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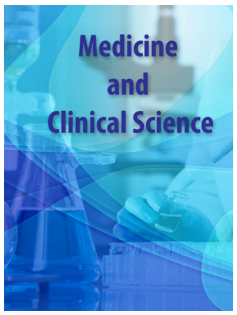
Mini Review



Glaucoma - A Window into Future Neurodegeneration

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Abstract

Glaucoma is the leading cause of irreversible blindness in the world. Recent studies propose glaucoma to be a neurodegenerative disease due to overlap with diagnoses such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis. Emerging reports have linked glaucoma as a risk factor for future certain neurodegenerative diseases, however, results have been conflicting. The development of degenerative brain disease consists of both a genetic and environmental component. If diagnosed with glaucoma, patients should take additional measurements to reduce the likelihood of developing additional nerve cell loss.

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Introduction

Glaucoma is a group of eye diseases that can lead to irreversible blindness due to damage to the optic nerve [1,2]. There are an estimated 80 million people worldwide with glaucoma and this number is predicted to surpass 111 million by 2040 [2]. Among the various types, open-angle glaucoma (OAG) is the most prominent and makes up more than 80% of glaucoma cases [2,3]. Patients will experience a gradual, painless loss of their peripheral vision [3]. Usually, once patients start noticing symptoms, the disease has progressed to a high severity [2,3]. The exact cause of glaucoma is debated with proposed risk factors including age, elevated eye pressure, corticosteroid use, diabetes, race, smoking, and family history of glaucoma or elevated eye pressure [1-3]. There currently is no cure for glaucoma, and treatments aim to prevent further damage by lowering the intraocular pressure [1-3].

Traditionally, glaucoma has been considered an ocular disease with monitoring involving a fundus exam and optic nerve imaging by an ocular practitioner. However, recent studies discuss glaucoma as a neurodegenerative disease, sharing similarities to Alzheimer's and Parkinson's diseases such as selective neuronal cell loss and transsynaptic degeneration [4-6]. Similar to a neurodegenerative disease, glaucoma has been linked to damage to specific brain structures such as the lateral geniculate nucleus and visual cortex [4,7].

Emerging studies have also implicated glaucoma as a risk factor in the development of future neurodegenerative disease [8-10]. The aim of this study is to review the current literature looking at this association. Using the information presented in this study, current evaluation for neurodegenerative disease can incorporate history of glaucoma as a predictive as well as diagnostic tool.

Dementia

Dementia is a general term used to describe loss of memory, problem-solving, language, and other forms of cognitive functioning [11]. Dementia is one of the leading causes of death with aspiration pneumonia being the most common cause [12]. There are many types, including Alzheimer's, vascular, Lewy body, frontotemporal, Huntington's, or mixed dementia. Alzheimer's makes up 60-80% of cases with treatments with anti-cholinergic medications used to temporarily relieve symptoms [11,13]. The cause of dementia is not well known with age being a key risk factor [11,12]. Recent studies have found glaucoma to be associated with the development of dementia [8,14]

Through unclear mechanisms, OAG patients are shown to be at an increased risk for cognitive impairment [8]. Data has shown OAG to be significantly associated with dementia with mixed reports on vascular dementia and Alzheimer's [8,10]. Studying this association, a large study in Sweden by Crump et al published this year, looked at 324,730 individuals diagnosed with glaucoma and compared it to an age- and sex-matched population-based control cohort without dementia [15]. With a median follow-up of 8 years, authors found the incidence of Alzheimer's disease, vascular dementia, and all-cause dementia to be significantly elevated in the glaucoma cohort

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over the control group in those diagnosed with glaucoma at 70 years or older. This association was found in OAG and normal-tension glaucoma (NTG). The same significance between glaucoma and dementia was not seen in patients diagnosed with glaucoma younger than 60 years of age. Independently, primary angle closure glaucoma was significant for all-cause dementia but not Alzheimer's or vascular dementia. These findings were adjusted for income, education, and comorbidities such as hypertension, diabetes, hyperlipidemia, and ischemic heart disease.

This study provided high statistical power while controlling for socioeconomic and comorbidities. As the patient population was largely Swedish patients and did not include the severity of dementia or glaucoma, future studies are warranted. Additional factors not noted in Crump et al include the influence of lifestyle factors such as physical activity, diet, or smoking. Previous studies have listed these factors to possibly delay or prevent the development of dementia [16-18]. Discrepancies seen in prior studies may be related to the type and age of glaucoma diagnosis. Monitoring for dementia symptoms in persons diagnosed with glaucoma, will allow for earlier detection and treatment.

Parkinson's Disease

Parkinson's affects both the motor and non-motor systems of the central nervous system [19]. Alpha-synuclein aggregates within Lewy bodies of neurons leads to cell death within the substantia nigra [19,20]. The substantia nigra produces dopamine, a key hormone needed by the basal ganglia to control voluntary motor control [19,20]. This leads to the characteristic tremors, bradykinesia, rigidity, and loss of balance seen in Parkinson's. In advanced stages, Parkinson's is also known to cause dementia, mood, and behavioral changes [19,20]. Most cases are sporadic, with an unclear cause. Current understanding is that Parkinson's is caused by a combination of genetic and environmental factors with advanced age being a key risk factor [19,20]. Diagnosis is made by patient history and a neurological exam looking for symptoms consistent with Parkinson's. Unfortunately, no cure exists, and treatments become less effective over time.

Glaucoma has been found to be one of the most common ocular pathological findings seen in Parkinson's, however, studies linking glaucoma as a risk factor for developing Parkinson's have shown conflicting results [8,9,21]. A large study looking at 24,892 OAG patients with an average age of 58.9 years, who were seen at Duke University, showed no correlation between OAG and the development of Parkinson's [8]. While a study in Taiwan found that patients who developed glaucoma at 65 years old and greater had a significantly elevated risk of developing Parkinson's [22]. A recent meta-analysis composed of three studies studying this association noted an elevated but non-significant risk of glaucoma patients developing Parkinson's when compared to a control cohort [9]. Future studies may need to further investigate the effect of a late diagnosis of glaucoma on the development of Parkinson's as a similar trend has been noted in dementia [23].

Current studies examining this association are too few to draw definitive conclusions and are limited by factors such as race and location. The type of glaucoma was not specified in all studies as well as the amount of physical activity by the patients. Although not absolute, physical activity has shown to prevent or delay the onset of Parkinson's [24,25]. With glaucoma showing an association with developing Parkinson's, especially if diagnosed at an older age, patients should consider an exercise regimen to prevent cognitive decline and muscle rigidity.

Amyotrophic lateral sclerosis (ALS)

ALS or Lou Gehrig's disease is the most common motor neuron disease and presents with the progressive loss of upper and lower motor neurons responsible for muscle control [26]. This predominantly sporadic, progressive disease is diagnosed based on symptoms and exclusion of alternate diagnoses. Rapid progression of this condition leads to the weakening of the diaphragm muscles with the inability to support breathing and life [27]. Current therapies aim to delay symptoms, however, there is no cure. Interestingly, studies have found connections between ALS and glaucoma [28,29].

An association exists between glaucoma and ALS through mutations in the optineurin (OPTN) gene [28-30]. The OPTN protein is involved in many pathways, not limited to membrane vesicle trafficking, exocytosis, cell survival, autophagy, and cell division. Mutations in OPTN can give rise to glaucoma, ALS, or both [28,31]. Glaucoma-associated mutations are more likely caused by single copy missense mutations in OPTN, whereas ALS-associated mutations are associated with nonsense and missense mutations or deletions [28,31]. In rare cases, a 2-base pair insertion in OPTN is associated with the development of glaucoma as well as ALS in the future [28]. The pathogenesis of how OPTN contributes to developing either disease is unclear but believed to be due to impaired autophagy, and thereby endoplasmic reticulum (ER) stress and cell death [28, 31].

Carreras has also proposed a similar pathogenesis between glaucoma and ALS [29]. The author reports the misdirection of the aqueous humor to the posterior pole of the eye leads to the development of glaucoma. The differing calcium ion concentration between the fluid and the optic nerve leads to damage and produces symptoms [29]. A similar difference in ionic concentration is seen when comparing the cerebrospinal fluid (CSF) to the gray central matter involved in carrying out muscle contraction [29]. This study proposes that, similar to aqueous humor in glaucoma, the misdirection of CSF leads to ALS.

Large clinical studies looking at OAG patients showed no correlation in developing ALS in the future when compared to the control cohort [8]. However, studies are limited due average life expectancy of ALS. ALS can present earlier than glaucoma and has an average life expectancy of 2-5 years after diagnosis [27]. Due to patients who are diagnosed with ALS not routinely following up with an ocular practitioner, a conclusion cannot be reliably made. With the possibility of overlapping genes and pathophysiology, a connection between the two disease states may exist.

Discussion

Developing a neurodegenerative disease is believed to contain both a genetic and environmental component. Factors such as obesity, vascular disease, diabetes mellitus, physical inactivity, social isolation, cigarette smoking, and depression have been shown to be lifestyle-related risk factors [16,17]. Studies have also expressed the importance of higher levels of education and activities enhancing cognitive abilities to provide resilience against dementia-related deterioration as well as brain changes from age [16,17]. Patients with untreated hearing loss are also at risk for developing dementia, stressing the importance of a hearing examination. Maintaining a healthy lifestyle, engaging in regular moderate exercise, and participating in intellectual activities can reduce the risk of neurocognitive dementia by up to 35% [16,17].

Current literature exploring glaucoma as a risk factor for neurodegenerative diseases is emerging, yet remains insufficient. As glaucoma is a term for a group of diseases, few studies examine this correlation between other glaucoma subtypes. Recent studies are starting to find normal-tension glaucoma (NTG) as a risk factor for dementia [31,32]. Unlike OAG, the eye pressure in NTG is within normal limits [31,32]. This may imply a different mechanism between types of glaucoma or a pressure-independent pathway. To further test this association, future studies can examine if an advanced stage of glaucoma is associated with an increased incidence of neurodegenerative diseases. Another possible question is testing if the use of intraocular pressure-lowering medications can mitigate the increased risk. As glaucoma is a disease most diagnosed around mid-life, it is difficult to assess a connection to pathology with a young age of onset and a high rate of mortality. With advancing treatments, and prolonging life expectancy, future studies can assist in determining if glaucoma is a risk factor or a co-morbidity to other neurodegenerative diseases.

Despite years of research and progress, glaucoma is a disease full of mystery. Although mainly treated by an ophthalmologist, the findings here demonstrate glaucoma is a disease that transcends the eyes. This study is novel because it highlights literature on glaucoma in developing several neurodegenerative diseases. As the incidence of glaucoma, Alzheimer's, Parkinson's, and ALS continues to rise, current research suggests that underlying similarities in mechanisms may be the cause. The lack of a cure for neurogenerative diseases stresses the importance of diagnosing early and adjusting for environmental risk factors if possible. The current management of glaucoma should include risk factor management of future neurodegenerative disease, especially in those with a late diagnosis and believed to be high risk.

Conflicts of Interest

The authors claim no personal or business interest in the information presented in this manuscript.

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