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Ocular Alzheimer's-Disease and Ayurveda- An Integrated Approach and New Insight for Research

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ABSTRACT

Glaucoma is a neurodegenerative disease of the optic nerve and the second leading causes of vision loss in the world among the geriatric population. Apoptosis is a programmed cell death causing damage to Retinal ganglion cells (RGCs) resulting in death of the cell. Alzheimer's disease (AD) is a neurodegenerative disease characterized by dementia in geriatric population. Glaucoma and Alzheimer's disease are having similarities in neuropathology and are progressive neurodegerative diseases. The loss of large magnocellular RGCs in optic nerve are seen in Glaucoma and Alzheimer Disease. The elevated glutamate level and nitric oxide synthase up regulation with reactive oxygen species formation are the excitotoxic triggers noted in both disease.

Brain is the seat of *Indriyas*, *Manas*, *Prana*. *Pradnya* or *Budhi* is the ultimate function of these three factors of brain. The anatomical or physiological disturbances in the brain will ultimately affect the *Pradnya*. Levels of management are

i. Primary: Natural protective provision,
ii. Secondary: Protective measures for healthy personnel,
iii. Tertiary: Protection at neurological level.

On these three levels Ayurveda can tackle the neurodegeneration and can prevents the neural loss in diseases like Glaucoma. The recent advances can also be considered in treatment of Glaucoma on following levels: Neuroprotection, Neuroenhancement, Retinal Ganglion Cell Replacement, optic nerve regeneration & vision restoration. The present paper will give a new insights and addition in the knowledge of scientific Ayurvedic community.

KEYWORDS

Glaucoma, Alzheimer, Apoptosis, Neuroprotection, Ayurveda

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INTRODUCTION

Adhimantha is a *Sarvagat Vyadhi* and can be symptomatically equally compared to Glaucoma which is the second cause of blindness and can cause irreversible damage in eyes leading to irreversible loss of vision[1]. The causative factors of development of retinal/optic nerve damage and loss of visual function are still unknown. The raised intraocular pressure (IOP), auto regulation of retinal blood supply, apoptosis of retinal ganglion cells (RGCs) in the individual patient, connective tissue at the lamina cribrosa, and perfusion pressure are the risk factors for the disease glaucoma. Medicinal line of treatment is only aimed towards the regulation of Intra Ocular Pressure but over the period of time apoptosis starts causing the damage to nerve fibers and retinal ganglion cell leading to visual field loss[2].

The number of glaucoma cases are increasing worldwide from 60 million to 80 million cases by 2020 with the prevalence rate 2.65% in people above the age of 40 years. The prevalence rate of Primary open angle glaucoma (POAG) is more than that of Primary angle closure glaucoma (PCAG). Glaucoma is the subsequent major reason of blindness after cataract and refractive errors and falls under the category of irreversible blindness. It is estimated that in excess of 3 million individuals are visually handicapped because of glaucoma[3].

EPIDEMIOLOGY

In India, 12 million cases are affected with glaucoma which is the one fifth of the global cases of glaucoma. According to Vellore Eye Study (VES), Prevalence of POAG, PACG, and ocular hypertension were 4.1, 43.2 and 30.8 per 1,000, respectively, that is, 0.41%, 4.32% and 3.08%, respectively. According to Andhra Pradesh Eye Disease Study (APEDS) definite POAG, suspected POAG, and OHT had an age- and gender adjusted prevalence of 1.62%, 0.79%, and 0.32% in those 30 years of age or more, and 2.56%, 1.11%, and 0.42% in those 40 years of age or more, respectively. According to Arvind Comprehensive Eye Survey, the prevalence of any glaucoma was 2.6%, of POAG it was 1.7%, and if PACG it was 0.5%, and secondary glaucoma excluding pseudoexfoliation was 0.3% [4].

So the average prevalence rate of POAG to be considered for the study is 1.24%. Most of the time the cases of glaucoma were undiagnosed and identified during the survey (98.6% in the Chennai Glaucoma Study and 93% in ACES). According to the National Blindness survey 2001, glaucoma

is the third major cause of blindness in India and cause 5.9% of blindness (VA <6/60)[5]. The proportion of blindness caused due to glaucoma has increased three times compared to that found in the previous National survey in between the years 1986–1989[6]. It is seen that glaucoma visual impairment is disparaged in these surveys as the blindness is characterized on visual acuity criteria rather than visual fields which is main feature of glaucoma.

Glaucoma is a chronic, neurodegenerative disease that originates with pressure-induced changes at the optic nerve head (ONH) and subsequent death of retinal ganglion cells (RGCs) with an associated loss of vision. Glaucoma research, similar to that of other neurodegenerative diseases, has seen an increasing focus on neuroprotection[7]. There is no specific targeted therapy for neuroprotection in glaucoma.

APOPTOSIS AND GLAUCOMA

Around half of the ganglion cells do not make central connection within the lateral geniculate nucleus in primates and die from apoptosis. Apoptosis was also involved in the IOP elevation process, by altering the structure of trabecular meshwork and disrupting aqueous humor outflow. Apoptosis is a programmed cell death initiated because of glutamate toxicity and oxidative stress in the cell which causes death of adjacent cell causing progressive visual field defect.

ALZHEIMER DISEASE

Alzheimer's disease (AD) is termed as a progressive neurodegenerative condition in which the progressive developement of dementia in older age occurs. Neuropathological findings in AD consist of neurofibrillary tangles and deposition of amyloid in neuritic plaques concentrated in the hippocampal and parahippocampal areas of brain[8]. Amyloid deposition occurs through the abnormal proteolytic processing of the integral membrane protein amyloid precursor protein (APP), yielding an abnormal accumulation of amyloid-beta peptide consisting of 40 or 42 amino acids[9]. Alzheimer's disease is an age-related, chronic, progressive neurodegenerative disease and is characterized by severe loss of memory, unusual behavior, changes in personality, and a decreased in cognitive function.

SIMILARITIES BETWEEN GLAUCOMA AND ALZHEIMER DISEASE

There are multiple similarities noted in neuropathology of Glaucoma and Alzheimer's disease which are chronic neurodegenerative conditions. Loss of large magnocellular RGCs seen in optic nerve in

patients of Alzheimer's disease. These type of cells dies earliest in glaucoma[10]. The triplet neurofilament proteins that are components of pathological neurofibrillary tangles also demonstrate localization to large RGCs[11,12]. The elevated glutamate[13, 14] and nitric oxide synthase up regulation with reactive oxygen species formation[15] have been seen in glaucoma which are excitotoxic triggers. The same process can be observed in Alzheimer's disease[16]. The increased susceptibility to excitotoxic injuries caused due to synaptic dysfunction in AD which is associated with deficient glutamate transport function[17,18] and caspase activity[19].

The perimetry of mildly affected AD patients shown the visual field defects reported by some studies[20]. The visual field defects in AD patients significantly seen in the infero-temporal and infero-nasal arcuate regions, in a pattern that is very much mimicking to visual field loss in glaucoma. As compare to the open angle glaucoma patients, the visual field loss has been more prominent and occurs at a greater rate in AD patients[21].

VASCULAR PATHOLOGY IN GLAUCOMA AND ALZHEIMER DISEASE

The cerebral amyloid angiopathy (CAA) are caused by vascular deposits of amyloid-beta in AD. The CAA causes degeneration of vascular endothelial and smooth muscle cells[22,23] and hemorrhagic stroke[24]. Amyloid-beta1-40 is found in vasculature of AD patients, whereas amyloid-beta1-42 is reported in senile plaques[25].

Some of the studies reported that vascular amyloid deposition may occur in glaucoma. The pathology of glaucoma is expected to occur because of the high levels of amyloid-beta1-40 and other APP fragments that cause a type of cerebral amyloid angiopathy (CAA) that affects the blood vessels of the retina and optic nerve head[26]. This provides a clue for pathology of splinter haemorrhages in glaucoma patients. Some study findings showed delayed course of apoptosis in AD patients because of caspase activation[27, 28].

AIMS & OBJECTIVES

Acharya Charaka stated in *Siddhisthana* about the importance of *Trimarma (Shiro, Hriday, Basti)* as "The vital breath of human resides in heart, head and urinary bladder. Therefore one needs to make every effort to protect them. Protecting vital parts means preventing imminent causes, adhering to code of conduct for the healthy and remedying the condition if it occurs[29]". So considering the principle of protection of the seat of *Prana* i.e. *Murdhni* (brain) the

neuroprotective levels can be planned for treatment.

MECHANISM OF *BUDDHIBHRANSHA*

The *Buddhi (Prajnya)* is the ultimate function of the factors Indryas, Manas and Prana residing within the brain. When any disruption occurs either at structural or functional level in the brain, the *Prajnya* is directly affected.

LEVELS OF NEUROPROTECTION

Since the neuroprotective strategies are gaining the uprising wave in the field of ophthalmology research, the current integration between AD and Glaucoma will help to discover the newer treatment modalities in *Ayurveda*. As per Acharya *Charaka* the *Marmapalana* (protection of *Trimarma*) *Siddhant* can be categorized on following three levels

i. Primary: Natural Protective provisions.

ii. Secondary: Protective measures for healthy personnel.

iii. Tertiary: Protection at neurological level.

Primary level of neuroprotection includes bony protection, soft tissue protection, CSF protection, healthy compartments of brain, auto regulation. As per *Ayurveda Murdha* (brain) is the seat of *Prana*, *Indriya* and *Mana*. The physiological aspect of the organ is essential in primary level of neuroprotection.

Secondary level of protection includes *Ayurvedic* strategies like *Garbhini Paricharya, Prasuti Paricharya, Shishu Paricharya, Swasthavritta Paricharya*, use of *Panchakarma* treatment, *Rasayan, Dharaniya* and *Adharniya Vega, Trayopastambha Paripalan* and *Yoga* and *Pranayam.*

According to modern science control of B.P, control of lipids, control of sugar, avoidance of narcotics, alcohol, smoking, stress, fast food, use of organic food, etc.

Tertiary protection includes the *Panchakarma* therapies like *Shirodhara, Shirobasti* to alleviate vitiated *Vata Dosha*. *Medhya Rasayana* is useful to nourish the brain tissue and *Sarvadehik Rasa Dhatu. Satvik* diet, *Satvovajay Chikitsha* i.e patient and family counselling. One can use *Suvarna Bhasma, Roupya Bhasma* or a combination of it.

NEWER AREA OF RESEARCH IN GLAUCOMA[30]

Glaucoma is a chronic condition in which there is gradual loss of vision due to damage to the optic nerve. In present era, no treatment modality can reverse the loss of vision due to glaucoma. New ways to treat, control and even cure glaucoma are important for patients and doctors. The key

areas of research in glaucoma identified as are

NEUROPROTECTION

It is a capacity to keep the retinal ganglion cells (RGCs) alive and strengthen their health regardless of the damage occurred by glaucoma. Neuroprotection can be studied with animal studies.

NEUROENHANCEMENT

It is the modality that one can give the cells a "booster shot" and make the sick cells functional again to gain vision in short time duration.

REPLACEMENT OF RGCS

Replacement is done with two key approaches:·

- Endogenous RGC Replacement requires the use of existing cell sources including Müller glia, retinal pigment epithelial cells, and stem cells. The efficient reprogramming of these cells is required to make functional RGCs.
- Exogenous RGC replacement includes using outside sources to generate RGCs, such as induced pluripotent stem cells.

REGENERATION OF OPTIC NERVE

Stimulates the development of axons through an optic nerve injury site to suitable target areas of the brain while preventing abnormal development.

RESTORATION OF VISION

The restoration of vision includes restoring vision that was already lost due to glaucoma. It depends on the ability of brain to recognize to retain some functions.

DISCUSSION

The present review suggest a hypothesis for RGC death in glaucoma involving chronic amyloid-beta neurotoxicity which is similar to that of Alzheimer's disease for the treatment objective in Ayurveda. The potential benefits from this review are that ayurvedic treatments contemplated for Alzheimer's disease may be used to treat glaucoma. Conversely, the neuroprotective approaches designed for the treatment of glaucoma may also be used for other chronic neurodegenerative conditions as per Ayurveda. The single herbs like *Ashwangadha (Withania somnifera), Haridra (Curcuma longa), Kapikachhu (Mucuna pruriens), Bramhi (Bacopa monniera), Punarnava (Boerhavia diffusa), Triphala* (trio of *T. chebula, T. bellerica* and *E. officinalis*) are some of the indigenous medicines which can be tested for the neuroprotective effect and their *Chakshyushya* properties. The animal models can be designed to study the neuroprotection in Glaucoma and the Ayurvedic drugs mentioned in Alzheimer's disease (particularly *Medhya Rasayan*) can be tested in animal models of glaucoma. The glaucoma that can be easily studied on

an animal model having key features as axonal injury at the nerve head as an initial feature of damage, and, selective RGC loss with sparing of other retinal neurons. The pathophysiology of glaucoma is complex and difficult to study in humans. As such, one can rely on animal models that faithfully reproduce important aspects of the condition for understanding mechanisms of disease and developing new therapies. Animal glaucoma models are important for our ongoing efforts to elucidate the disease's natural course and establish therapeutic approaches to delay or reverse the condition's progression. So the animals are necessary in the regards of neuroprotection study of Glaucoma. The present review emphasizes on the study of glaucoma pathway in regards with the pathophysiology of AD through Ayurvedic treatment modalities in animals.

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REFERENCES

1. Fiaz Shamsa. (2015). Concept of Adhimantha: Glaucoma in Ayurveda and modern Science. (1st ed). Varanasi. Choukhambha Orientalia.
2. Dutta, L., & Dutta, N. (2005). Modern Ophthalmology (3rd ed). Jaypee Brothers Medical Publishers Pvt Ltd. p. 1755
3. Saxena R, Singh D, Vashist P. (2013). Glaucoma: An Emerging peril. Indian Journal of Community Medicine. 38(3):135.
4. George R, Ve R, Vijaya L. (2010). Glaucoma in India: Estimated burden of disease. Journal of Glaucoma. 19(6):391-397.
5. Murthy G. (2005). Current estimates of blindness in India. British Journal of Ophthalmology. 89(3):257-260.
6. Mohan M. National Survey of Blindness-India. (1989). NPCB-WHO Report. New Delhi: Ministry of Health and Family Welfare, Government of India; NPCB 11th plan.
7. KUEHN, M., FINGERT, J., & KWON, Y. (2005). Retinal Ganglion Cell Death in Glaucoma: Mechanisms and Neuroprotective
Strategies. Ophthalmology Clinics of North America, 18(3), 383-395.
8. Katzman R. (1986). Alzheimer's disease. N Engl J Med. 314, 964-973.
9. Kang J, Lemaire H, Unterbeck A, Salbaum J, Masters C, Grzeschik K et al. (1987). The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Alzheimer Disease & Associated Disorders. 1(3):206-207.
10. Rosenbaum D, Kalberg J, Kessler J. (1994). Superoxide dismutase ameliorates neuronal death from hypoxia in culture. Stroke. 25(4):857-862.
11. Sadun A, Bassi C. (1990). Optic Nerve Damage in Alzheimer's Disease. Ophthalmology. 97(1):9-17.
12. Vickers J, Schumer R, Podos S, Wang R, Riederer B, Morrison J. (1995). Differential vulnerability of neurochemically identified subpopulations of retinal neurons in a monkey model of glaucoma. Brain Research. 680(1-2):23-35.
13. Vickers J, Hof P, Schumer R, Wang R, Podos S, Morrison J. (1997). Magnocellular and parvocellular visual pathways are both affected in a macaque monkey model of glaucoma. Australian and New Zealand Journal of Ophthalmology. 25:239-243.
14. Dreyer E. (1996). Elevated Glutamate Levels in the Vitreous Body of Humans and Monkeys With Glaucoma. Archives of Ophthalmology. 114(3):299.

15. Dreyer E, Pan Z, Storm S, Lipton S. (1994). Greater sensitivity of larger retinal ganglion cells to NMDA-mediated cell death. NeuroReport. 5(5):629-631.

16. Neufeld A, Sawada A, Becker B. (1999). Inhibition of nitric-oxide synthase 2 by aminoguanidine provides neuroprotection of retinal ganglion cells in a rat model of chronic glaucoma. Proceedings of the National Academy of Sciences. 96(17):9944-9948.

17. Ishii K. (2000). Subacute NO generation induced by Alzheimer's beta-amyloid in the living brain: reversal by inhibition of the inducible NO synthase. The FASEB Journal. 14(11):1485-1489.

18. Li S, Mallory M, Alford M, Tanaka S, Masliah E. (1997). Glutamate Transporter Alterations in Alzheimer Disease Are Possibly Associated with Abnormal APP Expression. Journal of Neuropathology and Experimental Neurology. 56(8):901-911.

19. Tominaga K, Uetsuki T, Ogura A, Yoshikawa K. (1997). Glutamate responsiveness enhanced in neurones expressing amyloid precursor protein. NeuroReport. 8(8):2067-2072.

20. Masliah E, Mallory M, Alford M, Tanaka S, Hansen L. (1998). Caspase Dependent DNA Fragmentation Might Be Associated with Excitotoxicity in Alzheimer Disease. Journal of Neuropathology and Experimental Neurology. 57(11):1041-1052.

21. Trick G, Trick L, Morris P, Wolf M. (1995). Visual field loss in senile dementia of the Alzheimer's type. Neurology. 45(1):68-74.

22. Bayer A, Ferrari F. (2002). Severe progression of glaucomatous optic neuropathy in patients with Alzheimer's disease. Eye. 16(2):209-212.

23. Roses A.D. (1996). Apolipoprotein E alleles as risk factors in Alzheimer's Disease. Annual Review of Medicine. 47(1):387-400.

24. Wisniewski H, Frackowiak J, Mazur-Kolecka B. (1995). In vitro production of β-amyloid in smooth muscle cells isolated from amyloid angiopathy-affected vessels. Neuroscience Letters. 183(1-2):120-123.

25. Mackic J, Weiss M, Miao W, Kirkman E, Ghiso J, Calero M et al. (1998). Cerebrovascular Accumulation and Increased Blood-Brain Barrier Permeability to Circulating Alzheimer's Amyloid β Peptide in Aged Squirrel Monkey with Cerebral Amyloid Angiopathy. Journal of Neurochemistry. 70(1):210-215.

26. Vinters H.V. (1987). Cerebral amyloid angiopathy. A critical review. Stroke. 18, 311-324

27. Prelli F, Castano E, Glenner G, Frangione B. (1988). Differences Between Vascular and Plaque Core Amyloid in Alzheimer's Disease. Journal of Neurochemistry. 51(2):648-651.

28. Zhang Y, Goodyer C, LeBlanc A. (2000). Selective and Protracted Apoptosis in Human Primary Neurons Microinjected with Active Caspase-3, -6, -7, and -8. The Journal of Neuroscience. 20(22):8384-8389.

29. Charakasamhita (1994), Sidhhisthana, 9/9-10, by Chakrapanidatta, 4th edition, published by Choukhamba Sanskrit Sansthan, Varanasi, 718.

30. New Priorities for Glaucoma Research. Glaucoma Research Foundation. (2020). Retrieved 17 April 2020, from https://www.glaucoma.org/news/blog/new-priorities-for-glaucoma-research.php