Research article

The impact of glaucomatous disease on lifestyle and healthy aging. Association between structural visual and auditory functional changes in glaucoma

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Abstract: In the last decade, it was concluded that glaucomatous optic neuropathy is part of the neurodegenerative diseases in which destructive neuronal lesions are located not only in the structure of the retina, but they are also present at the level of the central visual and nervous pathways. **The purpose of this study** was to evaluate the degree of involvement of the auditory system in patients with Primitive Open Angle Glaucoma (POAG), the structural changes in the optic nerve, and to establish correlation between the hearing loss and structural changes in the optic nerve. **Material and methods:** It is a prospective, cross-sectional study on 32 eyes of 16 subjects with POAG in a study group and 24 eyes of 12 healthy subjects in control group, with a mean age of 62 years in both groups. Both groups underwent ophthalmological, audiological and brain magnetic resonance imaging (MRI) evaluation. **Results:** In the Study group patients, compared to the Control group, the average levels of the left Pure-tone audiometry (PTA), the cup/disc (C/D) area in both eyes, and the C/D ratio in both eyes are increased. **Conclusions:** Patients with POAG show changes in audiometry test in correlation with ophthalmological parameters demonstrating that the auditory system can be affected in glaucoma.

Keywords: hearing loss, pure tone audiometry, structural changes in the optic nerve, RNFL, C/D ratio

1. Introduction

In 1922, Felix Lagrange of Bordeux noted that a glaucomatous eye is "a sick eye in a sick body"[1]. Nowadays, this intriguing statement remained a challenge in the study of glaucoma disease even after 100 years. Glaucoma has long been considered a multi-factorial optic neuropathy, slowly progressive characterized by irreversible damage to the optic nerve accompanied by the thinning and specific loss of retinal ganglion cells and the

visual field [2]. The pathophysiology of glaucomatous optic neuropathy is completely unknown, and several mechanisms involved are approved: mechanical stress, changes in ocular blood flow, oxidative stress and neurotrophic factors that affect the survival of Retinal Ganglionar Cells (RGCs) and some RGCs being more susceptible to destruction than others [3,4,5]. In 2007, Gupta and Yucel hypothesized that glaucomatous disease is a neurodegenerative condition, opening new perspectives in the pathophysiological approach of the disease with multiple implications both in the mechanisms of disease and in therapeutic management [6]. They were the first who stated that high intraocular pressure (IOP) and the destruction of the RGCs can be a trigger factor for transsynaptic degeneration in the lateral geniculate bodies (LGB) and visual cortex. Lowering IOP is the best way to prevent RGCs death and may decrease the risk of central nervous system degeneration in glaucoma. In 2009, Gupta showed that patients with glaucoma have degenerative lesions in the LGB of the thalamus in the magnocellular, parvocellular, and koniocellular layers [7]. These changes were related to IOP and the severity of optic nerve injury. Viewed as a neurodegenerative brain disease rather than a simple eye disease glaucoma has generated various studies which demonstrate that the complex connection between the eye and the brain is essential to the disease as stated by Jeffrey L. Goldberg in 2010 [8]. The key process in glaucoma is the loss of specific neuronal populations like in other neurodegenerative diseases such as Alzheimer's dementia [9]. Several mechanisms of neurodegenerative disorders also occur in glaucoma: oxidative stress, mitochondrial dysfunction, glutamate excitotoxicity, abnormal protein accumulations [5,10,11,12] and neuroinflammatory reactions, especially at the level of glial and microglial cells [13] with release of proinflammatory cytokines interleukines (IL1, IL6, TNFα) and chemokines (CCL2, CX3, CL1) at the first relay level central (LGB and superior quadrigeminal colliculi) [14]. Experimental studies have demonstrated that the loss of peripheral ganglion cells through increased IOP values causes metabolic changes at the cortical level, as in any degenerative disease, accompanied by an increase in the cortical reorganization capacity of the projection of several analyzers in the sense of functional reorganization [15]. The evaluation of the two visual and auditory analyzers has concerned the scientific community, but most of the research exploring non-visual sensory deficits has focused on the incidence of hearing loss in association with glaucoma, the findings being debatable and variable [16, 17]. The evidence supporting a link with peripheral hearing loss (related to a deficit at the cochlear level) is more consistent, in patients with pseudo-exfoliation glaucoma, where hearing loss is connected to the accumulation of pseudoexfoliation material in the extracellular matrix of the inner ear [18-24]. In this way, we look at glaucoma as a neurodegenerative disease, during the course of which complex neurosensory changes take place. The dual visual and auditory deficit, along with the increase in life expectancy and the aging of the population, generates a decrease in the quality of life of the patients, which is ultimately reflected in social life, turning the ophthalmological disease into a public health problem.

The idea of studying these two systems, visual and auditory, appeared as a natural consequence of the anatomical and functional cortical connections, but also of current clinical findings. This study aimed at establishing the existence of some corelations between damage to the optic nerve, a defining element in glaucomatous disease with possible hearing impairment, both systems being extremely involved in ensuring the quality of life. In this study, we wanted to demonstrate if there are connections between the structural lesions that appear in glaucoma and the auditory function as a starting point for the emergence of new diagnostic elements.

2. Results

2.1. Epidemiologic characteristics.

Distribution by age groups: the study included 16 POAG patients in a study group and 12 healthy individuals in control group. All 56 eyes and ears of the total 28 subjects were included in the evaluation. During the study, a number of eight patients were ex-

cluded from the study group for various reason: three patients were diagnosed with tympanic disorders (one had a hearing aid, one was diagnosed with a toxic hearing impairment, and one did not initially declare that is wearing a hearing aid), two patients were excluded to incomplete or unreliable optical coherence tomography (OCT), one patient with an ischemic stroke was identified and two patients did not continue the study protocol. The control group included 12 patients because only these patients met the rigorous inclusion criteria and signed the informed consent.

The series of values for age was homogeneous: variations in the range of 48-69 years; group average 61.64 years ± 6.53; groups median of 63 years; result of the Skewness test = -0.442; the average age in the Study group was significantly higher compared to the Control group (63.69 vs 58.92 years; p=0.05). Corroborating these results, age 65 is chosen as the threshold for further statistical comparisons. It was found that 56.3% of the patients in the Study group were over 65 years old, while 83.3% of the patients in the Control group were under 65 years old (p=0.039), as shown in Figure 1.
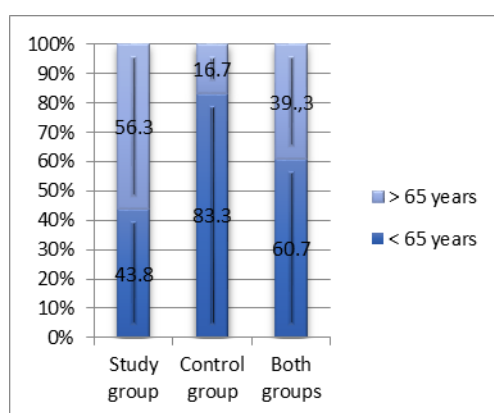

Figure 1. Structure by age groups (over 65 years, under 65 years)

Gender distribution: In the case study, female patients prevail (71.4%), the F/M ratio being 2.5/1. In the study groups, the percentage distribution was homogeneous (68.8% vs 75%; p=0.716), as shown in Figure 2.
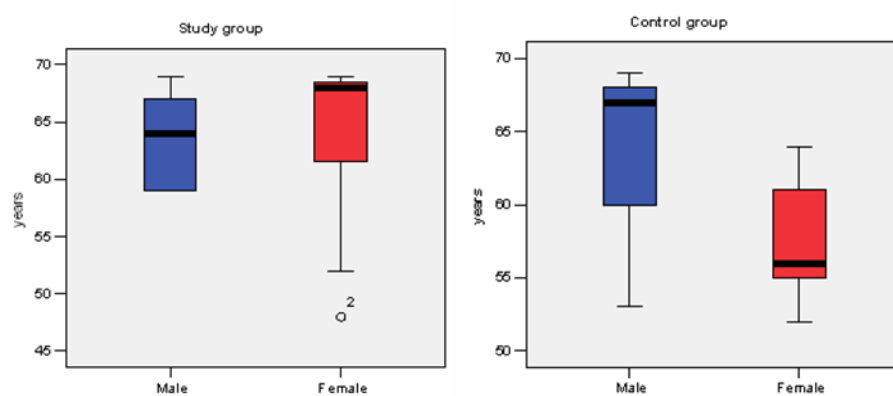

Figure 2. Average age compared by gender (study groups and control groups)

Following the analysis of the demographic data, it can be stated that there is an increase in the addressability of the female sex. Women go to the doctor easier than men and more easily accept all the investigations necessary to detect and monitor the disease.

Distribution by means of origin: in the case study, the urban patients prevail (82.1%), the C/D ratio being 4.6/1. In the study groups, all patients in the Control group and 68.8% of the Study group came from the urban environment (p=0.011).

Regarding the distribution according to educational status in the case study, over 70% of the patients completed their secondary (32.1%) or higher (39.3%) education. In the study groups, over 58% of the patients in the Control group and only 25% in the Study group completed their higher education (p=0.05).

2.2. Clinical parameters:
2.2.1. Pure tone audiometry (PTA):

PTA is a homogeneous variable in both the right and left ears, so statistical significance tests can be applied (Table 1). PTA in the right ear varied from 0 to 30 dB, the average level being 16.21 dB ± 7.14, close to the median value (15 dB), and the Skewness test result = 0.441; PTA in the left ear varied from 5 to 52 dB, the average level being 19.29 dB ± 10.87, close to the median value (18 dB), and the Skewness test result = 1.292. Both in the right ear (18.38 vs 13.33 dB; p=0.063), but especially in the left ear (23.25 vs 14 dB; p=0.023), the average level of PTA was higher in the Study group. Increased PTA values reflect a hearing loss according to the American Speech-Language-Hearing Association (ASHA) criteria (the classification is different depending on the PTA level) (see Table 1).

Table 1. Descriptive data of PTA compared to study groups

Lot	N	Average	Std. Dev	Std. error	Confidence Interval 95%		Min	Max	t-Student Test (p)
					-95%CI	+95%CI			
PTA (dB) right									
Study	16	18.38	7.949	1.987	14.14	22.61	0	30	0.063
Control	12	13.33	4.793	1.384	10.29	16.38	5	22	
PTA (dB) left									
Study	16	23.25	12.283	3.071	16.70	29.80	7	52	**0.023**
Control	12	14.00	5.560	1.605	10.47	17.53	5	23	

The multivariate analysis highlighted the fact that the PTA level both in the right ear (Model 2 p=0.001) and in the left ear (Model 2 p=0.031) has gender and age as good predictors, statistically significant.

Table 2. Multivariate analysis. PTA dependent variable linear regression

Model	R	R Square	Adjusted R Square	Standard Error	Change Statistics				
					R Square	F	df1	df2	p
The dependent variable PTA (dB) right									
1	0,342(a)	0,117	0.083	6.834	0.117	3.437	1	26	0,075
2	0,672(b)	0,452	0.408	5.491	0.335	15.269	1	25	**0,001**
3	0,672(c)	0,452	0.383	5.603	0.000	0,008	1	24	0,930
4	0,672(d)	0,452	0.357	5.724	0,000	0.000	1	23	0,995
The dependent variable PTA (dB) left									
1	0,390(a)	0,152	10.197	0.152	4.677	4,677	1	26	0,040
2	0,547(b)	0,300	9.452	0.147	5.259	5.259	1	25	**0,031**
3	0,548(c)	0,300	9.646	0.000	0.006	0,006	1	24	0,939
4	0,616(d)	0,380	9.275	0.080	2.960	2.960	1	23	0,099

a Predictors: (Constant), Sex
b Predictors: (Constant), Sex, years

c Predictors: (Constant), Sex, years, Environment
d Predictors: (Constant), Sex, years, Environment, Studies

2.2.2. The disc area: The disc area is a homogeneous variable in both the right and left eyes: RE (right eye) disc area varied from 1.02 to 3.21, the mean level being 1.91 ± 0.52, close of the median value (1.86 mm2), and the Skewness test result = 0.544; LE (left eye) disc area varied from 1.06 to 2.83, the average level being 1.66 ± 0.40, close to the median value (1.65 mm²), and the Skewness test result = 0.838. Both in RE (1.93 vs 1.90; p=0.886) and in LE (1.77 vs 1.52; p=0.096), the average level of the disc area was slightly higher in the Study group.

2.2.3. The rim area: In the RE rim area varied from 0.43 to 3.02, the mean level being 1.12 ± 0.54, close to the median value (1.04 mm²), and Skewness test result = 1.768; LE rim area ranged from 0.28 to 1.98, the average level being 1.03 ± 0.41, close to the median value (1.0 mm2), and the Skewness test result = 0.303. In the RE the average level of the rim area was significantly higher in the Control group (0.89 vs 1.42; p=0.007), in the LE the difference was not statistically significant (0.93 vs 1.17; p =0.121).

2.2.4. The area C/D ratio: In RE the area C/D ratio varied from 0.10 to 0.79, the average level being 0.43 ± 0.18, close to the median value (0.40 mm2), and the Skewness test result = 0.428; In the LE the area C/D ratio varied from 0.10 to 0.92, the average level being 0.40 ± 0.34, close to the median value (0.34 mm²), and the Skewness test result = 0.948. Both in the RE (0.52 vs 0.31; p=0.001), and in the LE (0.49 vs 0.28; p=0.007), the average level of the area C/D ratio was significantly higher in the Study group.

2.2.5. The vertical C/D ratio: In RE the vertical C/D ratio varied from 0.27 to 0.92, the average level being 0.64 ± 0.16, close to the median value (0.63), and the result of the Skewness test = -0.356; In LE the vertical C/D ratio ranged from 0.31 to 0.95, the mean level being 0.63 ± 0.16, close to the median value (0.60), and the Skewness test result = 0.380. Both in RE (0.70 vs 0.55; p =0.016) and in the LE (0.70 vs 0.54; p=0.009), the mean level of the vertical C/D ratio was significantly higher in the Study group.

2.2.6. RNFL average thickness (μm): In the RE ranged from 61 to 139 μm, the average level being 94.71 μm ± 16.07, close to the median value (94 μm), and the Skewness test result = 0.485; in the LE it varied from 0 to 128 μm, the average level being 98.57 μm ± 22.98, relatively close to the median value (100 μm), and the Skewness test result = 0.948. Both in RE (93.19 vs 96.75; p=0.571) and LE (95.56 vs 102.58; p=0.434), the average level of RNFL average thickness was slightly lower in the Study group.

2.2.7. Central corneal thickness (CCT) (μm): In the RE CCT varied from 507 to 572 μm, the mean level being 522.11 μm ± 89.72, relatively close to the median value (535 μm), and the result of the Skewness test = -1.903; in the LE CCT varied from 504 to 573 μm, the average level being 540.18 μm ± 18.73, close to the median value (539 μm), and the result of the Skewness test = -0.014. Both in the RE (482.75 vs 537 .85; p=0.145), and in the LE (542.13 vs 539.40; p=0.735), no significant differences in the average level of CCT were revealed.

2.2.8. Correlations between PTA values with structural elements of the optic nerve: vertical C/D ratio, area C/D ratio, Rim area, average RNFL, CCT, and demographic elements (age) emphasizes:

Right ear PTA correlated significantly, directly, moderately in intensity with age (r= 0.629; p= 0.001). Right ear PTA did not correlate significantly with RE vertical C/D ratio (r= +0.013; p= 0.946); RE area C/D ratio (r= +0.127; p= 0.521); disc area (r= -0.045; p= 0.820); Rim RE area (r= -0.216; p= 0.269); average RNFL structure RE (r= -0.112; p= 0.570); RE CCT (r= -0.072; p= 0.715) (see Figure 3).
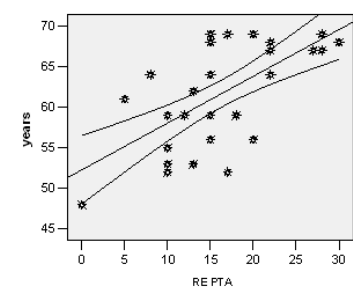
Figure 3. Correlation of PTA in the right ear with age .Viewpoint-based kernel fuzzy clustering with weight information granules

Left ear PTA correlated significantly with LE vertical C/D ratio (r= +0.434; p= 0.021), LE area C/D ratio (r= +0.452; p= 0.016) and indirectly, moderately in intensity with average RNFL structure LE (r= -0.438; p= 0.02) and with age (r= 0.445; p= 0.018). Left ear PTA did not significantly correlate with LE disc area (r= + 0.334; p= 0.082) or the LE Rim area (r= -0.271; p= 0.162) and LE CCT (r= -0.185; p= 0.345) (Figure 4).
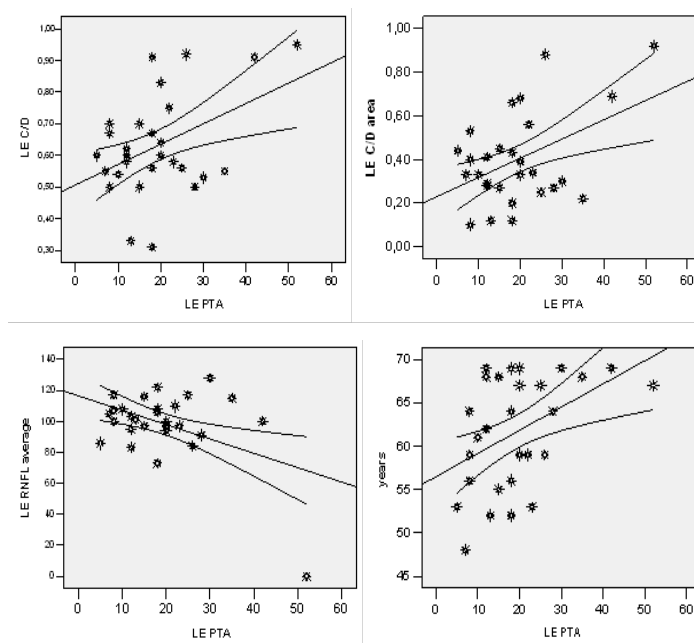

Figure 4. Correlation of left ear PTA with LE vertical C/D ratio, LE C/D area, LE average RNFL and age(years). Viewpoint-based kernel fuzzy clustering with weight information granules

By plotting the ROC curve, the following parameters were highlighted as good predictors of glaucoma in the RE (Figure 5): at values higher than 0.60 of the vertical C/D ratio, with a sensitivity of 75% and a specificity of 58.3% (AUC=0.753; IC95%: 0.569-0.937; p=0.024); at values higher than 0.33 of the area C/D ratio, with a sensitivity of 87.5% and a specificity of 58.3% (AUC=0.862; IC95%: 0.725-0.999; p=0.001) and at values higher than 14 of the right ear PTA with a sensitivity of 81.3% and a specificity of 58.3% (AUC=0.732; IC95%: 0.542-0.922; p=0.039) (Figure 5, Table 3).
By plotting the ROC curve, the following parameters were highlighted as good predictors of glaucoma in the LE (Figure 5): at values higher than 0.56 of the C/D ratio, with a sensitivity of 75% and a specificity of 42% (AUC=0.734; IC95%: 0.550-0.919; p=0.037); at values higher than 0.30 of the area C/D ratio, with a sensitivity of 75% and a specificity of 50% (AUC=0.763; IC95%: 0.588-0.938; p=0.019) and at values higher than 14 of the left ear PTA with a sensitivity of 75% and a specificity of 50% (AUC=0.745; IC95%: 0.562-0.928; p=0.029) (Figure 5, Table 3).
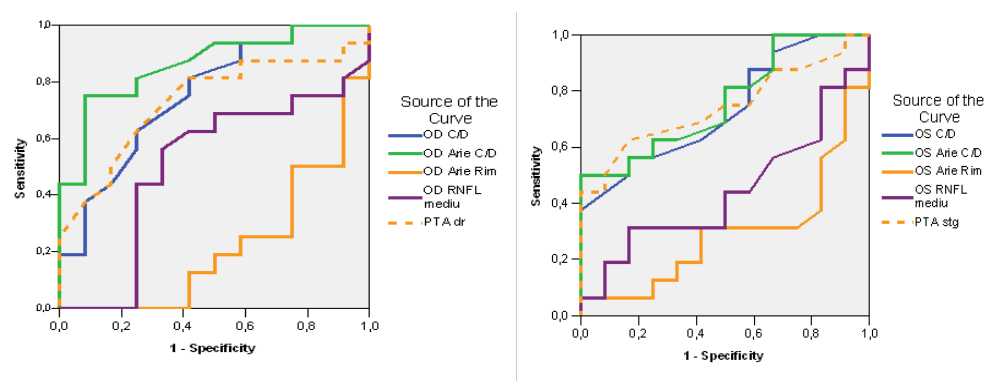
Figure 5. ROC curve in the RE (left image) and in the LE (right image).

Table 3. Predictors of glaucoma in the right /left eye

Test Result Variable(s)	Area	*Cut off*	Std. Error (a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
RE C/D ratio	0,753	0,60	0,094	0,024	0,569	0,937
RE C/D Area	0,862	0,33	0,070	0,001	0,725	0,999
RE Rim Area	0,219	1,11	0,090	0,012	0,043	0,395
RE RNFL average	0,505	95,00	0,118	0,963	0,275	0,736
PTA right	0,732	14,00	0,097	0,039	0,542	0,922
LE C/D ratio	0,734	0,56	0,094	0,037	0,550	0,919
LE C/D Area	0,763	0,30	0,090	0,019	0,588	0,938
LE Rim Area	0,292	1,11	0,100	0,063	0,095	0,488
LE RNFL average	0,443	100,00	0,111	0,610	0,226	0,659
PTA left	0,745	14,00	0,093	0,029	0,562	0,928

The test result variable(s): RE/LE C/D ratio, RE/LE area C/D ratio, RE/LE Rim area, RE/LE RNFL average, PTA right has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a Under the nonparametric assumption
b Null hypothesis: true area = 0.5

3. Discussions

The phenomenon of dual visual and auditory impairment in glaucoma has garnered interest among researchers, leading to studies that approach the topic from both ophthalmological and audiological perspectives. Opinions on the relationship between visual and auditory dysfunction in glaucoma are divided. Previous studies have examined various parameters to evaluate both visual and auditory dysfunctions. One study conducted in 1997 by Shapiro et al. [17] examined 67 glaucoma patients and found no connection between sensorineural hearing loss and visual loss beyond age-related losses. However, this study included patients with different types of POAG, which could explain the lack of significant findings. On the other hand, studies have investigated the association between hearing loss and pseudo-exfoliative syndrome, especially when accompanied by pseudo-

exfoliative glaucoma. Accumulation of pseudo-exfoliative material in both the eye and the cochlea, as well as vestibular damage, have been proposed as possible causes for the connection between pseudo-exfoliative syndrome and hearing loss [24]. Although the exact causes are not fully understood, several theories have been proposed regarding the relationship between glaucoma and hearing impairments. These theories include the common embryological origin of the inner ear and the anterior segment of the eye, the accumulation of pseudo-exfoliative material in both the anterior segment and cochlea, vascular wall involvement, and vestibular damage caused by pseudo-exfoliative material leading to vestibular compensation [18-23, 39, 40]. In 2004, Kremmer et al. conducted a study on patients with normotensive glaucoma and found that microcirculation disorders caused by microthrombi, which are a result of increased antiphospholipid antibodies [16], contribute to visual and auditory dysfunctions. In 2012, O'Hare, Crowston et al. approached glaucoma as a neurodegenerative disease and studied visual and auditory dysfunction from the perspective of cortical integration. They discovered temporal cortical abnormalities in auditory information processing among glaucoma patients, suggesting a theory of neuronal vulnerability [24]. Mudie et al. conducted a study in 2012 involving 215 patients and examined the impact of glaucomatous visual field loss and hearing impairment on glaucoma patients. They concluded that these impairments play a significant role in functional and cognitive decline, which greatly affects the social integration of patients [25]. Studies have also identified demographic factors associated with the co-occurrence of glaucoma and hearing impairments. Kim et al. conducted a study in 2019 involving 12,899 patients over the age of 40 and concluded that age, male sex, and triglyceride levels play a role in the association between glaucoma and hearing impairments [26]. Similarly, Chien et al., in a large-scale retrospective study in 2020 involving 15,686 patients, found a higher incidence of glaucoma in patients with hearing impairment. They recommended routine ophthalmological examination for glaucoma detection in individuals with a history of sensorineural hearing loss [27].

In the current study, the study group consisted mostly of urban females aged over 65. The study group showed significantly higher mean levels of PTA, area C/D ratio, and vertical C/D ratio compared to the control group. Higher PTA values indicated hearing loss according to the ASHA classification, suggesting different levels of hearing impairment based on PTA values. The mean level of RNFL thickness was slightly lower in glaucoma patients, while the average level of rim area was significantly higher in the Control group for both right and left eyes. Multivariate analysis revealed that gender and age can be good predictors of PTA in both eyes, with the influence of age on PTA being a known factor based on existing specialized literature [28]. Direct statistical correlations were observed between PTA values, which evaluate auditory function, and the vertical C/D ratio as well as the area C/D ratio, which define the structure of the optic nerve. An indirect correlation was observed with RNFL values, reinforcing the hypothesis of a connection between visual and auditory impairments. These correlations were identified mainly on the left side. Corneal thickness values do not correlate statistically significantly with hearing changes, quantified by PTA. Two elements are interesting in the study: the occurrence of changes in the value of PTA in both ears, together with the presence of correlations within the structure of the optic nerve only on the left side and the possibility of issuing some predictive factors from a statistical point of view in both eyes, in the study group. The average level of PTA was higher in the Study group. Maybe would be good to mention that all participants in the study are right-handed thinking of a possible cortical explanation.

The visual stimulus has a key role in the perception of the acoustic surroundings and in identifying the location of the stimulus [29,30]. Visual information confirms the location of the sound through direct (source position) and indirect (source environment) methods [31], the two stimuli acting simultaneously. Placing the auditory stim-ulus in a visual con-text improves both auditory and motor performance [32]. The con-text of visual perfor-

mance impairment generates simultaneous auditory adaptation, the auditory space spontaneously recalibrates to the visual space probably determined by cortical mechanisms of adaptation and restructuring of both intramodal and cross-modal plasticity [29].

There have been interesting scientific concerns regarding the establishment of some correlations between intraocular pressure, eyeball length, retinal thickness, choroidal thickness and stomatognathic apparatus elements: masticatory and neck muscle thickness [34]. The correlations between the visual and auditory clinical parameters established by our study allow the glaucomatous disease to be approached from a cortical aspect as well. Humans are the only species with asymmetrical, cross-lateralized motor behavior [35]. The phenomenon of cortical lateralization is known for several cognitive functions, but with the specification that some of them, such as language, have specific cortical areas. Taking into account these elements that combine with the phenomenon of crossmodal neuroplasticity that occurs as an adaptive cerebral response to various pathologies, we can think of the study results as a beginning in the complex evaluation of the patient with glaucoma.

The aim of the conducted study was to highlight a correlation between two of the most important systems of the human body: vision and hearing. The purpose of this work was to investigate the possible involvement of the two analyzers in a neurodegenerative disease such as glaucomatous disease. Of course, bilateral damage is important both in diagnosis, but it has an even greater value in ensuring the quality of life of glaucoma patients. When both systems have different degrees of disability, the medical problem becomes a big social problem.

Taking into account what has been stated, it is possible to take into consideration the dual evaluation of the hearing in the patient with glaucoma, but also the ophthalmological evaluation of the patients with hearing disorders.

The paper wants to emphasize the interdisciplinary nature of the evaluation of the patient with glaucoma in its preparation by participating specialists from various areas of medical interest whose concerns present areas of common interest: ophthalmology, otorhinolaryngology, radiodiagnostics, neurosurgery.

Also this study shows that glaucoma is a complex disease that requires a multidisciplinary approach, but it wants to highlight that using ophthalmological common tests combined with usual and frequently used auditive test may establish correlations with important impact on glaucoma diagnostic management.

As a conclusion, a multicenter, longitudinal study starting from the encouraging results of the work presented could provide valuable information, worthy of being included in the diagnosis and treatment algorithm of glaucoma patients.

However, the study has limitations due to the small number of participants in both groups, the short follow-up period, and the cross-sectional design. Further multicenter, longitudinal studies with a larger sample size are needed to explore the long-term association between hearing loss and visual loss in glaucoma. Such studies could provide valuable information for the diagnosis and treatment algorithm of glaucoma patients, combining ophthalmological and audiological assessments.

4. Materials and Methods

4.1. Study Design. A prospective, cross-sectional, observational study was conducted in the Ophthalmology Department of Clinical County Emergency Hospital of Braila during October 2021 and December 2022. Patients were evaluated for a period of 6 months after enrollment. This study was approved by the Ethic Commission of Clinical County Emergency Hospital of Braila, approval no. 1/03.09.2021 in accordance with the ethical and deontological rules for medical and research practice.

Informed consent forms were obtained from all the patients involved in the study, following the guidelines of the Declaration of Helsinki and in compliance with ethical considerations. The study was conducted with approval from the ethics commission.

The subjects included in the study were divided into two groups: a group of patients with glaucoma, compared to a group of patients without glaucoma, in terms of the evolution of structural changes in the optic nerve and audiometry evaluation. The study group consisted of 32 eyes of 16 subjects with POAG, while the control group consisted of 24 eyes of 12 healthy subjects, with an average age of 62 years in both groups. All 16 case participants were enrolled from the Ophthalmology Department of the Clinical County Emergency Hospital of Braila. The control participants were recruited from the same hospital's general Eye Department, as well as volunteer friends/relatives of the cases or staff members. In the study group, 11 patients were female, and 5 were male, while in the control group, 9 patients were female, and 3 were male.

Initially, the study group consisted of 33 patients diagnosed with glaucoma. However, after applying rigorous inclusion and exclusion criteria, 9 patients were excluded due to the severity of their glaucomatous disease. Among the remaining 24 patients, 8 were further excluded for not meeting the specified criteria, resulting in a final sample of 16 glaucoma patients included in the study. The control group included 12 patients who met the strict inclusion and exclusion criteria and provided informed consent.

It should be noted that all patients and participants underwent MRI examinations, which can be challenging for subjects to undergo (see Figure 6).

4.1.2. Inclusion criteria: The presence of glaucoma was defined by high IOP without treatment (initial IOP mean: RE: 27.38±4.67; LE: 28.69±5.41 for the Study group, and RE: 15.67±6.31; LE: 14.67±2.14 for the Control group), abnormal visual field defects on standard automated perimetry (SAP), and characteristic optic nerve head morphology (rim loss, corresponding retinal nerve fiber layer and visual field loss) in the presence of an open iridocorneal angle. To be included in the study, patients with glaucoma had to have the disease present in both eyes, be between the ages of 47 and 70, have refractive error not exceeding ±4 diopter sphere and 2 diopter cylinder, and have transparent ocular media. All glaucoma participants were receiving topical glaucoma medications, and their IOP was within normal limits. Only patients with moderate visual field and optic nerve damage remained in the study. The final IOP mean with topical treatment was RE: 16.14 mmHg ± 4.58; LE: 16.21 mmHg ± 2.85. Study participants who had undergone uneventful cataract surgery were also included. Healthy volunteers in the control group were required to have IOP less than 21 mmHg in both eyes, clinically normal optic discs, SAP results within normal limits, and no ocular or systemic abnormalities that could affect optic nerve structure or visual function (see Figure 6).

4.1.3. Ophthalmological exclusion criteria primarily referred to ocular diseases and systemic diseases known to affect visual and auditory processing for each participant in the study or control group. These criteria included best-corrected visual acuity worse than 20/100, refractive error greater than ±4 sphere diopters or 2 cylinder diopters, optically significant cataract, gonioscopy showing occluded angle or anterior peripheral synechiae, excessive pigmentation or deposits of exfoliating material, history of inflammatory eye disease, previous eye trauma, diabetic retinopathy, neuroophthalmological disease, optic nerve abnormalities (tilted disc, drusen), or angle anomalies, any retinal disease or other ocular or systemic disease capable of causing visual field loss or optic nerve damage, including intracranial injury or orbital disease. Patients with severe glaucomatous damage were not included in the study, which excluded patients with a cup/disc ratio (C/D) of 1, complete glaucomatous atrophy, and major perimetric deficits that prevented accurate functional evaluation. Participants who showed poor cooperation or experienced claustrophobia were also excluded (see Figure 6).

4.1.4. Hearing exclusion criteria included the following: conductive hearing loss, family history of hearing loss, neck muscle problems, high noise exposure, acute or chronic ear infection, tympanic membrane perforation, ear surgery, head trauma, active upper respiratory tract infection, cochlear ossification, active mastoiditis, cerebral tumor history of ototoxic drugs, and systemic diseases that affect hearing. Participants with chronic lesions of

the auditory apparatus were also excluded from the study. Patients and volunteers without other neurological diseases that could have affected the investigation were included in the study (see Figure 6).

Figure 6. Patient recruitment flow diagram (inclusion and exclusion criteria).

4.2. Evaluation protocol.

4.2.1 The study protocol included ocular examination, imaging evaluation, and ear examination. The patients were evaluated for a period of 6 months after enrollment, but the clinical parameters analyzed in the study were those evaluated at enrollment. These parameters included PTA, disc area, rim area, area C/D ratio, vertical C/D ratio, RNFL average thickness, and CCT.

4.2.2 Ocular examinations. All participants underwent detailed medical history and comprehensive ocular examinations, including best-corrected visual acuity (BCVA), refraction, IOP measurements, slit-lamp and fundus examinations, and CCT measurement. Refractive errors were evaluated using an autorefractokeratometer (Reichert RK600, Reichert Technologies Inc., NY, USA). Bilateral IOP was measured once in the morning between 10:00 AM using Goldmann applanation tonometry, and anterior segment evaluation was performed using a slit-lamp (Reichert Xcel 200, Reichert Technologies Inc., NY, USA) by ophthalmologists. CCT was measured using central corneal ultrasonic pachymetry (OcuScan RxP; Alcon Laboratories Inc., Irvine, CA). Fundus examinations were performed using a 90 D lens from Volk Optical USA. Anterior chamber angle was estimated using a 3-mirror lens from Ocular Instruments, USA. Visual field assessment was conducted using SAP and OCT. For SAP, at least two reliable tests were performed using Optopol Technology PTS 900, Glaucoma field, Strategy Fast threshold, Optopol Technology S.A., Zawiercie, Poland. Abnormal SAP results were defined as typical glaucomatous defects with integrated perimetric defect in the clinical context and mean defect (MD). Spectral-domain OCT imaging was performed using Optopol SOCT Copernicus (version 4.20, rev.5, SOCT Software 4, 3, Optopol Technology S.A., Zawiercie, Poland). The optic nerve assessment included evaluation of optic disc size, neuroretinal rim shape, RNFL measurements, cup diameter, cup maximal depth, horizontal rim size, temporal and nasal height, peripapillary RNFL thickness, and optic nerve head (ONH) parameters. Good-quality scans, defined as scans with a signal strength of at least 7, without RNFL discontinuity or misalignment, involuntary saccade, or blinking artifacts, were used for analysis. OCT imaging was performed in a quiet and dark room, and artificial tears were used before image acquisition for patient comfort.

4.2.3 Imaging evaluations. All participants underwent MRI to exclude other ear diseases such as cochlear ossification, active mastoiditis, or cerebral tumor. MRI was performed using General Electric Healthcare MRI Signa Explorer, USA, 2019; 1.5 Tesla, with the orbit and head protocol performed by a specialist radiologist. Participants were examined in a supine position with their heads stabilized using foam cushions to minimize head motion.

To minimize eye movement during image acquisition, participants were advised to look straight ahead. The axial plane of each MRI session was set parallel to the line from the anterior commissure to the posterior commissure on sagittal localizer images. For MRI scans of the optic nerve and cerebral tissue, the orbit and head tests were combined. No contrast substance was used for the MRI scans, which were performed using nine series of data: six for head investigations and three for orbit: 3-Plane localizer with field of view (FOV)= 30.0, echo time (TE)=1.8, slice thickness =5.0, Ax T2 Propeller FOV=25.0, repetition time (TR)=4019.0, TE=106.7, slice thickness = 4.0, AxT2 Flair with FOV= 24.0, TR=9000.0, TE=120.0, slice thickness = 4.0, 3D AxSwan(SWI) with FOV=24.0, TR=79.9, TE=50.0, slice thickness =3.0,AxDWI b1000 with FOV=24.0, TR=4543.0,TE= min, slice thickness =5.0, Sag3DT1 FSPGR with FOV=25.6, TR= 8.5, TE=min, slice thickness =2.0, CorT2STIR with FOV=20.0, TR= 2606.0, TE=55.0, slice thickness =2.0, Ax T2 Propeller with FOV=22.0, TR=3854.0, TE= 118.5,slice thickness = 3.0, 3DAx T2 Cube with FOV= 22.0,TR=2022.0, TE=150.0, slice thickness =1.0. The parameters used for the MRI scans, such as FOV, TE, TR, and slice thickness, were specific to the General Electric Healthcare MRI Signa Explorer.

4.2.4 Ears examinations. All patients and control participants underwent standard otolaryngological examinations, including medical history (past medical history, social history, family history) and clinical findings. Bilateral ear examinations were performed by a specialist otolaryngologist using a Heine beta 200 otoscope. Hearing sensitivity was evaluated using PTA in a double-walled soundproof booth. Air conduction pure-tone thresholds were measured using a MAICO MA25 audiometer with two channels (MAICO Diagnostic GmbH, Salzufer 13/14, D 10587 BERLIN), Noah 9 software. PTA was performed for each ear at six frequencies (125, 250, 500, 1000, 2000, 4000, and 8000 Hz) by a well-trained examiner, and the results were recorded. The MA 25's frequencies range from 125 Hz to 8000 Hz and signal intensities are adjustable in 1 or 5 dB steps from -10 to 100 dB HL (Hearing level). The "gold standard" of hearing sensitivity is the PTA.The audiogram displays the listener's detection thresholds (hearing level in dB according to the American National Standards Institute, 1996) for pure tone signals at octave frequency intervals in the range 250–8000 Hz, in both ears. This frequency range encompasses the spectrum of speech sounds. The standard method for measuring pure tone detection threshold is the modified Hughson-Westlake technique (American National Standards Institute, 1997; ASHA, 1978; Carhart and Jerger, 1959). This is a single stimulus technique that combines the ascending and descending methods of limit where the stimulus duration is 1-2 seconds and the signal can be steady state or pulsed. The definition of threshold is the lowest level at which a listener detects a signal. Pure tone thresholds are evaluated in air conduction mode (250-8000 Hz) and bone conduction mode (250-4000 Hz) [36]. Measurement of pure tone detection thresholds is essential for determining the degree of hearing loss. A classification scheme for the degree of hearing loss is that developed by ASHA. Hearing loss was defined as pure-tone average thresholds at 125, 250, 500, 1000, 2000, 4000 and, 8000 Hz averaged for both ears of > 40-dB. Hearing impairment was categorized by severity (mild or moderate-to-profound). The degree of hearing loss was assessed in accordance with ASHA recommendations thresholds of 0-25 dB (decibels) were evaluated as normal hearing, 26-40 dB as mild hearing loss, 41-55 dB as moderate hearing loss, 56-70 dB moderate-severe hearing loss, 70-90 dB severe hearing loss, and >90 dB as profound hearing loss [37-40]. Audiometry testing was repeated once if initial testing was deemed unreliable.

4.2.5 Statistical and data Analysis. The data were processed using SPSS version 18.0 software (SPSS Inc., Chicago, IL). Statistical tests, including ANOVA, coefficient of variation (CV%), skewness test, t-Student test, F-test (ANOVA), chi-square test, and Kruskal-Wallis test, were performed depending on the distribution of the variables and the number of groups being compared. The Pearson correlation coefficient was used to study the corre-

lation between different parameters. Multiple linear regression analysis was used to highlight the relationship between the dependent variable and a set of independent variables. The ANOVA test consisted in analyzing the dispersion of the dependent variable: intra and intergroup. The coefficient of variation (CV%) highlights the percentage deviation between two averages, providing results on the homogeneity of the series of values and the Skewness test (-2 < p < 2) validates the normality of the series of values; it is used when the examined variable has continuous values. In the calculation of the significant difference between two or more groups, depending on the distribution of the value series, at the significance threshold of 95%, for the quantitative variables, apply: the t-Student test: parametric test that compares the mean values recorded in 2 groups with normal distributions; the F-test (ANOVA) used when comparing 3 or more groups with normal distributions, combined with the application of the Bonferroni correction (Bonferroni post-hoc) to reduce the error rate when testing several hypotheses; the c2 test is a non-parametric test that compares 2 or more frequency distributions from the same population, and it is applied when the expected events are excluded; The Kruskal-Wallis test, a non-parametric test that com-pares 3 or more frequency distributions between groups; "Pearson" correlation coefficient (r) represents the correlation of 2 variables from the same group (direct/indirect correlation); The study of the correlation between different parameters was carried out with the help of the Pearson correlation coefficient, which reproduces the intensity of the statistical links and their meaning. The values of the correlation co-efficient are between [-1, +1]: if the correlation coefficient tends to +1 (direct correlation), or to −1 (indirect correlation), there is a strong linear dependence of the parameters; the closer the correlation coefficient is to 0, the lower the intensity of the link. Multiple linear regression aims to highlight the relationship between a dependent variable (explained, endogenous, result) and a set of independent variables (explanatory, factorial, exogenous, predictors).

5. Conclusions

This study provides evidence that patients with POAG exhibit changes in their audiometry tests, indicating a correlation between ophthalmological parameters and auditory function. These findings suggest that the auditory system can be affected in POAG, leading to hearing impairment. By combining the structural evaluation of the optic nerve with auditory functional analysis, it is possible to establish correlations that can enhance the diagnostic algorithm for glaucoma. Early detection of the disease is crucial for maintaining the quality of life for glaucoma patients.

Considering that both the visual and auditory systems play a role in ensuring quality of life, it is essential to integrate comprehensive medical care. As a perspective, it may be beneficial for patients with high PTA values, but without an identified organic ear disorder, to undergo ophthalmological evaluation. Similarly, patients with hearing impairments should undergo periodic auditory evaluations and be examined by an ophthalmologist to potentially receive a diagnosis of glaucoma.

By recognizing the interconnections between the visual and auditory systems and their impact on overall well-being, healthcare professionals can adopt a multidisciplinary approach to provide comprehensive care to patients with glaucoma and hearing impairments. Regular auditory evaluations and ophthalmological examinations can contribute to the early detection and management of glaucoma, thereby improving the quality of life for affected individuals.

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