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Renal damage induced by non-steroidal anti-inflammatory drug treatment

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively used worldwide due to their analgesic, antipyretic and anti-inflammatory effects. NSAIDs (both non-selective NSAIDs and selective cyclooxygenase-2 inhibitors) have nephrotoxic potential, particularly when used chronically.The principal mechanism of action of NSAIDs is cyclooxygenase inhibition, which prevents the conversion of arachidonic acid to prostaglandins, prostacyclins and thromboxanes. In the kidney, prostaglandins induce vasodilation and counter the action of the renin-angiotensin-aldosterone system and the sympathetic nervous system, ensuring optimal renal perfusion. Inhibition of this mechanism by NSAIDs can result in renal damage: acute kidney injury through hemodynamic mechanism, acute interstitial nephritis, glomerular disease, papillary necrosis, water and electrolyte imbalances, HTN. Chronic NSAID use may lead to chronic kidney disease.The nephrotoxic effect is reduced in young patients without renal disease or other comorbidities, but increases significantly in elderly patients with pre-existing kidney disease, nephrotic syndrome, diabetes mellitus, severe congestive heart failure, volume depletion, cirrhosis with ascites, HTN, atherosclerosis, or in patients under treatment with diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors.

Key words: *non-steroidal anti-inflammatory drugs, nephrotoxicity, kidney disease, cyclooxygenase, prostaglandins*

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used since ancient times (by Assyrians, Egyptians, Greeks) for their analgesic, antipyretic and anti-inflammatory effects. Initially, they were extracted from willow bark and leaves. At the end of the 17th century, in Europe, salicin was identified as the active ingredient in the willow extract. The German company Kolbe started the mass production of salicylic acid, and in 1899 the Bayer company changed it into acetylsalicylic acid and launched it on the market under the name of aspirin (1,2).

NSAIDs underwent a major development during the past century, especially after Sir John Vane, an English pharmacologist, identified their role in the inhibition of prostaglandin synthesis mediated by cyclooxygenases (1,3,4). They started to be increasingly used in the treatment of a wide range of conditions, from minor pain and fever to osteoarticular disorders (acute and chronic) or inflammatory intestinal diseases. With their extensive use, adverse reactions started to appear: digestive hemorrhage, ulcer, arterial hypertension, platelet dysfunction syndrome, cardiovascular adverse reactions and renal damage (1,5,6,7).

Currently, NSAIDs are among the most widely used drugs globally, and most of them can be bought over the counter. The most frequent users are those with chronic pain associated with rheumatic diseases (rheumatoid arthritis, osteoarthritis or other musculoskeletal disorders).

The pharmacological effect of NSAIDs depends on the dose and the duration of treatment. Prolonged use leads to organ damage, renal involvement ranking second in terms of frequency (8,9,10).

The mechanism of action of NSAIDs

The principal mechanism of action of NSAIDs is central and peripheral cyclooxygenase (COX) inhibition, which interferes with the conversion of arachidonic acid to prostaglandins (PG), prostacyclins and thromboxanes. Prostaglandins have a vasodilator effect, extremely important for the maintenance of preglomerular resistance, glomerular filtration rate and renal blood flow (1,5,11,12).

There are two COX isoforms, COX-1 and COX-2, which act at different levels. The COX-1 isoform has a role in regulating physiological processes and maintaining homeostasis; therefore, it is present in the majority of cells and tissues (endothelium, monocytes, platelets, renal collecting ducts, gastrointestinal tract, seminal vesicles). COX-2 is activated by inflammation and pro-inflammatory cytokines in the vascular endothelium, osteoclasts and macrophages (1,5,7,13,14). NSAIDs can be

classified into four categories, depending on their selectivity in inhibiting COX-1 and/or COX-2 (1,5,15) (Table 1).

Table 1. Classification of NSAIDs depending on inhibition of COX-1 and/or COX-2 (15).

Class	Properties	Examples
Group 1	NSAIDs that inhibit both COX1 and COX-2	Aspirin, ibuprofen, ketoprofen, diclofenac, indomethacin, naproxen, piroxicam
Group 2	NSAIDs that are preferential COX-2 inhibitors	Celecoxib, etodolac, meloxicam, nimesulide
Group 3	NSAIDs that are highly selective COX-2 inhibitors	Rofecoxib, NS-398
Group 4	NSAIDs that are weak inhibitors of both isoforms	5-aminosalicylic acid, sodium salicylate, nabumetone, sulfasalazine

The majority of adverse effects are related to COX-1 inhibition. In the kidney, COX-1 has an important role in maintaining glomerular filtration, which is why the renal adverse effects of using non-selective NSAIDs are greater in patients with pre-existing renal involvement. The action of COX-2 is associated with renal water and electrolyte balance; thus, renal adverse effects are enhanced by dehydration, decreased renal perfusion or pre-existing renal damage (5,14,16,17).

The mechanisms by which NSAIDs can induce renal damage

The kidneys achieve complex functions: they maintain homeostasis (fluid volume and osmolarity, water, electrolyte and acid-base balance), excrete metabolic end products, metabolize and excrete a series of exogenous substances, including drugs. Prostaglandin synthesis plays an important role in ensuring the filtration function by maintaining the glomerular filtration rate and renal homeostasis (1,5,18,19).

NSAIDs inhibit coenzymes COX-1 and/or COX-2 and implicitly, the formation of prostaglandins. In the kidney, prostaglandins (especially prostacyclin, PGE2, PGD2) have a vasodilator action on the afferent arteriole, increasing renal perfusion, with the distribution of blood flow from the renal cortex to the medulla. Furthermore, vasodilation has a negative feedback effect on the renin-angiotensin-aldosterone system and the sympathetic nervous system, ensuring adequate blood flow in the kidney. NSAIDs, through inhibition of PG synthesis, can lead to acute vasoconstriction and acute kidney injury (5,10,18,19,20).

In addition to its vasodilator action, PGE2 inhibits the transport of sodium and chloride in the ascending limb of the loop of Henle and in the collecting duct, resulting in natriuresis. PGE2 also has an antagonist effect on antidiuretic hormone receptors, favoring diuresis. The inhibition of PGE2 production by NSAIDs leads to sodium and water retention, with the development of edema and arterial hypertension (5,19,21,22,23,24).

Clinical renal syndromes associated with the use of NSAIDs NSAID treatment may affect cells in all nephron components through various mechanisms (1,9,25) (Table 2).

Table 2. Renal syndromes induced by NSAIDs (1,9).

Acute kidney injury	Hemodynamically mediated Acute tubular necrosis
Acute interstitial nephritis	
Glomerular disease	Minimal change disease Membranous nephropathy
Papillary necrosis	
Electrolyte abnormalities	Hyperkalemia Renal tubular acidosis Hyponatremia
Hypertension/edema	
Analgesic nephropathy/chronic tubulointerstitial nephritis	

Acute kidney injury (AKI)

The most frequent form of AKI induced by NSAIDs is hemodynamically mediated, and may occur following both non-selective NSAIDs and selective NSAIDs. AKI develops due to an alteration of intrarenal microcirculation and implicitly, of glomerular filtration by inhibition of PG synthesis (9,25,26,27).

Under euvolemic conditions, basal prostaglandin levels are not very high; this is why intrarenal circulation does not depend on these substances to maintain the glomerular filtration rate. Consequently, under these circumstances, prostaglandin synthesis inhibition induced by NSAIDs rarely affects renal circulation and function. In contrast, under conditions of volume depletion, severe hypotension, hemodynamic instability, prostaglandin synthesis is significantly increased to counterbalance vasoconstriction induced by angiotensin II, norepinephrine, endothelin and vasopressin, and to ensure adequate renal perfusion, with the maintenance of glomerular filtration and the reduction of ischemia. In these patients, prostaglandin synthesis inhibition by NSAIDs leads to a decrease in

the glomerular filtration rate, acute ischemia that increases the risk of acute tubular necrosis, an enhancement of vascular tone with antidiuretic and antinatriuretic effects (1,5,10,28,29).

AKI induced by NSAIDs is not frequent, but its incidence increases significantly in patients at risk such as: patients with volume and sodium depletion, congestive heart failure, cirrhosis with ascites, nephrotic syndrome, chronic kidney disease, arterial hypertension, diabetes mellitus, over 65 years of age (especially in the case of comorbidities) (28,29,30,31). Also, there is an increased risk for AKI in the case of the association of NSAIDs with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) or diuretics (1,5,7,10,29,32,33).

AKI clinically manifests with oliguria and an elevation in serum creatinine levels, which occur 3-7 days after administration of NSAIDs. Proteinuria, if present, is lower than 500 mg/day. Absence of hematuria and proteinuria in the presence of granular and epithelial cylinders is specific to ischemic injury. AKI treatment consists of immediate interruption of NSAIDs and volume repletion (if needed). Otherwise, the management of AKI is identical to that of AKI of other causes (1,9,10,28).

Acute interstitial nephritis

Acute interstitial nephritis is responsible for about 15% of AKI cases. It can have multiple causes, but is most frequently induced by drugs, among which NSAIDs play an important role (1,10,25,34,35).

Pathogenetically, a type IV delayed hypersensitivity reaction occurs, which is mediated by T helper 2 lymphocytes. Renal function alteration develops through acute inflammation and edema of the renal interstitium, associated with tubulitis and lymphocyte and eosinophil infiltration (35,36,37).

AIN induced by NSAIDs has several clinical particularities: it occurs after a long treatment duration, 6-18 months (for both non-selective and COX-2 selective NSAIDs), and patients do not present fever, rash or eosinophilia (which are probably masked by the anti-inflammatory effects of NSAIDs) (1,25,28,35).

Despite AKI that can be severe, treatment interruption is followed in the majority of cases by renal function restoration (1,25,35).

Glomerular disease

Glomerular disease induced by NSAIDs (selective and non-selective) is represented by minimal change disease (MCD) with nephrotic syndrome and rarely, by membranous nephropathy (MN) (25,38,39). Pathogenesis is not completely understood and is more probably due to an alteration of immune response secondary to COX inhibition than to direct toxic cellular effects. MCD can be associated with AIN. Interruption of treatment with NSAIDs usually results in remission of glomerular disease. If nephrotic syndrome persists after interruption of NSAID treatment, corticotherapy is associated, with favorable results (1,9,25,38).

Papillary necrosis

NSAIDs may cause acute, subacute or chronic papillary necrosis, which constitutes analgesic nephropathy. PG synthesis inhibition by NSAIDs leads to a diminution of blood flow in the renal medulla and papilla, with ischemia and even papillary necrosis. Administration of NSAIDs under volume depletion conditions (after vomiting, diarrhea, sepsis, diuretics, insufficient intake) increases the risk of acute tubular necrosis (1,40,41,42).

Clinically, there is an alteration of the urine concentration capacity, sterile pyuria, microscopic hematuria and low-level proteinuria, with an increase in serum creatinine values. Computed tomography can be useful for diagnosis (1,29,42).

Prognosis depends on the time of diagnosis and on the time of treatment interruption. Continuing NSAID treatment can lead to end-stage chronic kidney disease (1,29,41).

Alteration of water and electrolyte balance by NSAIDs

Hyperkalemia occurs by two mechanisms. In the first place, it inhibits renin secretion mediated by PG, with the development of hyporeninemic hypoaldosteronism, which results in decreased potassium secretion in the collecting duct cells with hyperkalemia. In the second place, NSAIDs induce AKI with a reduction of glomerular filtration.

The diminution of glomerular filtration leads to a decrease in sodium concentration in the distal nephron, with a decrease in potassium secretion at this level. Hyperkalemia is more severe in patients with intravascular volume depletion, heart failure, or patients receiving NSAIDs associated with ACEI, ARBs or aldosterone blockers (1,10,29,30,43).

Renal tubular acidosis occurs due to prolonged hyperkalemia, which leads to a decrease in renal ammonium ion excretion in the distal nephron, with type 4 renal tubular acidosis, a form of

hyperchloremic metabolic acidosis (1,10,43).

Hyponatremia develops because of PG secretion inhibition by NSAIDs and the disappearance of their regulatory effect on the antidiuretic hormone, with increased water reabsorption and dilution hyponatremia. The decrease in the glomerular filtration rate also favors water retention and hyponatremia (1,10,43).

Arterial hypertension

The inhibition of PG production by NSAIDs results in sodium and water retention, with the development of edema and increased blood pressure values. This effect is more intense in patients with pre-existing HTN, heart failure, chronic kidney disease or cirrhosis (1,10,28,44).

NSAIDs and chronic kidney disease

Both types of NSAIDs (selective and non-selective) inhibit intrarenal vasodilation mediated by PG, with a decrease in renal perfusion and an alteration of the glomerular filtration rate, which is why they should be avoided in patients with a glomerular filtration rate lower than 60 ml/min. In these patients, even small doses of NSAIDs can precipitate the development of renal failure with all the mechanisms described above. Moreover, these patients usually receive treatment with ACEIs, ARBs or diuretics for HTN, proteinuria or volume control, which in association with NSAIDs increase even more the risk of rapid alteration of the renal function (1,5,9,10,45).

Conclusions

NSAIDs, both non-selective and selective (including coxibs), can induce renal damage. The risk of renal involvement is lower in young patients without associated diseases, but increases significantly in elderly patients (who usually have several associated diseases requiring drug associations and have reduced renal hemodynamics), with pre-existing kidney disease, nephrotic syndrome, diabetes mellitus, severe congestive heart failure, volume depletion, cirrhosis with ascites, HTN, atherosclerosis, or in patients under treatment with diuretics, ACEIs or ARBs. This is why careful monitoring of the renal function during prolonged NSAID treatment is necessary, particularly in patients with risk factors. Early identification of renal damage and interruption of treatment with NSAIDs lead in the majority of cases to the recovery of renal function or at least, to its improvement.

Declaration of conflict of interests

The author does not have any financial interest involving the companies and/or materials mentioned in this article.

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Neurorehabilitation in basilar artery occlusion in a young patient with thrombophilia and antiphospholipid antibody syndrome – a case report

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Abstract

Twenty percent of strokes occurring in young patients are represented by posterior ischemic strokes. Acute basilar occlusion is a devastating, life-threatening condition, with the highest mortality in young patients. We present the case of a 33-year-old female patient, without vascular risk factors or oral contraceptive treatment, admitted to our department through the emergency ward for comatose state – Glasgow Coma Scale (GCS) 11 points, headaches, right-sided hemiparesis, dizziness and vomiting, with acute onset. CT angiography was performed, which showed left vertebral artery with no flow in the intradural section and absent flow in the basilar artery. After more than 12 hours from onset, endarterectomy was excluded; initiation of treatment with heparin 1000 IU/hour was decided. MRI performed after 24 hours revealed: subacute median and left paramedian pontine ischemic stroke, subacute stroke in the base of the left midbrain peduncle. The following diagnosis was established: pontine ischemic stroke caused by two autoimmune diseases: thrombophilia and antiphospholipid antibody syndrome. Our patient started rehabilitation very early and was discharged with the following neurological sequelae: tetraparesis with the predominance of left hemiparesis: 4/5 on the Medical Research Council strength scale (MRC) – right limbs, 3/5 on the Medical Research Council strength scale (MRC) – left limbs, and dysphagia for liquids.

Key words: *ischemic stroke, young patient, neurorehabilitation,*

Introduction

Twenty percent of strokes occurring in young patients are represented by posterior ischemic strokes. Acute basilar occlusion is a devastating, life-threatening condition, with the highest mortality in young patients (1). Studies on the outcome of basilar artery occlusion using a conventional treatment approach have been small and have described the outcome of highly selected patients or used very broad definitions, including vertebral and branch artery occlusions, finding a case fatality of 86% (2). Basilar artery occlusion represents 1% of all strokes and currently, there is no consensus on the best treatment strategy for these patients. While endovascular reperfusion therapy has been demonstrated to improve outcomes in anterior circulation stroke, its benefit in acute basilar artery occlusion (BAO) has not been confirmed in randomized controlled trials.

Antiphospholipid antibody syndrome is a rare cause of stroke in young patients, especially when associated with thrombophilia or other hypercoagulable states. These autoantibodies appear to cause clinical symptoms by working in concert with phospholipid-binding proteins, which subsequently bind to endothelial and other cells leading to a pro-inflammatory or hypercoagulable state. Stroke associated with antiphospholipid antibodies occurs most commonly in young people and should be considered as a possible cause in these groups (3).

If there is an association between inherited thrombophilias and arterial stroke, then it is a weak one, probably enhanced by other prothrombotic risk factors, such as antiphospholipid antibody syndrome or systemic lupus erythematosus (SLE) (4).

Ischemia may transiently induce antiphospholipid antibodies, and prospective studies examining stroke incidence among patients have found that the presence of lupus anticoagulant poses a greater risk than other antiphospholipid antibodies. Consistent associations between young ischemic stroke and the presence of lupus anticoagulant and anticardiolipin antibodies are seen, inflammation, especially IL-6, being highlighted as a risk factor in the development of stroke (5).

Case report

We present the case of a 33-year-old female patient, with neither vascular risk factors nor oral contraceptive treatment, admitted to our department through the emergency ward for comatose state – CGS 11 points, headaches, right-sided hemiparesis, dizziness and vomiting, with acute onset. At admission, the patient had a blood pressure value of 120/80 mmHg and a rhythmic heart rate, 100 b/min. She had no fever and no other abnormalities at the general examination. Neurological examination revealed: divergent strabismus of the left eye, right-sided hemiplegia, 0/5 MRC, diminished right osteotendinous reflexes, and right plantar extension. Our patient was not able to maintain her gait. In the emergency service, cerebral CT was performed which was not conclusive, showing no ischemic lesion. Blood tests revealed only mild leukocytosis. Due to the fact that the patient's condition worsened – tetraplegia with skew eye deviation, decerebration rigidity and a comatose state – GCS 4 points, CT angiography was performed. This showed left vertebral artery with no flow in the intradural section and absent flow in the basilar artery (Figure 1). After more than 12 hours from onset, endarterectomy was excluded; initiation of treatment with heparin 1000 IU/hour was decided. MRI performed in the Radiology Department after 24 hours revealed: subacute median and left paramedian pontine ischemic stroke, subacute stroke in the base of the left midbrain peduncle (Figures 2, 3). Differential diagnosis with other autoimmune disorders such as multiple sclerosis or Balo-like lesions and neuromyelitis optica (NMO) was discussed. In the case of Balo-like lesions, the lesions are characteristic, with rings of demyelination, surrounded by partially demyelinated regions, reflecting concentricity within the lesion (6), and even though brainstem involvement, with or without transverse myelitis, is rarely seen in the classic type of NMO, this diagnosis was also ruled out by MRI which showed an ischemic pontine lesion, knowing that the most characteristic brainstem lesion in NMO involves the area postrema (7).

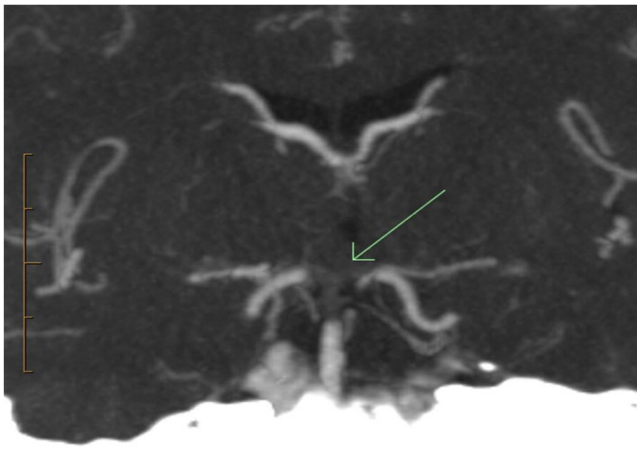

Fig. 1. CT angiography - Basilar occlusion

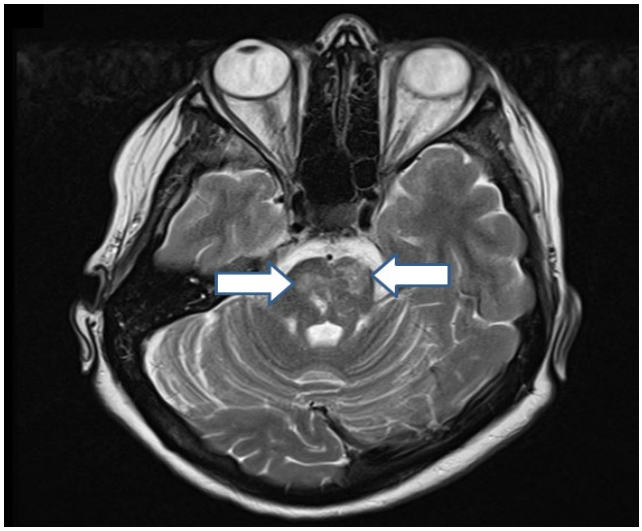

Fig. 2. T2 – FLAIR MRI – Subacute median and left paramedian pontine ischemic stroke

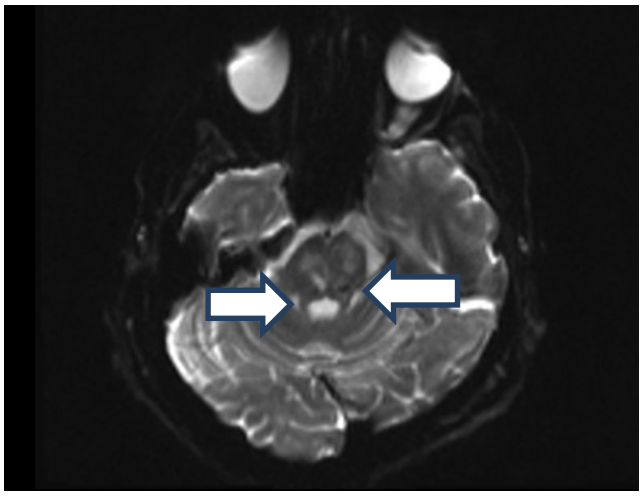

Fig. 3. DWI MRI – Pontine ischemic stroke

Based on all the information gathered, a hematological consultation was considered advisable. The hematologist recommended blood tests for different autoimmune disorders: thrombophilia, antiphospholipid antibody syndrome and lupus anticoagulant. For thrombophilia, the following were positive: factor VIII (heterozygous genotype), MTHFR C677T (homozygous genotype), and PAI1 (heterozygous genotype). Antiphospholipid syndrome and lupus anticoagulant antibodies were also positive. When deglutition was possible, dicumarin therapy was initiated. Due to the fact that the patient was in good condition, it was decided to start rehabilitation as soon as possible. Recent studies have shown that the greatest degree of recovery occurred relatively rapidly during the first 4 weeks of treatment (i.e. neurological impairments); recovery was also observed within 3 to 6 months of stroke, but to a lesser extent (8).

Rehabilitation was started early and the results did not take long to appear. Studies suggest that if a patient with a certain level of cognitive ability can acquire functional independence, one should focus more on treatment to maximize the recovery of impairment during the early post-stroke period. Our patient started rehabilitation very early: simple motor exercises and task-specific training, motor training being oriented towards achieving the goals relevant to the functional needs of the patient. Motor rehabilitation was accompanied by speech and swallowing therapy. It is known that the duration of rehabilitation therapy is not clearly established: for stroke survivors, rehabilitation should provide as much scheduled therapy (occupational therapy and physiotherapy) as possible, with a minimum of three hours a day (9). After 14 days, the patient was included in a rehabilitation program consisting of daily physical exercises, for 3 hours per day, performed in the Rehabilitation Department of our hospital. After the rehabilitation program, she was discharged with the following neurological sequelae: tetraparesis with the predominance of left hemiparesis: 4/5 MRC – right limbs, 3/5 MRC – left limbs, and dysphagia for liquids, with a Barthel Index score of 11 (at admission, the Barthel Index score was 0).

Discussions

In as many as 35% of cases, the underlying etiology of stroke in young adults is still unclear. While atherosclerosis remains an important risk factor (accounting for 15–25% of strokes in young adults), cardioembolic stroke is more common among younger patients (15–35% of cases). Other causes that are more frequent in young people include extracranial artery dissection (2–25% of cases), migraine (up to 20% of cases), and drug use (up to 5% of cases, depending on the frequency of use in a given population).

Oral contraceptive use has been implicated in up to 8% of young stroke cases in some populations (10). Apart from antiphospholipid antibody syndrome (5–10% of cases), inherited coagulation disorders do not appear to play an important role in young stroke in the absence of right-to-left venoarterial shunting (10). Cerebral venous thrombosis is an uncommon cause of young stroke – 1%; usually, the risk of CVT is considered high in women older than 35 years who use oral contraception for a long period of time (10, 11). Despite all this being known, the etiology of 30% of all strokes remains unknown – the ESUS concept.

One of the ESUS criteria is excluding a major-risk cardioembolic source of embolism, which in our case was ruled out by the fact that our patient was monitored in the intensive care unit for 24 hours/day.

Post-acute care and rehabilitation are often considered a costly area of care to be trimmed, but without recognition of their clinical impact and ability to reduce the risk of downstream medical morbidity resulting from immobility, depression, loss of autonomy, and reduced functional independence. The provision of comprehensive rehabilitation programs with adequate resources, dose, and duration is an essential aspect of stroke care and should be a priority in these redesign efforts (5).

The particularity of our case is that our patient was diagnosed with two autoimmune diseases that caused the procoagulant status, whereas each of them separately could not cause such extensive cerebral ischemia. It is known that thrombophilia by itself cannot induce a procoagulant state; another risk factor (for example, another autoimmune disease, smoking, contraceptive pills, etc.) should be present.

Conclusions

The presented case fits into the stroke statistics described by the literature, in which thrombophilia is rarely the etiology of arterial ischemia. Most often, thrombophilia is known to be the etiology of cerebral venous thrombosis. In addition, the association between thrombophilia and antiphospholipid antibody syndrome is known to raise thrombotic risk.

An improvement in lower motor function is observed in about 65% of patients with initial motor deficits. The rate of clinical recovery is relatively rapid during the first few weeks after a stroke, but then slows considerably between 1 and 3 months later. Between 3 and 6 months after stroke, recovery slows so much as to be barely noticeable, although there appears to be an overall trend toward some additional recovery during this time (6).

Conflict of interest

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.

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Pharmacological pain management in patients with chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is one of the most frequently seen comorbidities in patients suffering from musculoskeletal conditions; it is defined by a glomerular filtration rate (GFR) under 60 ml/min/1.73 m2. The following paper focuses on providing a dosage adjustment guideline depending on how advanced renal impairment is.

A literature search was carried out using the following items: pharmacokinetics, side effects, drug interactions and dosage, pain medication and antirheumatic drugs in renal failure.

The use of non-steroidal anti-inflammatory drugs is inadvisable for a GFR < 30 ml/min as they all pose the risk of inducing acute renal damage, as well as worsening of the underlying chronic renal disease. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided due to the possibility of kidney disease progression. Paracetamol is an analgesic often chosen in this category of patients. As far as opioid analgesics are concerned, methadone is the only one that can be used without dosage adjustment. Physiotherapy remains a good and safe option for treatment in patients with musculoskeletal complaints.

The use of analgesics in patients with CKD continues to be a challenge, as more research is needed.

Key words: *chronic kidney disease, pain, medication, antirheumatic drug,*

1. Introduction

Patients with chronic kidney disease (CKD) have a large number of comorbidities that modulate the response to pain. Chronic pain is common in CKD and affects 50% of hemodialysis patients. From this category, 82% show moderate to severe pain.

One study reported up to 47% chronic pain in CKD stage 5 patients (1).

The etiology of pain can be iatrogenic in some procedures, but is more often due to comorbidities such as arterial disease or diabetes. The most frequent cause of pain is represented by musculoskeletal disorders (63%), of which osteoarthritis is the most common, followed by peripheral vascular disease, bone diseases (renal osteodystrophy, osteoporosis with vertebral fractures), arthritis, and peripheral neuropathy (2).

CKD affects the renal excretion mechanism of drugs and the pharmacokinetic processes involved in their distribution (e.g., absorption, clearance, extrarenal distribution, metabolism). Improper dosage adjustment of medications is common in patients with renal impairment and may cause frequent adverse effects or poor therapeutic outcomes.

The general principles of assessment, pain management and analgesia should be prescribed taking into account the WHO recommendations for pain management in these patients, with careful and frequent monitoring of possible side effects of the drug itself or its metabolite accumulation data. Clinical management should be performed by a multidisciplinary team that includes a clinical nephrologist and a pharmacist (3).

The K/DOQI Advisory Board has divided the progression of CKD into five stages (see **Table 1**).

Table 1. Stages of CKD

Stages	CKD Stage	Glomerular filtration rate ml/min/1.73m^2	Creatinine clearance (CrCl) ml/min
Normal kidney function	1	>90	120
Mild decreased function	2	60-89	20-50
Moderate	3	30-59	10-20
Severe	4	15-29	<10
End-stage renal disease	5	<15	<10

Knowing the adverse drug reactions in patients with CKD is particularly important because only in this way can further damage of residual kidney function be prevented (4,5,6).

For patients with significant glomerular filtration rate (GFR) reductions, dose adjustment and avoidance of certain analgesics is necessary because of a change in the pharmacokinetics and pharmacodynamics of several analgesics or their metabolites. Patients with CKD have an increased risk of adverse effects due to several aspects such as: comorbidities, increased susceptibility to medication, reduction of muscle/body mass, reduced therapeutic and toxic dose, and accumulation of medication due to low excretion. These pharmacokinetic characteristics and pharmacodynamic changes depend on the pharmacological agent itself, the stage of renal insufficiency and whether the patient undergoes dialysis (7,8).

An increased number of patients with CKD are elderly, and this may further enhance the sensitivity of these patients to analgesics.

The quality of life of patients with CKD is impaired both by the underlying disease and the presence of pain (9,10).

Monitoring of renal function is required in all situations where the drug that needs to be administered has renal toxic effects or is renally excreted.

In most cases of acute and chronic pain in CKD patients, physiotherapy should be performed as a non-pharmacological alternative.

In what follows, the authors aim to review most of the drugs used in pain management and their restrictions in patients with CKD, using their own experience.

ANALGESICS

STAGE I ANALGESICS

Acetaminophen

It is considered the first option in the treatment of pain. It should be kept in mind that long-term use itself may cause nephrotoxicity. Many authors do not consider dose adjustment with a GFR = 50 ml/min (maximum dose 4 g/day), but frequent comorbidities in CKD patients require caution. A GFR below 50 ml/min requires dose reduction (11,12).

Non-steroidal anti-inflammatory drugs (NSAIDs)

They should be avoided even in minor/mild renal insufficiency, but in certain situations they are accepted in stage 1 CKD. Prostaglandins mediate the compensatory vasodilation of related arterioles that vascularize the glomerulus to maintain GFR states of hypovolemia and hypotension (13).

NSAIDs lead to the renal exhaustion of prostaglandins with vasodilatory effects and allow for uncontrolled vasoconstriction. From a clinical point of view, these mechanisms can have catastrophic and unpredictable effects by diminishing blood flow. Generally, the triad NSAIDs, diuretics and angiotensin-converting enzyme (ACE) inhibitors can severely affect GFR and renal function. However, in most cases, the effect may be transient, without clear evidence of long-term impaired renal function. The risk of using NSAIDs in this patient group should be considered in relation to benefit. If NSAIDs are to be used, they should be limited to the shortest possible duration and renal function should be monitored closely. NSAIDs should be avoided in patients with additional risk factors that may affect kidney function, such as older age, diabetes mellitus, and the use of ACE inhibitors. One of the limited indications of NSAID administration is gout attack (14,15,11,4).

Topical use of NSAIDs is recommended as an alternative to general administration.

STAGE II ANALGESICS

Codeine. Half-life is significantly prolonged in CKD. Accumulation of active metabolites may lead to severe adverse reactions (e.g., respiratory arrest, narcolepsy and severe hypotension).

In mild CKD, the normal daily dose is permitted with function monitoring. In moderate CKD, a 75% reduction of the normal dose is required, and in severe CKD, 50% of the normal dose is needed (16).

Tramadol. The active metabolite is renally excreted.

In mild CKD - 50-100 mg in a single dose can be administered, moderate impairment increases the dose interval - 50-100 mg divided into 2 doses, and in severe damage it should be avoided.

In end-stage renal disease, at CrCl <30 ml/min, 50-100 mg doses every 12 hours (maximum: 200 mg/day). Retard forms of tramadol will not be prescribed in patients with CrCl <30 ml/minute (16).

STAGE III ANALGESICS

Morphine

Morphine is metabolized by the liver; 5-10% is excreted unchanged by the kidney. The hepatic metabolites of morphine, such as morphine-6-glucuronide (M6G) and morphine-3-glucuronide, are associated with hyperalgesia and neurotoxicity when accumulated in patients with severe renal impairment. At a GFR of 50 ml/min, the dose is reduced to less than 50%, and morphine is avoided in patients with a GFR below 50 ml/min.
Morphine is removed by dialysis (4,2).

Oxycodone. It is metabolized in the liver and less than 10% is renally excreted. It should be used with great caution in moderate renal impairment; a second-line agent should be considered in CKD. Dosage adjustment is recommended (data is poor) according to the following schedule:
A GFR of 20-50 ml/min does not require dose adjustment; at a GFR <20 ml/min - to be avoided.
There is no data on the effect of dialysis on oxycodone and its breakdown products (2).

Fentanyl

It has a safe pharmacological profile in patients with CKD. Hepatic metabolism is reduced, less than 10% is renally excreted. Dosage adjustment is recommended according to the following schedule:
A GFR of 20-50 ml/min - normal dose. For a GFR less than 20 ml/min, it is recommended to reduce the dose due to the phenomenon of serum accumulation and increased risk of toxic reactions (11,8).

Methadone

Methadone is fecally excreted, with no active metabolites. It is not removed by dialysis. No dose reduction is needed up to a GFR of 10 ml/min (17).

ADJUVANT ANALGESICS

This category consists of drugs that can be administered in association with other medications, or in certain situations they can be administered individually.

1. Gabapentin

Gabapentin is excreted unchanged in the urine. In our practice we used the following dose adjustment (see **Table 2**):

GFR 30-50 ml/min - max 300-700 mg in two divided doses;

GFR 10-20 ml/min - max 300 mg in a single dose;

GFR <10 ml/min - max 300 mg every other day.

Due to other side effects such as dizziness, sleepiness, gabapentin can be difficult to tolerate in elderly patients (17).

Table 2. Gabapentin – dosage

Creatinine clearance (mg/ml)	Daily dose (mg/day)
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150-600
<15	150-300

2. Pregabalin

Dose adjustment is recommended according to the following schedule (see **Table 3**):

Table 3. Pregabalin – dosage (18)

Creatinine clearance (ml/min)	Total pregabalin daily dose (mg/day)				Dose regimen
≥60	150	300	450	600	TID = three divided doses or BID = two divided doses
30-60	75	150	225	300	TID or BID
15-30	25-50	75	100-150	150	BID or one dose
<15	25	25-50	50-75	75	One dose

3. Dexamethasone. It does not require dose adjustment, but attention should be paid to urea retention.

4. Amitriptyline. A tricyclic antidepressant with no renal excretion, it can be used in renal impairment at doses of 10-25 mg/day up to 75 mg/day, depending on the patient's response (19,20).

OTHER MEDICATIONS

1. Colchicine

In mild (CrCl: 50-80 ml/min) and moderate CKD (CrCl: 30-50 ml/min), dose adjustment is not required, but patients should be carefully monitored for possible side effects.

In severe CKD (CrCl <30 ml/min): no dose adjustment is required, but a treatment course should not be repeated more than once every two weeks. For patients requiring repeated treatment, alternative therapy should be considered. Colchicine is not eliminated by hemodialysis, so there is a risk of myo/neurotoxicity (21).

2. Allopurinol

Dosage adjustment in renal impairment is required depending on creatinine clearance (CrCl):
Parenteral doses:
CrCl less than 3 ml/min: 100 mg/day with prolonged dosing interval;
CrCl: 3-10 ml/ min: 100 mg/day;
CrCl: 10-20 ml/min: 200 mg/day.
Oral doses:
CrCl less than 10 ml/min: 100 mg, 3 times/week;
CrCl: 10 ml/min: 100 mg on alternate days;
CrCl: 20 ml/min: 100 mg once/day;
CrCl: 40 ml/min: 150 mg once/day;
CrCl: 60 ml/min: 200 mg once/day.
In hemodialysis patients, administration of allopurinol is unnecessary because uric acid is eliminated by hemodialysis. Switching to febuxostat is recommended in every case of CKD with hyperuricemia. In special cases where allopurinol is recommended, the dose administered at the end of the hemodialysis session should not exceed 200 mg/session (21).

3. Febuxostat

No dose adjustment is necessary in patients with mild or moderate CKD. There are no consistent data for GFR below 30 ml/min. The effects of delaying renal impairment in patients with CKD have been demonstrated in several studies, and not only in those with hyperuricemia or gout. In clinical trials, it has been demonstrated to reduce uremia faster than allopurinol (22,23,24).

Conclusions

Pain management in patients with CKD is challenging because of the difficulty in choosing between different drugs due to direct renal toxicity or comorbidity. Choosing a medicine should be done with caution using clinical judgment to avoid further deterioration in renal function. Knowing the pharmacokinetics of analgesic drugs helps the clinician predict renal tolerance and response to treatment.

Conflicts of interest

The authors of this paper state that there are no conflicts of interest regarding the study methodology, results and conclusions drawn.

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Post-stroke visual rehabilitation - the impact on life quality of the stroke survival patients - a brief review

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Abstract
Visual rehabilitation therapy (VRT) is one of the most important and difficult post stroke rehabilitation component that can considerably improve the quality of patient's life. There are also evidences that VRT contribute to a better motor recuperation, by offering a support for spatial and temporal orientation due to process of motor activity recuperation. Visual rehabilitation methods can be classified into the following groups: Visual Substitution Therapy, Visual Scanning Training (VST), Audio-Visual Scanning Training (AViST) and Vision Restoration Training (VRT). Even the evaluation of the results of training methods have an important subjective component, being assessed by various questionnaires, there are continues improving of these methods designed to achieve better results in post stroke rehabilitation therapy. Understanding the anatomical support and psysiological background of the visual process in brain networks, and also, the pathophysiology of visual function impairment after stroke, could be a good support for an personalized rehabilitation therapy adapted to each patient. This paper is aimed to emphasise the main methods of vision rehabilitation therapy in order to offer to the post stroke rehabilitation team an instrument for their day by day activities designed to improve the quality of life for stroke surviving patients.
Key words: *stroke, visual impairment, visual rehabilitation, neuroplasticity, hemianopsia, diplopia*,

Introduction

The World Health Organization (WHO) provides a specific definition for low vision as follows: impairment of visual function even after standard correction of refractive errors or specific treatments (medical or surgical) with visual acuity less than 6/18 (3/10 on Snellen chart assessment) or a visual field with concentric reduction at less than 10 degree from the fixation point, or the inability to use the vision for daily tasking execution or planning activities (1,2). According with WHO, visual disability classified by visual acuity grade can be represented by three categories: 1: moderate visual impairment (VA between 3/10 and 1/10), 2: severe visual impairment (VA between 1/10 and 1/20), 3: blindness (VA < 1/20) (1). According with visual field (VF) defect there are: moderate visual impairment (VA field restricted between 10 and 20 degrees), severe visual impairment (VF restricted between 10 and 5 degrees), and blindness (VF restricted to less than 5 degrees (1). According with orientation and mobility ability that is subjective, but influencing daily activities, there are also moderate impairment of vision when the patient is able to localize and avoid obstacles, severe visual impairment when the activity is restricted with aids, and blindness when the visual orientation is unreliable (patient is orientating by hearing) (1). One of the most important visual impairment is consequently to stroke, both ischemic or hemorrhagic stroke can lead to visual disabilities. Visual impairment after stroke is a frequent consequence in surviving patients and can affect approximately 60% of the patients (3). Where visual problems existed in patient's history, there is possible not to be immediately recognized as part of the stroke syndrome and attributed to other causes such are migraine with aura , where the visual disturbances can precede the migraine pain, due to their common pathophysiological pathways, or hypertensive crisis (4,5). Visual impairment can consists in visual field loss, double vision, nystagmus, blurred vision (usually on the same side with motor deficit) perceptual and psychological problems (6). The visual system disorders are close related to stroke topography (7). The stroke survival patients are also complaining of dry eyes, symptom related to their age or to the lack of attention to a proper treatment of eye dryness (8). The consequences of impairing of visual function can be very various, from loosing of confidence due to increased risk for falls and accidents with trauma, to increased rehabilitation

difficulties. Impact of visual problems on the quality of life after stroke it is also considerable (8). There are also serious difficulties to adapt to this new situation and despite of the patients efforts to reduce the visual impairment (by using a magnification glass, changing their posture, increasing light intensity or changing the distance to the visual target) they are often unable to increase the visual comfort by themselves. This article is designed to analyze the importance of identify the visual impairments consequently to a stroke, in surviving patients, and to systematize the patients clinical approaching, in order to improve their neurological rehabilitation. The aim of this paper is to enhance the main neurophysiologic processes that are the basis of visual perception and the most important rehabilitation therapies that can contribute to visual rehabilitation in stroke patients.

Neurophysiologic basis of vision and associated deficits

The human visual pathways that are implicated in perception, transmission and processing of the visual information are still under the study and the organizational principles within this region are not yet well understood. The integrity of visual pathways contribute to a correct decisional activity and constitute an important guidance for motor activity, properly integrated in time and space. Despite of the classical pattern of visual information transmission from retina to the occipital cortex, through the visual pathways via reticulo-geniculo route, there are alternative pathways for visual information transmissions that play an important role for vision rehabilitation due to neuroplasticity phenomenon (9). Modern neuroimaging techniques including functional magnetic resonance imaging (fMRI) and diffusion tensor MRI and fibre tractography (DTI) support the existence of an important circuitry for visual perception of words, colours, forms and faces in occipito-temporal cortex (10). There are other visual association cortex that contains a large number of specialized visual areas as are V4 specialized for colour perception or V5 area specialized for motion perception (11). Mainly, the information that are transmitted through extrastriatal cortex are directed along two pathways: ventral pathways (for forms recognition and colours), involving inferior temporal cortex and dorsal pathways (for spatial aspects), involving parietal cortex (12). This is highly relevant in understanding brain capacity to recover visual function in patients with brain lesions. These two pathways are complementary in environmental perception and essential for a spatial and temporal integration of the motor function (11,13). According with visual field impairment there are several lesions that can result in specific changes of visual field assessed by perimetry: unilateral defects as are centro-cecal scotoma that can result from retinal ganglion cells lesions (papillo-macular bundle area), or amblyopia that can result from interruption of the neural connections between the eye and the visual pathways from various causes including intraorbitar and prechiasmatic segment of the optic nerve (14,15). Hemianoptic, quadrianoptic and altitudinal defects that result from chiasmatic and post chismatic lesions of the visual pathways including occipital cortex (16). Visual integration disorders, associated with stroke, consist in failure of the visual cortical areas to process the visual information and can be classified as follow: alexia without agraphia associated with lesions of the corpus callosum (splenium) that connects the right occipital lobe and angular gyrus (patients in this situation are not able to read and failure to resolve their deficit by spectacle prescription) (17) ; visual agnosia that can be perceptive visual agnosia (the objects are not recognized and are associated with bilateral parieto-occipital lesions) and associative visual agnosia (where the visual perception of the objects can' t be associated with any visual experience or object memory) (18) ; Gertsmann syndrome represented by finger agnosia associated with right-left disorientation, agraphia and acalculia that occur dominance hemisphere lesions (inferior parietal lobe - angular gyrus) (19) ; colour agnosia associated with temporal associative cortex lesions (20).

Visual rehabilitation therapy can be supported by some residual structures that are typically spared by the damage: island of better vision in the blind field, visual field borders (at the level of visual field impairment), extrastriatal pathways spared by the damage, perilesional spared tissue and some high level neuronal networks preservation (15).

Visual rehabilitation methods

Patient’s ability to perform visual tasks and potential benefits of rehabilitation are needed to be estimated before the decision to apply the visual rehabilitation therapy. Influencing factors as hearing loss, cognitive troubles, tremor, sensory or motor deficit and depressive syndrome are also need to be identified (21,22).

Visual rehabilitation methods can be adressed to the central vision restoration, peripheral field restoration or the restoration of the vision due to hemianopia (23). According with the topography of the lesions, focal lesions are associated mainly with hemianoptic or sectorial defect and the lesions are represented mainly by stroke, since peripheral/central field defects are mainly associated with multifocal lesions due to diseases as is multiple sclerosis (24). Since multiple sclerosis has a pattern of demyelisation or remyelisation, that are cyclic processes, it is difficult to assess vision restoration therapies because the disease itself is naturally associated in evolution with spontaneous visual rehabilitation due to remyelisation process. Therefore, permanent lesions produced in ischemic conditions, are the situation where the visual restoration techniques can contribute to the improvements in visual function. Visual rehabilitation methods follow 2 concepts represented by restoration of visual function and compensation of the classical pathways of visual system with alternative pathways and cortical areas (25). Compensatory and restorative approaches have become intensive studied in recent researches because of the continued expansion of studies that reported plastic reorganization in the human visual system (26).Visual rehabilitation methods can be classified into the following groups: Visual Substitution Therapy, Visual Scanning Training (VST), Audio-Visual Scanning Training (AViST) and Vision Restoration Training (VRT) (25,27). The last method of rehabilitation, even if has the largest potential, is the most controversial. However, there are several factors that can impair visual rehabilitation therapies: fewer functional neurons in residual structures spared by the damage, less physiological functionality of these structures compared with main visual pathways, and failure to correct visual acuity by spectacles due to other concomitant eye conditions associated with patient age, as are optic nerve ischemia or age related macular degeneration (28).

Visual Substitution Therapy include refraction errors correction, prisms prescription, orthoptic exercises, low vision aids, and advice (29). Refraction error correction it is an important step towards the better visual acuity that is an essential contributor for the other rehabilitation methods applied to the patients. If the visual acuity is not the best possible after spectacle prescription, other training methods are not resulting in maximum rehabilitation. Prism prescription and orthoptic exercises designed to diplopia are only for visual comfort improvement but are also important for patient rehabilitation.

Visual Scanning Training is mostly addressed to compensatory mechanism of visual rehabilitation and consists in three types of exercise designed for compensatory pathways training : the first type of exercise based on visual search in which patients have to find one or more targets among distracters, second type based on finding a specific target that is not surrounded by distracters, and the third type when the targets are presented on the horizontal axes and the participants are making large and fast movements towards the target (30). Recent studies showed that VST applied to the patients with homonymous hemianopsia, due to postchiasmatic lesions, can specifically improves detection of peripheral visual stimuli and avoiding obstacles when moving around during mobility-related activities (31). Orientation difficulties after hemianoptic lesions have two different approach: rehabilitation of the deficitary visual field by visual stimulations and explorative eye movements in the direction of the hemianoptic field (32). Cerebral perception of visual information in cortical areas can be also affected, therefore, visual rehabilitation in hemianopsia can require and multidisciplinary team approaching (neurology and ophthalmology specialists) (32). Visual rehabilitation in visual field defect depends on surviving neurons and their topography on visual pathways and cortical area. Perceptual learning and receptive field plasticity also play an important role in vision restoration (33). Efficiency of VST is also in accordance with reaction time improvements, that indicate that the plasticity of temporal processing information can also contribute to a better rehabilitation of the vision (34). Functional imaging studies of the brain activity previous and after VST demonstrate the potential role of plasticity in vision rehabilitation therapy. The exact mechanism of this effect is still unknown, and evidence of visual improvement are only based on visual field assessment and subjective questionnaires. Despite that, a significant percentage of the patients reported a subjective improvement in daily activities, that is an important factor for life quality improvement (35). Mueller et al reported a notable subjective improvement in 70.9% of the patients, improvement that were independent of the lesion etiology and age, with most benefits for the patients older than 65 years

and for the patients who had a preservation of larger areas of residual function at baseline (35). Their results were validated by visual field assessment at baseline and at the end of therapy and by questionnaires (36). More complex training by this technique consist in daily training in a driving simulator where the patients are able to develop saccadic eye movements as a compensatory mechanisms, for a better localisation of the target in space and time, because the stimuli succession are more rapid and the patient have to focus on their presentation (37). Therefore, saccadic behaviour can constitute and important phenomenon that can be trained in order to rehabilitate the visual field in patients with hemianopia. Combined with immediate visualization of gaze behaviour the method provide a feedback mechanism for a better treatment strategy. Clinical research in this area can improve the understanding of the pathophysiological mechanisms that are on the basis of visual improvement by VST, and eventually can contribute to scientific improvements of the method.

Audio-Visual Scanning Training (multisensory stimulation training) consists in audio-visual stimulation toward the visual field defect and is considered to be based on stimulation of superior colliculus that is an important central nervous system structure involved in initiation and execution of saccades. The mechanism underlying on this process is not entirely known but is leading to improvement of the accuracy and searching time during the visual exploration (38). Furthermore, gradually decreasing of the temporal interval between acoustic stimulation and visual stimulation by a visual target, was reported to improve the visual restoration after 1 month of therapy, 4 h a day, with a long lasting results, for those who had audio-visual stimulation, compared with the patients with only visual or audio stimulation, in hemianoptic patients. This showed that multimodal sensory stimulation can improve visual restoration therapy in patients with brain lesions (39). Besides of the visual field improvements in patients with hemianopsia due to brain lesions, there are a studies that demonstrated that audio-visual stimulation therapy can be also useful in patients with visuospatial attention deficit as are patients with neglect, improving multisensory integration. Audio-visual stimulation was failed to show an improvement in patients who presented both deficits (hemianopsia and neglect) (40,41). The results were better if the audio and visual stimuli were aliniated in the same direction and were spatially closed (41). The visual function restoration is possible due to remapping processes of the cortex operating in higher-level visual perception areas of the parietal cortex offering a visual integration in time and space of the rapid successive of foveal retinal images and ensuring the environmental orientation by the spatial perception of the target (42). If the visual stimulus is associated with acoustic stimulus, the remapping process is enhanced due to cross-modal spatial integration between auditory and visual inputs that is an important phenomenon in space perception (41,42). The explanation of the improvements due to Audio-Visual Scanning Training technique is not yet completely understood some studies suggesting that multisensory integration and cross modal attention take place in different cortical areas that deserve visual function, while others show the involvement of early sensory specific areas (25). There are also studies that reported that multisensory cortical integration and attention are interacting, and are related to the lesion topography (43).

Vision Restoration Training. One of the most important component for visual function restoration is the improvement of visual stimuli discrimination together with the improvement of the ability to perceive various light intensity attributed to visual stimuli. Long term training (6 month of daily training) can improve the luminance sensitivity improvements in trained patients and perception area (44). Compensation and restoration are different forms of visual rehabilitation, and the difference between them consists in their different pathophysiological mechanisms: compensation is designed to recruit the alternative visual pathways and brain visual perception areas and restoration consist in stimulation of partially injured visual areas. Both of the process involve neuronal plasticity even there are serious controversies about the real possibility of restoration mechanism (45).

Consequences of vision rehabilitation therapy

In general terms, Visual Restoration Training aim at improving the magnitude of visual function, while Visual Scanning Training and Audio-Visual Scanning Training compensate for the visual field loss (25). While substantial spontaneous recovery can occur in the first few weeks to months brain lesions, cortical blind defects tend to become stable and permanent in a high percent of the patients (44). Most

of the therapies targeting visual rehabilitation are focused on developing of compensatory mechanisms as are eyes movement strategies, or prism lens indication for diplopia (46). Patients also develop head adapted position in order to improve visual function position and to compensate visual field defect (47). The methods for visual function rehabilitation are still under research and subjective control of results (based mostly on visual acuity assessment, visual field assessment and questionnaires about visual improvement in daily activities) rise difficulties in clinical implementation of these therapies. Regardless of these concerns and of the lack of evidences about the mechanisms of visual rehabilitation therapies, the results of vision rehabilitation therapy, regarding the methods, can have an important consequences in other medical disorders associated with stroke:

- falling - patients with visual disabilities have and increased risk to fall with the most severe consequences as is hip fracture (due to advanced age and associated osteoporosis). Improvement of visual function, physical therapy and adjuvant medication as is vitamin D supplementation can significantly reduce the risk for falling and for its complications (48).

-cognitive disorders - cognitive impairment is a frequent condition associated with stroke patient due to patient's age and due to other associated diseases (49). Visual improvement therapy can also improve cognition due to increasing the patient's ability to repeat the their daily task (50).

- depression: over than 30 % of the patients who have a low vision associated with various disorders have been reported to develop depression (51). Improving visual function shown improvement of the depressive symptoms (51).

Therefore, visual rehabilitation therapies added to other therapies (52,53,54), can constitute and important aid for post stroke rehabilitation patients.

Conclusions

Visual disabilities after stroke were considered to be irreversible. The researches in this area started to report significant result after various therapies that can prove a considerable potential for vision restoration even in adulthood. Visual rehabilitation after cerebral injury associated with a stroke are usual incomplete but can constitute an important component of stroke rehabilitation method that can lead to a better result in motor recuperation. The strategy for visual rehabilitation therapy has to be adapted to every patient situation and also has to be multidisciplinary. Visual rehabilitation is necessary to be aimed on the improvement of patient's daily life after stoke and constitute a gold target for clinicians who contribute to stroke rehabilitation. Early diagnosis of visual disabilities can substantial improve functional ability and other general aspects in stroke survivors. Post stroke rehabilitation is a activity of a multidisciplinary training that can offer a better social and psychological integration for the surviving patients.

Declaration of conflict of interests

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

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The influence of circadian variation in ischemic stroke onset on the evolution of the severity of the clinical picture and disability

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Abstract

Introduction. The chronobiology of ischemic stroke describes an occurrence pattern with the highest incidence in the morning according to most literature reports, but its influence on the evolution of the severity of the neurological picture and functional status is little studied. **Materials and method**. This cohort study included 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 followed up for 2 years by 5 successive evaluations. The onset time of ischemic stroke was assigned to one of the six hours intervals: 00.01-06.00 (night), 06.01-12.00 (morning), 12.01-18.00 (afternoon) and 18.01-24.00 (evening). For each patient, the National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) scores were recorded on the occasion of each evaluation. Statistical analysis was performed using Excel Microsoft, descriptive and ANOVA test. **Results and conclusions.** Our study confirms the incidence pattern of ischemic stroke with a morning peak, which is more obvious in the case of patients aged less than 65 years. Patients with stroke onset in the nocturnal interval have a less favorable neurological and functional evolution during the second year after ischemic stroke.

Key words: *ischemic stroke occurrence, circadian variation, NIHSS, mRS,*

Introduction

Over the past years, interest has increased in the study of chronobiological aspects involved in health maintenance as well as in the development of various diseases. The study of the temporal variation in the incidence of cerebrovascular pathology is part of this interest (1-4). Ischemic stroke describes a circadian variation pattern with the highest incidence in the morning, according to most literature reports (5-9).

The NIHSS Scale (the National Institute of Health Stroke *Scale)* reflects the severity of the neurological picture, and the mRS disability score (Modified Rankin Score) assesses the degree of functional impairment in post-ischemic stroke patients, both scores representing parameters that allow monitoring patient evolution (10). The evolution of the severity of the neurological picture and disability after ischemic stroke depending on the time of the day when ischemic stroke has occurred is little studied (11-13).

Materials and method

A prospective cohort study was conducted which included 63 patients with ischemic stroke occurring over the last 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. For each patient, demographic data were recorded and the time of onset was assigned to one of the 4 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 followed up on the occasion of 5 visits during 2 years: first visit (time "0"), at 1 month ("1"), 6 months ("6"), 12 months ("12"), and 24 months ("24"). Each patient was assessed based on the NIHSS and mRS scores. Four of these patients missed one visit.

Statistical analysis was performed using Excel Microsoft software. Categorical data were presented as diagrams, absolute and relative frequencies, and continuous variables were summarized using synthetic centrality, dispersion and location indicators or frequency histograms and linear diagrams. For the analysis of the differences between the mean scores at each visit across the 4 time intervals of the day, two-way ANOVA statistical analysis was used.

Results

In our study, ischemic stroke onset had the highest frequency in the 06.01-12.00 interval, followed by the 12.01-18.00 interval (Figs. 1 and 2), and the lowest frequency in the 00.01-06.00 interval. Patients were divided into two age groups (<65 years, ≥65 years) – Fig. 3, with the predominance of patients aged less than 65 years in the morning interval. Figures 4 and 5 show the descriptive evolution of the arithmetic mean of NIHSS and mRS scores across the 4 time intervals of the day during the 2 years (5 evaluations).

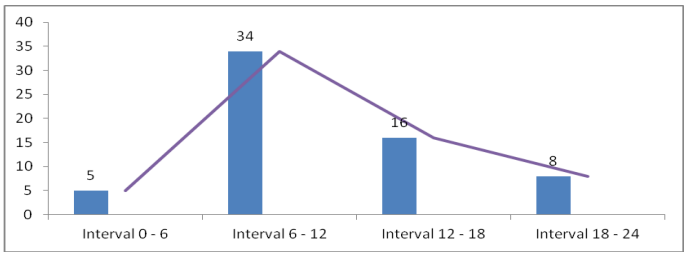

Fig. 1. Circadian variation of ischemic stroke onset in the studied group across the 4 time intervals of the day

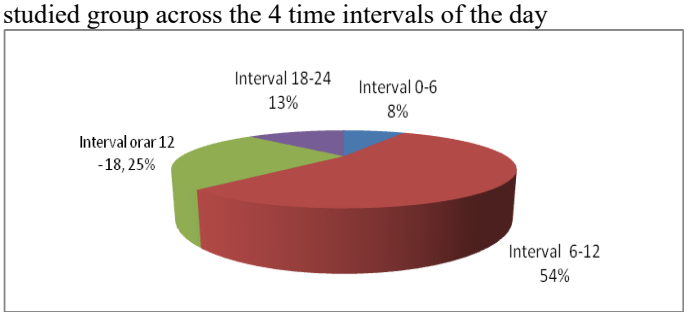

Fig. 2. Percentage representation of ischemic stroke onset in the studied group across the 4 time intervals of the day

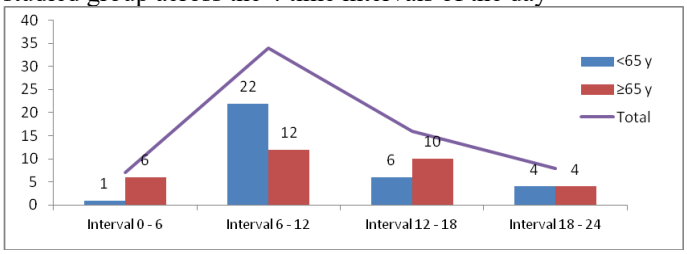

Fig. 3. Circadian variation of ischemic stroke onset in the studied group depending on age, across the 4 time intervals of the day

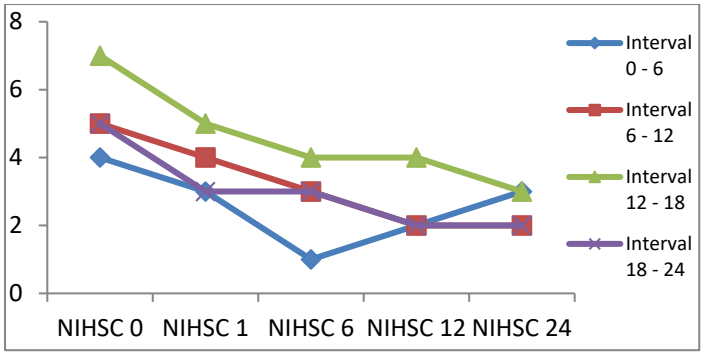

Fig. 4. Temporal evolution of the arithmetic mean of **NIHSS** scores over 2 years, across the 4 time intervals of the day (5 evaluations)

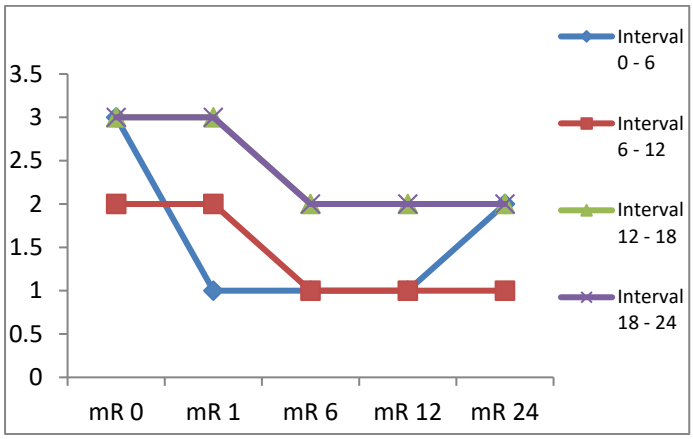

Fig. 5. Temporal evolution of the arithmetic mean of **mRS** scores over 2 years, across the 4 time intervals of the day (5 evaluations)

Following one-way ANOVA statistical analysis, statistically significant differences were found regarding patients' age (descriptively represented in Fig. 2) and the time interval of stroke onset ($F(3.59)=3.18$ (Welch), $p=0.011$), but the relationship between age and the stroke occurrence interval was of low intensity ($\omega^2=0.12$). Post-hoc data analysis evidenced a significant difference between the 06.01-12.00 and 00.01-06.00 intervals.

Two-way ANOVA statistical processing of NIHSS and mRS scores across the 4 time intervals of the day for the 5 evaluations (0, 1, 6, 12, 24 months) showed the following: no statistically significant differences were observed for NIHSS (but for NIHSS 6, $p=0.073$), while for mRS score, statistically significant differences were found for mRS1 ($F(3.55)=5.6$ (Welch), $p=0.028$). Post-hoc analysis indicated statistically significant differences between the 00.01-06.00 and 12.01-18.00 intervals, as well as between the 00.01-06.00 and 18.01-24.00 intervals.

Discussions

In the case of the studied group, the circadian variation pattern of ischemic stroke is confirmed, having the highest incidence in the 06.01-12.00 interval and the lowest incidence during the night (00.01-06.00) (Fig. 1), according to literature data derived from both retrospective (5-8,14) and prospective studies (15-17). This pattern is more obvious for patients aged less than 65 years.

By analyzing the diagrams for the evolution of NIHSS and mRS scores across the 5 evaluations during the 2 years of follow-up, it can be seen that NIHSS (reflecting the severity of the neurological picture) had a favorable evolution for all time intervals, excepting the nocturnal one (00.01-06.00), which was associated with its worsening after 6 months of resolution. This aspect was correlated with the evolution of the mean mRS score (reflecting the degree of disability or functional status), which also only for the nocturnal interval, after a rapid improvement by 2 points during the first month after stroke, remained unchanged for the rest of the first year, then started to worsen slowly by 1 point during the following 12 months. The highest mean NIHSS score at onset (NIHSS 0) was found for the 12.01-18.00 interval (7), but its evolution was favorable (decreasing by 3 points during the first year), similarly to that of the 06.01-12.00 and 18.01-24.00 intervals (5→2). The greatest disability (mRS) at onset was found for the 18.01-24.00 interval, along with the 00.01-06.00 interval mentioned before, but its evolution was favorable and similar to that of ischemic strokes with onset in the 06.01-12.00 and 12.01-18.00 intervals.

It can be concluded that these scores, reflecting clinical severity on the one hand and the degree of disability on the other hand, had an almost parallel evolution (Figs. 3 and 4).

Statistically significant differences between the 4 time intervals of stroke onset were found by multivariate ANOVA analysis only for mRS values at 1 month (mRS1), while for NIHSS the differences in values at 6 months (NIHSS 6) between the 4 time intervals of the day came close to statistical significance, most probably due to the small number of patients in the study group.

There are very few literature data on the evolution of NIHSS and mRS scores depending on the circadian interval in which stroke has occurred, the available data being derived only from the initial admission of patients with ischemic stroke (values at admission versus discharge), not from evolution during a longer follow-up period. However, the results are concordant, describing the best evolution of the functional score (mRS) from admission to discharge for patients with ischemic stroke onset in the 04.01-08.00 interval and the lowest score in the 20.01-24.00 interval, without statistically significant differences for NIHSS (8,11). The evolution of the mRS score is also consistent with the results of another study performed by us, in which the degree of disability was assessed based on ADL (activities of daily living) and IADL (instrumental activities of daily living) scores, with their least favorable evolution for ischemic stroke occurring in the nocturnal interval 00.01-06.00 and the greatest improvement for all time intervals during the first year after stroke (18).

Conclusions

This study confirms the circadian variation pattern for stroke of ischemic etiology, with the highest incidence in the morning and the lowest incidence during the night, our results being statistically significant for patients aged less than 65 years.

The evolution of NIHSS (reflecting the severity of the neurological picture in stroke) and mRS (reflecting the degree of disability) scores during the 2 years of follow-up, depending on the circadian interval of stroke onset, is similar for our study group, with the greatest improvement during the first year after stroke and relatively no changes during the second year, except for onset in the nocturnal interval (00.01-06.00), associated with a slight worsening after 12 months. The difference in the evolution of the functional status of patients with nocturnal stroke onset compared to patients with onset in the other time intervals of the day is statistically significant for the evaluation visit at 1 month.

Knowing the influence of the circadian variation in ischemic stroke onset on the evolution of the neurological and functional picture can be important in assessing long-term prognosis, which involves different degrees of use of medical and social resources.

Informed consent

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

Declaration of conflict of interests

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

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Headache occurring during rehabilitation in a migrainous patient with cervical spinal cord injury

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Abstract

Traumatic vertebral artery (VA) dissection is a severe consequence of a cervical injury, which usually involves the vertebrae and spinal cord. Traumatic VA dissection has been frequently underdiagnosed or misdiagnosed, mainly because many patients remain asymptomatic. The consequence of VA dissection is ischemia in the territory supplied by the affected artery. The VA dissection presents most often as a vertebrobasilary transient ischemic attack or ischemic stroke, usually preceded by local symptoms such as neck pain or headache. Headache is a common symptom in patients with cervical artery dissection, but its characters are not specific. Diagnosis of VA dissection usually requires a CT-angiography. Delayed onset of symptoms with a variable asymptomatic interval, ranging from several days to 3 months, has been reported. The risk of stroke remains high, especially in the first weeks after the confirmation of VA dissection. Treatment of traumatic VA dissections include anticoagulation or antiplatelet therapy and revascularization techniques. We present the case of a patient with spinal cord injury and operated C5 fracture, who was diagnosed with unilateral VA dissection 6 months after the traumatic event, during the rehabilitation program.

Key words: *vertebral artery dissection, cervical spinal cord injury, headache, rehabilitation*,

Introduction

Traumatic vertebral artery (VA) dissection is a relatively rare sequela of cervical trauma and can occur as a result of different trauma types that cause excessive cervical rotation or extreme flexion-extension of the neck. Traumatic VA dissection has been frequently underdiagnosed or misdiagnosed, mainly because many patients remain asymptomatic if the VA is damaged only unilaterally (1).

Headache is the common symptom in patients with cervical artery dissection (2). Delayed onset of symptoms with a variable asymptomatic interval, ranging from several days to 3 months, has been reported (1). We present the case of a patient who showed delayed symptoms of VA dissection, 6 months after the traumatic event.

Case report

A 37-year-old male patient with a history of migraine was involved in a car accident with traumatic cervical spinal cord injury, with fracture of the C5 vertebra. Neurosurgical intervention was performed in emergency with decompression and stabilization of the spine by posterior fixation with rods and screws **(Figure 1).**

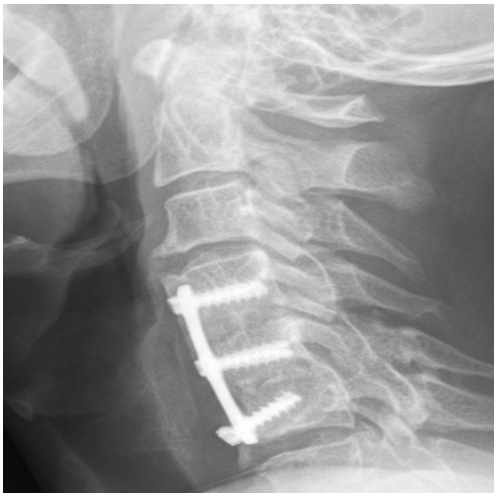

Fig. 1: Radiographies of the cervical spinal cord showing C5 fracture and stabilization of the spine with rods and screws

After surgery, the patient had an American Spinal Injury Association (ASIA) grade B. Six months after his traumatic event, the patient improved to an ASIA grade C, was admitted to our Rehabilitation Hospital, and started a physical therapy program. His neurological examination showed important motor deficit in the distal upper limbs (especially for wrist

extensors and finger flexors), spastic motor deficit in the lower limbs, brisk reflexes, bilateral Babinski sign, decreased pain and temperature sensations below D4 level, with preserved light touch and proprioception in the lower limbs, sphincterian troubles with urge micturition. He was able to walk a few steps with a rollator. Electrocardiogram (ECG) showed asymptomatic sinus bradycardia of 42/min. At admission, the patient's complaints were mild occipital headache and right side cervical pain. No signs of cranial nerve involvement were observed. The patient also reported an increased frequency of migraine attacks after the traumatic event.

The physical therapy program consisted of sedative massage of the cervical-dorsal-lumbar spine, passive postural changes and mobilization of the upper and lower limbs to prevent the effects of prolonged immobilization, respiratory gymnastics to maintain the respiratory function. For recovery of sphincter disorders, pelvic floor toning exercises and interferential electrostimulation were performed. Also, the patient was included in a virtual therapy and occupational therapy program to increase mobility and recover balance. For recovery of walking, the parallel bar system was used, as well as a robotic system which allowed support of the lower limb joints, particularly the knees, and intelligent control of walking assistance depending on the patient's movement capacity. The rehabilitation program was conducted over three weeks; at discharge, the indication was to continue the kinesitherapy program at home.

No manipulative techniques for the cervical area were performed.

Three days after admission, the patient complained of worsening of headache and right cervicalgia; the headache had different features than his usual migraine attack (increased intensity, continuous type, no pulsating character). No changes in neurological exam were noted. The pupils were symmetrical and reactive. Cervical spine plain radiographs were identical to previous examinations. Native cerebral CT scan was normal, showing no hydrocephalus.

Cervical MRI was performed, evidencing T2 hyperintensities at C5-C6 level of the spinal cord, consistent with traumatic myelopathy; there was no syringomyelia **(Figure 2).**

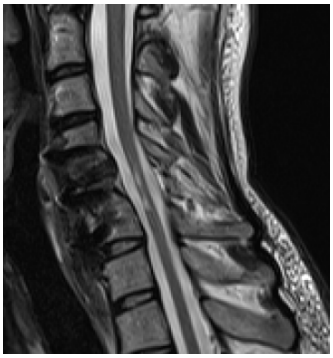

Fig. 2: Cervical MRI, sagital sequences, showing T2 hyperintensities in the spinal cord, correspponding to post-traumatic myelopathy

On axial sequences, absence of flow in the proximal V2 segment of the right vertebral artery was observed, and in distal V2 the blood flow was filiform. The left VA was dominant, without flow abnormalities **(Figure 3).**

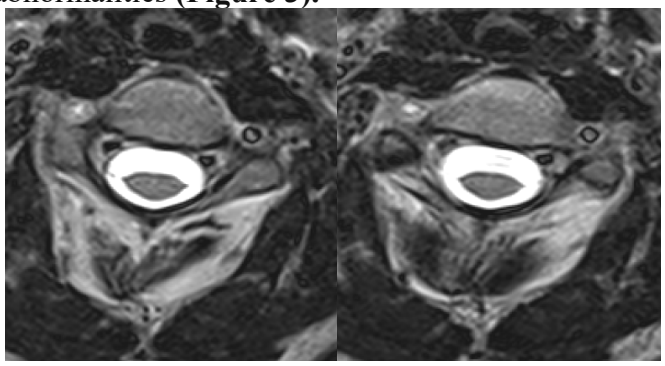

Fig. 3: Cervical MRI, axial sequences at C5-C6 level, showing normal flow in the left VA and absence of flow in the right VA, corresponding to VA occlusion

We obtained previous MRI of the patient, performed one month after surgical intervention **(Figure 4),** and we compared the aspect of vertebral arteries on axial sections, at the same level; we have not noticed any flow abnormalities, and we have presumed that, at the time when this MRI has been performed, the right VA flow have been normal.

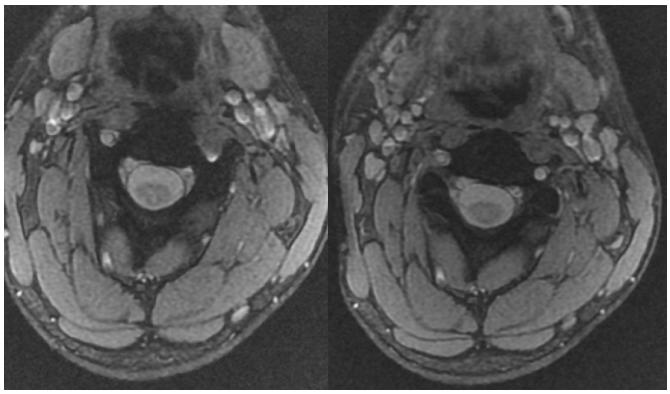

Fig . 4: Cervical MRI performed 1 month after traumatism, axial sequences at C5-C6 level, showing presence of blod flow in V2 segment of right VA

Doppler ultrasound examination of cervical and cerebral arteries revealed the absence of flow in the V2 segment of the right VA, normal flow in the dominant left VA, and increased intima-media thickness (IMT) bilaterally. Normal flow in both V3 segments and basilar artery was observed on transcranial Doppler ultrasound (TCD).
An angio-CT scan of cervical vessels was then performed, and dissection of the V2 segment of the non-dominant right VA was confirmed **(Figure 5).**

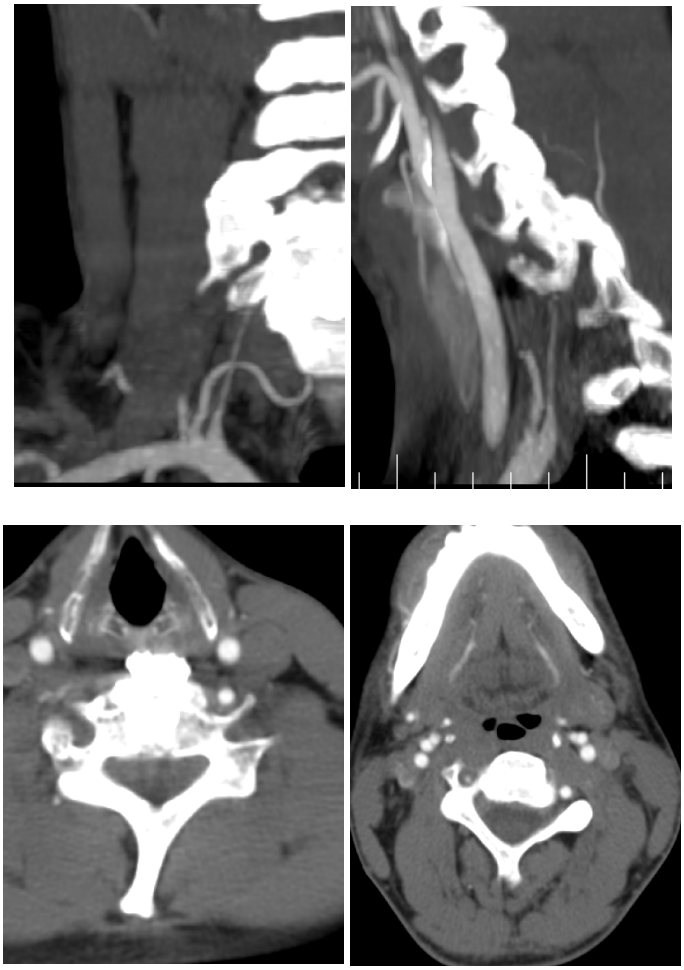

Fig. 5. Angio-CT scan of the neck showing signs of right VA dissection in V2 segment (A – coronal view, B – lateral view, C, D – axial view)

Antiplatelet treatment for VA dissection was started in our patient, associated with symptomatic analgesic treatment, with gradual improvement in the patient's headache. The patient was discharged after 21 days, with improved neurological status, but with the same ASIA grade C. Prophylactic treatment with curcumin for increased frequency of migraine attacks was initiated.

The patient returned for follow-up at 3 months. No new neurological symptoms were present from discharge, and his neurological condition remained stable. Doppler ultrasound of cervical arteries showed no recanalization of the V2 segment of the injured right VA. Antiplatelet treatment was stopped. The patient in stable condition was then referred for balneotherapy in a spa resort (3, 4) in the form of balneation and crenotherapy, with specific natural factors.

Results and discussion

Arterial injuries are not very rare consequences of cranial or spinal cord injuries. Cervical arteries are also exposed to traumatic factors, especially the extracranial parts of the VA which passes through the transverse foramina of the cervical vertebrae, having a higher incidence of dissection, especially in the V2 segment. Fractures involving the transverse foramina or the lateral vertebral masses, or vertebral subluxations may damage/tear/traction the artery, causing dissection (5). Some VA dissections may extend to more than one segment (6). During arterial dissection, a tear forms in the arterial wall, leading to intrusion of blood within the layers of the arterial wall resulting in an intramural hematoma (7).
The consequence of VA dissection is ischemia in the territory supplied by the affected artery: vertebrobasilary stroke or transient ischemic attack (TIA). The mechanism of stroke is presumed to be embolic from a local thrombus or hemodynamic by a decrease in blood flow in the absence of collateral circulation.
Clinically, VA dissection most often produces a vertebrobasilary TIA or ischemic stroke, usually preceded by local symptoms such as neck pain or headache. Headache is the common symptom in patients with cervical artery dissection (CAD), but the characteristics of pain associated with CAD are not specific and can sometimes resemble migraine or even cluster headache (2). A recent study showed that more specific headache characteristics in patients with intracranial vertebral artery dissection included: headache in the occipitonuchal region, with unilateral, pulsatile and acute onset, with severe intensity, and without nausea or vomiting (8). .
We assumed that patient's cervicalgia and headache were related to right VA dissection although the patient was a migraineur.

The persistence and intensity of pain raised the suspicion of another etiology than a migraine attack. First we looked for a possible dislocation of the fixation material used to stabilize the cervical spine, but the radiographs indicated a normal position of the rods and screws. A new cervical MRI was performed to rule out a possible post-traumatic syrinx, but the spinal cord showed only chronic post-traumatic changes.

However, headache rarely occurs in isolation, without focal neurological signs (2). If the damage is unilateral and has induced occlusion of the non-dominant VA, it may not cause ischemic symptoms. Outcome in VA dissections is dependent on perfusion of the contralateral VA: if inadequate, it can induce vertebrobasilary (VB) ischemia; dominant VA occlusion can result in a more severe clinical picture (5). In our case, Doppler ultrasound and angio-CT scan showed that the left VA was dominant, and the basilar artery had normal perfusion, so this could explain why our patient did not have ischemic symptoms.

The particularity of this case was the long time interval between the traumatism and VA dissection. A latent period between the time of injury and the appearance of clinical manifestations of a few hours or days is typically seen (9). Delayed onset of symptoms with a variable lucid interval, ranging from several days to 3 months, has also been reported (2). In a series of 500 patients with whiplash injury acquired in car accidents, the incidence of cervical arterial dissection occurring within 12 months after the traumatism was 1.6%, and the mean delay between the trauma and arterial dissection diagnosis was 72 ± 99 days (10). In 87.5% of cases from this study, the dissection was complicated by brain infarction, and the risk of cerebrovascular events was still increased 4-12 months after injury (10).

The risk of stroke remained important in our patient, especially in the first weeks after the confirmation of VA dissection. In a study of over 800 patients with traumatic cervical artery dissection without stroke, the risk of stroke was 1.43%, not significantly different from that of non-traumatic dissections (11), and was maximal during the first 2 weeks. In CADISS (Cervical Artery Dissection in Stroke Study), which randomized patients presenting with cervical artery dissection, an overall stroke recurrence rate of 2% at 3 months was observed, with all recurrences occurring within the first 10 days (12).

Therapeutic strategies in traumatic VA dissections include anticoagulation or antiplatelet therapy, revascularization techniques (stent-assisted arterial reconstruction), and endovascular permanent arterial occlusion (6). According to the literature, recanalization may occur weeks and even months (max. 24 months) after arterial dissection (10).

Migraine attacks were also disabling for the patient, with increased frequency after the traumatism. Prophylactic treatment had to be considered in this case. Our patient presented with bradycardia, so the use of beta-blockers for migraine prophylaxis was inappropriate. According to our recent research, curcumin was shown to be effective in migraine prophylaxis (13) and in migraine attacks due to its important anti-inflammatory effects (14), being also well tolerated by patients.

Patients with spinal cord injury need long recovery periods. Functional risk complications are possible, which cause long term or permanent disability requiring specialized medical rehabilitation care. Rehabilitation treatment in SPA resorts has also proved to be effective in ameliorating disability in patients with important neurological deficits (3). Also, SPA treatment is effective in different types of migraine, while behavioral interventions will be beneficial in reducing the risk of cronicisation (15).

Conclusions

Vertebral artery dissection are a severe complication of traumatisms in the cervical area. Diagnosing a VA injury could be difficult, because some dissections are asymptomatic, others have minor symptoms (as headache or cervicalgia), or in other cases the severity of the neurological picture in SCI could mask vascular symptoms. Because VA dissections carry an important risk of stroke in the vertebrobasilary system, screening for VA injury after cervical spine fractures should be performed when necessary, on a case-by-case basis (16). Screening criteria have been recently published, and CT-angiography is recommended for the detection of a VA dissection (17). An important point is the free interval between the traumatic event and the occurrence of symptoms of VA dissection, which was particularly long in our patient. At least 3 months of treatment is safe to prevent ischemic events in affected patients, but the choice between antiplatelet versus anticoagulant therapy is under debate. VA dissections carried good prognosis in treated patients.

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.

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Cardiac rehabilitation for older patients with cardiovascular pathology using robotic systems – A survey

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Abstract

In the last decades, we have witnessed a drastic increase in the proportion of elders in the western countries, and more than a third of worldwide population dies because of cardiovascular diseases. The elderly patients with cardiovascular diseases, but not only, are frail and need constant assistance, and so the healthcare system will slowly become incapable of properly address all the patients' medical problems and rehabilitation issues, while aiming towards a continuous increase of the life quality. The rehabilitation robotic systems have the potential to stimulate and support the re-learning of the functional motor pattern of over-ground walking in an optimal manner while increasing patient's motivation, which constitutes a crucial element in the subject's cardiac recovery. Thus, the present article aims at reviewing the robotic systems available for cardiac rehabilitation in elders with cardiac pathology.

Key words: *cardiac rehabilitation, older patients, cardiovascular diseases, heart failure, rehabilitation robotic systems, assistive robotics,*

Introduction

In the last decades, we have witnessed a drastic increase in the proportion of elders in the western countries, and more than a third of worldwide population dies because of cardiovascular diseases (1). Multiple recent investigations have documented an increase of 10%–25% in peak VO2 after exercise training in older patients with heart failure (2). The older patients with cardiovascular diseases, but not only, are frail and need constant assistance, and so the healthcare system will slowly become incapable of properly address all the patients' medical problems and rehabilitation issues, while aiming towards a continuous increase of the life quality (3,4). An important part of cardiac rehabilitation programs includes cardiac training exercises recommended by a medical team and supervised by therapists. An important consideration when prescribing an exercise regimen in cardiac rehabilitation is the level of supervision required. Patients at moderate to high risk cardiac complication should participate in a medically supervised program with trained personnel and equipment suitable for advance cardiac life support. Moreover, this level of medical supervision should be continued for at least 8 to 12 weeks (5). In a society where there is a growing demand place on the healthcare system, the cardiac rehabilitation programs would represent a great financial burden. In UK, for example, the annual potential cost of cardiac rehabilitation was estimated of around £42 million (6) .In the era of telemedicine and robots, the supervision of exercise training could be undertaken by robotic systems (7).

In order to be able to address these needs, the European Commission has identified several major areas of interest where robotics would play an important role (8), among which:

- Rehabilitation robotics: refer to robotic system that would be used following a medical condition (traumatic, post-operative, cardiac or neurological) where their direct physical interaction with the patient would either enhance the recovery process or act as a replacement for a lost function.
- Assistive robotics: refer to secondary aspects related to the medical process, providing assistance to the healthcare givers of the patients.

The scientific literature has demonstrated that physical exercise training improves parameters like aerobic capacity and muscular strength in cardiac patients (9). Rehabilitation of cardiac patients has always been a great challenge, due to the complexity of the recovery treatment and so there has been a strong motivation to the development of new systems for increasing the efficiency of rehabilitation procedures (10). From this

perspective, robotic assisted rehabilitation can be seen as an important tool that provide flexibility, customized training and enhanced recovery treatment for cardiac patients. However, as any other new technology, rehabilitation robotic systems should be refereed on its efficiency and cost-effectiveness and not only on its technical performance. The rehabilitation robotic systems have the potential to stimulate and support the re-learning of the functional motor pattern of over-ground walking in an optimal manner while increasing patient's motivation, which constitutes a crucial element in the subject's cardiac recovery (11).

Thus, the present article aims at reviewing the robotic systems available for cardiac rehabilitation in elders with cardiac pathology.

A survey of rehabilitation robotic systems and their adequacy for the cardiac rehabilitation

Repetitive task-oriented movements are the single most important variable of cardiac rehabilitation and have a therapeutic gain; the literature suggests that an elderly patient recovering from cardiac failure must play an active role in the rehabilitation process if improvement is to occur (9).

Several robotic systems designed for rehabilitation are presented in the scientific literature as prototypes while others are being on the market, already. Most of the developed robotic systems for rehabilitation were focus on neurological failure (ex. neuromuscular impairment) and less on heart failure. Furthermore, some of the robotic systems manufacturers defined heart failure as one of the exclusion criteria for robot-assisted gait therapy (Hocoma the Lokomat® system manufacturer) (10).

In this paper we will analyse the rehabilitation robotic systems which allow an over-ground gait training without exoskeletal support. Assessing whether they can be used or were designed especially for patients with cardiac problems.

The Lokomat® robotic system is a bilaterally driven gait training equipment that is used in conjunction with a body-weight support system (12).

It combines the advantages of robotic orthoses with advanced feed-back algorithms and Virtual Reality applications while providing a safe environment for the patient. The advantage of Lokomat's training is to impress a correct physiological movement scheme, more repetition than any classical approach, ensuring a high patient comfort by placing the patient in a virtually pleasant environment. The robotic system supports the weight of the patient in a manner appropriate to the functional capacity of the subject, which leads to rapid and sustained progress. There is at least one research study that highlight Lokomat® robotic system can be used on cardiac rehabilitation procedures (10).

The SoloWalk® is one of the other rehabilitation robots that is aimed towards helping individuals suffering from neurological fails and movements disorders. SoloWalk® is powered by DC gearmotors for its omnidirectional wheels while a harness system, attached to a pair of underarm supports, is designed to lift the patients and prevent them from falling (13).

A force sensor is integrated between the main frame and the harness that measures interaction force generated by the patient's intention of movement. Patients are supposed to be able to walk freely with the assistance of the SoloWalk while the robot simply follows the patient's motion. Based on the SoloWalk characteristics and training possibilities we can say that the robotic system could be used for cardiac rehabilitation (13).

The KineAssist® consists of an omnidirectional base, harness joining at the pelvic, force torque sensor that measures interaction force generated by the patient's intention of movement, and an active body weight support (14). The robotic system provides stability of the patient, and sustaining body weight, allowing the pelvic movement without any restriction. Unique harness system protects patients from losing their balance by gripping them before they can fall, which increase confidence in their abilities while they growth endurance and strength.

The development of this robotic system has met the doctor's need as it generates an intense, specific locomotion pattern and walking training by supporting the patient body weight. To provide an effective rehabilitation training, the KineAssist® is capable of seven modes of operation that can be used throughout the rehabilitation therapy.

Robo-K®, the walking rehabilitation robot developed by BA Healthcare is a prototype that helps patients to relearn to walk (15). This relearning process is basically limited by the patient's joint pains and the practitioners' available time. Due to the integrated intelligent suspension system that can relieve the patients from 50% of their weight, the

stresses on their joints are significantly reduced.
Additionally, the robot localization system offers an autonomous navigation within rehabilitation centre, releasing the physiotherapist who can then focus on his therapeutic approach and on encouraging the patient to make progress. The rehabilitation robotic system, Robo-K®, is equipped with a recording system that store the parameters of the training devoted to each patient, offering them a progressive therapy, adapted accordingly to their own particularities and needs (15).
Some clinical trials were made at the University Hospital in Rennes on a sample of 36 patients using ROBO-K® and significant improvements have been seen regarding their walking performance (15).
The above presented four rehabilitation robotic systems illustrate very well the "over-ground gait training without exoskeletal support" device structure and the training possibilities for relearning to walk, or to increase the functional capacity of the subject, which leads to rapid and sustained progress. Theoretically, and in several cases also practically by medical trials it has been shown that these rehabilitation robotic systems can also be used for rehabilitating heart failure patients. Certainly, more studies need to be done.

Discussions

A variety of rehabilitation robotic systems were developed for and tested in clinical and rehabilitation environments. These systems have the potential to facilitate long time training, reproduce repetitive movements, motivate patients and reduce the therapists' work. New technologies made possible the improvement of the function, usability and accessibility of the robots in medical and social environment. Robots could provide accurate and standardized assessment methods for cardiac rehabilitation, as to compare intra and inter-subject performance. Furthermore, rehabilitations robotic systems could be the gate to advanced technologies which provide novel training programs for patients with cardiovascular diseases. Thus, virtual and augmented reality technologies associated to rehabilitation robotic systems could increase both the motivation to participate to therapy and the engagement during walking training. Sensor added to these robotic systems would give an accurate image of the biological parameters modified by constant training, to quantify the short and long-term benefits of cardiac rehabilitation programs.
The majority of rehabilitation robots were designed for intensive locomotor training in patients suffering a movement disorder after stroke or spinal cord injury. The rehabilitations robots useful for patients with stroke were elegantly reviewed and classified by Ghannadi B et al. (8).
The data regarding rehabilitation robots in cardiac pathology are scarce. The group who developed Lokomat robotic system designed a study in order to assess feasibility and safety of a robot-assisted gait therapy in patients early after open heart surgery (16). They showed that the "results with robot-assisted training were comparable to early postoperative standard in hospital training and no deep sternal wound infection or any adverse event occurred in the robot- assisted training group" (16). Thus, the robot-assisted gait therapy with the Lokomat system proved to be feasible and safe for postoperative cardiac rehabilitation.
Another study, published recently, focused on the possibility to integrate a robotic agent into cardiac therapy (17). This work presents an exploratory experiment for on-line assessment of typical cardiac rehabilitation routines, and for integrating social robots in cardiac rehabilitation routine. Given the fact that cardiovascular patients, especially those diagnosed with heart failure have an increased psychological stress, rehabilitation robotic system could be helpful for the health care system, by precisely identifying risk factors, the potential risk of therapy and by increasing the patient's performance through motivation and engagement (17,18) .

Future trends

In the future, clinical and basic research is needed to investigate the role of rehabilitation robotic systems in cardiovascular patients. Close collaborations between clinical and basic research could improve the function of rehabilitations robotic system and the training protocols to obtain the best functional outcome for cardiac patients. Some parameters should be reconsidered such as: optimal training paradigms, duration, protocols parameters and the best way to integrate in both medical and social environment. Hopefully, the rehabilitation robotic systems might further help to investigate the cardiac rehabilitation benefits and the underlying mechanisms of recovery.

Declaration of conflict of interests

The authors does not have any financial interest involving the companies and/or materials mentioned in this article.

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Rehabilitation therapies in stable chronic obstructive pulmonary disease

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Abstract

Introduction. Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease. The pulmonary rehabilitation (PR) is a mutidisciplinary and comprehensive intervention in symptomatic patients with COPD. **Objective.** This review aims to synthesize evidence from available studies on the relative efficacies of different methods of rehabilitation therapies in patients with stable COPD. **Material and Methods.** A search was performed on the databases Pubmed, Embase, ResearchGate. Of the 410 articles retrieved from databases, only 20 met the inclusion criteria. Two reviewers independently reviewed selected eligible studies. **Results.** Rehabilitation is a multidisciplinary intervention in symptomatic patients with COPD, including speleotherapy, halotherapy, muscular training, soft tissue manual therapy and neuromuscular electrostimulation. All of the case-control studies using speleotherapy reported improved respiratory function to varying degrees and there were improvements in lung functional tests including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV 1), oxygen saturation, partial pressure of oxygen in arterial blood, and partial pressure of carbon dioxide in arterial blood. In addition, halotherapy has been associated with relief of respiratory conditions such as COPD, asthma and cystic fibrosis by its bactericidal effect, improvement of immunity and rheological properties of secretions. Respiratory muscle training is a part of rehabilitation for COPD subjects. In patients who can not perform physical activity, neuromuscular electrostimulation (NMES) increased 6 minute walking distance and time to symptom limitation exercising at a submaximal intensity and reduced the severity of leg fatigue on completion of exercise testing. **Conclusion.** The management of COPD should include a multidisciplinary therapy, including rehabilitation therapies as an adjuvant to the medical treatment, especially because due to the high prevalence, mortality, and morbidity, COPD will be one of the biggest public health challenges in the next century.

Key words: *Rehabilitation therapy, COPD, Halotherapy, Speleotherapy, Muscular Training*,

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease caused by alveolar and/or airway abnormalities and characterized by persistent respiratory symptoms and airflow limitation, usually due to significant exposure to noxious particles or gases (1). COPD has become a problem of public health that occurs in >10% of adults over 40 years old and accounts for >5% of physician office visits and 13% of all hospitalizations, with the majority of patients remaining undiagnosed and untreated (2,3,4). Obstructive sleep apnea (OSA), diabetes, osteoporosis, depression/anxiety, musculoskeletal impairment and cardiovascular diseases are frequent and important comorbidities in COPD, often under-diagnosed, and associated with poor health status and prognosis. Due to the high prevalence, mortality, and morbidity, COPD will be one of the biggest public health challenges in the next century.

To minimize the burden of COPD for the health care system, three cornerstones can be defined: smoking cessation, reduction of acute exacerbations and comorbidity management (5). Mutidisciplinary approach combines these aspects in an integrative intervention including other therapies such as speleotherapy, halotherapy, muscle training, soft tissue manual therapy intervention, neuromuscular electrostimulation. Because respiratory and limb muscle dysfunction have been recognized as indicators for disease progression independent of lung function (6), physical exercise has become an indispensable measure to invert skeletal muscle dysfunction (7), improve exercise capacity and health-related quality of life (HRQoL) and reduce exacerbations.

According to ATS/ERS pulmonary rehabilitation is a mutidisciplinary and comprehensive intervention in symptomatic patients with COPD. It becomes a part of an individual patient's plan of treatment and is initiated in order to optimize functional status, enhanced participation in physical and social activities, improve the quality of life and reduce healthcare cost by stabilizing or reversing the systemic manifestations of the disease (8). In the last five years some research has focused on the roles of rehabilitation therapy in chronic obstructive pulmonary disease and its comorbidities.

Objective. This approach aims to synthesize evidence from available studies on the relative effectiveness of different methods of pulmonary rehabilitation in patients with stable COPD.

Materials and methods

This search was performed on the databases Pubmed, Embase, ResearchGate. The following key words were used: Halotherapy, Speleotherapy, Muscular Training, Manual Therapy, Neuromuscular Electrostimulation (NMES). They were applied on following disease conditions: chronic obstructive pulmonary disease (COPD). Inclusion criteria were: studies evaluating short and long term effects of speleotherapy, halotherapy, inspiratory or expiratory muscle training, neuromuscular electrostimulation, manual therapy (soft tissue manual intervention), in stable COPD patients. Studies had to include one of these outcomes: dyspnea, quality of life, exercise capacity, 6 minute walking test. Exclusion Criteria: We excluded studies that did not meet the above criteria.

Results

Database search resulted in 410 titles and abstracts that were relevant for the present topic; after selecting articles published in the last five years, 106 articles remained for further selection. After exclusion of all the irrelevant studies for our purpose were regarding the aim, 20 articles were finally included in this research.

Key words	Study results	Study selected
Speleotherapy	9	3
Halotherapy	8	3
Muscular Training	28	5
Manual therapy	29	3
Neuromuscular electrostimulation	32	6

Key words „-Speleotherapy" OR „-Halotherapy" OR „-Muscular training" OR „-Manual Therapy" OR „-Neuromuscular electrostimulation"
n=410

Articles resulted after the application of inclusion and exclusion criteria
n=106

Articles included in the final review
n=20

Speleotherapy and halotherapy

Chronic airflow obstruction, often belonging to panting and reduced walking distance distinguish COPD (9,10) and chronic character of symptoms directly influences patient's quality of life. Respiratory physiotherapy, bronchodilators, smoking cessation, rehabilitation, inhaled drug treatments and antibiotics are available treatment methods. Severe medication side-effects and allergic responses made physicians prefer to use natural salt as an adjuvant treatment in stable COPD.

Speleotherapy in the treatment of COPD imply applying normal salt in a reserved atmosphere as a therapy for disease treatment (11). It is recommended by the broader community and is often described as a reviewed treatment method for people with chronic and allergic respiratory diseases, using the specific and unique feature of the environment, especially particles contained in the air of underground spaces, mostly karst caves. In Eastern Europe, natural salt caves were used for the relief of respiratory symptoms. The unique properties of the microclimate in caves are the constant air temperature of moderate to high humidity, the presence of fine aerosol elements (sodium, potassium, magnesium and calcium), as well as the lack of airborne pollutants and pollen in the air. Nowadays, salt caves are used for treatment at health centers in Austria, Poland, Slovakia, Romania, Azerbaijan, Kyrgyzstan, Russia and Ukraine (12).

All of the case-control studies reported improved respiratory function to varying degrees and improvements in lung functional tests including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), oxygen saturation, partial pressure of oxygen in arterial blood and partial

pressure of carbon dioxide in arterial blood (13). On the other hand, the results are contradictory because another study showed no significant difference of FEV1/FVC in patients using speleotherapy (11). Also, there was statistically significant improvement in recorded 6-minute walk distant parameter in subjects with speleotherapy (P=0.02), while in control group there was no significant improvement (P=0.23). These findings were similar to a previous study reporting that patients in the case group had a statistically significantly improved six minutes walking test (6MWT) by 90 meters ($p<0.01$) (14) and another study reported an improvement by with 75 meters ($p<0.01$) (15). Moreover, patients receiving speleotherapy improved their clinical condition which was scored each day by the participants and physician jointly in the basis of symptoms and complaints. It was suggested that the improved clinical state for stable COPD patients improved their life quality by decreasing exacerbations, reducing hospitalization, improving physical tolerance and reduces fatigue (13).

Speleotherapy has beneficial impact on the immunological status which has improved by 97.8% in the treatment group, more exactly the reduction of inflammatory process during exacerbations and the normalization of the subpopulation of CD4+ and CD8+ lymphocytes with the increasing in the neutrophil phagocytosis activity (16). In addition, taking into account the importance of mental status, other studies showed that rehabilitation programs which included speleotherapy improved depression and anxiety in patients with stable COPD (17,18).

On the other hand, **halotherapy** is used as an alternative for speleotherapy in regions that do not have karst caves. Halotherapy is a treatment consisting of inhalation of small salt particles in a controlled environment of a halochamber. This room is designed to replicate the natural microclimate of a salt cave. Halotherapy treatment has been associated with relief of respiratory conditions such as COPD, asthma, cystic fibrosis, as well as relieving in tegumentary conditions such as eczema and dermatitis (13).

Although the claimed effects of halotherapy are plenty, such as bactericidal effect, improvement of immunity, improved rheological properties of secretions, a single study has looked at immunological changes during halotherapy and suggested changes in T-Lymphocyte activity (16). Halotherapy has been shown to relieve symptoms in smokers and in patients with respiratory symptoms in general. Another study which compared saline inhalation (inhalation of saline solution through specialized equipment without halochamber) with halotherapy in the treatment of patients with COPD reported an improvement in FEV 1% in both groups. Moreover, halotherapy has a beneficial statistically significant effect on 6 minute walking test and on the patient's quality of life, as measured by Saint George's Respiratory Questionnaire (SGRQ) (19). In addition, no patients experienced side effects, which indicates that the treatment is safe and well tolerated; halotherapy seems to be better tolerated than saline inhalation (20).

Patients with COPD and comorbidities such as OSA (Overlap syndrome, prevalence 0,5-1%) (21) have more exacerbations of the respiratory symptomatology, a situation in which the halotherapy and the CPAP therapy have many benefits, but the therapeutic success is primarily ensured by the patients' compliance (22). The presence of various microbiological and inorganic structures on the inner surface of CPAP masks and tubes emphasizes the risk of microbial and inorganic elements inhalation into the upper and lower airways, so the microclimate and the hygiene of CPAP device, including masks and tubing is very important (23,24,25).

Muscular Training program

In COPD, changes in the anatomy of the airways and lung parenchyma occur as the result of bronchial hypersecretion and bronchoalveolar instability. These changes cause expiratory flow limitation and air trapping, known clinically as dynamic hyperinflation. This phenomenon leads to increases in expiratory reserve volume, residual volume (RV) and end expiratory lung volume (EEV). The increase in EEV limits Tidal volume and inspiratory reserve volumes resulting in a negative impact on the inspiratory capacity (IC). The changes alter the position of the ribs causing a state similar to sustained inspiration over time, often referred to as "inspiratory block"(26).

COPD can cause systemic alterations such as systemic inflammation, skeletal muscle dysfunction, peripheral muscle weakness and inspiratory and expiratory muscle weakness by changes in the composition of muscle fibers and muscle atrophy (27,28). Thus, the treatment of this disease should be

multidisciplinary and respiratory physiotherapy may act by improving the functional capacity of these subjects (29).

Because of the COPD comorbidities, like cardiovascular diseases and Obstructive Sleep Apnea (OSA), the importance of screening programs for these pathologies is evident in COPD patients. Some studies showed that only overweight itself produces early changes in cardiovascular status of the patient by decreasing the left ventricular ejection fraction, thickening the interventricular septum, increasing left ventricular mass and implementing early diastolic dysfunction (30).

Respiratory muscle training is a part of rehabilitation for stable COPD subjects, as it promotes benefits such as improved pulmonary function and respiratory muscle strength, reduction of dyspnea severity, improved exercise tolerance and enhanced functionality and quality of life. Studies that prove the efficacy of inspiratory muscle training (IMT) in subjects with stable COPD show that this training leads to a reduction of dyspnea and improve the pulmonary function, respiratory muscle strength, and functional capacity (27). IMT improves inspiratory muscle strength, quality of life (SGRQ), exercise capacity (quantified by 6MWT) and decreases dyspnea. Dyspnea during constant load tests was significantly decreased with IMT alone and IMT improved the walked distance during 6MWT with 43 meters-, with a statistical significance (31).

Studies have shown that respiratory muscle weakness is associated with increased mortality in subjects with COPD (32). In obese COPD patients the clinicians have to introduce a weight reduction programme in order to minimize the effect of excessive adipose tissue on the disease evolution. McDonald et al. demonstrated that the association between diet and resistance exercise training in obese COPD patients determined an improvement of clinical outcomes including health status, symptoms and functional capacity. Importantly, when calorie restriction is coupled with resistance exercise training and protein intake is maintained, it does not result in reduced skeletal muscle mass (33). In addition, expiratory muscle weakness is a risk factor for readmission to hospital due to exacerbations (34), and a recent study showed that the degree of airflow obstruction and hyperinflation is related to expiratory muscle strength (35). A recent systematic review showed that in normal subjects, the combination of IMT plus expiratory muscle training (EMT) is more effective in increasing the performance exercise compared with IMT or the control group (36).

In addition, some important comorbidities of COPD are obesity, OSA and metabolic syndrome including type 2 diabetes, which can complicate the evolution of stable COPD (37). Between these pathologies there is a synergic relation, because due to anatomical and physiological factors and treatment with corticosteroids increases fat deposition in the neck region, central obesity becoming a risk factor for OSA in the general population (38,39). One of the most important interventions in the treatment of OSA is the nutrition program along with a training program in order to reduce OSA severity, improve sleep quality and increase respiratory muscle endurance in patients with COPD (40,41). The purpose is to obtain weight loss, to reduce the apnea-hypopnea index and the severity of OSA but, in selected cases with associated craniofacial deformities, early orthodontic treatment could be beneficial (42,43,44).

Soft tissue manual therapy intervention

Manual therapy (MT) has been described as a therapeutic intervention that uses the hands to provide treatment to the musculoskeletal and/or visceral systems. MT includes techniques such as massage, myofascial release, muscle energy technique, ligament balance, joint mobilization and joint manipulation. The suggestion that MT can deliver ongoing benefits for people with COPD is a new approach (45).

Cruz-Montecinos showed that management strategies which include manual therapy designed to address the soft tissues of the chest wall has the potential to produce immediate improvements in lung function in patients with severe and very severe COPD (26). Another study reported similar results, but included a combination of soft tissue therapy and thoracic mobilization (46). Moreover, reduced tonicity in the muscles, fascia and ligaments of the neck and chest would facilitate an improvement in the passive components of expiration by reducing the extent of any inspiratory block. In support of this concept are the results of a recent study, which reported a correlation between pulmonary function and postural alignment and mobility of the chest in patients with COPD (47). Improvements in mechanical efficiency may also explain the increase in oxygen saturation and decrease in respiratory rate, which if sustainable, could alter input to the central and peripheral

chemoreceptors. The decrease in heart rate may be the result of the decreased residual volume, where lower pressure within the lungs leads to a reduction in pulmonary hypertension. Therefore, a single application of an MT protocol consisting of several soft tissue techniques has the potential to deliver immediate improvements in lung function for people with severe and very severe COPD. The doctors should be trained in order to recommend the proper technique, because the MT techniques that use compression/decompression maneuvers can increase airway obstruction by accelerating airflow to the extent that airways collapse (26).

Neuromuscular electrostimulation

For a long time, COPD was considered to be a respiratory disease, but, additionally, COPD produces inactivity, which promotes further loss of exercise capacity (deconditioning) through the loss of muscle mass, creating a "vicious" circle. Weakness, atrophy, structural and metabolic changes have been observed in limb muscles, which in turn, can have a negative impact on exercise tolerance. Peripheral muscle dysfunction in people with COPD is characterized by: reduced percentage of the oxidative fibres (type I) in relation to glycolytic fibres (type IIa and IIb), decreased activity of most oxidative enzymes while glycolytic enzyme expression is increased, reduced capillary density or capillary-to-fibre ratio and mitochondrial dysfunction. Taken together, these changes contribute to an overall reduction in the oxidative capacity of the muscles of patients with stable COPD and overlap syndrome. Exercise protocols have traditionally focused on aerobic training, however, more recently, increased emphasis has been placed on resistive training because of the importance of maintaining or improving muscle bulk and strength in this group of patients. Unfortunately, some debilitated patients with COPD are unable to sustain an adequate training intensity and duration, leading to reduced activity or even to the patient being confined to their home or bed and accentuating the deterioration of the overall health status of this individual. Moreover, several investigations have reported the benefits of pulmonary rehabilitation beside using neuromuscular electrostimulation (NMES) to reverse some of the negative changes occurring in the peripheral muscles of patients with stable COPD. NMES has been extensively used as a technique to improve muscle function and structure in different areas of rehabilitation and sports training programs [48], required in patients with overlap syndrome that associate excessive daytime sleepiness, limited physical activity and a lower quality of life in order to improve sleep quality and to reduce OSA severity (49,50,51).

Kucio C et al. suggested that physical exercise results in decreased symptoms of skeletal muscles function disorders, which constitute the most common extrapulmonary symptoms of COPD. Physical training prevents further muscle damage which leads to decreased strength and endurance, while at the same time increasing exercise tolerance. The results of this study indicate that due to the application of traditional pulmonary rehabilitation in combination with NMES of 35 Hz frequency, a substantial increase of distance in the 6 minute walking distance in relation to the distance covered before the study was observed. The increase in exercise tolerance does not correlate with improvements in spirometric values (FVC, FEV1, FEV1%FVC), nor with gasometric parameters (partial oxygen pressure - pO2 and partial pressure of carbon dioxide - pCO2). However, the observed improvement of exercise tolerance results from increased strength and endurance of skeletal muscles of lower limbs subjected to NMES therapy (52). Another study showed that NMES, when applied in isolation, increased quadriceps force and endurance, 6MWD and time to symptom limitation exercising at a submaximal intensity, and reduced the severity of leg fatigue on completion of exercise testing (53).

Conclusion

COPD is an ever-growing global problem with systemic implication and multiple comorbidities. Although pharmaceuticals have been extensively studied and utilized, their disease-modifying effects are limited and dependent on patient adherence.

The management of COPD should include a multidisciplinary therapy; individualized pulmonary rehabilitation as an adjuvant to the medical treatment, by effective methods, such as speleotherapy, halotherapy, muscular training, manual therapy (soft tissue manual therapy) and neuromuscular electrostimulation.

Declaration of conflict of interests

The author does not have any financial interest involving the companies and/or materials mentioned in this article.

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Short narrative review on main winter sports-related accidents: epidemiology, injury patterns, arguments for prophylactic behavior to avoid orthopedic and catastrophic neurological injuries

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Abstract

Winter-sport participation may be associated with a risk of injuries. The article provides a brief overview of the epidemiology of winter sports-related trauma, referring to common skiing and snowboarding injuries in professional athletes or inexperienced ones (amateurs), to determine injury patterns, crash circumstances, their pathological repercussions, and possible preventive interventions.Known risk factors for the occurrence of injuries are: lack of experience in snow-sports, suboptimal skill and technical level, poor physical fitness level, fatigue, risk-taking behavior, alcohol consumption, absence or rented and/ or faulty equipment and protective devices, high speed, ice on the slope, bad weather conditions and poor visibility, crowd on the track. This short exposure aims to educate younger (recreational) skiers and snowboarders to prevent traumatic injuries to the limbs and especially the catastrophic ones, resulting in central nervous system lesions, with devastating consequences for athletes, their families, and communities. The paper has a multidisciplinary addressability: it may be useful for general practitioners and young specialists in orthopedics, neurology, physical medicine & rehabilitation, and kinetotherapy.

Key words: *winter sports; snowboarding injuries; skiing injuries; bobsleigh; luge; skeleton; spinal cord injury; traumatic brain injury; injury prevention; physical disability,*

Introduction

Being active in sports has many positive health effects, and provides many benefits to physical and mental health. The Latins had a famous proverb: "Mens sana in corpore sano / A sound mind in a healthy body".

Recreational or professional alpine skiing, snowboarding, luge, are increasing in popularity worldwide, enjoyed by million of participants of all ages and skill levels. In 2010 an estimated 11.5 million people in the United States participated in skiing, and 8.2 million engaged in snowboarding (1). Besides the beneficial health effects of an active life style, sport participation may be unfortunately associated with risk of injuries.

Sometimes devastating traumatic injuries can have dramatically consequences for the athletes, their families, and communities. Severe post traumatic neurological injuries can raise significant public health concern, and even may discourage participation in sport. Michael Schumacher's dramatic fate was an intensely covered topic in mass-media, five years ago.

Material and method

A systematic search of Pubmed Database focused on the above-mentioned keywords was conducted to identify relevant articles and systematic reviews published in English literature, reporting winter-sport related accidents.

This article is a short overview of the epidemiology of snow sport-related trauma, referring to the common skiing and snowboarding injuries in professional athletes or inexperienced (amateurs) tourists, to determine the injury patterns, crash circumstances, their pathological repercussions, and possible preventive interventions.

Known risk factors for the occurrence of injuries are lack of experience in snow-sports, technical errors, suboptimal technical level and poor physical fitness level, fatigue, risk-taking behavior, and alcohol consumption, presence of ice on the slope, bad weather conditions and poor visibility, crowd on the track, high speed, rented or faulty equipment or protective devices (2,3,4).

Local mountaineers ironically and generically call a category of amateurs, inexperienced athletes, as "*paltonari*" (term derived from "palton", similar to the English word "paletot"), referring to their unfit

mountain equipment and imprudent behavior. These inexperienced skiers and snowboarders are usually exuberant and defiant young persons, predisposed to alcohol consumption and risk-taking behavior with dramatic repercussions (severe limb fractures or catastrophic neurologic injuries).

Recent international literature reviews emphasize that the incidence of traumatic brain injury (TBI) and spinal cord injury (SCI) in winter sport activities are increasing, mainly in alpine skiing and snowboarding (5,38). Although uncommon, fatal and severe nonfatal (but with dramatic debilitating sequels) brain and spine injuries can occur during winter-sports, and induce enormous financial burden to society. These accidents may happen at all levels of play, from youth to professional athletes (6, 7). In Canada, all winter sports injuries are responsible for significant health care burden, with estimates of $400 million in direct and indirect annual health care costs (8).

Catastrophic **spinal injuries** in sports are rare but tragic events, and athletic competition has long been a known source of spinal cord injuries (SCIs). SCI is a rare but serious event and a major cause of morbidity and mortality for skiers and snowboarders. Approximately 8.7% of all new cases of SCIs in the United States are related to (general) sports activities; ice hockey, skiing and snowboarding are among the highest risk-spots for SCIs (7). Spine trauma is among the most devastating injuries in snow sports, comprising 1% to 17% of all injuries in skiers and snowboarders (9, 10). Different epidemiological studies emphasized that most SCIs occurred after intentional jumps, rather than collisions (11, 12).

In 13.4% patients, most commonly seen are “tandem injuries”: a closed head injury and cervical spine trauma, with possible catastrophic repercussions (13). Safety helmets decrease the risk for and the severity of head injuries. Although helmets do not protect the spine, they certainly do not increase the risk of neck and cervical injuries (14, 15).

The common mechanism of SCI for all at-risk winter sports is represented by an axial compression force to the top of the head with the neck in neutral position of slightly flexed (7). The biomechanical dynamic proprieties of the head and spine, the force vector applied during impact, the intrinsic strength and anatomy of vertebral bodies and their surrounding spinal elements (16) concur to SCI. In neutral, vertical position, the average weight of human head is around 4.5 to 5 kg at rest. As the head is bending forward, its weigh increases from 13 kg (at 15°), to 20 kg (at 30°), 24,5 kg (at 45°), 30 kg (at 60°) (17). These biomechanical variable factors may explain a cervical SCI after an accidental fall on the ischial tuberosities.

Spinal injury patterns among snowboarders and skiers associated cervical spine trauma in 19.6% cases vs. 10.9% of thoracic and 6% of lumbar injuries (13).

A systematic review of published literature (1980 - 2015) reporting the epidemiology of sport-related SCIs emphasized that the greatest majority of cervical SCIs were encountered in hockey and skiing, whereas in snowboarding over half of the spinal lesions were fond with predilection in the thoracic or lumbosacral levels (18). In snowboarders falling backward represent the mechanism of spine injury (typically in the fragile thoracolumbar junction), causing an axial load or a flexion-distraction moment (11, 19).

Lower trunk lesions (pelvis, hip, lumbar spine) are usually characteristic of snowboarders (20). Acrobatic jumping or accidental collisions with trees or ski towers are responsible for snowboarding-related pelvic ring fractures, associated or not with sacral fractures. Incidence of pelvic fractures was 2%, and in about 14.5% patients have occurred axial biomechanical stability problems (21).

Pending of the vertebral lesion and neurological level of injury, immediate and sometimes life-long catastrophic neurological consequences can occur: more or less severe paralysis of the entire body (tetraplegia), or only paralysis of the lower limbs (paraplegia), infra-lesional anesthesia, neurogenic bladder requiring artificial voiding (using indwelling or intermittent urinary probes), neurogenic bowel, respiratory dysfunction, predisposition to pressure ulcers, pulmonary or urinary infections.

Another catastrophic winter-sport event is TBI, the leading cause of death and severe disability in skiing and snowboarding. Approximately 600,000 ski- and snowboarding-related injuries occur in North America each year, and head trauma accounts for 20% of all injuries (14).

Amateurs (“week-end athletes”) aged between 46 to 55 years, and those who never had a professional instruction, or those with rented equipment are predisposed to catastrophic neurological lesions (22).

Cerebral trauma was reported in 28% of all ski injuries, respectively in 15% (23) up to 33.5% (24) of all reported snowboarding injuries.

One must stress that TBI can have fatal outcomes among snowboarders and skiers of all ages, and is the culprit for up to 88% of all winter sport-related deaths (14). Little research has been conducted on sport-related concussion and injury prevention strategies in competitive sledding sports, like bobsleigh, luge, and skeleton.[Skeleton is a winter sliding sport in which a person rides a small sled, known as a skeleton bobsled (or sleigh), down a frozen track, while lying face down and head-first (25). Prevention strategies are limited, with no possibility of attenuating a catastrophic collision to the head, by interposing the hands. Concussions are a common occurrence in elite sledding sport athletes, affecting 13-18% of all, and this risk factor was entitled "sled head" (26).

Recreational sledging (tobogganing), very popular in Alpine regions, consists in ascending and sledging down on the same track. Apparently safe and stable, about 9% participants reported sledging-related injuries to: lower extremities (41%), arms (22%), shoulder and back (11%), or head (10%) (4).

Overall, 22% of head injuries can be serious enough to cause clinical signs of concussion (14); acute subdural hematoma represents the most common neurosurgical indication for intervention (27).

Immediate consequences can be devastating, consisting of serious neurological and psychological disorders: different degrees of alteration of the cognitive and executive functions, aphasia, hemiplegia or even tetraplegia, neurogenic bladder, vegetative status and feeding by percutaneous endoscopic gastrostomy (PEG). Unfortunately, most of these severe impairments may persist as life-long disabilities. Due to the violent energy impact, head trauma is the leading cause of mortality after injuries related to skiing and snowboarding (15).

Due to actual objective limitations of therapeutic possibilities of intervention to restore neurological function after TBI and SCI, the best treatment is prevention. Safety helmets are strongly recommended during recreational skiing and snowboarding (14). There is evidence that helmets reduce the risk of head injury by 22-60% (5).

Helmets are used by most snowboarders (72%) and skiers (74%), but more than 25% of all skiers and snowboarders remain at increased risk of serious brain injury, by not wearing a helmet. Females are more “conscious” to wear helmets than males (80% vs. 70%), and fortunately the highest rates of use were found among 4- to 12-years-old children (8).

In Netherlands was developed an evidence-based tailored Web-based advice tool (Wintersportklaar) for online intervention, addressed to skiers and snowboarders. It promotes adequate protection equipment, correct information and sustained media education initiatives advocating injury preventive behavioral attitude essential to counteract the “adverse effects” of winter-sports (28).

Severe injuries are more common in snowboarding accidents. Referring to snowboarders: wrist injuries, shoulder soft tissue injuries, ankle injuries, concussions, and clavicle fractures were most frequently seen, whereas in skiers anterior cruciate ligament (ACL) sprain or tear, medial collateral ligament (MCL) sprains, or lateral collateral ligament (LCL) sprains of the knee, lower extremity contusions, and tibia fractures were mostly encountered (1, 19, 29).

Shoulder injuries were reported in 4 to 11% of all alpine skiing injuries and in 22 to 41% of all upper-extremity ones (31). During snowboarding, shoulder girdle injuries account for 8 to 16% of all injuries and for 20 to 34% of all upper-extremity ones (1, 30).

Most common shoulder injuries during skiing and snowboarding were [30]: glenohumeral dislocations (5.5% of all injuries) (21), rotator cuff strains, acromioclavicular dislocation, and clavicle fractures (4% of all reported injuries(9,1).

Falls, in addition to pole planting during skiing and aerial maneuvers during snowboarding are the most common causes of shoulder injury (31).

Overall, upper limb injuries in snowboarding have a double frequency, compared to those registered during alpine skiing (22, 29). Most common fractures were noticed at the radius (48%), clavicle (11%), humerus (11%), and ulna (7-8%) (32).

Wrist represents the most common location of upper extremity injuries related to snowboarding, accounting for 32% (33) - up to 44% of all upper extremity injuries (34]), and fractures accounted for 31% (33) - up to 78% of total wrist lesions (34). Snowboarding-related wrist lesions registered between 2010 to 2016 in the emergency departments in the United States included wrist strains/sprains (25.2%), contusions (10.9%), concussions (10.0%), and dislocations (4.0%) (34).

Usually beginner snowboarders are predisposed to falling and wrist fractures. Snowboarding-related hand injuries accounted for 8.4% of the total upper extremity lesions (34).

The natural defense reflex during falling down represents the physiopathological mechanism of the shoulder and/ or wrist injuries. The severity of arm injuries in snowboarding seems to be caused by direct force on the wrist and elbow, which receive the full impact of a fall (29). Analyzing the falling kinematic mechanisms one emphasized that falling backward leads to a wrist injury, whereas a fall forward (toe side) is more predictive of a shoulder injury (19). These aspects explain why upper extremities fractures in snowboarders are three times more common than in skiers, affecting mainly the left upper extremity, with the exception of wrist fractures (35).

Knee is the most common region of the lower extremity injured during skiing, with a mean incidence of 42 injuries per 1,000,000 person-years, and a higher incidence in adults, mainly in males (46 per 1,000,000 person-years) (20).

The anterior cruciate ligament (ACL) is involved in approximately 50% of all knee serious injuries, due to forced internal rotation and / or valgus loading, in the effort to restore the trajectory of the skis (36).

It is frequently associated with concomitant (other) injuries, such as medial collateral ligament (MCL) sprains, meniscal tears, or tibial plateau fractures (36).

Foot and ankle injuries (ankle fractures and sprains) are most prevalent type of injuries associated with snowboarding, estimated at 15% of all lesions encountered in this sport **(**37). Fracture of the lateral process of the talus is relatively unique to snowboarding, and is commonly called the "snowboarder's fracture" (37).

The greatest majority of snowboard-related lesions were encountered in persons who did not have a correct initial instruction from professional staff (93%) and did not use protective equipment (87%) (35). Sustained information on specific technical procedures and biomechanical particularities in each winter sport, the correct application of the learned techniques on the slopes, and the encouragement of adequate use of protective equipment are mandatory to avoid possible serious accidents.

This short exposure aims educational approach to stimulate injury preventive behavior among amateur skiers and snowboarders. In a beautiful lyric song Jacques Brel said: “On a beau faire on a beau dire, Qu`un homme averti en vaut deux “/ An informed man is worth two! “).

Conclusion

In conclusion, referring to winter-sport related catastrophic lesions of the central nervous system, PREVENTION IS CURE !

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Abbreviations

ACL, anterior cruciate ligament
LCL, lateral collateral ligament
MCL, medial collateral ligament
SCI, spinal cord injury
TBI, traumatic brain injury

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A statistical study on the recovery of pubalgic syndrome in football players

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Abstract

According to pathology description, pubalgic syndrome affects increasingly more people, especially athletes practicing sports such as football, hockey, rugby, etc. Once this pathology has been established, in addition to pain in the pubic region, a decrease in mobility and muscle strength, it also induces changes in footprint and, implicitly, in the level of plantar pressure. The study was conducted on a number of 35 subjects, of which 30 healthy subjects and 5 subjects affected by pubalgic syndrome (pubis osteitis). The 5 football players affected by pubalgic syndrome (pubis osteitis) benefited from kinesiotherapy. All data, both initial and final, as well as the data recorded for the 30 healthy football players, were statistically processed and compared. The kinesiotherapeutic plan led to positive effects by reducing the symptomatology recorded at plantar level, and ANOVA tests helped in obtaining a qualitative contribution to the recovery program, as well as a socio-economic benefit for the patient.

Key words: *pubalgic syndrome, kinesiotherapy, statistical analysis, postural test*

Introduction

The football game has evolved considerably over the last decade, so players have to resort to "overtraining" to cope with the new standards imposed by the game. The "overtraining" that athletes use to compete consists of: increasing the number of weekly workouts, inadequate dosage of effort, weight before the recommended age, etc. All these "methods" used by athletes plus the high number of matches in both domestic and international championships have led to the emergence of new pathologies.

One of these new pathologies affecting football players is pubalgic syndrome (pubis osteitis). This condition was first described by Dr. Edwin Beer in 1924. Beer described it as a complication following surgery of the pubic symphysis, later migrating as an inflammatory process in athletes. In 2011, Demetrius E.M.L. wrote that this syndrome frequently occurs in football and accounts for 10-13% of all accidents every year (1).

Since the onset of the syndrome in football, most specialists have approached this problem from a pharmacological, imaging, radiological and surgical point of view (2, 3, 4, 5, 6). A small number of specialists also addressed the issue of musculoskeletal impairment, syndrome classification, incidence and rehabilitation programs (7, 8, 9, 10, 11, 12). In 2012, Vijayakumar P. rehabilitated a soccer player affected by pubalgic syndrome (pubis osteitis) with the help of manual therapy and proprioceptive neuromuscular facilitation techniques, successfully used in the recovery of osteoarthritis and migraine cases as well (13, 14, 15). Ceatham S.W. contradicted Vijayakumar P. in 2016, writing that there is little evidence of the effectiveness of recovery and reintegration programs in competitive activity (16).

Materials and methods

The statistical study was performed on a group of 35 male football players (30 healthy subjects and 5 subjects affected by osteitis pubis), aged between 18 and 35 years. Both healthy and affected patients underwent initial and final testing, based on a postural test. Data were used from the article *Assessment of Pubalgic Walking with the Help of a Podiatry Platform in Football Players* (17).

Patients affected by this syndrome benefited from personalized kinetic treatment:

- physical exercise;
- PNF techniques;
- massage.

The results were analyzed using the two ANOVA specific hypotheses: the null hypothesis (there is no relationship between variables), and the alternative hypothesis (relationships are established between variables, so they are dependent).

The results showed a correlation between the group of healthy players and those who benefited from the recovery plan.

The subjects were assessed by a postural test "Pedana OEM/DF, DISP MED. CLASSE I", along with "Dr. Foot Analysis 4.0" (Figure 1) (17, 18). Using them, data were collected on plantar footprint and plantar pressure for both the right and the left foot.

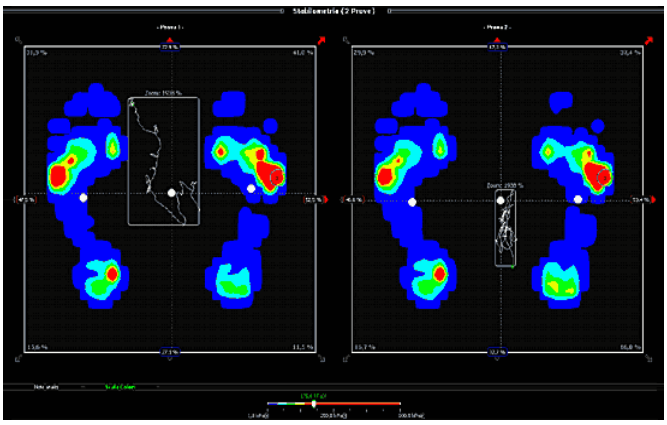

Fig. 1*. Dr. Foot Analysis 4.0 - plantar surface, plantar footprint, pressure points together with the position of the center of gravity (16)*

Results

After processing the data using the ANOVA test in the study *Pubalgic Walking with the Help of a Podiatry Platform in Football Players*, we identified that (Tables 1 and 2) (17):

Applying the statistical tests to regularize the experimental data led us to the following results:

- the sum of squares for both the left and the right foot is 573.975, but with notable differences for weighted (568 for the right foot and 98.335 for the left foot), and deviation (21.163 for the right foot and 16.926 for the left foot);
- the number of degrees of freedom is equal for the right foot and the left foot;
- the major interest resides in F; the value associated with the F-test is 10.214 with p <0.243 for the right foot, with a repeat of 1.147 with p <.532 for the left foot, which leads us to the assumption that the weight is distributed on the left foot.

Figures 2 and 3 are graphical representations of Tables 1 and 2. In the figures mentioned below, it can be seen how the plantar footprint is inversely proportional to the pressure exerted at plantar level, namely:

- the right foot of healthy football players (Figure 2) - the plantar footprint is smaller compared to the left foot, but the pressure exerted at plantar level is higher for the right foot;
- the left foot of healthy football players (Figure 3) - the plantar footprint is larger compared to the right foot, but the pressure exerted at plantar level is lower for the left foot.

This can be explained by the fact that the football players used in the study *Pubalgic Walking with the Help of a Podiatry Platform in Football Players* are right-footed (17). While a larger left plantar footprint provides increased stability necessary for directional changes, kicks of the ball, etc., a lower plantar pressure favors the mobility of the segment for easy handling of the ball.

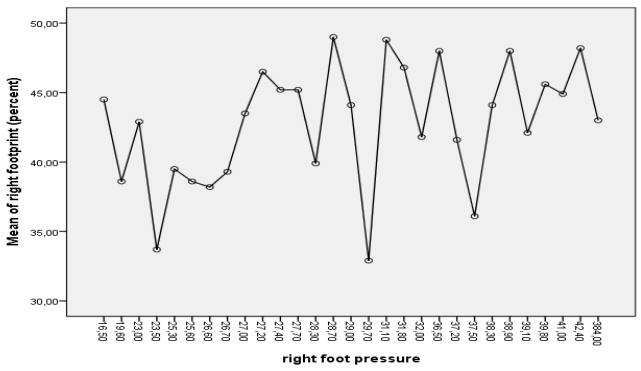

Fig. 2*. ANOVA TEST - the correlation between plantar footprint and plantar pressure - right foot (healthy football players)*

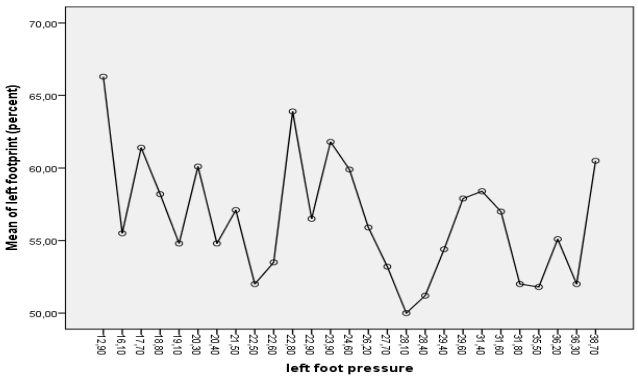

Fig. 3. *ANOVA TEST - the correlation between plantar footprint and plantar pressure – left foot (healthy football players)*

After kinetic treatment, the patients affected by pubalgic symptoms also had the final evaluation, and the data obtained are presented in Table 3.

Table 3 shows the differences obtained following the application of kinetic treatment for the right footprint, left footprint, right foot plantar pressure, left foot plantar pressure, and the center of gravity. The differences can be more easily observed in Figures 4 and 6 for the right foot and Figures 5 and 7 for the left foot.

If in healthy football players (Figures 2 and 3) the plantar footprint was inversely proportional to the pressure exerted at plantar level, with the development of the disease the ratio between the plantar footprint and the pressure exerted at plantar level became directly proportional (Figures 4 and 5) (initial testing). This is explained by the defense of the body, trying to limit as much as possible the contact of the right foot with the ground, thus modifying the general center of gravity.

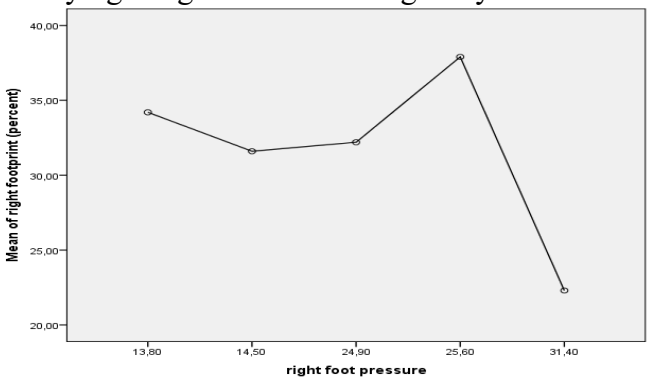

Fig. 4*. ANOVA TEST - the correlation between plantar footprint and plantar pressure - right foot (initial testing of affected football players)*

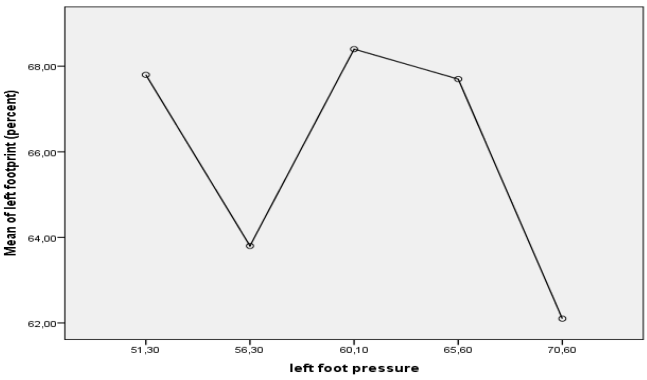

Fig. 5. *ANOVA TEST - the correlation between plantar footprint and plantar pressure – left foot (initial testing of affected football players)*

Following kinesiotherapy, as shown in Figures 6 and 7 (final tests), a tendency towards normalization occurred, with a change in the ratio from directly proportional to inversely proportional, like in the case of healthy football players.

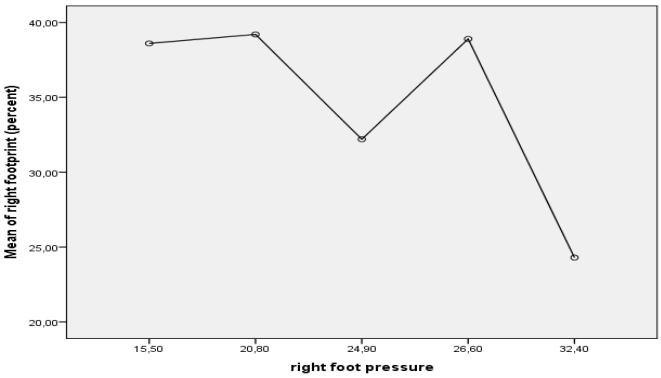

Fig. 6. *ANOVA TEST - the correlation between plantar footprint and plantar pressure - right foot (final testing of affected football players)*

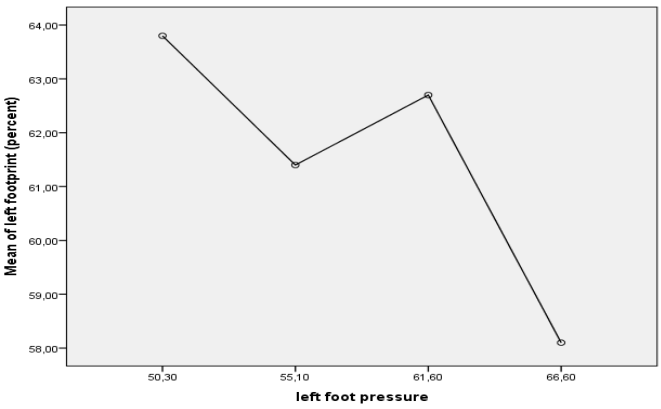

Fig. 7*. ANOVA TEST - the correlation between plantar footprint and plantar pressure – left foot (final testing of affected football players)*

Conclusion

Following analysis, it can be said that the treatment plan had beneficial effects by reducing the symptomatology recorded at plantar level.

The parameters registered in the initial testing (affected players) changed after treatment, so that final testing parameters were close to the parameters recorded in healthy players.

Once established, the pathology causes changes in both footprint and plantar pressure.

The kinesiotherapeutic program led to a positive change in the final assessment compared to the initial assessment. After treatment, based on comparison and statistical processing of the data, a tendency towards normality in the affected players was evidenced.

ANOVA tests helped in the processing and interpretation of the data obtained, thus allowing a qualitative contribution to the recovery program, as well as a socio-economic benefit for the patient by decreasing the duration of treatment sessions and implicitly reducing the costs of the rehabilitation program.

Informed consent

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

Declaration of conflict of interests

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

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Table 1. ANOVA TEST - the correlation between plantar footprint and plantar pressure - right foot (healthy football players)

			Sum of Squares	df	Mean Square	F	Sig.
Between Groups	(Combined)		571.975	28	20.428	10.214	.243
	Linear Term	Weighted	.568	1	.568	.284	.688
		Deviation	571.407	27	21.163	10.582	.239
Within Groups			2.000	1	2.000		
Total			573.975	29			

Table 2. ANOVA TEST - the correlation between plantar footprint and plantar pressure – left foot (healthy football players)

			Sum of Squares	df	Mean Square	F	Sig.
Between Groups	(Combined)		521.495	26	20.057	1.147	.532
	Linear Term	Weighted	98.335	1	98.335	5.621	.098
		Deviation	423.160	25	16.926	.968	.605
Within Groups			52.480	3	17.493		
Total			573.975	29			

Table 3. *Initial and final evaluation of the affected group*

S	**Apd (%)**			**Aps (%)**			**Ppd (kgf)**			**Pps (kgf)**			**SCg (cm^3)**		
	I	F	Dif.	I	F	Dif.	I	F	Dif.	I	F	Dif.	I	F	Dif.
1	34.2	39.2	5	63.8	60.8	3	13.8	20.8	7	56.3	50.3	6	0.145	0.17	0.025
2	31.6	38.6	7	68.4	61.4	7	14.5	15.5	1	60.1	55.1	5	0.121	0.161	0.04
3	37.9	38.9	1	62.1	58.1	4	25.6	26.6	1	70.6	66.6	4	0.171	0.211	0.04
4	32.2	32.2	0	67.8	66.8	1	24.9	24.9	0	51.3	50.3	1	0.125	0.139	0.014
5	22.3	24.3	2	67.7	62.7	5	31.4	32.4	1	65.6	61.6	4	0.116	0.126	0.01

*Legend: S = subjects, Apd = right footprint, Aps = left footprint, Ppd = right foot plantar pressure, Pps = left foot plantar pressure, SCg = center of gravity

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Autonomic dysfunction and peripheral nerve involvement in patients with Parkinson's disease

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Abstract

Introduction: Parkinson's disease (PD) is a chronic illness which damages central and peripheral nervous system. The presence of peripheral neuropathy (PN) in PD, it has been suggested to be the effect of treatment. The aim of this study was to investigate autonomic cardiac control in PD patients with normal serum levels of vitamin B12 by means of spectral analysis of short-term heart rate variability (HRV) and also to assess the prevalence of PN using electrophysiological examinations. **Methods:** 30 (18 male and 12 female) with PD were compared to 20 age- and sex-matched control subjects. Short-term ECG was used to calculate time domain and spectral parameters of HRV. The stimulodetection examination was realized in the motor fibers of median, peroneal and tibial nerves, and in the sensitive fibers of median and sural nerve according to the standard procedures. **Results:** Low and high frequency were lower in PD patients than in controls (LF: 332.±288.4 ms² PD vs 723.9±348.2 ms^2 C; HF: 283.72±241.97 ms² PD vs 530.54±226.5 ms² C, $p<0.01$). No differences between LF/HF ratio of PD and controls appeared. Sensory nerve action potential in sural nerve was reduced in PD patients. No differences between sensory and motor nerve conduction velocities of PD and controls appeared. **Conclusions**: PD causes dysfunction of autonomic cardiovascular regulation and peripheral nerve involvement.

Key words: *Parkinson's disease, heart rate variability, parasympathetic nervous system, low frequency, sensory nerve action potential, nerve conduction velocity*,

Introduction

Parkinson's disease (PD) is a chronic neurodegenerative movement disorder characterized by a progressive loss of the pigmented dopaminergic neurons of the substantia nigra pars compacta (SNpc) and by the presence of intra-neuronal aggregates called Lewy bodies (1). This degeneration affects not only the dopaminergic mesocorticolimbic system, but also the noradrenergic locus coeruleus (2), motor vagal nucleus, the serotonergic raphe nuclei (3) and many peptidergic brainstem nuclei containing substance P, somatostatin, and neuropeptide Y (4).

Clinical manifestations of Parkinson's disease include motor dysfunction such as rigidity, resting tremor, bradykinesia, postural instability and gait dysfunction. PD is also associated with many non-motor features, including autonomic dysfunction, pain, mood disorders, sleep impairment, and dementia (5).

The pathogenesis of PD is largely unknown but mitochondrial dysfunction, oxidative stress, glutamate induced excitotoxicity, intracellular protein accumulation of Lewy Bodies containing α-synuclein protein, inflammation, loss of neurotrophic factors and apoptosis appear to have a key role in the development and progression of PD (6-8). Also the genetic factors, genes like parkin and α-synuclein has been involved in pathogenesis of PD (9).

It is well documented that PD may be associated with a dysfunction of the autonomic nervous system. Histological studies have proven the presence of Lewi's bodies in sympathetic and parasympathetic preganglionic neurons and also in central structures associated with the autonomic regulation (10).

Analysis of heart rate variability (HRV) from ambulatory ECG recordings has become an important method for assessment of cardiovascular autonomic regulation.

To characterize the cardiovascular autonomic regulation in PD, Ewing tests were used. These tests require an active participation of the patients, and the rigidity and tremor characteristic of PD make these tests difficult to assess. The measurement of autonomic parameters using power spectrum analysis of heart rate (HR) does not require the active participation of patients. Decrease of spectral power in PD patients was documented in 24-hour examination (11). The presence of peripheral neuropathy (PN) in PD is a relatively new clinical fact. PD patients may have sensory abnormalities which in some cases precede motor dysfunction. Alpha-synuclein was found in peripheral sensory neurons in PD patients (12). The presence of PN in PD, it has been suggested to be an iatrogenic effect of levodopa treatment, by deficiency of vitamin B12 after treatment (13). Toth et al. found that high levels of methylmalonic acid (MMA) are associated with levodopa-treatment and PN in PD patients (14).

The aim of this study was to investigate autonomic cardiac control in PD patients in early stages of the disease, with normal serum levels of vitamin B12 (cobalamin) and methylmalonic acid, by means of spectral analysis of short-term HRV and also to assess the prevalence of PN using electrophysiological examinations.

Metthods

Participant recruitment and inclusion criteria

30 patients (18 male and 12 female) with PD were compared to 20 age- and sex-matched control subjects. Parkinson's disease was diagnosed according to the United Kingdom Parkinson Disease Society Brain Bank criteria (15). PD severity was determined using the Hoehn and Yahr scale (H&Y) (16). The patients included into the study also meet the criteria of normal serum levels of vitamin B12 (cobalamin) and methylmalonic acid.

Patients with stroke, epilepsy, coronary artery disease, arrhythmias, atrioventricular block or bundle branch block were excluded from the study. Inclusion criteria for the controls were the absence of any history of PD and with two normal consecutive ECG in the course of one month. Patients who had medication known to influence autonomic system (anticholinergic and monoamine oxidase inhibitor) were excluded. The study was carried out in accordance with the Helsinki Declaration. All subjects participated voluntarily after being given a detailed explanation of the purpose of the study.

Clinical and paraclinical assessment

All the subjects underwent detailed history taking and neurological examination. A standardized autonomic questionnaire was used to detect autonomic complaints.

Score of Unified Parkinson's Disease Rating Scale (UPDRS) part III (Motor section) was recorded when patients were at "on" state (17). The motor examination of UPDRS is the most used measure to assess motor symptoms such as rest and action tremor, rigidity, bradykinesia, gait and posture, facial masking. Each items are scored on a 0 (no impairment) to 4 (severe impairment), the total motor UPDRS exam score ranges from 0 to 108 (17).

For each person in the study we measured: body mass index (BMI) (calculated as weight divided by height squared-Kg/m²), fasting blood glucose, serum total cholesterol, high density lipoprotein cholesterol-HDL, low density lipoprotein cholesterol-LDL, triglycerides; systolic and diastolic arterial blood pressures in standard examination conditions.

Measurement of heart rate variability

Using BIOPAC Acquisition System, we monitored the HRV in basal condition (18-20). HRV was analyzed following the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (21). Short time ECG data were digitized and stored on computer for subsequent off-line analysis. The ectopic bits or artifacts were manually edited.

Time–domain parameters used were Mean-R-R, Standard deviation of all NN intervals (SDNN), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), percentage of differences between adjacent NN intervals differing more than 50 msec (pNN50 %). pNN50% has been proven to be a valid index of vagal tone. Frequency Domain HRV measured were: very low frequency (VLF) from 0.0033–0.04 Hz, low frequency (LF) from 0.04–0.15 Hz and high frequency (HF) 0.15–0.4 Hz. The HF fluctuation of RR intervals mainly reflects the cardio-vagal modulation and the inspiratory inhibition of vagal tone (21). We analyzed LF and HF power, ratio of LF/HF (considered an index of cardiac sympathetic/parasympathetic tone balance). All HRV tests were made always in the morning hours between 9 and 11 a.m.

Table 1. Recording and stimulation site for nerve conduction studies

Nerve	*Recording (surface electrodes)*	*Distal stimulation*	*Proximal stimulation*
mNCV Median nerve	*Abductor Pollicis Brevis Muscle*	*3 cm above the wrist*	*Elbow*
mNCV Peroneal nerve	*Extensor Digitorum Brevis Muscle*	*Ankle (between the extensor digitorum longus and extensor hallucis longus tendons)*	*behind the fibular head*
mNCV Tibial nerve	Abductor Hallucis Muscle	behind the medial malleous	popliteal fossa
sNCV Median nerve ortodromic stimulation	*3 cm above the wrist*	Finger II	
sNCV Sural nerve **antidromic stimulation**	behind the Lateral Malleolus	distal to the lower border of the bellies of the gastrocnemius, at the junction of the middle and lower thirds of the leg, just lateral to the midline.	

Nerve conduction studies

For electrophysiological investigations the electromyograph Neuro–MEP Micro was used. The stimulodetection examination was realized in the motor fibers of median, peroneal and tibial nerves, and in the sensitive fibers of median and sural nerve according to the standard procedures (22). The surface electrodes were used to obtain muscular response according to the principle "belly-tendon" (the active electrode was placed on the muscle belly and the reference electrode on its tendon). The ground was placed between distal stimulation and the recording electrodes. *Stimulation and collection points are shown in Table 1. The investigations were carried out in a warm room, the temperature of the patient's skin being at least 35°C.* For data acquisition specific settings were used: sensitivity (500 μV - 2 mV for motor and 2-5 μV for sensory nerve conduction velocity- NCV); frequency range (20 Hz - 5 kHz motor NCV and 20 Hz - 7 kHz sensory NCV); sweep (5 ms/division motor and 2 ms/division sensory NCV). Stimulation used single stimuli with duration of 0.1 ms and variable intensity to obtain maximum response (maximum 100 mA). For each motor nerve the following electro-physiological indices were studied: motor distal latency (MDL – ms), compound motor action potential (CMAP – mV), motor nerve conduction velocity (mNCV – m/s). At the examination of sensitive nerves the following parameters were measured: sensitive latency (SL - ms), sensory nerve action potential (SNAP – microV), sensory nerve conduction velocity (sNCV – m/s).

Statistical Analysis

The statistical analysis of the results was performed using the software package STATISTICA 6.0 (StatSoft Inc., USA). The values are presented as mean values and standard deviation. Test t- Student or variance analysis (ANOVA) was used to determine the differences between the groups. The Pearson correlation coefficient r was used for determining relationship between parameters. The values $p<0.05$ were considered statistically significant.

Results

We studied 30 patients (18 males and 12 females) with PD in 1-2 H&Y stage (mean age 63.2±3.47 years, body mass index 24.44±1.74kg/m²). These were compared to 20 normal patients (10 males/10 females, age 61.84±3.54 years, BMI 25.63±1.56 kg/m²) without history of PD and cardiovascular event.

Characteristic of study groups, time and frequency domain parameters of HRV are summarizes in Table.2. UPDRS motor was 19.2±5.2 in PD, orthostatic hypotension was found in 13 PD patients (43.3%) and in 5 controls (25%) patients with $p<0.01$. Mean systolic and diastolic blood pressure did not differ when compared to the control group, but heart rate was found increased in PD patients with $p<0.05$. Mean RR showed statistically significant reduction in PD patients (822 ±115 ms in PD vs 983.2±116.8 ms in controls, $p<0.05$). The SDNN (38.7±16.7 ms PD vs 51.36±21.65ms C, $p<0.01$), rMSSD (36.9±14.7 ms PD vs 43.1±8.6 ms C, $p<0.05$) were reduced in PD patients when compared to the control group.

Both LF and HF were lower in PD patients than in

controls (LF: 332.±288.4 ms² PD vs 723.9±348.2 ms² C; HF: 283.72±241.97 ms² PD vs 530.54±226.5 ms² C, p<0.01). No differences between LF/HF ratio of PD and controls appeared.

Table 2. Characteristic of study groups, according to morphometric and comparison of time domain and spectral parameters of HRV

Parameter	Control n=20	PD n=30
Age (years)	61.84±3.54	63.2±3.47
BMI (Kg/m²)	25.63±1.56	24.44±1.74*
UPDRS motor	-	19.5±5.2
Fasting blood sugar (mg/dl)	91.1±22.12	95.3±17.34
Total cholesterol (mg/dl)	196.6±29.6	185.4±21.33
HDL-cholesterol (mg/dl)	47.2±3.1	41.34±3.53*
Triglyceride (mg/dl)	158.2±14.96	162.5±32.32
Vitamin B12 (pg/ml)	581.9±108.4	597.75±149.5
Acid folic (ng/ml)	9.27±2.19	9.34±2.31
Mean SBP (mmHg)	131.86±20.5	129.6±14.87
Mean DBP (mmHg)	69.21±8.01	71.17±9.17
HR (b/min)	68.81±8.96	73.31±9.82*
Mean RR (ms)	983.2±116.8	822 ±115*
SDNN (ms)	51.36±21.65	38.7±16.7**
rMSSD (ms)	43.1±8.6	36.9±14.7*
pNN50 (%)	16.09±4.6	12.41±4.8*
LF (ms²)	723.9±348.2	332.±288.4**
HF (ms²)	530.54±226.5	283.72±241.97**
LF/HF	1.59±0.37	1.79±0.97

BMI – body mass index, UPDRS- Unified Parkinson's Disease Rating Scale, MMSE- Mini-Mental Status Examination, BDI- Beck depression inventory
SBP - systolic blood pressure, DBP - diastolic blood pressure, MAP-mean arterial pressure, PP- pulse pressure, HR- heart rate
Mean RR, SDNN, rMSSD, pNN50, LF, HF, LF/HF: explanation in method section.
Data: expressed as means±standard deviation;
*- P< 0.05; ** - P< 0.01 for difference between controls and PD

The results of Pearson correlation test, for a confidence interval of 95% indicate a significant inverse correlation between the age and LF values (r= - 0.41, p<0.02) and triglycerides with HF (r=-0.36, p<0.05). Also HF was correlated with BDI score (r=0.43, p<0.001).

Sensory nerve action potential in median nerve was reduced in PD patients: 9.81±5.2μV vs 11.53±5.5μV in controls, but we didn't find any statistical significance (Table 3). For median motor nerve parameters didn't show any differences between the study groups. The results of sural nerve exploration show that the sensitive potential amplitude was 8.16±2.36 μV vs 10.95±2.73 μV for the control group, difference with high statistical significance (p<0.01). No differences in sNCV of sural nerve, mNCV of tibial or peroneal nerves between PD patients and controls appeared. Also we found differences between CMAP of tibial nerve in PD 3.72±1.73 μV and controls 5.34±1.71μV with p<0.01.

Table 3. Results of neuroelectrophysiological examination on controls and PD patients

Parameter	Control n=20	PD n=30
Median		
CMAP(μV)	7.23±2.2	6.8±2.6
mNCV (m/s)	48.3±3.2	48 ±3.23
MDL (ms)	2.92±1.5	2.82±1.5
SNAP (μV)	11.53±5.5	9.81±5.2
SL (ms)	1.84±0.01	1.9±0.01
sNCV (m/s)	50.3±6.4	48.73±6.5
Sural		
SNAP (μV)	10.95±2.73	8.16±2.36**
SL (ms)	3.4±0.1	3.5±0.1
sNCV (m/s)	46.28±6.29	45.8±6.5
Tibial		
CMAP(μV)	5.34±1.71	3.72±1.73**
mNCV (m/s)	43.71±4.15	43.78±4.6
MDL (ms)	4.32±1.2	5.4±1.21*
Peroneal		
CMAP (μV)	4.15±1.2	3.9±1.6
mNCV (m/s)	48.41±2.28	46.15±5.21
MDL (ms)	2.93±1.21	3.36±1.33

SL-sensitive latency, SNAP-sensory nerve action potential, sNCV - sensory nerve conduction velocity, MDL- motor distal latency, CMAP- compound motor action potential, mNCV - motor nerve conduction velocity.
*- P< 0.05; ** - P< 0.01 for difference between controls and PD

The results of Pearson correlation test, for a confidence interval of 95% indicate a significant inverse correlation between age and the sensory nerve conduction velocity value of the sural nerve (r= -0.47, p<0.05).

Discussion

PD is a neurodegenerative disorder, with an average age at onset of about 60 years and with the aging of the population it is anticipated that the prevalence of PD will increase dramatically in the coming decades. Recent studies suggest that PD may start in the gastrointestinal tract. According to the 'Braak's' hypothesis, protein aggregation in enteric neurons

spreads to the brain through the dorsal motor nucleus of the vagus (10). Pre-symptomatic PD patients had protein aggregation in the peripheral nervous system but not in the central nervous system (1). Protein aggregation ascended into the central nervous system and correlated with the development of motor dysfunction. Braak had postulated that the early Stages 1 to 3 of disease develop in patients who have not yet been diagnosed with classical motor symptoms of disease. Motor symptoms start to develop in Stage 3, when pathology has spread to the substantia nigra. Cognitive problems and dementia would occur when the neocortex becomes affected in Stages 5 and 6.

Alpha synuclein deposits have been found in the autonomic nervous system, in sensory and motor peripheral nerves (12, 23). Existing reports indicate that autonomic nervous system dysfunction occurs in the very early stages of PD. Evidence shows that both parasympathetic and sympathetic functions are impaired in PD (24).

123I-MIBG myocardial scintigraphy (Metaiodobenzylguanidine-a physiological analogue of noradrenaline) is clinically used to evaluate myocardial sympathetic nerve damage in PD. Reduced uptake of 123I-MIBG is considered to reflect cardiac sympathetic denervation, which precedes the neuronal loss of the paravertebral sympathetic ganglia, suggesting distal-dominant degeneration (25).

Patients with PD have shown suppressed heart rate responses to deep breathing indicating parasympathetic dysfunction (26). PD patients have low supine blood pressure levels and orthostatic hypotension is frequent because degeneration of sympathetic neurons is found (27). That can increase susceptibility to falls in PD patients.

HRV is widely accepted non-invasive, providing information on sympathetic and parasympathetic modulation of the sinus node. HF is regard as a marker of cardiac vagal activity. LF represents the sympathetic activity with vagal modulation. Goldstein et al, 2011, suggests that LF power should be seen as an index of baroreflex function rather than cardiac sympathetic tone (28). SDNN, pNN50%, time domain indicator of the HRV, represents the activity of the vagal nerve.

In our study the analysis of HRV demonstrated that both parasympathetic and sympathetic nerve functions were impaired in PD patients because the measures of SDNN, pNN50%, HF and LH were significantly lower than in controls. No differences between LF/HF ratio of PD and controls appeared. Our results agree with other studies demonstrating that both branches of autonomic nervous system are affected early in the course of PD.

In PD recent clinical and pathological studies point to defects in function of the peripheral nervous system in patients with early onset PD due to *parkin* mutation (29). The occurrence of peripheral neuropathy in a genetic type of PD suggests that a link may be present between central and peripheral neuronal degeneration. Reichling and Levine, 2011, suggest that in PD we can saw a combination of peripheral afferent abnormalities with central pathological changes resulting in neuropathic pain. They suggest that it is the result of the same neurodegenerative processes, but occuring in the peripheral nervous system (30, 31).

In a longitudinal study of PD patients Toth et al., 2008, found that over half of the patients tested had peripheral neuropathy (14). The severity of the PN correlated with increased exposure to L-DOPA. Blood testing showed that the PD patients with PN had increased serum levels of methylmalonic acid (14). They also suggested that treatment with cobalamin will prevent the formation of methylmalonic acid, and thus could help protect against PN during long term L-DOPA therapy (14).

Abnormalities in SNAP or CMAP amplitude and a conservation of the nervous conduction velocity reflect axonal loss or degeneration (22). The signs of demyelination are decrease of the nervous conduction velocities, decrease of the action potentials, and an extension of the distal latencies (22). In our study we found reduced SNAP of sural nerve in PD patients. Therefore we concluded that the neuropathy in PD patients was mostly of a sensory axonal-predominant type. Our PD patients had normal levels of cobalamin suggesting that the presence of PN in early stages may be intrinsic to PD. PN may contribute to distal limb weakness, pain and risk of falling. A possible limitation of our study is the presence of a small number of subjects this decreases the statistical power to detect differences between the groups. Therefore, more research and longer observation of a larger group of patients are needed, including the most advanced form of Parkinson's disease.

Conclusions

PD causes dysfunction of autonomic cardiovascular regulation and peripheral nerve involvement especially axonal neuropathy even in early stage of the disease. The neurodegeneration process occurs both in the central and peripheral nervous systems so we can consider that PD is a multi-systemic disorder. Future work will seek to clarify pathophysiological mechanisms inducing the peripheral nerve damage seen in idiopathic Parkinson's disease.

Conflict of Interest Statement: The Authors declare that they have no conflict of interests.

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Nullius in verba: "Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes" in NEJM

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Dear Editor,

I read with great interest the valuable article by De Benedetti and colleagues, the leading scientists in the relevant field, about canakinumab for autoinflammatory recurrent fever syndromes, which was recently published in the New England Journal of Medicine (1). I would like to raise some worthwhile issues that need to be clarified.

The "Statistical Analysis Plan" (2, 3) of the study stated "all efficacy evaluations will be performed on the full analysis set" and "The Full Analysis Set (FAS) Epoch 2 will consist of all randomized patients in the randomized treatment epoch who received at least one dose of study drug in epoch 2. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization". According to CONSORT 2010 Explanation and Elaboration, "Intention-to-treat analysis corresponds to analysing the groups exactly as randomised", "The simple way to deal with any protocol deviations is to ignore them: all participants can be included in the analysis regardless of adherence to the protocol, and this is the intention-to-treat approach. Thus, exclusion of any participants for such reasons is incompatible with intention-to-treat analysis", and "The term 'modified intention-to-treat' is quite widely used to describe an analysis that excludes participants who did not adequately adhere to the protocol, in particular those who did not receive a defined minimum amount of the intervention. An alternative term is 'per protocol'" (4). Hence, the study efficacy analysis appears to be modified intention-to-treat analysis, even though the authors incorrectly called an intention-to-treat approach. Interestingly, in the literature, several systematic reviews addressed whether investigators who expressed that an intention-to-treat analysis was used really did what they say (5, 6) and found that 13% (5)-23% (6) of the reviewed articles did not analyze according to intention-to-treat. This is similarly the case in De Benedetti and colleagues' study (1). The majority of P values in Figure 2 (1) are not matched with the records of ClinicalTrials.gov (7, 8). Namely, the primary outcome and all three secondary outcomes in mevalonate kinase deficiency (MKD) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS); and serum amyloid A (SAA) in colchicine-resistant familial Mediterranean fever (crFMF). These discrepancies cannot simply be attributed to rounding numbers.

Last and very least, the number of the actual enrolment in the article (i.e. 181 or 203) (1) is higher than the anticipated sample size (i.e. 180) (2, 3, 9). According to CONSORT, "If the actual sample size differed from the originally intended sample size for some other reason (for example, because of poor recruitment or revision of the target sample size), the explanation should be given" (4). However, it was surprising to see that the article did not contain any description of sample size and power estimations for the study. More seriously, the authors, in the article, failed to justify why the study recruited more patient than intended.

In conclusion, I believe that the efficacy analysis should be re-performed using the intention-to-treat (all patients as randomized regardless of adherence to the protocol (4) population. Also, I strongly believe that the discrepancies in P values require immediate clarification.

I end with the Royal Society's motto "Nullius in verba" and with an elegant Viewpoint (10).

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Note: The letter could not be submitted through NEJM online submission system, because it is not possible to submit a letter after three weeks of the publication date of the article. I submitted a presubmission inquiry requesting consideration of the letter for publication. The editors replied that the editorial policy is firm and letters regarding the 17 May issue are no longer being considered.

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