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PATHOGENESIS OF GLAUCOMA: INTEGRATION OF BIOMEDICAL AND AYURVEDIC PERSPECTIVES

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Abstract: Glaucoma is the second most common cause of visual loss in the world and causes irreversible loss of vision. The current approaches to deal with primary open angle glaucoma are chiefly based on reduction intraocular pressure, the most significant controllable risk factor. It is being increasingly recognized that lowering IOP is not adequate in a significant population of primary open angle glaucoma (normal tension glaucoma included) patients. Even in patients those who respond well to IOP lowering drugs, it is more rational to adopt an integrated approach which takes care of multiple risk factors for glaucoma. Ayurveda can play a significant role in the integrated management of this condition. This paper correlates the information on pathogenesis available in biomedical system and system of Ayurveda in order to provide an integrated perspective which can form the basis for further interdisciplinary studies.

Keywords: Glaucoma, Intraocular pressure, Neuroprotection, Normal tension glaucoma, Oxidative stress, Apoptosis, Ayurveda.

Introduction

Glaucoma is the second most common cause of visual loss in the world.[1] A study estimated that there are approximately 11.2 million persons aged 40 years and older with glaucoma in India of which 6.48 million persons suffer from primary open angle glaucoma.[2] Primary open angle glaucoma is the most common type of glaucoma.

The current approach to manage primary open angle glaucoma are primarily based on reduction of intraocular pressure, its most significant controllable risk factor. It is being increasingly felt that IOP lowering approach needs to be supplemented by measures which can deal with all the known factors involved in pathogenesis of glaucoma.

The research in *Ayurveda* can provide new leads, pharmacological or non-pharmacological, for the management of glaucoma. The conceptual studies which correlate basic concepts of *Ayurveda* and Biomedicine will form the basis for further research. This paper explores the possible areas of integrative research in the field of glaucoma.

Glaucoma

The glaucoma is a diverse group of disorders characterized by a chronic, slowly progressive loss of retinal ganglion cells and their neurons resulting in characteristic optic nerve head cupping and visual field loss.[3] The intraocular pressure (IOP) elevation need not be present to make the diagnosis of glaucoma.[4] The intraocular pressure (IOP) in glaucoma patients, however, is raised above the tolerance limits of retina.[5] It is now recognized that elevated IOP, though most important, is only one amongst many risk factor for glaucoma.

A number of studies indicate that the progression of glaucoma cannot be fully controlled by lowering IOP in all patients.[6,7,8] It is being increasingly recognized that retinal ganglion cells (RGC) are more susceptible to damage in glaucoma patients. Therefore, RGC loss continues

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to occur despite of IOP lowering treatment in many patients. Glaucoma is also being recognized as neurodegenerative disease. As RGC do not regenerate, the measures to strengthen the neurons are considered and being tried for glaucoma management. The focus of research is shifting from IOP reduction to neuroprotection.

As already mentioned, IOP is not always elevated in glaucoma. The characteristic visual field changes and optic disc damage may be present at normal intraocular pressure. This condition is referred as normal tension glaucoma (NTG) or low tension glaucoma (LTG). The visual fields remain normal in some individuals despite of raised intraocular pressure. They are known as glaucoma suspect and subjected to periodic ophthalmic evaluation. The distinction between primary open angle glaucoma is arbitrary as involvement of similar mechanisms has been observed in both of these conditions.[9]

From the diagnostic point of view the glaucoma can be divided into three phases *viz.* asymptomatic undetectable, asymptomatic detectable and symptomatic phase.

The early neuronal damage cannot be detected due to the lack of high sensitivity tools. The most common method of visual function assessment for glaucoma is perimetric measurements of visual sensitivity. On average, statistically significant abnormalities of visual sensitivity require neural losses of 20 – 50 %, depending on the retinal eccentricity.[10]

The symptoms of glaucoma do not usually appear until moderate neuronal damage has occurred; therefore, it remains largely unreported and untreated in early stages of disease. Most of the patients seek medical advice due to painless loss of vision only after significant optic atrophy has already taken place. Glaucoma does not seem to be single disease as multiple pathological mechanisms converge to result in characteristic glaucomatous changes.

Systemic Associations with Glaucoma

Cardiovascular Conditions

Many studies have reported, association of glaucoma with cardiovascular diseases.

Blood Pressure

Hypertension as well as hypotension are found to be associated with glaucoma.[11,12,13] Arterial hypertension is identified as an important risk factor for POAG.[14] In some studies arterial hypertension and NTG are reported to be associated[15,16,17] A study has found significantly higher levels of blood pressure in NTG patients. In another study the nocturnal dip of blood pressure was found to be associated with NTG.[18]

Hypotension is also implicated as risk factor in some studies.[19,20,21] A study demonstrated a significant difference between blood pressure in supine and upright positions in NTG and HTG patients, the difference being higher among NTG patients.[22]

Sustained blood pressure drop during sleep and markedly low systolic blood pressure in day time have also been observed as risk factors for rapid progressive visual field loss. [23,24]

These studies show that changes in blood pressure, particularly nocturnal drop in blood pressure, may play an important role in pathogenesis of glaucoma in some patients.

The pressure changes in circulatory system are considered as *vata* abnormality from *Ayurvedic* point of view. The mechanisms involved in performing regulatory functions in the body are classified under the umbrella term, *vata*.[25] The hypertension or hypotension can be considered as the abnormalities of these control mechanisms and can be attributed to a sub-class of *vata* called *vyana vayu*, a term that describes the regulatory mechanisms responsible for generalized body functions and movements.[26]

Vasospasm

Vasospasm, or vascular dysregulation, is defined as inappropriate constriction or dilatation

responses in microcirculation to stimuli, such as coldness or emotional stress.[27] Numbers of studies have found the role of vasospasm in pathogenesis of glaucoma, which support the hypothesis that vascular dysregulation interferes with the auto-regulation and predisposes the eye to the damage by raised IOP and hypotension.[28,29] Auto-regulation of retinal circulation is carried out primarily by the balance of two regulatory mechanisms. Endothelium derived substances, like endethelin-1 (ET-1), cause vasoconstriction and nitric oxide (NO) leads to dilatation of vessels. Their imbalance leads to vasospasm. [30] Increased plasma levels of ET-1 are reported in patients with glaucoma.[31] The vascular dysregulation may partly occur due to dysregulation of autonomic nervous system.[32]

From *Ayurvedic* point of view, vasospasm (*sankocha*) is also attributed to abnormality of *vata*. The therapeutic measures which normalize *vata* should be considered as options in glaucoma management. A study conducted on *Ginko biloba*, a herbal drug, is found to increase ocular perfusion.[33] In a rat model of chronic glaucoma it improved retinal ganglion cell survival.[34] *Ginko biloba* has improved visual field defects in some patients with NTG.[35]

Headache and Migraine

The migraine is known to be associated with vasospasm of blood vessels of brain. There is a possibility of retinal vasospasm in glaucoma patients. Some studies conclude that migraine is an independent risk factor for progression of glaucoma.[36] From *Ayurvedic* point of view the migraine is considered as predominantly *vata* abnormality. The stress related factors may also play role in glaucoma progression as they precipitate the attacks of migraine.

Platelet Aggregation

The platelet aggregation is positively related to progressive visual field loss in glaucoma patients as compared to patients with stable visual fields.[37] Theoretically, platelet aggregation may reduce the blood flow, contributing in ischemic damage in glaucoma.

From Ayurvedic point of view, the reduction in blood circulation in a particular area signifies *srotavrodha* (the term *srotavrodha* means obstruction in conduit or channel) and results in *dhatu kshaya* (tissue loss) occurring due to lack of *poshana* (nutritional supply).[38]

Autonomic Nervous System

Intraocular pressure level is influenced by autonomic nervous system. A number of drugs acting on autonomic nervous system have pressure lowering effect.[39] In glaucoma patients a diminished oculo-cardiac response had been demonstrated. A study demonstrated the parasympathetic neuropathy is POAG patients.[40] Another study showed 73% of sympathetic nervous systems under-activity and 86% of parasympathetic under-activity in patients of POAG when compared with normal control group.[41]

The dysfunction of autonomic nervous system, again an abnormality of control mechanism, can be attributed to abnormality of *vata*.

Autoimmunity

The immunological findings described in literature are related to glaucoma are reviewed by **Mona Pache and Josef Flammer**[42] It has been suggested[43] that an autoimmune mechanism may be responsible for the optic nerve head damage in NTG patients. The signaling mechanisms of immune system initiated by high IOP, ischemia, and excessive excitatory amino acids can cause neuronal cell death.[44]

The antibodies against heat shock proteins present in photorecepters and glycosaminoglycans in optic nerve head were observed in glaucoma patients. The heat shock proteins which are expressed in photoreceptors and may participate in rhodopsin processing, are also the target of auto-antibodies in glaucoma patients.

Glycosaminoglycans maintain the structure as well as various cell functions and cell-to-cell interactions at ONH. Presence of serum autoantibodies against ONH glycosaminoglycans

in glaucoma patients, especially in those with NTG, was observed. A lack of cell-mediated immunity has been observed as leukocyte migration inhibition is found in POAG patients. The glycosaminoglycan antibodies may get deposited in the lamina cribrosa and disturb the extracellular melieu leading to increased neuronal susceptibility to damage by high IOP.

This pathogenesis can be interpreted, from *Ayurvedic* point of view, as abnormal *vata* causing *agnidushti* which then leads to formation of *ama* and *mala samchaya*. *Malasamchaya* causes further vitiation of *doshas*, *srotavrodha* and *dhatu dushti*. *Ama* or *malasamchaya* means deposition of unwanted or waste materials in the body tissues which disturbs the homeostasis, ultimately leading to functional and structural damage.

Neurodegenerative Diseases

Some studies suggest relation between neurodegenerative diseases and glaucoma. A high frequency of glaucoma has seen found in patients of senile and presenile dementia.[45] Ganglion cell degeneration has been observed in Alzheimer disease. It is found in a study that 23.7% of Parkinson's disease patients suffer from glaucoma.[46]

The neurodegenerative diseases, in general, are considered as *vata* predominant disorders in *Ayurveda*.

Sleep Apnea

Several studies have found a positive association between glaucoma and sleep apnea syndrome.[47,48] In a study glaucoma was observed in 7.2% of patients with sleep apnea syndrome.[49] In another study conducted on 30 glaucoma patients, 20% found to be suffering from glaucoma. Sleep apnea syndrome patients also have increased levels of endothelin-1.[50,51] It is possible that the impaired profusion of optic nerve head during sleep apnea causes damage.[52,53,54]

From *Ayurvedic* point of view, the sleep apnea may be regarded as *pranavaha srotodushti* as it results in retinal tissue hypoxia. *Pranvaha srotas* is considered as a transport system, - controlled by regulatory mechanisms *(prana vayu)*,- involved in the oxygen supply (respiration) to tissues.[55] *Pranvaha srotas* involves structures right from respiratory system to the capillaries, transport mechanisms through cell membrane and up to mitochondria where oxygen is ultimately utilized for its conversion into biological energy. Ischemic damage in glaucoma, therefore, can result from disorder of *Pranvaha srotas*.

Psychological Factors

It has been observed in some studies that in healthy individuals the stress has IOP increasing effect while the relaxation techniques have IOP-lowering effect.[56,57,58] Emotional instability has been associated with POAG. In a study conducted on 27 POAG patients, it was observed that two-third of these patients exhibited marked deviations on personality scale showing a trend towards depression and hysteria for male patients and paranoia and schizophrenia for female patients.[59]

In one study, glaucoma patients were found to be generally more depressive, conscious, meticulous, introverted, submissive and emotionally unstable than healthy controls.[60]

The personality characteristics described above are features of *vata prakriti* patients and are also found in conditions associated with increased *vata*.

Pathophysiology

The cellular mechanisms implicated in the pathogenesis of glaucoma are not well understood. The following patho-physiological mechanisms have been implicated in glaucoma.

Increased Stress Conditions

Historically, glaucomatous optic nerve damage has been attributed to either mechanical compression of retinal ganglion cell axons or to the ischemia caused by compression of capillaries supplying these axons. These mechanisms partially explain the damage in glaucoma.

Mechanical Hypothesis

The lamina cribrosa is a sieve like structure made up of scleral tissue having pores, through which bundles of optic nerve axons pass. Elevated IOP can cause posterior bowing of the lamina cribrosa.[61] The lamina cribrosa gets compressed in POAG patients[62] either due to raised IOP or inherent weakness of the tissue leading to distortion and damage to axons. The structural changes in lamina cribrosa are caused by changes in extracellular matrix. These changes include basement membrane thickening, disorganized and fragmented laminar beams, increased level of certain types of collagen, and structural changes in elastin.[63]

Elevated IOP in glaucoma patients can decrease axoplasmic flow in retinal ganglion cell axons.[64,65] Normal axonal transport is important for cell survival as it communicates neurotrophic factors and its lack may induce apoptotic changes.

Vascular Hypothesis

Chronic hypoxia or ischemia is believed to cause optic neuropathy.[66,67,68,69] It may occur due to compression caused by elevated pressure. Microvascular changes in the optic nerve head have been implicated in pathogenesis of glaucoma in many studies.[70] Reduced capillary network at optic nerve head has been observed in some studies. But this may be the result and not necessarily the cause of loss of tissue at optic nerve head. Some epidemiologic association between POAG and diabetes retinopathy, a disease with capillary dropout, has been reported.[71]

Hypoxia inducible factor-1 (HIF-1), an oxygen regulated transcription activator, was found up-regulated in postmortem human glaucomatous eyes, suggesting hypoxia as the cause of RGC damage.[72]

The *Ayurvedic* interpretation of the mechanical and vascular mechanisms refers to reduced supply of oxygen, nutritional factors and survival factors to optic nerve head. The hypoxia at ONH indicates *pranavaha srotodushti*. As the circulation of *rasa-rakta* (the vehicle of nutritional factors for *dhatus*, the structural elements) is impaired *rasavaha srotodushti* leading to *dhatu kshaya* (degeneration) can be considered as a component of pathogenesis.

Glutamate Induced Excitotoxicity

Raised glutamate levels were found in the vitreous of glaucomatous patients.[73] Prolonged exposure to high level of glutamate has been found to be toxic to all neurons. Neuron damage is identified in *Ayurveda* as *vata* abnormality.

Oxidative Stress and Apoptosis

The levels of reduced form of glutathione are found decreased in the blood which indicates the reduced oxidative protection.[74] The RGC death in glaucoma is thought to occur by apoptosis. It is a slow degenerative process characterized by cell shrinkage, plasma membrane blebbing. It may occur due to cytoskeleton degeneration.[75] Apototic cell death (*dhatu shosha*) and oxidative stress[76] have been compared with *vata* abnormality.

Increased Flow Resistance

Aqueous humor flows out of the anterior chamber through trabecular meshwork (TM). It is then drained via canal of Schlemn in conventional pathway and, via cilliary tissue in uveoscleral pathway.

Normal outflow of aqueous through TM depends upon the integrity of TM structure. It has been observed in several studies that there is increased extracellular matrix (ECM) deposition and decreased cellularity in TM. Elevated IOP results from increased outflow resistance at TM level.[77]

Flow through conventional pathway is controlled by balance between matrix metalloproteinases (MMPs) and tissue inhibiters of metalloproteinases (TIMPs). Both of these groups of molecules are continuously involved in remodeling of ECM. ECM deposition is caused by decreased activity or MMPs and increased activity of TIMPs. Argon laser treatment has been found

to increase the activity of MMPs and lower IOP. The imbalance of MMPs and TIMPs is also implicated in uveo-scleral outflow resistance. There is evidence of ECM deposition between the cellular components of ciliary body which imparts resistance to the fluid passing through it.

This mechanism of pathogenesis can be interpreted in terms of *Ayurveda* as deposition of *ama* or *mala* in the drainage channels leading to increased resistance. The formation of *ama* implies *agnimandya* (reduced activity of digestive or proteolytic enzymes). The deposition of extracellular matrix in trabacular mashwork and uveal tissue occurs due to reduced activity of proteolytic factors, the matrix metalloproteinases (MMPs). This correlates with *agnimandya* at *dhatu* (tissue) level with consequent deposition of *ama* which in turn disturbs the physiological milieu resulting in increased outflow resistance.

Conclusions

Majority of the risk factors and pathological mechanisms involved in pathogenesis of glaucoma indicate the role *vata* dysfunction. *Vata* regulates all activities of body including the activities of other two *doshas viz. pitta* and *kapha*. It is possible that in later stages of glaucoma all three *doshas* turn abnormal while *vata* continue to play a predominant role.

Agnimandya, *malasamchya*, *pranavaha* and *rasavaha srotodushti* also seem to play a significant role in glaucomatous damage. The therapeutic interventions contemplated against these factors can be studied for their role in modifying the pathogenesis of glaucoma.

The progression of glaucoma pathogenesis, though slow and silent, leads to irreversible blindness. An integrated approach dealing with all risk factors of glaucoma is more rational. Ayurveda can play a significant role in the integrated management of this condition. The correlations made in this paper regarding pathogenesis in systems of Biomedicine and Ayurveda propose an integrated perspective which can form the base for interdisciplinary studies in the field of glaucoma.

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