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Abstract

The knee joint is very complex in terms of degrees of mobility and for normal biomechanics it is necessary for all the anatomical structures at this level to be within physiological limits. Problems can be caused by a number of risk factors such as age, sex, weight, or local risk factors such as patellar changes represented by patella alta or patella baja, which can lead to instability of the lower limb. Risk factors that may influence the development and progression of knee osteoarthritis have been evaluated. Changes in patellar position in relation to knee osteoarthritis were also studied. A group of 377 patients hospitalized for unilateral or bilateral knee pain with instability were included in the study. 239 of the 377 starting group presented knee osteoarthritis, constituting the study group. The risk factors analyzed were age, patient sex, BMI, weight status, anatomical changes in position of the patella (patella alta and patella baja), COBB angle and spine deviation. The results indicated that obesity, anatomical changes in the position of the patella, (patella alta), COBB angle and spine deviations represent significant risk factors in the onset of knee osteoarthritis.

Key words: *risk factors, joint instability, knee osteoarthritis,*

Introduction

The knee is a very complex joint from a biomechanical point of view and for the joint to function properly it is necessary for all of the anatomical structures that make up the knee to be within normal limits (1).

The knee joint has a high degree of mobility in terms of flexion and extension, and is comprised of the femuro-tibial joint that has the role of bearing the weight of the body, and the patellofemoral joint with a role in reducing friction caused by muscle contractions (2).

There are various conditions that produce changes in the joint load distribution, which alter the mechanical properties at the level of the cartilage, muscles and ligaments as well as affecting their normal composition and structure (3).

Local risk factors that can lead to disturbances in knee joint biomechanics, such as anatomical changes in position involving the patella or abnormalities in the patellofemoral surface, in combination with a number of general risk factors (such as age, sex or obesity), in time could lead to osteoarthritis, in the absence of therapeutic measures (4,5).

Anatomical changes in patellar position are described using the terms patella alta and patella baja, both of which may be due to a congenital defect, however, patella alta could be the result of various conditions such as patellar dislocation, neurological pathologies or idiopathic.

Patella baja is associated with trauma, ischemia of the patellar ligament or with knee surgery (6).

In the context of local anatomical changes, alterations of the biomechanics lead to a reduction in the joint functions, in association with pain and instability, leading to progression of osteoarthritis in the femoral-tibial compartment (7).

The knee joint is one of the most frequently affected joints by osteoarthritis, along with the hip joint or interphalangeal joints (8).

One of the most frequently encountered articular pathology in the USA is osteoarthritis; 19% of adults aged 45 and above are affected, and the alarming fact is that the number of people diagnosed is constantly increasing, and despite the ongoing research so far, the clear causes of osteoarthritis have not been fully elucidated (9).

The purpose of this study is to evaluate the modification of patellar position in relation to knee osteoarthritis, and the risk factors involved in the development of knee osteoarthritis.

Material and methods

The retrospective study included 377 patients, admitted to the Emergency Military Clinical Hospital "Dr. Iacob Cziha" Iasi, between July 2017 and July 2018. The patients included in the study were hospitalized due to knee pain (uni- or bilateral), accompanied by instability.

The exclusion criteria from this study was a history of knee surgery. Radiographs were obtained with a conventional radiology machine: Telediagnostic Philips Optimies.

Measurements of the narrowing of the tibio-femoral joint space and the Insall-Salvatti index were performed on radiographs, digitized in the FCR Prima Console Viewer program.

In order to grade the severity of knee osteoarthritis, according to the Kellgren-Lawrence classification, radiographs of the knee in the anterior view in orthostatic position were studied.

I performed the measurements using as a reference the middle portion of the lateral and medial joint spaces of each knee, and determined the maximum height of the radiotransparent area between the edges of the tibio-femoral articular surfaces.

Radiographs that showed a joint space of less than 5 mm were graded according to the Kellgren-Lawrence classification.

The Kellgren-Lawrence classification (10):

- Grade 0: Absence of radiological changes;
- Grade 1: possible narrowing of the joint space with a tendency for osteophyte formation;
- Grade 2: detecting osteophytes and possible narrowing of the joint space;
- Grade 3: definite narrowing of the joint space, significant osteophytosis and possible bone deformities;
- Grade 4: marked narrowing of the joint space accompanied by deformations, bone sclerosis and major osteophytes.

Using the Kellgren-Lawrence classification, two study groups were established. The first group consisted of 138 patients without knee osteoarthritis (grade 0), the second group consisted of 239 patients with knee osteoarthritis (grades I-IV).

Patellar instability is caused by the abnormal positioning of the patella, characterized by high or low positions; patella alta and patella baja.

To determine the patellar position, I calculated the Insall-Salvatti index, which represents the ratio between the length of the patellar tendon and the height of the patella. Insall-Salvatti index normal values are between 0.8-1.2, an index lower than 0.8 suggests patella baja; and greater than 1.2, patella alta.

Technique: I evaluated lateral knee radiographs with the knee flexed at 30°. In order to determine the length of the patellar tendon, I measured the distance between the lower pole of the patella and the tibial tuberosity. To obtain the height of the patella, I measured the greatest pole-to-pole length.

Patients were classified according to weight and height using the BMI index: underweight - BMI <18.5; normal weight - BMI between 18.51 - 24.99; overweight - BMI between 25.00 - 29.99; grade I obesity - BMI between 30.00 - 34.99; grade II obesity - BMI between 35.00 - 39.99; morbid obesity - BMI of 40.00 or above.

The study evaluated the risk factors with significant predictability in the presence of knee osteoarthritis.

Results

In this study group 52.72% of cases had grade I knee osteoarthritis on the left while 51.88% had grade I knee osteoarthritis on the right. Grade II was found at 19.67% on the left and 20.92% on the right, III on 10.04% on the left, respectively 10.04% on the right, and Grade IV had a proportion comparable to the III, 10.04% on the left and 14.23% on the right (Table 1). The mean age in patients with knee osteoarthritis was significantly ($p < .001$) higher (64.39 ± 10.26) compared to the age of patients without knee osteoarthritis (43.83 ± 13.42).

Insall-Salvatti index on both left and right showed significantly higher values for patients with knee osteoarthritis ($P < .001$). Abnormal patella positioning such as patella alta frequency is 91.82% in patients with knee osteoarthritis, a significantly higher value ($p < .001$) compared to its frequency in the patients without knee osteoarthritis (8.18%). Also, the frequency of patella baja was significantly higher for patients with knee osteoarthritis (90.24%) (Table 1).

Spine deviations were represented in the study group of 95.24% dextroscoliosis and 99.01% levoscoliosis (Table 1).

Table 1. Characteristics of patients in the study group and the control group

	Knee osteoarthritis (n=239) †		Control group (n=138) †	Test statistic	p-value‡
Age (year)	64.39±10.26		43.83±13.42	-12.71	<.001*
Male/Female	86/153 (44.33%/83.61%)		108/30 (55.67%/16.39%)	62.60	<.001*
BMI	29.72±4.09		26.81±3.5	48.65	<.001*
Normal weight	20 (39.22%)		31 (60.78%)		
Over weight	113 (56.78%)		86 (43.22%)		
obesity grade I	91 (82.73%)		19 (17.27%)		
obesity grade II	12 (85.71%)		2 (14.29%)		
obesity grade III	3 (100%)		0 (0%)		
Kellgren-Lawrence classification	<u>left</u>	<u>right</u>			
Grad 0	18 (7.53%)	7 (2.93%)		348.29	<.001*
Grad I	126 (52.72%)	124 (51.88%)			
Grad II	47 (19.67%)	50 (20.92%)			
Grad III	24 (10.04%)	24 (10.04%)			
Grad IV	24 (10.04%)	34 (14.23%)			
Insall-Salvatti index left	1.18±0.14		1.07±0.13	4.393	0.0125*
Insall-Salvatti index right	1.29±0.12		1.09±0.13	4.006	0.0097*
Anatomical changes of position: patella: <i>norma / alta / baja left</i>					
<i>normală / alta / baja right</i>	88(41.71%)/146(91.82%)/5(71.43%)		123(58.29%)/13(8.18%)/2(28.57%)	98.34	<.001*
	86(41.75%)/148(90.24%)/5(71.43%)		120(58.25%)/16(9.76%)/2(28.57%)	92.73	<.001*
COBB angel (grade)	5.824±6.05		2.12±3.48	-3.842	.0001
Spine deviation					
Normal	79 (37.09%)		134 (62.91%)	146.25	<.001*
Dextroscoliosis	60 (95.24%)		3 (4.76%)		
Levoscoliosis	100 (99.01%)		1 (0.99%)		

† Values were expressed as number (%) mean ± SD or percent at%;

‡ ANOVA or Mann-Whitney U Test; Chi-square test or Fisher's exact test

(*) Marked effects are significant at $p < .05$

Table 2. Model coefficients and Wald test in logistic regression on predictive factors for knee osteoarthritis onset

Multiple regression, dependent variable: knee osteoarthritis onset	B	SE	Wald	Sig. p	Odd ratio Exp(β)	95% CI for Exp(B)	
						Lower	Upper
Age	.694	.126	3.984	.026*	1.532	1.113	3.505
Female	1.687	.215	5.816	.003*	1.976	1.769	4.587
BMI	2.874	.307	4.682	.001*	2.064	1.668	5.669
Normal weight	.614	.019	.664	.237	.879	.687	.991
Over weight	.889	.208	.795	.069	.785	.432	.875
obesity grade I	2.684	.067	6.804	.004*	2.687	1.864	6.881
obesity grade II	3.632	.817	5.972	.002*	2.935	1.904	8.557
obesity grade III	3.314	.061	5.991	.000*	4.588	2.671	9.644
Anatomical position abnormality							
Patella alta	2.464	.154	9.331	.000*	5.971	4.677	9.471
Angel COBB	6.541	.249	5.615	.025*	3.587	1.694	7.871
Spine alignment							
dextroscoliosis	1.336	.607	10.063	.021*	2.571	1.864	3.541
levoscoliosis	1.864	.239	8.004	.038*	2.108	1.526	2.875

SE- standard error; 95%CI - Confidence Interval

(*) Marked effects are significant at $p < .05$

The assessment of the risk factors was performed on the basis of multiple logistic regression assessing the predictive power of several independent variables introduced simultaneously regarding the occurrence of knee osteoarthritis. Logistic regression (binomial: the present absence of an event) is a form of regression that is used when the dependent variable is dichotomous and the independent variables are of any type. Even if the independent variables are introduced in the model simultaneously, it will evaluate the degree of independent prediction for each variable, but the prediction will be adjusted considering the full context of the model. The variables included in the analysis, which in the univariate analysis (Table 1) showed a significant association with the presence of knee osteoarthritis. The independent variables (presumed predictive factors) introduced in the study were: age, female gender, BMI, obesity (normal weight, overweight, grade I obesity, grade II obesity, morbid obesity), anatomical position abnormality (patella alta), COBB angle, spine deviation (dextroscoliosis, levoscoliosis). The ENTER model was applied in which all the independent variables were introduced in one step.

The results indicated that the most significant risk factors are the presence of patella alta (OR=5.97, 95% CI: 4.677-9.471, $p < .001$), followed by obesity grade III (OR = 4.588, 95% CI: 2.671- 9.644, $p < .001$) and COBB angle value (OR = 3.587, 95% CI: 1.694, 7.871, $p = .025$) (Table 2). Although there is a slightly lower risk of spine deviation, BMI, female gender, and high age are important risk factors for knee osteoarthritis ($p < .001$) (Table 2).

Discussion

A normal patellar position is a very important element in the biomechanical function and its alteration is associated with the appearance of symptomatology (11).

In the literature, patellofemoral osteoarthritis is reported to affect 65% of persons aged over 50 years old (12) and the association of patellofemoral osteoarthritis with an abnormal patellar position is emphasized (13).

All the patients included in this study with at least grade 1 according to the Kellgren-Lawrence classification had patellofemoral osteoarthritis in varying degrees; further research is needed on this aspect.

Knee osteoarthritis is addressed in most studies as a combination of pathophysiological processes that produce cartilage destruction, pain and disability, which have an effect on the social and professional life of patients; this pathology in advanced stages produces disability (14,15). Patients with knee osteoarthritis demonstrate instability during gait due to pain, with or without patellar height changes.

In this study a series of risk factors associated with the occurrence or progression of the pathology are represented by age, sex, body mass index, anatomical or biomechanical changes or various pathologies (Table 2), as well as the literature report (16). Although in theory, it can develop at any age, osteoarthritis is found especially in adults over 40 years old and affects both sexes.

Comparative studies in the international literature highlight an increased prevalence of knee osteoarthritis in women (17).

The results obtained from the group show the same conclusions and demonstrate that females are most affected by osteoarthritis (83.61%).

The data obtained in the study supports the research carried out so far and underlines that knee osteoarthritis has a high prevalence among individuals with high body mass index (29.7 ± 4.09).

In a meta-analysis of the literature, it was demonstrated that obesity is the risk factor with a major impact on knee osteoarthritis, joint pain and functional impotence (18).

Given that obesity has the potential of being reduced, it is possible to propose a physical exercise program and a rigorous diet (19,20).

The findings of a recent study on the influence of changes in patellar position in patellofemoral osteoarthritis, using magnetic resonance investigations, conclude that patella alta is a predictive factor for lateral patellofemoral osteoarthritis (21). In the analyzed group, patients with knee osteoarthritis presented patella alta with a frequency of 91.82% on the left and 90.24% on the right. The Cobb angle showed a significantly higher mean value ($p = .0001$) in the study group 5.824 ± 6.05 compared with the average value found in the patients in the control group 2.12 ± 3.48 .

Abnormal values of spine curvature angles, especially in the case of lumbar lordosis, has a positive association with knee osteoarthritis, explained by the fact that the spine forces the patient to bend their knees to maintain their centre of gravity (22).

Maintaining the physiological alignment in the sagittal plane at both the spine, the hip joints and the knee is essential for the prevention of increased mechanical stress in any of these segments, and for this, researchers emphasize the importance of postural and gait correction (23, 24).

B. Supartono outlines in his study that the changes in spine alignment have a great influence on the installation and progression of knee osteoarthritis, the risk being 7.5 times higher in patients with moderate changes in the Cobb angle (25).

The literature highlights the importance of detecting risk factors in the installation and progression of knee osteoarthritis and also underlines and attempt to eliminate or reduce them (26, 27).

Conclusion

Unfortunately, knee osteoarthritis cannot be treated curatively yet; it is important to evaluate and eliminate risk factors involved in its installation and progression as much as possible. Risk factors such as obesity, anatomical changes in position and spinal deviation may be considered to prevent the installation of knee osteoarthritis.

Since a vicious cycle is generated by the fact that joint instability influences the installation and progression of osteoarthritis, which in turn aggravates instability, it is important to take measures to eliminate them.

Pain and functional impotence are important causes of disability. Pain and its psychological impact are subjective from one individual to another and it offers researchers perspectives that can aid doctors in their practices, since in general a physician's view on the real degree of the loco-regional changes can be distorted by the patient.

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References

1. Stefano Zaffagnini, David dejour, Alberto Grassi, et al. Patellofemoral anatomy and biomechanics: current concepts *Joints*. 2013; 1(2):15–20.
2. Jawad F. Abulhasan, Michael J. Grey Anatomy and physiology of knee stability *J Funct Morphol Kinesiol*. 2017; 2:34.
3. Farshid Guilak Biomechanical factors in osteoarthritis *Best Pract Res Clin Rheumatol*. 2011;25(6):815-823.
4. Farshid Guilak, Ph.D. Biomechanical factors in osteoarthritis *Best Pract Res Clin Rheumatol*. 2011; 25(6): 815–823.
5. Ashraf Ramadan Hafez, Aqeel Mohammed Alenazi, Shaji John Kachanathu, Abdulmohsen Meshari Alroumi and Elham Saed Mohamed Knee osteoarthritis: A review of literature *Phys Med Rehabil Int*. 2014;1(5): 8.
6. Konstantinos Anagnostakos, Olaf Lorbach, Sarah Reiter, Dieter Kohn Comparison of five patellar height measurement methods in 90° knee flexion *Int Orthop* 2011;35(12):1791–1797.
7. E.M. Macri, D.T. Felson, Y. Zhang, et al. Patellofemoral morphology and alignment: reference values and dose-response patterns for the relation to MRI features of patellofemoral osteoarthritis *Osteoarthritis and Cartilage* 2017;25(10):1690-1697.
8. Belluzzi E, El Hadi H, Granzotto M, et al. Systemic and Local Adipose Tissue in Knee Osteoarthritis *J Cell Physiol*. 2017;232(8):1971-1978.
9. Ian J. Wallace, Steven Worthington, David T. Felson, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century *Proc Natl Acad Sci U S A*. 2017;114(35): 9332–9336.
10. Mark D. Kohn BA, Adam A. Sassoon, Navin D. Fernando, Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis *Clin Orthop Relat Res*.2016;474(8): 1886–1893.
11. Fitzpatrick CK, Baldwin MA, Laz PJ, FitzPatrick DP, Lerner AL, Rullkoetter PJ Development of a statistical shape model of the patellofemoral joint for investigating relationships between shape and function. *J Biomech*. 2011;44(13):2446-52.

12. E.M. Macri, D.T. Felson, Y. Zhang, et al. Patellofemoral morphology and alignment: reference values and dose-response patterns for the relation to MRI features of patellofemoral osteoarthritis *Osteoarthritis and Cartilage* 2017;25(10):1690-1697.
13. Lu W, Yang J, Chen S, Zhu Y, Zhu C Abnormal Patella Height Based on Insall-Salvati Ratio and its Correlation with Patellar Cartilage Lesions: An Extremity-Dedicated Low-Field Magnetic Resonance Imaging Analysis of 1703 Chinese Cases. *Scand J Surg*.2016;105(3):197-203.
14. Jones G What's new in osteoarthritis pathogenesis? *Intern Med J*. 2016;46(2):229-36.
15. Spinoso DH, Bellei NC, Marques NR, Navega MT Quadriceps muscle weakness influences the gait pattern in women with knee osteoarthritis *Adv Rheumatol*.2018;58(1):26.
16. Behzad Heidari Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I *Caspian J Intern Med* 2011;2(2): 205–212.
17. Plotnikoff R, Karunamuni N, Lytvyak E, et al. Osteoarthritis prevalence and modifiable factors: a population study *BMC Public Health*.2015;15:1195.
18. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis *Osteoarthritis Cartilage*. 2015;23(4):507-15.
19. Brosseau L, Taki J, Desjardins B, et al. The Ottawa panel clinical practice guidelines for the management of knee osteoarthritis. Part two: strengthening exercise programs *Clin Rehabil*.2017;31(5):596-611.
20. Yázigi F, Espanha M, Marques A, Teles J, Teixeira P Predictors of walking capacity in obese adults with knee osteoarthritis *Acta Reumatol Port*.2018;43(4):256-263.
21. Haj-Mirzaian A, Guermazi A, Pishgar F, et al. Association of patella alta with worsening of patellofemoral osteoarthritis-related structural damage: data from the Osteoarthritis Initiative *Osteoarthritis Cartilage*. 2019;27(2):278-285.
22. Ryoji Tauchi, Shiro Imagama, Akio Muramoto, Masaki Tsuboi, Naoki Ishiguro, Yukiharu Hasegawa Influence of spinal imbalance on knee osteoarthritis in community-living elderly adults Nagoya J Med Sci. 2015;77(3): 329–337.
23. W. J. Wang, F. Liu, Y.W. Zhu, M.H. Sun, Y. Qiu, W. J. Weng Sagittal alignment of the spine-pelvis-lower extremity axis in patients with severe knee osteoarthritis *Bone Joint Res*. 2016; 5(5): 198–205.
24. Hiroshige TATEUCHI Gait- and postural-alignment-related prognostic factors for hip and knee osteoarthritis: Toward the prevention of osteoarthritis progression *Phys Ther Res*. 2019; 22(1): 31–37.
25. B. Supartono, R. Gamma, S. Wiyono, S. Yuli The influence of scoliosis towards secondary osteoarthritis of the knee joint in athletes *BMJ Journals* 2016;50(1)A33.1-A33.
26. Michl GL, Katz JN, Losina E Risk and risk perception of knee osteoarthritis in the US: a population-based study. *Osteoarthritis Cartilage*. 2016;24(4):593-6.
27. Boiculescu, V. Lucian, Dimitriu, Gabriel, Moscalu, Mihaela, Nearest neighbor classification with improved weighted dissimilarity measure, *Proceedings of the Romanian Academy Series A-Mathematics Physics Technical Sciences Information Science*, 2009;10(2): 205-213.

Rehabilitation protocol with or without mobile health in overweight and obese knee osteoarthritis patients - a pilot study

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Abstract

Knee osteoarthritis (OA) is a degenerative and weight bearing joint disease that resulted from wear and tear of articular cartilage. It is more common in the overweight and obese knee OA patients. The objectives of pilot study were to assess the feasibility, acceptability and challenges of study design, study setting and tools of lower limb rehabilitation protocol among the knee OA patients who are overweight and obese. Twelve overweight and obese knee OA patients attending a Teaching Bay in the Pakistan were enrolled in the study and completed 6 training sessions over 2 weeks. The participants were divided randomly into Intervention Group with Mobile Health (IGW-mH), Intervention Group without Mobile Health (IGWO-mH) and the Control Group (CG). Both intervention groups were provided fifteen days of lower limb rehabilitation protocol but the CG did not. Two text messages per day for three days a week were sent to IGW-mH as a reminder to carry on their training session and instructions of daily care. All participants of intervention groups showed willingness to randomization and adherence to training sessions. The results indicated that eligibility criteria, recruitment rate and randomization procedures were feasible and there were no adverse events from training sessions. The participants demanded Urdu translation and pictures of lower limb rehabilitation protocol.

Key words: *mobile health technology, overweight, knee, osteoarthritis,*

1 Introduction

The most common form of arthritis is osteoarthritis (OA). It is characterized by a progressive destruction of articular cartilage, resulting in severe pain and disability (1). OA has been described as a condition characterized by use-related joint pain experienced on most days in any given month, for which no other cause is apparent (2). The wear and tear of articular cartilage in the knee OA disease is not only the main cause, but it is also considered a disorder of physiological processes that is manifested by progressive lesions of articular cartilage and other structures (3). Worldwide 250 million people, both men and women, are affected with symptomatic knee injury (4). Obesity is a significant as well as rapidly increasing global health issue. More than 39% and 13% of adults were considered overweight (body mass index > 25 kg/m²) and obese (body mass index > 30 kg/m²) respectively in 2014, and the prevalence of overweight and obesity has doubled

globally since 1980 (5). A recent published research study concluded that the excess of weight and adiposity had a negative impact in increasing pain perception of patients with OA (6). There is a gap in literature for utilizing mHealth to increase the effectiveness of OA self-management intervention delivery (7, 8). Health related services via a mobile device are known as mHealth (9). There is need of mHealth especially for the overweight or obese knee OA patients in order to reduce weight and enhance the quality of life. The objectives of pilot study were to assess the feasibility, acceptability and challenges of study design, study setting and tools of lower limb rehabilitation protocol among the knee OA patients who are overweight and obese. In the current pilot study the training sessions of lower limb rehabilitation protocol were performed in sitting or lying positions without putting mechanical pressure at the knee.

2 Methodology

2.1 Participants

The Participants were recruited via word of mouth by contacting with political and welfare organizations. A published research article suggested that active recruitment strategies were 66.5 times more effective and personal compared to passive recruitment strategies (10). Participants were recruited from the urban area of Punjab, Lahore. Inclusion criteria were both males and females overweight and obese knee OA patients, age between 45 and 60 years, having OA of one or both knees and fulfilling the second mild and three moderate grade criteria of Kellgren and Lawrence Scale (KLS). Grade 0, 1 and 4 of KLS were not included in the pilot study. Exclusion criteria were one or more of the identified flat feet, spinal deformities, knee surgery, corticosteroid injection at the knee, spinal deformities, cardiac problem or hormonal problem. The study was approved by the ethical committee of Rehmatul-Lil-Alameen Postgraduate Institute of Cardiology with reference No. RAIC PESSI/Esst/2019/487, and all participants provided written informed consent before participation in the study.

2.2 Study design

It was a single blinded randomized controlled study design. The participants were unaware about the intervention in the pilot study and therefore it was a single blinded randomized controlled study design. In randomization each participant has an equal chance of selection. Randomization was done by a computer generated number.

2.3 Study population

Study population were overweight and obese knee OA patients from the urban area of District, Lahore, Punjab, Pakistan. Normal weight participants were not included in the pilot study.

2.4 Study randomization

The researcher randomized the 12 participants equally into three groups, intervention group with mobile health (IGW-mH), intervention group without mobile health (IGWO-mH) and the control group (CG). Instructions of daily care were provided to all three groups.

2.5 Measurements and groups protocol

All participants completed baseline measurements of pain, body mass index, mobility, quality of life, activities of daily living, functional capacity,

functional strength, patient satisfaction, exercise adherence and self-management.

After baseline measurements, participants were randomly allocated into three groups by a computer generated number. Participants in two intervention groups were asked to complete six sessions over 2 weeks with their training sessions at their homes. Two weeks rehabilitation protocol was carried out three times a week for two weeks. It was consisted of warming up of 10 minutes followed by lower limb rehabilitation exercises in sitting or lying position. The resistance was provided with the help of elastic bands, force of gravity and ankle weights. At the end of training sessions a cooling down of 10 minutes was performed (table 1).

Table 1. Two weeks rehabilitation protocol

Muscle Group	Frequency	Duration
Hip flexors and extensors	Three times a week	Two weeks
Hip abductors and adductors		
Knee flexors and extensors		
Ankle dorsiflexors, plantarflexors		
Ankle invertors and evertors		
10 minutes warm up at the start and 10 minutes cooling down at the end of each training session.		

Both intervention groups (IGW-mH and IGWO-mH) followed the lower limb rehabilitation protocol and instructions of daily care for two weeks. Two text messages per day for three times a week for two weeks with the help of mHealth were provided only to IGW-mH as a reminder to carry on two week exercise protocol and instructions of daily care. The instructions of daily care are shown in table 2. The control group did not get text messages as a reminder. The CG only followed the instructions of daily care (Table 2).

After completion of the two week exercise protocol, the measurements of pain, body mass index, mobility, quality of life, activities of daily living, functional capacity, functional strength, patient satisfaction, exercise adherence and self management were again retested. These measurements were taken as a testing purpose and were not analyzed.

2.6 Feasibility, acceptability and challenges of study

The feasibility of the study was assessed by eligibility criteria, recruitment rate, dropout (lost to follow up) rate, willingness to the randomised and adverse events of pilot study. The acceptability of study was assessed by patient satisfaction and exercise adherence. The participants demanded the need of Urdu translation and pictures of lower limb rehabilitation protocol in their interviews. The interviews were conducted by the researcher.

Table 2. Instructions of daily care

Activity Name	Explanation
Sitting	Always prefers to sitting than standing.
Walking	Always walk with a stick.
Stair climbing	Avoid stair climbing.
Exercise	Do not walk, jog or run as an exercise plan.
Exercise positions	Always exercise in non-weight bearing positions. e.g sitting or lying positions
Body weight	Reduce your weight by avoiding taking of drinks and fat foods

The participants were also interviewed of future need in the real study. The questions regarding feasibility, acceptability and challenges are shown in table 3.

3 Results and Discussion

Recruitment began and completed in July, 2019. Fourteen participants were selected from the urban area of District, Lahore, Pakistan and assessed for enrollment in the Teaching Bay of Rehmatul-Lil-Alameen Postgraduate Institute of Cardiology. Two participants were excluded, one due to normal weight and the remaining one due to the cardiac problem. Twelve were randomized and completed the pilot study. Enrollment, allocation, follow-up and analysis of pilot study are shown in the flow chart of study (Figure 1).

Eight participants of intervention groups completed six training sessions in two weeks and followed the instructions of daily care, while four participants of

the CG followed the instructions of daily care. All participants showed willingness to randomization. An adverse event, withdrawal or dropout rate was zero. All participants of intervention groups showed exercise adherence to training sessions. All participants of intervention groups showed satisfaction with the rehabilitation protocol.

Table 3. Feasibility, acceptability and challenges of pilot study

Investigations	Questions	Answers
Feasibility	Good eligibility criteria	Yes or No
	Good Recruitment rate	Yes or No
	Dropout (lost to follow up) rate present	Yes or No
	Willingness to the randomised	Yes or No
	Adverse events present	Yes or No
Acceptability	Are you satisfied with the pilot study?	Yes or No
	Are you satisfied with exercise adherence?	Yes or No
Challenges	Do you need Urdu translation of lower limb rehabilitation protocol?	Yes or No
	Do you need pictures of lower limb rehabilitation protocol?	Yes or No
	Do you feel to recommend any future need in real study?	Yes or No

As shown in Figure 2, Researcher identified that the majority participants of intervention groups had following three challenges. These challenges were identified through the interview of participants. The participants demanded Urdu translation and pictures of two weeks lower limb rehabilitation protocol. The participants also demanded the support of the family member for the completion of their rehabilitation protocol. The results of pilot study identified that the participants of IGW-mH resulted more satisfaction and exercise adherence to the lower limb rehabilitation protocol than IGWO-mH and CG.

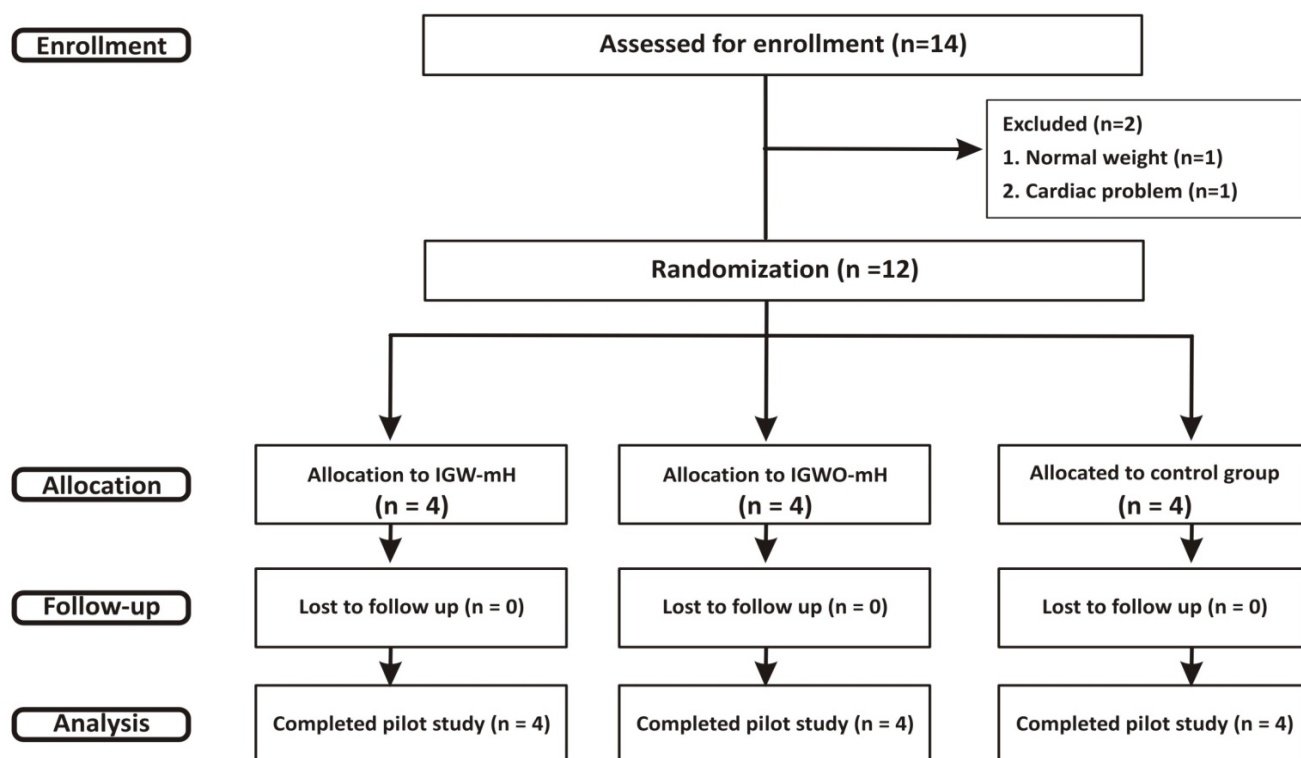


Fig. 1. Flow chart of pilot study

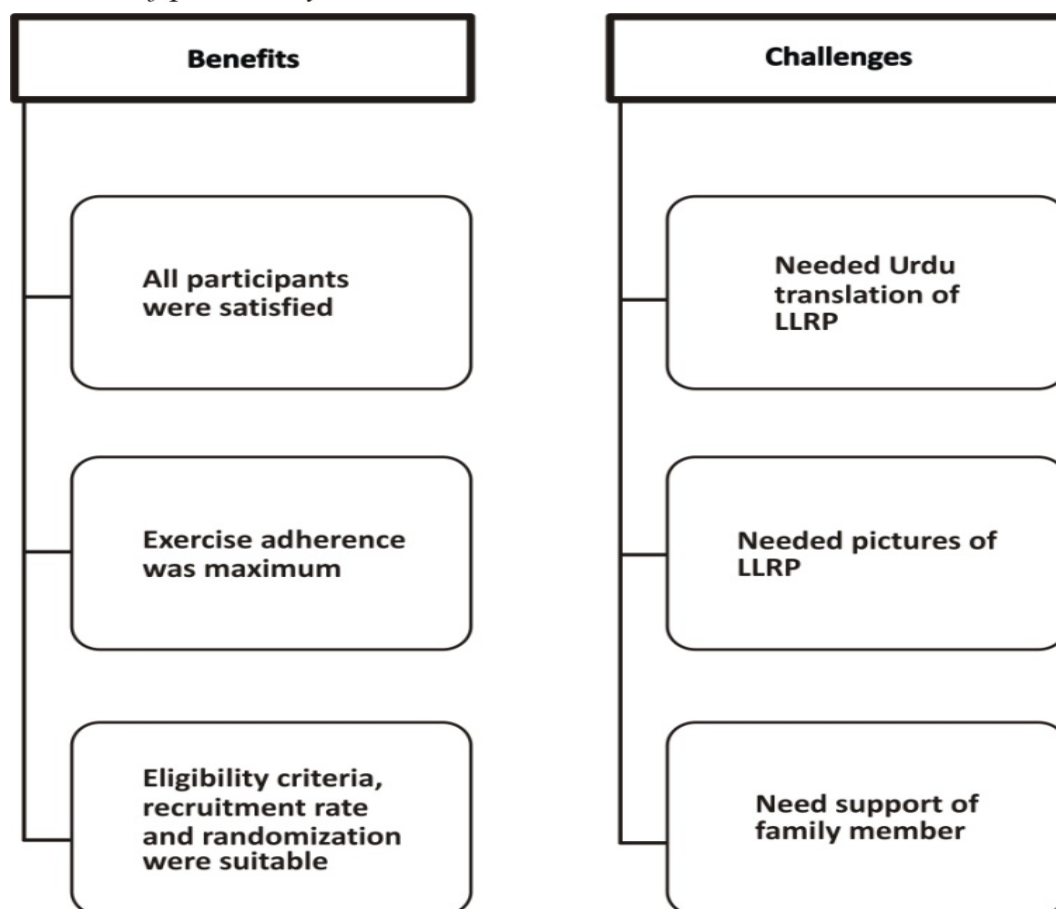


Fig. 2. Output from participant interview

4 Conclusion

The objectives of pilot study were to assess the feasibility, acceptability and challenges of study design, study setting and tools of lower limb rehabilitation protocol among the knee OA patients who are overweight and obese. The results indicated that eligibility criteria, recruitment rate and randomization procedures were feasible and there were no adverse events from training sessions. The participants demanded not only the translated version of lower limb rehabilitation protocol into Urdu language but also in the forms of pictures. However, the aims, methodology and results of current study would require a future trial of long duration to see the effectiveness of rehabilitation protocol using mHealth among the overweight and obese knee OA patients.

References

1. Warner SC, Valdes AM. The genetics of osteoarthritis: A review. *Journal of Functional Morphology and Kinesiology*. 2016 Mar;1(1):140-53.
2. Agel J, Akesson K, Amadio PC, Anderson M, Badley E, Balint G, Bellamy N, Bigos S, Bishop N, Bivans B, Bjorke PA. The burden of musculoskeletal conditions at the start of the new millennium. *World Health Organization-Technical Report Series*. 2003(919)
3. Ali A, Rosenberger L, Weiss TR, Milak C, Perlman AI. Massage therapy and quality of life in osteoarthritis of the knee: A qualitative study. *Pain Medicine*. 2016 Sep 1;18(6):1168-75.
4. O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. *Best Practice & Research Clinical Rheumatology*. 2018 Nov 22.
5. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, Farzadfar F. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *The Lancet*. 2011 Feb 12;377(9765):557-67.
6. Alfieri FM, Silva NC, Battistella LR. Study of the relation between body weight and functional limitations and pain in patients with knee osteoarthritis. *Einstein (São Paulo)*. 2017 Sep;15(3):307-12.
7. Choi W, Zheng H, Franklin P, Tulu B. mHealth technologies for osteoarthritis self-management and treatment: a systematic review. *Health informatics journal*. 2019 Sep;25(3):984-1003.
8. Grünloh C, Myreteg G, Cajander Å, Rexhepi H. "Why do they need to check me?" patient participation through eHealth and the doctor-patient relationship: qualitative study. *Journal of medical Internet research*. 2018;20(1):e11.
9. Labrique AB, Vasudevan L, Kochi E, Fabricant R, Mehl G. mHealth innovations as health system strengthening tools: 12 common applications and a visual framework. *Global health: science and practice*. 2013 Aug 1;1(2):160-71.
10. Mody L, Miller DK, McGloin JM, Freeman M, Marcantonio ER, Magaziner J, Studenski S. Recruitment and Retention of Older Adults in Aging Research: (See editorial comments by Dr. Stephanie Studenski, pp 2351–2352). *Journal of the American Geriatrics Society*. 2008 Dec;56(12):2340-8.

Effectiveness of pulmonary rehabilitation in improving quality of life in patients with different COPD stages

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Abstract

Introduction. Anxiety and depression are frequently associated conditions in COPD patients, and have also significant impact on their quality of life (QoL) and on the course of the disease. Pulmonary rehabilitation (PR) is an adjuvant, non-pharmacological method used in symptomatic COPD patients. The study aimed to evaluate the impact of COPD on QoL depending on disease severity, and to assess the supposedly positive effects of a pulmonary rehabilitation program (PRP) for COPD patients. **Material and method.** This research included patients with COPD GOLD stages II-IV undergoing bronchodilator therapy. QoL was assessed with the self-administered St George's Respiratory Questionnaire (SGRQ), and depression with the Beck Depression Inventory (BDI). PRP included 3-5 weekly physical training sessions for an average period of 12 weeks, but not less than 3 weeks. **Results.** The degree of QoL impairment was moderate in stage II (41.07) and severe in stages III (70.28) and IV (81.02). The most severe depression (score 26.6 vs 2.5 in healthy subjects) was also recorded in this group. After the patients underwent all PRP, QoL reassessment at 6 months revealed statistically significant improvements in all 3 groups ($p < 0.05$). In the GOLD COPD stage II group the average reduction was -4.38 units, in the group GOLD COPD stage III -5.37 units, and in the GOLD COPD stage IV -6.75 units. The depression score correlated with the SGRQ score, both of them being higher in the severe stages of disease. BDI administered again 6 months after PRP revealed a significant improvement in average score in all groups, respectively a decrease of -2.17 units in the COPD II group, -2.03 units in the COPD III group and -1.88 units in group COPD IV B group. **Conclusion.** The results of this study demonstrate a favorable impact of PRP on improving COPD associated symptoms, depression, and QoL in all the 3 monitored COPD patient groups, with statistically significant and persistent positive results over time (6 months after completion of PRP).

Key words: COPD, pulmonary rehabilitation program, Quality of life (QoL), depression,

Introduction

Patients diagnosed with chronic obstructive pulmonary disease (COPD) present with different symptoms that significantly impair health-related quality of life (QoL). Anxiety and depression are frequently associated conditions in COPD patients, and have also significant impact on their QoL and on the course of the disease. Pulmonary rehabilitation (PR) is an adjuvant, non-pharmacological method used in symptomatic patients with chronic lung disease. Chronic obstructive pulmonary disease (COPD) is the first indication for referral to a pulmonary rehabilitation program (1). Given the chronic and disabling nature of this disease, the quality of life (QoL) of these patients is profoundly altered. COPD patients have chronic symptoms, especially dyspnea, cough and asthenia. The course of disease is characterized by exacerbations mainly

due to respiratory tract infections, noxious exposure, non-adherence to chronic inhaled medication or long-term oxygen therapy, or decompensation of associated diseases (2-7). Systemic inflammatory changes, weakness and muscle atrophy (8) occur in advanced stages of disease. All of these result in limited exercise capacity, restriction in activities of daily living (ADL) and occurrence of depression (9). The reported frequency of depression in COPD patients differs between studies (10-55%), but is higher than in other chronic diseases and worsens in severe or exacerbated forms (10-86%) (10,11). The study aimed to evaluate the impact of COPD on QoL depending on disease severity, and to assess the supposedly positive effects of a pulmonary rehabilitation program for COPD patients.

Materials and methods

This research is part of a study conducted at the Pulmonology Department of the Timisoara "Victor Babes" Hospital, aimed to determine the effectiveness of PR on lung function, exercise tolerance and QoL in patients with COPD GOLD stages II-IV undergoing bronchodilator therapy. The inclusion and exclusion criteria had been described in a previous publication (12). QoL was assessed with the self-administered St George's Respiratory Questionnaire (SGRQ), and depression with the Beck Depression Inventory (BDI).

SGRQ, developed by PW Jones et al., is one of the most frequently used questionnaires for assessing QoL in chronic respiratory diseases (13). The questionnaire is structured as follows: Part I addresses the symptoms: presence of cough, expectoration, dyspnea, wheezing; frequency, duration and time of occurrence of dyspnea episodes, number of good days/week; Part II assesses activity (16 items about activities limited by dyspnea) and impacts (26 items), gradually following the impact of the disease on ADL, psychosocial, professional, material status and treatment options. Patients are asked to tick a box for each question, and three domain scores and a total score are obtained. The highest score is 100 units, a higher score indicating poorer quality of life (14). A minimal decrease in time or an over 4-unit difference between groups is considered clinically significant (15).

The degree of depression was assessed using a specific questionnaire, namely the BDI, the most popular depression screening tool (14). The assessment consisted of a 21-question interview aimed at measuring the depressive symptoms and irritability, guilt, fatigability, weight loss, and sexual dysfunction. For each question there are 4 answers, rated 0-3, and the total score reflects the degree of depression.

The pulmonary rehabilitation program (PRP) included 3-5 weekly physical training sessions (25 to 45 minutes each) for an average period of 12 weeks, but not less than 3 weeks, according with previous published data (16). After warming-up and stretching, patients proceeded to endurance exercises, such as treadmill walking or cycling. Later on, the patients continued with aerobic exercises for respiratory muscle, arm, and lower limb training. Strength training included weight lifting exercises or the use of multifunctional machines. Patients received education about

diaphragmatic breathing exercises. Intensity of exertion was established so that the patients to have a dyspnea score between 4 and 8 on the Borg scale. Joint educational meetings of the multidisciplinary team with the patient groups were organized.

Results

The pre-rehabilitation assessment included 141 patients and 32 healthy subjects. QoL was visibly impaired in patients with severe COPD forms (Table 1).

Table 1. General data and initial assessment. Comparison by stages of disease severity

Parameters	Heathy subjects	COPD GOLD stage		
		GOLD II	GOLD III	GOLD IV
No. subjects	32	43	45	53
No. of subjects who completed the PRP		12	29	33
Mean age, years	55.6	62.9	63.1	64.2
FEV1%	96.2±9.8	64.21±9.5	39.50±5.86	24.49±7.54
SGRQ score	17.8±5.09	41.07±29.11	70.28±24.37	81.02±6.86
BDI score	2.5±2.0	17.5±4.22	23.33±8.07	26.6±4.49
Patients with comorbidities (no, %)	9 (28.12)	18 (41.8)	23 (51.1)	38 (71.6)

The degree of QoL impairment was moderate in stage II (41.07) and severe in stages III (70.28) and IV (81.02). The most severe depression (score 26.6 vs 2.5 in healthy subjects) was also recorded in this group. We found an average increase of 24.72 units from the GOLD COPD stage II group to GOLD COPD stage III group (the highest increase, equivalent to the most marked alteration in QoL), and an average increase of 5.78 units from the COPD stage III group to COPD stage IV group. Increases in the degrees of QoL impairment were encountered in all the three sections assessed by the SGRQ (symptoms, activity, and impacts, respectively). After the patients underwent all PRP phases, QoL reassessment at 6 months revealed statistically significant improvements in all 3 groups ($p < 0.05$). Thus, significant reductions in the score were obtained in each group. In the GOLD COPD stage II group the average reduction was -4.38 units, in the group GOLD COPD stage III -5.37 units, and in the GOLD COPD stage IV -6.75 units.

The depression score correlated with the SGRQ score, both of them being higher in the severe stages of disease (Table 2).

Table 2. Comparison of QoL and depression measures according to COPD severity stage

COPD GOLD stages	QoL score			BDI score		
	Baseline	6 months after PRP	Diff	Baseline	6 months after PRP	Diff
GOLD II	42.46 (DS±5.98)	38.08 DS±5.2 0	4.38	17.83 DS±2.98	15.66 DS±2.50	2.17
Outpatient PRP	42.47	38.67	3.8	17.5	16.25	1.25
Inpatient PRP	42.45	36.9	5.55	18.5	17	1.5
GOLD III	68.17 DS±10.52	62.80 DS±9.54	5.37	22.75 DS±4.13	20.72 DS±4.17	2.03
Outpatient PRP	66.04	61.26	4.78	21.6	19.2	2.4
Inpatient PRP	70.45	64.46	5.99	23.9	22.2	1.7
GOLD IV	75.33	68.58	6.75	24.84	22.96	1.88

In the groups receiving PRP we found the same tendency, with the gradual increase of the average score from the COPD stage II group (17.83 units - mild depression) to the COPD stage III group (22.75 units - moderate depression), with the highest score recorded in the COPD stage IV group (24.84 units - severe depression). BDI administered again 6 months after PRP revealed a significant improvement in average score in all groups, respectively a decrease of -2.17 units in the COPD II group, -2.03 units in the COPD III group and -1.88 units in group COPD IV B group.

Patients who underwent inpatient PRP had a poorer QoL than those on outpatient PRP, both at baseline and at 6 months. The difference between the outcomes of inpatient and outpatient PRP was not statistically significant ($p > 0.05$). Both groups had a favorable evolution, respectively with a decrease at 6 months (Table 3).

Table 3. Comparative statistical analysis of QoL evolution after PRP in COPD by disease severity stages

Table Analyzed	QoL COPD II	QoL COPD III	QoL COPD IV
Column A	baseline	baseline	baseline
vs	vs	vs	vs
Column B	6 month	6 month	6 month
Paired t test			
P value	<0.0001	<0.0001	<0.0001
P value summary	***	***	***
Are means significantly different? (P < 0.05)	Yes	Yes	Yes
One- or two-tailed P value?	Two-tailed	Two-tailed	Two-tailed
t, df	t=7.846 df=11	t=7.722 df=28	t=15.71 df=32
Number of pairs	12	29	33
How big is the difference?			
Mean of differences	4.383	5.366	6.755
95% confidence interval	3.154 to 5.613	3.943 to 6.788	5.879 to 7.630
R square	0.8484	0.6805	0.8853
How effective was the pairing?			
Correlation coefficient (r)	0.9497	0.9350	0.9816
P value (one tailed)	<0.0001	<0.0001	<0.0001
P value summary	***	***	***
Was the pairing significantly effective?	Yes	Yes	Yes

Of the total of 141 individuals initially assessed, 79 had one associated disease (56%). More than half (64.3%) of the elderly patients (≥ 65 years) had comorbidities, some of them having 3 to 5 associated diseases. The most common chronic diseases associated with COPD were: cardiovascular diseases (ischemic heart disease, high blood pressure, and lower limb arteriopathy), rheumatic diseases, neurological diseases, diabetes, obesity, sleep apnea.

Discussion

Assessment of QoL with SGRQ demonstrated that QoL was affected in all COPD groups, and the degree of impairment correlated strongly with disease severity. However, QoL impairment was found even in patients with milder disease stages (17). Symptoms may have an earlier age of onset when associated with other lung tissue diseases besides emphysema (18). The study by Nonato et al. showed a significant correlation between COPD severity, BODE (Body mass index, airflow Obstruction, Dyspnea and Exercise capacity) score and QoL, the results being comparable (SGRQ score 52.3 ± 19.0 regardless of COPD severity) (17). Medinas-Amoróset al. also reported that the total SGRQ score of 48.26 ± 16.84 correlated with the GOLD classification and BODE score. The SGRQ score was 44.06 in stage II; 46.68 in stage III and 53.37 in stage IV COPD, slightly lower than in our study, especially in patients in a very severe disease stage (19).

It is increasingly recognized that, although used as a measure of severity in COPD, FEV1 does not describe all disease manifestations. Thus, besides dyspnea index, exercise capacity index, BODE index, QoL assessment is important as it reflects patient health status (20). As in bronchiectasis, in COPD attempts are being made to find biomarkers predictive of unfavorable course, exacerbations and QoL impairment (21-23).

The comorbidities commonly associated with COPD further affect the health-related quality of life (24). Metabolic disorders and the presence of sleep apnea worsen both the respiratory symptoms and the associated diseases such as type II diabetes, high blood pressure, heart failure (25-29). Along with conventional treatment, patients suffering of anxiety and depression associated with these chronic conditions (30-32) occasionally use complementary and alternative therapies and balneal specific rehabilitation (33-37).

Anxiety and depression assessment is important in COPD patients. Several scales can be used in this respect: Anxiety Inventory for Respiratory disease (AIR), COPD Anxiety Questionnaire (CAF), Primary Care Evaluation of Mental Disorders (PRIME-MD), Patient Health Questionnaire (PHQ), Generalized Anxiety Disorder 7-item (GAD-7), Hospital Anxiety and Depression Scale (HADS), Beck Anxiety Inventory (BAI), and Beck Depression Inventory (BDI). In our study, we used the BDI, which confirmed depression as a symptom in COPD, its severity being correlated with disease stages (11). Patients with COPD and depression are at higher risk of continuing smoking, progression of lung function decline, decreased lung function, exacerbations, hospitalizations and death (38). Although the disease prognosis is not as gloomy as in other lung or infectious diseases, COPD remains a condition that carries significant mortality and morbidity rates (39-42).

Conclusions

The results of this study demonstrate a favorable impact of PRP on improving COPD associated symptoms, depression, and QoL in all the 3 monitored COPD patient groups, with statistically significant and persistent positive results over time (6 months after completion of PRP). QoL assessment and recognition of COPD-induced depression or anxiety and associated diseases are extremely important. Non-pharmacological interventions (cognitive behavioral therapy), psychoemotional therapy sessions, as well as pulmonary rehabilitation programs can improve the QoL of COPD patients.

Declaration of conflict of interests/Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this article.

Informed consent

Informed consent was obtained from all patients included in this study.

References:

1. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine*. 2013;188:e13-e64

2. Hoge S-P, Tudorache E, Fildan AP, Fira-Mladinescu O, Marc M, Oancea C. Risk Factors of Chronic Obstructive Pulmonary Disease Exacerbations Clin Respir J. 2020;00:1–15
3. Rajnoveanu RM, Antoniu S, Ulmeanu R Combined long-acting bronchodilator single therapy for COPD. Expert Opinion on Pharmacotherapy 2014;15(1): 139-142
4. Davis JR, Wu B, Kern DM, Tunceli O, Fox KM, Horton J, et al. Impact of nonadherence to inhaled corticosteroid/LABA therapy on COPD exacerbation rates and healthcare costs in a commercially insured US population. Am Health Drug Benefits. 2017;10(2):92–100.
5. Tofolean D, Popescu G, Arghir IA, Frandes M, Fildan AP. A Different Approach of Chronic Obstructive Pulmonary Disease Severity and Plastic Medical Devices Used for Oxygenotherapy. Materiale Plastice. 2019; 56(2): 295-300
6. Motoc NS, Man MA, Tudorache SI, Rusu E, Brailescu CM, et al. The Importance of Mask Type and Mask Materials in Sleep Apnea Patients. Revista de Chimie. 2019; 70(9), 3273-3276.
7. Munteanu LA, Fildan AP, Tudorache E, Fira-Mladinescu O, Frandes M, Timar B, Oancea C, Tofolean DE. Inhaler technique errors in Romanian patients with asthma - a multicenter study. Patient Preference and Adherence. 2019; 13:1401-1414
8. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med. 1996; 153:976–980
9. Singer J, Yelin EH, Katz PP, et al. Respiratory and skeletal muscle strength in chronic obstructive pulmonary disease: impact on exercise capacity and lower extremity function. J Cardiopulm Rehabil Prev. 2011; 31(2):111–119
10. Willgoss TG, Yohannes AM. Anxiety disorders in patients with COPD: a systematic review. Respir Care. 2013;58(5):858-866.
11. Yohannes AM, Kaplan A, Hanania NA. Anxiety and Depression in Chronic obstructive Disease: recognition and management. Cleveland Clinic Journal of Medicine.2018; S11-S18 doi: 10.3949/ccjm.85.s1.03
12. Tudorache E, Motoc NS, Pescaru C, Crisan A, Ciumarneau L. Impact of pulmonary rehabilitation programs in improving health status in COPD patients. Balneo Research Journal. 2019; 10(4):472-477
13. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991;85(Suppl B):25–31.
14. Mc Dowell I. Measuring health: a guide to rating scales and questionnaires. 3rd ed. New York: Oxford University; 2006
15. Kon SS, Canavan JL, Jones SE, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. Lancet Respir Med. 2014;2(3):195–203.
16. Zeng Y, Jiang F, Chen Y, Chen P, Cai S. Exercise assessments and trainings of pulmonary rehabilitation in COPD: a literature review. Int J Chron Obstruct Pulmon Dis. 2018;13:2013–2023.
17. Nonato NL, Díaz O, Nascimento OA, Dreyse J, Jardim JR, Lisboa C. Comportamiento de la calidad de vida (SGRQ) en pacientes con EPOC según las puntuaciones BODE. Arch Bronconeumol. 2015; 51:315–321.
18. Deacu M, Tofolean DE, Bosoteanu M, Pulmonary alveolar lipoproteinosis associated with emphysematous areas. Rom J Morphol Embryol. 2012; 53(1): 173-177
19. Medinas-Amorós M, Mas-Tous C, Renom-Sotorra F, Rubí-Ponseti M, Centeno-Flores MJ, Gorriz-Dolz MT. Health-related quality of life is associated with COPD severity: a comparison between the GOLD staging and the BODE index. Chron Respir Dis 2009; 6(2):75–80.
20. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005–12.
21. Lesan A, Man M A, Nemes R M, Harsovescu T, Tudorache IS, Boca BM, Pop CM. Serum Interleukin 4 and 6 Levels Measured Using the ELISA Method in Patients with Acquired Bronchiectasis Compared to Healthy Subjects. Rev Chim (Bucharest) 2019; 70(7), 2410-2414.
22. Motoc NS, Martinovici P, Boca B M, Tudorache IS, Harsovescu T, Furtunescu F L, Man MA, Pop CM. Neutrophil-to-lymphocyte ratio (NLR) and Platelets-to-lymphocyte (PLR) Ratio in Patients with Exacerbation of Bronchiectasis. Rev Chim (Bucharest). 2019; 70(11): 3889-3892.

23. Jimborean G, Arghir OC, Cambrea SC, Dantes D, Socaci A, Otelea MR, Bechir ES, Ianosi ES. The Clinical Implications of Carbon Dioxide Increased Level in Arterial Blood Related to Severe Exacerbations of Chronic Obstructive Pulmonary Disease. *Revista de Chimie*, 2018, vol 69(8): 2050-2053.
24. Hillas G, Perlikos F, Tsiligianni I, Tzanakis N. Managing comorbidities in COPD. *Int J Chron Obstruct Pulmon Dis*. 2015;10:95-109.
25. Trenchea M, Arghir IA, Popescu G, Rascu S, Bechir ES, Tofolean D, Fildan AP, Ion I, Dantes E. The Triad Nocturia, Smoking and Obstructive Sleep Apnea. *Rev Chim (Bucharest)* 2019; 70(5):1839-1842.
26. Anton A, Tofolean DE. Obstructive sleep apnea and metabolic syndrome: is there a correlation? *Sleep Medicine*. 2017;40(1): E16-E16.
27. Jimborean G, Szasz S, Szathmary M, Csipor A, Arghir OC, Nemes RM, Postolache P, Ianosi ES. Association between Chronic Obstructive Pulmonary Disease and Sleep Apnea Experience of Pulmonology Clinic Tg Mures, Romania. *Rev. Chim. (Bucharest)*. 2018; 69(4):1014-1017.
28. Boldova A, Celli BR, Marin JM, Carrizo SJ, Soriano JB. Outcomes in Patients with Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea. *Am J Respir Crit Care Med*. 2010;182(3):325–31.
29. Rusu A, Nita C, Todea D, Rosca L, Bala C, Hancu N. Correlation of the daytime sleepiness with respiratory sleep parameters in patients with sleep apnea and type 2 diabetes. *ActaEndocrinologica*. 2011; VII(2):163-171.
30. Lupu AA, Ionescu EV, Iliescu MG, Almasan RE, Oprea C, Ion I, Iliescu DM. Effect of Techirghiol specific climate factors on the patients quality of life with degenerative lumbar pain. *J Environ Prot Ecol*. 2018,19 (4), 1857.
31. Tica I, Lupu A, Botnariuc M, Petcu L, Oprea C, Badiu RG, Iliescu DM, Ionescu EV, Tica VI; Iliescu MG. Brain - Derived Neurotrophic Factor - a Marker for the Balneal Treatment of Chronic Low Back Pain? *Rev.Chim.(Bucharest)* 2019, 70(9): 3180
32. MG. Iliescu, AA. Lupu, EV. Ionescu, I. Tica, RE Almasan, C. Oprea, DM. Iliescu. Water, nature, techirghiol – long – term therapeutic benefits using aquatic exercise for patients with degenerative low back pain. *J Environ Prot Ecol*. 2019; 20(3):1505-1516.
33. Kessler RC, Soukup J, Davis RB, Foster DF, Wilkey SA, et al. The use of complementary and alternative therapies to treat anxiety and depression in the United States. *Am J Psychiatry*. 2001;158(2):289-94.
34. Oprea C, Ionescu EV, Iliescu MG, Almasan RE, Calota N, Iliescu DM. Monitoring and evaluation of patients satisfaction in medical units that use natural factors for treatment. *J Environ Prot Ecol*. 2019;20(1):447-452.
35. Tucmeanu AI, Popescu DM, Ionescu EV, Almasan RE, Oprea C, Mociu A, Iliescu MG, Iliescu DM. Management Consultancy for Organisational Change in Health from the Manager Perspective. *J Environ Prot Ecol*. 2017, 18 (3), 1238.
36. Solomon D, Adams J. The use of complementary and alternative medicine in adults with depressive disorders. A critical integrative review. *J Affect Disord*. 2015;179:101-13.
37. Almasan RE, Ionescu EV, Iliescu MG, Oprea C, Iliescu DM, Nenciu MI, Golumbeanu M. Techirghiol lake in the context of the integrated development of health tourism. *J Environ Prot Ecol*. 2019;20(1):206–213.
38. Iliescu MG, Profir D, Surdu O, Marin V, Demirgean S, Almasan RE, Stanciu LE, Oprea C, Iliescu DM, Ionescu EV. Statistical View Through Balneal Activity In Techirghiol Medical Area. *J Environ Prot Ecol*. 2018;19(1):382.
39. Montserrat-Capdevila J, Godoy P, Marsal JR, et al. Overview of the impact of de- pression and anxiety in chronic obstructive pulmonary disease. *Lung*. 2017;195(1):77-85.
40. Cambrea SC, Petcu LC, Iliescu DM. Relations of Environmental Factors and Evolution of Boutonneuse Fever in the County of Constanta – Romania. *J Environ Prot Ecol*. 2018; 19(2):914-922.
41. Cambrea SC, Popescu GG, Resul G, Petcu LC. The spectrum of infectious diseases hospital mortality by HIV status. *Acta Medica Mediterranea*. 2019; 35(6): 3517-3522.
42. Decramer M, Rennard S, Troosters T, Mapel DW, Giardino N, et al. COPD as a lung disease with systemic consequences—clinical impact, mechanisms, and potential for early intervention. *COPD*. 2008;5:235–256.

A review of antimicrobial photodynamic therapy (aPDT) in periodontitis

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Abstract

Introduction: Periodontitis is an inflammatory disease caused by a multitude of pathogens, that eventually affects the entirety of all periodontal tissues and may lead to tooth mobility or even tooth loss. The destruction of said tissues occurs via 2 pathways: a direct pathway (defense mechanisms belonging to the pathogens) and an indirect pathway (the host's immune system). Therapy is complex and requires strict follow-ups in order to prevent relapse. **Aim:** Our objective was to determine whether or not aPDT can be considered to be an effective adjunctive approach to the current standard initial treatment method when dealing with periodontitis (scaling/root planing). **Methods:** We performed an electronical search of the PubMed and ScienceDirect data bases starting from January 2014 and up to May 2019. Eligibility criteria included English-language systematic reviews and randomized clinical trials which evaluated the efficiency of aPDT, and that had been carried out on human subjects with permanent dentition. We excluded studies and reviews that were focused on the microbiology and/or immunology in photodynamic therapy and also those that used other LASER treatment modalities than aPDT. **Results:** Current literature displays many opinions regarding periodontal therapy with adjunctive aPDT, but it seems to be mainly regarded as a safe, effective and easy-to-use approach. **Conclusion:** aPDT seems to be efficient in the treatment of periodontitis when carried out additionally to classical scaling/root planing. Residual pockets seem to respond well to aPDT, as opposed to subsequent debridement flap elevation and its consequences on hard and soft tissues. However, further studies with a stricter treatment protocol and subsequent follow-ups are required in order to obtain a firmer conclusion.

Key words: *periodontitis LASER, periodontitis aPDT, periodontitis photodynamic therapy,*

Introduction

Periodontitis is defined as an inflammatory disease caused by various pathogenic microorganisms, which leads to the destruction of all periodontal tissues: gingiva, periodontal ligaments, alveolar bone and cementum. The destruction occurs not only due to the direct damage caused by the pathogens, but also due to the indirect destruction produced by the host's immune response. Therapy must be multidisciplinary and the main goal is to reduce inflammation.

When left untreated, periodontitis may not only lead to tooth mobility and eventually tooth loss, but it can also cause other systemic diseases. Being a chronic oral infection, periodontitis represents a continuous source for subsequent co-morbidities and even mortality in respective patients. Examples include cardiovascular diseases, cerebrovascular diseases, respiratory diseases and low birth weight (1, 2).

Conventional approach is based on the removal of hard deposits and plaque from the root surface by subgingival scaling and root planing, thus leading to a reduction of the bacterial load in the periodontal pocket. Frequent associated consequences to this maneuver are bleeding, pain, swelling and overall patient discomfort, all of which have a negative impact on the postoperative quality-of-life (QoL) factor.

The use of LASERs has evolved since the first LASER was introduced in 1985. Research in hard and soft tissue LASERs is continuously advancing through the discovery of newer wavelengths. Nowadays, science has come a long way and has been developing increasingly modern devices with the aim to improve hemostasis, patient comfort, healing and provide less postoperative swelling and pain (3).

There are many LASERs commercially available that advertise to be able to achieve all of these positive features.

It is already known that photodynamic LASER therapy is unable to remove subgingival calculus on its own. The principle of soft tissue LASER therapy is based on the reduction of bacterial population and removal of necrotic epithelial tissue (3). In antimicrobial photodynamic LASER assisted procedures (also known as “aPDT”), LASER energy is absorbed by the chromophores within the diseased periodontal pocket and transformed into photothermic energy. Pathogens contain different amounts of wavelength-specific chromophores and, according to these, require different LASER parameters in order to be neutralised.

Laser wavelengths can be classified into soft and hard tissue LASER types. Soft tissue LASERs are the CO₂, Nd:YAG and diode LASERs, while Erbium-based wavelengths produce effects both on soft, as well as on hard tissues.

Among the LASER types applied in periodontology are the CO₂-LASER (very efficient in cutting and vaporizing soft tissues), the diode LASERs (efficient in cutting, decreasing bacterial loads in periodontal pockets and hemostasis), Erbium-based LASERs (effective in cavity preparations and caries removal, as well as the removal of soft and hard deposits from root surfaces, furcations and infrabony defects) and Nd:YAG LASERs (which have an affinity to chromophores similar to that of the diode LASERs, thus leading to good bacterial reduction).

Antimicrobial photodynamic therapy relies on three components: photosensitizer, light in a spectrum that is appropriate to activate the photosensitizer, and oxygen. The photosensitizer is transferred from its basic singlet state into an activated singlet state after irradiation with a specific wavelength. This reaction pathway is recognized as the major course of microorganism destruction. As far as the photosensitizer is concerned, Methylene blue and Toluidine blue O seem to have the strongest bactericidal effect among medical photosensitizers (4). They are the most commonly used and are very efficient in killing Gram-positive and Gram-negative periodontopathic bacteria, but also the influenza virus, *Helicobacter pylori* and *Candida albicans* after they are activated by light (5). Thus, it can be stated that aPDT is a fairly novel antimicrobial approach with less complications and side effects when compared to conventional antibiotic therapy, one of which's well known side effects is bacterial

resistance. Thus, LASER-assisted therapy seems to be a very desirable approach in contemporary dentistry, which helps keep treatment at a minimally invasive level.

The question that arises is if aPDT is effective as an adjunctive approach to the current standard treatment method of periodontitis cases. Therefore, our objective in this systematic review was to assess the efficiency of photodynamic therapy when treating periodontitis in a combined fashion: standard scaling/root planing with additional aPDT.

Methods

Search strategy and selection criteria

We performed an electronic search of the PubMed and ScienceDirect data bases starting from January 2014 and up to May 2019. Our aim in this systematic review was to assess the clinical outcomes of aPDT when used as an adjunctive to scaling and root planning in periodontal treatment. The following eligibility criteria was established: systematic reviews and randomized clinical trials which evaluated the efficiency of aPDT. Our search was limited to the last 5 years (January 2014 - May 2019) and only took studies in human population with permanent teeth into account. Also, only articles that were published in English were included. The search protocols on the different databases were similarly constructed, respective to each site's individual search engine design. The following key word constructions were used: periodontitis LASER, periodontitis aPDT, periodontitis photodynamic therapy. We did not include studies and reviews that investigated the effects of the photodynamic therapy from a microbiological or immunological point of view. Moreover, all studies that used LASER treatment modalities other than aPDT were also not included in this review (mainly those using CO₂, Nd:YAG and Erbium-based LASERs).

Study selection and data extraction

Initially, 10 articles were found on ScienceDirect and 93 articles on PubMed. After excluding all articles that did not meet our inclusion criteria, a total of 23 articles remained. All articles were either systematic reviews or randomized clinical. After applying the above mentioned exclusion criteria, 8 articles about aPDT remained, 7 of which were systematic reviews and 1 was a randomized clinical trial. In the aforementioned 7 articles there were 47 studies involved.

Data extracted from the included studies contained: general information about the publication (year, author), number of patients taken into consideration, treatment-related information (type of LASER used and its characteristics, treatment duration, number of meetings) and clinical outcomes (Table 1).

Results

Current literature contains a wide range of results concerning treatment options in periodontitis. aPDT is mainly regarded as being a safe and easy-to-use approach.

The review of Fahim Vohra et al. (6) showed that aPDT was effective as an adjunct approach to SRP (i.e., scaling and root planing) in aggressive periodontitis – now considered to be an outdated diagnostic - in generally healthy patients. More randomized clinical trials with properly defined control groups are needed to assess the best parameters for adjunctive aPDT application.

The review of Dong Xue (7) showed a significant improvement in PD (i.e., probing depth) and CAL (i.e., clinical attachment level) gain after the usage of SRP with aPDT in non-smoking patients. However, more trials with clearer treatment protocols and similar study designs are recommended to reduce bias.

The review of Zohaib Akram et al. (8) showed that it was debatable whether or not aPDT was effective. Due to the reduced sample size and high heterogeneity of the studies, it is necessary to be cautious with the interpretation of the outcomes and further trials are needed to obtain a more convincing conclusion.

The article of M. Meimandi et al. (9) contained 16 studies, out of which 9 were included in this review. 5 out of these 9 clinical trials showed a significantly better outcome of periodontal parameters after SRP with aPDT (10-14), while 1 study showed short-term efficiency (15). The other 3 studies (16-18) showed no significant difference regarding the clinical outcomes when SRP was combined with aPDT or in comparison with SRP alone. In most of the studies, bleeding on probing (BoP) was improved after additional LASER application. Further studies with higher homogeneity and clearer treatment protocols are needed to firmly conclude efficiency.

The systematic review of E. Souza et al. (19) concluded that further clinical trials which include aggressive periodontitis patients are needed and that the follow-up should be carried out on a time frame longer than 6 months. Also, a strict treatment protocol should be set in order to reach stronger

evidence regarding aPDT efficiency. Identifying a most effective number of necessary applications/sessions could contribute to clarifying treatments protocols.

The systematic review of Dong Xue et al. (20) concluded the following: 4 studies (21- 24) showed a positive outcome for the adjunctive use of aPDT, while 2 studies (25, 26) showed no additional benefits for adjunctive aPDT. The clinical trials show a significant improvement of the clinical parameters after SRP with adjunctive aPDT when smokers are not involved.

The study of Betsy and Joseph et al. (27) determined aPDT to be efficient as an adjunctive therapy to SRP. It showed improvements in the gingival index and gingival bleeding index after 1 month of treatment, and also an enhancement of PD and CAL after 3 and 6 months, respectively, after aPDT.

Conclusions

Regarding all conclusions of the presented studies, it can be stated that aPDT is efficient when carried additionally to standard SRP, especially regarding gingival bleeding. Also, residual pockets might be alternatively treated with aPDT (as opposed to subsequent SRP/debridement flap elevation, which may lead to increased hard/gingival tissue loss). Furthermore, patients with HIV and chronic periodontal infections might have additional benefits when adjunctive aPDT is used.

In the case of the disease formerly classified as “aggressive periodontitis”, aPDT cannot replace the antibiotic adjunctive treatment, a fact confirmed by better clinical outcomes when antibiotics rather than aPDT were used additionally to SRP. In most of the studies, adjunctive aPDT demonstrated better outcomes in PD, CAL gain and gingival bleeding. However, aPDT efficiency seems to be compromised in smokers. It has no reported side effects. If side effects appear, they seem to be related to allergic reactions to the photosensitizer.

All outcomes have to be interpreted with great caution due to the heterogeneity among the studies. More studies with a strict treatment protocol are needed to strengthen the current positive conclusion, as well as to assess the best treatment parameters for establishing a future firm therapeutic protocol.

Conflicts of Interest

The authors declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Table 1. General information about the studies included in this article.

Author/Date	Concept/theoretical model	Context/Setting/Sample	Control groups
Fahim Vohra & Zohaib Akram/2015 (6)	Systematic Review	5 studies - aPDT performed adjunct to SRP; 2 studies – aPDT alone	SRP alone and SRP + ABX
Dong Xue & Ying Zhao/2016 (7)	Systematic Review & Meta-analysis	4 studies – SRP + aPDT, non-smoker and smoker	Only SRP
Zohaib Akram & Tahira Hyder/2017 (8)	Systematic Review & Meta-analysis	SRP + aPDT	SRP + ABX
Mansour Meimandi & mohammed Reza Talebi Ardakani/2017 (9)	Literature Review	[1] PDT, SRP + aPDT, [2] SRP + aPDT, [3] SRP + aPDT, [4] SRP + aPDT, [5] SRP + aPDT, [6] SRP + aPDT, [7] SRP + aPDT, [8] SRP + aPDT, [9] aPDT; aPDT + PS, [10] SRP + aPDT (HIV), [11] SRP + aPDT, [12] SRP + aPDT, [13] SRP + aPDT, [14] SRP + aPDT, [15] 1x TB + aPDT, [16] SRP + PS; SRP + aPDT.	- SRP, - SRP, - SRP, - SRP, - SRP, - SRP, - SRP, - SRP, - SRP, - SRP, - SRP, - SRP, - SRP, - SRP, - No aPDT, - SRP.
Emmanuel Souza & Ana Claudia Madeiros/2015 (19)	Systematic Review & Meta-analysis	SRP + aPDT	SRP
Betsy Joseph & Chandra Sekhar Prasanth/2014 (26)	Randomized Clinical Trial	SRP + aPDT	SRP
Dong Xue, Lu Tang/2017 (20)	Systematic Review & Meta-analysis	SRP + aPDT	SRP

References

- Arigbede AO, Babatope BO, Bamidele MK. [Internet]. Advances in pediatrics. U.S. National Library of Medicine; 2012 [cited 2018Jul4]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3590713/>
- Roman A, Soanca A, Petrutiu SA, Condor D, Cioban C. Parodontologie 2 Ghid de tratament. Ed.Med. Univ. Iuliu Hatieganu 2018.
- Coleton S. The Use of Lasers in Periodontal Therapy. Alpha Omegan. 2008;101(4):181–7.
- Wilson M, Dobson J, Sarkar S. Sensitization of periodontopathogenic bacteria to killing by light from a low-power laser. Oral Microbiol Immunol. 1993; 8: 182–187.
- Wiebe CB, Putnins EE. The Periodontal Disease Classification System of the ... [Internet]. 2000 [cited 2018Jul3]. Available from: <https://www.bing.com/cr?IG=94E349692BD643D3B1726278F7A9CD4C&CID=12B0F7FD23FA607E1BDFFBDC2207612B>
- Vohra F, Akram Z, Hasnur S, Devi R, Ghanem A, Sergis K, et al. Photodiagnosis and Photodynamic therapy Role of antimicrobial photodynamic therapy in the treatment of aggressive periodontitis : A systematic review. Photodiagnosis Photodyn Ther [Internet]. Elsevier B.V.; 2016;13:139–47. Available from: <http://dx.doi.org/10.1016/j.pdpdt.2015.06.010>
- Xue D, Zhao Y. Photodiagnosis and Photodynamic Therapy Clinical effectiveness of adjunctive antimicrobial photodynamic therapy for residual pockets during supportive periodontal therapy : A systematic review and meta-analysis. Photodiagnosis Photodyn Ther [Internet]. Elsevier B.V.; 2017;17:127–33. Available from: <http://dx.doi.org/10.1016/j.pdpdt.2016.11.011>
- Akram Z, Hyder T, Al-hamoudi N, Binshabaib MS, Alharthi SS, Hanif A. Photodiagnosis and Photodynamic Therapy E ffi cacy of photodynamic therapy versus antibiotics as an adjunct to scaling and root planing in the treatment of periodontitis : A systematic review and. Photodiagnosis Photodyn Ther [Internet]. Elsevier. 2017;19(May):86–92. Available from: <http://dx.doi.org/10.1016/j.pdpdt.2017.05.007>
- Meimandi M, Reza M, Ardakani T, Nejad AE, Yousefnejad P. The Effect of Photodynamic

- Therapy in the Treatment of Chronic Periodontitis : A Review of Literature. *Laser Appl Med Sci Res Cent* [Internet]. 2017;8(Suppl 1):S7–11. Available from: <http://dx.doi.org/10.15171/jlms.2017.s2>
10. Aykol G, Baser U, Maden I, et al. The effect of low- level LASER therapy as an adjunct to non-surgical periodontal treatment. *J Periodontol*. 2011;82(3):481–488. doi:10.1902/jop.2010.100195.
 11. Cappuyns I, Cionea N, Wick P, Giannopoulou C, Mombelli A. Treatment of residual pockets with photodynamic therapy, diode LASER, or deep scaling. A randomized split- mouth controlled clinical trial. *Lasers Med Sci*. 2012;27(5):979–986. doi:10.1007/s10103-011-1027-6.
 12. Noro Filho GA, Casarin RC, Casti MZ, Giovani EM. PDT in non- surgical treatment of periodontitis in HIV patients:a split–mouth, randomized clinical trial. *Lasers Surg Med*. 2012;44(4):296–302. doi:10.1002/lsm.22016.
 13. Berakdar M, Callaway A, Fakhrddin M, Rob A, Willershausen B. Comparison between scaling–root planning and SRP/photodynamic therapy: six–month study. *Head Face Med*. 2012;8:12.
 14. Giannelli M, Formigli L, Lorenzini L, Bani D. Combined photoablative and photodynamic diode LASER therapy as an adjunct to non-surgical periodontal treatment
 15. Lui J, Corbet EF, Jin L. Combined photodynamic and low -level LASER therapies as an adjunct to non-surgical treatment of chronic periodontitis. *J Periodontol Res*. 2011;46:89–96.
 16. Polansky R, Haas M, Heschl A, Wimmer G. Clinical effectiveness of photodynamic therapy in treatment of periodontitis. *J Clin Periodontol*. 2009;36:575–580.
 17. Ruhling A, Fanghanel J, Hushmand M, et al. Photodynamic therapy of persistent pockets in maintenance patients - a clinical study. *Clin Oral Investig*. 2010;14(6):637–644. doi:10.1007/s00784-009-0347-4.
 18. Balata ML, Andrade IP, Santos DB, et al. Photodynamic therapy associated with full-mouth ultrasonic debridement in the treatment of severe chronic periodontitis:a randomized–controlled clinical trial. *J Appl Oral Sci*. 2013;21(12):208–214. doi:10.1590/1678-7757201302366.
 19. Souza E, Medeiros AC, Gurgel BC, Sarmiento C. Antimicrobial photodynamic therapy in the treatment of aggressive periodontitis: a systematic review and meta-analysis. 2015;
 20. Xue AD, Tang L, Bai Y, Ding Q, Wang P, Zhao Y. Clinical efficacy of photodynamic therapy adjunctive to scaling and root planing in the treatment of chronic periodontitis: a systematic review and meta-analysis. *Photodiagnosis Photodyn Ther* [Internet]. Elsevier B.V.; 2017; Available from: <http://dx.doi.org/10.1016/j.pdpdt.2017.01.183>
 21. Christodoulides N, Nikoldakis D, Chondros P, et al. Photodynamic therapy as an adjunct to non-surgical periodontal treatment a randomized controlled clinical trial. *J Periodontol* 2008;79(9):1638–44.doi:10.1902/jop.2008.070652.
 22. H.A. Alwaeli, S.N. Al-Khateeb, A. Al-Sadi, Long-term clinical effect of adjunctive antimicrobial photodynamic therapy in periodontal treatment: a randomized clinical trial, *Lasers Med. Sci*. 30 (2013): 801–807.
 23. S. Malgikar, S. Reddy, P. Babu, et al., A randomized controlled clinical trial on efficacy of photodynamic therapy as an adjunct to nonsurgical treatment of chronic periodontitis, *J. Dent. Lasers* 9 (2015) :75–79.
 24. R. Birang, M. Shahaboui, S. Kiani, et al., Effect of nonsurgical periodontal treatment combined with diode LASER or photodynamic therapy on chronic periodontitis: a randomized controlled split-mouth clinical trial, *Lasers Med. Sci*. 6 (2015) :112–119.
 25. S.H. Bassir, N. Moslemi, R. Jamali, et al., Photoactivated disinfection using light-emitting diode as an adjunct in the management of chronic periodontitis: a pilot double-blind split-mouth randomized clinical trial, *J. Clin. Periodontol*. 40 (2013) :65–72.
 26. A.C. Queiroz, F.A. Suaid, P.F.D. Andrade, et al., Adjunctive effect of antimicrobial photodynamic therapy to nonsurgical periodontal treatment in smokers: a randomized clinical trial, *Lasers Med. Sci*. 30 (2015) :617–625.
 27. Betsy J, Prasanth CS, Baiju KV, Prasanthila J, Subhash N. Efficacy of antimicrobial photodynamic therapy in the management of chronic periodontitis: a randomized controlled clinical trial - Betsy - 2014 - *Journal of Clinical Periodontology* - Wiley Online Library [Internet]. *Journal of Clinical Periodontology*. John Wiley & Sons, Ltd (10.1111); 2014 [cited 2019May16]. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/jcpe.12249>

Effect of Low Level Laser Therapy (LLLT) on muscle pain in temporomandibular disorders – an update of literature

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Abstract

Introduction: Temporomandibular disorders are complex pathologies with multifactorial aetiology. Due to this matter, different therapeutic approaches have been developed, one of them being physical therapy (also known as physiotherapy). Low-level laser therapy is often used in treating musculoskeletal diseases, TMJ pain and, although the exact mechanism of LLLT has not yet been completely elucidated, it seems that this kind of therapy induces analgesic, anti-inflammatory and bio-stimulating effects. *The aim* of this study was to create an update of scientific literature regarding the clinical use of LLLT in patients with temporomandibular disorders, and to identify the impact of this therapy on reducing pain in the masticatory muscles. **Methods:** A research of literature was performed - articles published over the last 10 years (January 2009 until December 2019) were searched for by introducing a combination of different keywords on the PubMed and ScienceDirect databases. **Results:** A total number of 294 articles were found. After applying inclusion and exclusion criteria, 28 articles were taken into consideration for our study, and among them, 9 were systematic meta-analyses or literature reviews and 19 were clinical studies. **Conclusion:** Low level laser therapy may effectively reduce pain in patients suffering from muscular- and/or joint-specific TMDs, but the effect appears to last only for a short period of time, and can be achieved only in less complex cases. LLLT may also improve oro-facial functions by reducing muscular activity. This research also reveals the need for better-designed clinical trials with larger sample sizes, in order to evaluate the efficacy of LLLT on improving the signs and symptoms of TMDs.

Key words: Low-level laser therapy, temporomandibular disorders, muscle pain,

1. Introduction

Temporomandibular muscles and joint disorders (TMDs) represent a complex pathology in the craniofacial region that affects more than 10% of the population worldwide (1). Typical signs and symptoms of this condition include muscle and joint pain, headache, limitation and/or deviation in the range of motion of the mandible, tenderness of masticatory muscles and temporomandibular joints, as well as joint noises (2).

Several classifications of the TMDs can be found in literature. The most common classification is the one proposed by the International Association for the Study of Pain: *myofascial pain*, *myositis*, *muscle spasm* and *muscle contracture* are considered to be Temporomandibular Muscle Disorders, while *disk displacements with or without reduction*, *TMJ subluxation or dislocation*, *osteoarthrosis*, *ankylosis*, *traumatic injuries* and *neoplasma* are considered Temporomandibular Joint Disorders (2).

As the aetiology of TMDs is considered to be multifactorial, different approaches have been developed, such as occlusal equilibration, manual therapy, occlusal splint therapy, and physical therapy (1).

Low level laser therapy (LLLT) is a non-surgical treatment that uses a non-thermal type of light, which has been put under the spotlight in the last few years, due to its easy protocol of application, limited number of necessary sessions and minimum contraindications. Low-laser therapy is often used in treating musculoskeletal diseases and TMJ pain. Although the exact mechanism of LLLT is not completely elucidated, it seems that this kind of therapy has an analgesic, anti-inflammatory and bio-stimulating effect (3).

The aim of this study was to create an update of the scientific literature concerning the clinical use of LLLT for patients with temporomandibular disorders, and to identify the impact of this therapy on reducing the pain of the masticatory muscles.

2. Methods

2.1 Search strategy. We systematically searched for scientific articles on the PubMed and ScienceDirect databases. Our search interval included the last 10 years, starting from January 2009 until December 2019. In our electronic search, we used a combination of the following search terms: “temporomandibular disorder”, “TMD”, “temporomandibular joint disorder”, “TMJ disorder”, “TM disorder”, “low-level laser therapy”, “LLLT”, “laser therapy”, “diode laser”. We performed the last search in December 2019.

Before initiating the search, we took into consideration the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (4).

2.2 Selection criteria. *Inclusion criteria* were as follows: a) studies in which LLLT was the treatment for TMD; b) meta-analysis studies; c) articles written in English; and d) randomized clinical trials including patients with TMD. *Exclusion criteria* were as follows: a) abstracts that did not report data for the outcomes of interest; b) studies with participants suffering from systemic disease or with pain not related to TMJ.

2.3 Data extraction. A screening of the possible relevant titles and abstracts was performed by all the authors involved in the present research. Afterwards, the full-text was obtained for the articles taken into consideration. We extracted different data like: general information about the publication (year, author), number of the patients taken into consideration, treatment related information (type of device used and its characteristics, duration, number of meetings) and clinical outcomes regarding the effect of low-level laser therapy on patients with TM disorders.

3. Results

A total number of 294 articles were found. After applying the inclusion and exclusion criteria, 28 articles were taken into consideration for the present study.

4. Discussion

Although there is a multitude of treatment options available for TMDs, low level laser therapy is considered to be a promising approach, being able to relieve pain soon after application (a few minutes after) (15).

The aim of this study was to review literature in the above mentioned time frame and to create an update

regarding the clinical use of LLLT for patients with temporomandibular disorders. We also intended to identify the impact of this type of therapy on reducing muscle pain in patients suffering from this pathology.

Out of the 28 articles included, 9 were meta-analysis, systematic reviews, or literature reviews (3,5,6,25,26,28,29,30,32) and 19 were clinical trial studies

(7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,31). Therefore, the authors analyzed the articles included in this research and organized the findings based on topic and on answering on some focused questions.

Which is the mechanism of action and what are the indications for LLL Therapy?

Although the exact mechanism of action of LLL therapy is not clear, there are several theories explaining its function in more detail. One theory suggests that analgesia occurs as a consequence of minimizing the PGE2 level, one of the most important proinflammatory mediators in our body (5). More than that, laser irradiation levels-up the synthesis of ATP and generates reactive oxygen radicals, which leads to the inhibition of COX-2, the enzyme responsible of synthesizing PGE2 (3,6). Another theory is focused on the effect of the laser on neuronal cells by disrupting their physiology and altering the axonal flow, a reversible process that causes no nerve damage and manages to interrupt pain formation (5,7).

LLLT's main indications in TM disorders are: pain in TMD, presence of joint sounds, sensitivity of masticatory muscles and alteration of mandibular function (15).

What are the working protocols for LLL therapy in TMD?

Regarding the working protocols, we noticed different approaches depending on laser type, wavelength and TMD severity. These were summarized in Table 1.

What are the effects of LLL therapy on masticatory muscles?

Muscular activity increases in TMDs, leading to pain and limitation of jaw movements. As a result, sensitivity or pain of the masticatory muscles and TMJs are the main complaints of patients suffering from temporomandibular disorders (11).

One study concentrated on masticatory muscles and used electromyography (EMG) to evaluate muscle activity before and after low-level laser therapy, but no significant differences were found for the masseter and temporal muscle; the only improvement obtained was pain reduction (13). In another study, published by the same authors (11), muscle relaxation for both temporal and masseter muscle was obtained, but only in the case of the superior head of the masseter muscle sensitivity was reduced. Although there were no significant modifications in mouth opening, after scanning the patients with T-Scan™ III (Tekscan, Inc., Boston, USA), even distribution of occlusal contacts (50% on each side) was demonstrated after LLL therapy.

Other studies (12,15) reported an improvement in pain symptoms and EMG activity of both masseter muscles in habitual occlusion, but no significant changes in the temporal muscle or mandibular function were identified.

When evaluating orofacial functions after LLL therapy, Haddad Leal de Godoy et al. (13) obtained pain relief for all fibres of the temporalis and masseter muscle, except for one patient, who continued to report pain in the middle masseter head. They also observed unmodified occlusal loading, maximum bite force and occlusal contact area after LLLT. This data is summarized in Table 2.

What other results can be obtained after LLL therapy in TMDs?

The main effect of this therapy is the reduction of pain, which was demonstrated by many studies (7, 9, 11, 12, 16, 17, 18, 19, 20), but also a positive psychological effect of laser therapy was obtained in the placebo group. Pain relief and an increase of the values of mandibular movement ranges after a single laser application was also observed by Santos et al. (15).

Concerning the duration of pain relief, LLLT is considered to be a rapid means of reducing pain, with effects appearing immediately after treatment, but pain recurrence occurred to some degree, thus no long-term effect has been identified so far (8).

Low-level laser therapy also has the capacity of improving mouth opening, which can be frequently observed in TMD patients. A significant improvement of the maximum mouth opening after treatment was observed (9,17,18,19), except for one study (19) which reported a non-significant increase in the LLLT group, as well as in the placebo group.

Although one research study (16) concluded that only pain reduction was obtained after using LLLT, without any modification of the maximum bite force, occlusal load and occlusal contact area, another study (11) obtained (using T-Scan™ III, Tekscan, USA, after LLLT) important differences regarding the distribution of occlusal contacts after treatment, namely approximately 50% on each side.

Studies also reported the reduction of joint sounds that are frequently present in TMD patients. Sayed et al. (18) observed that, alongside pain relief and an increase of the active range of motion, joint sounds were also reduced after LLLT.

Does the use of LLL therapy cause adverse effects?

One comparative study regarding the effects of LLLT and red and infrared led therapy (9) reported an increase of temperature during irradiation, followed by a cooling for 3-4 minutes, until initial temperature was reached again, concluding that LEDs can be a good alternative to LLLT.

No other studies declared any side effects during or after LLLT, or they were not reported.

5. Future/ongoing research

Many studies are currently ongoing (21,22,23,24,10), evaluating the effects of low-level laser therapy in patients with temporomandibular disorders, all of them containing a large sample size in order to increase the relevance of future data.

6. Conclusion

Based on the findings of this literature research we can conclude that low level laser therapy may effectively reduce pain for patients suffering of muscular and joint TMDs, but the effect appears to be only shortly maintained, and only for less complex cases. Furthermore, LLLT may also improve oro-facial functions, reducing muscle hyperactivity. This literature update also highlights the need for better-designed clinical trials with larger sample sizes, in order to evaluate the efficacy of LLLT on improving the signs and symptoms of TMDs.

Table 1. Working protocols for LLLT

Author	Type	Wavelength (nm)	No. of subjects	Irradiation site	No. of irradiations	Exposure time
Melchior et al.	Gaalas	780	12	4 points: 3 points for the upper, medium and lower thirds of masseter m., 1 point for the anterior region of temporalis m.	8 sessions, sessions/week	2 40 sec/point
Rodrigues et al.	Gaalas	780	89	3 points: upper, middle and lower masseter m. 3 points: anterior, middle and posterior fibres of the anterior temporal m. 5 points for TMJ, lateral pole.	8 sessions, sessions/week	2 20 sec/point for the muscles 50 sec/point for TMJ
Panhoca et al.	Led Infrared led	630 850	30	5 points: 3 around TMJ, 1 point for the temporal m., 1 point for the masseter muscle	8 sessions, twice a week	60 sec/point
De Godoy et al.	Diode laser	780	9	4 points: 3 points for the superior, medial and inferior heads of the masseter m., 1 point for the anterior temporal m.	12 sessions, sessions/week	2 20 sec/point
De Godoy et al.	Gaalas	780	16	4 points: 3 for the superior, medial and inferior heads of masseter m., 1 point for the anterior temporal m.	12 sessions, sessions/week	2 20 sec/point
Hotta et al.	Gaalas	780	10	Chinese acupuncture points: ig4, c3, e6, e7	10 sessions, once a week	20 sec/point

Table 2. Effects of LLLT on muscles

Author	Masseter m.	Temporal m.	Mandibular function	Follow-up
De Godoy et al.	m. relaxation ↓sensitivity of the superior head of the right masseter m.	m. relaxation no significant difference in m. sensitivity	Nonsignificant increase in mouth opening; ↑distribution of occlusal contacts	6 weeks
Rohlig et al.	↓pain, except from 1 patient—moderate pain in the masseter middle	↓pain for all heads	Unmodified occlusal contact area, occlusal pressure and maximum bite force	4 weeks
De Godoy et al.	↓pain No changes in EMG activity	↓pain No changes in EMG activity	Not evaluated	6 weeks
Hotta et al.	↓pain ↓EMG	No significant changes	No significant improvement	1 month

References

1. Fertout A, Manière-ezvan A, Lupi L, Ehrmann E. Management of temporomandibular disorders with transcutaneous electrical nerve stimulation : A systematic review. *CRANIO® J Craniomandib SLEEP Pract* [Internet]. 2019;00(00):1–12. Available from: <https://doi.org/10.1080/08869634.2019.1687986>
2. Friction RJ. Clinical Updates. *Pain - Clin Updat*. 2004;XII(2):1–6.
3. Petrucci A, Sgolastra F, Mattei A. Effectiveness of Low-Level Laser Therapy in Temporomandibular Disorders: A Systematic Review and Meta-Analysis. *J Orofac Pain*. 2011;25(4):298–307.
4. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;349:g7647
5. Tuner J, Hosseinpour S, Fekrazad R. Photobiomodulation in Temporomandibular Disorders. *Photobiomodulation Dent*. 2019;XX(XX):1–11.
6. Chang W.D., Lee C.L., Lin H.Y., Hsu Y.C., Wang C.J., Lai P.T. A meta-analysis of clinical effects of low-level laser therapy on temporomandibular joint pain. *J.Phys.Ther.Sci*. 26: 1297-1300, 2014.
7. Carolina Almeida Rodrigues DDS, MS, PhD, Melissa de Oliveira Melchior SLPs, MS, Laís Valencise Magri DDS, MS, PhD & Marcelo Oliveira Mazzetto DDS, MS, PhD (2018) Can the severity of orofacial myofunctional conditions interfere with the response of analgesia promoted by active or placebo low-level laser therapy?, *CRANIO®*, DOI: [10.1080/08869634.2018.1520950](https://doi.org/10.1080/08869634.2018.1520950)
8. Melchior M.O., Venezian G.C., Machado B.C.Z., Borges R.F. MM. Does Low Intensity Laser Therapy Reduce Pain and Change Orofacial Myofunctional Conditions ? *J Craniomandib Sleep Pract*. 2013;31(2):133–9.
9. Panhoca VH, Lizarelli Z, Nunez SC, Campi de Anadrade Pizzo R, Grecco C, Paolillo FR, et al. Comparative clinical study of light analgesic effect on temporomandibular disorder (TMD) using red and infrared led therapy. *Laser Med Sci*. 2015;30:815–22.
10. Haddad Leal De Godoy C, Da Costa Silva PF, Araujo DS, Motta LJ, Biasotto-Gonzalez DA, Politti F, et al. Evaluation of effect of low-level laser therapy on adolescents with temporomandibular disorder : study protocol for a randomized controlled trial. *Trials* [Internet]. 2013;14(229):1–6.
11. Haddad Leal de Godoy C, Motta Jansiski L, Fernandes Santos K, Mesquita-ferrari RA, Deana AM, Bussadori SK. Effect of Low-Level Laser Therapy on Adolescents With Temporomandibular Disorder: A Blind Randomized Controlled Pilot Study. *J Oral Maxillofac Surg* [Internet]. 2015;73(4):622–9. Available from: <http://dx.doi.org/10.1016/j.joms.2014.09.018>
12. Hotta T, Hotta TH, Bataglione SA, Coronatto DS, Sie S, Cecilio S, et al. Emg analysis after laser acupuncture in patients with temporomandibular dysfunction (TMD). Implications for practice. *Complement Ther Med*. 2010;16:158–60.
13. Haddad Leal de Godoy C, Motta LJ, Garcia EJ, Fernandes KPS, Mesquita-Ferrari RA, Sfalain A, et al. Electromyographic evaluation of a low-level laser protocol for the treatment of temporomandibular disorder: a randomized , controlled , blind trial. *J Phys Ther Sci*. 2017;29:2107–11.
14. Rodrigues M.F., Rodrigues M.L., Bueno K.S., Aroca J.P., Camilotti V., Busato M.C.A., Mendonca M.J. Effects of low-level laser auriculo-therapy on the physical and emotional aspects in patients with temporomandibular disorders: a blind, randomized, controlled clinical trial. *Complementary therapies in medicine*. 2019; 42:340-346.
15. Santos TDS, Piva MR, Ribeiro MH, Antunes AA, Melo AR, Dias DenOliveira e Silva E. Lassertherapy efficacy in temporomandibular disorders: control study. *Braz J Otorhinolaryngol*. 2010;76(3):294–9. Available from: <http://dx.doi.org/10.1590/S1808-86942010000300004>
16. Gökçen-Röhligh B, Kipirdi S, Baca E, Keskin H, Sato S. Evaluation of orofacial function in temporomandibular disorder patients after low-level laser therapy. *Acta Odontol Scand*. 2013;71:1112–7.
17. Salmos-Brito JAL, Menezes RF De, Teixeira CEC, Gonzaga RK, Rodrigues BHM, Braz R, et al. Evaluation of low-level laser therapy in patients with acute and chronic

- temporomandibular disorders. *Lasers Med Sci*. 2012; DOI: 10.1007/s10103-012-1065-8
18. Sayed N, Murugavel C, Gnanam A. Management of Temporomandibular Disorders with Low Level Laser Therapy. *J Maxillofac oral Surg*. 2014;13(4):444–50.
 19. Abbasgholizadeh ZS, Evren B, Ozkan Y. Evaluation of the efficacy of different treatment modalities for painful temporomandibular disorders. *Int J Oral Maxillofac Surg*. 2019;YIJOM-4267:1–8. Available from: <https://doi.org/10.1016/j.ijom.2019.08.010>
 20. Huang Y, Lin J, Yang H, Lee Y-H, Yu C-H. Clinical effectiveness of laser acupuncture in the treatment of temporomandibular joint disorder. *J Formos Med Assoc [Internet]*. 2014;113(8):535–9. Available from: <http://dx.doi.org/10.1016/j.jfma.2012.07.039>
 21. Carvalho FR, Barros RQ, Gonçalves AS, Freitas PM. Photobiomodulation therapy on the palliative care of temporomandibular disorder and orofacial / cervical skull pain: study protocol for a randomized controlled clinical trial. *Trials*. 2019;20(200):1–8.
 22. Langella LG, Silva PFC, Costa-santos L, Gonçalves MLL, Motta LJ, Deana AM, et al. Photobiomodulation versus light-emitting diode (LED) therapy in the treatment of temporomandibular disorder : study protocol for a randomized , controlled clinical trial. *Trials*. 2018;19(71):1–7.
 23. Melchior MO, Machado BCZ, Cristina R, Magri LV, Mazzetto MO. Effect of speech-language therapy after low-level laser therapy in patients with TMD : a descriptive study Efeito do tratamento fonoaudiológico após. *CoDAS*. 2016;28(6):818–22.
 24. Herpich CM, Leal-junior ECP, Amaral AP, Tosato JDP, Phillip I, Barbosa M, et al. Effects of phototherapy on muscle activity and pain in individuals with temporomandibular disorder : a study protocol for a randomized controlled trial. *Trials*. 2014;15(491):1–8.
 25. Xu G, Jia J, Jin L, Li J, Wang Z, Cao D. Low-Level Laser Therapy for Temporomandibular Disorders : A Systematic Review with Meta-Analysis. *Pain Res Manag*. 2018;2018:1–13.
 26. Maia M.L.M., Bonjardim L.R., Quintans J.S.S., Ribeiro M.A.G., Maia L.G.M., Conti P.C.R. Effect of low-level laser therapy on pain levels in patients with temporomandibular disorders: a systematic review. *J Appl Oral Sci*, 2012; 20(6):594-602.
 27. Chen J, Huang Z, Ge M, Gao M. Efficacy of low-level laser therapy in the treatment of TMDs : a meta-analysis of 14 randomised controlled trials. *J Oral Rehabil*. 2014;1–9.DOI: 10.1111/joor.12258
 28. Gil-Martinez A, Paris-Alemany A, Lopez-de-Uralde-Villanueva I LTR. Management of pain in patients with temporomandibular disorder (TMD): challenges and solutions. *J Pain Res*. 2018;11:571–87.
 29. Melis M, Di Giosia M, Zawawi KH. Low Level Laser Therapy for the Treatment of Temporomandibular Disorders : A Systematic Review of the Literature. *J Craniomandib Pract*. 2012;30(4):304–12.
 30. Buduru S, Talmaceanu D, Baru O, Culcitchi C, Cosgarea R. Low-level LASER therapy effects vs. placebo in the treatment of temporomandibular joint disorders. *Balneo Res J*. 2018;9(3):281–4.
 31. Buduru S, Baru O, Mesaros A. The low- level laser therapy in temporo-mandibular disorders- an update of the current literature. *Balneo Res J*. 2018;9(3):277–80.

The control of cardiovascular risk factors – an essential component of the rehabilitation of patients with ischemic heart disease. What are the current targets?

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Abstract

Cardiovascular diseases continue to cause the highest mortality in Europe, among both men and women. Ischemic heart disease is responsible for most of these deaths. An important role in decreasing mortality and improving the prognosis of patients diagnosed with this disorder is played by cardiovascular rehabilitation programs. The short hospitalization period of patients with acute coronary syndromes who undergo revascularization procedures (in-hospital rehabilitation) becomes extremely useful to determine the cardiovascular risk factors underlying the development of these diseases and to implement lifestyle changing measures. Patients with ischemic heart disease included in rehabilitation programs will not only have the advantage of an increased exercise capacity, but they will also be monitored by qualified medical personnel for the evolution of cardiovascular risk factors. We aim to summarize the objectives to be targeted regarding these risk factors in the presence of a patient with ischemic heart disease included in cardiovascular rehabilitation programs.

Key words: *cardiovascular risk factors, cardiovascular rehabilitation,*

1. Introduction

Cardiovascular diseases continue to cause the highest mortality in Europe, among both men (41%) and women (49%) (1) while remarkable progress has been made over the past 25 years to reduce inequalities between the different European regions in terms of socioeconomic conditions (2). Ischemic heart disease is responsible for most of these deaths (1). An important role in decreasing mortality and improving the prognosis of patients diagnosed with this disorder is played by cardiovascular rehabilitation programs (3). The short hospitalization period of patients with acute coronary syndromes who undergo revascularization procedures (in-hospital rehabilitation) becomes extremely useful to determine the cardiovascular risk factors underlying the development of these diseases and to implement lifestyle changing measures. Patients with ischemic heart disease included in rehabilitation programs will not only have the advantage of an increased exercise capacity, but they will also be monitored by qualified medical personnel for the evolution of

cardiovascular risk factors. At the same time, compliance and persistence to the recommended medication, which acts on these factors and has cardioprotective effects (antiplatelet drugs, statins, beta-blockers, angiotensin converting enzyme inhibitors/sartans) are important (4). The main cardiovascular risk factors are smoking, unhealthy diet, hypertension, diabetes mellitus, dyslipidemia, obesity, metabolic syndrome, sedentary lifestyle and psychosocial stress. Ideally, the so-called “new cardiovascular risk factors” and associated diseases, especially autoimmune disorders, should also be taken into consideration (4,5,6).

The new European guidelines that address classical risk factors propose extremely ambitious targets for patients with very high cardiovascular risk, this risk class being specific to patients with ischemic heart disease. In what follows, we will summarize the objectives to be targeted regarding these risk factors in the presence of a patient with ischemic heart disease included in cardiovascular rehabilitation programs.

Hypertension

Currently, this extremely important risk factor causes the highest cardiovascular mortality (7). All patients with blood pressure values higher than 140/90 mmHg should be advised to make lifestyle changes, as well as to follow drug therapy. In the case of patients aged over 80 years, treatment should be initiated only if the systolic blood pressure value is higher than 160 mmHg (8). Thus, it is recommended to consume less than 1500 g salt/day, optimally less than 1000 g/day, which can contribute to decreasing systolic blood pressure by up to 5-6 mmHg (9). At the same time, regular physical exercise, either aerobic or resistance exercise, may induce a decrease in systolic blood pressure between 4 and 8 mmHg (9). European recommendations regarding the therapeutic targets that should be reached by combining lifestyle changing measures with drug therapy are less than 130 mmHg for systolic blood pressure, but not less than 120 mmHg, for the general population (8). For patients aged over 65 years and those with chronic kidney diseases, the target is less than 140 mmHg, but not less than 130 mmHg, if these values are tolerated. For all patients with hypertension, the diastolic blood pressure value should be less than 80 mmHg, but not less than 70 mmHg (8).

Dyslipidemia

The main therapeutic target that will be taken into consideration for the treatment of dyslipidemia will be LDL cholesterol, because both primary and secondary prevention studies have demonstrated that the lower its value, the lower the risk of cardiovascular events (4,10). The targets that should be reached are: LDL cholesterol < 3 mmol/l (< 116 mg/dl) for subjects with a low risk, LDL cholesterol < 2.6 mmol/l (< 100 mg/dl) in the case of moderate risk, LDL cholesterol < 1.8 mmol/l (< 70 mg/dl) in the presence of high cardiovascular risk, LDL cholesterol < 1.4 mmol/l (< 55 mg/dl) or a reduction of at least 50% of the initial value in subjects with a very high risk (10).

Diabetes mellitus

Obviously, patients with diabetes mellitus should strictly follow the specific dietary measures recommended by the diabetologist.

Systolic blood pressure values will be lower than 130, but not lower than 120 mmHg, and diastolic blood pressure values will be lower than 80 mmHg (without decreasing below the value of 70 mmHg) (11). Glycated hemoglobin will be reduced to less than 7% (11).

Obesity and metabolic syndrome

Patients with coronary diseases will be informed that both overweight and obesity are associated with an increase in the risk of death caused by cardiovascular diseases (4).

Mortality of any cause is reduced when the body mass index is 20-25 kg/m² (in persons aged < 60 years), and an additional reduction of weight does not lead to a decrease in cardiovascular risk (4).

At the same time, patients should know the fact that reaching and maintaining normal weight also has a favorable effect on other cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus) (4). For overweight and obese adults, counseling and calorie restriction are recommended to reach and maintain weight loss (12).

Recently, it was demonstrated that regardless of the body mass index value, persons with metabolic syndrome have a higher risk of developing ischemic heart disease than their healthy peers (13).

In contrast, regardless of the presence of metabolic syndrome, overweight and obese persons had a higher risk of coronary diseases than normal weight persons (13). These findings entail the concept of “metabolically healthy obesity”, which encourages obesity fighting strategies in the population (13).

Smoking

Many patients with acute coronary syndromes are smokers. They should be made aware of the implication of smoking in the pathogenesis of ischemic heart disease. Quitting smoking is the most effective cardiovascular prevention method in terms of cost-effectiveness ratio (4).

This is why during the entire rehabilitation program, the so-called strategy of the “five Aces” should be applied: A-ASK – the patients will be inquired on the occasion of each visit to the doctor about their smoking status; A-ADVISE – all subjects will be advised to quit smoking; A-ASSESS – determining the degree of dependence and willingness to quit smoking for each individual; A-ASSIST – establishing together with the patient smoking-quitting strategies, including a deadline for quitting smoking, behavioral counseling and pharmacological support; and A-ARRANGE – developing a follow-up program (4). In order to emphasize the importance of quitting smoking, we will give the example of the results of a meta-analysis published in 2018 (14). Its data demonstrate that men who smoke about a cigarette per day have a 48% higher risk of coronary disease than non-smokers and a 25% higher risk of stroke (14). Estimates are even higher for women: 57% for ischemic heart disease and 31% for stroke compared to never smokers (13). In fact, the conclusion is that persons who smoke about a cigarette per day have about 40-50% of the cardiovascular risk associated with smoking 20 cigarettes per day (14).

Stress

Regarding the psychosocial status of patients with coronary diseases, the ESC guidelines on cardiovascular disease prevention recommend establishing the presence of diseases such as anxiety, depression, as well as of a lower socioeconomic status, workplace or family stress, type D personality, social isolation (4). The presence of these conditions contributes to decreasing adherence to cardiovascular rehabilitation programs and drug treatment. The fact that the cardiovascular rehabilitation team must include a psychiatrist and a psychologist is well known. All these patients should receive counseling from them.

Healthy diet

All patients must be advised to adopt a healthy diet, rich in vegetables, fruit, walnuts, integral cereals, plant proteins and fish, and poor in trans fats, red meat and processed red meat, refined carbohydrates and sweetened beverages (4). Obviously, in establishing concrete measures, the dietician as a member of the rehabilitation team will also take into consideration the presence of hypertension, diabetes mellitus, dyslipidemia, obesity.

Sedentary lifestyle represents one of the most important cardiovascular risk factors, which is why by including patients with coronary diseases in long-term exercise training programs, this factor will be effectively fought.

Conclusion

In conclusion, including patients with coronary diseases in cardiovascular rehabilitation programs can contribute to reaching the therapeutic targets indicated by guidelines on the control of cardiovascular risk factors responsible for the development of these diseases.

References

1. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J*. 2016;37(42):3232-3245.
2. Di Girolamo C, Nusselder WJ, Bopp M, Brønnum-Hansen H, Costa G, Kovács K, Leinsalu M, Martikainen P, Pacelli B, Rubio Valverde J, Mackenbach JP. Progress in reducing inequalities in cardiovascular disease mortality in Europe. *Heart*. 2020; 106(1):40-49.
3. Sandesara PB, Dhindsa D, Khambhati J, Lee SK, Varghese T, O'Neal WT, Harzand A, Gaita D, Kotseva K, Connolly SB, Jennings C, Grace SL, Wood DA, Sperling L. Reconfiguring Cardiac Rehabilitation to Achieve Panvascular Prevention: New Care Models for a New World. *Can J Cardiol*. 2018;34(10 Suppl 2):S231-S239.

4. Piepoli MF, Hoes AW, Agewall S, Albus C, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 2016;37(29):2315-2381.
5. Pop D, Dădârlat A, Zdrengea D. Novel cardiovascular risk markers in women with ischaemic heart disease. *Cardiovasc J Afr.* 2014;25(3):137-41.
6. Gușetu G, Pop D, Pamfil C, Bălaj R, Mureșan L, Cismaru G, Matuz R, Roșu R, Zdrengea D, Rednic S. Subclinical myocardial impairment in SLE: insights from novel ultrasound techniques and clinical determinants. *Med Ultrason.* 2016 ;18(1):47-56.
7. Poulter NR, Prabhakaran D, Caulfield M. Hypertension. *Lancet.* 2015. 22;386(9995):801-12.
8. Williams B, Mancia G, Spiering W et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39(33):3021-3104.
9. Whelton PK, Carey RM, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e13-e115.
10. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2019. pii: ehz455. doi: 10.1093/eurheartj/ehz455
11. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J.* 2019 Aug 31. pii: ehz486. doi: 10.1093/eurheartj/ehz486.
12. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.
13. Garcia-Moll X. Obesity and prognosis: Time to forget about metabolically healthy obesity. *Eur Heart J.* 2018;39(5):407-409.
14. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenković D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *BMJ.* 2018;360:j5855.

Clinical-evolutive particularities and therapeutic-rehabilitative approach in the rare case of acute disseminated encephalomyelitis following an episode of viral meningitis of unknown etiology

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Abstract

Acute disseminated encephalomyelitis (ADEM) is a disease mainly affecting children, however, adult cases have been also reported. The disease represents a demyelinating disorder of the central nervous system, with a monophasic evolution and mostly full recovery. Mortality is documented at only 2%, but there are risks of complications in the acute phase, mostly due to the vast number of lesions and their distribution in the cerebrum. We present the case of a 40 year-old female patient who presented with visual impairment, coordination issues with walking difficulties, hypoesthesia of the entire body, back and upper limbs paresthesia, upper limbs and torso tremor as well as speech impairment. Symptoms appeared on the same day after discharge from the Infectious Disease Hospital where she was treated for viral meningitis. MRI findings on admission described multiple demyelinating lesions located bilaterally in the white matter and in the cervical spine. The patient was started on high dose parenteral methylprednisolone 1g/day for 5 days and afterwards was switched to oral corticoids with dose tapering over a period of 40 days. Rehabilitation treatment was started during hospitalization and continued after discharge. Evolution was favorable, with almost complete recovery, the patient presenting with only minor hypoesthesia of the torso at discharge.

Key words: *acute disseminated encephalomyelitis, ADEM, meningitis, rehabilitation,*

1. Introduction

Acute disseminated encephalomyelitis (ADEM) represents a demyelinating disorder commonly believed to be immune-mediated. It mostly affects the white matter of the brain and the spinal cord and is usually preceded by an infection (1, 2).

The incidence is 0.4/100.000/year, mostly appearing in younger individuals, under the age of 20 with mean age of presentation being 5 to 8 years, however, cases have also been documented in adults ranging between the ages of 18 and 82 (2, 4). Incidence among genders is almost equal, with a slight male predominance (2). Seasonal distribution suggests only a moderate increase during winter and spring time (2). Mortality rates are currently considered to be low, at approximately 2% (2), death occurring mostly in fulminant cases (3).

The risk of developing ADEM resides in the individual's genetic composition, as well as the exposure to various microorganisms.

In most cases the disease appears after a viral or bacterial infection (4). Implicated microorganisms include CMV, EBV, herpes simplex virus, HIV, influenza, enterovirus and measles -previously considered the main virus leading to the development of ADEM (1, 5).

Clinical manifestations are comprised of multifocal neurological abnormalities, reflecting the widespread involvement of the nervous system (2). Complications, although rare, can lead to fatal consequences such as respiratory failure due to brainstem involvement (2).

The difficulty in diagnosing this particular disease is due to the lack of a specific test or laboratory finding and changes present on imagistic studies such as MRI are not pathognomonic for ADEM (1). Furthermore, differentiating from a first episode of multiple sclerosis is often times impossible.

2. Case presentation

We present the case of 40 years-old female admitted to the Neurological Emergency Department with the following complaints: visual impairment (difficulty in focusing), coordination issues with gait abnormalities, hypoesthesia of the entire body, paresthesia of the back and upper limbs, tremor of the upper limbs and speech impairment. The patient had no history of chronic pathologies, but was recently discharged from the Infectious Disease Hospital where she was successfully treated for an acute episode of viral meningitis of unknown etiology.

The symptoms started nine days prior to admission, on the same day she was discharged from the Infectious Disease Hospital with paresthesia and hypoesthesia of the back and right upper limb, after which extended to the left upper limb and was accompanied by visual impediment. The ophthalmologic consult revealed slight papillary focal edema and retinal nervous fibers edema. Five days before admission, the patient started developing both resting and intentional tremor of the upper limbs. Two days before admission was noted the debut of coordination impairment of the lower limbs with walking difficulties and the hypoesthesia engulfing the whole body. The day before admission, the patient shows muscle weakness, thus rendering independent walking impossible. On the day of admission, speech impediment in the form of dysarthria had developed.

The cerebral contrast MRI conducted describes multiple demyelinating lesions located in the with subcortical matter, periventricular bilateral, left internal capsule, right external capsule, cerebral peduncle, middle cerebellar peduncle, corpus callosum and medial spinal column. Some lesions present DWI contrast diffusion restriction (figure 1 a, b).

Upon admission the patient presented with normal BMI, normal BP and respiratory values and urinary retention (the patient describing difficulty in coordinating urinary emission). The first neurologic examination showed normal mental status, temporally and spatially oriented, no signs of meningeal irritation. The patient presented postural, action and resting tremor located at the upper limbs, normal visual field, difficulty in visual focus, normal eye movement, hypoesthesia of the right hemiface, no sign of facial palsy, bilateral horizontal exhausting nystagmus, unsteady gait, possible only with bilateral help, decreased motor strength (4/5 in

both lower limbs and 4+/5 in the upper left limb), bilateral dysmetria with hypermetria during finger to nose test and heel to shin test, exaggerated reflexes in both upper limbs, abolished abdominal reflexes, Babinski sign positive bilaterally, hypoesthesia of the whole body, paresthesia located in the back and superior limbs and dysarthria.

The patient was placed on high dose corticoid treatment, starting with 1 g a day of methylprednisolone administered intravenously for five days, followed by a dose of 16 mg po with a rate of 2-1-0 for three days, then 1-1-0 for five days and followed by further gradual tapering (30 days in total).

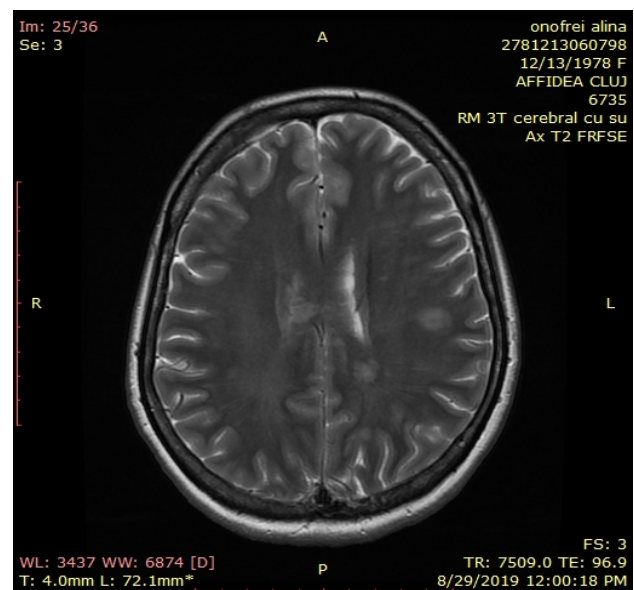


Fig. 1a: Axial T2 MRI shows lesions in the left white matter.

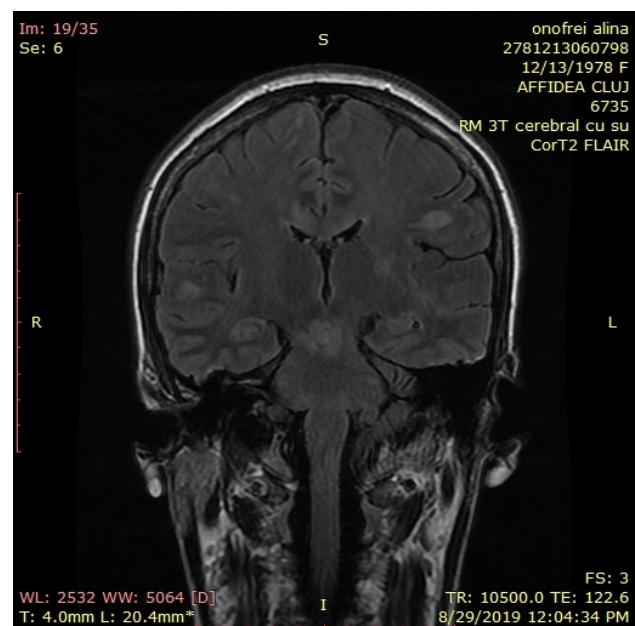


Fig. 1b: Coronal T2 FLAIR MRI shows multiple lesions.

During her stay the patient received physical and occupational therapy with emphasize on coordination and reestablishment of muscle force and walking exercises. Bed exercises were performed during the first days with both passive and active mobilization and afterwards introducing stretching exercises. Both fine and gross motor skill exercises were done daily under the surveillance of a specialist. Our aim was also to restore efficient and independent functional walking, rehabilitation being done in order to obtain a coordinated gait and increased walking distance.

During hospitalization a number of tests were ordered, starting with routine blood test which showed high cholesterol, iron deficiency anemia (Hb – 11,3 g/dl – NV: 12 – 15,5 g/dl, iron blood value – 22 ug/dl – NV: 60 – 180 ug/dl), elevated markers of

conducted (electroneurographic examination, visual evoked potentials, ophthalmological examination, internal medicine and cardiological consults, echocardiography, abdominal echography and pulmonary radiography) – all proving to be within normal margins.

MRI of the cervical and dorsal spine was conducted which showed millimetric contrast enhancing lesions located posterior to the C2 and C7-T1 vertebrae (figure 2a, b).

Lumbar puncture was already done during the previous admission in the Infectious Disease Hospital, which showed elevated CSF total protein (7,3), lymphocytic pleocytosis and no bacterial growth. Testing for various microorganisms was also already conducted, with no positive test (*E. coli*, *H. influenzae*, *Listeria monocytogenes*, *N. meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, CMV, Enterovirus, Herpes simplex virus 1,2 and 6, *Cryptococcus neoformans*, Parechovirus and Varicella Zoster Virus).

During her stay, the patient's symptoms slowly regressed, with improvement in coordination and the regained ability to stand and walk independent. Paresthesia almost disappeared and only minor hypoesthesia of the back still being present at the time of discharge.

The patient was discharged with the following recommendations: continue corticoid treatment (methylprednisolone 16 mg po) with tapering until discontinuation with association of a proton pump inhibitor, iron and folic acid substitution, Neurossen Injekt 1-0-0 intramuscular injections for seven days and continuation of physical rehabilitation.

The patient was advised to enroll in a specialized program which combined functional rehabilitation with physical procedures. The duration and difficulty of daily exercises will be slowly increased given the fact that the patient still presented fatigue at discharge. Therefore, daily rehabilitation will consist of coordination, balance and walking exercises as well as stretching and relaxation techniques. The patient will also undergo aerobic training, and exercises which will strengthen all group muscles with emphasize on the lower limbs.

Approximately one month after the initial debut of symptoms, another cerebral Gadolinium contrast MRI was conducted revealing almost complete resolution of lesions – in number and size (figure 3 a, b, c).



Fig. 2a: Sagittal T2 - cervical spine



Fig. 2b: Sagittal STIR dorsal spine

inflammation (mostly due to corticoid treatment) and low folic acid. Multiple paraclinical tests were



Fig. 3a: Sagittal T2 – one lesion in the brainstem

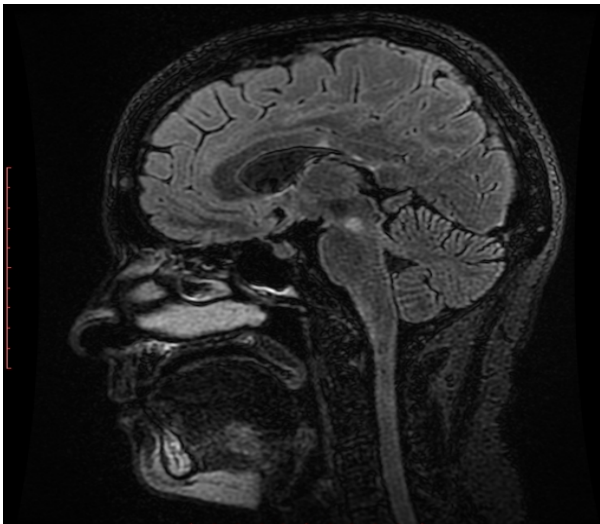


Fig. 3b: Sagittal FLAIR – shows the same unique brainstem lesion

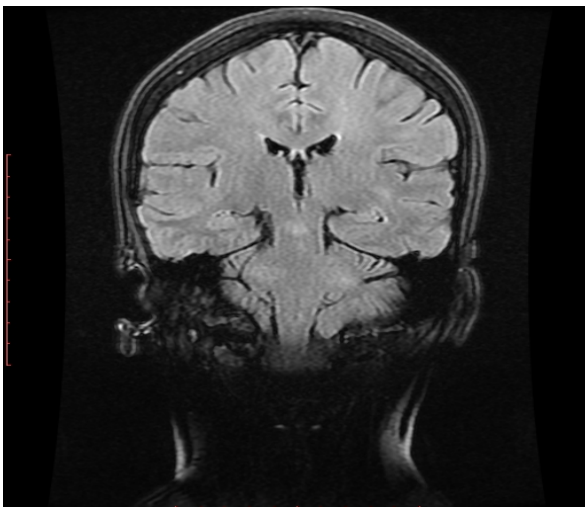


Fig. 3c: Coronal T2 FLAIR – lesion in the brainstem

3. Discussions

Patients with ADEM usually have an excellent outlook, as they can look forward to a complete recovery or to the persistence of only mild deficits (1). Our patient's symptoms regressed almost in full at discharge, with only minor sensory deficits of the back still being present. Routine follow up is mandatory for the control of appropriate diagnosis, efficacious treatment and the surveillance of developing MS, as the long-term risk is approximately 25% (1). Features that have been found to predict relapses include female sex and absence of encephalopathy at presentation (7).

The onset of ADEM occurs in the immediate wake of a febrile illness (1) between two days and four weeks after it's resolution (2), with a general rule of having at least one afebrile day between the two diseases (1).

Clinical symptoms include specific neurologic manifestations such as encephalopathy (represented by change in mental status ranging from lethargy to coma), meningeal signs, muscular weakness, ataxia, cranial nerves palsies, loss of visual acuity, seizures, impairment of speech, paresthesia, and is usually accompanied by nonspecific symptoms such as fever, lethargy and vomiting (2, 4).

Paraclinical studies usually include imagistic exams and biological testing.

MRI is executed in helping to distinguish ADEM from other demyelinating disorders. T1, T2, FLAIR and T1 postcontrast sequences are mostly used to determine the disease's activity. Typical lesions seen on MRI are usually asymmetrical, bilateral with slightly inhomogeneous increased signal on T2 and FLAIR and with greater size than in MS, rounding up at approximately 4 cm. Some lesions may be even larger and confluent. (6).

Cerebrospinal fluid findings are unspecific, including lymphocytic pleocytosis and mildly elevated *CSF* total *protein* (as is the case of our patient) (6). Testing for oligoclonal bands and immunoglobulin elevation is conducted in need of differentiating ADEM from multiple sclerosis, as these markers are mostly elevated in the second disease (1).

Blood work is mostly unspecific, with platelet counts seen elevated in some cases and high values of sedimentation rate appearing in 30% of patients (1).

Diagnosis criteria proposed by IPMSSG (International Pediatric Multiple Sclerosis Study Group) are generally used in children, but can be

correlated in adult ADEM. According to IPMSSG, four criteria are required in making the diagnosis of ADEM (table 1) (5,8). In our patients' case 3 out of the 4 criteria were established, with the three month MRI still is awaiting to be conducted.

Treatment for acute disseminated encephalomyelitis often represents administration of high-dose intravenous corticoids, usually using methylprednisolone 20 – 30 mg/kg/day (maximum dose of 1g/day) for 3 – 5 days (1). This approach is followed by oral medication with tapering the dose of corticoid over a period of 14 to 21 days (2).

The main alternative is administering immune globulin at a dose of 2 g/kg intravenous over the course of 3 – 5 days (1).

Some clinicians prefer the approach of combining the two medications, but there is no convincing evidence of any advantages to such measures (1).

In our case, corticoid treatment was used, with evident improvement of the patient.

The main problem in approaching ADEM or any form of demyelinating disease is establishing the diagnosis. Various monophasic and relapsing illnesses must be considered as there are a broad spectrum of symptoms that overlap over numerous diseases. Clinical features and imaging findings must be closely analyzed (2). The most challenging disease to differentiate is multiple sclerosis. Certain clinical features may be used in support of the diagnosis: history of a recent viral illness and widespread central nervous system signs and symptoms with or without encephalopathy usually suggest ADEM (3). Imaging findings can also be used as ADEM presents with more lesions than MS and also larger and more poorly defined (3).

Table 1. IPMSSG diagnosis criteria (8)

Multifocal, clinical CNS event with presumed inflammatory demyelinating cause;
Encephalopathy that cannot be explained by fever, systemic illness or post-ictal fever;
No new clinical and MRI finding 3 months or more after onset;
Brain MRI is abnormal with changes consistent with demyelination during the acute, 3 month phase.

4. Conclusions

Acute disseminated encephalopathy is an auto-immune demyelinating disease, mostly appearing after an infection or immunization. Even though the evolution is usually monophasic and benign with symptoms resolving almost completely, there are risks of fatality if certain regions of the cerebrum are

involved. The main problem is in successful diagnosis, treatment in order to decrease the risk of residual deficits and progressive early passive and active exercise therapy. It is pertinent to emphasize the difficulty and importance of differentiating ADEM from other diseases of the central system, demyelinating or not.

Informed consent

An informed consent was obtained from the patient participating in the study.

Declaration of conflict of interests

The authors declare that there was no conflict of interest regarding the publication of this paper.

References

1. Brenton JN., Ramachandran TS. (21st October 2019) Acute Disseminated Encephalomyelitis. Medscape.
2. Gulay Alper, MD. Acute Disseminated Encephalomyelitis. Journal of Child Neurology. 2012; 27(11): 1408-1425.
3. Waldman AT., Gonzalez-Scarano F., Dashe JF., Acute disseminated encephalomyelitis in adults. Post TW, ed. UpToDate. Waltham, MA: UpToDate. Inc. <https://www.uptodate.com> (Accessed on October 20, 2019.)
4. Anilkumar AC., Foris LA., Tadi P. Acute Disseminated Encephalomyelitis (ADEM). Treasure Island (FL): StatPearls Publishing; 2019 Jan.
5. Adesina O., Boellstorff DM., Thompson R. Acute disseminated encephalomyelitis. American Academy of Ophthalmology. <https://eyewiki.aao.org/> (Accessed on October 07 2019).
6. Brinar VV., Habek M., Diagnostic imaging in acute disseminated encephalomyelitis. Expert Rev. Neurother. 10(3): 459 – 467 (2010).
7. Koelman DL, Chahin S, Mar SS, Venkatesan A, Hoganson GM, Yeshokumar AK. et all. Acute disseminated encephalomyelitis in 228 patients: A retrospective, multicenter US study. Neurology. 2016 May 31;86(22):2085-93.
8. Krupp LB., Tardieu M., Amato MP., et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revision to the 2007 definitions. Mult Scler J. 2013; 19(10):1261 – 1267.

Therapeutic difficulties in vegetative epileptic seizures as a sign of acute viral encephalitis: case presentation

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Abstract

Acute encephalitis is a severe pathology represented by the inflammation of the brain parenchyma associated with neurological dysfunction. The etiology is predominantly viral or autoimmune, with different therapeutic approach. The typical manifestations include fever, epileptic seizures and neurological focal signs. The treatment consists in specific drug therapies regarding the etiology and rehabilitation therapies in case of incomplete recovery.

We present a case of a 43-year-old woman with occipital cephalalgia and dizziness, associated with vesperal high blood pressure levels at the same hour daily. The brain MRI described possible acute encephalitis, with FLAIR and T2 hypersignal area on right parietal region and diffusion restriction. The lumbar puncture revealed no modifications and the EEG recordings showed irritative patterns. The acyclovir intravenous treatment and an antiepileptic drug were initiated. The repeated MRI revealed laminar necrosis which explained the vegetative epileptic seizures manifested with high blood pressure. The clinical status of the patient majorly improved due to specific treatment including rehabilitation interventions.

Key words: *acute viral encephalitis, vegetative epileptic seizures, laminar necrosis, cephalalgia, rehabilitation,*

1. Introduction

Encephalitis represents the inflammation of the cerebral parenchyma associated with a neurological dysfunction, caused by the infection of the central nervous system or by an immune-mediated mechanism (1).

Clinical manifestations of encephalitis include fever, epileptic crisis, focal neurologic signs, pleocytosis in CSF, neuroimages and EEG manifestations (2, 3).

The most common cause of encephalitis is the viral infection. In many cases, it can be difficult to determine the etiology considering that are over 100 pathogens which can be involved, most common being herpes simplex virus 1 and 2 (HSV). Almost 50% of encephalitis cases remain undiagnosed (4).

The diagnostic approach includes lumbar puncture, the analysis of the cerebrospinal fluid (CSF) and MRI (5). On the MRI, the main abnormalities include the presence of hypersignal in the temporal and frontal lobe and in the insular cortex, diffusion restriction and contrast enhancement (4). If the etiology is not determined the empiric treatment is with intravenous Acyclovir for 10-14 days. Following the above-mentioned treatment, the mortality in these cases decreases from 70% to just 8%. (4).

Some patients remain with neurological sequelae that can be partially diminished by specific

rehabilitation therapy. The recovery from encephalitis is variable according to the patient predisposition and the severity of the case, from a complete and fast recovery to an incomplete or prolonged recovery that might last several months. Some of the chronic deficits that the patient may experience include neurological impairments, movement disorders, aphasia, behavioral abnormalities, and intellectual deficit. The general outcome can be improved by rehabilitation methods which can be applied according to each case particularity (6).

Cognitive therapy interventions, measuring for example memory and language processing, have a positive change in neuropsychological tests from baseline to follow-up, but with no complete recovery for the majority of patients. Behavioral therapy methods following infectious encephalitis also show an improved result. Physical therapy interventions are very important in improving motor and sensory deficits, with lower need of assistance for daily life activities (6).

The combination of physical, psychological, occupational and speech therapy plays a major role in the rehabilitation of these patients, and studies reveal a significant improvement in scores, but with incomplete recovery for some patients (6).

2. Case presentation

The patient, a 43-year-old woman with no pathological history, presented to the Neurology Department for pulsating occipital headache, dizziness and drowsiness. These symptoms suddenly started 5 days prior to the admission and at the beginning they included tremor, parenthesis in the upper and lower limbs, giddiness and headache.

At the general examination, there were no signs of pathological modifications.

When the neurological assessment was performed, the patient was conscious, spatially and temporally oriented, without any signs of meningeal irritation or intracranial hypertension, not showing any involuntary movements, without any pathological modifications on cranial nerves, except from a slightly positive unsystemised Romberg, independent walking, with no motor deficit, motor strength=5/5, normotonia, without dysmetria, deep tendon reflexes and abdominal cutaneous reflexes present bilaterally, plantar cutaneous reflex in flexion, without pathological reflexes, pain when palpating the bilateral Arnold points, sharp pain when palpating the occipital region, without subjective or objective sensibility disorders, continent sphincters.

Biologic: VEM 99,8fl slightly raised (VN 90-95fl), Vitamin B12 deficiency (150 pg/ml, VN=180-914pg/ml), microscopic hematuria.

Taking into consideration the uncharacteristic pathology and the multitude of differential diagnosis, an emergency native cerebral CT scan was performed with no pathological findings.

The investigations were continued with radiography of the cervical spine, but no degenerative or static changes were noticed. The ENT assessment found normal hearing and vertiginous syndrome of neurologic cause.

As the patient displayed persistent high blood pressure (of 145/90mmHg-180/90mmHg) which did not improve when given IECA and indapamide, a cardiologic examination was made, with normal EKG and echocardiography.

As the patient showed anxiety and panic attacks, a psychological assessment was completed and it revealed only signs of anxiety caused by the sudden appearance of the symptoms, with no suspicion of depression or somatization.

During this time, the patient followed a symptomatic treatment which showed a slight improvement, although the low intensity vertigo and the headache persisted. During the day, the patient presented

normal-high blood pressure with a maximal value of 130/90mmHg, measured in the morning. In the evening, after 7pm, her general mood would worsen, with accentuated occipital headache and her blood pressure would be as high as 190/100mmHg. These symptoms would persist through the night until early morning, at around 4am. A chronic treatment with enalapril and indapamide was administrated with no success, followed by angiotensin-II-receptor antagonists and calcium channel blockers as a possible resistivity to IECA was taken into consideration, also unsuccessfully. During the moments of elevated blood pressure, numerous hypertensive medications were administrated, such as IECA, angiotensin II receptor blockers, beta blockers, furosemide, calcium channel blockers and anxiolytics when the patient presented panic attacks, but blood pressure continued to follow the same daily pattern: in the evening, blood pressure would suddenly increase over the values she presented during the day, the headache would aggravate along with anxiety. These symptoms would go for hours, only fade away back to normal in the morning with or without the medication.

A native cerebral MRI is performed and described a discrete FLAIR and T2 hypersignal coming from the right parietal region, as seen in Figure 1, and moderate diffusion restriction, as showed in Figure 2. The cortical distribution affected two gyri near a sulcus, with no SWI and T1 expression. The aspect of the MRI indicated a possible focal encephalitis.

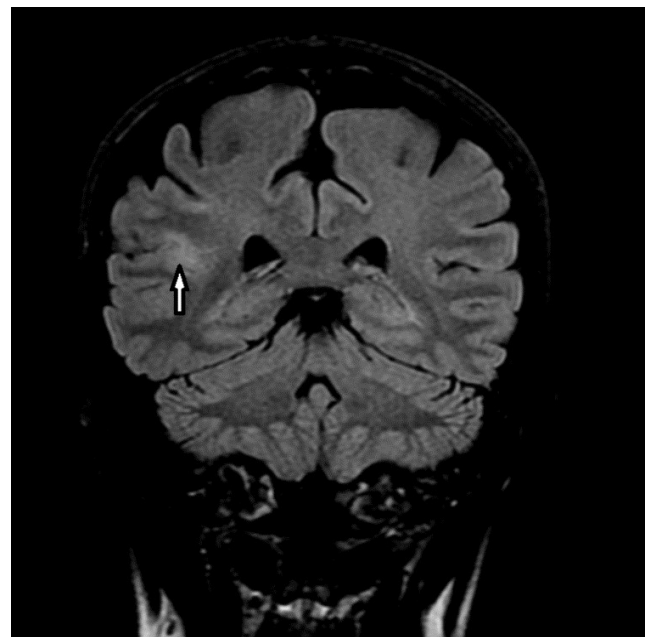


Fig. 1: Native cerebral MRI, T2 FAIR, coronal section, hypersignal in the right parietal area

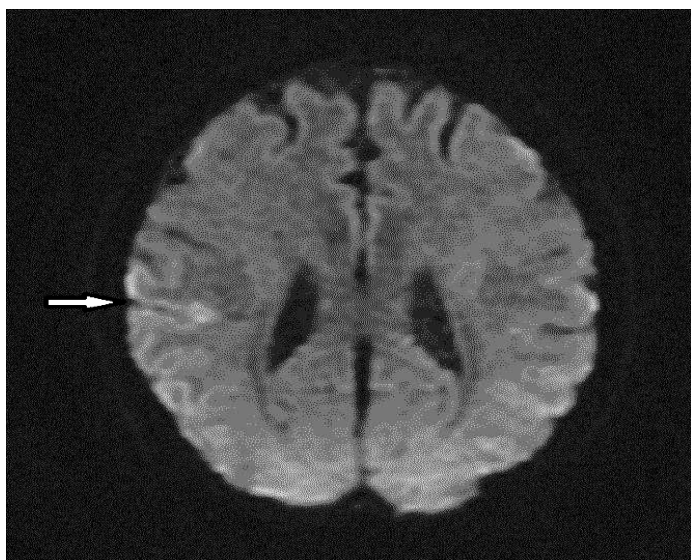


Fig. 2: Native cerebral MRI, DWI, axial section, moderate diffusion restriction area

As the suspicion of viral encephalitis arose, the Infectious Diseases clinic was contacted and recommended an emergency lumbar puncture and an intravenous treatment with Acyclovir 1500mg a day for 7 days, Mannitol 20% for 3 days and Dexamethasone.

The CSF analysis revealed no pathological modifications in biochemistry (normal amylase, chlorides, glucose, LDH, total proteins), normal leukocyte count, CSF bacteriologic exam (absent *Streptococcus pneumoniae*, *Streptococcus beta hemolytic*, *Staphylococcus aureus*, *Enterobacteriaceae*, *Enterococcus spp*, *Pseudomonas spp*, *Acinetobacter spp*.). The multiplex PCR Panel was undetectable for *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, Cytomegalovirus, Enterovirus, Herpes simplex virus 1,2,6, Human Parechovirus, Varicella zoster virus, *Cryptococcus neoformans/gattii*.

The immunologic analysis from serum did not reveal any IgM anti-Herpes type 1,2, CMV reactivity, but there was IgG reactivity for HSV, VVZ, CMV and an uncertain result for EBV. Although the blood and CSF analysis did not reveal the encephalitis etiology, the clinical status and the imagistic aspects indicate viral encephalitis from the Herpesviridae category. From this reason, the Infectious Diseases specialists recommended that the empiric treatment with Acyclovir should continue.

During the treatment, the clinical state of the patient has considerably improved: the headache reduced in frequency, appearing only occasionally, the dizziness got better, the drowsiness and the high blood pressure which were present during hospitalization disappeared. Although the injectable treatment with Acyclovir usually is administrated for 10-14 days, the patient followed it only for 7 days because of the hepatic cytolysis syndrome which appeared. After that, the treatment was discharged with oral treatment of Acyclovir 400mg 2 pills 4 times a day for 14 days, while the hepatic and renal functions were monitored.

EEG: alpha rhythm 11 cycles/sec in posterior progressing towards the anterior area, with rare pathological irritative elements at the C4-P4 (right parietal and central) level (Figure 3). Taking into consideration the cortical damage showed on the cerebral MRI and the irritative changes in the right parietal region which correspond to the focal lesion, a prophylactic antiepileptic treatment was recommended: Levetiracetam 500mg one pill two times a day.

After three weeks from onset, a follow up cerebral MRI with contrast was performed and it revealed two areas of hypersignal T1, T2 and FLAIR, without a diffusion restriction, at frontal parietal level and right parietal with cortical distribution and a reduction of the hypersignal T2 zone in the right parietal region compared to the preceding examination (Figure 4). There was a suspicion for a possible cortical laminar necrosis in the right frontal parietal region.

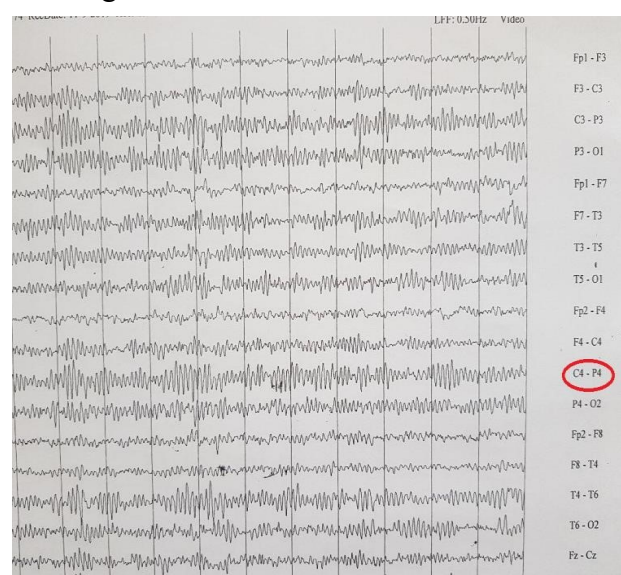


Fig. 3: EEG- pathological elements of irritative type at C4-P4 (right parieto-central) level.

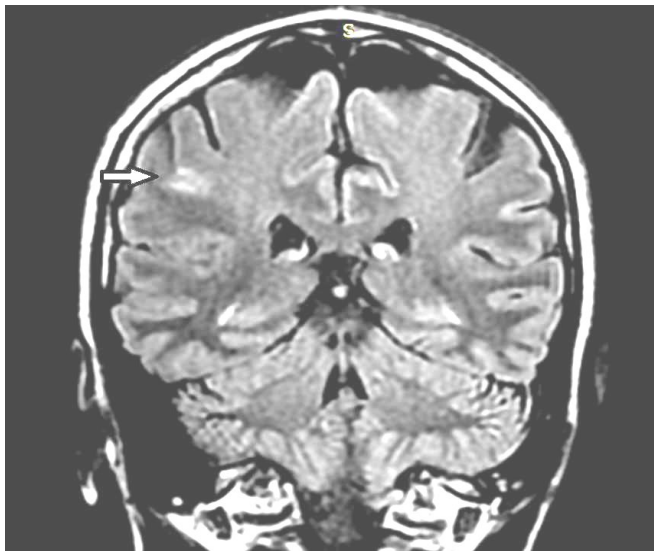


Fig. 4: Cerebral MRI with contrast, T2 FLAIR, coronal section, hypersignal area in the right parietal level.

At the release from hospital, the outcome was favorable, with an improved general condition under the medication mentioned above.

At a few weeks follow-up examination, the patient still complained about a remaining dizziness sensation, although majorly improved compared to the acute phase and a low intensity headache. Also, she developed general anxiety due to the medical condition, for which she refused to practice any psychotherapy or any other activity that will diminish it.

3. Discussions

Encephalitis represents a pathology with significant mortality and morbidity, which, if detected early on, can change the outcome for the patient.

The etiology can be infectious (viruses, bacteria, parasites, fungi), post infectious (Acute disseminated encephalomyelitis), non-infectious (autoimmune, paraneoplastic). Its frequency varies dependent on the geographical region and age, from 0.7 to 13.8 in 100,000 people (2).

The Herpes virus encephalitis caused is the most frequent in developed countries, with a predominance of 90% for HSV type1, not being favored by immunosuppressant. The HSV 1 affects especially the temporal and orbital and frontal lobe. A third of the cases are attributed to the primary infection which spreads through the olfactory nerves by nasopharyngeal and two thirds are caused by the viral reactivation and its spreading in the intracranial portion of the trigeminal nerve (1). Clinically, it

manifests itself through fever, headache, personality disorders and epileptic seizures (4). The CSF exam discovers pleocytosis, normal glucose levels, and possible xanthochromia. The PCR test is an elective test with 98% sensibility and 94% specificity but can be negative initially (4). The cerebral CT in the case of the herpetic virus can show no visible changes, sometimes a hypo intensity at temporal level (7). The cerebral MRI T1 sequence shows an edema and sometimes, a hyper signal in the regions with hemorrhage and delayed enhancement under different shapes: gyrus, leptomeningeal, diffuse and annular. On the T2 sequences there can be noticed a hypersignal at the level of white substance of the cortex and hypo signal at the levels of hemorrhages. On the DWI and ADC sequences, a diffusion restriction is seen due to the cytotoxic edema, which is less intense compared to the one from a stroke (8,9).

The EEG is modified in 80% of the cases of viral acute encephalitis. It can be useful to make the differential diagnosis between an organic pathology and a psychiatric one, and also to identify the non-motor crisis. The changes are unspecific and include slow, high amplitude waves, with activity in the temporal lobe and periodic epileptiform discharges. There are no pathognomonic elements for the herpetic encephalitis (2).

The criteria for diagnosing encephalitis include:

- Major criteria: the alteration of the consciousness and the personality for over 24 hours, without any other possible alternative cause
- Minor criteria: documented fever, epileptic seizures present in the case of a patient not registered with epilepsy, focal neurologic signs which appear suddenly, the presence of leucocytes in CSF, suggestive neuroimages, EEG abnormalities.

The diagnosis of suspecting encephalitis is attributed when a major criteria is present along with two minor criteria, while the diagnosis of probable or definite encephalitis needs three minor criteria (1).

Acyclovir is an antiviral medication utilized for many species from the Herpesviridae category. The treatment should be initiated even in the cases which are not confirmed, even before the lumbar puncture or if this is delayed, and can be stopped in the case that another diagnosis is discovered to be more probable. This treatment implies a dose of 10 mg per body kilogram three times a day for approximately 14 days (2).

Because the herpetic encephalitis has also a necrotic effect, with a possible epileptogenic effect, the patients can be recommended a prophylactic antiepileptic treatment. A controversial treatment is the one with corticosteroids in the case of viral infection, as it is proven to be beneficial in certain bacterial infections, but there aren't enough clinical proofs to sustain its administration in the cases of viral infections as well (1).

The cortical laminar necrosis represents the lesions of neurons from the cerebral cortex when the oxygen and glucoses contribution cannot meet the necessities in the local tissue. The cause can be ischemia, hypoglycemia, hypoperfusion, epileptic crisis especially in epileptic status. The pathogenesis of this dysfunction which is predominant at the cortex level consists of the fact that these neurons are much more metabolically active compared to the white substance or to the glial cells around them, necessitating much more energy (10).

The changes seen on the cerebral MRI in the case of laminar cortical necrosis include in the beginning the diffusion restriction on DWI, after two weeks, the T1 hypersignal with a peak at week 4 and progressive disappearance for a few months. The T1 hypersignal shows that the denatured proteins accumulate in the damaged and macrophage cells and excludes the presence of hemorrhage or of calcium deposits. T2 Sequence presents a hypersignal (11).

The epileptic seizures are generally associated with high blood pressure because of the stimulation of the sympathetic nervous system and the secretion of catecholamine (12). Some patients can have vegetative epileptic seizures manifested only through dysfunctions of the autonomic nervous system and clinically through sudden and periodic increases in blood pressure which don't respond to usual antihypertensive medication (13).

In the case of our patient, we discovered a cortical laminar necrosis on the cerebral MRI, which was associated with the vegetative epileptic crisis from the encephalitis foci. The crises manifested through high blood pressure can be explained through rhythmicity, as these increases manifested at the same time every day, uninfluenced by numerous antihypertensive medications, through the irritative changes on the EEG and their disappearance after the antiepileptic treatment with levetiracetam has been initiated.

Regarding the long term rehabilitation, our patient experienced severe fatigue for several weeks, thus

we created a lifestyle changes plan. We advised her to maintain a reasonable activity schedule, reduction of work hours, moderate and regular exercise such as walking, no intake of stimulant substances or alcohol and a healthy diet. The fatigue was significantly improved after a few days. For the persisted headache we recommend to the patient to keep a cephalalgia journal to monitor the frequency and intensity of the headache. We also encouraged psychotherapy combined with cognitive therapy to manage stress and anxiety, since the emotional component was an important reaction for our patient, but she was no compliant to this treatment and the anxiety syndrome still persisted. In our case, patient's behavior status, anxiety and cephalalgia are mandatory to be monitor in the future visits.

The quality of the rehabilitation care is not dependent of age, sex, type of infectious agent or intervention type, but is related more to establishing the correct diagnosis, the initial clinical picture, as well as the unique central nervous system characteristics of each individual (6).

The particularities of this case lay in the atypical symptomatology of encephalitis manifested through headache, without the alteration of the conscious state or other neurological signs, vegetative epileptic crisis manifested through high blood pressure, associated with cortical laminar necrosis and in the fact that the pathogen agent wasn't detected through the currently available methods.

4. Conclusions

Viral acute encephalitis is a serious pathology which can have long term consequences if it is not properly identified. The clinical manifestations can be atypical or unspecific. The treatment should be recommended to every patient with this possible diagnosis and not be delayed by the investigation process. General rehabilitation interventions can lead to a better outcome for the patient.

Informed consent

An informed consent was obtained from the patient participating in the study.

Declaration of conflict of interests

The authors declare that there was no conflict of interest regarding the publication of this paper.

References

1. Halperin JJ. Diagnosis and management of acute encephalitis. *Handbook of Clinical Neurology*. 2017;140:337-47.
2. Solomon T, Michael BD, Smith PE, Sanderson F, Davies NW, Hart IJ et al. Management of suspected viral encephalitis in adults e Association of British Neurologists and British Infection Association National Guidelines. *Journal of Infection* (2012) 64, 347-373.
3. Ellul M, Solomon T. Acute encephalitis diagnosis and management. *Clinical Medicine*. 2018;18(2):155-9.
4. Piquet AL, Cho TA. The Clinical Approach to Encephalitis. *Curr Neurol Neurosci Rep*. 2016;16:1-8.
5. Ekmekci H, Ege F, Ozturk S. Cerebrospinal Fluid Abnormalities in Viral Encephalitis. *IntechOpen*.2013. DOI: 10.5772/54590. Available from: <https://www.intechopen.com/books/encephalitis/cerebrospinal-fluid-abnormalities-in-viral-encephalitis>
6. Christie S, Chan V, Mollayeva T, Colantonio A. Systematic review of rehabilitation intervention outcomes of adult and pediatric patients with infectious encephalitis. *BMJ Open*. 2018. doi:10.1136/bmjopen-2017-015928.
7. Jayaraman K, Rangasami R, Chandrasekharan A. Magnetic Resonance Imaging Findings in Viral Encephalitis: A Pictorial Essay. *J Neurosci Rural Pract*. 2018;9(4):556–560. doi:10.4103/jnpr.jnpr_120_18
8. Granerod J, Davies NW, Mukonoweshuro W, et al. Neuroimaging in encephalitis: analysis of imaging findings and interobserver agreement. *Clin Radiol*.2016;71(10):1050–1058. doi:10.1016/j.crad.2016.03.015
9. Bertrand A, Leclercq D, Martinez-Almoyna L, Girard N, Stahl JP, De-Broucker T. MR imaging of adult acute infectious encephalitis. *Médecine et Maladies Infectieuses*, Elsevier Masson, 2017, ff10.1016/j.medmal.2017.01.002ff. fffal-01490868f.
10. Donaire A, Carreno M, Gómez B et-al. Cortical laminar necrosis related to prolonged focal status epilepticus. *J. Neurol. Neurosurg. Psychiatr*. 2006;77 (1): 104-6.
11. Arman F¹, Kaya D, Dincer A, Sav A, Pamir MN. Serial EEG and MRI changes in status epilepticus-induced excitotoxic neuronal necrosis. *Epileptic Disord*. 2011 Dec;13(4):446-51. doi: 10.1684/epd.2011.0472.
12. Nass RD, Hampel KG, Elger CE, Surges R. Blood Pressure in Seizures and Epilepsy. *Front Neurol*. 2019;10:501.
13. Kanner AM. Epilepsy and Activity of the Autonomic Nervous System. *Epilepsy Curr*. 2002;2(5):159–160.

The efficacy of pulmonary rehabilitation in improving the clinical status in idiopathic pulmonary fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fatal lung disease with a median survival rate of 2-4 years after diagnosis, occurring primarily in older adults. The diagnosis is suggested by histology or radiologic evidence of a usual interstitial pneumonia (UIP) pattern and exclusion of known cases of pulmonary fibrosis. There are some comorbidities associated with IPF such as pulmonary hypertension, emphysema, chronic obstructive pulmonary disease (COPD), asthma, lung cancer, cardiovascular disorders, gastroesophageal reflux disease (GERD), sleep disorders and psychiatric disturbances. The management of IPF focuses on the amelioration of symptoms, preserving lung function, improving health status, minimizing the adverse effects of therapy and improving survival. Pulmonary rehabilitation is suggested for IPF patients when adequate medical therapy controls poorly the disease progression and mental, physical or social consequences of the illness persist during daily life. Currently, there are only two approved available antifibrotic therapies, pirfenidone and nintedanib, capable to reduce disease progression and physical deterioration, but cure is elusive and improvements are hardly observed. In addition, there is a continuous need of non-drug therapy components which should be included in IPF patient management: education, psychosocial support, exercise training, nutrition, symptom management and palliative care, non-invasive ventilation and pulmonary transplant. These complementary therapies have been proven to improve dyspnea, exercise capacity, fatigue and quality of life.

Key words: *idiopathic pulmonary fibrosis, rehabilitation, quality of life, palliative care,*

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic lung disease with poor prognosis and rapid progression, with a median survival rate between 2-5 years after diagnosis (1). IPF is characterized by fatigue and dyspnea, which impairs daily living by decreasing the quality of life. As fibrosis evolves, these symptoms worsen, patients becoming unable to perform physical activities. Also, these subjects associate skeletal muscle deconditioning, depression and social isolation (2). IPF has a limited response to pharmacological treatment and new approaches and complementary therapies to improve IPF control are urgently required (3).

Prevalence

IPF affects about 3 million people worldwide, with an incidence increasing dramatically with age (4). IPF is more prevalent in males, but it can also affect women, especially the heaviest smokers (5). A

recent analysis based on healthcare claims data of a large health plan in the United States yielded a prevalence estimate of between 14.0 and 42.7 per 100,000 persons depending on the used case definition (6). Generally, the prevalence is higher in America than in Europe or Asia, and it is unclear whether this is due to differences in geographic, ethnic and cultural aspects or due to different types of disease management (5).

Etiology

Even though idiopathic pulmonary fibrosis is, by definition, a disease of unknown etiology, a number of potential risk factors have been described such as cigarette smoking, environmental exposures, microbial agents, chronic viral infections and certain comorbidities (4, 6). Smoking is strongly associated with the development of IPF, especially for individuals with a smoking history of more than 20

packs/year (6). It is a well-known fact that cigarette smoking is the main factor responsible for the development of IPF, but there are some debates regarding the implication of this exposure on the evolution of this disease. King Jr. et al. reported a better survival in subjects who were current smokers at the time of diagnosis, explained by the earlier presentation because of smoking-related symptoms, facilitating an accurate diagnosis in a mild stage of the disease (7, 8). Numerous environmental exposures that target the lung epithelium increase the risk of IPF, the most important being cigarette smoking. Also, an increased risk has been linked to exposures such as agriculture and farming, metal and wood dust, stone dust and silica (4).

Taking into account the microbial agents, it is known that the Epstein-Barr virus has primarily been detected in the alveolar epithelia of IPF patients (4, 6). Viruses include cytomegalovirus, human herpes viruses (HHV-7, HHV-8), which have been associated with IPF development. Several studies have also suggested that bacteria might play a part in the pathogenesis of IPF. The lungs of patients with IPF have higher bacteria loads and significant differences in the composition of their microbiota compared to healthy subjects. The most common pathogenic bacteria are *Staphylococcus* spp and *Streptococcus* spp. These modifications have been associated with the clinical markers of disease evolution (4).

An association between serum *Helicobacter Pylori* (HP) antibody positivity and more severe diseases was recently described. In a recent study, the prevalence of HP infection in IPF was compared between two groups: HP-positive IPF patients and HP-negative IPF patients and revealed that those with HP positive infection had significantly lower FVC, FEV1 than the other group (9).

Pathophysiology

Despite the fact that lungs are exposed to many external factors, they possess a great ability to recover through various mechanisms. But, in an individual with susceptible state, a repetitive alveolar injury causes a premature and persistent epithelial damage, a release of pro-fibrotic mediators and a cascade of mesenchymal cell activation, all these mechanisms conducting to an ongoing development of IPF.

Ageing is the most important demographic risk factor, affecting epithelial type 2 cells (AEC2s) which have epigenetic changes, genomic instability,

mitochondrial dysfunction, altered intercellular communication, deregulated nutrient sensing, loss of proteostasis, genomic instability and a lower secretory capacity with a loss of surfactant (10,11). Moreover, in IPF the function of the epithelial type 1 cells (AEC1s) is affected, influencing the epithelial turnover. Besides ageing, in one-third of cases, the major risk factors are genetic variants (12, 13). Even if the certain mechanism of developing IPF is not clear, there are some multidirectional interactions between the risk factors and genetic susceptibility, causing alterations in the epithelial cells, extracellular matrix and mesenchymal cells, so all individuals diagnosed with IPF are considered mechanistically similar (14).

Comorbidities

Pulmonary and extra pulmonary comorbid conditions are progressively being recognized as important in patients with IPF (4). Comorbidities may differently influence prognosis of IPF patients (15).

IPF has been correlated with a considerable number of comorbidities such as pulmonary hypertension, emphysema, COPD, asthma, lung cancer, cardiovascular disorders, gastroesophageal reflux disease (GERD), sleep disorders and psychiatric disturbances (16). Kreuter et al. described the “comorbidome” of IPF, a new tool that can help clinicians to predict the survival in patients with IPF, which include cardiovascular (atherosclerosis, arterial hypertension, coronary arterial disease, pulmonary hypertension), metabolic (diabetes), gastroenterological (GERD) and neoplasia diseases (lung cancer) (16, 17).

Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) are two severe multifactorial pulmonary disorders characterized by quite distinct clinical and pathological features. COPD is characterized by a poorly reversible and progressive airflow limitation that is determined by the concurrence of airways inflammation and emphysema, whereas in IPF a restrictive pattern of lung volume abnormality is associated with impaired diffusion capacity. During imaging and pathological examinations COPD and IPF exhibit different appearances, as far as the involved pulmonary regions (upper lobes versus lower lobes), and the occurring parenchyma modifications are concerned (alveolar emphysematous dilation and bronchiolar

inflammation in COPD, versus interstitial fibrosis and honeycombing in IPF) (18).

Nevertheless, a number of similarities can be recognized between the two disorders. Firstly, both COPD and IPF are chronic and progressive diseases of elderly people (with male predominance), that severely affect the lung function and both are related to long term inhalation of external noxious agents (mainly tobacco smoking). Secondly, in both diseases a progressive loss of alveolar parenchyma takes place leading to severe impairment of respiratory function. Variants of pulmonary fibrosis associated with emphysema have been described and these cases have been grouped in a newly defined syndrome of combined pulmonary fibrosis and emphysema (CPFE). In CPFE, lung volumes are commonly within normal limits due to the opposing effects of hyperinflation and fibrosis. The CPFE syndrome is more frequent in male smokers and pulmonary hypertension can complicate all these disorders.

Finally, both IPF and COPD are associated with an increased risk of cancer development and several lines of evidence suggest that this increase is independent from the effect of cigarette smoking (18, 19).

Lung cancer (LC)

One of the most impacting comorbidity is the appearance of LC in the course of IPF. Interestingly, IPF itself increases the risk of LC development by 7% to 20%. There are various common molecular, genetic and cellular processes that associate lung fibrosis with LC like oxidative stress, myofibroblast activation and uncontrolled proliferation, myofibroblast/mesenchymal transition, alterations of growth factors expression, endoplasmic reticulum stress and other genetic and epigenetic variations that lead to the development of IPF and LC (20). The risk of developing LC of patients with IPF is up to 5 times greater than in the general population, with a prevalence ranging between 3% and 48% depending on different cohort studies (5, 20). The reason of this bizarre association is still unclear. Some studies demonstrated that both diseases share common risk factors such as aging, smoking history and male gender and similar pathogenic mechanisms. Usually lung cancer develops as nodules close to fibrotic areas and the most diagnosed subtypes are the adenocarcinoma and squamous cell carcinoma, worsening the evolution of IPF patients (21, 22).

Pulmonary hypertension (PH)

Pulmonary hypertension is a frequent complication of IPF and is now defined as mean pulmonary arterial pressures (mPAP) more than or equal to 25mm Hg at rest, confirmed by right heart catheterization (RHC) (23). Patients with PH and IPF presents a very poor survival rate with reduced quality of life. Usually they tend to have reduced exercise tolerance, lower arterial oxygen at rest, lower lung diffusion of carbon monoxide (DLCO) values, right ventricular hypertrophy and/or pulmonary artery enlargement on imaging scans. Currently, the only approved treatment for PH in IPF is lung transplant in selected cases (15).

Obstructive Sleep Apnea (OSA)

Sleep apnea is increasingly evident in patient with IPF. The relationship between obstructive sleep apnea (OSA) and IPF is complex. The restrictive condition can reduce upper airway tone increasing their collapsibility and the nocturnal oxygen desaturation leads to an increased oxidative stress (25), both of these conditions leading to a poor prognosis of IPF. By using therapy with continuous positive air pressure we can see significant improvements in activities of daily living, quality of sleep, survival and ultimately quality of life (15, 21, 24, 25).

Gastroesophageal reflux disease (GERD)

The finding of GERD in the context of IPF is not rare. However, how this mechanism has a pathogenic role in IPF is not clear. It is known that micro aspiration can cause a repetitive alveolar cell injury, leading to an irregular wound healing process and finally to lung fibrosis (15). Antacid therapy, mainly proton pump inhibitors (PPI) might decrease the frequency of acute exacerbations of IPF (AE-IPF) by reducing the acidity of the micro aspirate (16).

Asthma

Both asthma and IPF affect the architecture of the lung parenchyma and even if there is no connection between these two diseases, environmental triggers can determine hypersensitivity pneumonitis, which in evolution can cause pulmonary fibrosis. In an individual, both asthma and IPF can coexist, sharing common risk factors, even if in IPF lung injury is more important, progressing to destroyed lung tissue and respiratory failure (26).

Cardiovascular comorbidities (CVD)

Numerous cardiovascular comorbid conditions like arrhythmias, congestive heart failure and ischemic heart disease are very often associated with IPF (4, 27). Amongst them, an increased incidence of Atrial Fibrillation (AF) and Atrial Flutter (AFL), which have been the most commonly reported arrhythmias in patients with IPF, comorbidities that persist after a lung transplant according to Nielsen et al. (23, 28). Kizer et al. showed that pulmonary fibrosis was associated with an increased incidence of coronary artery disease (CAD) (17, 29). The causal relation where pulmonary fibrosis promotes atherosclerosis is evidenced by the increasing serum levels of interleukins, cytokines, circulating immune complexes and development of fibrosis in extra-pulmonary organs like the digits and mediastinum (4). Cardiovascular impairments among IPF patients are considered a significant limiting factor during physical exertion and are associated with exercise intolerance, severe signs and symptoms and lower prognosis outcomes (1).

Depression and anxiety

Symptoms like anxiety and depression are commonly observed in patients with IPF. Also they are related to the functional status of patients and can cause an increase in dyspnea, physical disability and mortality and decrease exercise tolerance (21). Given that, comorbidities should be systematically explored in IPF because an appropriate treatment and an early recognition may help in optimizing the management and improving quality of life (15).

Diagnostic

IPF is a fibro proliferative disease of unknown case, associated with histopathological and/or high resolution computed tomography (HRCT) pattern of usual interstitial pneumonia. To establish the diagnosis of IPF, an exclusion of other known cases of interstitial lung disease (ILD) is required, through a multidisciplinary discussion between pulmonologists, radiologists and pathologists experienced in the diagnosis of ILD (in particular those linked to the environment exposures, drug toxicity and connective tissue disease). The confirmation of the certain IPF diagnosis is challenging and it is based mainly on the radiological pattern. Given the high-quality evidence regarding HRCT specificity for the recognition of histopathologic UIP pattern (reticular opacities, honeycombing, secondary bronchiectasis), surgical

lung biopsy (SLB) is not essential. When surgical lung biopsy is indicated, the diagnosis is established in the presence of SLB aspects showing up a UIP pattern and specific combinations of HRCT (6, 30).

Management

The main goals of IPF management focuses on the amelioration of symptoms, preserving lung function, improving health status, minimizing adverse therapy effects and improving survival (4). The 2011 American Thoracic Society/European Respiratory Society/ Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) consensus guidelines recommend long-term oxygen therapy if hypoxemia is present, the treatment of comorbidities, pulmonary rehabilitation (PR), lung transplant for selected patients and clinical follow-up every 4–6 months. Also, an important aspect of care is the management of cough, dyspnea and psychological suffering, symptoms which nearly all patients with IPF develop as the disease evolves (31).

A comprehensive care approach that includes nonpharmacological and pharmacological treatment, patient education, palliative care and increased support throughout the course of the illness is needed.

Antifibrotic therapy

Apart from lung transplant, long term efficient treatment is still limited for most patients with IPF, despite some recent encouraging findings in pharmacotherapy. Currently, there are only two available approved antifibrotic therapies: pirfenidone (dose 801 mg 3 times daily) and nintedanib (dose 150 mg twice daily). Both antifibrotics are capable of reducing disease progression and physical deterioration, but improvements are hardly ever observed and cure is elusive (31).

Oxygen therapy

In individuals with resting hypoxemia, the 2011 ATS/ERS/JRS/ALAT treatment guidelines advise the initiation of long-term oxygen therapy, maintaining a SaO₂ between 92–95% at rest and around 88% during physical activity (6). In evolution, the titration of oxygen therapy is required every 60-90 days, or more frequently if needed (32). Also, patient education is required in order to encourage self-monitoring at home by pulse oximetry, both at rest and with exertion, to provide

the sufficient supply of oxygen in order to achieve the individual need (31). The current guidelines do not encourage clinicians to perform cardiopulmonary exercise testing for routine monitoring, but the 6-minute walking test (6MWT) instead, a useful tool to appreciate the physical exercise capacity of the patient. This test should be done at baseline and at an interval of 3 to 6 months, moreover because IPF subjects which are not hypoxic at rest in the early stage of the disease can experience a fall in oxygen saturation during minimum exercise (6).

Smoking cessation

Since tobacco exposure is the main risk factor in IPF, and it is involved in pathogenesis, prognosis and evolution, smoking cessation needs to be implemented in all active smoker subjects. In order to obtain smoking cessation, the clinicians should adopt an individualized management plan including behavioral support and necessary pharmacotherapy. Also, the medical team is encouraged to give intensive cessation advice that has been proven to be more helpful in making smokers quit compared with brief advice. In addition, it was proved that these methods can be augmented by telephone quit-lines, group-based counseling programs, self-help materials and internet-based interventions. Recommendations are based on relaxation training, problem-solving skills and group counseling adding elements of peer support (33, 34). In subjects with IPF, smoking addiction should be avoided because nicotine and other excipients of the cigarette smoke interact with the action mechanism of antifibrotic therapy, resulting in lower medication concentration with a lack of efficiency (35, 36).

Rehabilitation Programs

Pulmonary rehabilitation has become a multidisciplinary approach which includes a routine of education, exercise training and behavior modification techniques, used to improve symptomatology and self-management and to enhance the participation of these subjects in daily life activities, even if in the majority of clinical trials regarding PR programs patients with IPF have not been distinguished from other restrictive lung diseases, such as bronchiectasis, scoliosis and neuromuscular disease (37). Since the prognosis, the disease progression and the response to therapy of IPF subjects are heterogeneous, therefore the ideal moment to initiate a PR program is still unknown and requires further studies (3).

Education

Comprehensive pulmonary rehabilitation plays a significant role in the management of patients with IPF, including its educational intervention. Patients should be informed about disease progression and health deterioration and need to be prepared for the future (31). It has been suggested that educational programs should cover exacerbation and symptom management, oxygen therapy, mood disorders, medications, lung transplantation, energy conservation and end of life care (38).

Psychosocial support

A priority of IPF patient management is psychosocial support in order to improve the quality of life and to reduce the symptomatology. In this group of patients, depression and anxiety affects the daily living, especially in those with a severe, progressive form of IPF. Psychosocial programs need to provide individual and group support to increase the adherence to antifibrotic and symptomatic therapy (39). Subjects who live in rural areas or have limited mobility may benefit from online support groups, such as the Pulmonary Fibrosis Foundation website. Also, an efficient tool in monitoring is represented by the community medical support system with specialists that can detect the decline of clinical status or the need of additional measures, before the next clinic visit. This means that, for the management of an IPF individual, the intervention of a multidisciplinary team is required (40).

Exercise training (ET)

In literature, the majority of studies proposed a training program based on a combination of strength and endurance exercises with a duration between 6 and 12 weeks. The majority of the programs include aerobic exercise (walking, cycling), resistance training and flexibility exercises for peripheral skeletal muscles (41), besides breathing exercises and respiratory muscle training (42). In patients with IPF, due to reduced daily physical activity, a significant loss of muscle strength and endurance was observed, especially of the quadriceps muscle (43). The changes in quadriceps strength in IPF patients was evaluated by Kozu et al. during an 8-week outpatient PR program and an increase of 10% in the maximal isometric knee extension maneuver (41) was observed. After the exercise training program, Nishiyama et al. concluded that there were no significant effects on the arterial blood gases,

dyspnea scale or lung function, but the 6-minute walking distance (6-MWD) had been 46,3 m higher in patients who had physical activity as recommendation (44). These findings are confirmed by Huppmann et al., which found an improvement of 45 ± 55 m of the 6-minute walking distance in patients receiving rehabilitation programs (45).

It has been stipulated that physical activity and regular exercise have an important effect on patients with mild-moderate IPF than in more severe IPF conditions so, as Kozu et al. demonstrated that in patients with severe dyspnea, a home-based rehabilitation program had no effect on 6-MWD, dyspnea or the quality of life (41). The heterogeneity of these findings can be explained by the differences between certain exercise programs, proving that home-based training is not so efficient in patients with IPF which require a more supervised management. Vainshelboim et al. observed that patients included in a supervised exercise training program showed an improvement in exercise tolerance, pulmonary function (FVC), ventilatory response, dyspnea, functional capacity and quality of life. So, since these parameters influence the prognosis of IPF subjects, the ET has an impact on the morbidity and mortality of these individuals (42).

IPF patients usually have a restrictive pathophysiology, with inefficient breathing and lower lung compliance (46). It is plausible that the stretching of thoracic muscles, chest expansion during deep breathing and repetitive stimulus of high ventilation demands that were used in several programs to be responsible of the effectiveness of the breathing pattern with the decreasing of dyspnea. Nykvist et al. demonstrated that by adding inspiratory muscle training on the PR program in patients with IPF, an improvement of dyspnea, exercise capacity, fatigue and quality of life was obtained (47).

Management of IPF and Comorbidities

COPD

COPD is a frequent comorbidity in patients with IPF and the rehabilitation programs have proven their efficacy. In these subjects, there were improvements in dyspnea, functional exercise-capacity (measured by 6MWT) and health-related quality of life (44, 48). Despite the fact that the mechanism of exercise intolerance differs between COPD and IPF, the rehabilitation therapies approved for COPD patients are effective to achieve a suitable exercise capacity

in patients with IPF. The management of COPD and IPF should include a multidisciplinary approach, including individualized rehabilitation intervention as an adjuvant to the medical treatment, through effective methods such as muscular training, speleotherapy, soft tissue manual therapy, neuromuscular electrostimulation and halotherapy (49, 50).

ASTHMA

Asthma is a heterogeneous condition that is associated with IPF, influencing the prognosis of these patients and remaining poorly controlled despite optimum management. The additional interventions in asthma and IPF management, such as physical training, smoking cessation, environmental control practices, inspiratory muscle training, breathing techniques, speleotherapy and halotherapy have been proven to improve muscle strength, symptomatology, exercise capacity and quality of life (15,51).

OSA

The reason of association between OSA and IPF remains unclear. Some possible interactions are explained by the reduction of upper airway tone which determines an increased collapsibility, and by the alterations of the respiratory drive found in subjects with IPF. As showed by Bosi et al., the presence of OSA in IPF patients influences the prognosis by worsening the nocturnal oxygen desaturations (52, 53). In these conditions, the continuous positive pressure treatment (CPAP) is highly advised in patients diagnosed with OSA and IPF, despite the fact that the efficacy of this treatment in reducing disease progression and mortality is not yet proven in large clinical trials (15,54).

LUNG CANCER

The patients diagnosed with IPF have a high risk of developing lung cancer, diseases with several common risk factors, which shares many pathogen mechanisms. Individualized pulmonary rehabilitation in patients with IPF and lung cancer has been shown to increase exercise tolerance, reduce symptomatology and improve quality of life. Complementary therapies include adequate nutrition, physical activity, smoking cessation and psychosocial support. However, at this moment, there is a lack of evidence in the benefit of these therapies on the survival period, symptomatology and the health-related quality of life (55, 56).

Symptom management and palliative care

IPF is a progressive, disabling disease responsible for the deterioration of lung function which determines a progressive increase in fatigue, shortness of breath, and cough. As the pathology evolves, this symptom management represents a major point of interest, the purpose being maintaining an adequate quality of life (57). Even if it is known that the disease has a fatal prognosis, it is challenging for the patient and the caregivers to accept the poor outcome despite maximum conventional and additional therapy (58).

The main goal of palliative care focus is to reducing the symptomatology and to provide comfort for patients, decreasing the physical and emotional distress by introducing the psychological and spiritual support. The persistence of symptoms such as dyspnea and cough affects the daily living of IPF patients, which can be managed with corticosteroids, thalidomide or chronic opioids, but there is a lack of data in this direction (59). Patients with IPF with severe physiological impairment and important co morbid conditions should benefit from advanced directives and end-of-life plan (6).

Nutrition

Patients with IPF which associate gastro-esophageal reflux have an inappropriate nutritional status, so the BMI should be taken into consideration in the management decision. Nutritional support refers to the optimization of calorie intake, with a rigorous adjustment of protein and fat content. Dietary control includes the management of symptoms and of the weight with a focus on reducing the body weight, especially because obesity is a contraindication for lung transplant. An important direction is the management of symptoms related to antifibrotic therapy, such as nausea and reduced appetite, which can require symptomatic therapy and reduction of antifibrotic therapy doses (31).

Non-invasive ventilation (NIV)

NIV is used as a first line respiratory management for AE-IPF, especially because there is an extremely poor prognosis of subject treated with invasive mechanical ventilation (IMV). Although mechanical ventilation has become an indispensable support for critically ill patients with acute respiratory failure, it is well known that MV can initiate and exacerbate lung lesions and can increase the patient morbidity and mortality. Non-invasive ventilation was used in CPAP mode or BiPAP S/T mode in all patients, but it seems that CPAP is less effective in acute

respiratory failure, despite the fact that many patients can be successfully managed by using CPAP mode. The patients with IPF have a poor prognosis, with a controversial evolution, as Yokoyama et al. highlighted in their study, a mean duration of NIV of 12.3 days and a high rate of mortality. However, almost half of the subjects can avoid intubation and have a greater survival rate with the application of NIV, initiated to avoid the severe hypoxemia in acute exacerbation (60, 61).

Pulmonary transplant

Taking into account that the patients with IPF have a poor prognosis and there is a lack of therapy that can reduce mortality, pulmonary transplant has to be taken into consideration. The International Society for Heart and Lung Transplantation (ISHLT) recommends that lung transplant should be indicated in chronic lung disease in subjects who have a high (> 50%) risk of death within two years. Worldwide, the percentage of IPF patients which benefit from lung transplant has gradually increased and even if most evidence supports both lung transplants, the single lung transplant has the advantage of a lower waiting time and can also prevent the higher rates of mortality. During clinical evaluation of IPF patients, a prognosis assessment should be completed in order to refer for lung transplant at the most appropriate moment. Factors that can determine a poor prognosis include older age, low pulmonary function, higher dyspnea score (Modified Medical Research Council, Scala Borg), history of respiratory exacerbation, higher oxygen need, low six-minute walk distance, especially if there is a decline of these parameters over a 6-12 month time period (62). Contrary, higher body mass indices, better pulmonary function and lower mean pulmonary artery pressures have been associated with a better survival five years after the initial diagnosis (63). Clinical prediction models incorporating these variables have been formulated in an effort to improve a clinician's ability to predict prognosis (64).

Conclusion

The management of patients diagnosed with IPF is challenging and integrate disease-specific strategies for slowing disease progression and extending patient survival, simultaneously with palliative care, in order to improve symptom management and quality of life. The major components of the treatment are represented by: early initiation of

antifibrotic therapy, oxygen therapy, psychosocial support, adequate nutrition, education of patient and family, symptom management and palliative care and specific rehabilitation programs, designed in order to prolong the survival period and to enhance the quality of life.

Declaration of conflict of interests

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All authors have equal rights as the first author of this paper.

References

1. Vainshelboim B, Kramer RM, Fox DB, Izhakian S, Sagie A, Oliveira J. Supervised exercise training improves exercise cardiovascular function in idiopathic pulmonary fibrosis. *European Journal of physical and rehabilitation Medicine*. 2017 April;53(2):209-18.
2. Swigris Jeffrey J., Fairclough Diane L., Morrison Marianne, Make Barry, Kozora Elizabeth, Brown Kevin K., Wamboldt Frederick S. Benefits of Pulmonary Rehabilitation in Idiopathic Pulmonary Fibrosis. *Respir Care*. 2011 June;56(6): 783–9.
3. Kenn K., Gloeckl R., Behr J. Pulmonary Rehabilitation in Patients with Idiopathic Pulmonary Fibrosis A Review. *Respiration*. August. 2013; 86:89–99.
4. Martinez Fernando J. , Collard Harold R., Pardo Annie, Raghu Ganesh, Richeldi Luca, et al. Idiopathic pulmonary fibrosis. *Nature Reviews Disease Primer*. October 2017; 3:1-19.
5. Caminati Antonella, Madotto Fabiana, Cesana Giancarlo, Conti Sara, Harari Sergio. Epidemiological studies in idiopathic pulmonary fibrosis: pitfalls in methodologies and data interpretation. *Eur Respir Rev*. 2015 June; 24(137): 436–44.
6. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Schünemann HJ. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *American Journal of Respiratory and Critical Care Medicine* 2011; 183(6):788–824.
7. King Jr. T. E., Tooze J. A., Schwarz M. I., Brown K. R., Cherniack R. M. Predicting survival in idiopathic pulmonary fibrosis: scorings ystem and survival model. *American Journal of Respiratory and Critical Care Medicine*. 2001 October;164(7):1171–81.
8. Budin C.E., Marginean C, Bordea I.R., Enache L.S., Enache E.L., Grigorescu B.L., et al. The Influence of Smoking on Nicotine Exposure Biomarkers and Inflammatory Profile Among Foster Care Teenagers, Romania. *Rev.Chimia*, 2018;69(12):3659-63.
9. Bennett David, Bargagli Elena, Refini Rosa Metella, Campagna Maria Stella, Gennari Luigi, et al. Helicobacter pylori infection in IPF patients is associated with higher rates of mortality and PFTs decline. *Eur Respir J*. 2014 September; 43: 635–8.
10. Wolters P. J., Collard H. R., Jones K. D. Pathogenesis of idiopathic pulmonary fibrosis. *Annu. Rev. Pathol*. 2014; 9:157–79.
11. Selman M.,Pardo A. Revealing the pathogenic and aging-related mechanisms of the enigmatic idiopathic pulmonary fibrosis. an integral model. *Am. J. Respir. Crit. Care Med*. 2014;189:1161–72.
12. Ley B, Collard HR. Epidemiology of idiopathic pulmonary fibrosis. *Clinical Epidemiology*. 2013 November; 5, 483–92.
13. Mathai SK, Newton CA, Schwartz DA, Garcia CK. Pulmonary fibrosis in the era of stratified medicine. *Thorax*. 2016 December; 71, 1154–60.
14. Selman, M., Lopez-Otin, C. & Pardo, A. Age-driven developmental drift in the pathogenesis of idiopathic pulmonary fibrosis. *Eur. Respir. J*. 2016 August; 48, 538–52.
15. Torrisi SE, Vancheri A, Pavone M, Sambataro G, Palmucci S, Vancheri C, Comorbidities of IPF: How do they impact on prognosis, *Pulmonary Pharmacology & Therapeutics*. 2018 September; 53: 6-11.
16. Kreuter M, Ehlers-Tenenbaum S, Palmowski K, Bruhwyler J, Oltmanns U. Impact of Comorbidities on Mortality in Patients with Idiopathic Pulmonary Fibrosis. *PLoS One*. 2016 March; 11(3): e0151425.
17. Alexescu TG, Bordea IR, Cozma A, Rajnoveanu R, Buzoianu AD Nemes RM, Tudorache SI, Boca BM, Todea AD. Metabolic Profile and the Risk of Early Atherosclerosis in Patients with Obesity and Overweight. *Revista Chimia*. 2019; 70(10):3627- 33.
18. Chilosi M., Poletti V., Rossi A. The pathogenesis of COPD and IPF: Distinct horns of the same

- devil? *Respiratory Research*.2012; 13(1):3. Available at: <http://respiratory-research.com/content/13/1/3>.
19. Budin CE Alexescu TG, Bordea IR, Gherginescu MC, Aluas M, Grigorescu BL, Biro L, Buzoianu AD, Nemes RM, Tantu MM, Todea DA. Nicotine Addiction Objective in Educational Programs for Smoking Prevention in Young People. *Revista Chimia* , 2019; 70(6): 2168- 72.
 20. Ballester B, Milara J, Cortijo J. Idiopathic Pulmonary Fibrosis and Lung Cancer: Mechanisms and Molecular Targets. *International Journal of Molecular Sciences*. 2019 Feb; 20(3):593.
 21. Caminati A, Lonati C, Cassandro R, et al. Comorbidities in idiopathic pulmonary fibrosis: an underestimated issue. *European Respiratory Review* 2019; 28:190044.
 22. Todea D, Cosma C, Dicu T, Roșca L, Cucuș(Dinu) A, Rîșteiu M, Iancu D, Papuc I, Rădulescu D. Lung cancer risk induced by residential radon in CLUJ and Alba Counties, ROMANIA. *Environmental Engineering and Management Journal*. 2013.12(6):1281-5.
 23. Agrawal A, Verma I, Shah V, Agarwal A, Sikachi RR. Cardiac manifestations of idiopathic pulmonary fibrosis. *Intractable & Rare Diseases Research*. 2016 April; 5(2):70–5.
 24. Todea DA, Herescu A, Rosca L. Obstructive Sleep Apnea Syndrome - a matter of public health, *Transylvanian Review Of Administrative Sciences*,2012;37E:186-201.
 25. Rusu A, Nita C, Todea D, Rosca L, Bala C, Hancu N. Correlation of the daytime sleepiness with respiratory sleep parameters in patients with sleep apnea and type 2 diabetes. *Acta Endocrinologica*. 2011;VII(2):163-71.
 26. Pulmonary Fibrosis Now!. Can Asthma cause Pulmonary Fibrosis. 2018 September. Available at: <https://pulmonaryfibrosisnow.org/2018/09/16/can-asthma-cause-pulmonary-fibrosis/>.
 27. Zalar DM, Pop C, Buzdugan E, Todea D, Mogosan CI. The atherosclerosis inflammation relationship- a pathological approach. *FARMACIA*. 2019;67(6): 941-947.
 28. Nielsen TD, Bahnson T, Davis RD, Palmer SM. Atrial fibrillation after pulmonary transplant. *Chest*. 2004; 126:496-500.
 29. Kizer JR, Zisman DA, Blumenthal NP, Kotloff RM, Kimmel SE, Strieter RM, Arcasoy SM, Ferrari VA, Hansen-Flaschen J. Association between pulmonary fibrosis and coronary artery disease. *Arch Intern Med*. 2004; 164:551-556.
 30. Cottin V, Crestani B, Valeyre D, Wallaert B, Cadranel J, Dalphin J-C, et al. Diagnosis and management of idiopathic pulmonary fibrosis: French practical guidelines. *European Respiratory Review*. 2014 Jun; 23(132):193–214.
 31. Onofre MM, Colman R, Kalluri M, Cabalteja C, Harle I. A comprehensive and practical approach to the management of idiopathic pulmonary fibrosis. *Expert Review of Respiratory Medicine*. 2019, Jun;13(7):601-14.
 32. Jacobs SS, Lindell KO, Collins EG, et al. Patient perceptions of the adequacy of supplemental oxygen therapy. results of the American Thoracic Society nursing assembly oxygen working group survey. *Ann Am Thorac Soc*. 2018;15(1):24–32.
 33. Vremarioiu-Coman A, Alexescu TG, Negrean V, Milaciu MV, Buzoianu AD, Ciumarnean L, Todea DA. Ethical aspects of smoking cessation among the population from Transylvania. *Balneo Research Journal*.2018;9(3):254–9.
 34. Hughes JR. An updated algorithm for choosing among smoking cessation treatments. *J Subst Abuse Treat* 2013;45:215-21
 35. Esbriet (pirfenidone) [monograph]. Mississauga, ON, Canada: F. Hoffmann-La Roche Ltd.; 2018.
 36. Ofev (nintedanib) [monograph]. Burlington, ON, Canada: Boehringer Ingelheim (Canada) Ltd..
 37. Medical Section of the American Lung Association. Standardization of spirometry: 1994 update. *Am. J. Respir. Crit. Care Med*. 1995; 152: 1107–36.
 38. Holland AE, Fiore JF., Goh N, Symons K, Dowman L, Westall G, Glaspole I. Be honest and help me prepare for the future. *Chronic Respiratory Disease*. 2015; 12(2), 93–101.
 39. Duck A, Pigram L, Errhalt P, et al. IPF care: a support program for patients with idiopathic pulmonary fibrosis treated with pirfenidone in europe. *Adv Ther*. 2015;32(2):87–107.
 40. Sampson C, Gill BH, Harrison NK, et al. The care needs of patients with idiopathic pulmonary fibrosis and their carers (CaNoPy): results of a qualitative study. *BMC Pulm Med*. 2015;15:155.
 41. Kozu R, Jenkins S, Senjyu H. Effect of disability level on response to pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology*. 2011; 16: 1196– 1202.
 42. Vainshelboim B, Oliveira J, Yehoshua L, et al. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic

- pulmonary fibrosis. *Respiration* 2014; 88: 378–388.
43. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M et al. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2005; 171: 972–7.
 44. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, et al: Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008; 13:394–9.
 45. Huppmann P, Szczepanski B, Boensch M, Winterkamp S, Schönheit-Kenn U, Neurohr C, Behr J, Kenn K: Effects of in-patient pulmonary rehabilitation in patients with interstitial lung disease. *Eur Respir J* 2012;42:444–5.
 46. Meltzer EB, Noble PW: Idiopathic pulmonary fibrosis. *Orphanet J Rare Dis* 2008; 3:8.
 47. Nykqvist M, Sköld M, Ferrara G, Faager G. Inspiratory muscle training in addition to physical exercise for idiopathic pulmonary fibrosis. *European Respiratory Journal*.2016 Sep; 48 (60): OA1518.
 48. Alexescu TG, Tarmure S, Negrean V, Cosnarovici M, Ruta VM, Popovici I. Para I, Perne MG, Orasan OH, Todea DA. "Nanoparticles in the treatment of chronic lung diseases," *Journal of Mind and Medical Sciences*, (2019) 6:Iss. 2 , Article 7.
 49. Casaburi R,Patessio A,Ioli F,Zanaboni S,Donner CF, et al. Reduction in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lungdisease.*Am Rev Respir Dis*.1991;143:9–18.
 50. Alexescu TG, Maiercan A, Ciumarnean L, Budin C, Dogaru G, Todea DA. Rehabilitation therapies in stable chronic obstructive pulmonary disease. *Balneo Research Journal*. 2019; 10(1):37–44.
 51. Maiercan A, Ciumarnean L, Alexescu TG, Domokos B, Rajnoveanu R, Arghir O, Todea D, Buzoianu AD, Dogaru G, Bordea RI. Complementary therapeutic approaches in asthma. *Balneo Research Journal*. 2019; 10(3):204–12.
 52. Bosi M., Milioli G., Fanfulla F., Tomassetti S., Ryu JR, et al. OSA and Prolonged Oxygen Desaturation During Sleep are Strong Predictors of Poor Outcome in IPF, *Lung*. 2017;195(5):643–51.
 53. Rusu A, Todea D, Rosca L, Nita C, Bala C. The development of a sleep apnea screening program in Romania type 2 diabetic patients: a pilot study. *Acta Diabetologica*.2012.49(2):105–9.
 54. Radescu OD, Albu S, Baciut M, Bran S, Coman AC, et al. Results in the Treatment with Twin Block Polymeric Appliance of the Retrognathic Mandible in Sleep Apnea Patients, *MATERIALE PLASTICE*. 2017; 54(3):473–6.
 55. Wang H, LiuX, Rice SJ, Belani CPPulmonary Rehabilitation in Lung Cancer. *Physical Medicine and Rehabilitation*, 2016; 8(10): 990–6.
 56. E Dantes, CS Cambrea, L Tuta, C Mihalov, D Todea, et al. Environmental asbestos exposure – a possible risk factor for mesothelioma in siblings. *Journal of Environmental Protection and Ecology* 20, 2019; 2:640–7.
 57. McKibbin KA. Systematic reviews and librarians. *Libr Trends* 2006;55: 202–15.
 58. Yoshida M, Taguchi O, Gabazza EC, Yasui H, Kobayashi T, Kobayashi H, Maruyama K, Adachi Y. The effect of low-dose inhalation of nitric oxide in patients with pulmonary fibrosis. *Eur Respir J* 1997;10:2051–4.
 59. Allen S, Raut S, Woollard J, Vassallo M. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. *Palliat Med* .2005;19:128–130.
 60. Yokoyama T, Kondoh Y, Taniguchi H, Kataoka K, Kato K, Nishiyama O, Kubo K. Noninvasive Ventilation in Acute Exacerbation of Idiopathic Pulmonary Fibrosis. *Internal Medicine*. 2010; 49(15), 1509–1514.
 61. Coman AC, Todea DA, Popa E, Radu T, Cadar O, et al. Multilateral characterization of masks and tubes surfaces in contact with respiratory system through ventilation, *Journal Of Optoelectronics And Advanced Materials*. 2015 October; 17(9): 1563–71.
 62. Collard HR, King TEJr, Bartelson BB, Vourlekis JS, et.al. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2003 Sep 1;168(5):538–42.
 63. Brown AW, Shlobin OA, Weir N, Albano MC, et al. Dynamic patient counseling: a novel concept in idiopathic pulmonary fibrosis. *Chest*. 2012 Oct;142(4):1005–10.
 64. du Bois RM, Weycker D, Albera C, Bradford WZ, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2011 Aug 15;184(4):459–466.

Cardiovascular surgery complication and the benefits of pulmonary rehabilitation in preventing COPD exacerbation

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Abstract

Introduction. Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide, and the burden of the disease is constantly increasing. Although COPD is primarily characterized by the presence of airflow obstruction, in many patients, it is associated with systemic manifestations that can result in impaired functional capacity, reduced quality of life, and increased mortality. Pulmonary rehabilitation (PR) consists of a multidisciplinary and comprehensive non-pharmacological intervention that is designed to improve health status in COPD patients, along with pharmacologic treatment. PR has also been shown to improve the diaphragmatic mobility in patients with different conditions that affect the diaphragm. The aim of the paper is to describe the clinical and functional features of a COPD patient with unilateral paralysis of the phrenic nerve and the role of PR as a major component of the case management. **Material and method.** This paper presents the case of a 66-year-old patient, diagnosed with COPD Gold stage III, which suffered a surgical intervention for an aorta aneurysm and later complicated with phrenic nerve injury and left diaphragmatic paralysis. This condition worsened the respiratory functional status and the patient needed a tailored treatment. **Results and discussions.** The treatment included besides inhaled dual long acting bronchodilator and corticoid therapy, pulmonary rehabilitation with complex methods, consisting in training of the respiratory musculature and techniques of bronchial drainage using devices with positive inspiratory and expiratory pressure, with good clinical and functional outcomes. A PR program should be included into a personalized management plan, along with pharmacological therapy. **Conclusion.** Although there is no standard treatment for COPD associated with unilateral paralysis of the phrenic nerve, it is important to diagnose these conditions promptly, and to recommend the adequate pharmacological treatment for controlling the symptoms along with a personalized complex respiratory rehabilitation program, in order to increase functional status and quality of life.

Key words: *respiratory rehabilitation, COPD, phrenic nerve paralysis,*

Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of mortality worldwide, with a constantly increasing prevalence, mainly due to smoking and different exposures to noxious particles (1,2). The progressive decline in lung function that defines COPD is commonly associated with a significant reduction in exercise capacity and psychological issues, all of which contribute to greater patient's disability, poor quality of life and reduced survival (3,4). Pulmonary rehabilitation (PR) consists in a multidisciplinary and comprehensive non-pharmacological intervention that is designed to improve health status in COPD patients (3-5). PR has also been shown to improve the diaphragmatic mobility in patients with different conditions that affect the diaphragm (6-8). The aim of the paper is to describe the clinical and functional features of a COPD case associated with unilateral paralysis of the phrenic nerve and the role of PR as a major component of the case management.

Material and method

This paper reports the case of a 66-year-old patient, with a 42-pack year history of smoking, diagnosed with COPD Gold stage III, in 2011, and treated with a fixed combination of inhaled corticosteroid and beta-2 agonist bronchodilator (fluticasone/salmeterol 50/500 µg, 2 inhalations/day) and salbutamol as needed. The initial values of spirometry parameters were: reduced forced expiratory volume in 1 second (FEV1) 1.42 L (41.3%) and forced vital capacity (FVC) 2.43L (52.3%) corresponding to a decreased FEV1/FVC ratio of 58.4%. The patient was regularly monitored, including clinical and functional assessment.

In December 2012, the patient was admitted in Pulmonology department for severe infectious exacerbation of COPD with left upper lobar pneumonia and minimum left pleural effusion, cured under broad-spectrum intravenous antibiotic therapy (ceftazidime 3g/day, gentamicin 160mg / day, and

ciprofloxacin 1000mg /day) administered for 10 days. Chest computed tomography (CT scan) exam, performed after the pneumonia resolution, revealed the presence of a sacciform dilation of the aortic cross, distal of the emergence of the left subclavian artery, with a diameter of 35/25mm.

The patient was referred to Cardio-vascular surgery department and suffered a curative intervention for aorta aneurysm. Phrenic nerve injury occurred during the cardiothoracic surgery intervention, led to left diaphragmatic paralysis, revealed by chest X-ray (fig 1). This complication affected the health status condition both functionally (FEV1 decreased to 1.25L, corresponding to 35% of predicted value) and regarding the quality of life.

Results

The post-operative evaluation revealed an overweight patient (BMI = 28.7kg/m²), presenting dyspnea on exertion (grade 3-4 mMRC), decreased breath sounds on the left lower hemithorax, dullness to percussion in the same area, and inward movement of the epigastrium during inspiration. Pulmonary function tests suggested severe irreversible obstructive disease: post-bronchodilator values of FEV1, FVC and FEV1/FVC ratio were lower (34%, 50% and 54.5% respectively). CT exam of the chest revealed the presence of accessory hemiazygos vein, calcified micronodular lesions in both upper lobes, left supradiaphragmatic lamellar atelectasis, bronchiectasis in lingula and left lower lobe (fig. 2) and a highly elevated left hemidiaphragm (fig. 3). The walked distance on the 6 minutes walking test (6 MWD) was 390 m, representing 70% of predicted value, and a significant desaturation up to 85% during the test. The treatment included besides inhaled dual bronchodilator and corticoid therapy, pulmonary rehabilitation with complex methods, consisting in the training of the respiratory musculature, pursed lip breathing, arm and chest exercises, resistance training exercises including walking on a treadmill, and, also, techniques of bronchial drainage using devices with positive inspiratory and expiratory pressure (fig 4). PR included also the educational and nutritional support. The patient followed the rehabilitation program twice daily for one month in the rehabilitation department.

The PR program, along with the pharmacological therapy had good clinical and functional outcomes. Dyspnea was reduced to grade 2-3 mMRC, the values of FEV1, FVC, and FEV1/FVC ratio increased to 44.7%, 58.3%, and 55% respectively.

The 6 MWD increased up to 82% of predicted value, and the lower value of SpO₂ during the test was 90%.

Two years after cardiothoracic surgery, patient reported persistent low back pain in the chest, and he was referred to Balneal and Rehabilitation Sanatorium of Techirghiol, Romania, where specific balneal therapy was started, consisting in peloidotherapy – cold mud baths and adjuvant procedures such as: electrotherapy, massage and kinetotherapy. After seven years of monitoring, the patient remains stable, with no respiratory exacerbation. He is under pulmonology and cardiologic pharmacological treatment.

Discussions

COPD represents a major public health problem, the main cause of global morbidity and mortality (1,8). Along with pulmonary tuberculosis, HIV infection and lung cancer, obstructive lung diseases represent a major component of health care system burden (10-15). COPD exacerbations and associated comorbid conditions, such as cardiovascular diseases, obstructive sleep apnoea, metabolic syndrome or other rare diseases, are responsible for much of the morbidity and mortality (15-20), along with suboptimal adherence to pharmacological treatment (21,22). Although COPD is a progressive respiratory disease, it also has diverse manifestations beyond the lungs, known as systemic effects (23). The most important systemic dysfunction in COPD patients is the peripheral muscle impairment resulting from both systemic inflammation and physical inactivity (24). Skeletal muscle dysfunction is a frequent and important feature of COPD (5), especially in advanced stages and it is associated with reduced quality of life, exercise capacity and survival.

Pulmonary rehabilitation is a well-proven complex and multidisciplinary treatment approach that includes patient evaluation and education, smoking cessation intervention, physical training and skeletal muscle strengthening, nutritional intervention, occupational therapy and psychosocial support (25). A PR program should be included into a personalized management plan, along with pharmacological therapy (26,27) and long term oxygen therapy when needed (28,29). Patients who should benefit the most from a PR program are COPD patients from groups B–D, according to the Global initiative for Obstructive Lung Disease (GOLD) guidelines (30).

However, the American College of Physicians evidence-based practice guideline supports the indication of PR for symptomatic COPD patients with FEV1 <50% of predicted (strong recommendation) (31), conditions which were present in our reported case, because the patient was initially diagnosed with COPD Gold stage III, with a FEV1 of 41.3% of predicted value, and dyspnea of 3-4 mMRC scale.

In the next year after the COPD diagnosis, the patient suffered a surgical procedure for an aorta aneurysm, after which he presented in the pulmonary department with left diaphragmatic paralysis. Usually, this unilateral diaphragmatic paralysis is incidentally found on routine chest X-ray (32,33). Most patients diagnosed with asymptomatic hemidiaphragmatic paralysis do not require treatment (32). In this case, the patient did not consent for a surgical procedure for the correction of unilateral diaphragm paralysis by plication of the affected site. This option is considered if the patient has important symptoms, or if the patient has bilateral diaphragmatic paralysis (32,33).

In our case, the respiratory status of the patient was already impaired due to obstructive disease. After cardiovascular surgery intervention, he presented a worsened dyspnea and functional status, with post-bronchodilator values of FEV1, FVC and FEV1/FVC ratio of 34%, 50% and 54.5% respectively. The pharmacological treatment consisted in adding a long acting anticholinergic to his inhaled combination of corticosteroid and long acting beta2-agonist. The patient also benefited from a complex PR program, twice daily for one month in the rehabilitation department, having a favourable evolution, with significant clinical and functional improvement of respiratory symptoms and spirometric parameters. Balneal therapy for degenerative low back pain done consisting in peloidotherapy – cold mud baths and adjuvant procedures such as: kinetotherapy, electrotherapy, massage therapy, had a very good clinical response. Data from literature also support the beneficial clinical effectiveness of balneal treatment (34-36). After seven years of monitoring, COPD remains stable, with no further respiratory exacerbation.

Conclusion

Although there is no standard treatment for COPD associated with unilateral paralysis of the phrenic nerve, it is important to diagnose promptly these conditions and to recommend the adequate pharmacological treatment for controlling the

symptoms along with a personalized complex respiratory rehabilitation program, in order to increase functional status and quality of life.



Fig 1. Chest CT scan revealed a sacciform dilation of the aortic cross, distal of the emergence of the left subclavian artery, with a diameter of 35/25mm.



Fig 1. Chest radiography - elevated left hemidiaphragm, diffuse right pulmonary hyperlucency and enlargement of intercostal spaces

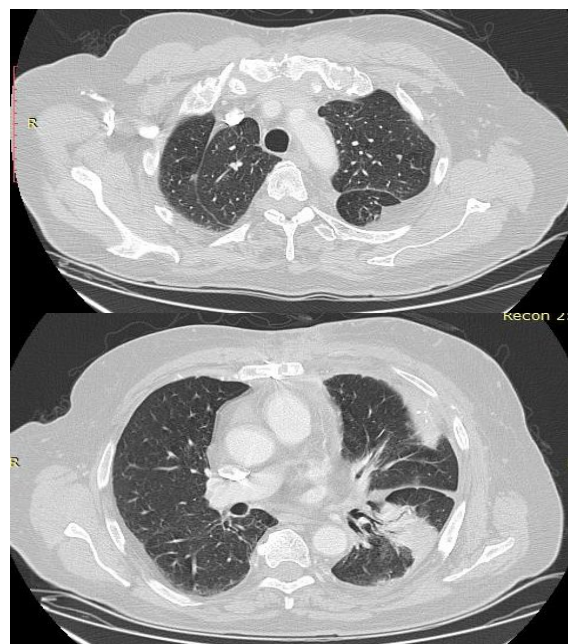


Fig 2. Chest CT scan revealed accessory hemiazygos vein, calcified micronodular lesions (upper); left supra-diaphragmatic lamellar atelectasis, and bronchiectasis in the lingula and in the left lower lobe (lower)



Fig 3. Chest CT scan by lung window (upper) and mediastinal window (lower) revealed highly elevated left hemidiaphragm

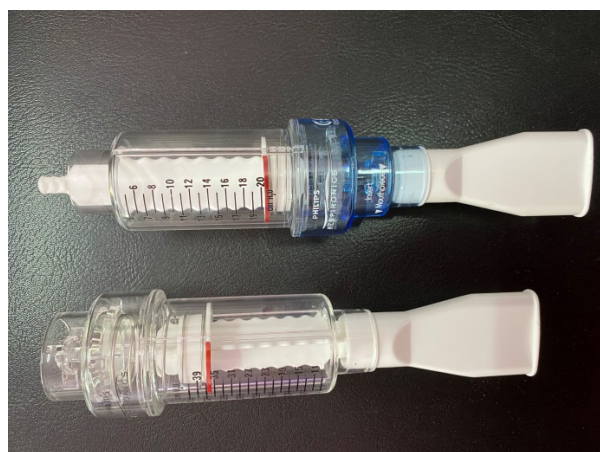


Fig 4. Training devices with positive inspiratory and expiratory pressure

Author contributions.

The authors contributed equally to the work.

Declaration of conflict of interests.

There is no conflict of interest for any of the authors regarding this paper.

Informed consent.

An informed consent was obtained from the patient included in this study.

References

1. Quaderi SA, Hurst JR. The unmet global burden of COPD. *Glob Health Epidemiol Genom.* 2018;3:e4.
2. Alexescu TG, Tarmure S, Negrean V, Cosnarovici M, Ruta VM, Popovici I, Para I, Perne MG, Orasan OH, Todea DA. Nanoparticles in the treatment of chronic lung diseases. *J Mind Med Sci.* 2019; 6(2): 224-231.
3. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2013; 187(4):347–365.
4. Corhay JL, Nguyen Dang D, Van Cauwenberge H, Louis R. Pulmonary rehabilitation and COPD: providing patients a good environment for optimizing therapy. *Int J Chron Obstruct Pulmon Dis.* 2014; 9:27–39.
5. Hopkinson N. Pulmonary Rehabilitation for COPD. *Tanaffos.* 2017; 16(Suppl 1):S7–S8.
6. Corbellini C, Boussuges A, Villafañe JH, Zocchi L. Diaphragmatic mobility improves after pulmonary rehabilitation. A study using M-mode ultrasonography. *Eur Respir J.* 2016; 48:OA3047.
7. Longoni A, Paddeu A, Mangiacasale D, Pozzi P, Cattaneo L, et al. Sonographic evaluation of the diaphragm muscle before and after pulmonary rehabilitation. *Eur Respir J.* 2017;50:PA4901
8. Alexescu TG, Maiercan A, Ciumarcan L, Budin C, Dogaru G, Todea DA. Rehabilitation therapies in stable chronic obstructive pulmonary disease. *Balneo Research Journal.* 2019;10(1):37–44.
9. Lopez-Campos JL, et al. Global burden of COPD. *Respirology* 2016; 21: 14–23.
10. Grobusch MP, Kapata N. Global burden of tuberculosis: where we are and what to do. *Lancet Infect Dis.* 2018; 18(12):1291-1293.
11. Fildan AP, Toma CL, Tofolean D, Arghir OC, Dantes E. TB Risk in Patients with Biological Therapy for Psoriasis. *Chest.* 2016; 150(4_S):201A.
12. Cambrea SC, Popescu GG, Resul G, Petcu LC. The spectrum of infectious diseases hospital mortality by HIV status. *Acta Medica Mediterranea.* 2019; 35(6): 3517-3522.
13. Barta JA, Powell CA, Wisnivesky JP. Global Epidemiology of Lung Cancer. *Ann Glob Health.* 2019; 85(1):8.
14. Ulmeanu R, Antohe I, Anisie E et al. Nivolumab for advanced non-small cell lung cancer: an evaluation of a phase III study. *Expert review of anticancer therapy.* 2016; 16(2): 165-167.

15. Hoge Stanca P, Tudorache E, Fildan AP, Fira-Mladinescu O, Marc M, Oancea C. Risk Factors of Chronic Obstructive Pulmonary Disease Exacerbations. *Clin Respir J*. 2019; doi:10.1111/crj.13129.
16. Trenchea M, Arghir IA, Popescu G, Rascu S, Bechir ES, Tofolean D, Fildan AP, Ion I, Dantes E. The Triad Nocturia, Smoking and Obstructive Sleep Apnea. *Revista de Chimie*. 2019; 70(5):1839-1842.
17. Anton A, Tofolean DE. Obstructive sleep apnea and metabolic syndrome: is there a correlation? *Sleep Medicine*. 2017; 40(1):E16-E16.
18. Deacu M, Tofolean DE, Bosoteanu M, Pulmonary alveolar lipoproteinosis associated with emphysematous areas. *Rom J Morphol Embryol*. 2012; 53(1):173-177.
19. Todea D, Herescu A, Rosca L. Obstructive Sleep Apnea Syndrome - a matter of public health. *Transylvanian Review Of Administrative Sciences*. 2012;37E:186- 201.
20. Budin CE, Marginean C, Bordea IR, Enache LS, Enache EL, Grigorescu BL, Biro L, Rusu E, Nemes RE, Todea DA. The Influence of Smoking on Nicotine Exposure Biomarkers and Inflammatory Profile Among Foster Care Teenagers, Romania. *Rev.CHIM. (Bucharest)*.2018; 69(12):3659-63
21. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. *Respir Med*. 2013 Oct; 107(10):1481-90.
22. Munteanu LA, Fildan AP, Tudorache E, Fira-Mladinescu O, Frandes M, Timar B, Oancea C, Tofolean DE. Inhaler technique errors in Romanian patients with asthma - a multicenter study. *Patient Preference and Adherence*. 2019; 13:1401-1414.
23. Agustí A, Soriano JB. COPD as a systemic disease. *COPD*. 2008; 5(2):133–138.
24. Wüst RC, Degens H. Factors contributing to muscle wasting and dysfunction in COPD patients. *Int J Chron Obstruct Pulmon Dis*. 2007;2(3):289–300.
25. Spruit MA, Singh SJ, Garvey C et al. An official American thoracic society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013; 188(8):e13–e64.
26. Rajnoveanu RM, Antoniu S, Ulmeanu R. Combined long-acting bronchodilator single therapy for COPD. *Expert Opinion on Pharmacotherapy*. 2014;15(1):139-142.
27. Alexa I, Alexa-Stratulat T, Antoniu S, Antohe I, Arghir O, Grigorescu C. Roflumilast in patients with advanced chronic obstructive pulmonary disease: towards a better-targeted use. *Expert Opin Pharmacother*.2019; 20(1): 91-93.
28. Jimborean G, Arghir OC, Cambrea SC, Dantes E, Socaci A, Otelea MR, Bechir ES, Ianosi ES. The Clinical Implications of Carbon Dioxide Increased Level in Arterial Blood Related to Severe Exacerbations of Chronic Obstructive Pulmonary Disease. *Rev Chimie (Bucharest)*, 2018; 69(8): 2050-2053.
29. Tofolean D, Popescu G, Arghir IA, Frandes M, Fildan AP. A Different Approach of Chronic Obstructive Pulmonary Disease Severity and Plastic Medical Devices Used for Oxygenotherapy. *Materiale Plastice*. 2019; 56(2):295-300.
30. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2019 Report. Available from: <https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf>
31. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med*. 2011; 155(3):179–191.
32. Mandoorah S, Mead T. Phrenic Nerve Injury. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing. 2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482227/>
33. Hart N, Nickol AH, Cramer D, Ward SP, Lofaso F, et al. Effect of severe isolated unilateral and bilateral diaphragm weakness on exercise performance. *Am. J. Respir. Crit. Care Med*. 2002;165(9):1265-70
34. Lupu AA, Ionescu EV, Iliescu MG, Almasan RE, Oprea C, Ion I, Iliescu DM. Effect of Techirghiol specific climate factors on the patients quality of life with degenerative lumbar pain. *J Environ Prot Ecol*. 2018, 19 (4), 1857.
35. Iliescu MG, Profir D, Surdu O, Marin V, Demirgean S, Almasan RE, Stanciu LE, Oprea C, Iliescu DM, Ionescu EV. Statistical View through Balneal Activity In Techirghiol Medical Area. *J Environ Prot Ecol*. 2018; 19(1):382.
36. Almasan RE, Ionescu EV, Iliescu MG, Oprea C, Iliescu DM, Nenciu MI, Golumbeanu M. Techirghiol lake in the context of the integrated development of health tourism. *J Environ Prot Ecol*. 2019; 20(1):206–213.

Pseudotumor cerebri-Case report

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Abstract

An 46-year-old Caucasian woman was diagnosed with idiopathic intracranial hypertension (IIH) after presenting with papilledema and bilateral visual blurring. Lumbar puncture revealed an opening pressure of more than 550 mmH₂O. Cerebral magnetic resonance imaging (MRI) showed bilateral flattening of the posterior sclera, enhancement of the prelaminar optic nerve, distension of the perioptic subarachnoid space, intraocular protrusion of the prelaminar optic nerve and empty sella. The main purpose of the treatment was to release the symptoms and preserve the vision. It was initiated the general treatment with Mannitol 20%, 250 ml/day, Acetazolamide 2x500 mg/day and B-vitamins. After discharge the patient followed a treatment with acetazolamide 2x250 mg/ daily doses and oral potassium supplements 30 mg bid/day.

Key words: *pseudotumor cerebri, idiopathic intracranial hypertension, papilledema,*

Introduction

Pseudotumor cerebri is a rare condition which is characterized by an idiopathic increased intracranial pressure (IIP) manifested with papillary edema and other neurologic signs such as headache, visual loss, tinnitus, diplopia. Often this syndrome appear in young overweight women of childbearing age. The funduscopy reveal bilateral papilledema. Visual field examination by perimetry and ocular coherence tomography are important examination for the diagnostic. Because the symptoms are similar to cerebral mass lesion, for this reason the name of pseudotumor cerebri was associated with “false brain tumor”. The diagnosis is an exclusion one, other causes of increased intracranial pressure (ICP) have to be excluded with imaging methods (brain MRI) and lumbar puncture. The main purposes of treatment are releasing of the symptoms and conservation of vision. Treatment options for this potentially low vision disease include diet and life style, certain medications (e.g., vitamin A derivatives, tetracycline, and lithium), carbonic anhydrase inhibitor (Acetazolamide or Diamox) (1), steroids (2), Furosemide (3). In case of medical treatment failure, surgical treatment is indicated. Cerebrospinal fluid shunting (CSF) (e.g., ventriculo-peritoneal and lumbar-peritoneal shunting) (4-8) and optic nerve sheath fenestration (ONSF) (9-16), and management of transverse sinus stenosis are indicated (17).

Case report

We present the case of a 46 year old female patient, known with ovarian cyst, asthma, who was admitted in our department accusing ocular discomfort in both eyes felt as retro bulbar pressure. The patient reported no allergies and no fever in the past days. The onset of these symptoms started 2 months before the presentation in our department. The family history was not relevant. She had no chronic treatment. The general clinical exam was normal. The body mass index was normal. She did not have any history of recent ear infection, treatment for acne vulgaris, vitamin A supplementation, lead exposure, seizure disorder, oral contraceptives, steroid intake or withdrawal. There was no history of tick bites, target rash or joint pains. Her medical, surgical and family history was all unremarkable. The ocular examination at the presentation in our department revealed a best corrected visual acuity of 1 without correction in both eyes. The refraction showed at right eye: +0,75D sph-0.25 D cyl ax 150° and at left eye: +0.75 D sph, 0.25 D cyl, ax 10°. The intraocular pressure was 17 mmHg measured by applanationometry in both eyes. The light perception and projection was present at both eyes. The papillary light reflex was present in both eyes. The ocular motility was normal. Slit lamp examination revealed a normal examination in both eyes.

The ophthalmoscopy of both eyes showed at both eyes papilledema, the optic nerve head without edges, prominent, dilated retinal veins and a chrysanthemum flower appearance in the right eye (RE).(Fig.1).



Fig.1. Ophthalmoscopy aspect seen at retinophotography at RE and LE

The visual field examination discovered enlarged blind spot both eyes with some paracentral scotoma in both eyes.(Fig 2).

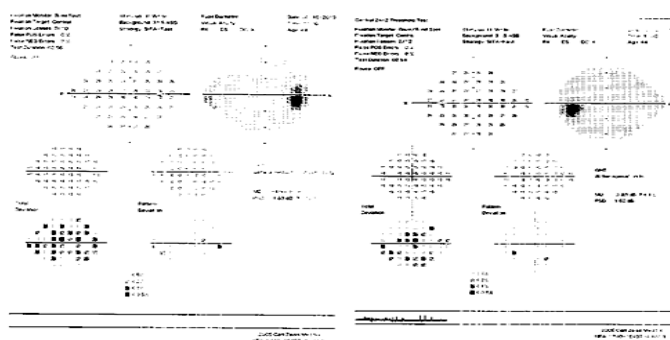


Fig.2. Visual field aspect in both eyes

The optical coherence tomography (OCT) of the optic nerve revealed a swollen optic nerve in both eyes but no retinal nerve damage. (Fig.3).

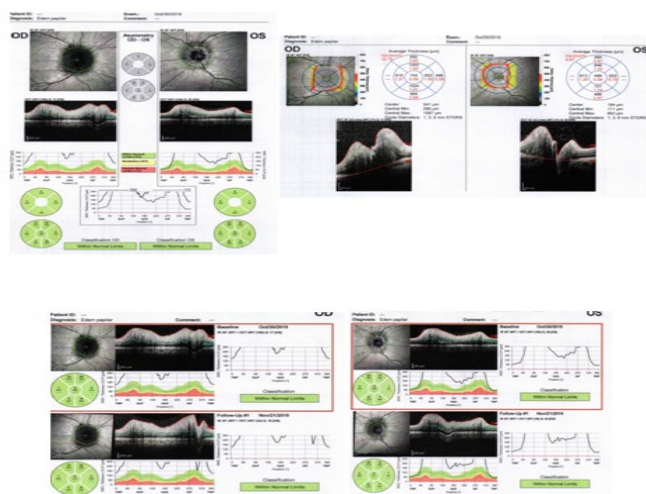


Fig. 3. OCT aspect at both eyes

Other examinations:

The standard blood tests were within normal parameters: RBC= $4,60 \times 10^{12}/L$, hemoglobin = 13,6 g/dL, WBC= $5,18 \times 10^9/l$, creatinine = 0,68 mg/dL, blood glucose =104 mg/dL, CRP= 0,27 mg/dL, BUN=30 mg/dL, fibrinogen= 316 mg/dL, platelets= $245 \times 10^9/l$, erythrocyte sedimentation rate =3 mm/h. Antibodies IgG anti-Borrelia and IgM anti-Borrelia, anti-RNP, anti-SSA, anti-cardiolipin, p-ANCA, c-ANCA, antiSCL70, anti-mitochondrial, ANA and the circulating immune complexes were normal. The serum vitamin B12 was 251 pg/ml and folic acid 15,17 ng/ml. Thyroid tests were normal. No inflammatory markers were positive.

The neurologic examination concluded a conscious patient, temporal and spatial oriented, symmetrical and reactive pupils, normal eye movements, no meningeal signs, with no cranial nerve deficits, no motor deficit, normal tendon reflexes, slightly brisk in the lower limbs, no Babinski's sign present, no ataxia, no sensitivity disorders, no sphincter disorders. The recommended treatment was Mannitol 20% 100 ml/day iv, neurotrophics and B1 (100 mg/day), B2 (10 mg/2 ml/ day) and B6 (50 mg/2ml/day) vitamins.

The cerebral magnetic resonance imaging (MRI) examinations revealed signs of idiopathic intracranial hypertension and few small focal lesions suggestive for demyelinating disease.(Fig.4).

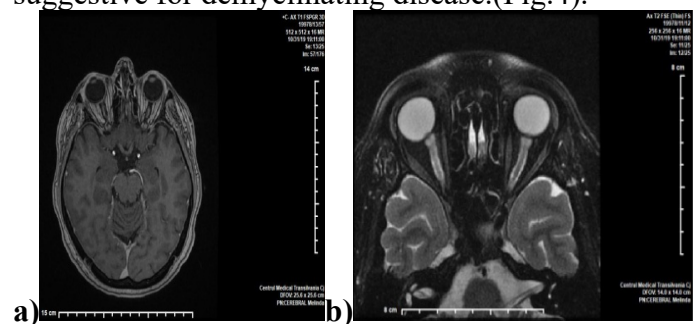


Fig.4. (a) - Brain MRI aspect T1W + contrast axial images at the level of the optic nerve(ON) reveal bilateral tortuous ON with prominent cerebrospinal fluid spaces around the ON.

(b) - T2-W1sequence reveal- flattening of the posterior sclera, bilateral hyperintensity and swelling of the optic nerve.

Lumbar puncture was done and the opening pressure was 550mmH₂O. Examination of cerebrospinal fluid (CSF) composition revealed normal cell count and differential glucose and protein.

The positive diagnose for both eyes was: papillar oedema, mild hyperopia, idiopathic increased intracranial pressure, folic acid deficiency.

The differential diagnosis for a bilateral papillary edema included structural cerebral lesions such as cerebral tumors (benign or malignant), vascular lesions, inflammation / infections (cerebral abscess), all which were ruled out by the neurologic examination and by the cerebral MRI examination. Because all the inflammatory tests were negative an autoimmune was excluded.

Chronic intracranial hypertension can be caused by many conditions including certain drugs such as tetracycline, a blood clot in the brain, excessive intake of vitamin A, or brain tumor. It can also occur without a detectable cause excluded by medical history of the patient.

Treatment

The main purpose of the treatment was to release the symptoms and preserve the vision. During the hospitalization, because of the mild visual field loss it was initiated the general treatment with Mannitol 20% 250 ml/day, Acetazolamide 2x500 mg/day, B1 (100 mg/day), B2 (10 mg/2 ml/ day) and B6 (50 mg/2ml/day) vitamins.

The evolution was stable during the admission. Recommendations at hospital discharged were to avoid the physical effort and indicated the treatment with Acetazolamide 2x250 mg/ daily doses and oral potassium supplements 30 mg bid/day.

The follow-up examination at one and 6 months after discharge showed a maximum visual acuity without correction at both eyes. The ophthalmoscopy exam revealed bilateral mild papillar oedema. The visual field examination revealed mild modifications (enlarged blind spot and few paracentral small scotomas) (Fig.5).

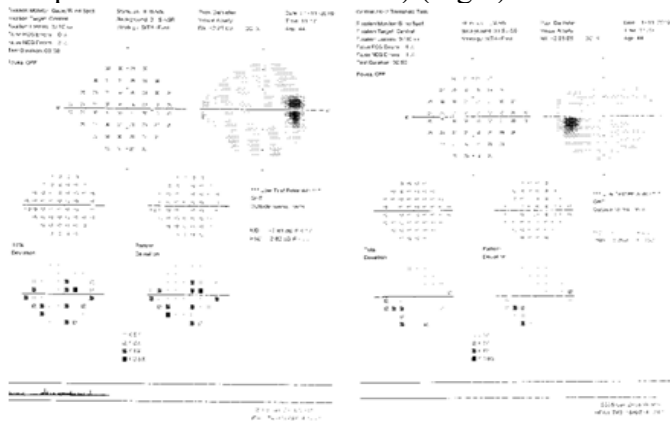


Fig.5. - Visual aspect at both eyes -6 months follow-up. Enlarged blind spot and few paracentral small scotomas.

Discussion

Idiopathic increased intracranial pressure (IICP), called also benign intracranial hypertension is a demanding disorder which is leading to increased intracranial pressure (ICP), in the absence of identifiable cause (18,19). The incidence of the condition is estimated to be 20 per 100,000 (20) and it is expected to increase rapidly. There are studies which showed that obesity is the main underlying etiological factor, knowing that obesity can affect children and males to a similar degree as females (21-23). What is interesting that our patient was not obese not fulfilling the profile for IIP.

At presentation, the most common symptom is headache (24,25) which is pulsatile in over 80% of patients (26) and 70% of patients report a focal component of the headache (e.g. occipital or retro-orbital pain)(26). After the decrease of intracranial pressure (ICP) the headache can be improved. Sometimes when patients have coexisting headache disorders (18) it may not respond well to treatment that decrease ICP and require conventional agents (pain relievers drugs) to control the symptom (19). In our case the headache was not so severe, had retro-orbital location but it was associated with papilledema.

Visual symptoms are common in IICP and are linked with papilledema. The common sign is represented by bilateral papilledema, sometimes symmetric sometimes asymmetric. Papilledema is present in 97% of IICP cases and is the hallmark features of the illness (27). In the absence of papilledema, abducens nerve palsy is a major criteria for the positive diagnosis of IICP (28). In our case, the abduces paralysis was absent.

The patients complain about transient visual loss precipitated by postural changes and Valsalva procedure –like maneuvers with duration of few seconds. The visual disturbances were present as progressive and early changes of visual field, enlargement of blind spot and a nasal step defect in visual field examination. In the late stages, if the papilledema persists, nasal defects, arcuate defects and severe visual field constriction can appear (29). Visual acuity is not decreased if visual field examination does not reveal any disturbances. That is why the examination of visual field by static perimetry is essential to establish management decision.

Abducens nerve palsy may be another sign in IIP and is due to the increased ICP on this nerve, which

has the longest intracranial pathway (25). Abducens nerve palsy was not present in our case.

Some authors revealed the possible correlation between IICP and iron-deficiency anemia (30). In our case, the patient did not present this type of anemia.

MRI has been of particular interest linked with the ability to provide the visualization of eyeball, optic nerve, orbit and optic tract.(31). Increased ICP may lead to several abnormalities on MRI, including: flattening of the posterior sclera, enhancement of the prelaminar optic nerve ; distension of the perioptic subarachnoid space, intraocular protrusion of the prelaminar optic nerve and empty sella (31).

Without any treatment, papilledema can cause progressive irreversible visual loss and optic atrophy. The principle objectives of treatment are reduction of symptoms, including headache, and preservation of vision. All overweight patients should be encouraged to enter a weight-management program with a goal of 5% to 10% weight loss, along with a low-salt diet. In our case the patient was not obese which represent a particularity of the case. We initiated a medical treatment with Acetazolamide in order to reduce the papilledema. When symptoms and visual loss are mild a lot of medical and surgical treatments are recommended.

In cases of mild visual field loss, as it was in our case, the treatment with Acetazolamide has to be initiated. Acetazolamide, a carbonic anhydrase inhibitor, decrease the cerebrospinal fluid production and decrease the ICP (32). Steroids were commonly used in the past for treating IIP but because of several side effects such as weight gain, rebound intracranial pressure after withdrawal, increase of glycemia, osteoporosis, psychosis ,peptic ulcer disease, hypertension, renal failure should not be used routinely (33,34).

Lumbar puncture improves the symptoms of IIP in most cases for a short period (35, 36). In our case the patient felt better after the procedure although the headache was not typically for IIP from the very beginning.

When visual loss is more severe or rapidly progressive, surgical interventions, such as optic nerve sheath fenestration or cerebrospinal fluid shunting, may be required to prevent further irreversible visual loss. Various other ophthalmologic pathologies have to be considered for young patients, as causes of visual function deterioration. The choice of intervention depends on the severity of symptoms and visual loss (37, 38).

The optic nerve sheath fenestration is reserved for cases with vision loss secondary to papilledema and mild symptoms of ICP. The cerebrospinal fluid shunting is preferable in patients with visual loss due to papilledema and increased symptoms of ICP (29).

Conclusion. Our case showed an uncommon presentation of IIP with a headache localized retro-bulbar, with bilateral papilledema (more severe at RE) and absence of obesity, iron-deficiency anemia and abducens nerve paralysis.

Informed consent. An informed consent was obtained from the patient included in this article

Conflict of interest. Authors declare no conflict of interest.

References

1. Ball AK, Howman A, Wheatley K, et al. A randomised controlled trial of treatment for idiopathic intracranial hypertension. *J Neurol.* 2011;258:874–881.
2. Thambisetty M, Lavin PJ, Newman NJ, Biousse V. Fulminant idiopathic intracranial hypertension. *Neurology.* 2007;68:229–232.
3. Schoeman JF. Childhood pseudotumor cerebri: clinical and intracranial pressure response to acetazolamide and furosemide treatment in a case series. *J Child Neurol.* 1994;9:130–134.
4. Johnston I, Besser M, Morgan MK. Cerebrospinal fluid diversion in the treatment of benign intracranial hypertension. *J Neurosurg.* 1988;69:195–202.]
5. Rosenberg ML, Corbett JJ, Smith C, et al. Cerebrospinal fluid diversion procedures in pseudotumor cerebri. *Neurology.* 1993;43:1071–1072.
6. Eggenberger ER, Miller NR, Vitale S. Lumboperitoneal shunt for the treatment of pseudotumor cerebri. *Neurology.* 1996;46:1524–1530.
7. Burgett RA, Purvin VA, Kawasaki A. Lumboperitoneal shunting for pseudotumor cerebri. *Neurology.* 1997;49:734–739.
8. Maher CO, Garrity JA, Meyer FB. Refractory idiopathic intracranial hypertension treated with stereotactically planned ventriculoperitoneal shunt placement. *Neurosurg Focus.* 2001;10:E1.
9. Corbett JJ, Nerad JA, Tse DT, Anderson RL. Results of optic nerve sheath fenestration for pseudotumor cerebri: the lateral orbitotomy approach. *Arch Ophthalmol.* 1988;106:1391–1397.
10. Sergott RC, Savino PJ, Bosley TM. Modified optic nerve sheath decompression provides long-term visual improvement for pseudotumor cerebri. *Arch Ophthalmol.* 1988;106:1384–1390.

11. Berman EL, Wirtschafter JD. Improvement of optic nerve head appearance after surgery for pseudotumor cerebri. *JAMA*. 1992;267:1130.
12. Kelman SE, Heaps R, Wolf A, Elman MJ. Optic nerve decompression surgery improves visual function in patients with pseudotumor cerebri. *Neurosurgery*. 1992;30:391–395.
13. Chandrasekaran S, McCluskey P, Minassian D, Assaad N. Visual outcomes for optic nerve sheath fenestration in pseudotumour cerebri and related conditions. *Clin Experiment Ophthalmol*. 2006;34:661–665.
14. Yazici Z, Yazici B, Tuncel E. Findings of magnetic resonance imaging after optic nerve sheath decompression in patients with idiopathic intracranial hypertension. *Am J Ophthalmol*. 2007;144:429–435.
15. Wilkes BN, Siatkowski RM. Progressive optic neuropathy in idiopathic intracranial hypertension after optic nerve sheath fenestration. *J Neuroophthalmol*. 2009;29:281–283.
16. Kaye AH, Galbraith JE, King J. Intracranial pressure following optic nerve decompression for benign intracranial hypertension. *J Neurosurg*. 1981;55:453–456.
17. Fridley J, Foroozan R, Sherman V, Brandt ML, Yoshor D. Bariatric surgery for the treatment of idiopathic intracranial hypertension. *J Neurosurg*. 2011;114:34–9.
18. Friedman D. The pseudotumor cerebri syndrome. *Neurol Clin*. 2014;32: 363–396.
19. Friedman D., Liu G., Digre K. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology*. 2013;81: 1159–1165.
20. Friedman D., Rausch E. Headache diagnoses in patients with treated idiopathic intracranial hypertension. *Neurology*. 2002; 58: 1551–1553.
21. Radhakrishnan K., Ahlskog J., Cross S., Kurland L., O'Fallon W. Idiopathic intracranial hypertension (pseudotumor cerebri). Descriptive epidemiology in Rochester, Minn, 1976 to 1990. *Arch Neurol*. 1993;50: 78–80.
22. Bruce B., Kedar S., Van Stavern G., Monaghan D., Acierno M., Braswell R., et al. Idiopathic intracranial hypertension in men. *Neurology*. 2009;72: 304–309.
23. Standridge S. Idiopathic intracranial hypertension in children: a review and algorithm. *Pediatr Neurol*. 2010;43: 377–390.
24. Giuseffi V, Wall M, Siegel PZ, Rojas PB. Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): a case-control study. *Neurology*. 1991;41:239–244.
25. Wall M., Kupersmith M., Kiebert K., Corbett J., Feldon S., Friedman D., et al. The idiopathic intracranial hypertension treatment trial: clinical profile at baseline. *JAMA Neurol*. 2014;71: 693–701.
26. Wall M. The headache profile of idiopathic intracranial hypertension. *Cephalgia*. 1990;10:331–335.
27. Dai Y, Jia N, Wang XL, Chen XH, Sun HL, Zhang XJ: Analysis of characteristics of ocular manifestations of benign intracranial hypertension. *Zhonghua Yan Ke Za Zhi*. 2010;46:1071–1074
28. Friedman DI: Papilledema and idiopathic intracranial hypertension. *Continuum* 2014;20:857–876
29. Matthew J. Thurtell, Michael Wall. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Recognition, Treatment, and Ongoing Management. *Curr Treat Options Neurol*. 2013 Feb; 15(1): 1–12. doi: 10.1007/s11940-012-0207-4
30. Costa F, Neto FM, Gago G, Martins OG, Gibbon F, Nogueira LM. Pseudotumor cerebri presenting unilateral papilledema associated with iron-deficiency anemia. *Arq Bras Neurocir*. 2018;37:58–62
31. Thakkar DK, Patil A., Dolly Thakkar, Patil P., Jantre MN. Magnetic resonance imaging in pseudotumor cerebri: A case report. *Medical Journal of DY Patil University*. 2014.;7 (6):802–805
32. Ball AK, Howman A, Wheatley K, et al. A randomised controlled trial of treatment for idiopathic intracranial hypertension. *J Neurol*. 2011;258:874–881.
33. Liu GT, Kay MD, Bienfang DC, Schatz NJ. Pseudotumor cerebri associated with corticosteroid withdrawal in inflammatory bowel disease. *Am J Ophthalmol*. 1994;117:352–7.
34. Neville BG, Wilson J. Benign intracranial hypertension following corticosteroids withdrawal in childhood. *BMJ*. 1970;3(5722):554–556
35. De Simone R, Marano E, Fiorillo C, et al. Sudden re-opening of collapsed transverse sinuses and longstanding clinical remission after a single lumbar puncture in a case of idiopathic intracranial hypertension: pathogenetic implications. *Neurol Sci*. 2005;25:342–4.
36. Bulboaca AE, Angelo Bulboaca, Ioana Stanescu, Paul-Mihai Boarescu, Ioana Chirilă, Alexandra Bulboaca, Gabriela Dogaru. Homonymous hemianopsia versus unilateral spatial neglect rehabilitation strategies in stroke patients. *Balneo Research Journal*. 2019;10(2):67–73 DOI 10.12680/balneo.2019.242.
37. Rosca C, Munteanu M, Tamasoi I, Petrovic Z, Balica N, Nicula C, Cretu O. Calcification of hydrophilic acrylic intraocular lens in eyes with silicone oil tamponade - an interventional case series report. *Acta Ophthalmol*. 2016 Sep;94(6):625–7. doi: 10.1111/aos.12887. Epub 2015 Oct 28.
38. Nicula C, Nicula D, Popescu R, Saplonțai-Pop A. Corneal collagen cross-linking in keratoconus -- long-term prospective study. *J Fr Ophtalmol*. 2015 Mar;38(3):199–205. doi: 10.1016/j.jfo.2014.10.007. Epub 2015 Feb 11.

Abstract

Introduction. Cardiovascular diseases are recognized as worldwide (1) and national public health issue (2, 3). This is argued by having a leading position in the structure of general mortality and disability, the substantial loss of quality of life and the health system needs for increased costs. Prevention and control of cardiovascular disease has become one of the priority directions for global and national noncommunicable disease control strategies developed to reduce premature mortality (1, 5). The major cardiovascular diseases mortality was identified some aspects of premature mortality among the adult population in the Republic of Moldova. Overall decrease of mortality due to cardiovascular diseases among adults (-5.9%) has been accompanied by a relatively slower decrease in premature mortality (-2.4%) in the Republic of Moldova (6). Primary, secondary and tertiary prevention measures are essential in reducing the burden of cardiovascular disease and contribute to improving cardiovascular health at the population level. Nature is helping people to maintain their health through mechanisms much closer to them than pharmaceutical ones through the curative action of the various natural factors that form the climate of the respective territorial area.

Material and method. There is a descriptive study based on statistical data of the World Health Organization and official vital statistics of the Republic of Moldova.

Results and discussions. The climatic conditions of Moldova are favorable to cardiovascular prevention and rehabilitation. Moldova is located in the temperate continental climate influenced by the proximity of the Black Sea and the interference of warm-humid air from the Mediterranean. The annual air temperatures average in the country is 9,3°C. In the Republic of Moldova the warm weather with a comfortable temperature lasts 175 days and the relative humidity oscillates in the average from 66 to 87%. The country's thermal regime is the most important curative factor for treating chronic diseases and opportunity for the amplification of medical rehabilitation programs for patients with cardiovascular diseases. Application of methods based on the action of climatic factors in cardiovascular rehabilitation process contributes to its efficiency. Increasing the role of tertiary prevention is a good practice for the quality improvement of medical services for this category of patients. By making appropriate, timely and complex measures of primary, secondary and tertiary prevention cardiovascular disease can be substantially prevented.

Conclusions. Strengthening cardiovascular prevention centered on a complex approach to all its primary, secondary, and tertiary components is an opportunity to reduce premature mortality in the population.

Key words: Cardiovascular diseases, prevention, premature mortality,

Introduction

Cardiovascular diseases are the main public health issues at the global and national level (1, 2, 3, 4). The leading position of cardiovascular diseases in the distribution of general mortality and disability, the substantial loss of quality of life and the health system needs for increased costs are recognized as worldwide (1). Cardiovascular disease prevention is one of the priority directions for global and national noncommunicable disease control strategies in terms of reducing premature mortality (1, 5).

The major cardiovascular diseases mortality identified some aspects of premature mortality among the adult population in the Republic of Moldova. Overall decrease of mortality due to cardiovascular diseases among adults (-5.9%) has

been accompanied by a relatively slower decrease in premature mortality (-2.4%) in the Republic of Moldova (6).

The intensity of mortality due to diseases of the circulatory system in men in the age group 50-54 years in the Republic of Moldova corresponds to the intensity of similar mortality in the age group 70-74 years in the developed countries. Adjusted cardiovascular mortality rates are about 4 times higher in the Republic of Moldova compared to similar rates in Europe (6, 7).

WHO established the premature mortality target of a 25% reduction in overall mortality from major noncommunicable diseases (cardiovascular disease,

cancer, diabetes or chronic respiratory diseases) by 2025 (8).

WHO determined the indicator unconditional probability of dying between the ages of 30 and 70 years for monitoring progress of premature mortality reduction. This indicator expresses the probability (%) of dying of 30-year-old individuals from one of the main noncommunicable diseases before his or her 70th birthday (8).

The analysis of the change of the unconditional probability of dying between the ages of 30 and 70 years allowed the estimation of the premature cardiovascular mortality in the aspect of monitoring the intermediate progresses (2013-2016) in the Republic of Moldova. This identified a trend to decrease more slowly (-1%) compared to the expected one (-4.5%). In addition, the opposite directions of percentage evolution by sex were highlighted, in men with increasing tendency (+2.1%) vs. women with decreasing tendency (-5.4%). There is a delay in achieving the planned annual reduction (2013-2016) of premature mortality from cardiovascular diseases, which implies a risk for achieving the 2020 national targets and a future trend of premature death is not in line with the expected one (6).

Of all risk factors for noncommunicable diseases determined by the WHO for monitoring, only in case of one risk factor (insufficient physical activity) is identified a lower prevalence at the national level comparing to global level (8, 9, 10).

The assessment of cardiovascular health in the Republic of Moldova highlighted the substantial prevalence of poor cardiovascular health metrics (81.0%; 95% CI, 79.4% to 82.6%) compared to ideal cardiovascular health (0.6%; 95% CI, 0.3% to 0.9%) as a total and by sex and ages variables, as well (11). The results regarding the cardiovascular health assessment underlined the optimization needs in the prevention and control of major cardiovascular diseases.

Primary, secondary and tertiary prevention interventions are essential in reducing the burden of cardiovascular disease and contribute to improving cardiovascular health at the population level.

At once, nature is helping people to maintain their health through mechanisms much closer to them than pharmaceutical ones through the curative action of the various natural factors that form the climate of the respective area.

Material and Methods

There is a descriptive study based on statistical data of the World Health Organization and official vital statistics of the Republic of Moldova.

The aim of this article is to bring forward and to underline the importance of climatic factors and natural resources of the Republic of Moldova in providing opportunities for cardiovascular prevention and rehabilitation improvement.

Results and discussions

Recent research shows that the reduction of cardiovascular mortality is attributed to about 50% of the reduction of modifiable risk factors and another half of the risk is attributed to evidence based medical treatments (12, 13, 14, 15, 16, 17, 18, 19).

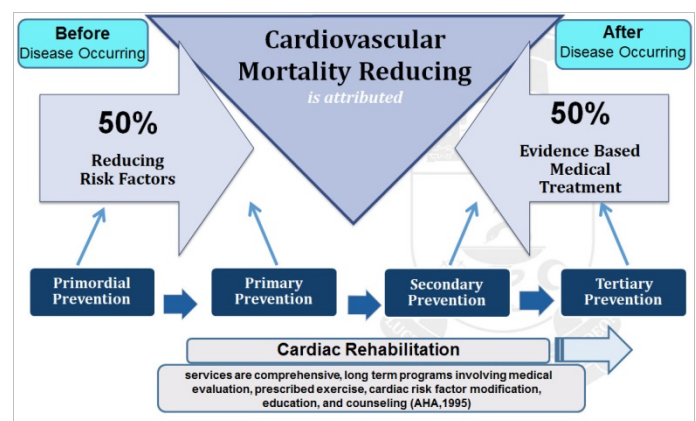


Fig. 3. The main directions of intervention in terms of cardiovascular prevention and control.

Cardiovascular rehabilitation in all its aspects is considered to be a consistent contribution to the prevention after disease occurring. Recent research offers more and more evidence of the benefits of cardiovascular rehabilitation for reducing mortality, morbidity and unplanned hospitalization, as well as improving the quality of life (Figure 3).

International guidelines underling the role of rehabilitation in the prevention and control of cardiovascular diseases recommend the cardiac rehabilitation services (20, 21).

In accordance with current recommendations at global and European level, the national clinical protocol and the standardized clinical protocol for physicians on cardiovascular rehabilitation was approved in the Republic of Moldova. Mentioned protocols regulate the cardiovascular rehabilitation in early stages (in the acute period of hospitalization) until the stable period, which provides rehabilitation services in an outpatient

regime, including rehabilitation services in the balneal-climatic facilities.

The climatic conditions of Moldova are favorable to cardiovascular prevention and rehabilitation and it is an opportunity to strengthen the cardiovascular prevention in the country.

Republic of Moldova is located in the temperate continental climate influenced by the proximity of the Black Sea and the interference of warm-humid air from the Mediterranean. The seasons are clearly defined with a short winter with a little snow and a long summer sometimes very hot and dry. The annual air temperatures average in the country is 9,3°C.

The continuous insolation in the average per year is in the North – 2064 hours, the Center – 2115 hours and the South – 2327 hours. Number of days without sun are as follows: North - 80, Center – 71, South - 63 days.

During the year in the Republic of Moldova the wind direction is more frequent to the northwest and less rarely to the southeast, with speeds deviating within the limits 3.3 to 6.1 m / sec. For the Republic of Moldova there are characteristic low and medium speed winds, which reach an average of 5 m / sec.

Seasonal weather conditions of the Republic of Moldova are determined in winter by unstable conditions with an average monthly temperature from 1.2°C to 3.3°C below zero. The coldest month of the winter is January: its average monthly temperature is 3-5°C below zero. During the winter season in the territory fall on average of 85-110 mm of precipitation, or 16-20% of the average annual amount. Precipitation falls mainly in the mixed phase: in the form of rain and snow, their daily maximum reached 50-70 mm. The unstable nature of the weather for the winter season does not determine it as an absolutely negative factor (22, 23).

In the spring the average of temperature ranges from + 8°C to + 10°C. In this season the number of hours of continuous isolation is increased, as follows: the North – 593 hours, the Center – 605 hours and the South – 642 hours. During the spring, the average precipitation falls 105-150 mm, or about 24% of the annual rainfall (22, 23).

The average temperature for the summer season range is from + 18.5°C to + 21°C. The hottest month of the summer is July, in which it is reported the

highest air temperature for the entire measurement period +41.5 °C. Summer is characterized mainly by high temperatures and stable weather. During this time of year, the favorable temperature is recorded in 30-40% of days. Atmospheric precipitations in the hot season (April-November) are recorded in the average, as follows: the North – 380 mm and the South – 346 mm. The average monthly relative humidity is up to 45-47%.

Autumn is characterized by the gradual decrease of the air temperature, the increase of the wind speed and the number of days with precipitation. Autumn in the Republic of Moldova is mostly hot with clear days, the average air temperature is in the North + 9°C and in the South + 10.8°C. The first frosts appear in the North and the Center of the country after October 10 and in the South area even later.

In the Republic of Moldova warm weather with comfortable temperatures lasts 175 days and the relative humidity ranges from 66 to 87% on average. The thermal regime of the country climatic conditions is the most important curative factor for the treatment of chronic diseases.

The comparative analysis of the data on the weather conditions in the Republic of Moldova, based on the degree of negative exposure of the weather elements, confirmed that the climate of the Republic of Moldova belongs to the "favorable" and partially - "relatively favorable" climate group for the rehabilitation of patients with chronic diseases, including cardiovascular (22, 23). The climatic conditions of the Republic of Moldova are sufficiently favorable for carrying out cardiovascular prevention and rehabilitation using nature resources.

The main methods of climate therapy accessible to the Republic of Moldova are:

Heliotherapy – the beneficial action of sunlight is indicated for the treatment of skin diseases and nervous system;

Aerotherapy – the complex action of the weather elements on the body (temperature, humidity, wind movement, solar radiation and barometric pressure) by performing the doctor's prescribed walks in patients with various diseases, including cardiovascular;

Land-therapy – dosage walking on special routes for curative and rehabilitation purposes;

The main methods that use the natural resources

accessible to the Republic of Moldova are:

Ampelotherapy – the dosed use of grape juice for the treatment of various diseases is indicated for liver, kidney and circulatory system disorders.

Peloidotherapy – The dosage application of the curative sludge is indicated for the diseases of the musculoskeletal, gynecological, nervous, and circulatory system.

Balneotherapy – mineral water treatment that is done by internal and external administration. When administering, the chemical composition of the water is taken into account.

The favorable climate is a natural therapy with multiple possibilities to treat different chronic conditions. Large use of climatic factors in cardiovascular prevention programs will help improve cardiovascular health in the Republic of Moldova. Application of methods based on the action of climatic factors in cardiovascular rehabilitation process contributes to its efficiency improvement. Increasing the role of tertiary prevention is a good practice for the quality improvement of medical services for this category of patients. By making appropriate, timely and complex measures of primary, secondary and tertiary prevention cardiovascular disease can be substantially prevented.

Conclusions

Strengthening cardiovascular prevention centered on a complex approach to all its primary, secondary, and tertiary components is an opportunity to reduce premature mortality in the population.

References

1. World Health Organization (WHO). Global action plan for the prevention and control of noncommunicable diseases 2013-2020 [internet]. Geneva: WHO; 2013. Available from: http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf
2. Programul național de prevenire și control al bolilor cardiovasculare pentru anii 2014-2020. Hotărârea Guvernului nr. 300 din 24 aprilie 2014 [internet]. În: Monitorul Oficial al Republicii Moldova, 06.05.2014, nr.104-109, art. Nr:327.
3. Strategia națională de prevenire și control al bolilor netransmisibile pe anii 2012-2020. Hotărârea Parlamentului nr. 82 din 12 aprilie 2012 [internet]. În: Monitorul Oficial al Republicii Moldova, 22.06.2012, nr.126-129, art. Nr:412. Available from: <http://lex.justice.md/index.php?action=view&view=doc&lang=1&id=352739>
4. Ford E. et al. Ideal Cardiovascular Health and Mortality from All Causes and Diseases of the Circulatory System Among Adults in the United States. *Circulation*, 2012 [internet]. DOI: 10.1161/CIRCULATIONAHA.111.049122. Available from: <http://circ.ahajournals.org/content/early/2012/01/30/CIRCULATIONAHA.111.049122>
5. Strategia națională de sănătate publică pentru anii 2014-2020. Hotărârea Guvernului nr. 1032 din 20 decembrie 2013 [internet]. În: Monitorul Oficial al Republicii Moldova, 27.12.2013, nr.304-310, art. Nr:1139. <http://lex.justice.md/index.php?action=view&view=doc&lang=1&id=350833>
6. Raevschi E. Mortalitatea cardiovasculară prematură în Republica Moldova. Chișinău: Elan Poligraf, 2017. 162 p.
7. World Health Organization (WHO). Regional office for Europe. European Health for All family of databases, July 2016 [internet]. Available from: <http://www.euro.who.int/en/data-and-evidence/databases/european-health-for-all-family-of-databases-hfa-db>
8. World Health Organization (WHO). Global status report on noncommunicable diseases 2014 [internet]. Geneva: WHO, 2014. Available from: <https://www.who.int/nmh/publications/ncd-status-report-2014/en/>
9. World Health Organization (WHO). Regional office for Europe. Prevalence of Noncommunicable Disease Risk factors in the Republic of Moldova. STEPS 2013 [internet]. Denmark, 2014. Available from: <https://extranet.who.int/ncdsmicrodata/index.php/catalog/230>

10. World Health Organization (WHO). Noncommunicable Diseases Progress Monitor, 2017 [internet]. Geneva: WHO, 2017. Available from: <http://apps.who.int/iris/bitstream/handle/10665/258940/9789241513029-eng.pdf?sequence=1>
11. Raevschi E., Ababii I., Sperling L., Vataman E. Status of cardiovascular population health in the Republic of Moldova. *Sănătate Publică, Economie și Management în Medicină*. Chișinău, 2018; nr.1-2 (75-76):13-16. ISSN 1729-8687.
12. Capewell S., O'Flaherty M. What explains declining coronary mortality? Lessons and warnings. *BMJ, Heart*, 2008, 94, p.1105-1108. Available from: <http://dx.doi.org/10.1136/hrt.2008.149930>
13. Ezzati M. et al. Contributions of risk factors and medical care to cardiovascular mortality trends. *Nat Rev Cardiol*. 2015; 12 (9): 508-530.
14. Ford E. et al. Explaining the Decrease in U.S. deaths from Coronary Disease, 1980-2000. *The New England Journal of Medicine*. 2007; 356 (23):2388-2398.
15. Mensah G. et al. Decline in Cardiovascular Mortality Rate: Possible Causes and Implications. *Circulation Research*. 2017; 120:366-380. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5268076/>
16. Nichols M. et al. Trends in age-specific coronary heart disease mortality in the Europe Union over three decades: 1980-2009. *European Heart Journal*. 2013; 34:3017-3027. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23801825>
17. Mensah G. et al. Decline in Cardiovascular Mortality Rate: Possible Causes and Implications. *Circulation Research*. 2017; 120:366-380 [internet]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5268076/>
18. Nichols M. et al. Trends in age-specific coronary heart disease mortality in the Europe Union over three decades: 1980-2009. *European Heart Journal*. 2013; 34:3017-3027. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23801825>
19. Capewell S., O'Flaherty M. What explains declining coronary mortality? Lessons and warnings. *BMJ Journals, Heart*. 2008; 94:1105-1108. Available from: <http://dx.doi.org/10.1136/hrt.2008.149930>
20. Hasnain M Dalal, Patrick Doherty and Rod S Taylor. *Cardiac Rehabilitation*. *BMJ*. 2015 Sep 29. doi: 10.1136/bmj.h5000.
21. European Society of Cardiology (ESC). *CVD Prevention in Clinical Practice (European Guidelines on)*, 2016 [internet]. Available from: <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/CVD-Prevention-in-clinical-practice-European-Guidelines-on>
22. Raportul Național de Dezvoltare Umană. 2009-2010. Schimbările climatice în Republica Moldova [internet]. Available from: http://www.undp.md/publications/2009NHDR/NHDR_rom_Capitol3.pdf
23. Serviciul Hidrometeorologic de Stat. *Climatologie* [internet]. Available from: <http://www.meteo.md/index.php/researches/climatologie/>
24. World Health Organization (WHO). *European Action Plan for Strengthening Public Health Capacities and Services* [internet]. Copenhagen: WHO; 2012. Available from: <http://www.euro.who.int/en/health-topics/Health-systems/public-health-services/publications/2012/european-action-plan-for-strengthening-public-health-capacities-and-services>
25. World Health Organization (WHO). *Prevention of recurrent heart attacks and strokes in low and middle income populations: Evidence-based recommendations for policy makers and health professionals* [internet]. Geneva: WHO; 2003. Available from: [\(http://www.who.int/cardiovascular_diseases/resources/pub0402/en/](http://www.who.int/cardiovascular_diseases/resources/pub0402/en/)

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Abstract

The purely spinal form of multiple sclerosis, presenting as a progressive spastic paraparesis, hemiparesis, or, spastic monoparesis of a leg with varying degrees of posterior column involvement, is a special source of diagnostic difficulty. We present the case of a 47 years old patient, with no personal pathological antecedents, admitted in our department through the emergency ward for motor deficit of the lower limbs, symphomatology that had an acute onset the day before admittance. The neurologic examination revealed: orthostatism and gait not possible, spastic paraparesis – 3/5 MRC (medical research council), deep tendon reflexes were found to be hyperactive on both lower extremities, bilateral plantar extension, a dermatomic level of sensory disturbance at T10 – T11 vertebral segment and urinary retention. The cerebral MRI revealed no pathological findings. The lumbar puncture revealed oligoclonal bands and the spine MRI outlined multiple focal images with demyelination aspect reaching the cervical and dorsal level of the medullary cord. The patient had two more relapses each at approximately 6 months, and this allowed us to establish the final diagnostic: Pure spinal multiple sclerosis.

Key words: *spinal multiple sclerosis, paraparesis, neurorehabilitation,*

Introduction

The purely spinal form of multiple sclerosis, presenting as a progressive spastic paraparesis, hemiparesis, or, spastic monoparesis of a leg with varying degrees of posterior column involvement, is a special source of diagnostic difficulty. Such patients require careful evaluation for the presence of spinal cord compression from neoplasm or cervical spondylosis. The diagnosis of multiple sclerosis is based on neurological signs and symptoms, alongside evidence of dissemination of CNS lesions in space and time. MRI is often sufficient to confirm the diagnosis when characteristic lesions accompany a typical clinical syndrome, but in some patients, further supportive information is obtained from cerebrospinal fluid examination and neurophysiological testing (1). Multiple sclerosis (MS) it is thought to be a complex disease, and poorly understood with regards to aetiology. Observational research has suggested genetic and environment influences through an underlined pathophysiology widely believed to be autoimmune in nature. The spinal cord is a critical structure and its damage can lead to dysfunction of motor and/or sensory systems, as occurs in cases of various musculoskeletal and neurodegenerative

diseases such as degenerative disc disease and multiple sclerosis. Spinal cord lesions on MRI correspond to areas of demyelination, neuroaxonal loss and gliosis, affecting spinal cord structure and function. Postmortem spinal cord studies have described a larger proportion of demyelination in the grey matter (33%) than in the white matter (20%), with lesions involving either both grey matter and white matter, or grey matter isolately. No difference in the extent of grey matter demyelination was seen between different cord levels (2).

Case report

We present the case of a 47 years old patient, with no personal pathological antecedents, admitted in our department through the emergency ward for motor deficit of the lower limbs, symphomatology that had an acute onset the day before admittance. At admission blood pressure and heart rate were in normal range. No fever and no other abnormalities were found in the general examination. The neurologic examination revealed: orthostatism and gait not possible, spastic paraparesis – 3/5 MRC (medical research council), deep tendon reflexes

were found to be hyperactive on both lower extremities, bilateral plantar extension, a dermatomic level of sensory disturbance at T10 – T11 vertebral segment and dysfunction of the urinary bladder – urinary retention. The differential diagnosis included: myelitis, neuromyelitis optica, motor neuron disorders, vascular diseases and nutritional deficiencies. A presumptive diagnosis of multiple sclerosis has been outlined too, therefore further investigations have been made. Biological it was emphasized a mild hepatocytolysis, vitamin B12, folic acid, complete blood count, ionogram were in normal ranges.

The cerebral MRI revealed no pathological findings. A MRI of the thoracic spine and a lumbar puncture were performed. The lumbar puncture revealed oligoclonal bands and the spine MRI outlined multiple focal images with demyelination aspect reaching the cervical and dorsal level of the medullary cord, some of them gadolinophilic (active), that were less than 2 vertebral bodies in length (this also helped us to exclude Neuromyelitis Optica). We excluded all the above mentioned with the spine MRI, the lumbar puncture and, of course, the clinical exam. Neuromyelitis optica was excluded by negative aquaporin 4 antibodies and negative anti MOG antibodies.

There are new studies that discuss the effect of plasmapheresis in MS patients, but it should be taken into account that patients can develop multiple adverse effects, for example hypotension, tachycardia and severe allergies (3). Our patient responded to treatment with methylprednisolone (1g/day, for 5 days).

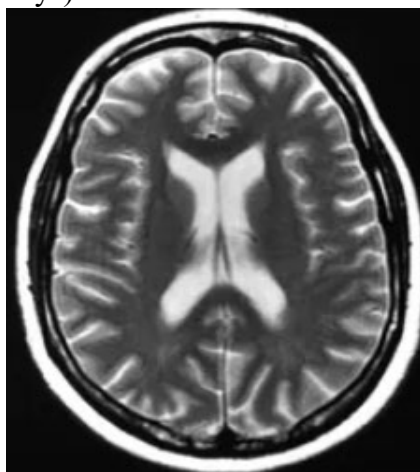


Fig. 1 .– Cerebral MRI (axial T2 sequence) – with no pathological findings



Fig .2 .– Spinal MRI (sagittal T2 flair sequence) – focal image with demyelination aspect reaching the dorsal level (T10-T11) of the medullary cord.

The patient was tested for Hepatitis B and C, and she was positive for hepatitis B (agHBs positive). She received a recommendation to see a gastroenterologist and to make further investigation. After this admittance, the patient had two more relapses each at approximately 6 months. During this time the patient received treatment with Baclofen 10 mg 2 tablets/day for the spasticity. For the urinary retention, the patient learned to catheterize herself. Of course she started physiotherapy – kinetotherapy. Because of Hepatitis B diagnosis we did not start any interferon or other immunosuppressive treatment. All in all, all these gathered together, allowed us to establish the final diagnostic: Pure spinal multiple sclerosis.

Discussions

Motor symptoms are common and disabling across the phases and forms of multiple sclerosis (MS). Disease modifying treatments help to prevent their development, but most of their management is through rehabilitation. Current rehabilitation approaches are based on physical therapy focused on the individual's needs (1). The efficacy of these approaches, however, is limited, as it is purely based on clinical grounds, and is largely unpredictable in the individual case, where several factors, including location, extent, and severity of MS damage, can contribute to individual variation in rehabilitation outcomes (4).

Therefore, an improved understanding of the neural processes underlying functional recovery and driven by rehabilitation, remain a clinical necessity and a research priority that should fully exploit the individual patient's potential to recover motor function (5).

The complexity of the disease, the difficulty in determining the appropriate treatment and a wide range of symptoms call for a comprehensive approach to the patient, which would involve both pharmacology and neurorehabilitation. Our patient definitely needed physiotherapy, which is an integral part of rehabilitation and consists in kinesitherapy, physical therapy and massage (6).

Generally speaking and, even more, in this case, physiotherapy is aimed at improving mobility through compensation mechanisms that involve the activation of capabilities of effectors, which results in the patient regaining functioning, not movement. All applications included in physiotherapy should be recommended in such a way as to act upon the largest possible number of motor deficits. The introduction of physical activity, regardless of the severity of the disease, will reduce the negative effects of akinesia, and thus increase the functional capabilities of all body systems (7).

Patients with MS can develop in time, especially if there are cerebral lesions, problems with balance and coordination, so the inclusion of balance and coordination exercises into the therapy is necessary. Coordination and balance exercises are carried out according to the Frenkel method, in which footprints painted on the floor are used to learn proper gait. The exercises are performed in 3 phases (right foot steps forward, shift weight, left foot joins the right one). The movement is divided into three phases (feet withdrawn, forward leaning of the trunk, straightening of the legs and getting up) (8,9).

Spasticity was one of the main symptoms of our patient and is one of the symptoms that often makes rehabilitation and care difficult and most importantly deepens the disability. Spastic paresis affects both lower and upper limbs with greater severity of pathological tension in the lower extremities. Our patient had a spastic paraparesis which made walking very difficult. It is a symptom of the impairment of upper motor neuron which reveals excessive activity of alpha cells of the anterior horn of the spinal cord. High degree of spasticity (3 or 4 in Ashworth scale) causes contractures, joint deformities and bedsores which lead to infections (10). Sometimes spasticity from Multiple Sclerosis or even Neuromyelitis Optica can be accompanied by painful spasms that are paroxysmal episodes lasting seconds or minutes, accompanied by intense

pain and tonic postures of the limbs. Ephaptic transmission between abnormal demyelinated tracts could explain the spasms. Recently, the presence of these manifestations seems to be associated to NMO rather than MS or idiopathic acute transverse myelitis, and we excluded both of these pathologies (11). Apart from pharmacotherapy, physiotherapy plays an important role in the cases of severe spasticity. The plan of the rehabilitation program should take into account the fact that the use of physical applications before kinesiotherapy has positive effects while greater physical efforts can increase muscle tension (7).

Passive stretching is a contraindication, as it reduces the excitability of the motor neurons and maintains elasticity properties of muscles and joints. Other physical methods used in the treatment of spasticity are electrotherapy and magnetic therapy (10).

Electrical stimulation of neuromuscular system (NMES), transcutaneous electrical nerve stimulation (TENS), Hufschmidt method and functional electrical stimulation (FES) are listed among the applications of electrotherapy. Electrical stimulation seems to be the best method because damage to Upper Motor Neuron does not alter the excitability of the muscles to electrical stimuli, so that the impaired bioelectrical function of muscles can be replaced. Studies have shown that both methods result in a reduction of muscle tension, which leads to a wider range of motion in the joints and improved gait efficiency (8).

Physical activity in patients with multiple sclerosis improves not only their physical capacity, but also their mood and attitude towards the exercises. Better cardiorespiratory efficiency has been proven to enhance the cerebrovascular function, which suggests that movement can also significantly improve the brain function in patients with multiple sclerosis. Aerobic training increases muscle strength of the lower limbs, which manifests itself in reducing spasticity without the risk of relapse or the symptoms of fatigue (8). Recent recommendations for patients with multiple sclerosis suggest performing physical activities 2–3 times per week at an intensity of 60–80% of maximum heart rate. The duration of the exercise should not exceed the initial period of 40 min. The intensity should increase gradually depending on the degree of disability (10, 12).

As far as the medical treatment is concerned, patients suffering from RRMS will begin their treatment with a first-line drug, fingolimod and dimethyl fumarate being the most active ones in this category, having the great advantage of the oral administration. IFNs and GA are somewhat less efficient, but they passed the test of time, showing a good safety profile, however most forms of multiple sclerosis are remissive and recurrent on the onset, and later they turn progressive, and no treatment has proven to be efficient, so far (13). If the cognitive impairment appears it should be differentiated from other forms of dementia like Alzheimer disease, for example, where p-tau /A β 42 or t-tau/A β 42 ratio is used, with a sensitivity of up to 92% and a specificity of up to 86%. The ratio between A β 42 and p-tau is significantly lower in AD patients compared to those with vascular dementia. Research studies on the treatment for cognitive impairment in MS patients are ongoing (14).

Conclusions

We have presented an atypical case of spinal multiple sclerosis, with late onset, in a 47 years old patient that had a good evolution receiving cortisonic treatment in the acute phase, followed by treatment with central antispastics and kynetotherapy.

Conflict of interest

No conflict of interest for any of the authors regarding this paper.

Informed consent

An informed consent was obtained from the patient included in this article

References

1. A. Hardy, Prof Franz Fazekas, Prof David H, Miller F, Diagnosis of multiple sclerosis: progress and challenges. *The Lancet*, VOLUME 389, ISSUE 10076, 2016, P1336-1346.
2. Lublin FD Reingold SC Cohen JA et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014; 83: 278-286.
3. Sava Mihai, Catană Maria-Gabriela, Roman Corina, The importance of early neurorehabilitation in the recovery of post-vaccination Guillain-Barre syndrome – a case report. *Balneo Research Journal*. 2019;10(2):98–102 . 10.12680/balneo.2019.246.
4. Sombekke MH Wattjes MP Balk LJ et al. Spinal cord lesions in patients with clinically isolated syndrome: a powerful tool in diagnosis and prognosis. *Neurology*. 2013; 80: 69-75.
5. Wallner-Blazek M Rovira A Fillipp M et al. Atypical idiopathic inflammatory demyelinating lesions: prognostic implications and relation to multiple sclerosis. *J Neurol.* 2013; 260: 2016-2022.
6. Kwolek A, Podgórska J, Rykała J. Own experience in the rehabilitation of multiple sclerosis patients. *Przegląd Medyczny Uniwersytetu Rzeszowskiego*. 2010;2:213–220.
7. Steiborn B, Łuczak-Piechowiak A. Kinesytherapeutic methods in the treatment of spasticity. *Polski Przegląd Nauk o Zdrowiu*. 2006;1:95–103.
8. Miller L, Mattison P, Paul L, Wood L. The effects of transcutaneous electrical nerve stimulation (TENS) on spasticity in multiple sclerosis. *Mult Scler*. 2007;13:527–533.
9. Frago YD, Santana DLB, Pinto RC. The positive effects of a physical activity program for multiple sclerosis patients with fatigue. *Neurorehabilitation*. 2008;23:153–157.
10. Dalgas U, Ingemann-Hansen T, Stenager E. Physical exercise and MS. *Recommendations Int MS J*. 2009;16:5–11.
11. Corina Roman-Filip, A. Ungureanu, M. Cernusca Mitariu, "Paniful tonic spasms and brainstem involvement in a patient with neuromyelitis optica spectrum disorders" *Polish Journal of Neurology and Neurosurgery*, ISSN 0028-3843, Vol.50.Nr.1 pag.55-58, 2016
12. Sandroff BM, Dlugnski D, Weikert M, et al. Physical activity and multiple sclerosis: New insights regarding inactivity. *Acta Neurol Scand.* 2012;126:256–262.
13. Carmen Adella Sirbu, Emilia Furdu-Lungut, Cristina Florentina Plesa, Alina Crenguța Nicolae, Cristina Manuela Dragoi. Pharmacological treatment of relapsing remitting multiple sclerosis-where are we?. *Farmacia.* 2016, Vol. 64, 5.

Satisfaction of Generations X and Baby Boomers with tourist services in resorts from the Subcarpathians of Oltenia, in line with sustainable tourism destination development

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Abstract

Introduction. In the context of sustainable tourism development, tourist satisfaction looked at from the perspective of the experience lived in the destination and the quality of services rendered by service providers is one of the directions in which researchers point their attention. In this context, the purpose of this study is to measure the satisfaction of Generations X (GX) and Baby Boomers (GBB) with tourist services in balneal resorts, seen through the perspective of the sustainable development of tourism destinations. **Material and method.** Methodology consisted in the survey method, by applying the semi-structured questionnaire tool on a sample of tourists visiting the balneal resorts in the Subcarpathians of Oltenia between July and October 2019. **Results and discussions.** The results show that satisfaction with the access to and inside the destination is good, but the infrastructure requires modernization. Satisfaction with tourist services is good, but it requires the improvement of recreational facilities and treatment services, especially for the members of Generation X. As far as accommodation services are concerned, even though they received the most positive feedback, the vast majority of facilities have medium level classification. Direct or indirect interaction with locals, hotel staff, and local authorities is valued as good towards very good. On the whole, it is necessary to increase satisfaction for GX and GBB tourists, as this will bring greater benefits for all interested parties: hotel owners and staff, tourists, local authorities, and even the local community, who can become more actively involved in the tourist market. **Conclusions.** This study is useful for local authorities in order to develop sustainable tourism, and for economic agents in obtaining the projected benefits.

Key words: *tourist satisfaction, generational cohorts, Subcarpathians of Oltenia, sustainable tourism, balneal services.*

Introduction

Spa tourism in Romania dates back to the period of Roman conquest, stimulated by the presence of mineral and geothermal springs in a period when numerous baths, especially thermal baths, were used in spa therapy. In the Subcarpathians of Oltenia, excavations at Săcelu revealed parts of the installations of the old Roman baths used for balneal purposes (1).

However, major developments can only be mentioned starting with the second half of the 18th century, when research and facility building have intensified in this field (2,3). This was favoured by the complex geological structure of Romania, which allowed the formation of a large variety of mineral water types, amounting to 2000 springs throughout the country (4).

In this context, a continuous development of spa tourism in Romania followed during the 19th and 20th centuries, with different visions in the capitalist versus the communist eras (1948-1999). The latter

was oriented towards the development of social tourism, which is verified by the boom in mid- and lower-class structures and the emergence of economic mono-functional territorial units (5,6).

Currently, Romania is in a continuous socio-economic transformation, and spa tourism is important in the local economic system due to complex economic influences, manifested both vertically and horizontally (7,8). Moreover, Romania is also facing demographic ageing, a complex process involving socio-economic and cultural effects; therefore, policies related to the aging population should revolve around the concept of health and increasing their life span (9), with spa treatments being just one of the possible solutions. Predictions on demographic ageing at a planetary level are not optimistic, and Romania has also set course on this trajectory. Specialists estimate the senior population older than 65 will rise to 22% of the world's population by the year 2050; they also

foresee a drastic drop in population under the age of 5 (5%) (10). Therefore, society should prepare to facilitate active ageing and a higher healthy life expectancy.

Literature review

Satisfaction is a basic element in assessing how competitive a tourist destination is and a key feedback element for tourist experience. The term "tourist satisfaction" was identified by Pizam, Neumann, and Reichel (11) as a vague concept, insufficiently researched or operationalised at the time. Cho (12) noted that even though there was a continuous increase in research on the satisfaction of tourists, it contained elements of confusion about what tourist satisfaction actually implies, as many people tended to confuse it with service quality, since this represents a global and holistic assessment (13).

Although studies on both service quality and tourist satisfaction have gaps, tourist satisfaction is a very important concept for the (sustainable) management of a destination (14). There are authors who believe that tourist satisfaction is related to a destination's attributes (15) or that it represents the result of the interaction between a tourist's experience and their expectations regarding the destination (11,16,17). Economic studies correlate tourist satisfaction to profitability (18), and Yuksel et al. (19) argue that satisfaction and loyalty are basic elements on which a business is built.

Drawing from Kozak's analyses (20) on the measurement of tourist satisfaction, Pou and Alegre (21), referring to it as customer feedback, state that it can be collected using various methods, one of which is the consumer satisfaction survey. These assessments make it possible to reconsider the continuous improvement of services (22), including better understanding of tourists' needs and desires, which is essential for destination management organisations (23).

On the other hand, Peterson and Wilson (24) argue that there is no measurement of true satisfaction because it is affected by numerous intangible issues from various spheres, such as individual tourist characteristics, multidimensional tourist subsystems (16), similar attractions, hotels, restaurants, and methodological or geographical considerations. The authors conclude that it is impossible to solve all these issues, given that a negative personal

experience can alter other spectacular aspects of the destination. Incidentally, satisfaction depends on many factors, either internal, such as tourist motivation or feelings, or external, such as tourist activities offered by a destination and/or the price-quality balance (25).

To maintain or raise satisfaction, efforts to improve services should be carried out at the same time as improving the infrastructure and technical base of the destination. Fuchs and Weiermair (26) argue that tourism service quality and tourist satisfaction are two complex, multidimensional, dynamic concepts, which are usually influenced by the individual features of customers/tourists, such as gender and age, as well as by the market. The authors conclude that measuring tourist satisfaction is indeed a difficult theoretical and empirical task.

Liljander and Strandvik (27) suggested that perceived service quality can be viewed as an external perspective, a cognitive judgement of a service that doesn't even have to be from personal experience, but it can rely on the knowledge of a company's services or on the way it is advertised. According to Liljander and Strandvik, satisfaction refers to a personal perspective gained through the client's own experiences and within which the result was assessed in terms of value received or in terms of what the customer had to give in order to obtain something.

When viewed as such, tourist satisfaction differs from one individual to another, but also from a generation to another. Age plays a key role in determining consumer behaviour or satisfaction. Dividing the population into groups called generational cohorts was proposed by Inglehart (28). A generational cohort is defined according to birth years and lasts 20-25 years or however long it generally takes for a group to be born, grow up, and have their own children (29). These cohorts share the same attitudes, ideas, values, and beliefs based on their being born during the same period of time and living through joint experiences, with the same social, political, and economic events on a macroeconomic level taking place during their lifetime (29). According to Meredith and Schewe (30), witnessing specific experiences and events will be reflected in their core values related to jobs, money, tolerance, and sexual behaviour. These values, beliefs, expectations, and behaviours remain

constant throughout the lifetime of a generation and create a generational identity (29,28,31,32). When referring to consumers, this can significantly influence shopping patterns and behaviour (33). According to cohort theory (34), using generational cohorts could make it possible to gain additional understanding of consumers, since each cohort is comprised of people who were born in a certain period, and who have similar experiences, values, and priorities that will remain relatively stable throughout their lives (35). UNWTO uses in its reports the terms of consumer generations: Generation X, Y, Z, α (36), terms adopted in tourism research (37,38).

Generation X (GX) refers to people born between 1961 and 1979 (39), it is one of the most highly educated generations in history and is characterized by technological and media savvy, scepticism and pragmatism (40,41).

On a global level, before Generation X, came the Baby Boom/Boomers generation (GBB), which is comprised of people born between 1946 and 1964 (41). Romania did not go through the same demographic boom during this period, but actually later, prompted by the pro-natalist policy enforced during the communist era. However, based on research homogeneity considerations, Romania aligns to this classification as well (39). The GBB cohort members, just as the other generations, have different experiences that influence their values, preferences, and purchase behaviour (42,43,44,45).

The purpose of this study is to assess the satisfaction of Generations X and BB with tourist services provided by the resorts in the Subcarpathians of Oltenia, in accordance with the sustainable development of destinations.

The research objectives are:

1. Outline the balneal characteristics of the study area.
2. Analyse the satisfaction of the two cohorts of tourists regarding access, tourist services (including balneal), and the social climate of the resorts.
3. Identify solutions for raising tourist satisfaction in the context of sustainable development.

Setting scene of the study area

The Subcarpathians of Oltenia, seen as a tourist destination of particular complexity, have a large

number of tourist attractions, a continuously developing infrastructure and various tourist activities, all included in the Northern Oltenia Tourist Region (2). This destination is home to five tourist resorts that show important similarities when it comes to their natural curative factors and the affections they treat.

Călimanești-Căciulata resort has balneal resources such as chlorosodic water, bicarbonate or calcic alkaline water, magnesium sulphur water, and sometimes brom-iodine water. The mineral waters are used in external treatments such as baths or topical applications for disorders of the musculoskeletal system and peripheral nerves, for gynaecological issues, varicose veins and vascular ulcers, and disorders of the upper airways. Internally, they are used to treat the digestive tract and its appendages, the kidneys and urinary tract, and various occupational diseases (46,47,48). Additionally, they are used to heat accommodation units and for recreational purposes (49).

Băile Olănești resort has sulphurous, chlorosodic, iodized, bromine, bicarbonate, calcic, and magnesium waters (1,46). They are used internally for metabolic diseases, kidney disorders, and digestive issues. In external treatments, they are recommended for disorders of the musculoskeletal system and peripheral nerves, skin conditions, and professional diseases (1,47,48).

Băile Govora Resort benefits from chlorosodic and strongly iodized waters, as well as from bicarbonate, sulphurous, bromine, and sodium waters. In addition to mineral waters, spa treatments here use the mud accumulated in the collapsed areas of the old Ocnele Mari salt mines. The resort is recommended for the treatment of rheumatic musculoskeletal disorders, of the peripheral nervous system, the respiratory tract, in otorhinolaryngology and in some nutritional disorders (46,47,48).

Săcelu resort, somewhat geographically isolated from the Vâlcea resort cluster, has natural curative resources such as chlorosodic, iodized, bromine, calcic, sulphurous, and bicarbonate waters. The resort is recommended for the external treatment of musculoskeletal, peripheral nervous system, and gynaecological disorders, and for the internal treatment of diuresis (urinary lithiasis), hypoacidic gastritis, and liver diseases (1,47,48).

The only resort with high concentration chlorosodic mineral water is the town of Ocnele Mari. The second substance used in balneal treatments is the therapeutic mud accumulated in the collapsed areas of the old salt mines. The mineral water in Ocnele Mari is recommended for the treatment of musculoskeletal, peripheral nervous system, and gynaecological disorders (46,47,48).

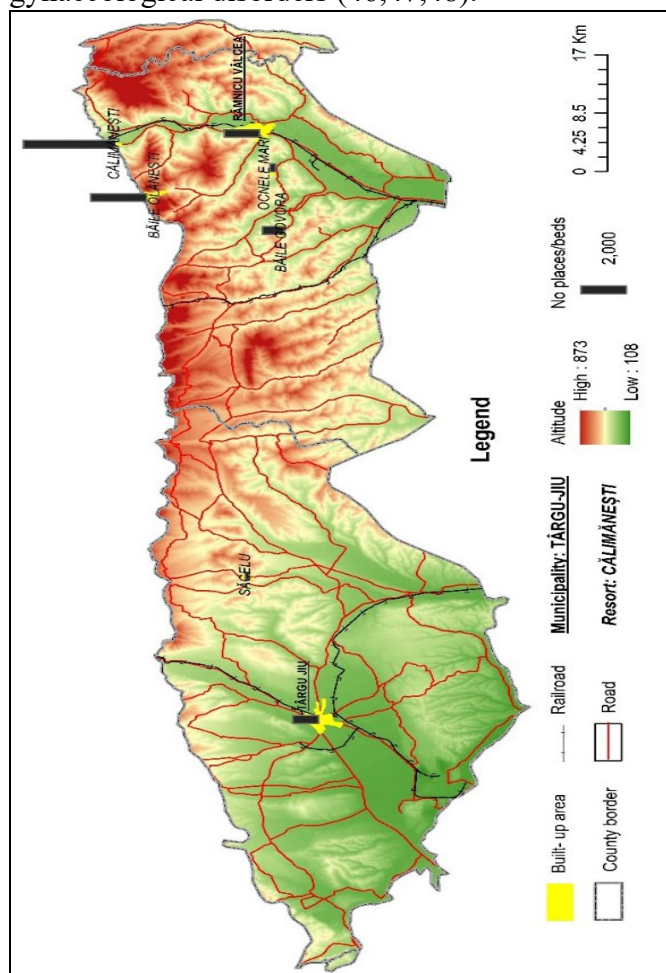


Fig. 1. Subcarpathians of Oltenia: resorts, municipalities, and their tourism capacity

Research methodology and data management

This research is based on a multidimensional approach to the sustainable development of tourism, by guiding the assessment of elements belonging to the environmental, tourist-economic, and social component.

The social component is the central element that interacts with the others and from which derives tourist satisfaction. In order to do this, samples of GX and GBB tourists were analysed to investigate their satisfaction with tourist services. In order to achieve this, satisfaction was investigated by connecting it with the general experience in the

destination, the quality of services received during their stay, and tourist interaction with locals and with the staff of economic agents and local authorities.

This satisfaction assessment was carried out using the investigation method and the semi-structured questionnaire applied face-to-face between July and October 2019; the questions chosen targeted two parts: socio-demographic characteristics and tourist satisfaction measured by access to the destination, and conflict situations. The questionnaire includes questions with multiple binomial answers, questions using the Likert scale (from 1 to 5, where 1 is Very poor, 2 is Poor, 3 is Average, 4 is Good, and 5 is Very good), as well as open questions. The sample consists of 144 responders, equally divided according to gender inside the two generational cohorts, with 59% being part of GX and 41% of GBB. Furthermore, 86% of the respondents come from urban areas and 14% from rural areas. In terms of education, 7.6% have undergone elementary studies (no high school), 35.4% high school studies, 22.2% postgraduate studies, 29.2% university studies, and 5.6% post-university studies. In terms of income, 9% have an income lower than 275€, 31.9% have incomes between 276€ and 500€, 20.8% have incomes between 501€ and 700€, 26.4% have incomes between 701€ and 900€, and 11.8% have an income higher than 900€ (Table 1).

Table 1. Socio-demographic profile of the sample

Socio-demographic profile		Percent (%)
Gender	Male	50%
	Female	50%
Age	45-64 years	59%
	≥65 years	41%
Education level	Lower secondary school	7.6%
	High school	35.4%
	Post-secondary school	22.2%
	University	29.2%
	Postgraduate	5.6%
Income	≤ 275 €	9%
	276-500 €	31.9%
	501-700 €	20.8%
	701-900 €	26.4%
	≥ 900 €	11.8%
Residence area	Urban	86%
	Rural	14%

Sample size was confirmed by χ^2 test, which showed a large number of statistical correlations with $p < 0.05$ (Table 2).

Table 2. Chi-squared test: correlations among sociodemographic variables and respondents' answers.

Correlations	Value	df	P value
Residence-Leisure	309.846	261	0.020
Residence-Means of transport used	311.749	261	0.017
Residence-Minimum travel distance	418.276	348	0.006
Gender-Complaint to police or authorities	15.689	3	0.001
Gender-Interaction with the staff of economic agents	9.525	4	0.049
Age-Satisfaction with treatment services	14.048	5	0.015
Age-Satisfaction with leisure and recreation services	9.985	3	0.019
Age-Complaint to police or authorities	11.854	3	0.008
Age-Minimum travel distance	9.621	4	0.047
Education- Means of transport used	22.876	12	0.029
Education-Use of local/public transport	13.000	4	0.011
Education-Interaction with locals	26.874	16	0.043
Education-Interaction with local authorities	33.403	16	0.007
Income- Satisfaction with treatment services	32.112	20	0.042
Income - Means of transport used	24.089	12	0.020
Income- Minimum travel distance	36.730	16	0.002

Source: SPSS v 25 output.

Data were processed in SPSS 25 using descriptive statistics, Frequency, and Mean, and the Chi-squared test (χ^2) for statistical and descriptive statistical significance.

GIS was used for the visual representation of the study area, by processing the data referring to access

ways and tourist capacity by resorts and municipalities. The source of the data regarding tourist capacity was the TEMPO-Online database of the INS (50).

Results and discussions

Tourist satisfaction concerning access to and inside the destination

Given that access to the destination is mainly done in two ways – by road and by rail, the means of transport predominantly used to reach the destination is personal car (51.4%), followed by coach with 17.4%, and train with 7.6%. Furthermore, 23.6% of respondents use more than one means of transportation to reach the destination. Comparing the two generations, it is noted that GXs choose their personal car (57% versus 44% for GBB), and BBs prefer the train (12% versus 5% for GX), especially thanks to the facilities offered by railway carriers (Table 3:3.1.).

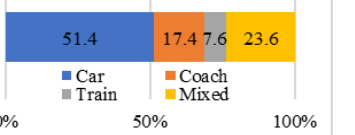
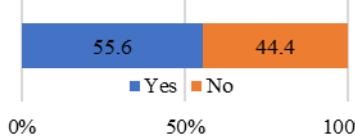
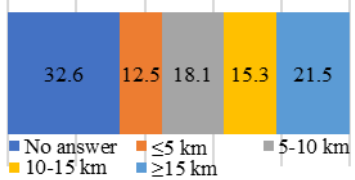
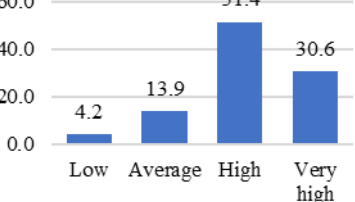
Tourist mobility inside the destination is ensured solely by road transport. More than half of the respondents claimed to use public transport inside the destination (55.6%) and they were divided almost equally between the two generations (Table 3:3.2).

One of the reasons for this is the very profile of the resorts, as facilities here usually recommend walking inside the destination as part of the treatment, combined with getting plenty of rest. Another motivation tied to tourist mobility is the proximity of the resorts to larger towns, as is the case of Călimănești-Căciulata, Băile Olănești, Băile Govora, and Ocnele Mari, all of which are close to Râmnicu Vâlcea. The distance tourists travel inside the destination ranges from 5 km or less (12.5%) to between 5-10 km (18.1%), between 10-15 km (15.3%), and to more than 15 km (21.5%). However, it must be stated that 32.6% of tourists did not answer this question. As for how the two generations compare in this aspect, it is noted that GXs travel a distance of more than 15km (30%) inside the destination, while BBs travel 5-10km (24%) (Table 3:3.3).

The overall satisfaction of the generational cohorts with destination accessibility is Good (Mean = 3.56), since 41.7% of respondents give it a value of 4 and 36.8% give it a 3 (Average), but it's not Very good because only 12.5% give it a 5 (Very good) on the

Likert scale (Table 3:3.4.). Comparing the two generations, it is noted that there is a slight difference in the satisfaction for BBG (Mean = 3.49) as opposed to GX (Mean = 3.60).

Table 3. Tourist satisfaction concerning access to and inside the destination

3.1. Means of transport used (What means of transport did you use to get to the destination?)	 <table border="1"> <thead> <tr> <th>Means of transport</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Car</td> <td>51.4</td> </tr> <tr> <td>Train</td> <td>17.4</td> </tr> <tr> <td>Coach</td> <td>7.6</td> </tr> <tr> <td>Mixed</td> <td>23.6</td> </tr> </tbody> </table>	Means of transport	Percentage	Car	51.4	Train	17.4	Coach	7.6	Mixed	23.6		
Means of transport	Percentage												
Car	51.4												
Train	17.4												
Coach	7.6												
Mixed	23.6												
3.2. Do you use local/public transport to travel inside the destination?	 <table border="1"> <thead> <tr> <th>Response</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Yes</td> <td>55.6</td> </tr> <tr> <td>No</td> <td>44.4</td> </tr> </tbody> </table>	Response	Percentage	Yes	55.6	No	44.4						
Response	Percentage												
Yes	55.6												
No	44.4												
3.3. If yes, what is your minimum travel distance?	 <table border="1"> <thead> <tr> <th>Distance</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>No answer</td> <td>32.6</td> </tr> <tr> <td>≤5 km</td> <td>12.5</td> </tr> <tr> <td>5-10 km</td> <td>18.1</td> </tr> <tr> <td>10-15 km</td> <td>15.3</td> </tr> <tr> <td>≥15 km</td> <td>21.5</td> </tr> </tbody> </table>	Distance	Percentage	No answer	32.6	≤5 km	12.5	5-10 km	18.1	10-15 km	15.3	≥15 km	21.5
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No answer	32.6												
≤5 km	12.5												
5-10 km	18.1												
10-15 km	15.3												
≥15 km	21.5												
3.4. Infrastructure. On a scale from 1 to 5 (where 1 is Very poor and 5 is Very good), how do you assess the quality of access to the destination?	 <table border="1"> <thead> <tr> <th>Assessment</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Low</td> <td>4.2</td> </tr> <tr> <td>Average</td> <td>13.9</td> </tr> <tr> <td>High</td> <td>51.4</td> </tr> <tr> <td>Very high</td> <td>30.6</td> </tr> </tbody> </table>	Assessment	Percentage	Low	4.2	Average	13.9	High	51.4	Very high	30.6		
Assessment	Percentage												
Low	4.2												
Average	13.9												
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Very high	30.6												
<table border="1"> <thead> <tr> <th></th> <th>Mean</th> </tr> </thead> <tbody> <tr> <td>Total Mean</td> <td>3.56</td> </tr> <tr> <td>GX Mean</td> <td>3.60</td> </tr> <tr> <td>GBB Mean</td> <td>3.49</td> </tr> </tbody> </table>		Mean	Total Mean	3.56	GX Mean	3.60	GBB Mean	3.49					
	Mean												
Total Mean	3.56												
GX Mean	3.60												
GBB Mean	3.49												

Source: Primary data collected through the questionnaire and processed by the author.

Satisfaction with service quality

To quantify their satisfaction with service quality, tourists were questioned concerning their experience inside the destination and the main services they received here (accommodation, food, treatment and recreation).

The data show that tourists' satisfaction with the experience lived inside the destination is Good (Mean = 4.08), since 51.4% give it a value of 4 (Good), and 30.6% give it a 5 (Very good) (Table

4:4.1.). Differences between the two generations are not so noticeable and consist in the fact that, although both generations believe they are satisfied, the Mean of the GBB responders is slightly higher (4.17) than that of the GX responders (4.02).

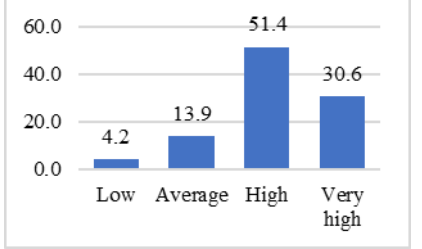
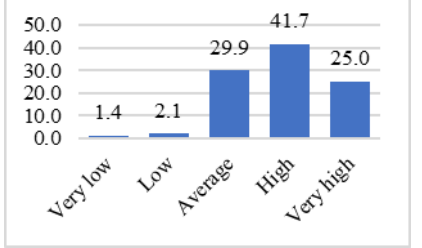
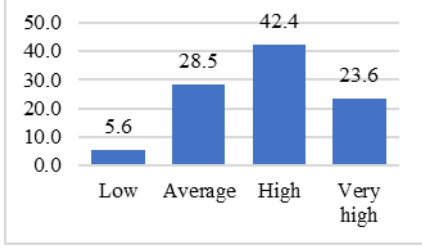
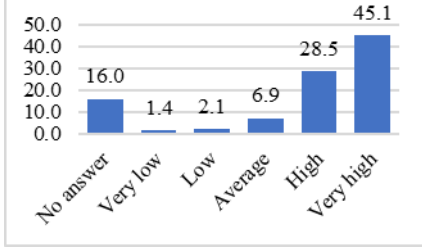
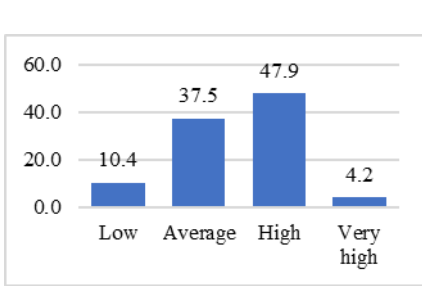
As far as accommodation services are concerned (Table 4:4.2.), data show that tourists' satisfaction is High (41.7%), Average (30%), and Very high (25%). Analysing each of the two generations, it is noted that while most GX respondents fall under the High (48%) and Average (29%) categories, GBB respondents fall under the High category in a slightly higher proportion (32%) than under the Average category (30%), but all in all the Very high category is in the lead (36%). These values can be correlated with the amounts they spend transposed into higher expectations of GXs for accommodation services, which is also confirmed by the average general value of the two generations (Mean GBB = 4, and Mean GX = 3.78).

In terms of satisfaction with public food services (table 4:4.3.), data show that satisfaction is High and Very high for 66% of respondents, which remains valid to a great extent when analysing the two generations separately. This analysis is based on Mean GX = 3.93 and Mean GBB = 3.71 and can be corroborated with the dietary requirements that the older GBB members are advised to follow for a better outcome of their treatments.

Viewed from the perspective of treatment services (Table 4:4.4.), data show that satisfaction is High and Very high for approximately 74% of tourists. As for the two generational cohorts, GBB's satisfaction is High (value 4) and Very high (value 5) in proportion of 86%, as opposed to only 65% of the GX. This is explained by the fact that within the GX sample there are members who have not benefited from treatment services or have benefited to a lesser extent, visibly shown by the Mean values of each generations, where Mean GX = 3.29 and Mean GBB = 4.19.

Tourists' satisfaction with the leisure and recreation services in the destination is Average (37.5%) and High (47.9%) (Table 4:4.5.). There is only one significant difference between the two generations, i.e. GBB members (Mean = 3.56) are more satisfied than GX members (Mean = 3.36). This can be correlated with the fact that paying for leisure and recreation activities is more specific to GX rather than to GBB given the latter's lower revenues.

Table 4. Tourist satisfaction with the quality of tourist and balneal services.

<p>4.1. On a scale from 1 to 5 (where 1 is Very low and 5 is Very high), how satisfied are you with your experience in the destination?</p> <table border="1"> <tr> <td>Total Mean</td> <td>4.08</td> </tr> <tr> <td>GX Mean</td> <td>4.02</td> </tr> <tr> <td>GBB Mean</td> <td>4.17</td> </tr> </table>	Total Mean	4.08	GX Mean	4.02	GBB Mean	4.17	 <table border="1"> <thead> <tr> <th>Satisfaction Level</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Low</td> <td>4.2</td> </tr> <tr> <td>Average</td> <td>13.9</td> </tr> <tr> <td>High</td> <td>51.4</td> </tr> <tr> <td>Very high</td> <td>30.6</td> </tr> </tbody> </table>	Satisfaction Level	Percentage	Low	4.2	Average	13.9	High	51.4	Very high	30.6				
Total Mean	4.08																				
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Satisfaction Level	Percentage																				
Low	4.2																				
Average	13.9																				
High	51.4																				
Very high	30.6																				
<p>4.2. On a scale from 1 to 5 (where 1 is Very low and 5 is Very high), how satisfied are you with accommodation services?</p> <table border="1"> <tr> <td>Total Mean</td> <td>3.87</td> </tr> <tr> <td>GX Mean</td> <td>3.78</td> </tr> <tr> <td>GBB Mean</td> <td>4.00</td> </tr> </table>	Total Mean	3.87	GX Mean	3.78	GBB Mean	4.00	 <table border="1"> <thead> <tr> <th>Satisfaction Level</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Very low</td> <td>1.4</td> </tr> <tr> <td>Low</td> <td>2.1</td> </tr> <tr> <td>Average</td> <td>29.9</td> </tr> <tr> <td>High</td> <td>41.7</td> </tr> <tr> <td>Very high</td> <td>25.0</td> </tr> </tbody> </table>	Satisfaction Level	Percentage	Very low	1.4	Low	2.1	Average	29.9	High	41.7	Very high	25.0		
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<p>4.3. On a scale from 1 to 5 (where 1 is Very low and 5 is Very high), how satisfied are you with public food services?</p> <table border="1"> <tr> <td>Total Mean</td> <td>3.84</td> </tr> <tr> <td>GX Mean</td> <td>3.93</td> </tr> <tr> <td>GBB Mean</td> <td>3.71</td> </tr> </table>	Total Mean	3.84	GX Mean	3.93	GBB Mean	3.71	 <table border="1"> <thead> <tr> <th>Satisfaction Level</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Low</td> <td>5.6</td> </tr> <tr> <td>Average</td> <td>28.5</td> </tr> <tr> <td>High</td> <td>42.4</td> </tr> <tr> <td>Very high</td> <td>23.6</td> </tr> </tbody> </table>	Satisfaction Level	Percentage	Low	5.6	Average	28.5	High	42.4	Very high	23.6				
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<p>4.4. On a scale from 1 to 5 (where 1 is Very low and 5 is Very high), how satisfied are you with treatment services?</p> <table border="1"> <tr> <td>Total Mean</td> <td>3.66</td> </tr> <tr> <td>GX Mean</td> <td>3.29</td> </tr> <tr> <td>GBB Mean</td> <td>4.19</td> </tr> </table>	Total Mean	3.66	GX Mean	3.29	GBB Mean	4.19	 <table border="1"> <thead> <tr> <th>Satisfaction Level</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>No answer</td> <td>16.0</td> </tr> <tr> <td>Very low</td> <td>1.4</td> </tr> <tr> <td>Low</td> <td>2.1</td> </tr> <tr> <td>Average</td> <td>6.9</td> </tr> <tr> <td>High</td> <td>28.5</td> </tr> <tr> <td>Very high</td> <td>45.1</td> </tr> </tbody> </table>	Satisfaction Level	Percentage	No answer	16.0	Very low	1.4	Low	2.1	Average	6.9	High	28.5	Very high	45.1
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Very high	45.1																				
<p>4.5. On a scale from 1 to 5 (where 1 is Very low and 5 is Very high), how satisfied are you with leisure and recreational services?</p> <table border="1"> <tr> <td>Total Mean</td> <td>3.46</td> </tr> <tr> <td>GX Mean</td> <td>3.36</td> </tr> <tr> <td>GBB Mean</td> <td>3.56</td> </tr> </table>	Total Mean	3.46	GX Mean	3.36	GBB Mean	3.56	 <table border="1"> <thead> <tr> <th>Satisfaction Level</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Low</td> <td>10.4</td> </tr> <tr> <td>Average</td> <td>37.5</td> </tr> <tr> <td>High</td> <td>47.9</td> </tr> <tr> <td>Very high</td> <td>4.2</td> </tr> </tbody> </table>	Satisfaction Level	Percentage	Low	10.4	Average	37.5	High	47.9	Very high	4.2				
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Source: Primary data collected through the questionnaire and processed by the author.

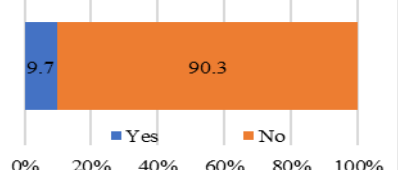
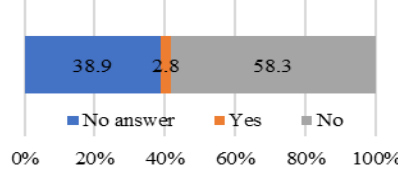
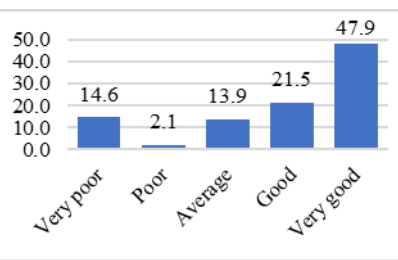
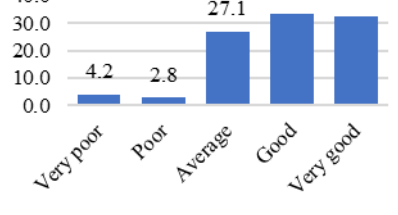
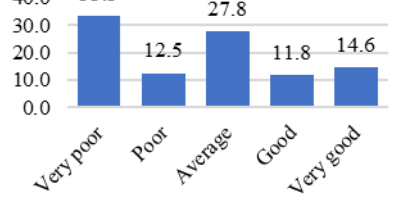
Satisfaction with local community interaction

Tourist satisfaction is also influenced by the social atmosphere of the destinations. Therefore, the possibility of a conflicting situation emerging can have a defining role in tourist satisfaction, which, in turn, may or may not lead to a follow-up visit. This is why conflict situations are an important indicator to consider when it comes to the sustainable development of a tourist destination, and therefore they must be carefully identified in order to find a solution. In this study, 9.7% of respondents (Table 5:5.1.) had conflict situations during their stay, and more exactly 15% of the GBB tourists and 6% of the GX tourists. Of these, only 2.8% (0% GX and 7% GBB) filed a report with the police or other authorities in a position to solve conflicts or problems (Table 5:5.2.). In terms of tourists' interaction with the locals (Table 5:5.3.), 48% of tourists believe that their interaction was Very good (value 5), with unnoticeable differences between the two generations (48% for GX and 47% for GBB).

In order to detect the main problems leading to tourist dissatisfaction, tourists were questioned concerning the destination's stakeholders (economic agents, residents, and local authorities). As far as economic agents are concerned, data show that approximately two thirds (66%) of responders consider that interaction with the staff of local economic agents is Good or Very good, while about 7% consider it to be Poor or Very poor (Table 5:5.4.). As for analysing each generation, it is observed that the Mean is 3.87 for both, with very slight variations between them. 37% of GX respondents believe that the interaction is rather Good (value 4), and 34% of GBB respondent believe that the interaction is Average (value 3).

Concerning tourists' interaction with local authorities (Table 5:5.5.), data show that 33.3% of respondents assign value 1 (Very poor), and 27.8% assign value 3 (Average), these characteristics also defining each generation. There are no significant differences between generations in terms of Mean either (GX Mean = 2.58 and GBB Mean = 2.68) because most of the time tourists did not come into direct contact with local authorities, although they did feel that authorities do not develop their subordinate areas in the right directions.

Table 5. Tourist satisfaction with local community interaction. Calculated in SPSS v25 and Microsoft Excel 2016.

5.1. Did you experience any conflict situation during your stay in the destination?	 <table border="1"> <thead> <tr> <th>Response</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Yes</td> <td>9.7</td> </tr> <tr> <td>No</td> <td>90.3</td> </tr> </tbody> </table>	Response	Percentage	Yes	9.7	No	90.3												
Response	Percentage																		
Yes	9.7																		
No	90.3																		
5.2. If yes, did you file a complaint with the police or the authorities?	 <table border="1"> <thead> <tr> <th>Response</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>No answer</td> <td>38.9</td> </tr> <tr> <td>Yes</td> <td>2.8</td> </tr> <tr> <td>No</td> <td>58.3</td> </tr> </tbody> </table>	Response	Percentage	No answer	38.9	Yes	2.8	No	58.3										
Response	Percentage																		
No answer	38.9																		
Yes	2.8																		
No	58.3																		
5.3. On a scale from 1 to 5 (where 1 is Very poor and 5 is Very good), how do you assess your interaction with the locals? <table border="1" data-bbox="108 902 325 1059"> <tbody> <tr> <td>Total Mean</td> <td>3.86</td> </tr> <tr> <td>GX Mean</td> <td>3.92</td> </tr> <tr> <td>GBB Mean</td> <td>3.78</td> </tr> </tbody> </table>	Total Mean	3.86	GX Mean	3.92	GBB Mean	3.78	 <table border="1"> <thead> <tr> <th>Category</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Very poor</td> <td>14.6</td> </tr> <tr> <td>Poor</td> <td>2.1</td> </tr> <tr> <td>Average</td> <td>13.9</td> </tr> <tr> <td>Good</td> <td>21.5</td> </tr> <tr> <td>Very good</td> <td>47.9</td> </tr> </tbody> </table>	Category	Percentage	Very poor	14.6	Poor	2.1	Average	13.9	Good	21.5	Very good	47.9
Total Mean	3.86																		
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Very good	47.9																		
5.4. On a scale from 1 to 5 (where 1 is Very poor and 5 is Very good), how do you assess your interaction with the staff of local economic agents? <table border="1" data-bbox="108 1305 325 1462"> <tbody> <tr> <td>Total Mean</td> <td>3.87</td> </tr> <tr> <td>GX Mean</td> <td>3.88</td> </tr> <tr> <td>GBB Mean</td> <td>3.86</td> </tr> </tbody> </table>	Total Mean	3.87	GX Mean	3.88	GBB Mean	3.86	 <table border="1"> <thead> <tr> <th>Category</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Very poor</td> <td>4.2</td> </tr> <tr> <td>Poor</td> <td>2.8</td> </tr> <tr> <td>Average</td> <td>27.1</td> </tr> <tr> <td>Good</td> <td>33.3</td> </tr> <tr> <td>Very good</td> <td>32.6</td> </tr> </tbody> </table>	Category	Percentage	Very poor	4.2	Poor	2.8	Average	27.1	Good	33.3	Very good	32.6
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Poor	2.8																		
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Good	33.3																		
Very good	32.6																		
5.5. On a scale from 1 to 5 (where 1 is Very poor and 5 is Very good), how do you assess your interaction with the local authorities? <table border="1" data-bbox="108 1686 325 1843"> <tbody> <tr> <td>Total Mean</td> <td>2.62</td> </tr> <tr> <td>GX Mean</td> <td>2.58</td> </tr> <tr> <td>GBB Mean</td> <td>2.68</td> </tr> </tbody> </table>	Total Mean	2.62	GX Mean	2.58	GBB Mean	2.68	 <table border="1"> <thead> <tr> <th>Category</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Very poor</td> <td>33.3</td> </tr> <tr> <td>Poor</td> <td>12.5</td> </tr> <tr> <td>Average</td> <td>27.8</td> </tr> <tr> <td>Good</td> <td>11.8</td> </tr> <tr> <td>Very good</td> <td>14.6</td> </tr> </tbody> </table>	Category	Percentage	Very poor	33.3	Poor	12.5	Average	27.8	Good	11.8	Very good	14.6
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Source: Primary data collected through the questionnaire and processed by the author.

Conclusions

The area has a wide tourist offer generated by five resorts with balneal resources that especially attract tourists from GX and GBB.

The location of this cluster of resorts is close to the main tourist generating areas of Romania, but access to the destination is primarily by road and secondly by rail. This draws attention to the development of a better transport management such as the modernisation of roads and railways, investments in public transport, etc.

Access to the resorts is considered good, but with gaps in investments towards modernization. There is a need for bypass routes (which partially exist to the East of Vâlcea and Călimănești Căciulata) because the main transport axes go through the centre of each resort.

Tourist services are good, which results in a predominantly high and average satisfaction, but the study shows a demand to enhance both the entertainment and the treatment offer; this is especially true for GX tourists who do not entirely find the services to satisfy their requirements at maximum level. It has also been observed that public food services should specialize on consumer categories and corroborate their offer with the various therapeutic diets recommended by the local spas and treatment centres.

Although accommodation services have received the highest value in the evaluation, close to the Good level, investments and programs/offers are needed to increase the satisfaction at maximum level. Therefore, the accommodation structures presently classified at 2-3 stars could be upgraded to 3-4 stars since the revenues have increased, but so have the tourists' demands and their culture.

The same level of satisfaction is observed in relation to the locals, the authorities, and especially the hotel staff. Development in the local community would benefit all the stakeholders, and a number of indicators would be achieved regarding the sustainable development of tourism destinations. On the one hand, the number of visitors and repeat visits would increase, and the destination would become more competitive; on the other hand, this would help raise the awareness and involvement of the local community in the tourist market. This is why we recommend creating a system for information to flow inside the local community concerning its

involvement in the life of the tourist destination; this can be achieved through the media and through workshops and trainings for tourism staff in consensus with the demands of sustainable development.

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Bibliography

1. Pricăjan A. Apele minerale si termale din România. Ed. Tehnica, Bucuresti, 1972.
2. Ielenicz M, Comănescu L. Romania - Potential turistic. Ed. Universitară, București, 2006.
3. Matei E, Vijulie I, Manea G, Tîrlă L, Dezsi S. Changes in the Romanian Carpathian tourism after the communism collapse and the domestic tourists' satisfaction. *Acta geographica Slovenica*. 2014;54(2):335-344.
4. Feru A. Bottled natural mineral waters in Romania. *Environmental Geology*. 2004;46(5):670-674.
5. Matei E, Dumitrache L, Nae M, Vijulie I, Onetiu A. Evaluating sustainability of urban development of the small towns in Romania, SGEM, Conference proceedings. 2011;3:1065-1072.
6. Matei E, Dumitrache L, Manea G, Vijulie I, Tîrlă L, Matei D. Urban sustainable development of the Romanian small towns in the local communities and authorities' perception, SGEM, Conference proceedings. 2013;3.
7. Ianos I, Peptenatu D, Pintilii RD, Draghici C. About sustainable development of the territorial emergent structures from the metropolitan area of Bucharest. *Environmental Engineering and Management Journal*. 2012;11(9):1535-1545.
8. Peptenatu D, Drăghici C, Merciu C. Characteristics of entrepreneurial profile in some emergent territorial structures in Romania. *Actual Problems of Economics*. 2012;12(138):448-458.
9. Matei E, Saghin D, Dumitrache L, Nae M. Multidimensional Approach on Sustainability of Ageing in Romanian Residential Care Centres for Elders. *Sustainability*. 2018;10(9):1-16
10. Pison G. Le vieillissement démographique sera plus rapide au Sud qu'au Nord. *Population et Sociétés*. 2009;457:1-4.
11. Pizam A, Neumann Y, Reichel A. Dimensions of tourist satisfaction with a destination area. *Annals of Tourism Research*. 1978;5:314-322.
12. Cho BH. Assessing tourist satisfaction: An exploratory study of Korean youth tourists in Australia. *Tourism Recreation*. 1998;23(1):47-54
13. Du Plessis E, Martin JC, Roma C, Slabbert E. Fuzzy logic to assess service quality at Arts festivals. *Event Management*. 2018;22:501-516.
14. Asmelash AG, Kumar S. The structural relationship between tourist satisfaction and sustainable heritage tourism development in Tigray, Ethiopia. *Heliyon*. 2019;5(3):e01335
15. Zabkar V, Brencic MM, Dmitrovic T. Modeling perceived quality, visitor satisfaction and behavioural intentions at the destination level. *Tourism Management*. 2009;31:537-546.
16. Shahrivar RB. Factors that influence tourist satisfaction. *Journal of Travel & Tourism Research*. 2012;12(1):61.
17. Milman A, Tasci, ADA. Exploring the experiential and sociodemographic drivers of satisfaction and loyalty in the theme park context. *Journal of Destinations Marketing&Management*. 2018;8:385-395.
18. Grönroos C. *Service Management and Marketing*. Lexington Books, Toronto. 1990.
19. Yuksel A, Yuksel F, Bilim Y. Destination attachment: Effects on customer satisfaction and cognitive, affective and conative loyalty. *Tourism Management*. 2010;31(2):274-284.
20. Kozak M. A critical review of approaches to measure satisfaction with tourist destinations. J.A. Mozanec, G.I. Crouch, J.R.B. Ritchie, A.G. Woodside (Eds.), *Consumer psychology of tourism, hospitality and leisure*. CABI Publishing, New York. 2001;2:303-319.
21. Pou L, Alegre J. The determinants of the probability of tourism consumption: An analysis with a family expenditure survey. 2002.
22. Truong TLH, Lenglet F, Mothe C. Destination distinctiveness: Concept, measurement, and impact on tourist satisfaction. *Journal of Destination Marketing & Management*. 2018;8: 214-231.
23. Alrawadieh Z, Prayag G, Alrawadieh Z, Alsalamdeen M. Self-identification with a heritage tourism site, visitors' engagement and destination loyalty: The mediating effects of overall

- satisfaction. *Service Industries Journal*. 2019;1-18.
24. Peterson RA, Wilson WR. Measuring customer satisfaction: Fact and artifact. *Journal of the Academy of Marketing Science*. 1992;20(1):61-71.
25. Teodorescu N, Pârgaru I, Stăncioiu FA, Matei E, Botoș A. Modelarea cercetării imaginii unei destinații turistice. *Revista Amfiteatrul Economic*. 2014;8:857-869
26. Fuchs M, Weiermair K. New perspectives of satisfaction research in tourism destinations. *Tourism Review*. 2003;58(3):6-14.
27. Liljander V, Strandvik T. The Relation between Service Quality, Satisfaction and Intentions. Kunst, P. and Lemmink, J. (Eds), *Quality Management in Services II*, Van Gorcum, Assen/Maastricht, The Netherlands, 1994.
28. Inglehart R. *The Silent Revolution: Changing Values and Political Styles Among Western Publics*. Princeton University Press, 1977.
29. Strauss W, Howe N. *Generations: The History of America's Future*. Quill William Morrow, New York, 1991.
30. Meredith GE, Schewe CD. The power of cohorts. *American Demographics*. 1994;16(12): 22-31.
31. Egri C, Ralsston D. Generation cohorts and personal values: a comparison of China and the United States. *Organization Science*. 2004;15:210-220.
32. Hung K, Gu F, Yim C. A social institutional approach to identifying generation cohorts in China with a comparison with American consumers. *Journal of International Business Studies*. 2007;38:836-853.
33. Parment A. Generation Y vs. Baby Boomers: shopping behavior, buyer involvement and implications for retailing. *Journal of Retailing and Consumer Services*. 2013;20(2):189-199.
34. De Pelsmacker P, Geuens M, Van den Bergh J. *Marketingcommunicatie*. Pearson Education Benelux, Amsterdam, 2005.
35. Meredith G, Schewe CD, Karlovich J. *Defining Markets, Defining Moments: America's Seven Generational Cohorts, Their Shared Experiences, and Why businesses Should Care*. John Wiley & Sons, New York, 2002.
36. United Nations World Tourism Organisation and World Youth Student & Educational Travel Confederation (UNWTO and WYSE Travel Confederation) "Affiliate members global reports, volume thirteen – the power of youth travel", 2018.
37. Gardiner S, Grace D, King C. The Generation Effect: The Future of Domestic Tourism in Australia. *Journal of Travel Research*. 2014;53:705-720.
38. Prayag G, Del Chiappa G. Hotel disintermediation in France: perceptions of students from Generation Y. *Anatolia*. 2014;25:417-430.
39. Gurău C. A life-stage analysis of consumer loyalty profile: comparing Generation X and Millennial consumers. *Journal of international consumer marketing*. 2012;29(2):103-113
40. Jackson V, Stoel L, Brantley A. Mall attributes and shopping value: differences by gender and generational cohort. *Journal of Retailing and Consumer Services*. 2011;18(1):1-9.
41. Littrell MA, Jin MaY, Halepete J. Generation X, baby boomers, and swing: Marketing fair trade apparel. *Journal of Fashion Marketing and Management*. 2005;9(4):407-419.
42. Holbrook MB, Schindler RM. Some exploratory findings on the development of musical tastes. *Journal of Consumer Research*. 1989;16:119-124.
43. Schuman H, Scott J. Generations and collective memories. *American Sociological Review*. 1989;54:359-381.
44. Holbrook MB, Schindler RM. Age, sex and attitude toward the past as predictors of consumers' aesthetic tastes for cultural products. *Journal of Marketing Research*. 1994;31:412-442.
45. Parment A. *Generation Y in Consumer and Labour Markets*. Routledge, New York, 2011.
46. Pricăjan A. *Substanțele minerale terapeutice din România*. Ed. Științifică și Enciclopedică, București, 1985.
47. Țișcovschi AA. *Balneoclimatologie*. Ed. Credis, București, 2005.
48. Munteanu C. *Ape minerale terapeutice*. Ed. Balneară, București, 2013.
49. Antics M, Rosca M. Geothermal development in Romania. *Geothermics*. 2003;32(6): 361-370.
50. INS. *Capacitatea turistică din Romania pe localități în anul 2019*.

Remission of progressive multifocal leukoencephalopathy in HIV- positive patient after multidisciplinary rehabilitation: a case report

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Abstract

Introduction: One of the most common neurologic disease in Acquired Immunodeficiency Syndrome (AIDS) caused by Human Immunodeficiency Virus (HIV) is represented by progressive multifocal leukoencephalopathy (PML), being caused by John Cunningham (JC) polyoma virus.

Case presentation: We report a case of a 27 years old women, HIV-positive since childhood, under specific antiretroviral therapy with good adherence to it in that period but starting with adolescence adherence to highly active antiretroviral therapy (HAART) decreased. In this context her HIV viral load increased to a 690.000 copies/ml, and CD4 collapsed at 57 cells/mm³. She presented in our clinic with ataxic left hemiparesis, truncal ataxia and left hemi-hypoesthesia. Cerebrospinal fluid (CSF) showed a slightly pleocytosis and polymerase chain reaction performed from CSF diagnosed John Cunningham (JC) virus. Once diagnosis established, we reinitiated HAART, but some neurologic disorders persisted like difficulty of the left upper member, having the modified Rankin scale (mRS) of 5. The patient started a multidisciplinary rehabilitation (MDR) treatment, specifically adapted. It consisted of 4 sessions of neuromotor treatments, 20 sessions of massages, and 12 sessions of occupational therapy. According to MDR, the patient improved the ataxic walking, without support, presenting an improvement mRS of 3.

Conclusions: AIDS patients with PML could require a prolonged MDR treatment for neurological disorders and rehabilitation treatment promptly should be applied when such diagnosis is suspected.

Key words: *progressive multifocal leukoencephalopathy, human immunodeficiency virus, neurological disorder, multidisciplinary rehabilitation,*

Introduction

Known as an opportunistic disorder, progressive multifocal leukoencephalopathy (PML) is usually caused by John Cunningham (JC) polyomavirus. First PML case mentioned in the literature was for a patient with chronic lymphocytic leukemia (1). Nowadays, considering the plethora of different viruses like Human Immunodeficiency Virus (HIV), the PML incidence has raised, AIDS patients accounted for about 85% of PML (2). AIDS represent the late stage of HIV infection which occurs when immune system is damaged by the virus and immunity, expressed by CD4 count, decreased less than 200 cells/mm³.

Generally, the clinical symptomatology of patients with PML is very poor, which will lead to death in approximately 6 months from onset of symptoms. Interestingly, only a rate between 7 till 9% of PML patients showed a higher survival rate, without any etiologic therapy (3,4).

The suspicion of PML arises in AIDS patients with a low CD4 cell count, considering the clinical manifestations such as insidious onset, with focal and behavior deterioration. Symptoms noticed in HIV-positive patients with PML are motor weakness, especially hemiparesis, visual deficits such as hemianopsia, diplopia, mental changes, aphasia, limb apraxia, ataxia and so on (4-6).

Regarding the treatment options, multidisciplinary rehabilitation (MDR) should be positively seen by the physician in PML patients in order to counteract the clinical effects of many brain injury, like stroke, spinal cord injury, respiratory diseases or rheumatologic disorders (7-12). In accordance with the same aim, the National Institutes of Health retrospective study, evaluated HIV-positive patients which were further analysed by the different rehabilitation therapy point of view (13,14). In this regard, although neurological abilities were

improved at the end of this study, some degree of disability still remains and many neurological regressions were reported (15-19).

The area from central nervous system most affected by PML is parieto-occipital white matter. More profound, white matter showed single or multiple lesions without mass effect and magnetic resonance imaging (MRI) sustain the hypointense on T1-weighted images and hyperintense on T2-weighted together with fluid-attenuated inversion recovery (FLAIR) sequences (20).

CSF is usually normal, but sometimes pleocytosis less than 20/ μ L can occur and protein levels may be slightly elevated (20).

Because there is no specific anti-JC treatment, some patients have experienced spontaneous improvements with highly active anti-retroviral therapy (HAART) (4-6). HAART is a very potent regimen for HIV-AIDS patient which initially included three classes of medication: protease inhibitors associated with nucleoside reversetranscriptase inhibitory and nonnucleoside reversetranscriptase inhibitors.

Therefore, the dynamics of neural plasticity in HIV-positive patients with PML are still unknown. The present case report describes the positive effect of MDR therapy in a HIV-positive patient with PML.

Case presentation

We report a case of a 27 years old women, diagnosed with HIV at age of 3, with different diseases in her childhood (i.e. extrapulmonary TB, recurrent bacterial pneumonia, recurrent parotiditis, chronic diarrhea, chronic hepatitis B, and oral candidiasis). After her HIV diagnosis, the patient was under specific antiretroviral therapy, with a good adhesion in childhood but with decreased adherence to HAART (i.e. lopinavir/ritonavir in associating with zidovudine/lamivudine) in adolescence.

In evolution her HIV viral load increased to a 690.000 copies/ml, and CD4 collapsed at 57 cells/mmc. At clinical and neurologic examination, the patient was awake but drowsy and oriented to time, place, and person. In this context she was hospitalized conscious, having coordination normal on the right side, whereas some ataxia was recorded on the left, with cerebellar dysarthria, diplopia at distance, ataxic left hemiparesis, truncal ataxia, and left hemihypoesthesia. The patient was further bedridden. Cerebrospinal fluid (CSF) examination evidenced a slightly pleocytosis (10 cells/mmc),

with no other changes. Polymerase chain reaction (PCR) performed from CSF evidenced presence of JC virus. Other etiology like Toxoplasma, Cryptococcus, Mycobacterium tuberculosis, gram positive or negative bacteria and fungi were excluded by specific CSF examination.

Cranio-cerebral MRI examination performed before and after administration of intravenous contrast showed confluent areas of hyperintense signal T2-FLAIR/hypointense T1, without restriction of diffusion, or contrast enhanced, symmetric in the periventricular white matter with subcortical bilateral extension. Lesions with the same characteristics were described in the cerebellar hemispheres, with a greater extension in the left cerebellar hemisphere. It also showed an inactive communicating hydrocephalus, probably induced by the aqueductal stenosis caused by the adherences (Figure 1). In this case clinical manifestation, biological and imaging changes sustained the PML diagnosis.



Fig. 1. Confluent areas of hyperintense signal T2-FLAIR/hypointense T1, without restriction of diffusion, symmetric in the periventricular white matter with subcortical bilateral extension.

After the established diagnosis, a symptomatic treatment was introduced and further reinitiated HAART (i.e. darunavir/ritonavir, raltegravir, associated with zidovudine/ziagen), but some neurologic disorders persisted like orthostatism and walking with great difficulty, supporting by another person, coordination and balance disorders, showing partial recovery in speech disorders and using with

difficulty the left upper member. The degree of disability was measured using the modified Rankin scale (mRS) in which after 5-years of follow-up, the patient presented a mRS of 3 (moderate disability; requires some help, but able to walk unassisted-according with mRS) from initially 5 (severe disability; requires constant nursing care and attention, bedridden, incontinent, according to mRS). The mRS present a score from 0 to 6 in which 0 are patients with no symptoms and 6 were dead persons (20).

In this context, the patient started a MDR treatment according to a neurologist and specialist in balneo-rehabilitation. The treatment was applied 5 years, 4 days/week, specifically adapted having the aims: muscle-ligament trophicization, recovery of the coordination of the left upper member function in order to increase muscle strength. Moreover, the program also included 4 sessions of neuromotor treatments, 20 sessions of massages, and 12 sessions of occupational therapy. The program ensures the more passive mobilization of the fingers, increasing the patient's ability in grasping in a functional position, according to special guiding techniques.

A control cerebral MRI was performed after 4 years which shows the sequelae of the lesions previously described, the same hydrocephalus, but with an evident cortical atrophy (Figure 2). Images correlated with the physical improvement but also with the cognitive decline and behavior disturbances. The patient has been also showed an increased CD4 to 430/ mmc and became undetectable 7 months after HAART resumption.

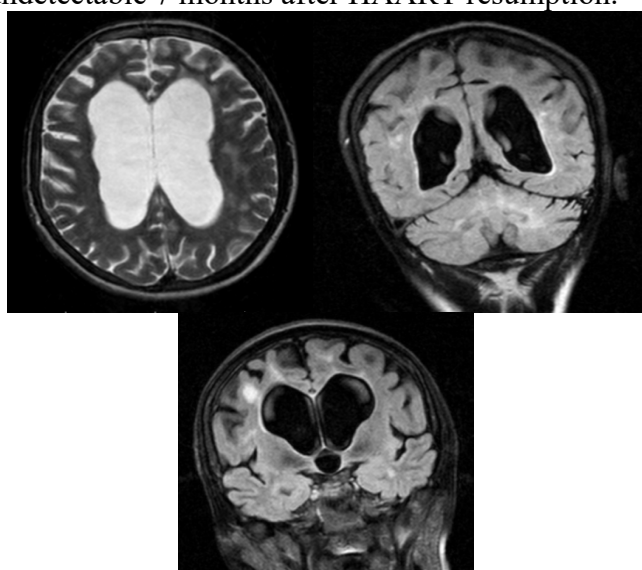


Fig. 2. MRI imaging of diffusion coronal sequence. The sequelae of the lesions previously described, presenting an evident cortical atrophy.

The patient improved the ataxic walking, performing short distance walking, without support, with an improved mRS of 3, without any severe sequelae.

Discussion

Worldwide epidemiology and morbidity by different infectious diseases changed over the last years. In some diseases like boutoneuse fever, shigella or salmonella, evolution is related with environmental factors (21-24), in other diseases evolution is related with outbreaks that can appear in absence of vaccination (25–28). In other diseases like TB or HIV evolution and mortality changed over the years according with early or late diagnosis and also with availability and adherence of specific treatment (29-34).

If, at the onset of the HIV pandemic, both physicians and patients were concerned only with prolonged survival, as this was achieved through complex treatment and specialized care, new clinical and therapeutic challenges are emerging for these patients. Currently, the medical approach of HIV-positive patients has changed. The care only by the infectious doctor has been switched to multidisciplinary approach, according with health problems of these patients. In our case neurologic and balneo-rehabilitation support were essential for treatment strategy.

PML showed to be a disease of a white matter cause by JC virus in which diagnosis can be made by using brain imaging investigation and even biopsy (35,36). Although there is no anti-JC treatment until present, in HIV positive patients have been showed an improvement along HAART. In HIV, before HAART survival for PML at one year was only 10%, but in the last years survival is at least 50% (20,37,38). The new biologic therapy (i.e. rituximab, efalizumab or natalizumab), for chronic diseases like rheumatoid arthritis, psoriasis, multiple sclerosis or Crohn's disease contribute to appearance of PML in other diseases, non-HIV related (39). Although survival increased, long term neurological sequelae in PML patients were not very well known. As long as PML is not a curable disease, by an specific treatment, persistence of immune restoration is essential for survival of these patients. Many patients from literature achieving this goal maintain this status and no reactivation or relapses were noticed (40, 41).

In developing rehabilitation strategies for PML in HIV-positive patients, both caregivers and professionals must take into consideration their

external support (42). The attitude and rehabilitation program should be constructed similar with those for patients with cancer, or multiple sclerosis (43,44).

Our study sustain the introduction of MDR program in HIV-positive patients, especially when is complicated by neurological disorders such as PML. At the end of the treatment, our patient showed better performances at left upper member, despite the ataxic left hemiparesis deficits. We can further admit that clinical PML symptoms were ameliorated by physical rehabilitation, although the treatment was applied after few months of symptoms appearance. The increased activation could be recorded by neurological abilities or hydro-kinetotherapy (7), along with climatic factors among the effects of balneal cures which influence the quality of life of patients (8, 11), admitting the idea of the consultants' professionalism and experience in the management of changes specific to health systems (9).

In this context, we only can assume that MDR might be used by routine in the practice of HIV-positive patients like in different other disability disorders. Although the number of patients remains limited, physical exercises have been showed to contribute an improving aerobic capacity, along with immune restoration in HIV patients (45,46).

Therefore, in patients with HIV and PML the role of physical rehabilitation could play an important role in achieving their health along with integration in their communities.

Conclusions

Although our study showed that MDR treatment can be highly encouraging in HIV-positive patient with PML, additional studies are demanded in order to achieve this aim. Therefore, larger studies should be acquired in order to identify potential candidates for achieving rehabilitation outcome.

Author contributions.

The authors contributed equally to the work.

Declaration of conflict of interests.

There is no conflict of interest for any of the authors regarding this paper.

Informed consent.

An informed consent was obtained from the patient presented in this case report

References

1. Astrom KE, Mancall EL, Richardson EP Jr. Progressive multifocal leuko-encephalopathy: a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. *Brain*. 1958; 81: 93-111.
2. Tyler, KL. The uninvited guest: JC virus infection of neurons in PML. *Neurology*. 2003; 61:734-5.
3. Berger JR. Progressive multifocal leukoencephalopathy. *Curr Treat Options Neurol*. 2000; 2: 361-368.
4. White MK, Khalili K. Pathogenesis of progressive multifocal leukoencephalopathy – revisited. *J Infectious Dis*. 2011; 203(5): 578-586.
5. Cambrea SC, Pascu C, Rugina S, Iancu AM. Evolution of progressive multifocal leukoencephalopathy in HIV-infected patients. Two case reports. *Archives of the Balkan Medical Union*. 2017; 52(1): 89-94.
6. Major EO, Amemiya K, Tornatore CS, Houff Sa, Berger JR. Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JC-Virus induced demyelinating disease of the human brain. *Clin Microbiol Rev*. 1992; 5(1): 49-73.
7. Lupu AA, Ionescu EV, Iliescu MG, Almasan RE, Oprea C, Ion I, Iliescu DM. Effect of Techirghiol Specific Climate Factors on the Patients Quality of Life with Degenerative Lumbar Pain. *J Environ Prot Ecol*. 2018; 19(4): 1857- 1863.
8. Iliescu MG, Lupu AA, Ionescu EV, Tica I. Almasan RE, Oprea C, Iliescu DM. Water, Nature, Techirghiol – Long -term therapeutic benefits for patients with degenerative low back pain. *J Environ Prot Ecol*. 2019; 20 (3): 1505 - 1516.
9. Tucmeanu AI, Popescu DM, Ionescu EV, Almasan RE, Oprea C, Mociu A, Iliescu MG, Iliescu DM. Management of consultancy for organizational change in health from the manager perspective. *J Environ Prot Ecol*. 2017; 18 (3): 1238-1248.
10. Stanciu LE, Pascu EI, Ionescu EV, Circo E, Oprea C, Iliescu MG. Anti-Ageing potential of Techirghiol mud therapy through the modulation of pituitary adrenal axis activity. *J Environ Prot Ecol*. 2017; 18 (2): 728-736.

11. Oprea C, Ionescu EV, Iliescu MG, Almasan RE, Calota N, Iliescu DM. Monitoring and evaluation of patients satisfaction in medical units that use natural factors for treatment. *J Environ Prot Ecol*. 2019; 20(1): 447-452.
12. Alexescu TG, Maierian A, Ciumarnean L, Budin C, Dogaru G, Todea DA. Rehabilitation therapies in stable chronic obstructive pulmonary disease. *Balneo Research Journal*. 2019;10(1):37-44.
13. O'Connell PG, Levinson SF. Experience with rehabilitation in the acquired immunodeficiency syndrome. *Am J Phys Med Rehabil*. 1991; 70: 195-200.
14. O'Dell MW, Hubert HB, Lubeck DP et al. Physical disability in a cohort of persons with AIDS: data from the Time-Oriented Health Outcome study. *AIDS*. 1996; 10: 667-673.
15. Crystal S, Sambamoortg U. Functional impairment trajectories among persons with HIV disease: a hierarchical lineal models approach. *Health Serv Res*. 1996; 31: 469-488.
16. Fleishman JA, Crystal S. Functional status transitions and survival in HIV disease evidence from the AIDS Costs and Services Utilization Survey. *Med Care*. 1998; 36: 533-543.
17. Missmer SA, Spiegelman D, Gobach SL. Et al. Predictors of change in the functional status of children with human immunodeficiency virus infection. *Pediatrics*. 2000; 106: E24.
18. Wilson IB, Cleary PD. Clinical predictors of functioning in persons with acquired immunodeficiency syndrome. *Med Care*. 1996; 34: 610-623.
19. Wilson IB, Cleary PD. Clinical predictors of declines in physical functioning in persons with AIDS: results of a longitudinal study. *J Acquir Immune Defic Syndr*. 1997; 16: 343-349.
20. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009; 58 (RR-4):1-207.
21. Hatefi D, Hirshman B, Leys D, Lejeune J, Marshall L, Carter BS, et al. Hemisphericectomy in the management of malignant middle cerebral artery infarction: Lessons from randomized, controlled trials. *Surg Neurol Int*. 2014; 5: 72.
22. Cambrea SC, Petcu LC, Iliescu DM: Relations of Environmental Factors and Evolution of Boutonneuse Fever in the County of Constanta – Romania. *J Environ Prot Ecol*. 2018; 19(2): 914 - 922.
23. Cambrea SC, Petcu LC, Mihai CM, Hangan TL, Iliescu DM. Influence of environmental factors about evolution of Shigellosis in Constanta County of Romania. *J Environ Prot Ecol*. 2019; 20(2): 986-994.
24. Halichidis S, Balasa AL, Ionescu EV, Iliescu MG, Cambrea SC, Petcu LC, Mihai CM: Evolution of Salmonellosis in Constanta area in correlation with environmental factors. *J Environ Prot Ecol*. 2019; 20 (3) :1496 - 1504.
25. Cambrea SC, Ilie MM, Carp DS, Dumea E, Halichidis S, Petcu LC. Correlation of an Acute Viral Hepatitis Type A Outbreak in the Constanta County with Environmental Risk Factors. *J Environ Prot Ecol*. 2014, **15** (1): 340 - 347.
26. Cambrea SC, Arghir OC, Rascu A, Petcu CL: Biochemical Features of an Acute Viral Hepatitis A Outbreak. *Revista de Chimie*. 2018, **69** (6): 1447-1450.
27. Diaconu S., Cambrea SC, Petcu LC, Rugina S: Aspects of Nosocomial Gastroenteritis with Rotavirus in Children Hospitalized in Constanta – Romania. *Acta Medica Mediterranea*. 2017;**33** (Special Issue 2): 1289 - 1293.
28. Cambrea SC, Halichidis S, Mihai CM, Carp DS, Stoicescu RM, Arghir OC: Environmental risk factors for influenza AH1N1 among children in south east Romania. *J Environ Prot Ecol*. 2013;15 (3): 1132 - 1139.
29. Arghir OC, Dantes E, Otelea M, Rascu A, Borgazi E, Cambrea SC. Eight year survey of tuberculosis in-hospital mortality in the South Eastern part of Romania, *Romanian Journal of Legal Medicine*. 2018;26 (2): 183-187.
30. Cambrea SC, Popescu GG, Resul G, Petcu LC. The spectrum of infectious diseases hospital mortality by HIV status. *Acta Medica Mediterranea*. 2019; 35(6): 3517-3522.
31. Arghir OC, Pereira PMA, Rascu A, Dantes E, Borgazi E, Iliescu DM, Otelea RM, Cambrea SC: The impact of Migrant Tuberculosis on the Chimioresistance Pattern of Antituberculosis Drugs in a Low Burden Tuberculosis European Country. *Farmacia*. 2018, **66** (3): 537-540.
32. Cojocaru V, Dantes E, Novac MG, Ionescu AM, Ianosi ES, Rush E, Nemes RM: The value of

- Adenosine Deaminase Enzyme level in the positive diagnosis of tuberculous pleural effusion. *Revista de Chimie*.2018; 69(12): 3688-3691.
33. Fildan A, Toma C, Tofolean D, Arghir O, Dantes E, Davila C: TB risk in patients with biological therapy for Psoriasis. 2016, *CHEST* 150(4) Supplement:S: 201A-201A
 34. Dantes E, Tofolean DE, Fildan AP, Craciun L, Dumea E, Tofolean IT, Mazilu L: Lethal disseminated tuberculosis in patients under biological treatment – two clinical cases and short review. *Journal of International Medical Research*.,2018; 46(7):2961 – 2969.
 35. Skiest DJ. Focal neurological disease in patients with acquired immunodeficiency syndrome. *Clin Infect Dis*. 2002; 34: 103-115.
 36. von Einsiedel RW, Fife TD, Aksanit AJ et al. Progressive multifocal leukoencephalopathy in AIDS: a clinicopathological study and review of the literature. *J Neurol*. 1993; 240: 391-406.
 37. Falco V, Olmo M, del Saz SV, Guelar A, Santos JR, Gutierrez M, et al. Influence of HAART on the clinical course of HIV-1-infected patients with progressive multifocal leukoencephalopathy: results of an observational multicenter study. *J Acquir Immune Defic Syndr*. 2008; 49(1): 26-31.
 38. Cambrea SC, Petcu LC. Failure under cART including Lopinavir/ritonavir in adherent adolescents and young adults from Constanta. *Acta Medica Mediterranea*. 2015; 31 (3): 673 - 680.
 39. Dalhaus S, Hoepner R, Chan A, Kleiter I, Adams O, Lukas C, et al. Disease course and outcome of 15 monocentrically treated natalizumab-associated progressive multifocal leukoencephalopathy patients. *J Neurol Neurosurg Psychiatry*. 2013; 84: 1068-1074. doi:10.1136/jnnp-2013-304897.
 40. Lima MA, Bernal-Cano F, Clifford DB, Gandhi R, Koralnik IJ. Clinical outcome of long-term survivors of progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry*. 2010; 81(11): 1288-1291.
 41. Giudici B, Vaz B, Bossolasco S, Casari S, Brambilla AM, Luke W, Lazzarin A, Weber T, Cinque P. Highly active antiretroviral therapy and progressive multifocal leukoencephalopathy: Effects on Cerebrospinal fluid markers of JC virus replication and immune response. *Clinical Infectious Diseases*. 2000; 30(1): 95-99.
 42. Goodkin K, Wilkie FL, Coucha M, et al. Subtle neuropsychological impairment and minor cognitive-motor disorder in HIV-1 infection: neuroradiological, neurophysiological neuroimmunological, and virological correlates. *Neuroimaging Clin N An*. 1997; 7: 561-579.
 43. Ferraro SJ, Diagnosis and treatment of HIV-associated neurocognitive disorders. *New Directions for Mental Health Services*. 2000; 87: 25-35.
 44. Budin CE, Alexescu TG, Bordea IR, Gherginescu MC, Aluas M, Grigorescu BC, Biro L, Buzoianu AD, Nemes RM, Tantu MM, Todea DA. Nicotine Addiction Objective in Educational Programs for Smoking Prevention in Young People. *REV.CHIM.(Bucharest)*.2019; 70(6): 2168- 72
 45. Gluck T, Degenhardt E, Scholmerich J, et al. Autonomic neuropathy in patients with HIV: course, impact of disease stage, and medication. *Clin Auton Res*. 2000; 10: 17-22.
 46. Simpson DM. Neuromuscular complications of human immunodeficiency virus infection. *Semin Neurol*.1992;12:34-42.

Neuromuscular electrostimulation as an adjuvant therapy to pulmonary rehabilitation programs in chronic obstructive pulmonary disease

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Abstract

Introduction. Chronic obstructive pulmonary disease (COPD) is commonly associated with a vicious circle of sedentary lifestyle - deconditioning - muscular dysfunction. High-frequency neuromuscular electrostimulation has demonstrated beneficial effects among subjects with muscle weakness. This study aimed to evaluate the benefits of merging pulmonary rehabilitation program (PRP) with neuromuscular electrostimulation in patients with very severe COPD. **Material and methods.** The study included 38 males with clinically stable COPD, who were divided in 2 groups: group A-19 patients that underwent a PRP of 5 sessions/week for 4 weeks and group B-19 patients that underwent intercostal and lower extremity muscle electrostimulation (5 sessions/week for 4 weeks, 60 min /session) in association with the same type of PRP. Saint Georges's Respiratory Questionnaire (SGRQ), Modified Medical Research Council (mMRC) dyspnea scale, spirometry, maximal inspiratory pressure (P_Imax) and maximal expiratory pressure (P_Emax), six minutes walking test (6MWT) and bio-electrical impedance were examined before and after the intervention. **Results.** Electrostimulation applied in group B increased muscle mass ($50.15 \pm 0.61\text{kg}$ vs $53.97 \pm 0.87\text{kg}$, $p < 0.001$), P_Emax (5.41 ± 0.25 vs post 6.79 ± 0.22 , $p < 0.0003$) and improved mMRC score (2.68 ± 0.15 vs 2.10 ± 0.15 , $p < 0.0109$), 6MWT ($369.6 \pm 10.77\text{m}$ vs post: $445.6 \pm 6.03\text{m}$) and SGRQ (61.32 ± 1.83 vs. 44.95 ± 1.94 , $p < 0.0001$). In group B only SGRQ score (55.05 ± 1.32 vs. 50.05 ± 1.51 , $p = 0.018$) was improved after PRP. **Conclusion.** A protocol which combines PRP with neuromuscular electrical stimulation in patients with very severe forms of COPD, has grater beneficial effect on dyspnoea, exercise tolerance, muscle mass toning and quality of life, compared with PRP alone.

Key words: COPD, muscular dysfunction, neuromuscular electrostimulation, pulmonary rehabilitation program,

Introduction

In the last century, due to medical innovations, we are facing a decrease in the morbidity and mortality caused by respiratory infections like pneumonia or tuberculosis and a rise in life expectancy (1). On the other hand, in developed countries this phenomenon has led to an increased prevalence of age-related chronic respiratory diseases (2-3): COPD, asthma, emphysema, lung cancer, obstructive sleep apnoea, idiopathic pulmonary fibrosis etc. which represent a significant burden for the health care services (4-10). COPD is a disorder characterized by chronic incomplete reversible airway limitation (11-12). During the chronic evolution of this disease, patients develop dyspnoea, fatigue, limited exercise capacity, symptoms that will lead to a vicious circle of sedentary lifestyle - deconditioning - muscular dysfunction (13,14) Muscle weakness is independent of airflow obstruction severity of and is a significant risk factor for falls in this population (15-16).

International guidelines recommend that patients with COPD should be included in PRP, in order to slow down the respiratory decline and to prevent muscle loss (11,12). These programs have been designed to optimize physical function, social performance and autonomy of patients with chronic respiratory diseases.

High-frequency neuromuscular electrostimulation has demonstrated beneficial effects among subjects with muscle weakness, especially in quadriceps muscle (17). It can be used alone or in association with other rehabilitation techniques.

Study aim

The objective of this study was to investigate if the association of neuromuscular electrostimulation to a pulmonary rehabilitation program will have greater benefits on muscle toning and exercise tolerance, then PRP alone, in patients with very severe COPD.

Materials and methods. Study design

Before participating in the study, patients signed an informed consent form. The ethical board of the “Victor Babes” Hospital for Infectious and Lung Diseases, Timisoara, Romania approved the study.

Thirty-eight males with clinically stable COPD participated in this prospective study. All subjects were diagnosed with very severe COPD according to GOLD/ATS criteria. The inclusion criteria were age of 40–75 years, eligibility to participate in exercise training, no acute exacerbations within the 3 month and no change in respiratory medication within the past 4 weeks. Exclusion criteria: orthopedic impairment, neuromuscular disorders, recent stroke or heart attack, advanced heart failure, aortic stenosis or pulmonary artery pressure >50 mmHg.

Subjects were divided in two study groups: Group A included 19 patients that underwent a PRP of 5 sessions/week for 4 weeks and Group B included 19 patients that underwent intercostal and lower extremity muscle electrostimulation (5 sessions/week for 4 weeks, 60 min per session) in association with the same type of PRP.

The PRP consisted in stretching exercises and endurance training: 60 min of treadmill and stationary bicycle, at 80% of each patient’s maximal heart rate. The PRP also included quadriceps resistance training and breathing exercises. The neuromuscular electrostimulation was performed using a Cefar Activ device. A prefigured software which combined aerobic exercises, strength exercises and body toning for the quadriceps and for intercostal muscles, was used. The procedure consisted in applying the electrodes to proximal and distal endpoints of quadriceps and intercostal muscle body. A commutative, symmetric current of 20-35 Hz frequency and 15-90 mA intensity, was used for 60 minutes per day, 5 days/week. The intensity was enlarged until a strong muscle contraction was visible or to the maximum toleration level.

At the beginning of the study, all subjects demographic information, smoking and medical history, physical examination were recorded. They completed SGRQ questionnaire, performed spirometry (Vitalograph ALPHA), P_{Imax} and P_{Emax}, 6MWT test. The body composition was analysed via bioimpedance (BFAT Model IOI 353). The body mass index (BMI), muscle mass (kg) and fat-free mass (%) were recorded. Dyspnoea was evaluated using the mMRC dyspnoea scale. The same investigations were performed at the end of the 3 weeks PRP.

The SGRQ as used to assess the health-related quality of life. The SGRQ includes 50 items. Total score is ranging from 0 to 100. A zero score indicates no impairment of health-related quality of life (18).

Respiratory muscle strength can be evaluated by measuring P_{Imax} and P_{Emax}. The P_{Imax} correlates with the diaphragm and other inspiratory muscles strength, while P_{Emax} correlates with abdominal muscles and expiratory muscles strength.

The 6MWT is used to assess aerobic capacity and endurance. The distance covered in 6 minutes reflects the changes in performance capacity after a pulmonary rehabilitation program.

Statistical analysis

Data were collected using GraphPad Prism 7. The results are presented as mean \pm standard deviation for continuous variables with Gaussian distribution, median (interquartile range) for continuous variables without Gaussian distribution, and percentage for categorical variables. A P value of <0.05 was considered statistically significant.

Results

The baseline characteristics of the studied groups are listed in table 1. Subjects from group B were older then those from group A (Table 2,3).

No statistically significant differences were noted in the spirometric values between the studied groups both pre- and post-intervention.

Table 1. Baseline characteristics of the studied groups			
	Group A	Group B	P
Age	57.53 \pm 1.49	63.11 \pm 1.72	0.019*
FVC (L)	2.46 \pm 0.14	2.22 \pm 0.12	0.221
FVC (%)	62.05 \pm 3.34	60.05 \pm 3.55	0.684
FEV1 (L)	1.02 \pm 0.06	0.92 \pm 0.05	0.260
FEV1 (%)	32.89 \pm 2.51	32.11 \pm 2.39	0.821
FEV1/FVC	44.89 \pm 3.26	46.26 \pm 2.77	0.751
BMI	27.21 \pm 0.69	27.42 \pm 1.07	0.870

In group B, P_{Emax} has significantly increased after the program (P_{Emax} pre 5.41 \pm 0.25 vs post 6.79 \pm 0.22, p<0.0003). There was no significant effect of pulmonary rehab or pulmonary rehab combined with electrostimulation on P_{Imax}. (Table 3).

Table 2. Pre-rehabilitation and post-rehabilitation characteristics for Group A			
	PRE (Mean \pm SEM)	POST (Mean \pm SEM)	P
PIMAX	7.12 \pm 0.34	7.35 \pm 0.33	0.647
PEMAX	5.66 \pm 0.16	5.78 \pm 0.41	0.774
mMRC	2.26 \pm 0.12	2.10 \pm 0.16	0.463
MM	51.21 \pm 0.89	51.65 \pm 0.99	0.742
FFM	33.16 \pm 0.88	34.18 \pm 0.73	0.382
6MWD	359.8 \pm 15.6	381.6 \pm 16.43	0.345
SGRQ	55.05 \pm 1.32	50.05 \pm 1.51	0.018*

Group B registered a decreased dyspnoea after the intervention (mMRC pre 2.68 ± 0.15 vs mMRC post 2.10 ± 0.15 , $p < 0.0109$) (Table 3) while in group A showed no statistically significant improvement.

Table 3. Pre-intervention and post-intervention characteristics for Group B

	PRE (Mean \pm SEM)	POST (Mean \pm SEM)	P
PIMAX	7.09 ± 0.29	7.89 ± 0.34	0.0891
PEMAX	5.41 ± 0.25	6.79 ± 0.22	0.0003*
mMRC	2.68 ± 0.15	2.10 ± 0.15	0.0109*
MM	50.15 ± 0.61	53.97 ± 0.87	0.001*
FFM	33.04 ± 0.65	34.41 ± 0.92	0.241
6MWD	369.6 ± 10.77	445.6 ± 6.03	$< 0.0001^*$
SGRQ	61.32 ± 1.83	44.95 ± 1.94	$< 0.0001^*$

The body composition changed in the electrostimulation group (Table 3). Muscle mass (MM) increased only in group B (pre: 50.15 ± 0.61 kg vs post: 53.97 ± 0.87 kg, $p < 0.001$) while in group A (pre: 51.21 ± 0.89 kg vs post 51.65 ± 0.99 kg, $p = 0.742$) no significant improvements were noticed.

Pre-rehabilitation, the 6MWT results did not differ significantly between the studied groups. Post-rehabilitation, a significant increase of distance walked in the 6MWT was observed only in group B (pre: 369.6 ± 10.77 m vs post: 445.6 ± 6.03 m) (Figure 1). The increase in the distance walked was 76 m for group B and only 21.8 m for group A. Patients from both groups reported an improvement of health-related quality of life (group A, SGRQ pre 55.05 ± 1.32 vs. SGRQ post 50.05 ± 1.51 , $p = 0.018$ and group B SGRQ pre 61.32 ± 1.83 vs. SGRQ post 44.95 ± 1.94 , $p < 0.0001$) (Figure 2)

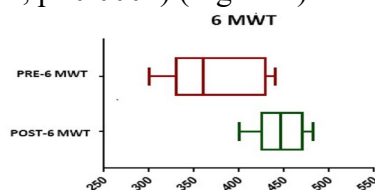


Fig.1. Pre-rehabilitation, the 6MWT results did not differ significantly between the studied groups. Post-rehabilitation, a significant increase of distance walked in the 6MWT was observed only in group B

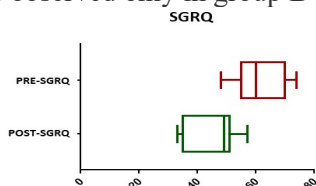


Fig.2. Patients from both groups reported an improvement of health-related quality of life (group A, SGRQ pre 55.05 ± 1.32 vs. SGRQ post 50.05 ± 1.51 , $p = 0.018$ and group B SGRQ pre 61.32 ± 1.83 vs. SGRQ post 44.95 ± 1.94 , $p < 0.0001$)

Discussion

The present study showed that association of neuromuscular electrostimulation to a PRP, will have greater benefits on muscle toning, exercise tolerance and quality of life, then pulmonary rehabilitation program alone, in patients with very severe COPD.

Subjects from the electrostimulation group were older then those from standard pulmonary rehabilitation group. This observation correlated with better results in this group, emphasizes the benefits of electrostimulation.

We used electrostimulation on the intercostal muscles but no significant differences in the spirometric values between the studied groups both pre- and post-intervention, were noticed. This observation is supported also by other authors (19). However, Vieira et al. assessed the effect of electrostimulation on the dynamic hyperinflation after 8 weeks of therapy. The neuromuscular stimulation increased FEV1, FEV1/FVC, 6MWT and reduced SGRQ ($P < 0.01$) (20). Lau et al., using a different protocol on the stellate ganglion region, have demonstrated a significant increase in FEV1 post electrostimulation program (21). Thus, we can assume that a longer period of therapy and a different thoracic stimulation region, could be the keys for an effective respiratory function rehabilitation.

We observed an increased expiratory muscle strength after the electrostimulation, but the inspiratory muscle strength change did not reach the statistical significance cut off. This observation is supported also by other papers (20). We can assume that a longer period of therapy could be more efficient on respiratory muscle strength.

The muscle mass has increased in the electrostimulation group, but no modification was recorded in the pulmonary rehabilitation group. Dal Corso et al. did not find significant changes in muscle mass, but an increase in type II muscle fibres and a decrease in type I (22).

A significant difference in the 6 MWT test was observed in the electrostimulation group. According to ATS/ERS guidelines a 47 m improvement in the 6MWT after an PRP intervention is a clinically significant (23). We observed an increase of 76 m after electrostimulation and only 21.8 m in the standard rehabilitation program. We have to keep in mind that these results are obtained in cohorts who included only severely deconditioned patients with COPD, GOLD 4.

It is important for clinicians to assess the health related quality of life among COPD patients, as this is a good indicator of disease severity (24). Among many specific instruments available in literature, SGRQ reflects the most complex image of diseases impact on patients daily life. In the current study, patients from both groups reported an improvement of health related quality of life (group A, SGRQ pre 55.05 ± 1.32 vs. SGRQ post 50.05 ± 1.51 , $p=0.018$ and group B SGRQ pre 61.32 ± 1.83 vs. SGRQ post 44.95 ± 1.94 , $p<0.0001$) observation also supported by other authors (20).

The disparities between the results obtained in different studies available in literature, can be explained by distinct electrostimulation and pulmonary rehabilitation protocols. A difference in the intensity and duration of muscular stimulation can highly influence the outcome of the intervention (25-26). Studies who used electrostimulation with higher intensities (15-90 mA) and lower frequencies (5-35 Hz) showed an increase in muscle mass (27-28) whereas other studies (22,29) who used lower intensities (10-45 mA) and higher frequencies (50 Hz) found no changes in muscle mass.

Future research on electrostimulation, should also address other pathologies who associate dyspnoea and muscle dysfunction, due to the high prevalence of age-related chronic respiratory diseases.

Limitations. The first limitation of this research was the short period of observation due to the fact that Romanian National Health System provides financial support only for a three-week pulmonary rehabilitation programme. In contrast, other studies lasted around 4 to 8 weeks. Secondly, the small sample size did not allow us to analyse sub-groups which could clarify some of the clinical changes. Further studies are needed to analyse the effects of merging neuromuscular stimulation with pulmonary rehabilitation programs in COPD patients and to evaluate the impact on hospitalizations rate and survival.

Conclusion. A protocol which combines pulmonary rehabilitation with neuromuscular electrical stimulation of the intercostal and lower limbs muscles, in patients with very severe forms of COPD, has grater beneficial effect on dyspnoea, exercise tolerance, muscle mass toning and quality of life, compared with pulmonary rehabilitation alone.

Declaration of conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Fildan AP, Toma CL, Tofolean D, Arghir OC, Dantes E. TB Risk in Patients with Biological Therapy for Psoriasis. *Chest*. 2016; 150(4_S):201A.
2. Tudorache E, Fildan AP, Frandes M, Dantes E, Tofolean DE. Aging and extrapulmonary effects of chronic obstructive pulmonary disease. *Clin Interv Aging*. 2017;12:1281–1287.
3. Todea D, Herescu A, Rosca L. Obstructive Sleep Apnea Syndrome - a matter of public health. *Transylvanian Review Of Administrative Sciences*. 2012;37E:186- 201.
4. Munteanu LA, Fildan AP, Tudorache E, et al. Inhaler technique errors in Romanian patients with asthma - a multicenter study. *Patient Prefer Adherence*. 2019;13:1401–1414.
5. Deacu M, Tofolean DE, Bosoteanu M, Pulmonary alveolar lipoproteinosis associated with emphysematous areas. *Rom J Morphol Embryol*. 2012; 53(1): 173-177.
6. Tudorache V, Traila D, Marc M, et al. Impact of moderate to severe obstructive sleep apnea on the cognition in idiopathic pulmonary fibrosis. *PLoS One*. 2019;14(2):e0211455.
7. Anton A, Tofolean DE. Obstructive sleep apnea and metabolic syndrome: is there a correlation? *Sleep Medicine*. 2017; 40 (1): E16-E16; DOI: 10.1016/j.sleep.2017.11.039.
8. Trenchea M, Arghir IA, Popescu G, Rascu S, Bechir ES, Tofolean D, Fildan AP, Ion I, Dantes E. The Triad Nocturia, Smoking and Obstructive Sleep Apnea. *REVISTA DE CHIMIE* . 2019; 70(5): 1839-1842 .
9. Traila D, Oancea C, Tudorache E, Mladinescu OF, Timar B, Tudorache V. Clinical profile of unclassifiable interstitial lung disease: Comparison with chronic fibrosing idiopathic interstitial pneumonias. *J Int Med Res*. 2018;46(1):448–456.
10. Vogelmeier, C.F., Criner, G.J., Martinez, F.J., Anzueto, A., Barnes, P.J., et al. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease 2017 report. *Respirology*, 22: 575– 601.
11. Tofolean D, Popescu G, Arghir IA, Frandes M, Fildan AP. A Different Aproach of Chronic Obstructive Pulmonary Disease Severity and Plastic Medical Devices Used for Oxygenotherapy. *Materiale Plastice* .2019; 56(2): 295-300.

12. Alexescu TG, Maiercan A, Ciumarnean L, Budin C, Dogaru G, Todea DA. Rehabilitation therapies in stable chronic obstructive pulmonary disease. *Balneo Research Journal*. 2019;10(1):37–44.
13. Maria A. Ramon, Gerben Ter Riet, Anne-Elie Carsin, Elena Gimeno-Santos, Alvar Agustí, Josep M. Antó, David Donaire-Gonzalez, Jaume Ferrer, Esther Rodríguez, Robert Rodríguez-Roisin, et al. The dyspnoea-inactivity vicious circle in COPD: Development and external validation of a conceptual model. *Eur Respir J*. 2018 Aug 2 Published online 2018 Aug 2. doi: 10.1183/13993003.00079-2018).
14. Alexescu TG, Tarmure S, Negrean V, Cosnarovici M, Ruta VM, Popovici I, Para I, Perne MG, Orasan OH, Todea DA. Nanoparticles in the treatment of chronic lung diseases. *J Mind Med Sci*. 2019; 6(2): 224-231.
15. Voica, Alina Sorina et al. “Chronic obstructive pulmonary disease phenotypes and balance impairment.” *International journal of chronic obstructive pulmonary disease* vol. 11 919-25. 29 Apr. 2016.
16. Tudorache E, Oancea C, Avram C, Fira-Mladinescu O, Petrescu L, Timar B. Balance impairment and systemic inflammation in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1847–1852. Published 2015 Sep 8.
17. Neder JA, Sword D, Ward SA, Mackay E, Cochrane LM, Clark CJ. Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax*. 2002;57(4):333e7.
18. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Analysis of clinical methods used to evaluate dyspnea in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;158(4):1185e9.
19. Kucio C, Niesporek J, Kucio E, Narloch D, Wegrzyn B. Evaluation of the effects of neuromuscular electrical stimulation of the lower limbs combined with pulmonary rehabilitation on exercise tolerance in patients with chronic obstructive pulmonary disease. *Journal of Human Kinetics*. 2016;54:75–82.
20. Vieira PJ, Chiappa AM, Cipriano G Jr, Umpierre D, Arena R, Chiappa GR. Neuromuscular electrical stimulation improves clinical and physiological function in COPD patients. *Respiratory Medicine*. 2014;108(4):609–20.
21. Lau KS, Jones AY. A single session of Acu-TENS increases FEV1 and reduces dyspnoea in patients with chronic obstructive pulmonary disease: a randomised, placebo-controlled trial. *Aust J Physiother*. 2008;54(3):179e84.
22. Dal Corso S, Napolis L, Malaguti C, Gimenes AC, Albuquerque A, Nogueira CR, De Fuccio MB, Pereira RD, Bulle A, McFarlane N, Nery LE, Neder JA. Skeletal muscle structure and function in response to electrical stimulation in moderately impaired COPD patients. *Respir Med*. 2007; 101: 1236-1243
23. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111e7.
24. Hoge Stanca P, Tudorache E, Fildan AP, Fira-Mladinescu O, Marc M, Oancea C. Risk Factors of Chronic Obstructive Pulmonary Disease Exacerbations *Clin Respir J* 2019; doi:10.1111/crj.13129.
25. Bourjeily-Habr G, Rochester CL, Palermo F, Snyder P, Mohsenin V. Randomised controlled trial of transcutaneous electrical stimulation of the lower extremities in patients with chronic obstructive pulmonary disease. *Thorax*. 2002; 57: 1045-1049.
26. Tasdemir F, Inal-Ince D, Ergun P, Kaymaz D, Demir N, Demirci E, et al. Neuromuscular electrical stimulation as an adjunct to endurance and resistance training during pulmonary rehabilitation in stable chronic obstructive pulmonary disease. *Expert Review of Respiratory Medicine*. 2015;9:493–502.
27. Vivodtzev I, Pepin JL, Vottero G, Mayer V, Porsin B, Levy P, et al. Improvement in quadriceps strength and dyspnea in daily tasks after 1 month of electrical stimulation in severely deconditioned and malnourished COPD. *Chest* 2006;129(6): 1540e8.
28. Vivodtzev I, Debigare R, Gagnon P, Mainguy V, Saey D, Dube ME, Pare ME, Belanger M, Maltais F.. Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD. *Chest*. 2012; 141: 716-725.
29. Maddocks M, Nolan CM, Man WD, Polkey MI, Hart N, Gao W, et al. Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomised double-blind, placebo-controlled trial. *Lancet Respiratory Medicine*. 2016;4:27–36.

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Abstract

Introduction. It is already known and accepted that cerebrovascular disease onset has a temporal variation pattern, the best documented being the circadian variation pattern, with a frequency peak in the morning and a second lower peak during afternoon. The impact of this circadian variation on post-stroke cognitive status has been little studied.

Materials and method. The study included a cohort of 63 patients with ischemic stroke, admitted to the Neurology Departments I and II of the Rehabilitation Hospital in Cluj-Napoca between 1 June 2008 and 1 June 2009, who were evaluated for their cognitive status over 2 years, during 5 successive visits. The onset time of ischemic stroke was assigned to one of the six-hour intervals: 00.01-06.00 (night), 06.01-12.00 (morning), 12.01-18.00 (afternoon), and 18.01-24.00 (evening). Statistical analysis was performed using Excel Microsoft, descriptive and ANOVA test.

Results and conclusions. The circadian variation pattern of stroke onset is confirming in our study the known incidence pattern of ischemic stroke, with the morning peak. There are differences in the evolution during dynamics of the MMSE score depending on the time of the day when stroke occurs. Patients with stroke onset during the night have seems to have a less favorable cognitive evolution in the second year after ischemic stroke compared to patients with stroke onset during the other intervals of the day.

Key words: *ischemic stroke occurrence, circadian variation, cognitive status,*

Introduction

The focus on the need to understand as much as possible of the factors involved in the development of various diseases including stroke, a devastating disorder worldwide due to the severe disability induced, includes the interest in the study of the chronobiological aspects involved (1, 2). It is already known that ischemic stroke onset has a circadian, circaseptan and circannual cyclicity pattern. The best studied and documented pattern, which does not depend on the geographical area, climate or lifestyle, is the circadian variation pattern. This is described as having a morning incidence peak, according to the majority of the literature reports, and a second, less impressive peak, during afternoon, described inconsistently (3-7).

Post-stroke cognitive impairment is frequent. Post-stroke cognitive deterioration represents one of the main causes of dependence in neurovascular patients. It has a multifactorial etiology (vascular lesions, lesions associated with Alzheimer's dementia, white matter changes) and can be assessed by various neuropsychological scores, of which the most widely used and available is MMSE (Mini Mental State Examination) which, along with the degree of disability, correlates with subcortical white

matter lesions (8-10). The evolution of cognitive status is closely related to functional status alongside the severity of the clinical picture. There are extremely few data regarding the influence of the circadian variation pattern on the evolution of cognitive status, and the influence on disability is reflected in some studies which suggest that patients with ischemic stroke onset during the night have a less favorable clinical (NIHSS) and functional (mRs, ADL, IADL) evolution compared to other patients with ischemic stroke (11-14).

Materials and method

Our study was based on a cohort of 63 patients who had an ischemic stroke over the past 6 months, admitted to the Neurology Departments I and II of the Rehabilitation Hospital in Cluj-Napoca, in the period 1 June 2008 - 1 June 2009. The diagnosis of ischemic stroke was defined according to updated World Health Organization criteria and was confirmed by neuroimaging. We recorded demographic data for each patient and the time of onset was assigned to one of the four 6-hour intervals of the day: 00.01-06.00 (night), 06.01-12.00 (morning), 12.01-18.00 (afternoon), and 18.01-24.00 (evening).

The 63 patients were assessed for their cognitive status using the MMSE scale during 5 visits over 2 years: at the first visit (time “0”), at 1 month (“1”), 6 months (“6”), 12 months (“12”) and 24 months (“24”).

Statistical analysis was performed using Excel Microsoft, categorical data were presented as diagrams, and continuous variables were summarized using synthetic centrality, dispersion and location indices. For the analysis of differences between the mean scores at each visit for the 4 time intervals of the day, two-way ANOVA statistical analysis was used.

Results

The circadian cyclicity pattern of ischemic stroke symptom onset in the studied group revealed the highest incidence in the morning, in the 6-12 interval, and the lowest incidence during the night, in the 0-6 interval (Fig. 1).

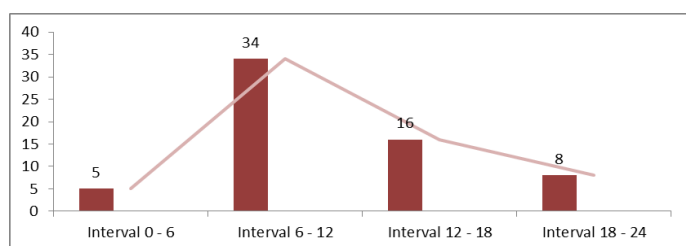


Fig. 1: Circadian cyclicity of ischemic stroke onset in our cohort across the 4 time intervals of the day

Figure 2 represents the descriptive evolution of the arithmetic mean of the MMSE score in patients with stroke onset across the 4 time intervals of the day over the 2 years of follow-up, on the occasion of the 5 evaluations.

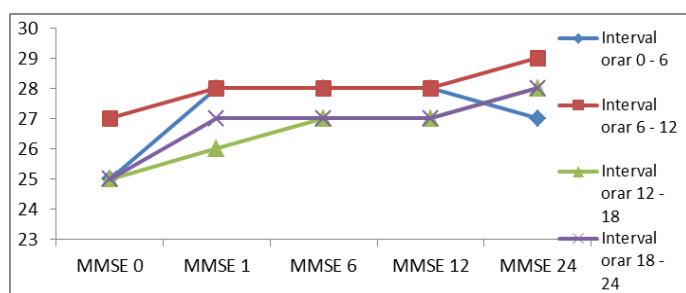


Fig. 2. Temporal evolution of the arithmetic mean of the MMSE scores during 2 years, across the four time intervals of the day (5 evaluations).

Following two-way ANOVA statistical processing of MMSE scores across the 4 time intervals of the day and the 5 time points for their evaluation (0,1,6,12,24): statistically significant differences

($p \leq 0.05$) were found at each evaluation visit (time point), between the morning and the afternoon time interval, at the first 3 visits (the first 6 months): at time 0 (first visit – MMSE 0), at 1 month (MMSE 1) and at 6 months (MMSE 6). In addition, at the 6-month visit (MMSE 6) there was a statistically significant difference between the morning and the evening intervals (Table 1).

Table 1. Statistically significant differences in the evolution of the MMSE score of patients with ischemic stroke depending on the onset intervals .

- **MMSE 0: 6.01-12.00 ---- 12.01-18.00 ($p=0.021$)**
- **MMSE 1: 6.01-12.00 ---- 12.01-18.00 ($p=0.03$)**
- **MMSE 6: 6.01-12.00 ---- 12.01-18.00 ($p=0.05$)**
- **--- 18.01-24.00 ($p=0.04$)**
- **MMSE 12, MMSE 24 - no statistically significant differences**

Discussions

The known circadian cyclicity pattern of ischemic stroke onset was confirmed in the case of the cohort of our study, with the incidence peak in the 06.01-12.00 interval and the lowest incidence during the night. (3, 4, 8, 15).

An analysis of the evolution during dynamics of the MMSE score across the 5 evaluations over the 2 years of follow-up shows a favorable evolution for all time intervals in the first month, with a subsequent relative plateau period up to 1 year, followed by a new improvement up to 2 years, except for the night interval of onset (00.00-06.00), for which MMSE worsened again after the first year. Statistically significant differences between the 4 time intervals of stroke onset by multivariate ANOVA analysis were detected for the MMSE values recorded on the occasion of the first 3 visits (initial time, at 1 month and at 6 months), more precisely between the 6-12 interval and the 12-18 interval, the 18-20 interval, respectively. No statistically significant differences were found regarding the evolution of MMSE values in patients with stroke onset during the night interval compared to patients with stroke onset in the other intervals of the day, despite the differences observed by descriptive analysis, most probably due to the small number of patients.

We found literature data related to the evolution of cognitive status depending on the circadian interval in which stroke occurred. The evolution of the MMSE score correlates with the results of other personal studies, in which the degree of disability

was evaluated using the scores ADL (activities of daily living), IADL (instrumental activities of daily living), mRs (modified Rankin score) associated with clinical severity assessed by NIHSS, with the least favorable evolution of these for ischemic stroke onset in the 00.00-06.00 night interval and the greatest improvement for all onset intervals during the first year after stroke (13, 14).

The more severe evolution of stroke with onset in the night interval from a clinical, functional and cognitive point of view is due to a number of factors: frequent late discovery on the occasion of wake-up which leads to waste of precious time, favoring endogenous factors such as variability of blood pressure values and autonomic system activity, nocturnal hypercoagulability along with possible sleep-disordered breathing as a risk factor for nocturnal stroke occurrence, and alteration of the post-stroke sleep-wake cycle, maintaining a vicious circle (15,16).

Conclusions

In our study group, the circadian variation pattern was similar to that found in the literature, with the highest incidence in the 6-12 morning interval and the lowest incidence in the 0-6 night interval, the latter seeming to be responsible for the least favorable evolution of cognitive status at 2 years. There are differences in the evolution during dynamics of the MMSE score depending on the time of the day when stroke occurs; more extensive studies in terms of number of patients and length of follow-up are required. Information about the influence of circadian variation in the occurrence of ischemic stroke on the evolution of cognition can help to estimate long-term prognosis and implicitly, the necessary medical and social resources.

References

- Kelly-Hayes M, Wolf PA, Kase CS, Brand FN, McGuirk JM, D'Agostino RB. Temporal Patterns of Stroke Onset. *Stroke*. 1995;26(8):1343-7.
- Gallerani M, Manfredini R, Ricci L, Cocurullo A, Goldoni C, Bigoni M, et al. Chronobiological aspects of acute cerebrovascular diseases. *Acta Neurol Scand*. 1993;87(6):482-7.
- Turin TC, Kita Y, Rumana N, Nakamura Y, Takashima N, Ichikawa M, et al. Is there any circadian variation consequence on acute case fatality of stroke? Takashima Stroke Registry, Japan (1990-2003). *Acta Neurol Scand*. 2012;125(3):206-12.
- Manfredini R, Boari B, Smolensky MH, Salmi R, la Cecilia O, Maria Malagoni A, et al. Circadian Variation in Stroke Onset: Identical Temporal Pattern in Ischemic and Hemorrhagic Events. *Chronobiology International*. 2009;22(3):417-53.
- Fodor DM, Fodor M, Perju-Dumbravă L. Seasonal variation of stroke occurrence: a hospital based-study. *Balneo Research Journal*. 2018;9(2):82-7.
- Raj K, Bhatia R, Prasad K, Srivastava MV, Vishnubhatla S, Singh MB. Seasonal differences and circadian variation in stroke occurrence and stroke subtypes. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2015;24(1):10-6.
- Ripamonti L, Riva R, Maioli F, Zenesini C, Procaccianti G. Daily Variation in the Occurrence of Different Subtypes of Stroke. *Stroke research and treatment*. 2017;9091250.
- Elnimr EM, Kondo T, Suzukamo Y, Satoh M, Oouchida Y, Hara A, et al. Association between white matter hyperintensity and lacunar infarction on MRI and subitem scores of the Japanese version of mini-mental state examination for testing cognitive decline: the Ohasama study. *Clin Exp Hypertens*. 2012;34(8):541-7.
- Liou LM, Chen CF, Guo YC, Cheng HL, Lee HL, Hsu JS, et al. Cerebral white matter hyperintensities predict functional stroke outcome. *Cerebrovasc Dis*. 2010;29(1):22-7.
- Liou LM, Lin HF, Tsai CL, Lin RT, Lai CL. Timing of stroke onset determines discharge-functional status but not stroke severity: a hospital-based study. *The Kaohsiung journal of medical sciences*. 2013;29(1):32-6.
- Ghandehari K. Challenging comparison of stroke scales. *Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences*. 2013;18(10):906-10.
- Fodor DM, Stănescu IC, Perju-Dumbravă L. The evolution of disability after ischemic stroke depending on the circadian variation of stroke onset. *Balneo Research Journal*. 2018;9(4):411-3.
- Fodor DM, Fodor MM, Stănescu IC, Dogaru G, Perju-Dumbravă L. The influence of circadian variation in ischemic stroke onset on the evolution of the severity of the clinical picture and disability. *Balneo Research Journal*. 2019;10(1):24-7.
- Gupta A, Shetty H. Circadian variation in stroke - a prospective hospital-based study. *Int J Clin Pract*. 2005;59(11):1272-5.
- Hepburn M, Bollu PC, French B, Sahota P. Sleep Medicine: Stroke and Sleep. *Missouri medicine*. 2018;115(6):527-32.
- Kulesh AA, Lapaeva TV, Shestakov VV. [Chronobiological characteristics of stroke and poststroke cognitive impairment]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2014;114(11):32-5.

The quality of life - an indicator for assessing the recovery program in patients diagnosed with degenerative disorders

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Abstract

Introduction. Osteoarthritis is a chronic joint disease, a progressive non-inflammatory arthropathy-type. Globally, around 1.7 billion people are affected by musculoskeletal and rheumatic diseases, which indicates an increase in the last 20 years of around 45%. **Material and method.** The objectives of the treatment of patients diagnosed with osteoarthritis were: decreasing the pain, increasing joint mobility, muscle strength, trophic and muscle tone, increasing the quality of life and reintegration into the social and family environment. Demographic data and the functional status were assessed using the VAS scale, the WOMAC scale, the QOL scale. **Results and discussions.** The pain, the most important symptom in osteoarthritis, was diminished in the patients from the group, the evaluation on the VAS scale, but also on the WOMAC scale has showed the value reduction and the statistical significance of this decrease. The quality of life in the group patients after the application of the complex recovery treatment, especially of the kinetotherapy program. **Conclusions.** The application of the individualized recovery treatment and adapted to the age group has allowed the improvement of the values of the parameters of pain, rigidity, functional capacity. The recovery of patients aged 55-65 is important to ensure the percentage of professionally active persons, to reduce medical costs, as well as those generated by absenteeism, and the socio-professional reintegration of these patients.

Key words: *osteoarthritis, the quality of life, the complex recovery treatment, kinetotherapy,*

Introduction

Osteoarthritis is a chronic joint disease, a progressive non-inflammatory arthropathy-type, which is characterized by the damage of articular joint, the subchondral bone, changes at the level of the periarticular structures, of the synovium. Osteoarthritis is determined by genetic factors (1,2,3) and environmental factors (sex, age, life-style, weight, endocrine-metabolic disorders) (4). For the bearing joints (hip, knee) the inflammatory process involves the damage of walking, the decrease of muscle strength in the lower body, joint deformities, instability at the knee level. Coxartrosis is a chronic disease, with a long evolution, characterized by joint limitation, functional disability and difficulty in performing daily activities. Frequently, patients diagnosed with coxarthrosis also have associated comorbidities (respiratory, cardiovascular, digestive, renal, metabolic conditions) (5,6). Knee osteoarthritis is a chronic joint disease that causes pain and the decrease of the functional capacity with negative

consequences on social integration, mental capacity, and the quality of life. A review of 62 studies from 4 databases has evaluated the quality of life through several questionnaires. Thus, it was found that obesity, the decrease of the physical activity (7) and the female sex were the factors that decreased the quality of life. Additionally, the patients' educational level, the psychological stress, the depression, the social and inter-family relations (8,9).

A study from 2019 (10) on 6472 participants shows that osteoarthritis at the level of the lower limb affects between 10-20% of people over 60 (11) involving economic and social costs (12), but also medical costs increasing by 80-90 % the costs for possible hip or knee prostheses (13,14,15).

A study performed in South Korea on 9512 participants over 50 allowed the evaluation of the risk factor and the quality of life in patients with osteoarthritis. It was found a higher prevalence in women (43.8%) compared to 21.1% in men.

The prevalence of obesity in a higher percentage in women has also determined the decrease of the quality of life in this population group (16, 17,18) .

The study presents the results from databases for 2 years, corresponding to patients diagnosed with osteoarthritis, noticing an increased opioid use in the treatment of the condition. Of the 2857999 patients with knee osteoarthritis, 12.2% have received opioid treatment as first treatment. The factors associated with osteoarthritis (depression or comorbidity) have represented the reason for the administration of these drugs (19,20).

Also, they should benefit from a proper quality of life, to delay the cognitive degeneration (21) as much as possible by interacting with their friends, participating in physical, social activities, maintaining control over their own lives (diet, weight, exercise, physical exercises, daily walks, avoiding sedentariness and isolation).

An observational and transversal study published in 2014 in which 1849 patients with gender and hip osteoarthritis over 50 were evaluated. The average age was 68.5 +/- 9.5 years. Of the patients, 61.5% had knee osteoarthritis, 19% hip osteoarthritis and 19.5% both, the latter also having a low quality of life (22). Globally, around 1.7 billion people are affected by musculoskeletal and rheumatic diseases, which indicates an increase in the last 20 years of around 45% (23).

The consequences of these conditions have an impact in the socio-economic field and are found in the absenteeism from the professional activity (50%) and in the incapacity for work and disabilities (60%), which leads to the early retirement of patients. This is why it is important to early diagnose and apply individualized and complex treatment (24,25).

The treatment for osteoarthritis of the joints of the hand, hip and knee takes into account the recommendations of the American College of Rheumatology (ACR) in 2012, the Osteoarthritis Research Society International (OARSI) in 2008 and 2014, but also the recommendations of the European League Against Rheumatism (EULAR) of the National Institute for Clinical Excellence (NICE) in England, as well as the American Academy of Orthopedic Surgeons (AAOS). (26,27,28,29).

For patients diagnosed with osteoarthritis, the recovery procedures must be individualized and involve the use of the two treatment possibilities, namely the pharmacological one and the non-

pharmacological one which involves electrotherapy and kinetotherapy procedures. (26,30,31)

The therapeutic management of osteoarthritis has the purpose of reducing the pain and the inflammation, improving physical function, educating the patient to practice therapeutic exercise, weight control and use of support walking devices (32). Also, the administration of simple analgesics and NSAIDs for pain control and increase of the quality of life (33).

Also, the recovery program in osteoarthritis includes a physical exercise program for increasing the muscle strength and endurance, increasing the joint mobility, maintaining muscle tone, as well as occupational therapy (34, 35).

In the recovery program, electrotherapy (36) is recommended by applying low and medium frequency currents and ultrasound (37,38,39).

Taking into account the adverse effects at the cardiovascular and digestive level, NSAIDs represent the second step in the management of osteoarthritis, being useful for the improvement of the symptoms, but the guides recommend them on the short term (ACR, 2008), (26,40,41).

However, to reduce the occurrence of gastrointestinal complications, it is recommended the associate with a selective non-steroidal anti-inflammatory, COX 2 inhibitor, a proton pump inhibitor (42,43,44,45). Also, the administration of non-steroidal anti-inflammatory medicine under topical form is better tolerated than the oral administration (46,47,48).

Another review from 2019 had as purpose evaluating the effectiveness of physical exercise on pain, joint function and quality of life in a knee / hip osteoarthritis. From 9 electronic databases, were evaluated the results obtained from 6472 patients who confirmed the benefits of physical exercise for decreasing the pain, increasing the functional performance, increasing the quality of life in 8 weeks of treatment. The better results, especially the pain perimeter, were obtained in patients diagnosed with osteoarthritis, under the age of 60 (49).

In another study published in 2019, it allowed a review of the effects of physical exercise on pain, physical function, quality of life, progress of disease in people with osteoarthritis on the lower body. For a period of 7 years, the published studies were analyzed and it was found that performing physical exercises for 150 min per week allowed the decrease of pain, the improvement of physical function and the quality of life for a period of up to 6 months (50).

The purpose of the study was to evaluate the quality of life after applying a medical recovery program in patients diagnosed with degenerative disorders

Material and method: The study was performed over a period of 6 months, under ambulatory regime. 72 patients were evaluated at the beginning and the end of the treatment, as well as at the examination performed eight weeks after the end of the treatment. The study inclusion criteria were the following:

- patients diagnosed with degenerative disorders (clinically and radiologically)
- over 50 years of age
- a diagnosis of degenerative disorder for at least 6 months
- agreement to take part in the study

The study exclusion criteria were:

- [1] patients diagnosed with degenerative disorders, but with arthroplasty (hip, knee)
- [2] associated, decompensated comorbidities
- [3] neuro- psychiatric disorders
- [4] patients who did not consent to take part in the study

The objectives of the treatment of patients diagnosed with osteoarthritis were: decreasing the pain, increasing joint mobility, muscle strength, trophic and muscle tone, increasing the quality of life and reintegration into the social and family environment. Demographic data (sex, age, weight, height, body mass index) and the functional status were assessed using the VAS scale (for pain), the WOMAC scale (for pain, rigidity, disability), the QOL scale (for the quality of life). At the clinical evaluation, the symptoms represented by pain (assessed with the VAS scale (0 = minimum pain, 10 = maximum pain) and joint rigidity accompanied by limited mobility (assessed with the goniometer) were used. Also, questionnaires were used to evaluate the functional joint capacity (WOMAC for supporting joints, Lequesne Index). The WOMAC scale evaluates the pain parameter (static and while moving), joint rigidity (at different moments) and functional capacity. The Lequesne functional index evaluates the pain that occurs during the first movements, as well as the discomfort that occurs during joint mobility.

During the study period (10 days) all the patients received pharmacological treatment (selective non-steroidal anti-inflammatory drugs, pain-killers) and performed kinetotherapy under the supervision of the physiotherapist, and, at home, they continued the recovery program (3 times a week). Electrotherapy has also been applied: low frequency currents (TENS), ultrasound.

Conventional TENS - electric current with frequency of 50-100 Hz, duration of 30-200ms, I = 10-40mA. The effect quickly installs (10-15 min) and lasts for several hours. The ultrasound was applied due to their physiological effects, that is: pain-killer (effect similar to that of the low-frequency currents), muscle relaxant (which is explained by the vibrational action of ultrasonic waves on tendon and muscle proprioceptors and which reacts to frequencies of 150 Hz), hyperaemic (activating blood circulation), anti-inflammatory (due to metabolic and vasomotor action) and fibrolytic (38,29). The chosen coupling form was direct, using the ultrasonophoresis process to allow the anti-inflammatory action of the applied gel (Voltaren gel in our case) (36). The application of ultrasound in impulse regime was preferred (the impulse duration/ pause duration rapport being 1: 4) in order to reduce the thermic effect and to potentiate the decontracting effect, allowing therefore to avoid the adaptation and the overloading of the tissues on which they were applied. In the study, the impulse frequency of 1 Hz, that is 60 impulses/min was used, and the impulse period was 1 second (Physiologic with ultrasound).

All the applied procedures took into account application indications and contraindications.

The kinetotherapy program lasted for 30 minutes per session and included passive, active and active with resistance mobilizations, coordination exercises, maintaining static and dynamic balance (25).

During the recovery program, but also at home, the patients received indications regarding the healthy lifestyle that involves: healthy diet, weight loss or maintaining their weight, avoiding exposure to coldness and moisture, avoiding prolonged standing, walking on uneven ground, lifting heavy weights (51).

Statistical analysis

The data obtained from the evaluation were processed statistically (median, standard deviation) using Microsoft Excel 10. The t-student test was useful for comparing the obtained results and verifying the working hypothesis. The statistical significance level is established at 5% ($p < 0.05$)

Results

The study group consisted of 72 patients aged over 55 (the average was 58).

Table 1. Distribution of group according to sex and age

age/sex	55-64years	65-74 years	>75 years
female	21	12	9
male	14	10	6

Of these, 58.34% were female and 41.66% male.

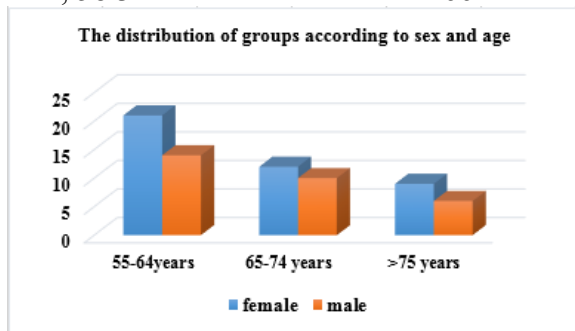


Fig. 1. Distribution of group according to sex an age
It is worth mentioning the patients' origin environment. Thus, it is observed a higher percentage of the urban area (57.14% in women and 53.34% in men) in both sexes compared to the rural area (42.86% in women and 46.67% in men).

Table 2. The distribution of groups according to sex and environment

sex/environement	urban	rural
female	24	18
male	16	14

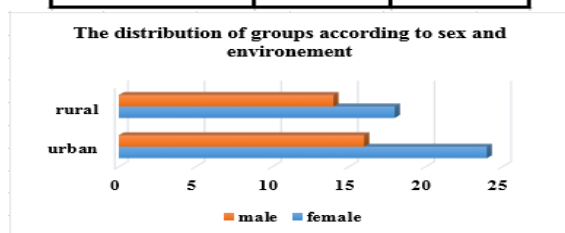


Fig. 2 The distribution of groups according to sex and environment

The pain evaluation on the VAS scale shows a statistically significant evolution at the 3 evaluation moments, and the t-student test is statistically significant with $p < 0.05$. Also, for the pain parameter evaluated by the WOMAC scale, the results are statistically significant at the 3 evaluation moments, with $p < 0.05$

Table 3 The evolution of the pain

scale	VAS		
moment	initial	final	control
mediana and std dev	7±1.42	5±1.22	3±0.67
t-student test	0.0215	0.0491	

Table 4 The evolution of the parameters of the WOMAC Index

scale/moment/statistically	initial	final	control
WOMAC pain	15±1.49	11±1.18	8±0.92
WOMAC rigidity	6±0.68	3.5±0.06	2±0.45
WOMAC functional capacity	53±2.79	39±3.35	25±2.45
WOMAC total	73.5±3.59	53.5±3.81	35±2.75

The evaluation of the parameters of articular rigidity, but also the functional capacity using the WOMAC scale allowed to obtain significant data, for each parameter and at the 3 moments of

evaluation, the t-student test being statistically significant, with $p < 0.05$.

By analyzing the results of the evaluation on the three parameters of the WOMAC Index, it is found a favorable evolution after the applied treatment, materialized by obtaining statistically significant data, with $p < 0.05$.

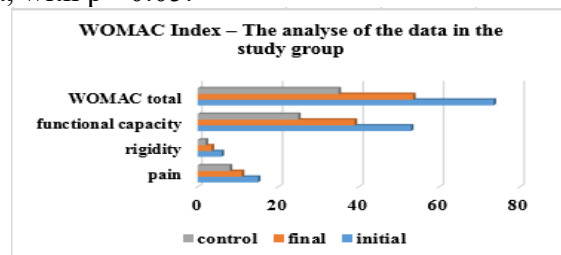


Fig. 3 The analyse of the data in the study group
Table 5 WOMAC Index – The analyse of the data in the study group

t student test WOMAC	initial	final
pain	0.0142	0.0152
rigidity	0.0409	0.0497
functional capacity	0.0128	0.0267
total	0.0134	0.0237

Also, the parameter for the quality of life evaluated using the QOL scale has pointed a good evolution of the studied patients, with statistically significant results, $p < 0.05$

Table 6 The evolution of the quality of life

scale	QOL		
moment	initial	final	control
mediana and std dev	81±9.91	90±6.88	100±5.27
t-student test	0.0018	0.0016	

Discussion

The study group has predominantly female patients (as shown by some published studies), especially from the urban area. By age groups, there is a higher percentage for both sexes in the 55-64 age group (50% in women and 46.66% in men), as well as in the 65-74 age group (28.57% in women and 33.34% in men). In this context, we can also think about the medical-socio-economic impact of degenerative diseases. The pain, the most important symptom in osteoarthritis, was diminished in the patients from the group, the evaluation on the VAS scale (a 28.5% reduction at the end of treatment and a 57.1% reduction at the control examination), but also on the WOMAC scale (26.66% reduction at the end of the treatment and with 46.66% at the control examination) has showed the value reduction and the statistical significance of this decrease. Also, the joint rigidity was reduced by 41.6% at the end of the treatment and by 66.7% at the control examination. The functional capacity has improved by 26.41% at the end of treatment and by 52.83% at control

examination. The quality of life in the group patients after the application of the complex recovery treatment, especially of the kinetotherapy program, improved by 11% at the end of the treatment and by 23.45% at the control examination.

Conclusions

The application of the individualized recovery treatment and adapted to the age group has allowed the improvement of the values of the parameters of pain, rigidity, functional capacity. The decrease of the pain and the increase of mobility and functional capacity allow a functional status proper to the age. The improvement of the values of the evaluated parameters has allowed the increase of the patients' quality of life, values appreciated based on the QOL questionnaire

In the recovery of patients over 55 with degenerative diseases, the non-pharmacological treatment (physical therapy and physical exercise) as well as pharmacological therapy, according to age, was also important. The recovery of patients aged 55-65 is important to ensure the percentage of professionally active persons, to reduce medical costs, as well as those generated by absenteeism, and the socio-professional reintegration of these patients.

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References

1. Stoicănescu D, Cevei M, Suciu R., Cseppento C. Calitatea vieții la pacienții cu coxartroză și afecțiuni cronice asociate. *Acta Medica Transilvanica*. 2013;2(1):118-121.
2. Cornelis FM, Luyten FP, Lories RJ. Functional effects of susceptibility genes in osteoarthritis. *Discov Med*. 2011;12:129-139.
3. Valdes AM, Spector TD. Genetic epidemiology of hip and knee osteoarthritis. *Nat Rev Rheumatol*. 2011;7:23-32.
4. Lane NE. Clinical practice. Osteoarthritis of the hip. *N Engl J Med*. 2007;357:1413-1421.
5. Van Dijk GM, Veenhof C, Schellevis F, Hulsmans H, Bakker JP, Arwert H, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. *BMC Musculoskelet Disord*. 2008;9:95.
6. Reeuwijk KG, de Rooij M, van Dijk GM, Veenhof C, Steultjens MP, Dekker J. Osteoarthritis of the hip or knee: which coexisting disorders are disabling? *Clin Rheumatol*. 2010;29:739-747.
7. Silisteanu SC, Silisteanu AE. The importance of physical exercise-bone mass density correlation in reducing the risk of vertebral and non-vertebral fracture in patients with osteoporosis. *Balneo Research Journal*. 2018, 9(2), 64-68.
8. Vitaloni M, Botto-van Bemden A, Sciortino Contreras RM, Scotton D, Bibas M, Quintero M, Monfort J, Carné X, de Abajo F, Oswald E, Cabot MR, Matucci M, du Souich P, Möller I, Eakin G, Verges J. Global management of patients with knee osteoarthritis begins with quality of life assessment: a systematic review. *BMC Musculoskelet Disord*. 2019 Oct 27;20(1):493.
9. Duica L, Antonescu E, Pirlog M, Purnichi T, Szakacs J, Totan M, .. & Bota, G. Clinical and biochemical correlations of aggression in Young patients with mental disorders. *Revista de Chimie*. 2018, 69(6), 1544-1549.
10. Siew-Li Goh, Monica S.M. Persson, Joanne Stocks, Yunfei Hou, Jianhao Lin, Michelle C. Hall, Michael Doherty, Weiya Zhang. Review Efficacy and potential determinants of exercise therapy in knee and hip osteoarthritis: A systematic review and meta-analysis. *Annals of Physical and Rehabilitation Medicine*. 2019;62: 356–365.
11. Pereira D, Peleteiro B, Araujo J, et al. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthritis Cartilage*. 2011;19:1270–85.
12. Sharif B, Kopec J, Bansback N, et al. Projecting the direct cost burden of osteoarthritis in Canada using a microsimulation model. *Osteoarthritis Cartilage*. 2015;23:1654–63.
13. Katz JN, Losina E, Barrett J, et al. Association between hospital and surgeon procedure volume and outcomes of total hip replacement in the united states medicare population. *J Bone Joint Surg* 2001;83:1622.
14. Katz JN, Barrett J, Mahomed NN, et al. Association between hospital and surgeon procedure volume and the outcomes of total knee replacement. *J Bone Joint Sur* 2004;86:1909.

15. Culliford D, Maskell J, Beard D, et al. Temporal trends in hip and knee replacement in the United Kingdom. *Bone Joint* 2010;92:130–5.
16. Lee S, Kim SJ Prevalence of knee osteoarthritis, risk factors, and quality of life: The Fifth Korean National Health And Nutrition Examination Survey, *Int J Rheum Dis.* 2017 Jul;20(7):809-817.
17. Silișteanu SC, Antonescu E. The influence of the body weight index (BMI) in the recovery of the degenerative diseases of the joints. *Balneo Research Journal*, 2016;7(2):66-71
18. Totan M, Antonescu E, Catana MG, Mitariu M M C, Duica L, Filip CR, ... & Mitariu, S. I. C. C-Reactive Protein-A Predictable Biomarker in Ischemic Stroke. *Revista de Chimie.* 2019, 70(6), 2290-2293.
19. Cho SK, Jung SY, Choi S, Im SG, Kim H, Choi WS, Jang EJ, Sung YK. Factors related to the use of opioids as early treatment in patients with knee osteoarthritis. *Arthritis Res Ther.* 2019 Nov 4;21(1):222. doi: 10.1186/s13075-019-2004-x.
20. Duica Lavinia, Depression - multiple psychopathological facets, Mental Health-actual views in psychology, medicine and anthropology. Sep. 2016, p 20-24.
21. Birlutiu V, Stef L, Mitariu S I C, Filip C R, Duica L, Antonescu E, ... & Manea, M. M. The Biochemical Biomarkers Determination in Alzheimer Dementia. *REVISTA DE CHIMIE.* 2018 69(11):4055-4059.
22. Bernad-Pineda M, de Las Heras-Sotos J, Garcés-Puentes MV. Quality of life in patients with knee and hip osteoarthritis. *Rev Esp Cir Ortop Traumatol.* 2014 Sep-Oct;58(5):283-9. doi: 10.1016/j.recot.2014.04.005. Epub 2014 Jul 8.
23. Hosu CD, Moisoiu V, Stefancu A, Antonescu E, Leopold LF, Leopold N, & Fodor, D. Raman spectroscopy applications in rheumatology. *Lasers in medical science*, 2019; 34(4): 827-834
24. Antonescu E, Bota G, Serb B, Atasie D, TATARU CD, Totan M, ... & Oswald, I. Study of the Total Serum Concentration of Serrum Ionized Magnesium in Children and Adolescents from Sibiu Area. *REVISTA DE CHIMIE*;2018;69(12), 3389-3392.
25. Silisteanu SC, Silisteanu AE. The importance of the elemental functional mobility coefficient in assessing the functional status of the coxofemoral joint. *Balneo Research Journal.* 2018; 9(1): 38-42.
26. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip and knee. *Arthritis Care Res.* 2012; 64: 465-74.
27. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis: II. OARSI evidence-based expert consensus guidelines. *Osteoarthritis and Cartilage*, 2008; 16: 137-62.
28. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis: I. Critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage*, 2007; 15: 981-1000.
29. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage*.2010; 18: 476-99.
30. Silisteanu SC, Antonescu E, Szakacs J, Totan M, Filip CR, Serb B H, ... & Mitariu SIC. Study on Changes in Some Physiological Parameters Under the Action of Therapeutic Ultrasound. *Rev. Chim. (Bucharest).* 2017; 68: 1306-1309.
31. Hugo L, Hoeksma D, Cornelia HM, et al. A comparison of the OARSI response criteria with patient's global assessment in patients with osteoarthritis of the hip treated with a non-pharmacological intervention. *OsteoArthritis and Cartilage*; 2006; 14, 77-81.
32. Silisteanu SC, Haidamac, AD. The purpose of the complex treatment for patients with posttraumatic lesions at the hand level. *Balneo Research Journal.* 2016; 7(4): 135-142.
33. Val Jiménez CL, López-Torres Hidalgo J, García Atienza EM, Navarro Ruiz MS, Hernández Cerón I, Moreno de la Rosa L. Functional status, self-rated health and level of physical activity of patients with osteoarthritis. *Aten Primaria.* 2017 Apr;49(4):224-232. doi: 10.1016/j.aprim.2016.06.002. Epub 2016 Jul 26.
34. Deyle GD, Allison SC, Matekel RL, et al. Physical therapy treatment effectiveness for osteoarthritis of the knee: a randomized comparison of supervised clinical exercise and manual therapy procedures versus a home

- exercise program. *Phys Ther.* 2005; 85: 1301-1317.
35. Silisteanu SC, Antonescu E, Moisii V. The importance of the recovery treatment in increasing the quality of the lives of the patients with the carpal tunnel syndrome. *Balneo Research Journal.* 2016; 7(3): 81-88.
 36. Rutjes AW, Nuesch E, Sterchi R, et al., 2009, Transcutaneous electrostimulation for osteoarthritis of knee. *Cochrane Database Syst Rev*, 4: CD002823.
 37. Silisteanu SC, Mitariu L, Ranga R, Antonescu E, Duica CL, Racheriu M, ... & Manea M. M. Potentiating the Effect of Treatment with Voltaren Gel Using Ultrasonic Frequencies of 1 MHz. *Revista de Chimie.* 2018; 69(7): 1749-1751.
 38. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendation and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U. S. Bone and joint initiative. *Seminars in Arthritis and Rheumatism*; 2014; vol. 43(6) :701-712.
 39. Silisteanu SC, Silisteanu AE, Antonescu E. The study on the importance of effects after the ultrasound use in the recovery of patients with lower lumbar discopathy. *Balneo Research Journal.* 2018; 9(4): 433-437.
 40. Bjordal JM, Klovning A, Ljunggren AE, et al. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: a meta-analysis of randomised placebo-controlled trials. *Eur J Pain.* 2007; 11: 125-38.
 41. Chou R, Helfand M, Peterson K, et al. Comparative effectiveness and safety of analgesics for osteoarthritis. *Comparative Effectiveness Review No.4*, 2006.(Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-02-0024). Rockville, Md: Agency for Healthcare Research and Quality
 42. Chan FK, Abraham NS, Scheiman JM, et al. First International Working party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. Management of patients on nonsteroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. *Am J Gastroenterol.* 2008; 103: 2908-18.
 43. Rostom AM, Muir K, Dube C, et al. Prevention of NSAID-related upper gastrointestinal toxicity: a meta-analysis of traditional NSAIDs with gastroprotection and COX-2 inhibitors. *Drug Health Patient Saf.* 2009; 1: 47-71.
 44. Rostom A, Moayyedi P, Hunt R. Canadian Association of Gastroenterology Consensus Group. Canadian consensus guidelines on long-term nonsteroidal antiinflammatory drug therapy and the need for gastroprotection: benefits versus risks. *Aliment Pharmacol Ther.* 2009; 29: 481-96.
 45. Bhatt DL, Scheiman J, Abraham NS., et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* 2008; 52: 1502-17.
 46. Latimer N., Lord J, Grant RL, et al. Cost effectiveness of COX-2 selective inhibitors and traditional NSAIDs alone or in combination with a proton pump inhibitor for people with osteoarthritis. *BMJ*, 2009, 339: b2538.
 47. Bjordal JM, Klovning A, Ljunggren AE, et al. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: a meta-analysis of randomised placebo-controlled trials. *Eur J Pain.* 2007;11: 125-38.
 48. Makris UE, Kohler MI, Fraenkel L. Adverse effects of topical nonsteroidal anti-inflammatory drugs in older adults with osteoarthritis: a systematic literature review. *J Rheumatol.* 2010; 37: 1236-43.
 49. Goh SL, Persson MSM, Stocks J, Hou Y, Lin J, Hall MC, Doherty M, Zhang W. Efficacy and potential determinants of exercise therapy in knee and hip osteoarthritis: A systematic review and meta-analysis. *Ann Phys Rehabil Med.* 2019 Sep;62(5):356-365.
 50. Kraus VB, Sprow K, Powell KE, Buchner D, Bloodgood B, Piercy K, George SM, Kraus WE . Effects of Physical Activity in Knee and Hip Osteoarthritis: A Systematic Umbrella Review. *Med Sci Sports Exerc.* 2019 Jun;51(6):1324-1339.
 51. Silisteanu SC, Silisteanu AE. The importance of the nutrition and of the body weight index in the recovery of the patients older diagnosed with coxarthrosis. *Balneo Research Journal.* 2017; 8(1): 15-20.

Study on the correlation between knee osteoarthritis and anxiety in patients aged over 55

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Abstract

Introduction. Osteoarthritis, which is a cause of chronic pain and disability with manifestation in any joint, with greater frequency in the joints of the lower limbs, upper limbs, but also at the spine level, affects around 250 million people in the entire world. This condition affects around 10% of the global population (18) and has an impressive impact on people, as it is one of the first 5 causes of disability. **Material and method.** The objectives of the treatment made by the patients diagnosed with knee osteoarthritis were: pain reduction, increased joint amplitude, increased muscle strength, increased muscle tone, increased quality of life and reintegration into the family and social environment. In the study, there were discussed demographic data regarding the patients. In order to assess the pain parameter, the VAS scale was used, as well as WOMAC subscales. To assess the quality of life of patients with knee osteoarthritis, the QOL scale (Quality of Life) was used. Anxiety was assessed with the help of a test that comprises the evaluation of symptoms at the cognitive, behavioral and physical level. **Results and discussions.** The pain was evaluated on the VAS scale, having a statistically significant evolution for the evaluation moments. Also with the help of the WOMAC index, two other parameters were evaluated, namely joint rigidity and functional capacity, the results being statistically significant in the 3 evaluation moments. The patients' anxiety was evaluated with the help of the anxiety test; the results obtained were statistically significant at the 3 evaluation moments. **Conclusions.** It is vital that the recovery treatment in osteoarthritis be individualized and adapted to the age group. In our group, it enabled the reduction of pain and anxiety, the increase of the functional capacity and the quality of the patients' lives. Taking into account the fact that the most affected group in the study group was the active professional one, we can evaluate the size of the recovery and the social, family and professional integration for these patients.

Key words: *knee osteoarthritis, the quality of life, anxiety, kinetotherapy,*

Introduction

Osteoarthritis, which is a cause of chronic pain and disability with manifestation in any joint, with greater frequency in the joints of the lower limbs (knee, hip, ankle), upper limbs (shoulder, hand), but also at the spine level (1), affects around 250 million people in the entire world (2). Osteoarthritis affects the joint structure, the subchondral bone, the capsule, the ligaments and the synovial membranes (3). The main symptom in osteoarthritis is the pain that causes the limitation of mobility (4), but also tiredness (5), decreased quality of life (6), but also muscle weakness (7), impaired muscle strength (8), changes in walking (9), all these worsening the preexisting pain (10). The patients diagnosed with osteoarthritis describe the occurrence of pain in static, but also dynamic activities, the affected joints being sensitive upon palpation and pressure (11) or at temperature difference (12). Some patients

describe pain as a burning sensation (13), electric current, with perception disorders in evaluating the painful segment and mobilization difficulty (14). The pain is fluctuating during the day (15) or does not show changes (16). However, between 12-30% of the patients diagnosed with osteoarthritis report the decrease of pain intensity on the long term (17). This condition affects around 10% of the global population (18) and has an impressive impact on people, as it is one of the first 5 causes of disability (19). The osteoarthritis diagnosis involves clinical manifestations (joint pain) (20, 21) and radiological elements (22). Among the people diagnosed with knee osteoarthritis, 70-80 % have radiological diagnosis of the disease, but they do not show frequent pain at the joint level (23) while 10-15 % have been radiologically diagnosed and show frequent pain (24).

Studies (25) revealed the relationship between joint pain in osteoarthritis and the changes that occur and can be imaginistically seen (by magnetic resonance) at the level of the knee joint- injuries at the bone or synovial level (26). The bone lesions of the subchondral bone microfracture type can determine nociception by increasing intra-bone pressure (27).

The imaginistic result by joint magnetic resonance may sometimes not be consistent with the pain phenomenon. Thus, the changes on the images obtained by magnetic resonance can be found in over 80% of the patients that do not show pain (28), and 30% also have synovitis without pain (29).

In this context we can say that there are changes of neuronal signaling in the spinal cord and brain in the case of a continuous joint nociception, a phenomenon called central sensitization, to which the sensory input is amplified when it reaches nociceptive ways at the medullary level and in the brain, causing the frequency and gravity of pain (30).

Therefore, the central sensitization present in an important percentage of people with osteoarthritis (31) is an element of pain gravity (32, 33), explaining the difference between the intensity of the pain and the joint structures changes in this condition (34).

In the case of the synovitis, certain inflammatory molecules can directly activate the nociceptors in the joint, causing the phenomenon of peripheral sensitization. (35). The study of synovial fluid in osteoarthritis of the knee is now performed by modern methods: resonant Raman spectroscopy and surface-enhanced Raman scattering (SERS)(36).

An important risk factor in causing and evolving pain and radiological changes (37) in people with knee osteoarthritis is represented by the body weight. Each weight gain by 3-4 Kg / m², therefore of the body mass index, doubles the risk of knee osteoarthritis (38). Also, obesity is associated to the pro-inflammatory condition that can accelerate the process of joint degeneration (39) and increases the nociceptive sensitization by increasing pain (40, 41). Osteoarthritis should be understood in a biopsychosocial setting. The pain felt in knee osteoarthritis involves complex mechanisms represented by the joint pathology, the status of nociception at the central level; that is why the treatment is based on the improvement of the pain, the improvement of the physical and mental function (42) by using the pharmacological therapy (43,44).

Osteoarthritis is a chronic disease requiring long-term management. Patients diagnosed with this condition are behaviorally inhibited, avoid assuming the active role in the self-management of pain and continue having chronic pains (45). This is why self-management interventions are recommended as part of the effective management of osteoarthritis (46,47) It is essential for the self-management concept, including the notions of motivation, expectation, belief to model the experience of pain and accompanying behaviors contributing either to the adaptation to chronic pain or to disability.

Recommended self- management interventions include information on the health condition, the stress management techniques, the physical exercises, the skill to solve personal problems, which allows people diagnosed with osteoarthritis to effectively manage long-term disease symptoms (48).

The results of a meta-analysis on 13 studies published in 2009 proved the beneficial effect of self-management programs on pain, the improvement of the quality of life, which would play an important role in the treatment of osteoarthritis (49). The authors of this study presented that the weak effects for self-management programs are represented by the patient's perception of the disease, associated comorbidities and patient's education (50,51).

Osteoarthritis involves high economic costs (52), absenteeism from the professional activity (65), decrease in the work efficiency, decrease in the the work performance, decrease in the productivity. Pain, anxiety and the decreased quality of life caused by the disease should be also taken into consideration (53). The indirect costs caused by osteoarthritis are increased, more in women compared to men. Due to the demographic changes, the aging of the population, it is expected that the prevalence of this disease will increase in the coming years.

The non-pharmacological treatment includes, besides the elements of education of the person, (losing weight, avoiding prolonged standing, walking on the ground with elevations, weight lifting) physical exercise and the use of electrotherapy (54,55).

The electrotherapy procedures frequently used involve ultrasound with pain-relief effect and muscle relaxation (56). The muscle relaxation is explained by the vibrational action of the ultrasound waves in the tendons and muscles, and the effect of hyperemia

determines, with the help of the vegetative nervous system, arteriolar vasodilation at the capillary level, activating blood circulation (57).

The pharmacological treatment consists of the administration of selective NSAIDs (COX-2 inhibitors), pain-killers (opioids), but also of “slow acting medication”.

A 2019 study (analysis of study) evaluated the effectiveness of physical exercise in reducing pain, increasing joint function and quality of life in the hip and knee osteoarthritis, all these worsening the preexisting pain (10). According to a study that analyzed the data from 9 electronic databases, until 2017 it was found that physical exercise has significant benefits in reducing pain, increasing functional capacity and quality of life for a period of 8 weeks, the results being better for people under the age of 60 (58). The physical exercise can improve the patient's symptoms, being a relatively safe alternative compared to the pharmacological treatment.

For the walking parameter (time, distance), physical exercise involved the increase of the strength, especially for knee extensors/flexors, hip abductors, but also for other muscle groups (59,60). The favorable results were recorded at a time interval of up to 8 weeks.

Physical exercise is recommended in the treatment guidelines for osteoarthritis (61,62), having benefits in reducing pain, improving physical function (63, 64), improving the mood (65), lowering the risk of developing other diseases (cardiovascular, metabolic, bone, neurodegenerative) (66, 67). Thus, physical exercise inhibits nociception at the central level (68, 69), at the local one (70) and at the systemic level and plays a role in reducing inflammation (83) and degenerative action at the joint level (71,72, 73). In addition, physical exercise has the same results in reducing pain compared to pain-killers (73), but with very few adverse effects (74,75). However, it is necessary that the physiotherapist individualize the exercise, to adjust and modify the training parameters in order to manage the symptoms.

Weight reduction programs used to improve disability and reduce pain (76) also help in reducing inflammatory biomarkers (77).

Research has shown that human lifestyle, sleep-wake rhythm and psychosocial factors can reduce or amplify pain (78), having a role in continue central sensitization (79).

These factors play a role in disability, which is why it is considered that sleep issues are related to the increased sensitivity of the patient with osteoarthritis and to the intensification of joint pain (80), which is why sleep may be a target for pain reduction treatment in osteoarthritis (81).

Among the people diagnosed with knee osteoarthritis, 40% have anxiety, depression, or both (82, 83,84), leading to a more serious pain (85). Anxiety (86) is associated with increased pain sensitivity in these people.

The study (87) published in 2019 investigated for 12 months the effect and role of anxiety in causing pain in osteoarthritis in a group of 4,730 people. It was found that higher anxiety, regardless depression, was associated to increased pain scores at people with knee osteoarthritis.

Some studies (88) proved that negative influences with changing vigilance lead to increased pain sensitivity, while positive influences decrease pain.

The purpose of this study was to evaluate the correlation between knee osteoarthritis and the manifestations of anxiety caused by the disease in people aged over 55.

Material and method. The study was performed in an outpatient regime, over a period of 6 months, being evaluated 123 patients.

The inclusion criteria in this study were:

- [1] patients diagnosed with knee osteoarthritis of the knee (clinically and radiologically)
- [2] diagnosis of knee osteoarthritis for at least 6 months
- [3] aged over 55
- [4] agreement to take part in the study

The exclusion criteria from the study were:

- patients diagnosed with knee arthroplasty
- decompensated associated comorbidities (cardiovascular, renal, pulmonary, digestive, neurological, metabolic)
- patients with mental disorders
- patients who did not agree to take part in the study

The objectives of the treatment made by the patients diagnosed with knee osteoarthritis were: pain reduction, increased joint amplitude, increased muscle strength, increased muscle tone, increased quality of life and reintegration into the family and social environment.

In the study, there were discussed demographic data regarding the patients (age, gender, living environment, height, weight, body mass index).

In order to assess the pain parameter, the VAS scale (0-100, 0 = no pain, 100 = maximum pain) was used, as well as WOMAC subscales (with 5 items regarding pain in standing, dorsal decubitus, sitting, walking, climbing stairs). By using WOMAC subscales, joint rigidity (in the morning and during the day), functional capacity (possibility of daily activities) and disability were assessed.

To assess the quality of life of patients with knee osteoarthritis, the QOL scale (Quality of Life) was used.

Anxiety was assessed with the help of a test that comprises the evaluation of symptoms at the cognitive, behavioral and physical level.

Also, for the patients' mental state (taking the age into account), the MMSE test (Mini test for the examination of the mental state) was used, the most used instrument in this context.

The study was performed for a period of 12 days, and the patients' evaluation was made at the beginning and the end of the treatment whereas the control was made 45 days later.

All patients received, according to the guidelines, pharmacological treatment with selective non-steroidal anti-inflammatory medication (general and topical administration) and pain-killers.

The recovery treatment included electrotherapy (medium frequency currents, ultrasound) and kinetotherapy in the outpatient regime, then the patients continued at home the kinetotherapy program for 30 minutes per day, 3 times a week.

The medium frequency currents have been used due to the physiological effects they present – pain-relief action, vasomotor, decontracting and trophic action. This type of current is a sinusoidal alternating current with a frequency between 3-10 kHz. In the study, it was used the interfering current with variable (modulated) rhythmic frequencies (“spectrum”) and modulation 0-100 Hz or “spectrum” 0-100 Hz. Thus, the difference of the two currents linearly varies both ascending and descending on a period from 0-100Hz. The rhythmic alternation of inhibitory/exciting effects is, therefore, achieved with the following consequences: the activation of cellular functions, hyperemia at the level of the deep vessels, the performing of a deep micro-massage for the striated muscles.

Ultrasounds (54) were used for biological effects, that is: the increase of cell membrane permeability,

molecular activation by increasing the energetic level of the external atomic electrons, by increasing the respiratory activity at the cellular level and the activation of oxidative processes. The pursued physiological effects were those of pain relief, hyperemia and muscle relaxation.

The pain relief effect is similar to the mechanism of low frequency current for pain relief and consists of inhibiting the painful transmission from the mechanical proprioceptors. Sonophoresis was chosen as an applying methodology (direct coupling) by using gel with a non-steroidal anti-inflammatory effect (55). In this context, the depth action was reduced and the contact material was denser. According to “the ultrasonophoretic index”, the quantity of pharmacological substance entered into the skin is directly proportional to the intensity and duration of the application, but it also depends on the thickness of the tissues crossed and the physiological state of the skin. The use of ultrasound in this form improves the resorption capacity for the next sessions. The dynamic method of ultrasound application was used, having the advantage of homogenizing the ultrasounds effects in different tissue structures, under impulse regime. The application dose was $0.5\text{W}/\text{cm}^2$, the impulse frequency was 1 Hz (54).

For all the procedures that were applied to patients, the indications and contraindications of application were considered.

The kinetotherapeutic program was daily performed, it lasted for 30 minutes per session and passive mobilizations were used, but also active or active with resistance. Also, exercises for coordination and for continuing the static and dynamic balance were used, which were useful in achieving the walking.

Statistical analysis

The recording of the data obtained in the evaluation was done in Microsoft Excel files and the values for the median and the standard deviation were used, and the application of the t-student test was useful to compare the obtained results and to observe if the working hypothesis was confirmed. After calculating the t test, we can appreciate the value of the p index, which shows the possibility of an error regarding the hypothesis. The results are statistically significant for $p < 0.05$.

Results

The present study included 123 patients aged over 55 and for which the average was 62. There were 69 female patients and 54 male.

Table 1. Distribution of the group by gender and age

age/gender	55-64 years	65-74 years	75-84 years
female	42	22	5
male	34	15	5

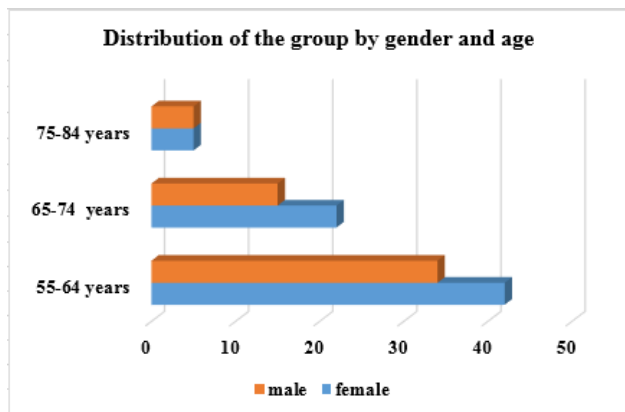


Fig. 1. Distribution of the group by gender and age

After their origin, patients come from the urban area in higher percentage (52.03%) compared to the rural area (47.96%)

Table 2. Distribution of the group by gender and environment

gender/environment	urban	rural
female	39	25
male	37	22

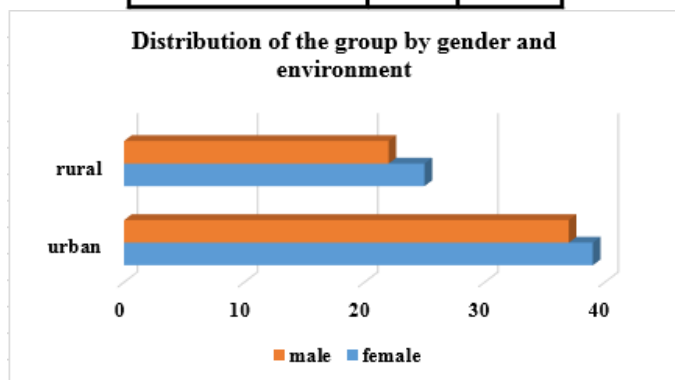


Fig. 2. Distribution of the group by gender and environment

The pain was evaluated on the VAS scale, having a statistically significant evolution for the evaluation moments, the applied student t test showed a value for $p < 0.05$.

Table 3. The evolution of pain on the VAS scale

scale	VAS		
moment	initial	final	control
mediana and std dev	7±1.47	5±1.39	3±1.11
t-student test	0.0223	0.1974	

The evaluation of the same parameter using the WOMAC index has also showed statistically significant results, with $p < 0.05$

Also with the help of the WOMAC index, two other parameters were evaluated, namely joint rigidity and functional capacity, the results being statistically significant in the 3 evaluation moments and with $p < 0.05$.

Table 4. The evolution of the WOMAC index

scale/moment/statistically	initial	final	control
pain	15±1.38	11±1.11	8±8.26
rigidity	6±0.69	3±0.45	2±0.45
functional capacity	53±2.72	39±3.27	26±3.22
WOMAC total	73±3.52	53±3.69	36±2.56

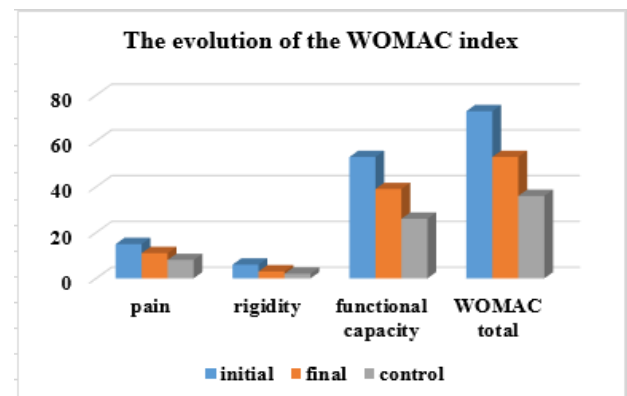


Fig. 3. The evolution of the WOMAC index in the study group

The quality of life parameter was very useful in our study, so it was evaluated with the help of the QOL scale. The results obtained after the recovery treatment are statistically significant, with $p < 0.05$.

Table 5. The evolution of the QOL scale

scale	QOL		
moment	initial	final	control
mediana and std dev	81±14.61	86±10.01	94±7.95
t-student test	0.0011	0.0012	

The patients' anxiety was evaluated with the help of the anxiety test; the results obtained were statistically significant at the 3 evaluation moments.

Table 6. The evolution of the anxiety scale

scale	Anxiety scale		
moment	initial	final	control
mediana and std dev	35±2.3	26±2.37	19±1.83
t-student test	0.0123	0.0142	

Discussions

The group of patients studied has a higher percentage of female patients (56.09%) compared to male patients (43.91%).

The distribution of patients by age and sex shows higher percentages in the 55-64 age group with 76 patients, among whom 42 (34.15%) were women and 34 (27.64%) were men.

The next one is the second age group with 22 (17.88%) female patients and 15 (12.19%) male patients.

For the age group between 75-84, the number of patients was 5 (4.07%).

Taking into consideration the above, we can state that the active professional group is affected, which leads to costs for professional treatment and reintegration.

One of the symptoms of knee osteoarthritis, which is the pain, was decreased in the study group, the results obtained by evaluation using the VAS scale (28.57% decrease of the pain at the end of treatment and 57.14% during the examination) and WOMAC (26.67% decrease at the end of treatment and 46.67% during the examination) being valid.

The joint rigidity was reduced by 50% at the end of the treatment and by 66.67% during the examination.

The functional capacity registered an increase of 26.42% at the end of the treatment and 69.81% during the examination.

The test for evaluating the anxiety caused by the disease also registered a decrease with 25.71% at the end of the treatment and of 45.72% during the examination.

Conclusions

It is vital that the recovery treatment in osteoarthritis be individualized and adapted to the age group. In our group, it enabled the reduction of pain and anxiety, the increase of the functional capacity and the quality of the patients' lives.

Taking into account the fact that the most affected group in the study group was the active professional one, we can evaluate the size of the recovery and the social, family and professional integration for these patients.

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References

1. Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, Goldring SR, Jones G, Teichtahl AJ, Pelletier J-P. Osteoarthritis. *Nat. Rev. Dis. Primers*. 2016;2:16072.
2. Lim SS, Vos T, Flaxman A.D., Danaei G., Shibuya K., Adair-Rohani H., AlMazroa MA, Amann M, Anderson HR, Andrews KG. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study *Lancet*. 2012;380:2224–2260.
3. Madry H, Luyten FP, Facchini A. Biological aspects of early osteoarthritis. *Knee Surg. Sports Traumatol. Arthrosc.* 2012;20:407–422. doi: 10.1007/s00167-011-1705-8
4. Vincent HK, Lamb KM, Day TI, Tillman SM, Vincent KR, George SZ, Morbid Obesity Is Associated with Fear of Movement and Lower Quality of Life in Patients with Knee Pain-Related Diagnoses. *PmR*. 2010;2:713–722.
5. Hawker G, Gignac M, Badley E, Davis A, French M, Li Y, Perruccio A, Power J, Sale J, Lou W. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. *Arthritis Care Res.* 2011;63:1382–1390.
6. Abbott JH, Usiskin IM, Wilson R, Hansen P, Losina E. The quality-of-life burden of knee osteoarthritis in New Zealand adults: A model-based evaluation. *PLoS ONE*. 2017;12:e0185676.
7. Henriksen M, Rosager S., Aaboe J., Graven-Nielsen T., Bliddal H. Experimental knee pain reduces muscle strength. *J. Pain*. 2011;12:460–467.
8. Rice DA, McNair PJ, Lewis GN, Mannion J. Experimental knee pain impairs submaximal force steadiness in isometric, eccentric, and concentric muscle actions. *Arthritis Res. Ther.* 2015;1:1–6.
9. Henriksen M, Graven-Nielsen T, Aaboe J, Andriacchi TP, Bliddal H. Gait changes in patients with knee osteoarthritis are replicated by experimental knee pain. *Arthritis Care Res.* 2010;62:501–509.
10. Oiestad BE, Juhl CB, Eitzen I, Thorlund J.B. Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. *A*

- systematic review and meta-analysis. *Osteoarthr. Cartil.* 2015;23:171–177.
11. Cedraschi C, Delézay S, Marty M, Berenbaum F., Bouhassira D., Henrotin Y, Laroche F, Perrot S. Let's talk about OA pain: A qualitative analysis of the perceptions of people suffering from OA. Towards the development of a specific pain OA-related questionnaire, the Osteoarthritis Symptom Inventory Scale (OASIS) *PLoS ONE*. 2013; 8:e79988.
 12. Moss P, Knight E, Wright A. Subjects with knee osteoarthritis exhibit widespread hyperalgesia to pressure and cold. *PLoS ONE*. 2016;11:e0147526.
 13. Blikman T, Rienstra W, van Raay JJ, Dijkstra B., Bulstra S.K., Stevens M., van den Akker-Scheek I. Neuropathic-like symptoms and the association with joint-specific function and quality of life in patients with hip and knee osteoarthritis. *PLoS ONE*. 2018; 13:e0199165.
 14. Nishigami T, Mibu A, Tanaka K, Yamashita Y, Yamada E, Wand BM, Catley MJ, Stanton TR, Moseley GL. Development and psychometric properties of knee-specific body-perception questionnaire in people with knee osteoarthritis: The Fremantle Knee Awareness Questionnaire. *PLoS ONE*. 2017;12:e0179225.
 15. Parry E, Ogollah R, Peat G. Significant pain variability in persons with, or at high risk of, knee osteoarthritis: Preliminary investigation based on secondary analysis of cohort data. *Bmc Musculoskelet. Disord.* 2017;18:80.
 16. Collins J, Katz J, Dervan E, Losina E. Trajectories and risk profiles of pain in persons with radiographic, symptomatic knee osteoarthritis: Data from the osteoarthritis initiative. *Osteoarthr. Cartil.* 2014;22:622–630.
 17. Nicholls E, Thomas E, van der Windt D, Croft P, Peat G. Pain trajectory groups in persons with, or at high risk of, knee osteoarthritis: Findings from the Knee Clinical Assessment Study and the Osteoarthritis Initiative. *Osteoarthr. Cartil.* 2014;22:2041.
 18. CG Helmick and DT Felson and RC Lawrence et al, “Estimates of the prevalence of arthritis and other rheumatic conditions in the United States”, Part.I, *Arthritis and Rheumatology* 58 (2008): 15-25.
 19. CJL Murray and AD Lopez, “Global mortality, disability, and the contribution of risk factors: global burden of disease study”, in *The Lancet*, vol. 349, no. 9063 (1997): 1436-1442.
 20. R Altman and E Asch and D Bloch and G Bole and D Borenstein and K Brandt et al, “Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association,” *Arthritis and Rheumatology* 29 (1986): 1039-49.
 21. Antonescu E, Bota G, Serb B, Atasie D, Tataru CD, Totan M, .. & Oswald, I. (2018). Study of the Total Serum Concentration of Serrum Ionized Magnesium in Children and Adolescents from Sibiu Area. *REVISTA DE CHIMIE*, 69(12), 3389-3392.
 22. JH Kellgren and JS Lawrence and “Osteoarthritis and disk degeneration in an urban population,” *Annals of Rheumatic Diseases* 17 (1958): 388-97.
 23. Kim C, Nevitt MC, Niu J., Clancy MM, Lane NE, Link TM, Vlad S, Tolstykh I, Jungmann PM, Felson DT. Association of hip pain with radiographic evidence of hip osteoarthritis: Diagnostic test study. *Bmj.* 2015:351.
 24. Kim C, Nevitt MC, Niu J, Clancy MM, Lane NE, Link TM, Vlad S, Tolstykh I, Jungmann PM, Felson DT. Association of hip pain with radiographic evidence of hip osteoarthritis: Diagnostic test study. *Bmj.* 2015:351.
 25. Barr AJ, Campbell TM, Hopkinson D, Kingsbury SR, Bowes MA, Conaghan PG. A systematic review of the relationship between subchondral bone features, pain and structural pathology in peripheral joint osteoarthritis. *Arthritis Res. Ther.* 2015;1:1–36.
 26. Alliston T, Hernandez CJ, Findlay DM, Felson DT, Kennedy OD. Bone marrow lesions in osteoarthritis: What lies beneath. *J. Orthop. Res.* 2018;36:1818–1825.
 27. Alliston T., Hernandez CJ, Findlay DM, Felson DT, Kennedy OD. Bone marrow lesions in osteoarthritis: What lies beneath. *J. Orthop. Res.* 2018;36:1818–1825.
 28. Kumm J, Turkiewicz A, Zhang F, Englund M. Structural abnormalities detected by knee magnetic resonance imaging are common in middle-aged subjects with and without risk factors for osteoarthritis. *Acta Orthop.* 2018;89:535–540.
 29. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain.* 2011;152:S2–S15.

30. Skou ST, Graven-Nielsen T, Lingsøe L, Simonsen O, Laursen MB, Arendt-Nielsen L. Relating clinical measures of pain with experimentally assessed pain mechanisms in patients with knee osteoarthritis. *Scand. J. Pain.* 2013 ;4:111–117.
31. Lluch E, Torres R, Nijs J, Van Oosterwijck J. Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review. *Eur. J. Pain.* 2014;18:1367–1375.
32. Duica L, Antonescu E, Pirlog M, Purnichi T, Szakacs J, Totan M,... & Bota, G. (2018). Clinical and biochemical correlations of aggression in Young patients with mental disorders. *Revista de Chimie.* 69(6), 1544-1549.
33. Skou ST, Graven-Nielsen T, Lingsøe L, Simonsen O, Laursen MB, Arendt-Nielsen L. Relating clinical measures of pain with experimentally assessed pain mechanisms in patients with knee osteoarthritis. *Scand. J. Pain.* 2013 ;4:111–117.
34. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, Campbell CM, Haythornthwaite JA, Edwards RR, Smith MT. Discordance between pain and radiographic severity in knee osteoarthritis: Findings from quantitative sensory testing of central sensitization. *Arthritis Rheum.* 2013 ;65:363–372. doi: 10.1002/art.34646
35. Eitner A, Hofmann G, Schaible H. Mechanisms of Osteoarthritic Pain. *Studies in Humans and Experimental Models. Front. Mol. Neurosci.* 2017 ; 10:349.
36. Bocsa CD, Moisoiu V, Stefancu A, Leopold LF, Leopold N, & Fodor D. (2019). Knee osteoarthritis grading by resonant Raman and surface-enhanced Raman scattering (SERS) analysis of synovial fluid. *Nanomedicine: Nanotechnology, Biology and Medicine*, 20, 102012.
37. Tuncer T, Cay FH, Altan L, Gurer G, Kacar C, Ozcakil S, Atik S, Ayhan F, Durmaz B, Eskiurt N, et al. 2017 update of the Turkish League Against Rheumatism (TLAR) evidence-based recommendations for the management of knee osteoarthritis. *Rheumatol. Int.* 2018;38:1315–1331.
38. Silisteanu SC, Silisteanu AE. . The importance of the nutrition and of the body weight index in the recovery of the patients older diagnosed with coxarthrosis. *Balneo Research Journal.* 2017;8(1), 15-20.
39. Wang X, Hunter D, Xu J, Ding C. Metabolic triggered inflammation in osteoarthritis. *Osteoarthr. Cartil.* 2015;23:22–30.
40. Lee YC, Lu B, Bathon JM, Smith MT, Haythornthwaite JA, Page GG, Edwards RR. Pain sensitivity and pain reactivity in osteoarthritis. *Arthritis Care Res. (Hoboken)* 2011;63:320–327.
41. Hosu CD, Moisoiu V, Stefancu A, Antonescu E, Leopold LF, Leopold N, Fodor, D. (2019). Raman spectroscopy applications in rheumatology. *Lasers in medical science.* 34(4), 827-834.
42. Royal Australian College of General Practitioners . *Guideline for the Management of Knee and Hip Osteoarthritis.* 2nd ed. Royal Australian College of General Practitioners; Melbourne, Australia: 2018.
43. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr. Cartil.* 2014;22:363–388.
44. Juhl C, Christensen R, Roos EM, Zhang W, Lund H. Impact of exercise type and dose on pain and disability in knee osteoarthritis: A systematic review and meta-regression analysis of randomized controlled trials. *Arthritis Rheumatol.* 2014;66:622–636.
45. Wesseling JJ, Bastick AA, ten Wolde S, Kloppenburg MM, Lefeber FF, Bierma-Zeinstra SS, Bijlsma HJ. Identifying trajectories of pain severity in early symptomatic knee osteoarthritis: A 5-year followup of the cohort hip and cohort knee (CHECK) study. *J. Rheumatol.* 2015;42:1470–1477.
46. The National Institute for Health and Care Excellence . *Osteoarthritis: Care and Management—Clinical Guideline.* National Institute for Health and Care Excellence; London, UK: 2014.
47. American Academy of Orthopaedic Surgeons . *Treatment of Osteoarthritis of the knee: Evidence-Based Guideline.* 2nd ed. American Academy of Orthopaedic Surgeons; Rosemont, IL, USA: 2013.
48. Mann EG, LeFort S, VanDenKerkhof EG. Self-management interventions for chronic pain. *Pain Manag.* 2013;3:211.

49. Birlutiu V, Stef L, Mitariu SIC, Filip CR, Duica L, Antonescu E, Manea MM (2018). The Biochemical Biomarkers Determination in Alzheimer Dementia. *REVISTA DE CHIMIE*. 69(11), 4055-4059.
50. Smith C, Kumar S, Pelling N. The effectiveness of self-management educational interventions for osteoarthritis of the knee. *Jbi Database Syst. Rev. Implement. Rep.* 2009;7:1091–1118.
51. Kroon FP, van der Burg LR, Buchbinder R, Osborne RH, Johnston RV, Pitt V. Self-management education programmes for osteoarthritis. *Cochrane Database Syst. Rev.* 2014
52. Rabenda V, Manette C, Lemmens R et al. Direct and indirect costs attributable to osteoarthritis in active subjects. *Journal of Rheumatology*.2006; 33 (6): 1152-58.
53. Hermans J, Koopmanschap MA, Bierma-Zeinstra SMA et al. Productivity costs and medical costs among working patients with knee osteoarthritis, *Arthritis Care and Research* .2012;64 : 853-861.
54. Silisteanu SC, Silisteanu AE, Antonescu E. The study on the importance of effects after the ultrasound use in the recovery of patients with lower lumbar discopathy. *Balneo Research Journal*.2018;9(4), 433-437.
55. Silisteanu SC, Mitariu L, Ranga R, Antonescu E, Duica CL, Racheriu M, Manea, MM. Potentiating the Effect of Treatment with Voltaren Gel Using Ultrasonic Frequencies of 1 MHz. *Revista de Chimie*.2017;69(7), 1749-1751.
56. Radulescu A. *Electroterapie*. Editura Medicala, 2014
57. Silisteanu SC, Antonescu E, Moisii V. The importance of the recovery treatment in increasing the quality of the lives of the patients with the carpal tunnel syndrome. *Balneo Research Journa*.2016; 7(3), 81-88.
58. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Osteoarthritis and absenteeism costs: evidence from US national survey data. *Journal of Occupational and Environmental Medicine*, vol. 52, no. 3, (2010): 263-68.
59. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommen-dations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Semin Arthritis Rheum* 2014;43:701–1
60. Dobson F, Hinman R, Hall M, Terwee C, Roos EM, Bennell K. Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. *Osteoarthritis Cartilage*. 2012;20:1548–62.
61. Wright AA, Hegedus EJ, Baxter GD, Abbott JH. Measurement of function in hip osteoarthritis: developing a standardized approach for physical performance measures. *Physiother Theory Pract* .2011;27:253–62.
62. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr. Cartil*.2014;22:363–388.
63. Larmer PJ, Reay ND, Aubert ER, Kersten P. Systematic Review of Guidelines for the Physical Management of Osteoarthritis. *Arch. Phys. Med. Rehabil*. 2014;95:375–389.
64. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: A Cochrane systematic review. *Br. J. Sports Med*. 2015;49:1554–1557.
65. Hoffman MD, Hoffman DR. Does aerobic exercise improve pain perception and mood? A review of the evidence related to healthy and chronic pain subjects. *Curr. Pain Headache Rep*. 2007;11:93–97.
66. Li Y, Su Y, Chen S, Zhang Y, Zhang Z, Liu C, Lu M, Liu F, Li S, He Z. The effects of resistance exercise in patients with knee osteoarthritis: A systematic review and meta-analysis. *Clin. Rehabil*. 2016;30.
67. Pedersen BK, Saltin B. Exercise as medicine: Evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand. J. Med. Sci. Sports*. 2015;25:1–72.
68. Totan M, Antonescu E, Catana MG, Mitariu MMC, Duica L, Filip CR, Mitariu SIC. (2019). C-Reactive Protein-A Predictable Biomarker in Ischemic Stroke. *Revista de Chimie*, 70(6), 2290-2293.
69. Sluka KA, Frey-Law L, Bement MH. Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation. *Pain*. 2018;159:S91–S97.
70. Rice D, Nijs J, Kosek E, Wideman T, Hasenbring MI, Koltyn K, Graven-Nielsen T,

- Polli A. Exercise induced hypoalgesia in pain-free and chronic pain populations: State of the art and future directions. *J. Pain.* 2019 doi: 10.1016/j.jpain.2019.03.005
71. Helmark IC, Mikkelsen UR, Børglum J, Rothe A, Petersen MC, Andersen O, Langberg H, Kjaer M. Exercise increases interleukin-10 levels both intraarticularly and peri-synovially in patients with knee osteoarthritis: A randomized controlled trial. *Arthritis Res. Ther.* 2010;12:R126.
 72. Runhaar J, Beavers D, Miller G, Nicklas B, Loeser R, Bierma-Zeinstra S, Messier S. Inflammatory cytokines mediate the effects of diet and exercise on pain and function in knee osteoarthritis, independent of BMI. *Osteoarthr. Cartil.* 2019;27:S453.
 73. Foster N, Thomas M, Holden M. Is long term physical activity safe for older adults with knee pain: A systematic review. *Osteoarthr. Cartil.* 2015;23:1445–1456.
 74. Van Ginckel A, Hall M, Dobson F, Calders P. Effects of long-term exercise therapy on knee joint structure in people with knee osteoarthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum.* 2019;48:941–949.
 75. Bricca A, Juhl C.B, Steultjens M, Wirth W, Roos EM. Impact of exercise on articular cartilage in people at risk of, or with established, knee osteoarthritis: A systematic review of randomised controlled trials. *Br. J. Sports Med.* 2018
 76. Silisteanu SC, Silisteanu AE. The importance of physical exercise-bone mass density correlation in reducing the risk of vertebral and non-vertebral fracture in patients with osteoporosis. *Balneo Research Journal.* 2018; 9(2), 64-68.
 77. Department of Veterans Affairs/Department of Defense, Clinical Practice Guideline for the Non-Surgical Management of Hip & Knee Osteoarthritis. Department of Veterans Affairs/Department of Defense; Washington, DC, USA: 2014.
 78. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, Beavers DP, Hunter DJ, Lyles MF, Eckstein F, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. *JAMA.* 2013;310:1263–1273.
 79. Bushnell MC, Čeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat. Rev. Neurosci.* 2013;14:502.
 80. Chen Q, Heinricher M. Descending Control Mechanisms and Chronic Pain. *Curr. Rheumatol. Rep* 2019;21:13.
 81. Fu K, Makovey J, Metcalf B, Bennell KL, Zhang Y, Asher R, Robbins SR, Devezza LA, Cistulli P.A., Hunter D.J. Sleep Quality and Fatigue are Associated with Hip Osteoarthritis Pain Exacerbations: An Internet-Based Case-Crossover Study. *J. Rheumatol.* 2019.
 82. Ho KKN, Ferreira PH, Pinheiro MB, Aquino Silva D, Miller CB, Grunstein R, Simic M. Sleep interventions for osteoarthritis and spinal pain: A systematic review and meta-analysis of randomized controlled trials. *Osteoarthr. Cartil.* 2019;27:196–218.
 83. Silisteanu SC, Antonescu E, Totan M. Study on the importance of medical treatment and physical methods in recovering patients with knee osteoarthritis, *Balneo Research Journal.* 2019, 10(2), 90-97.
 84. Axford J, Butt A, Heron C, Hammond J, Morgan J, Alavi A, Bolton J, Bland M. Prevalence of anxiety and depression in osteoarthritis: Use of the Hospital Anxiety and Depression Scale as a screening tool. *Clin. Rheumatol.* 2010;29:1277–1283.
 85. Duica Lavinia, Depression - multiple psychopathological facets, *Mental Health-actual views in psychology, medicine and anthropology*, sep 2016, p 20-24.
 86. Hawker G, Gignac M, Badley E, Davis A, French M, Li Y, Perruccio A, Power J, Sale J, Lou W. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. *Arthritis Care Res.* 2011;63:1382–1390.
 87. Burston JJ, Valdes AM, Woodhams SG, Mapp PI, Stocks J, Watson DJ, Gowler PR, Xu L, Sagar DR, Fernandes G. The impact of anxiety on chronic musculoskeletal pain and the role of astrocyte activation. *Pain.* 2019;160:658.
 88. Rayahin JE, Chmiel JS, Hayes KW, Almagor O, Belisle L, Chang AH, Moio K, Zhang Y, Sharma L. Factors Associated with Pain Experience Outcome in Knee Osteoarthritis. *Arthritis Care Res.* 2014;12:1828–1835.

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