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Review Article

A REVIEW ON PATHOGENESIS OF PRIMARY OPEN ANGLE GLAUCOMA: ON BASIS OF AYURVEDIC PERSPECTIVES

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ABSTRACT

Glaucoma is the second most common cause of visual loss in the world. 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. 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. This type of glaucoma can be correlated to Kaphaja Adhimantha as there is negligible pain or no pain and give rise to chronic visual defect. Ayurveda can play a significant role in the integrated management of this condition. Hence a minor attempt to correlate 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, IOP, Kaphaja, Adhimantha, Ayurveda

INTRODUCTION

Glaucoma is the second most common cause of visual loss in the world.[1] In Vedic literature and Samhitas all Acharayas have emphasized on importance of eyes. Netra Rogas have been given prime importance which is evident from the fact that 19 chapters among the 28 chapters of Shalakya Tantra in Sushruta Samhita are devoted to the eye diseases and their management. While describing 76 types of eye diseases, Acharya Sushruta has described a separate chapter for Sarvagata Roga in Uttartantra. Adhimantha comes under the Sarvagata Roga.

Adhimantha is one such eye disease, which has severe pain in eyes and one half of head.[2]It is categorized as Vataj, Pittaj, Kaphaj, Raktaj according to predominance of Doshas manifested through clinical features[3]. Based on the clinical features, Kaphaja Adhimanta may be correlated to Primary Open Angle Glaucoma (POAG). The classical features of Kaphaja Adhimantha are Nati-Sopha (mild or no swelling), Nati-Raga, (mild or no redness), Nati-Samrambha (mild or no congestion), Roop Pasyati Dukhena (difficulty in seeing), Siro-Dukhayutum[4](headache). All the above features are present in Primary Open Angle Glaucoma in which there is gradual progressive loss of vision, heaviness in eye and head without any complaints of redness and swelling.

Ayurveda can play a significant role in the integrated management of this condition. Hence a minor attempt to correlate 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.

DISCUSSION

Systemic Associations of Glaucoma with Cardiovascular Conditions

Many studies have reported association of glaucoma with cardiovascular diseases. Blood Pressure Hypertension as well as hypotension is found to be associated with glaucoma[5-6-7] Arterial hypertension is identified as an important risk factor for POAG[8]**.** Hypotension is also implicated as risk factor in some studies**.**[9-10-11] 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**.**[12]

The pressure changes in circulatory system are considered as Vata and Kapha abnormality from Ayurvedic point of view. The mechanisms involved in performing regulatory functions in the body are classified under the umbrella term, Vata[13]. 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**.**[14] Change in viscosity of blood in hypertension and hypotension is considered as Kaphaj abnormality.

Vasospasm

Number of studies have been found to have a role in the role of vasospasm in pathogenesis of Glaucoma, which support the hypothesis that vascular deregulation interferes with the auto regulation and predisposes the eye to the damage by raised IOP and hypotension.[15-16] 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 like Eranda Moola, Rasna etc.

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.**[17]** From Ayurvedic point of view migraine is considered as predominantly Vata abnormality. The stress related factors may also a 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[18]. 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 Shrotavrodha (obstruction in conduit or channel) and results in Dhatu Kshaya (tissue loss) occurring due to lack of Poshana (nutritional supply).[19]Shrotavrodha is also considered as Kapha abnormality and Dhatu Kshaya is due to vitiated Vata Dosha.

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.[20]. In glaucoma patients a diminished oculo-cardiac response had been demonstrated. A study demonstrated the parasympathetic neuropathy is POAG patients.**[21]** 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.**[22]** The dysfunction of autonomic nervous system, again an abnormality of control mechanism, can be attributed to abnormality of Vata.

Autoimmunity

It has been suggested that an autoimmune mechanism may be responsible for the optic nerve head damage in NTG patients[23]. The signaling mechanisms of immune system initiated by high IOP, ischemia, and excessive excitatory amino acids can cause neuronal cell death.[24]

This pathogenesis can be interpreted, from Ayurvedic point of view, as abnormal Kapha causing Agnidushti which then leads to formation of Ama and Mala Sanchaya. Malasanchaya causes further vitiation of Doshas, Srotavrodha and Dhatu Dushti. Ama or Malasanchaya 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 pre-senile dementia.**[25]** 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[26]. 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.**[27-28]** In a study glaucoma was observed in 7.2% of patients with sleep apnea Syndrome[29]. In another study conducted on 30 Sleep apnea patients, 20% found to be suffering from glaucoma.

From Ayurvedic point of view, the sleep apnea may be regarded as Pranavaha Shrotodushti 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.[30] 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.**[31-32-33]** Emotional instability has been associated with POAG. In one study, glaucoma patients were found to be generally more depressive, conscious, meticulous, introverted, submissive and emotionally unstable than healthy controls.**[34]** The personality characteristics described above are features of Vata prakriti patients and are also found in conditions associated with increased Vata.

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.**[35]** The lamina cribrosa gets compressed in POAG patients**[36]** 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.**[37]**

Elevated IOP in glaucoma patients can decrease axoplasmic flow in retinal ganglion cell axons.**[38-39]**. 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.[40-41-42-43] it may occur due to compression caused by elevated pressure. Micro vascular changes in the optic nerve head have been implicated in pathogenesis of glaucoma in many studies.**[44]** 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.[45] 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.[46]

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 Shrotoavrodha. As the circulation of Rasa-Rakta

(the vehicle of nutritional factors for Dhatus, the structural elements) is impaired Rasavaha Shrotodushti or vitiation of Kapha Dosha leading to Dhatu Kshaya or vitiation of Vata Dosha (degeneration) can be considered as a component of pathogenesis.

Glutamate Induced Excitotoxicity

Raised glutamate levels were found in the vitreous of glaucomatous patients.[47] 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.[48] 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.[49] Apototic cell death (Dhatu Shosha) and oxidative stress has been compared with Vata abnormality.

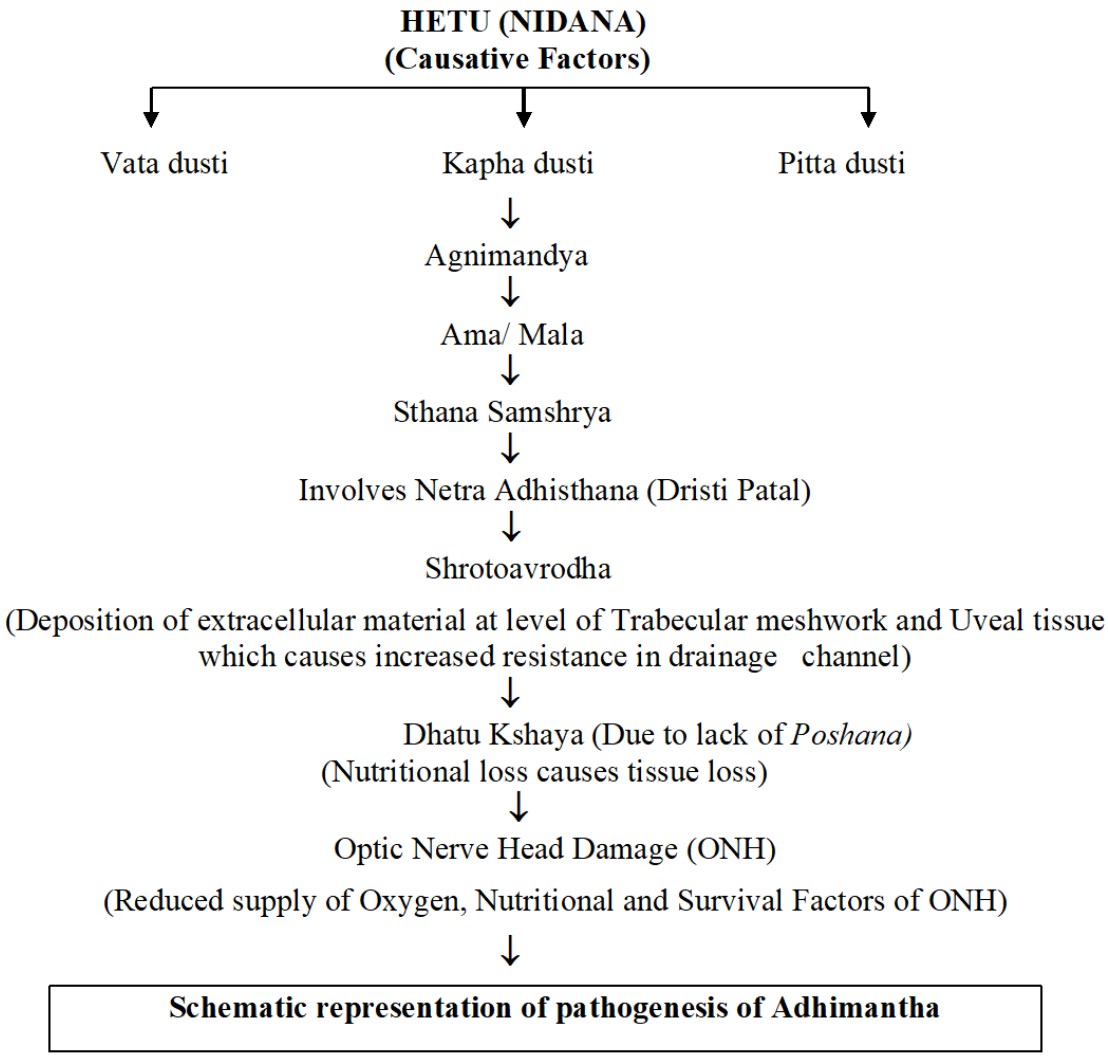
Increased Flow Resistance

Flow through conventional pathway is controlled by balance between matrix metalloproteinases (MMPs) and tissue inhibiters of metalloproteinases (TIMPs). Both of these group 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 the 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[50].

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 trabecular meshwork 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.

CONCLUSION

From above discussion it can be concluded that majority of the risk factors and pathological mechanisms involved in pathogenesis of glaucoma indicate the role Vata and Kapha 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 Shrotodushti also seem to play a significant role in Primary open angle glaucoma. The therapeutic interventions contemplated against these factors can be studied for their role in modifying the pathogenesis of Glaucoma.



Schematic representation of pathogenesis of Adhimantha

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