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Relation between Primary Open Angle Glaucoma and Neurodegenerative Diseases-A Case Control Study

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Introduction

Glaucoma is nowadays considered as a disease of optic nerve where in it is susceptible to damage from many factors. The nerve is susceptible to the existing IOP, or `the damage can be due to IOP independent mechanisms. The damaging IOP can be much lower than the statistical normal range .The seemingly non IOP dependent damage seen in some patients even after control of the IOP factor, made us think about other alternative pathogenesis factors and this concept of Normal Tension Glaucoma has influenced our understanding of glaucoma, resulting in elimination of IOP from the diagnostic criteria of POAG.

Neurodegenerative (NDD) disease was accidentally discovered to have an association with POAG when Chandra et al[1] found an increased incidence of POAG in the death registry record of people with dementia. The association was seen consistently in a few subsequent observational studies. Research also suggests common pathogenesis and terminal cellular events (apoptosis) in both.

Understanding POAG is important considering its prevalence, silent nature, and grievous impact on vision which is undetected until late. Ideally to manage such a problem we have to screen the population. Early diagnosis of glaucoma is difficult in population screening which needs a comprehensive evaluation involving technology. So population screening is not considered cost effective in POAG at this point of time[2]. A practical approach would be screening of the target groups considering the risk factors[3].It will also help us find out the pathogenetic mechanisms, invent newer interventional strategies and preventive measures.

In diagnosed cases of POAG especially with normal tension the factors that predict progression is another mystery to be unrevealed. Reasonable association is known to exist between POAG and age & family history especially in certain racial groups .Old age, disc hemorrhage, bilateral disease and advanced disease at diagnosis are few factors noted to cause progression. What more in the list? .Can NDD considered a risk factor for POAG? or is it vice versa? The road ahead has to elucidate its exact cause.

Glaucoma and Neurodegenerative diseases show selective loss of neurons in excess of normal aging process and they share the common risk factors like age and positive family history. Because neurons from various CNS regions share many common properties and glaucoma has reported associations with other neuro degenerative diseases[4] pathogenetic mechanism can be similar in Neurodegenerative diseases and Glaucoma. Present knowledge warrants an alertness[5]towards the issue. Hence this study investigates an association between the two.

Aim of study

The aim of the study was to find the proportion of Primary Open Angle Glaucoma cases in Neurodegenerative Diseases.

Review of Literature

Current status of Glaucoma

Magnitude of Glaucoma Worldwide

As evident from the statistics glaucoma is a major public health problem. Blindness prevalence for glaucoma is 8 million of which 4million is caused by POAG alone. Glaucoma is the leading cause of irreversible blindness worldwide accounting for 15% that is, the second most common cause of blindness after Cataract[6,7]. In 2006 Quigley et al estimated the number of people with POAG worldwide from population based surveys. The estimated number was about 60 million persons by 2010.The calculated incidence of POAG is 2.4 million per year[7]. Glaucoma is a chronic disease of aging population. More than fifty percent of the disease remains undiagnosed due to its asymptomatic nature. Therefore the number of POAG patients is estimated to increase by 50% by 2020 in US and a higher proportional increase is expected in India also[6].

Magnitude of Glaucoma in India

Majority of people with POAG are estimated to be under diagnosed in India and the estimated number is 12 million[6].By 2020 this number is expected to increase to 16 million[8]. The reported prevalence of POAG varies between 1.62 and 3.51% from the various populations based studies. The regional prevalence is given in Table 2.1.As the major element of Glaucoma diagnosis is by case detection in developing countries, more than 90% Glaucoma remain undiagnosed[9,10]. Thomas et al[11] reported a 3.5% per year conversion of persons with ocular hypertension to POAG.

Table 2.1 Prevalence of Glaucoma in different studies in India

Studies (n)	Mean Prevalence	Age specific Prevalence			
		40 to 49	50- 59	60- 69	> 70
APEDS[10], 934	369	1.27	2.31	4.89	6.32
ACES[12], 5150	1.7	0.34	1.57	1.83	2.88
CGS Rural[13, 14], 3924	1.62	0.63	1.62	2.58	3.25
CGS Urban[13], 3850	4.08	2.26	3.57	4.08	6.42
WBGS[15], 1269	2.99		2.55	2.69	4.76

Risk factors

POAG is a disease of multifactorial causation, most of which or at least some of them are unidentified yet. Identifying risk factors is important because this information maylead to development of strategies for disease screening and prevention. It may be useful in identifying persons who need attention and followup.A risk factor precedes disease occurrence.

Demographic Risk Factors for POAG

Age

Among the risk factors reported increasing age was a consistent risk factor for POAG across all studies[9, 13, 14, 16]. In the Baltimore eye survey[17], the prevalence of glaucoma among whites was 3.5 times higher for individuals in their 70s than for those in their 30s.Among blacks the ratio was 7.4.Further Ocular Hypertension Treatment Study[18] confirmed on this. In India, the CGS (urban)[13] showed 5 times more risk in >70 year

age group. The collaborative initial treatment glaucoma study[19] found that visual field defects were 7 times commoner in >60 age group than in 40s. Although IOP was found to increase with ageing in many populations, studies in Japan showed a relation between glaucoma and age even without an increase in IOP with age in that population. This proves that age is an independent risk factor. POAG being a chronic disease the number increases due to increase in cumulative number of persons with the disease.

Race

In a metaanalysis of 46 population based studies, by Rudnicka et al[20] the pooled prevalence estimate for POAG is 1.4% in Asians, 4.2% in blacks and 2.1% in whites. POAG was found to be more prevalent in blacks and more aggressive in them with a younger age of onset, more advanced at the time of diagnosis, and blindness from glaucoma is 4- 8 times commoner in them than in white patients. Blacks have thinner corneas and larger baseline vertical cup to disc ratios[16].

Family history

Kassand Becker[18] first observed a strong correlation between family history and glaucoma. Prevalence of glaucoma among siblings of patients is approximately 10% and the life time risk for glaucoma was found to be 10 times more for first degree relatives of glaucoma patients compared to normal population[21]. The Baltimore eye survey[17] found 3.7 fold increased incidence in individuals with a sibling having POAG. Precise mechanism of inheritance is not clear probably polygenic inheritance with or without environm-ental influences may play a role in causation.

Gender

No consistent association with POAG and gender has been reported.

Ocular risk factors

IOP

Large epidemiological studies indicate that the mean IOP is 16 mm, with a SD of 3mmHg. IOP shows a non Gaussian distribution with a skew toward higher pressures especially after 40 yrs of age. IOP is the strongest risk factor known to be associated with POAG[18.]Higher the IOP greater the risk of damage and progression. The importance of IOP in causing glaucomatous damage is supported by the finding that in patients with asymmetric intraocular pressures, visual field loss is usually more severe in the eye with the higher intraocular pressure[22,23]. Approximately 10% of individuals with persistent OHT will convert to POAG over a ten-year period[24] .It has been proved that lowering of IOP is beneficial for those with POAG in the normal as well as for those with higher IOPs[25, 26].

In most studies 30 to 60% of subjects diagnosed as POAG had an IOP recording in the statistically normal range[10,13,14,15,27,28,29].So a screening based on IOP, may miss up to more than half of cases of glaucoma. Elevated IOP is no longer a criterion for glaucoma diagnosis. General agreement has now reached that for a population as a whole, there exists no clear line between safe and unsafe IOP; some eyes undergo damage at 18mm or less whereas others tolerate 30 mm or more.

In normal individuals IOP varies 2-6 mmHg over 24 hr period depending on aqueous production. A diurnal fluctuation of more than 10 mmHg is suggestive of glaucoma.

Myopia

Myopia was an inconsistent risk factor for POAG as identified by few studies[20].Large discs and abnormalities like tilted discs in myopia are difficult to evaluate for glaucoma. Myopic fundus changes leading to field defects and difficult perimetric evaluation in high refractive errors are some of the other associated problems in glaucoma diagnosis in myopia.

Systemic Risk Factors for POAG

Diabetes mellitus

Studies have reported higher prevalence of diabetes and abnormal glucose metabolism in glaucoma[30,31] inconsistently[32]. Some authorities believe it to be due to small vessel involvement at

optic nerve head making it more susceptible to pressure related damage.

Role of blood pressure and its control:

Positive associations between blood pressure and IOP and between blood pressure and POAG have been reported[31, 32], it was not consistent in many studies[10,13,14,15,16,27].

Systemic hypotension episodes particularly in hypertensives on treatment, while sleeping, has been suggested as a possible cause of decreased optic nerve perfusion resulting in damage[33, 34].Nocturnal hypotension was found to be a risk factor for disease progression[35].

The Baltimore Eye Study investigators examined the relationship between POAG and diastolic perfusion pressure (defined as the difference between diastolic blood pressure and intraocular pressure). They found a significant increase in the rates of POAG for lower diastolic perfusion pressures[32].

Probablerisks

The probable risk factors are Vascular dysregulation, Aberrant immunity,

Glutamate excitotoxicity, Oxidative stress and Genetic factors linked to regulation of apoptosis.

Theories of glaucomatous optic nerve damage:

Site of damage

Although it is unclear whether changes to the ONH are the primary events that precipitate RGC demise or whether glaucomatous RGC death induces events that lead to ONH changes, evidence indicates that IOP induced damage lead to compositional and structural changes at the ONH. Both of these theories of elevated intraocular pressure and impaired blood supply to the optic nerve were proposed in 1858[36]. Heinrich Muller, a German anatomist was the first to suggest that mechanical compression due to elevated intraocular pressure was the cause of glaucomatous damage. Eduard Von Jaeger[37], the ophthalmologist who proposed that eyes with poor vascular supply to the optic nerve head were predisposed to glaucoma. Remarkably, he suggested that optic nerve head ischemia could occur in patients with either elevated or normal IOP.

Mechanical theory

Optic nerve fiber bundles are supported and separated by pores of lamina cribrosa. Within the collagenous beams of lamina cribrosa are blood vessels along with extra cellular matrix components and the retrograde axonal transport of brain derived growth factors (BDNF) contributes to the nourishment ofaxons[38].The lamina cribrosa acts as a conduit for the axons and provide nourishment and some suggests this is the site of optic nerve damage due to IOP. The pores of lamina cribrosa are arranged in an hour glass pattern[39], through which pass the arcuate bundles which are susceptible to glaucomatous damage. The susceptibility may be due to that thinner separating connective tissue septae offer less support and more easily collapse due to IOP[40]. This causes mechanical impingement of axons which also compromises blood flow and delivery of nutrients to axons .Elongated pores in advanced glaucoma may be due to stretching and rupture of the lamina beams[41]which explains the progressive increase in susceptibility to damage in glaucoma. This damaged lamina is demonstrated to bow posteriorly giving the excavated appearance.

Trans lamina cribrosa pressure gradient is a proposed factor to cause this axonal transport blockade which was demonstrated to occur at the level of lamina in experimental studies[42].

Ageing changes in the extra cellular matrixmay offer less support to the axons and glia leading to primary or secondary damage.

Vascular theory

Considerable evidence suggests compromise of microvasculature of optic nerve head in glaucoma. Studies showed epidemiologic association between low diastolic perfusion pressure and POAG[43]. High IOP may stress optic nerve head blood flow and the normally existing autoregulatory mechanism corrects this hypoxia by vaso dilation. In POAG, insufficient auto regulation occur[44,45,46]. Association of normal

tension glaucoma with peripheral vasospasm is also seen.

The vascular theory proponents are further supported by two recent findings. Immunochemistry studies in postmortem human glaucomatous eyes found that the oxygen-regulated transcription activator hypoxia-inducible factor-1 (HIF-1) alpha was upregulated in retinal locations that were highly concordant with the location of the visual field defects recorded in these eyes[47,48]. Endothelin-induced chronic ischemia in monkey eyes elicits optic nerve damage that is non-IOP dependent and results in axon loss that is similar to the damage observed in human glaucoma[49].

Excitotoxicity Due to Excessive Glutamate

Glial cell activation may be an important factor contributing to RGC death in glaucoma[50,51]. Under normal conditions, glial cells support neuronal function through a variety of mechanisms, including removal of extracellular glutamate and synthesis of growth factors and metabolites. The discovery that glutamate is a potent neurotoxin in the late 1950s has led to the term excitotoxicity and the discovery that the vitreous humor of glaucomatous monkeys and man contained elevated glutamate[52] led to the hypothesis that excitotoxicity could be a significant pathogenic mechanism in glaucoma. Excitotoxic cell death also means that injury to neurons or glia make them vulnerable to even normal levels of glutamate when they get over stimulated and die. A selective glutamate receptor blocker, memantine is in the phase 3 trial[53].

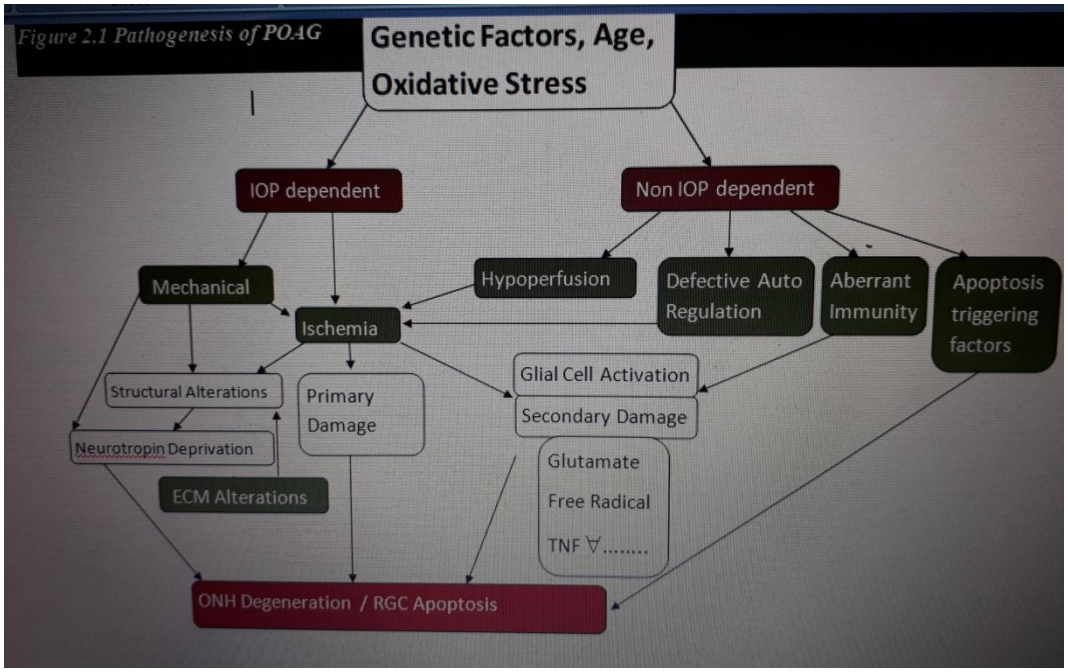
Reactive glial cells can exacerbate neuronal damage through the release of cytokines like TNF ∀[54,55], reactiveoxygen species, or nitric oxide. Various stimuli can initiate astrocyte activation, including demyelination of adjacent axons, ischemia, mechanical trauma, and increased hydrostatic pressure. Reactive astrocytes migrate to the nerve bundles and may form large cavernous spaces through the expression of matrix metalloproteinases possibly by an ischemia reperfusion injury[56]. It is possible that these changes weaken the architecture of the ONH and facilitate the collapse of the lamina cribrosa beams, eventually leading to injury of the RGC axons that pass through these structures.

TNF-∀ is a pro inflammatory cytokine that, when bound to its receptor, can induce apoptosis through acaspase-mediated pathway.

Oxidative Stress and Free Radical Damage

The role of oxidative stress, free radical damage, and mitochondrial function has been studied in various models of glaucoma including man. Mitochondrial dysfunction can trigger apoptosis signaling via activation of the mitochondrial permeability transition pore complex, which is a key regulator of oxidative stress-induced apoptotic cell death[57].

Now that the probable causes of glaucomatous damage are enlisted, the terminal cellular event in glaucomatous process in RGCs is thought to occur by apoptosis[58] - a slow degenerative process that features cell shrinkage, plasma membrane blebbing, nuclear DNA cleavage by endonucleases known as caspases, and cyto skeletal degeneration. The initial evidence for apoptosis in glaucoma was markers of nuclear DNA cleavage. Mitochondrial-dependent apoptosis involves the induction of pro-apoptotic proteins such as BAX that increase mitochondrial membrane permeability; this subsequently promotes activation of the cell executioner caspase enzymes, which in turn activate DNA breakdown. Caspase activation & noncaspase-dependent apoptosis may also be a viable mechanism of apoptosis induction in glaucoma[58,59]. Physiological cell stressors thought to underlie glaucoma may tip the balance between the apoptosis inducing intra cellular signaling proteins called BAX and anti apoptotic proteins called BCL. The stress conditions of neurotrophin deficiency ,oxidative stress and inflammatory cytokines impinge on cell fate by affecting the BAX/BCL “thermostat”or via different signaling cascades.



Glaucoma diagnosis

The current definition of POAG

American Academy of Ophthalmology (AAO) in 1996: "a multifactorial optic neuropathy" with "a characteristic acquired loss of optic nerve fibers"; the definitive characteristics of glaucoma are based on visual field loss or the appearance of the disc or retinal NFL.

Early or mild glaucoma is characterized by optic nerve abnormalities with normal visual fields[60]. Thus, visual field defects are no longer part of the case definition of glaucoma.

Moderate glaucoma is defined as visual field abnormalities in one hemifield, not within 5° of fixation.

Severe glaucoma involves visual field abnormal-lities in both hemifields or loss within 5° of fixation.

Operational definition of glaucoma proposed by Foster et al[61]: for population based surveys evaluate a set of criteria's which include: Category1- structural and functional evidence. Category 2- advanced structural damage with unproved field defect .Category 3- poor visual acuity with IOP >99.5th percentile of normal with evidence of glaucoma surgery or medication.

Glaucomatous optic neuropathy

It is the sine qua non of all forms of glaucoma. Structural optic nerve changes precede detectable functional loss. A change in appearance of the optic nerve can be the first sign of glaucoma in a patient. Thus a stereoscopic view of optic disc with systematic assessment to recognize characteristic features of glaucomatous optic neuropathy prevents any glaucoma from being missed[62, 63].

Histologically early glaucomatous cupping consists of loss of axons, blood vessels and glial cells. Loss of tissue seems to start at lamina cribrosa and is associated with compaction and fusion of the laminar plates which is most pronounced at the superior and inferior poles of the disc.Tissue destruction in more advanced glaucoma extends behind the lamina cribrosa and the lamina bows backward .Then the optic nerve head takes on an excavated and undermined appearance like a bean pot.

Evaluation of Optic Nerve Head

Normal optic nerve head

The ONH is composed of retinal ganglion cell axons, blood vessels, glial cells, and other support tissues. The axons, traveling in the retinal nerve fiber layer (RNFL) gather together from throughout the retina in the ONH .Approximately 1.2 million nerve fibers pass through the ONH, organized into bundles passing through the lamina

cribrosa, which provides the structural support to the neural tissue. The total number of nerve fibers passing through the ONH is related to the disc size, with larger discs composed of more fibers than smaller discs. The typical healthy disc is oval in shape with the long axis vertically oriented. The average diameter of the disc is 1.5 mm and average disc area is 1.8 mm^2. The two main structural components of ONH are: the neuroretinal rim (NRR) and the optic disc cup.

The neuro retinal rim(NRR): Therim is the location of all axons and pink in color .The typical configuration of the rim is, the thickest area is in the inferior quadrant followed by the superior, nasal, and temporal quadrants (ISNT rule)[64].

The ONH cup: is the space devoid of any axons. It is oval shaped and centrally located in healthy eyes with the long axis horizontally oriented. In eyes with a larger ONH, the cup can be larger than in eyes with a smaller disc .The spatial distribution of the fibers is organized so that the main arcuate bundles of the RNFL enter through the poles. The central retinal artery and vein enter the eye at the center of the ONH and divide into their branches while still within the optic disc area. Circumlinear vessels that leave the central blood vessels' lie superficially supported by the rim tissue at the edge of the cup. This typical shape of the ONH described can vary markedly between subjects.

Systematic Approach to Disc Assessment

Since 1960's Armaly's cup disc ratio was used for quantitative evaluation of disc. As it does not take into account the disc size, misdiagnoses were common.

Disc Damage Likelihood Score (DDLS)

Brought forth by Spaeth et al[65] in 2002(Appendix-1) to incorporate the effect of disc size and focal rim width into a clinical grading scale. It is highly reproducible and reliable[65]. It correlates strongly with degree of field loss[66]and correlates with the HRT-2 for distinguishing between normal and glaucoma or glaucoma suspects.

The DDLS relies on the optic nerve appearance as a direct indicator of disease. The system categorizes the disc as small (<1.5mm), medium (1.5-2.0mm) or large (>2.0mm). This ensures that the disc size is measured thereby reducing misclassification bias based on disc size.

Disc size can be measured using a fundus lens at the slit-lamp. A slit beam is directed onto the disc and the graticule at the top used to reduce the height of the beam until it corresponds in size to the disc. The lens used will determine the correction factor. A 66D gives the exact measure from the graticule. Correction factors for the other lenses are Volk60D-0.88, 78D-1.2,90D-1.33
Nikon - 60D-1.03, 90D-1.63.

The next stage is to measure the radial width of the thinnest part of the rim. The examiner evaluates the rim throughout its entire circumference in order to identify the area of greatest thinning. The measurement is expressed in rim: disc. Where there is no rim present at the thinnest point the value is 0. The circumferential extent of rim absence is then measured in degrees. A sloping rim is not taken as an absent rim.

Each grade is assigned a numerical value so the system can then be used in research settings to determine severity or degree of progression. Paying attention to the 5 R's: a concept created by Robert N Weinreb MD[67] can be utilized to further enhance the reliability of disc assessment by stereoscopic disc and the nerve fiber layer examination[68,69].

The Scleral Ring (optic disc size) - Vertical and horizontal cup disc ratios are noted. The margin of cup is delineated by the bending of the disc vessels. In general, a CDR of 0.7 in average disc or an asymmetry > 0.2 between disc could be glaucomatous.

The Neuroretinal rim evaluation (NRR) - Its thickness, color and contour should be compared in all 4 quadrants. Glaucomatous damage may be diffuse, focal or a combination. Diffuse damage results in enlargement of the cup with generalized rim thinning. Focal damage results in localized loss of NRR called a notch and it is highly suggestive of Glaucoma. A pale NRR suggests causes other than Glaucoma. In the evaluation of

glaucomatous disc damage it is the contour cup that is of relevance and not the colour cup.

Retinal and Optic Disc Hemorrhages - A splinter hemorrhage on the disc surface usually in the superotemporal or infero temporal rim are at high risk for developing glaucomatous progression.

Retinal nerve fiber layer defect - Examined with red free light through a dilated pupil. Wedge shaped defects of absent nerve fiber layer striations extending up to the disc are typical of Glaucoma. Advanced stages show diffuse atrophy of nerve fiber layer.

Peripapillary atrophy - Peripapillary atrophy in the beta zone is seen more in glaucomatous eye and it is found to be progressive in glaucoma[70].

Limitation of DDLS

Optic nerve heads come in many shapes and forms. No method of classification will fit all of these different patterns and forms. The DDLS cannot be used to evaluate a congenitally anomalous disc. Myopic discs may be difficult to grade. It is unwise in such situations to use any of the standard systems, such as cup/disc ratio, HRT evaluations, OCT evaluations, or the DDLS.

Another problem with the DDLS is that a disc may show progressive damage by having a continuing generalized narrowing of the neuroretinal rim, but not have an increase in the circumferential extent of rim absence. In such a situation the disc would unquestionably have become worse, but the DDLS score will not change. It takes some effort to learn to administer the tool.

Correlation of Field with Optic Disc

The disc finding and its attendant retinal nerve fiber layer change has to be correlated with the field abnormality which is the functional loss in glaucoma. Field evaluation by perimetry is a subjective test and is influenced by a number of factors .It is a difficult task in patients with poor vision, elderly, patients with physical or psychological disabilities. Even in healthy individuals there exists a learning curve before a reliable field is obtained. A good baseline field is obtained by repeated tests at short intervals and the results should be reproducible to diagnose the disease or its progression. Single study of disc or field has very poor sensitivity and specificity[71].

If correlation with field and optic disc is lacking, other causes should be considered like: Ischemic optic neuropathy[72], Demyelinating / other neurologic disease, Optic nerve or Chiasmal compression.

Features to note here are, shallow cupping ,pallor more impressive than cupping ,pattern of field loss not characteristic of glaucoma(it respects vertical meridian), location of cupping or thinning does not correspond to the location of visual field defect, progression of field loss seems to be excessive.

Normal Tension Glaucoma

Open angle glaucoma with IOP in the statistically normal range. The concept of NTG has influenced our understanding of glaucoma, and has resulted in elimination of IOP from the diagnostic criteria of POAG. It lead to the thought that other risk factors, most of which are currently unknown may play an important role in its causation. Drance SM[72] and coworkers described 2 forms of NTG (1) a non progressiveform, which is usually caused by a vascular shock(2) a more common progressive form probably resulting from chronic vascular insufficiency of the optic nerve head.

Features of NTG[73] arenormal IOP, Abnormal peripapillary changes, Disc splinter hemorrhages, features of vascular dysregulation and not just simple ischemia[74,56] as evidenced by history of migraine headaches, vasospasm in reaction to stress or cold, Family history of glaucoma. Systemic diseases associated with NTG are vasospastic phenomena like migraine and Raynauds phenomenon, vascular diseases like myocardial infarction, dyslipidemia, carotid artery disease, nocturnal hypotension, vascular dysregulation, shock, autoimmunity, diabetes mellitus, obstructive sleep apnoea syndrome.

Neuro degenerative diseases and their pathogenesis

Alzheimer's disease

Alzheimer's disease is the commonest dementing illness. It is a gradually progressive disorder of recent episodic memory, language, visuospatial functions and executive functions. Brain atrophy with the presence of amyloid and neuritic plaques and neurofibrillary tangles are the primary pathological features of AD. AD may be familial. Autosomal dominant AD has been traced to have genetic mutations[75]in 3 genes, namely, Amyloid Precursor Protein (APP) and the Presenelin 1 &2 (PS-1,PS-2) genes. The role of genetic risk factors for the more common late onset sporadic disease is the subject of intense research. Inheritance of the E4 allele of the apoprotein(Apo E) gene remains the most established genetic risk factor for AD.

Parkinson's Disease

Many of the neurodegenerative movement disorders share the property of neuron damage caused by the accumulation of proteins that have toxic effects. The most striking pathological change in PD is in the Substantia Nigra of the midbrain. The microscopic changes include neuronal loss, gliosis, and the presence of cytoplasmic inclusions called Lewy bodies in surviving neurons. The actual role of the aggregate remains a mystery. However potential mechanisms of neurodegeneration related to the aggregates include interaction of the mutant protein with the wild type protein, interaction with other proteins including transcription factors, caspase activation, apoptosis, interference with mitochondrial function, oxidative stress and microglial activation[76].

Parkinsons Plus Syndrome

The Parkinson Plus Syndrome includes Progressive Supranuclear Palsy (PSP), Multi system Atrophy (MSA) and Cotico Basal Degeneration (CBD).

PSP is characterized by vertical supranuclear ophthalmoplegia, axial rigidity, pseudo bulbar palsy, mild dementia and progressive worsening of balance with frequent falls. The degenerative process involves the midbrain, basal ganglia and diencephalon. Pathological findings include neuronal loss, gliosis and the typical neuronal lesion- globose neurofibrillary tangle. PSP almost always occur sporadically, an increasing number of familial cases suggest a genetic etiology in some cases. There is growing support for the notion of altered regulation of tau gene expression in PSP.

CBD is a Parkinsonian Plus Syndrome characterized by asymmetrical rigidity, apraxia, dystonia, tremor, clumpsy useless limb, alien limb phenomenon, myoclonus and cortical sensory dysfunction. Typical microscopic changes are tau positive neurons and glial lesions especially grey and white matter astrocytic plaques, thread like lesions and neuronal loss in the cortex and substantia nigra. As with other tauopathies, the etiology of CBD is unknown.

MSA is a disorder characterized by various combinations of pyramidal, extra pyramidal, autonomic and cerebellar features. At autopsy MSA shows neuronal loss and gliosis in the striatum, substantia nigra, locus ceruleus, inferior olive, pontine nuclei, Purkinje cells, intermediolateral cell colums and Oruf's nucleus of the spinal cord. Glial cytoplasmic inclusions containing ∀ synuclein are the most characteristic histological feature. The etiology is unknown. Genetic factors do not seem to play an important role.

Fronto temporal dementia

FTD are a group of neurodegenerative dementias in which the frontal or temporal lobes or both are affected, out of proportion to rest of the brain. The clinical phenotypes includes behavioral variant FTD, Primary Progressive Aphasia (PPA) and Semantic Dementia (SD). FTD has complex genetic underpinnings. The mutations that have been identified in FTD involve the MAPT gene on chromosome 17, Valosin gene on chromosome 9 and CHMP 2 ∃ gene on chromosome 3.

Motor Neuron Disease or Amyotrophic Lateral Sclerosis (ALS)

ALS is a neurodegenerative disease that primarily affects the motor neuron cells in the motor cortex, brainstem and spinal cord. The pathological hall

marks of ALS are the degeneration and loss of motor neurons with astrocytic gliosis and ubiquitinated inclusions in the neurons. The pathogenesis of ALS involves a complex chain of injurious events involving excitotoxins, oxidative stress[77], neurofilament dysfunctions, altered calcium homeostasis, mitochondrial dysfunction, and pro inflammatory cytokines. Genetic factors may also play a role. Proposed ALS susceptibility genes include ApoE, SMN, Peripherin, apex nuclease gene, vascular endothelial growth factor (VEGF) gene[78].

Neurodegeneration and Neuroprotection in Glaucoma

The greatest risk factor for NDD is aging.In these late-onset diseases, there is some factor that changes as a person ages for each disease .While many different forms of NDDs are recognized, the lines that separate one from the other is often not clear. With few exceptions, no diagnostic lab test exists that can clearly indicate the presence, absence or category of a NDD. Diagnoses are usually based on clinical evaluation.

The similarities that exist between NDD and POAG are common risk factors, selective loss of neuron populations, trans synaptic[79]and secondary neuronal degeneration, common mechanisms of cell injury and death. Therapies combining IOP lowering with neuro protection may be beneficial as it is imperative to keep the available neurons alive. The chronic neurodegenerative diseases where the exact etiology or its therapy is not known can only be helped by retarding or reversing apoptosis associated neuronal cell death resulting from the primary injury and preventing the secondary events.

Materials and Methods

Study Design: Cross sectional- Case Control study.

Study Setting: Medical College, Kottayam.

Duration of Study: March 2011 to August 2012

Study population: Experimental group: All patients with a diagnosis of neurodegenerative disease getting admitted to the neuro medicine wards of Medical College, Kottayam during the study period.

Control group: an age matched sample collected from normal population evaluated by neurologist and confirmed absence of any neurodegenerative disease. The following neurodegenerative diseases were included in the study: Alzheimer's disease, Parkinson's disease, and Parkinson's plus syndrome, Fronto- temporal dementia, Motor neuron disease/ amyotrophic lateral sclerosis, Multi system atrophy. They were diagnosed by standard diagnostic criteria by the neurologist.

Inclusion and Exclusion Criteria

Inclusion Criteria

Experimental Group

All patients with a diagnosis of Neurodegenerative Disease, from age 40 – 80.

Control Group

Age matched subjects without Neurodegenerative Diseases, evaluated by neurologist.

Exclusion Criteria

Experimental and Control Group

Cases in which evaluation of POAG is not possible due to Opaque Media.

Sample Size

The total number of cases available during the study period was the sample size. Forty cases of neurodegenerative disease constituted the experimental group. Neuro degenerative diseases being uncommon, 80 subjects without any neurodegenerative disease selected from general population constituted the control group. The total study sample is120.

Study Procedure

The Socio Demographic and Clinical Data Sheet were administered on the subjects of the age group 40 to 80. Subjects who satisfy the Inclusion and Exclusion Criteria were selected as the study sample and informed consent was obtained.

The proforma evaluated for history of risk factors like family history, myopia, migraine like vaso spastic phenomena, shock or haemorrhagic episode, auto immune diseases, cardiovascular diseases, diabetes mellitus ,systemic hypertension,

night dose of anti hypertensives, sudden onset defective visions, use of steroids and addictions.

The study sample was evaluated in outpatient department of Ophthalmology, Medical College Hospital, Kottayam with the following procedures.

1) The best corrected visual acuity was determined.
2) A slit lamp evaluation was done to rule out any abnormalities.
3) IOP by Goldmann Applanation Tonometry and a median of three consecutive measurements were taken.
4) Gonioscopy with Goldmann 3 mirror gonioscope was performed to rule out angle closure.
5) Visual field evaluation with 30-2 threshold testing with SITA standard strategy was done. In patients unable to perform SITA standard due to mental or physical limitations were evaluated with SITA Fast strategy. In experimental group subjects unable to co operate for the above were evaluated for Glaucoma by stereoscopic optic nerve head evaluation only.(Based on the operational definition for glaucoma by Foster et al).
6) Stereoscopic disc and nerve fiber layer evaluation with 90 D and Disc Damage Likelihood Score (DDLS) by a single observer at the Haag Streit slit lamp after pupillary dialation with Tropicamide Plus.

The system categorizes the disc as small (<1.5mm), medium (1.5-2.0mm) or large (>2.0mm). A slit beam is directed onto the disc and the graticule at the top used to reduce the height of the beam until it corresponds in size to the disc. A correction factor of 1.33 is multiplied to get the disc size .The next stage is to measure the radial width of the neuro retinal rim measured at its thinnest point. The unit of measurement is the rim/disc ratio- that is, the radial width of the rim compared to the diameter of the disc in the same axis. When there is no rim remaining the rim/disc ratio is 0. The circumferential extent of rim absence (0 rim/disc ratio) is measured in degrees. A sloping rim is not taken as an absent rim .Each grade is assigned a numerical value. Other factors taken into account for probable glaucomatous damage are a RNFL defect or disc hemorrhage.

In difficult to cooperate patients, clinical estimation of optic nerve head size is possible with a Welsch Allen Ophthalmoscope. The smallest white round spot of the Welsch Allen ophthalmoscope usually illuminates a cone angle of 5° and casts a light of 1.5 mm in diameter on the retina.

Therefore diagnosis of glaucoma included, 1) patients with structural and functional defect (ONH cupping, with corresponding visual field defect). 2) Advanced structural defect with unproved field defect (a DDLS score of >6 ie; definite rim loss) in patients who were unable to co operate for a field study.

All the experimental group were admitted and evaluated in the hospital for their neurological evaluation. Investigations were done including appropriate neuroimaging to rule out alternate diagnoses.

Results and Discussion

The present study was conducted in a total of 120 subjects. Out of which 40 persons with Neurodegenerative diseases were the experimental group and 80 people without Neurodegenerative disease were recruited as the control group.

Age Distribution

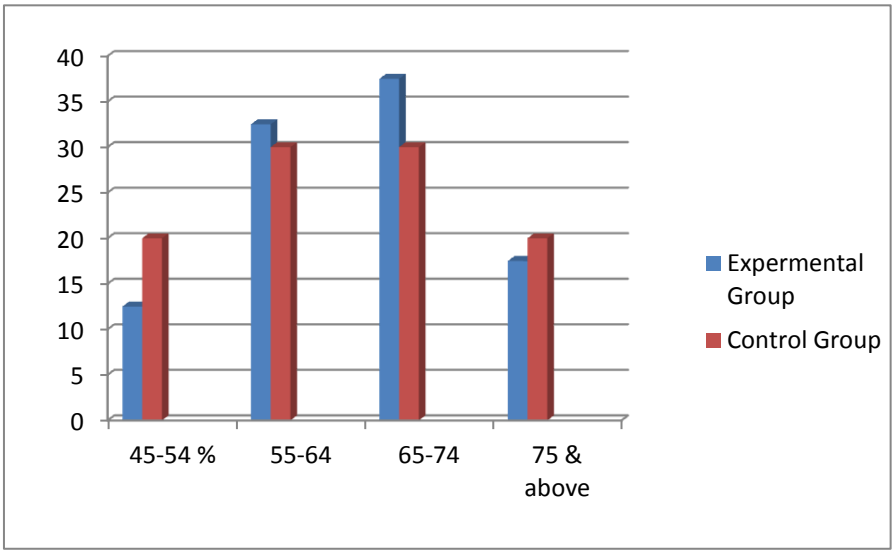
Age distribution is presented in Table No. 4.1, and Figure 4.1

Table 4.1 Age distribution of study sample

Age Groups	Group (N, %)			Chi- Square Value
	Experimental	Control	Total	
45-54	5, 12.5	16, 20	21, 17.5	1.460
55-64	13, 32.5	24, 30	37, 30.8	
65-74	15, 37.5	24, 30	39, 32.5	
>75	7, 17.5	16, 20	23, 19.2	

The Chi- Square test indicates that age is matched among study groups.

Figure 4.1, Age specific percentage of the study sample.



Distribution of Socio-demographic Variables

The distribution of Gender, Education, Employment, Socio- Economic status & Residence is given in Table 4.2.

Table 4.2, Gender, Education, Employment, Socio- Economic status & Residence distribution of the study sample

Socio- demographic Variables (SDV)	Sugroups of SDV	Group(N, %)			Chi- Square Value
		Experimental	Control	Total	
Gender	Male	29, 72.5	33, 41.3	62, 51.7	10.42**
	Female	11, 27.5	47, 58.8	58, 48.3	
Education,	<High School	23, 57.5	23, 28.7	46, 38.3	9.324**
	>High School	17, 42.5	57, 71.3	74, 61.7	
Employment,	Employed	11, 27.5	15, 18.8	26, 21.7	3.378
	Unemployed	28, 70	65, 81.3	93, 77.5	
Socio- Economic status	Low	7, 17.5	9, 11.3	16, 13.3	
	Middle	30,75	69, 86.3	99, 82.5	
	High	3, 7.5	2, 2.5	5, 4.2	
Residence	Urban	9, 22.5	23, 28.7	32, 26.7	
	Rural	31, 77.5	57, 71.3	88, 73.3	

** Significant at 0.01 level.

The Chi- Square test indicates that there is significant difference in the gender distribution between study groups. Males were significantly more in Experimental groups. Number of years of education is significantly more in control groupie; gender and education level was not matched.

Majority in both the groups were unemployed. This could be due to the higher age group of the selected sample. The study sample constituted mainly of middle class. The study sample constituted mainly of rural population.

The proforma evaluated for the risk factors of POAG like History of Sudden onset of Defective Vision, Recurrent Redness & Pain, Coloured Haloes, Defective Vision in Childhood, V asospastic Phenomenon, Ischemic vascular events, diabetes and its duration, Systemic Hypertension, night time dosing of antihypertensives.

No significant number with history of vasospastic phenomenon, autoimmune disease, Ischemic Vascular Eventwas found in the experimental or control groups (Appendix). There is no significant relationship seen between Diabetes Mellitus or Systemic Hypertension and POAG (Appendix). As the total number of patients with POAG is limited a large number study will be more reliable. Substance abuse is equally distributed in the study groups.

Family History of Study Groups

Table No. 4.3 Family History of Study groups

Family History	Group (N, %)		Chi-Square Value
	Experimental	Control	
Absent	35, 87.5	80, 100	10.435**
Neurodegenerative Disease	5,12.5	0, 0	

* Significant at 0.05 level.

In the experimental group 12.5 % of people were having family history of Neurodegenerative disease but none of the persons in control group had the same. None of the POAG cases had a positive family history of POAG or NDD.

Neurological Diagnosis of Study Groups

Table No. 4.4, Neurological Diagnosis, its frequency and percentage

Neurological Diagnosis	Frequency	Percent
Alzheimers Disease	5	12.5
Parkinsons Disease	9	22.5
Parkinsons Plus	11	27.5
Frontotemporal Dementia	5	12.5
Motor Neuron Disease	8	20.0
Multisystem atrophy	2	5.0
Total	40	100.0

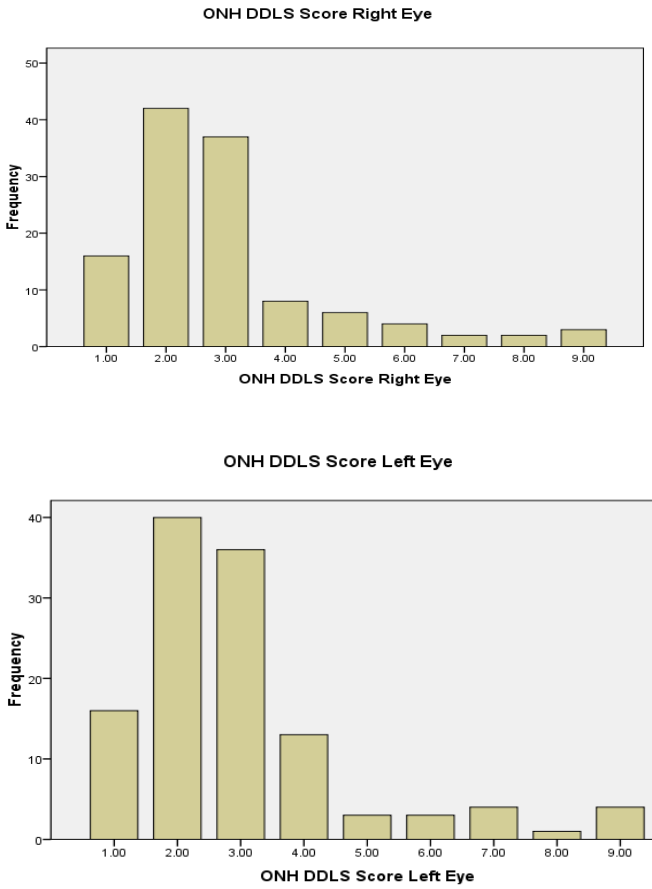
Disc Size distribution in study Groups

Table No. 4.5, Disc Size distribution in study Groups

Disc Size	Group (N, %)		
	Experimental	Control	Total
Small	3,7.5	13,16.3	16,13.3
Medium	35,87.5	55,68.8	90,75
Large	2,5	12,15	14,11.7

Disc size evaluation preceded DDLS scoring in the study sample. Majority had average sized discs.

Figure 4.2, Frequency of DDLS Score of Total Sample



The DDLS score distribution between right eye and left eye does not show any significant difference. The commonest score was DDLS 2 and 3 among the study groups.

The score of all glaucoma patients were above six. No anomalous or myopic disc with changes were included in the study.

Age Groups and Its Percentage of Glaucoma in Experimental Group

Table 4.6, Age Groups and Its Percentage of Glaucoma in Experimental Group

Age Groups	N and Percentages	Glaucoma		Total
		Absent	Present	
45 to 54	n	5	0	5
	% within Age in Groups	100.00%	0.00%	100.00%
	% of Total	12.50%	0.00%	12.50%
55-64	n	11	2	13
	% within Age in Groups	84.60%	15.40%	100.00%
	% of Total	27.50%	5.00%	32.50%
65-74	n	12	3	15
	% within Age in Groups	80.00%	20.00%	100.00%
	% of Total	30.00%	7.50%	37.50%
75 and above	n	5	2	7
	% within Age in Groups	71.40%	28.60%	100.00%
	% of Total	12.50%	5.00%	17.50%
Total	n	33	7	40
	% within Age in Groups	82.50%	17.50%	100.00%
	% of Total	82.50%	17.50%	100.00%

The average prevalence of POAG in experimental group is 17.5% .The age specific prevalence is found to increase steadily with increase in age by decades.

Table 4.7, Age Groups and Its Percentage of Glaucoma in Control Group

Age in Groups	Count, Percentage and Total Percentage	Glaucoma		Total
		Absent	Present	
45 to 54	Count	16	0	16
	% within Age in Groups	100.00%	0.00%	100.00%
	% of Total	20.00%	0.00%	20.00%
55-64	Count	24	0	24
	% within Age in Groups	100.00%	0.00%	100.00%
	% of Total	30.00%	0.00%	30.00%
65-74	Count	22	2	24
	% within Age in Groups	91.70%	8.30%	100.00%
	% of Total	27.50%	2.50%	30.00%
75 and above	Count	14	2	16
	% within Age in Groups	87.50%	12.50%	100.00%
	% of Total	17.50%	2.50%	20.00%
Total	Count	76	4	80
	% within Age in Groups	95.00%	5.00%	100.00%
	% of Total	95.00%	5.00%	100.00%

No cases of POAG were found in the control group up to 65 years of age. The average prevalence of POAG in the control group is 5%. Progressive increase in POAG cases is seen with increase of age in decades. The higher prevalances obtained may be due to that the control group was a hospital based sample.

Calculation of risk

The calculation of risk was done with estimation of Odds ratio

Table 4.8. Chi- Square test and Odds ratio of POAG in Study groups

Group	Glaucoma		Total	Chi-Square Value
	Absent	Present		
Experimental	31	9	40	8.454**
Control	76	4	80	
Total	107	13	120	

Mantel-Haenszel Common Odds Ratio Estimate

Estimate			.181
ln(Estimate)			-1.708
Std. Error of ln(Estimate)			.638
Asymp. Sig. (2-sided)			.007**
Asymp. 95% Confidence Interval	Common Odds Ratio	Lower Bound	.052
		Upper Bound	.633
	ln(Common Odds Ratio)	Lower Bound	-2.957
		Upper Bound	-.458

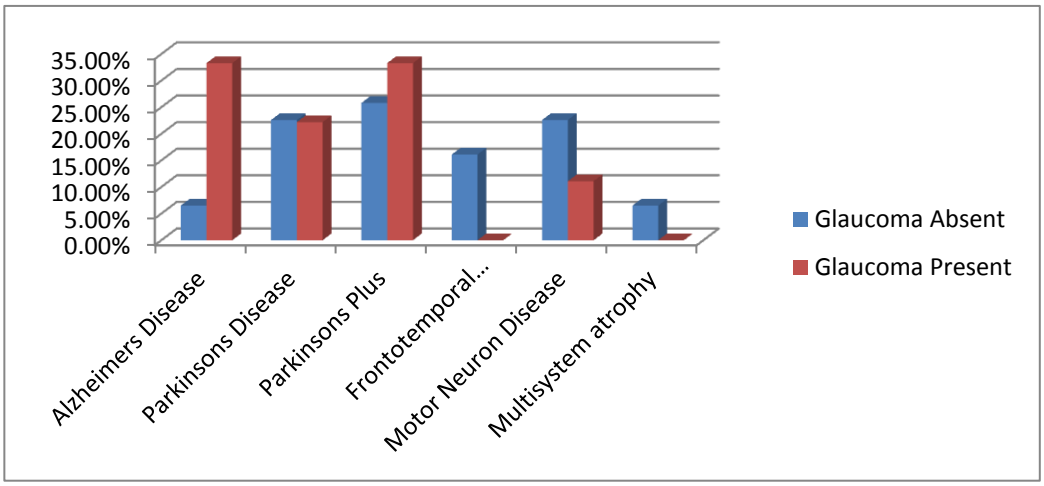
**Significant at 0.01 level

The finding of 17.5% glaucoma in the experimental group is significant when compared to the 5% occurrence in the control group. The Chi square shows significant difference and ODD's ratio calculated shows that NDD can be a risk factor for glaucoma. With the 95% confidence interval showing that this has not occurred by chance.

Table 4.9, POAG distribution among NDD

	Final Neurological Diagnosis(N,%)						Total
Glaucoma	Alzheimers Disease	Parkinsons Disease	Parkinsons Plus	Fronto- temporal Dementia	Motor Neuron Disease	Multisystem atrophy	
Absent	2, 6.5	7,22.6	8, 25.8	5, 16.1	7, 22.6	2, 6.5	31
Present	3, 33.3	2, 22.2	3, 33.3	0, 0	1, 11.1	0, 0	9
Total	5, 12.5	9, 22.5	11, 27.5	5, 12.5	8, 20.0	2, 5	40

Figure 4.3 POAG distributions among NDD



The table and figure indicates that among the various neurodegenerative diseases, together Alzheimers and Parkinsons disease constitute more than 60 percent of patients with Glaucoma. Alzheimers disease constitute 12.5% of the experimental group & 33.3% of patients with glaucoma.Of the 22.5% Parkinsons disease & 27.5% Parkinsons plus 20% of POAG were found.

Visual acuity in glaucomatous eyes

Table 4.10, Visual acuity in glaucomatous eyes

Visual Acuity in Right Eye			
	Group		Total
	Experimental	Control	
6/6 to 6/18	1	1	2
6/18 to 6/60	4	1	5
6/60 to 3/60	3	2	5
No PL	1	0	1
Total	9	4	13
Visual Acuity in Leftt Eye			
6/6 to 6/18	1	1	2
6/18 to 6/60	5	1	6
6/60 to 3/60	3	1	4
Less than 3/60	0	1	1
Total	9	4	13

Majority had visual impairment. Two out of thirteen had blindness in one or other eye.

Summary and Conclusions

Age

Comparison of age specific prevalence of POAG with other Indian estimates

Age specific glaucoma table of control group (Table 4.7) and that of other Indian studies (Table 2.1) indicates that the probable glaucoma in all population based studies show higher percentages in ages above 65 and significantly higher above 75. The present study show consistent results. This indicates that the pattern of Glaucoma incidence in present population shows similar incidence.

Risk factor evaluation by proforma

Features like History of Sudden onset of Defective Vision, Defective Vision in Childhood, Vasosp-astic Phenomenon, Ischemic vascular events, diabetes and its duration, Systemic Hypertension, night dose of antihypertensives which are found in association with Normal tension Glaucoma were not found in this study. This may probably due to the less number of cases evaluated.

Family history (given in results)

Family history is a known risk factor in POAG and Neurodegenerative disease. The present study confirms that there is significant family history in Neurodegenerative diseases (12.5%). This study could not find any family history in POAG group for POAG or Neurodegenerative disease. This could be due to less number of POAG cases evaluated.

Normal Tension Glaucoma in Present Study

Eight out of the 13 cases of glaucoma were on treatment. Seven were on drugs. One had history of surgery. High IOP was recorded in only one patient. All NDD cases had normal recorded tension. Cannot comment on this findings as most of them were on hypotensive medication.

POAG in NDD

The finding of 17.5% glaucoma in the experimental group is significant when compared to the 5% occurrence in the control group. The Chi square shows significant difference and ODD's ratio calculated shows that NDD can be a risk factor for glaucoma. With the 95% confidence interval showing that this has not occurred by chance.

Study by Bayer et al found an increased incidence among Alzheimers and Parkinson's patients. This study also came to a same conclusion. Bayer et al[80] commits the association could be due to selection bias. Similar finding in present study indicates that if the sample size was more the chance for getting a significant association is present. So possibly there could be an association.

Literature search showed higher occurance of POAG in Alzheimers and Parkinsons diseases and results of this study are also consistent.This study also highlights that POAG could also be found in other neuro degenerative diseases like motor neuron disease and multisystem atrophy.A further elaborative study including a more wider spectrum of neurodegenerative cases will be helpful to ascertain their exact distribution.

Limitation of the study

The study sample and period of study was small.

Conclusion and suggestion

There is significant association between neurodegenerative disease and primary open angle

glaucoma and neurodegenerative disease can be a risk factor for glaucoma. An extended period of study with a larger sample size matching all established risk factors will elicit more confirmatory evidence.

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