CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST
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PhD THESIS

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FUNCTIONAL AND STRUCTURAL EVALUATION IN GLAUCOMA FOR VALIDATING ESSENTIAL CORRELATIONS TOWARDS OPTIMIZING THE DIAGNOSTIC AND TREATMENT ALGORITHM

ABSTRACT

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List of published scientific papers

1. **Alina Mihaela Neacșu**, Corina Sporea, Nicoleta Anton, Lucian Lapușneanu, Maria Cristina Andrei, Mihaela Coșman, Dumitru Ferechide
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3. **Alina Mihaela Neacșu**, Dumitru Ferechide
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   Cap. 2: pag. 23-36

Contents

List of abbreviations and symbols

DNA: Deoxyribonucleic Acid

FA: Fractional Anisotropy

ATP: Adenosine Triphosphate

ADP: Adenosine Diphosphate

VA: Visual Acuity

CCT: Central Corneal Thickness

LGN: Lateral Geniculate Nucleus

MGN: Medial Geniculate Nucleus

RGC: Retinal Ganglion Cells

SC: Superior Colliculi

IC: Inferior Colliculi

VF: Visual Field

MD: Mean Deviation

MDev: Mean Deviation

dB: Decibel

dBHL: Decibel Hearing Level

EGCG: Epigallocatechin-3-gallate

GABA: Gamma-Aminobutyric Acid

GDP: Guanosine Diphosphate

GTP: Guanosine-5'-triphosphate

GMP: Guanosine Monophosphate

XFG: Exfoliation Glaucoma

POAG: Primary Open-Angle Glaucoma

FOV: Field of View

Hz: Hertz

RNF: Neuroretinal Ring

CSF: Cerebrospinal Fluid

ONH: Optic Nerve Head

ENT: Ear, Nose, Throat (Otorhinolaryngology)

OD: Right Eye

OS: Left Eye

PD: Pattern Deviation

IOP: Intraocular Pressure

PTA: Pure Tone Average

C/D Ratio: Cup-to-Disc Ratio

MRI 1.5T: Magnetic Resonance Imaging 1.5 Tesla

MRI 3T: Magnetic Resonance Imaging 3 Tesla

MRI 7T: Magnetic Resonance Imaging 7 Tesla

MRI: Magnetic Resonance Imaging

RNFL: Retinal Nerve Fiber Layer

SAP: Standard Automated Perimetry

SD-OCT: Spectral Domain Optical Coherence Tomography

CNS: Central Nervous System

VBM: Voxel-Based Morphometry

VIP: Vasoactive Intestinal Polypeptide

TE: Echo Time

TR: Repetition Time

ECF: Extracellular Fluid

μm: Micrometer

Introduction

Glaucoma is a multifactorial optic neuropathy characterized by the irreversible loss of retinal ganglion cells (RGC). The disease's irreversibility and its standing as the second leading cause of visual acuity (VA) loss after cataracts make glaucoma a significant public health issue.

In 2020, approximately 76 million people suffered from glaucoma, and it's estimated that this number will reach 111.8 million by 2040 [1]. The large number of existing and estimated patients, along with the degree of their visual impairment significantly affecting their quality of life, drives scientific efforts to identify early detection methods and innovative treatments aimed at preserving vision and its associated social integration.

Visual impairment affects life through its two elements: physical and social, while hearing impairment plays a key role in social functioning [2]. Dual sensory impairment – loss of both hearing and vision – compromises the two primary ways of communication, listening, and speech reading, potentially leading to social isolation. There's a reduction in the amount of information an individual can gather from their environment, leading to a functional limitation and significantly impacting quality of life [3,4].

Dual sensory loss affects cognitive function more than unilateral loss of vision or hearing [5–9], as these two functions are interconnected in the brain.

Looking ahead, the aging population is associated with an increased prevalence of glaucomatous disease, and indirectly, dual sensory loss will become more frequent, given the functional interconnection of these two functions [10].

Within this scientific context, research into the etiopathogenic mechanisms and clinical evaluation methods of glaucomatous disease has resulted in identifying useful elements for early diagnosis. Discovering auditory functional changes in patients with glaucoma opens new possibilities for early intervention and highlights the importance of interdisciplinary cooperation in medical practice.

The research hypothesis originated from a simple clinical observation resulting from years of ophthalmological practice. Patients with glaucoma in Romania tend to present themselves late to the doctor because this disease is not characterized by acute suffering or urgent elements that would prompt the patient to seek medical attention promptly. The observation from routine practice was that many of those evaluated and diagnosed with glaucoma exhibited a clear clinical decline in hearing. The natural question was whether these lesions were concurrent or consecutive and if a correlation could be established between them. The aim of the research, conducted on two perspectives – ophthalmological structural and functional and auditory functional – was to identify these connections between the obtained results and to potentially integrate them into a diagnostic algorithm.

The paper introduces three studies:
Study I: The impact of the association between structural changes in glaucoma and auditory function on the diagnostic algorithm of glaucomatous disease.
Study II: Dynamics of the association between visual and auditory functional changes in glaucoma.
Study III: Hypothesis of structural and functional reorganization at the cortico-thalamic level under conditions of acquired visual information deprivation: correlations between the results obtained from the conducted studies and the existent ones.

Patients with primary open-angle glaucoma (POAG) with moderate types of the disease were evaluated in these studies. All these patients were included in the research after an extremely rigorous ophthalmological and auditory evaluation. To exclude any central lesions that could affect the results, all patients and controls underwent imaging evaluation using 1.5 Tesla Nuclear Magnetic Resonance (MRI) with an orbital and cranial program. The results obtained after structural evaluation of the optic nerve through Optical Coherence Tomography (OCT), functional evaluation of the optic nerve through computerized perimetry, and auditory function through audiograms allowed for hypotheses to be stated.

The results of the conducted studies showed a structural impairment of the optic nerve quantified by OCT that correlates with an auditory functional impairment on the left side. Additionally, a functional impairment of the optic nerve associated with an auditory impairment on the same side was identified. It is worth mentioning that all patients included in the study are consistent right-hand users. In this regard, considering the cortical and subcortical visual and auditory cerebral interconnection, in relation to intense lateralization processes at this level, a supposition can be made regarding the existence of these modifications in both structures. As there is an abundant specialized literature on the subcortical and cortical connections of both analyzers, to collectively treat the results in a separate study accompanied by a meta-analysis of elements of the functional anatomy of the central nervous system (CNS) was considered useful.

If scientifically demonstrated hypotheses regarding the intense and continuous lateralization process of various cortical functions such as cognition, speech, and spatial visual attention are taken into account, it justifies both the working hypothesis and, most importantly, the obtained results. The number of participating patients is small but sufficient to generate statistically relevant conclusions and to open a new perspective on glaucomatous disease. Building upon the hypothesis of auditory functional impairment in glaucoma, future studies could expand to a larger number of patients, acquiring a longitudinal approach over a longer period.

The new element identified within the research, i.e. the dual nature of evaluating patients with glaucoma and those with recently installed non-detectable organic causes of hearing impairment can be mentioned. Interdisciplinary collaboration in this regard is evident since both elements identified during an ophthalmological consultation and those concerning the auditory apparatus can favor a comprehensive diagnosis. With relatively simple, cost-effective methods, an early diagnosis in glaucoma can be achieved, leading to an appropriate therapeutic course aimed at preserving vision. The interdisciplinary approach characterizes the entire research as it involves different medical specialties: otorhinolaryngology (ORL), audiology, radiology, neurology, neurosurgery, with complex elements of psychological development. Within this context, the phrase ‘a sick eye in a sick body’ grasps its reality and pertinence since 1922 when it was coined by Pierre-Félix Lagrange [11].

Chapter 1. Neuroanatomy and Neurophysiology of Visual and Auditory Analyzers

Visual and auditory sensory processes involving the reception and transmission of information associated with the perception and central cortical integration are extremely complex and presume the existence of correlated functionality from an anatomical and physiological standpoint in the visual and auditory pathways. The interrelation between many cortical and subcortical structures plays a key role in the pathology of ophthalmological diseases, especially the glaucomatous disease.

Cortical integration of visual information becomes a mechanism closely connected with many other cortical areas – motor, auditory, vestibular – because at the cortical level, systems and subsystems are defined, including sensory afferents from the retinal source, and each specific cortical region presents connections with other regions that ensure primary functions [12].

Glaucoma is the second leading cause of irreversible vision loss worldwide. The American Academy of Ophthalmology and the European Glaucoma Society define this disease as a multifactorial optic neuropathy characterized by a slow, progressive, irreversible destruction of retinal nerve fibers in the absence of other ophthalmological conditions, accompanied by the loss of visual field (VF) [13,14].

Nerve signals leave the retina through the optic nerves comprised of RGC axons. At the level of the optic chiasm, closely associated with the hypophyseal fossa, the optic nerve fibers from the nasal part cross and continue their path alongside fibers collecting information from the temporal part of the contralateral eye's retina to the lateral geniculate bodies (LGB) where they synapse with the second neuron of the visual pathway. Their axons form the geniculocalcarine tract as optic radiations reaching the primary visual cortex located at the edges of the calcarine fissure, in the medial area of the occipital lobe, where they synapse with the third neuron of the visual pathway. Visual pathway fibers send afferents to numerous older phylogenetically regions of the brain: to the suprachiasmatic nucleus of the hypothalamus involved in regulating the circadian rhythm, to the pretectal mesencephalic nuclei for reflex eye movements necessary for focusing on objects and pupillary reflex, and to the superior colliculi (SC) for rapid movement control [15,16].

The LGB has two main functions: it sends information with high fidelity to the primary visual cortex located at the edges of the calcarine fissure through Gratiolet's optic radiations or the geniculocalcarine tract and filters information reaching the visual cortex through corticofugal fibers and the reticular regions of the midbrain [15,16].

The primary visual cortex is located in the walls of the calcarine fissure, extending anteriorly from the occipital pole on the medial aspect of each occipital lobe. Impulses originating from the macular region project near the occipital pole, those from the peripheral retinal region into the concentric semicircular zones located anteriorly to the occipital pole and along the calcarine fissure, the superior retina in the upper occipital area, and the inferior retina in the lower area (primary cortex V1). The macular representation (fovea) is organized over a larger area compared to other retinal areas. Secondary visual cortical areas, also known as association areas, are located superiorly, inferiorly, laterally, and anteriorly to the primary cortex, and most of these extend to the lateral surfaces of the occipital and parietal cortices [15,16].

The central nervous system (CNS) has the capacity to receive, process, and generate appropriate responses for different types of apparatuses and systems. At this level, there are specialized neurons that cannot function alone but within complex systems where neuronal circuits play a vital role. The retina is a predominantly sensory neuronal circuit, and within the visual analyzer, the pathways collecting information from the retinal level under the term 'retinal somatotopy' are well-established. Retinal somatotopy [12,15,16] represents the specific transmission of information from each retinal zone through well-established pathways, both within the optic nerve and along the entire course of the main nerve pathways.

The Corti organ is the receptor organ for the auditory function. It is located within the cochlea, a bony semicircular canal in the inner ear. Neuron axons from the Corti ganglion synapse at the level of the bulb in the dorsal and ventral cochlear nuclei. A large part of nerve fibers pass to the opposite side and synapse in the superior olive nucleus, join the lateral lemniscus, and reach the medial geniculate bodies (MGB) in the thalamus, where they synapse. Neuron axons from the MGB project as auditory radiations to the superior gyrus of the temporal lobe – the primary auditory cortex. Auditory pathways have specific neuroanatomy, with impulses from both ears transmitted through bilateral auditory pathways, mostly contralateral [16].

The primary and associated auditory cortex has at least six tonotopic representations that separately analyze a sound feature. The frequency range at which cochlear nerve terminations are stimulated is wider than the intervals at which neurons in the auditory cortex are stimulated. This signifies a cortical ultra-specialization representing a process of fine-tuning a response to a frequency [12,16]. In the primary cortex, sound perception has different connotations; it is associated in certain regions with the mental sensation produced by noise or with sound localization.

Chapter 2. Glaucoma: A Neurodegenerative Disease with Elements of Brain Neuroconnectivity

Glaucoma is a chronic condition that results in irreversible vision loss. According to the European Glaucoma Society's guidelines [14], glaucoma is classified into Juvenile Glaucoma (congenital, congenital late detection, and secondary juvenile), Primary Open-Angle Glaucoma (POAG), Secondary Open-Angle Glaucoma, Primary Angle-Closure Glaucoma, and Secondary Angle-Closure Glaucoma. This terminology takes into account the iridocorneal angle as a classification element, an anatomical structure composed of five landmarks (Schwalbe's line, trabecular meshwork, Schlemm's canal, scleral spur, and ciliary body), while the secondary nature is conferred by various causes that can increase intraocular pressure (IOP) and lead to the destruction of the optic nerve and retinal nerve fiber layer (RNFL). The most well-known entity in the category of secondary glaucomas is Pseudoexfoliative Glaucoma (PEXG) determined by the Pseudoexfoliative syndrome (elastotic changes in the trabecular meshwork, genetically conditioned LOXL1) [17,18].

The most common form of glaucoma is POAG [14]. POAG is characterized by increased IOP due to trabecular meshwork dysfunction. The consistent elevation of IOP, combined with other local and general mechanisms, leads to the destruction of retinal ganglion cell (RGC) axons that make up the optic nerve. The consequence of this destruction is a concentric, progressive loss of the visual field.

Glaucoma is an insidious disease that remains asymptomatic for many years. Visual manifestations occur when RGC axons undergo permanent destructive damage, with RGC being universally recognized as the primary site of injury in glaucoma. Initially considered a multifactorial optic neuropathy causing slow, progressive destruction of RGC axons, resulting in irreversible visual acuity (VA) and visual field (VF) loss, since 2000, the definition has undergone significant changes. The concept of neuropathy has been replaced with that of a neurodegenerative disease of central visual pathways [19,20].

The primary risk factor remains IOP, which plays a crucial role in both the pathophysiology and progression of the disease. The etiopathogenic mechanisms in glaucoma are multiple but not entirely understood. Several theories are involved: the mechanical theory (related to IOP values and pressure effects on the optic nerve head: ONH), the vascular theory (decreased blood flow at the ONH due to various causes resulting in unfavorable pressure on the optic nerve), the biochemical theory (reduced neurotrophic factors in the retina, increased local neurotoxic products like glutamate), oxidative stress theory (excess of neurotoxic substances, mitochondrial dysfunction) associated with the apoptosis theory (programmed cell death of RGC initiated differently), the biomechanical theory (changes in the structure of the Lamina Cribrosa - an elastic structure, situated posteriorly through which optic nerve fibers exit the eye), the autoimmunity theory (immune-mediated mechanisms triggering apoptosis) [21].

Yucel Y. and Gupta N. [22] were among the first to hypothesize that increased IOP and RGC destruction could trigger transsynaptic degeneration and destructive changes both in the lateral geniculate nucleus (LGN) and in the visual cortex. Lowering IOP is the best strategy to prevent RGC death and, simultaneously, decrease the risk of CNS degeneration in glaucoma. Gupta showed that glaucoma patients have degenerative lesions in the LGN, involving the magnocellular, parvocellular, and koniocellular layers. These changes were linked to IOP and the severity of the optic nerve’s destructive injury [23]. After the publication of these studies, it was suggested that LGN atrophy could become a relevant biomarker for the deterioration and/or progression of visual system lesions in some glaucoma patients, considering evidence that glaucomatous neuropathy affects both the retina and the CNS [24-27]. Over time, increased IOP, combined with neuronal loss due to reduced metabolic activity, has caused injuries in the expression patterns of several synaptic plasticity markers present in LGN and the visual cortex of glaucoma patients and primate models [27]. The extension of neurodegenerative aspects to central visual pathways can affect information processing at this level and allows for the alteration of neural structures involved in the visual process, both directly and alternatively through other pathways implicated in visual information processing.

Etiopathogenic mechanisms of neurodegenerative diseases are present in glaucoma. Visual dysfunction in glaucoma mainly results from RGC death and axonal degeneration in the CNS [24,25,22,28,29,30]. In comparison, neurodegenerative disorders witness the destruction of specific neuronal groups: in Parkinson's disease, selective loss of nigrostriatal dopaminergic neurons leads to progressive movement disorders [31], whereas in Alzheimer's dementia, loss of hippocampal and cortical neurons [32] results in memory and cognitive impairments. Apoptosis, or the programmed cell death, is associated with neuronal destruction in glaucoma similar to other neurological diseases. Many pathological processes leading to apoptosis have been linked to mitochondrial dysfunction, oxidative stress, release of inflammatory mediators, glutamate excitotoxicity, and abnormal protein accumulations [30,33], but the triggering mechanisms remain unknown.

The notion that glaucoma is a neurodegenerative disease affecting central nerve pathways has opened new perspectives in terms of brain imaging. Studies employing state-of-the-art MRI machines investigate the appearance and size of the LGN and visual cortex in glaucoma patients. MRI can reveal central visual pathway degeneration following the damage to RGC axons [34]. LGN degeneration, geniculocortical projections, and cortical areas have been explored in glaucoma patients, identifying evidence of LGN atrophy [35]. Based on ONH and retinal evaluation data, in 2021, Beykin et al. [34] suggested that brain changes are primarily secondary effects of anterograde and even transsynaptic axonal degeneration. An injury at the ONH affects RGCs along its axons through direct anterograde degeneration or Wallerian degeneration and produces changes in the optic nerve, chiasm, and optic tract, but it can equally lead to direct retrograde degeneration of RGCs [36]. White and gray matter in multiple brain areas, especially in the occipital lobe, are affected with severity directly proportional to the glaucomatous disease stage [37]. Furlanetto et al. demonstrated in a cross-sectional study involving 41 glaucoma patients that there was a reduction in LGN height evaluated using 3T MRI imaging [38]. The connections of the visual apparatus with other brain structures open new approaches regarding changes in multiple neurosensory functions in glaucoma patients.

Chapter 3. Hypothesis and General Objectives

In the special section of the doctoral thesis, the results of three studies conducted during the doctoral research are introduced, addressing glaucomatous disease from the perspective of neurodegenerative impairment defined by localized lesions within the visual pathways interconnected with both the auditory analyzer and the central nervous system. The hypothesis underpinning these studies is based on proven anatomical and physiological principles of neuroconnectivity [28] between the visual and auditory analyzers at cortical and subcortical levels. Within these segments, there are associative areas receiving both visual and auditory information, which play a particularly significant role in the activity of complex integrative systems such as cognition and language. Remarkably important activity is observed within the superior colliculus (SC) and inferior colliculus (IC) of the midbrain, at the level of thalamic nuclei (pulvinar, lateral geniculate nucleus, and medial geniculate nucleus), as well as in cortical association areas.

The aim of these studies was to identify connections between the visual and auditory analyzers through a functional and structural analysis of the constituent elements of the optic tract from the retinal to the central level, establishing correlations between several measured parameters. The results of these studies consisted of establishing associations between: retinal changes quantified through structural assessment of the retina and direct optic nerve (ON) evaluation using Optical Coherence Tomography (OCT), visual field impairment assessed through computerized perimetry (functional analysis of the optic nerve), and Pure Tone Audiometry (PTA) values establishing hearing impairment (functional analysis of auditory pathways) through an audiogram.

To achieve this, a series of parameters defining the optic nerve and RNFL structure were measured using OCT: disc area, rim area (INR), cup-to-disc area ratio (C/D), vertical C/D ratio, average retinal fiber layer (RNFL) thickness, central corneal thickness (CCT), and Intraocular Pressure (IOP) values. Concerning visual fields, the following parameters were considered: Mean Defect (MD), Profile Slope, and Cal HOV. Audiogram values, specifically high-frequency sound levels, were studied. Both study groups underwent ophthalmological and audiological examinations, assessing the anatomical and functional integrity of the auditory system clinically and via imaging with a 1.5 Tesla MRI.

The general objectives of the studies were to evaluate the mentioned clinical parameters, analyze the demographic profile of the involved groups, and identify correlations between visual clinical parameters (structure and function) and auditory clinical parameters (function). Statistical tests were employed to scientifically validate the results. The subsequent consequence of the obtained results can manifest in the monitoring and treatment of patients.

Chapter 4. General Research Methodology

The studies conducted within this doctoral research are:

Study I: "The Impact of the Association Between Structural Changes in Glaucoma and Auditory Function on the Glaucomatous Disease Diagnostic Algorithm."
Study II: "The Dynamics of Association Between Visual and Auditory Functional Changes in Glaucoma."
Study III: "The Hypothesis of Structural and Functional Reorganization at the Cortico-Thalamic Level under Conditions of Acquired Visual Information Deprivation: Correlations between the Results Obtained from Conducted Studies and the Existent Ones."

The research was carried out on the same cohorts of patients and had the same inclusion and exclusion criteria, ophthalmological, otorhinolaryngological, and radiological clinical evaluations, but employed exploration methods with clear differentiations based on the objectives of each study.

Studies I, II, III are prospective, cross-sectional, observational clinical studies conducted in the Ophthalmology Department of the Emergency County Clinical Hospital Brăila between October 2021 and December 2022. Patients were evaluated over a period of 6 months since enrollment. As a personal contribution to the doctoral thesis these studies were approved by the Ethics Committee of the Emergency County Clinical Hospital Brăila, with approval documented as no. 1/3.09.2021, in compliance with ethical and deontological rules for medical practice and research. The studies were conducted following the Helsinki Declaration. Each patient was informed and signed a consent form to participate in the study.

The study group consists of 16 patients (32 eyes) with POAG, while the control group comprises 12 healthy subjects (24 eyes), with an average age of 62 years in both groups. All 16 patients were evaluated in the Ophthalmology Department of the Emergency County Clinical Hospital of Brăila. The healthy subjects in the control group were evaluated in the same ophthalmology department, consisting of friends, relatives, volunteers, and staff members. Of the 16 patients in the study group, 11 were women and 5 were men. Among the 12 healthy subjects in the control group, 9 were women and 3 were men. It is noteworthy that initially, the study group consisted of 33 investigated patients diagnosed with glaucoma. Based on rigorous and restrictive inclusion and exclusion criteria of the study, which will be explained in the study design, it began with 33 glaucoma patients, of which 9 were excluded due to the severity of the glaucomatous disease. Out of the remaining 24, 8 patients were further excluded for not meeting other criteria, resulting in 16 glaucoma patients included in the study. The control group included 12 subjects because only they met the rigorous inclusion and exclusion criteria (**Fig. 4.1**).

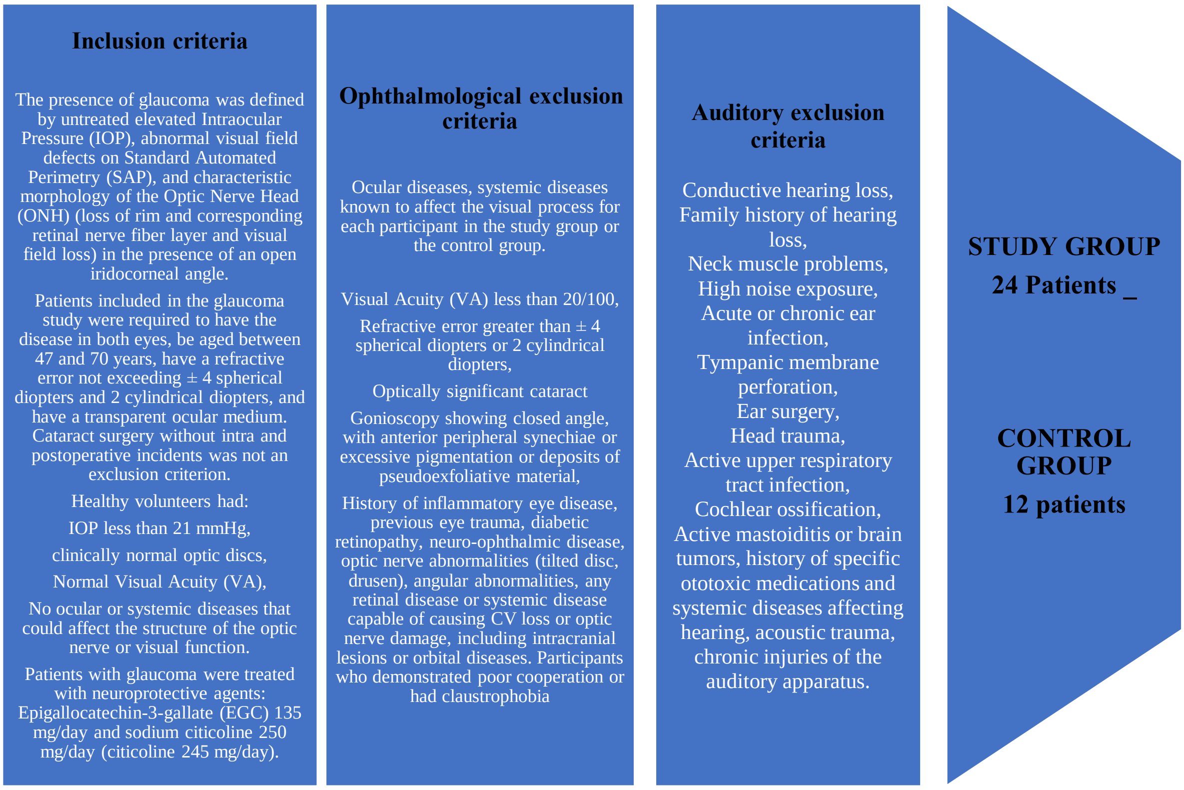

Fig.4 .1 Patient Recruitment Diagram

Ophthalmological and Auditory Inclusion and Exclusion Criteria

Chapter 5. Study I – The Impact of Association between Structural Changes in Glaucoma and Auditory Function on the Glaucomatous Disease Diagnostic Algorithm

The aim of this study is to evaluate the degree of involvement of the auditory system in patients with Primary Open-Angle Glaucoma (POAG) through structural changes in the optic nerve and establish correlations between structural changes in the optic nerve [39] and auditory assessment parameters. The subjects included in the study are grouped as follows:

a group of glaucoma patients compared to a group of volunteers without glaucoma concerning the evolution of structural changes in the optic nerve and audiometric evaluation. The study protocol included ophthalmological examinations, imaging, and ear examinations. Patients were evaluated over a 6-month period from enrollment; clinical parameters introduced into the study for analysis were those evaluated at enrollment: Pure Tone Audiometry (PTA), disc area, rim area (RA), cup-to-disc ratio (C/D), vertical C/D ratio, average retinal nerve fiber layer (RNFL) thickness, central corneal thickness (CCT), and Intraocular Pressure (IOP) values.

This was a prospective, cross-sectional study on 32 eyes from 16 subjects in a study group with POAG and 24 eyes from 12 healthy subjects in the control group, with an average age of 61.64 years ± 6.53 years in both groups. Both groups underwent ophthalmological, audiological, and imaging evaluations.

The coexistence of visual and auditory impairments in glaucoma has sparked the interest of many researchers. Interestingly, these studies have a dual nature, approaching the topic from both an ophthalmological perspective, linking vision loss in glaucoma with auditory dysfunction, and vice versa from an audiological perspective: age-related hearing loss correlated with glaucomatous disease.

If we take a historical evaluation of studies addressing visual and auditory impairments in glaucoma, we can observe that this topic has long been a focus of scientific attention.

In 1997, Shapiro et al. examined 67 glaucoma patients and found no association between sensorineural hearing loss and visual loss exceeding age-related losses among the study patients. However, this work included patients with various types of glaucoma: pigmentary, congenital, and ocular hypertension, which might explain the study's results [40]. Many studies have investigated hearing loss in patients with pseudoexfoliation syndrome, accompanied or not by pseudoexfoliation glaucoma [17,18,41,42,43]. In 2022, a meta-analysis conducted by Huang et al. regarding 14 eligible studies concluded a connection between pseudoexfoliation syndrome and hearing loss. Although the causes are not fully understood, several theories refer to a common embryological origin of the inner ear and anterior eye segment associated with the accumulation of pseudoexfoliative material in both the anterior segment and the cochlea, vascular wall involvement, vestibular impairment due to pseudoexfoliative material causing vestibular decompensation [44]. In 2004, in a study conducted on 34 patients with normal-tension glaucoma, Kremmer et al. claimed that microcirculation disorders generated by microthrombi produced by increased antiphospholipid antibodies [45] are the cause of visual and auditory dysfunctions. In 2012, O'Hare, Crowston et al. noted the limitations of previous studies and, considering glaucoma as a neurodegenerative disease, studied visual and auditory dysfunction from the perspective of cortical integration. They found that glaucoma patients processed auditory information differently, explaining these cortical temporal anomalies based on the neuronal vulnerability theory [46]. In 2012, in a study involving 215 patients, Mudie et al. examined the effect of glaucomatous vision loss and hearing impairment in glaucoma patients. After evaluating visual and auditory impairments, they concluded that these have a key role in functional and cognitive decline, significantly influencing the social integration of patients [47].

In 2019, in a large study involving 12,899 individuals over 40 years old, Kim et al. concluded that age, male sex, and triglyceride levels play a significant role in associating glaucoma with hearing deficiencies [48]. In 2020, in a large-scale retrospective study involving 15,686 patients over 16 years old, Chien et al. [49] investigated the incidence of glaucoma in patients with hearing impairments. After considering multiple potential risk factors, the study reported sensorineural hearing loss in correlation with an increased incidence of glaucoma. As a recommendation, the authors emphasize routine ophthalmologic examination for glaucoma detection in individuals with previous sensorineural hearing events.

In our study, female cases from urban areas, aged over 65 years, predominated in the study group. The mean age in the Study group was significantly higher compared to the Control group (63.69 vs 58.92 years; $p=0.05$). The mean age of both groups falls within the age range where age-related hearing dysfunction can occur due to changes in the inner ear. Presbycusis (age-related hearing loss) is multifactorial, involving genetic mechanisms, aging, oxidative stress, cochlear vascular changes, and environmental factors (such as noise, tobacco, alcohol, ototoxins) [50,51]. There is no universally accepted definition of hearing impairment or a universal scale for hearing loss.

In the Study group, there were more female cases over 65 years old from urban areas with a high educational level. The influence of the education level seems important, especially during the recruitment process when explanations regarding the study in general, necessary maneuvers, and the role or purpose of the study are more easily understood and accepted.

Regarding patients in the study group compared to the control group, the mean levels of PTA, disc-to-cup ratio in both eyes, and the vertical C/D ratio in both eyes were significantly higher on the left side. The mean level of RNFL thickness, both average and superior, was slightly lower in patients with glaucoma. Multivariate analysis demonstrates that sex can be a good predictor of C/D ratio and superior RNFL in the left eye and IOP in the right eye; sex and age can be good predictors of PTA values in both ears and the C/D ratio in the right eye, and sex, age, and environment of origin can be good predictors of disc area in the left eye. Structural changes precede functional changes in the optic nerve, a fact confirmed by existing literature [52]. Interestingly in this study, the impairment is more pronounced on the left side and less evident on the right side. One thought might involve the lateralization of cortical and subcortical functions, potentially providing an explanation in this regard.

The mean PTA was higher in the Study group: PTA in the right ear ranged from 0 to 30 dB, with a mean level of 16.21 dB ± 7.14, and PTA in the left ear ranged from 5 to 52 dB, with a mean level of 19.29 dB ± 10.87. These higher PTA values signify hearing loss according to the ASHA classification [53], categorized differently based on PTA values. Multivariate analysis shows that sex and age can be good predictors of bilateral PTA. Additionally, a direct correlation was observed between PTA values as an assessment of auditory function and the vertical C/D ratio and RA as elements defining the optic nerve's structure. An indirect correlation was observed with RNFL values, which reinforces the hypothesis of a connection between the two visual and auditory deficits. It is worth noting that these correlations were identified predominantly on the left side. Moreover, PTA values are correlated in both ears with age, a fact acknowledged by the existing literature [54].

The analysis of mean hearing values in the right/left ear shows that for higher frequencies in the Study group, there is an increase in sound intensity required for perception on the audiogram: for 4 kHz, in the right ear, 40.94 vs 29.17/left ear 46.25 vs 27.17; for 8 kHz, the values are significantly higher in the Study group: in the right ear, 56.56 vs 30.83/left ear 56.56 vs 27.92. Obviously, the sound intensity at higher frequencies is higher in glaucoma patients, which, according to the literature, signifies hearing loss for these frequencies. Although specialized literature defines these changes as age-related hearing losses, in the presented scenario, the values are different for similar age groups, living environment, and activities [53,54].

The mean level of average RNFL thickness was slightly lower in patients with glaucoma, but the mean level of rim area was significantly higher in the control group for both the right eye (0.89 vs 1.42) and left eye (0.93 vs 1.17). Corneal thickness values do not significantly correlate with auditory changes quantified by PTA.

A direct connection can be observed between the structure of the optic nerve (vertical C/D ratio, RA, and average RNFL thickness) and auditory nerve function (PTA values). By plotting the ROC curve, the specificity and sensitivity balance as a prognostic factor, the following parameters were identified as good predictors for glaucoma in the right eye: C/D ratio, with a sensitivity of 75% and specificity of 58.3% (AUC=0.753; 95% CI: 0.569-0.937; p=0.024); RA, with a sensitivity of 87.5% and specificity of 58.3% (AUC=0.862; 95% CI: 0.725-0.999; p=0.001); and PTA in the right ear, with a sensitivity of 81.3% and specificity of 58.3% (AUC=0.732; 95% CI: 0.542-0.922; p=0.039). For the left eye, the following parameters were identified as good predictors of glaucoma by plotting the ROC curve: C/D ratio, with a sensitivity of 75% and specificity of 42% (AUC=0.734; 95% CI: 0.550-0.919; p=0.037); RA, with a sensitivity of 75% and specificity of 50% (AUC=0.763; 95% CI: 0.588-0.938; p=0.019); and PTA in the left ear, with a sensitivity of 75% and specificity of 50% (AUC=0.745; 95% CI: 0.562-0.928; p=0.029). Through the performed analyses, a direct connection can be observed between the structure of the optic nerve (vertical C/D ratio, RA, and average RNFL thickness) and auditory nerve function (PTA values).

Two elements are intriguing in the study: the appearance of changes in PTA values in both ears, together with correlations in the optic nerve's structure only on the left side, and the possibility of issuing predictive factors from a statistical point of view in both eyes within the study group. The mean PTA level was higher in the Study group. It's worth mentioning that all study participants exclusively used their right hand, allowing for speculation about a possible cortical explanation.

Chapter 6. Study II – Dynamics of Association between Visual and Auditory Functional Changes in Glaucoma

Dual sensory loss affects cognitive function more than unilateral loss of vision or hearing [5–9], as these two functions are interconnected in the brain. Patients with Primary Open-Angle Glaucoma (POAG) may have alterations in other neurosensory organs, such as hearing loss [55], making the study of both sensory systems extremely interesting and useful.

The aim of this study is to establish correlations between functional impairment in glaucoma and auditory impairment, elements that could enhance the diagnostic and treatment algorithm. Evaluating visual function is a crucial element in managing the diagnosis of glaucoma. In the conducted study, we prioritized assessing visual function by analyzing visual parameters rather than auditory ones because specialized literature indicates that peripheral involvement in glaucoma significantly influences quality of life, known cases with considerable peripheral visual field deficits while maintaining central visual acuity [52].

The study protocol included ophthalmological examinations, imaging, and ear examinations. Patients were evaluated over a 6-month period from enrollment, but the clinical parameters introduced into the study for analysis were those evaluated at enrollment: Mean Deviation (MD), Profile Slope, Central Hemi-Visual Field (CHVF) elements, and PTA values.

The demographic analysis of patients in this study shows a higher proportion of female patients (81.4%) compared to male patients (28.6%). Statistical analysis shows a high percentage of patients with moderate to high education (high school, university – 71.4%) in the studied groups. In this sense, it can be said that female patients were more compliant, and perhaps the higher level of education made it easier for them to participate in the study. Additionally, the increased number of functional investigations (visual field tests, audiograms) and brain MRI further reduced the acceptance rate beyond the restrictive inclusion criteria, justifying the small number of participants included in the study. Analyzing the area of origin, it is noted that the majority are from urban areas compared to those from rural areas (82.1% versus 17.9%). Each patient’s evaluation had to be conducted through functional tests where cognitive ability acquired through experience and personal exercise played a key role. As a primary conclusion resulting from the demographic analysis, it can be observed that women seek medical attention more rapidly and frequently, the urban origin combined with the higher level of education facilitated the performance of functional tests that require understanding and compliance from the patients. Additionally, origin and educational level are important anamnestic elements regarding the risk of developing hearing disorders due to various professional activities. Within the analysis, none of the patients in the study group reported working in environments characterized by noise pollution that might have led to professional hearing impairment or ototoxicity.

The results analysis of the functional clinical parameter evaluation highlighted variations in the expected visual field parameters in glaucomatous disease.

The correlations between the functional evaluation of the optic nerve and the auditory nerve are quite interesting. Following statistical analysis, an indirect correlation was observed at the right eye (OD) level, which was reduced in intensity between visual parameters: MD ($r= -0.108$; $p= 0.585$), CHVF ($r= -0.268$; $p= 0.168$), and Profile Slope ($r = -0.297$; $p= 0.1$) and PTA in the right ear. At the left eye (OS) level, the parameters MD ($r= -0.584$; $p= 0.001$) and Profile Slope ($r= -0.377$; $p= 0.048$) correlate indirectly, moderately, yet significantly with PTA in the left ear and to a lesser extent with CHVF ($r = -0.147$, $p = 0.456$).

Thus, the decrease in sensitivity from the center to the periphery of light, together with the overall loss of sensitivity to visual stimuli, are elements associated with decreased sensitivity to bilateral auditory stimuli, but more significantly on the left side.

The observed correlations could be explained by examining the embryological origin, anatomy, and physiology of visual and auditory pathways, as well as the somatotopic distribution of optic nerve fibers. Embryologically, the optic and auditory nerves have a common origin from the neuroectoderm [56]. In the central nervous system, there are neural circuits responsible for receiving afferent impulses, processing information, and generating other efferent responses. Considering all the complex connections between primary, secondary, and cortical association areas where visual and auditory information are processed, connections between changes in optic and auditory nerve function become possible. Brain neuroconnectivity [12] could explain many of the connections between the visual and auditory analyzers.

Although the working hypothesis is innovative, the study presents limitations that could be overcome in the future. The small number of included patients, conducted at a single study center, the cross-sectional aspect, short follow-up period, strict inclusion criteria resulting in few enrollments. Additionally, in this study, patients with mild glaucomatous impairment were included, and therefore, future studies might consider groups with different levels of glaucomatous impairment but still allowing for the proposed functional evaluations.

Chapter 7. Study III – Hypothesis of Structural and Functional Reorganization at the Cortico-Thalamic Level under Conditions of Acquired Visual Information Deprivation: Correlations between Results Obtained from Conducted and Existing Studies

The working hypothesis in this study was to evaluate the structural and functional aspects of the visual and auditory systems to observe whether the results obtained show a level of interrelationship. Obtaining statistically significant correlations predominantly on the left side of both analyzers generated new questions whose answers would justify this interrelation between the two analyzers and their causality. Considering that these elements were identified only unilaterally and all affirmatively affected patients are right-handed users, we considered the possibility of these changes occurring on the opposite side of the used hand as a consequence of cortical and subcortical lateralization processes. These are innovative elements regarding glaucomatous disease, explained by the immense and incompletely studied capacity of the human brain to develop connections throughout life through intense learning processes.

Descriptive data of Pure Tone Audiometry (PTA) in both study groups show mean values of 16.21±7.14 for the right ear and 19.29±10.87 for the left ear. Correlation analysis between the right ear PTA and age, vertical C/D ratio, mean RNFL in the OD indicates that the right ear PTA correlated significantly, directly, moderately with age (r= 0.629; p= 0.001), but the right ear PTA did not significantly correlate with vertical C/D ratio (r= 0.013; p= 0.946) or mean RNFL (r= -0.112; p= 0.570). The correlation of the right ear PTA was indirect, reduced in intensity, both with MD (r= -0.108; p= 0.585), Cal HOV (r= -0.268; p= 0.168), and Profile Slope (r= -0.297; p= 0.1).

Correlations between the left ear PTA and age, vertical C/D ratio, mean RNFL in the OS show that the left ear PTA correlated significantly, directly, moderately with age (r= 0.445;

p= 0.018), vertical C/D ratio (r= 0.434; p= 0.021), and mean RNFL (r= -0.438; p= 0.020). The correlation of the left ear PTA was indirect, moderately intense, statistically significant with both MD (r= -0.584; p= 0.001) and Profile Slope (r= -0.377; p= 0.048), and reduced in intensity with Cal HOV (r= -0.147; p= 0.456).

In conclusion, statistically evident correlations emerged between the visual and auditory structural and functional aspects on the left side. Furthermore, in a statistical analysis dedicated to these parameters, the results confirmed the lack of strongly supported connections on the right side. In the right ear and OD, multivariate analysis through the linear regression model highlights that 37% of the PTA value can be explained by age, vertical C/D area, mean RNFL, MD, and Cal HOV (R adjust = 0.370; p=0.146). In the left ear and OS, the linear regression model indicates that 49.6% of the PTA value can be explained by age, vertical C/D area, mean RNFL, and MD (R adjust = 0.496; p=0.01), and 60.2% of the PTA value can be explained by age, vertical C/D area, mean RNFL, MD, Cal HOV, and Profile Slope (R adjust = 0.602; p=0.01) with statistically significant values. The results statistically confirm the working hypothesis.

Based on the established interrelationships between the analysis of all evaluated clinical parameters in Study III, we formulated a hypothesis regarding a possible structural and functional reorganization at the cortico-thalamic level under the conditions of acquired deprivation of visual information due to optic nerve injury caused by glaucoma during life.

This highly complex process involves several structures related to the midbrain: SC/SI and thalamus: LGN, MGN, and the pulvinar nucleus. The SC is a midbrain structure involved in integrating visual, auditory, and somatosensory information necessary to initiate motor commands, playing an important role in integrating multimodal signals. Neurons at this level transmit information in local networks involved in various behavior-related responses. SC receives sensory information and forms cognitive maps related to multiple behaviors. Neurons in different layers process visual, auditory, and motor information, which are then transmitted to the cortex, contributing to various native or learned cognitive behaviors. Consequently, SC is involved in visual information processing, sensorimotor integration, spatial orientation, selective visual attention, and decision-making.

The engagement of both the visual and auditory analyzers involves not only diagnosis but also appropriate therapeutic approaches. Considering the neurodegenerative origin of glaucoma and validating the correlations between visual and auditory functional impairment in glaucoma, we consider the administration of neuroprotective therapy in glaucoma to be both opportune and necessary. Alongside topical medication for reducing intraocular pressure patients included in the presented studies received two neuroprotective medications: EGC 135mg/day and 245mg/day of citicoline. Their selection was justified by several scientifically proven criteria: EGC, besides its antioxidant and anti-inflammatory role in the retina, also acts hypotensively by reducing UA production, while citicoline, with its membrane protection function, acts on all neuronal structures involved from the retina to auditory pathways and cognitive function.

This general context highlighted by the studies presented here aims to provide a possible explanation for the results obtained in the studies conducted in this doctoral thesis. However, improving the study’s design and increasing the number of participants involved, even transforming this study into a multicenter study, could enrich the information and conclusions drawn from the data analysis.

Chapter 8. Conclusions and personal contributions

Glaucoma is a slow progressive optic neuropathy characterized by irreversible damage to retinal ganglion cells (RGCs), leading to visual field loss and characteristic changes in the optic nerve. The condition involves multiple etiopathogenic mechanisms, yet Intraocular Pressure (IOP) remains the only measurable and modifiable risk factor in the disease course. Despite stabilized IOP, the disease’s progression has led to the hypothesis that there are other pressure-independent mechanisms influencing its evolution.

The total loss of vision turns this condition into a public health issue, justifying the relentless global research interest in various aspects of the disease: etiopathogenesis, diagnostic algorithms, and innovative medical and surgical therapies. One intensively studied theory in recent years suggests that glaucoma is a neurodegenerative disease sharing similarities with known neurodegenerative conditions.

Building upon understanding of the involvement of both peripheral and central nervous pathways in glaucomatous disease, this doctoral research aims to evaluate glaucoma from a different perspective – assessing the structural and functional aspects of the two vital sensory systems: visual and cognitive functions.

The goal of the performed tests is to establish associations between retinal changes quantified by direct structural evaluation of the optic nerve and retina using Optical Coherence Tomography (OCT), functional evaluation of the optic nerve through computerized perimetry, and auditory pathway functional analysis through audiograms.

The results are promising, encouraging further research on larger, multicenter populations and at different disease stages. If these studies confirm our hypotheses, it could lead to a comprehensive, interdisciplinary approach both for glaucoma patients and those with unexplained hearing loss due to non-organic causes.

In the first study, patients with Primary Open-Angle Glaucoma (POAG) showed hearing alterations assessed by audiometry correlating with ophthalmologic parameters, indicating that the auditory system can be affected in POAG. The structural assessment of the optic nerve along with auditory functional analysis might establish correlations improving the glaucomatous disease diagnostic algorithm to detect the disease at its earliest stages for better quality of life in glaucoma patients.

The second study focuses on both visual and auditory functions. Associating changes in visual parameters like Contrast Visual Acuity (Cal HOV) and the profile of light sensitivity from the center to the periphery with auditory values from the same side might be explained embryologically, anatomically, and physiologically, based on functional and structural analysis of visual and auditory pathways. However, the final conclusions might be improved due to the study's limitations.

The third study establishes correlations between clinical structural and functional, visual, and auditory parameters. These modifications and associations should be viewed in a comprehensive context together with the evaluation of the optic nerve structure and its changes in glaucoma, opening new opportunities and longitudinal design approaches to track these parameters over time. Considering that both visual and auditory systems are involved in ensuring quality of life, a prospective dual evaluation – ophthalmologic and auditory – for patients consulted by ophthalmologists for glaucoma and those evaluated by otolaryngologists for hearing loss without organic causes could be beneficial.

Ensuring quality of life remains the primary objective as the global aging trend implies an increased number of diagnosed glaucoma patients. The advantages of these studies lie in the use of routine investigations in ophthalmology and otolaryngology practices, with the caveat that if MRI examination is involved, economic considerations may hinder the study's future development.

The main limitation of both studies was the low number of involved patients and volunteers, attributable to multiple reasons. Based on the experience gained from conducting these studies, reevaluating the design towards a longitudinal, multicenter study involving glaucoma patients at different disease stages, with well-established follow-up protocols, might be beneficial.

Once again, the research information confirms the idea expressed by Felix Lagrange in 1922 that the eye with glaucoma is "a sick eye in a sick body." The most important conclusion drawn from these studies is the rreiteration of the interdisciplinary nature of glaucomatous disease. The extensive implications of all utilized investigations, specialized literature from different medical fields, pose both a challenge and a contribution to a different approach to glaucoma.

Personal Conclusions and Contributions:

1. Role of Pure Tone Audiometry (PTA) values in the diagnostic algorithm - the correlations between elevated PTA values and characteristic glaucomatous values make audiometry a useful test in glaucoma patients.
2. If clinically and diagnostically detectable PTA/hearing loss exists without organic causes, ophthalmologic examination is advisable.
3. Role of PTA in staging glaucomatous disease: in perspective, PTA values could be correlated with the stage of glaucomatous disease.
4. Cerebral interconnectivity – role in bilateral involvement (due to central anatomical distributions and crossings at the visual and auditory analyzer levels) and expressed clinically through bilateral impairment of visual parameters, recommending rigorous

bilateral clinical and functional ophthalmologic and auditory examination.

5. The frequent nature of examinations allows for their consideration as defining elements of glaucoma.
6. Correlations between PTA values and IOP values reinforce the role that IOP plays, both directly and indirectly.
7. From the demographic analysis conducted in the two studies, a predominance of female participants in both the study and control groups was observed. Additionally, there was a high level of education. Consequently, it is advisable to evaluate health education possibilities in the general population as the likelihood of undiagnosed glaucoma and hearing-impaired patients is high.
8. Dual involvement of the visual and auditory analyzers requires, besides diagnosis, an appropriate therapeutic approach. Starting from the neurodegenerative origin of glaucoma and validating the correlations between visual and auditory functional impairment in glaucoma, neuroprotection is considered an opportune and necessary administration in glaucoma.
9. Neuroprotection has a dual role on both RGCs and the neuronal component of hearing. In this context, neuroprotection is considered an adjunctive therapy in glaucoma that should accompany any type of applied treatment, both medical and surgical.
10. Patients included in the studies presented in this doctoral thesis received, alongside topical medication for reducing IOP, two neuroprotective medications: EGC 135 mg/day and 245 mg/day citicoline. Their selection was justified by several scientifically proven criteria: EGC, besides its antioxidant and anti-inflammatory role in RGCs, also acts hypotensively by reducing UA production, while citicoline, with its membrane protection function, acts on all neuronal structures involved from RGCs, neurons in auditory pathways, to cognitive function.
11. Neuroprotective medication diversity includes substances like resveratrol and curcumin (natural polyphenols with antioxidant effects), lutein and zeaxanthin (natural carotenoids with antioxidant roles), NAD (direct mitochondrial effect), Ginko Biloba extract (vasodilator), Coenzyme Q10 (antioxidant). The choice of neuroprotective agent should align with the patient's general condition and comorbidities.
12. IOP reduction through various methods (medical, laser therapy, or surgical) has been shown to be insufficient in preventing the progression of neuronal damage. The supported neurodegenerative nature of glaucoma, including in this doctoral thesis, makes neuroprotection an integral part of glaucomatous disease treatment.

13. The final conclusion of this thesis is that:

Glaucoma is a neurodegenerative disease that substantially involves the entire nervous system, with dual sensory impairment, requiring a mandatory complementary approach of a neuroprotection and dynamic, multidisciplinary patient evaluation.

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