

Concurrence of Visual Alteration and Cognitive Decline: A Role for Aquaporins?

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Article Info

Received: April 29, 2022

Accepted: May 20, 2022

Published: June 06, 2022

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Citation: Reza Rastmanesh. (2022) "Concurrence of Visual Alteration and Cognitive Decline: A Role for Aquaporins?", *Ophthalmology and Vision Care*, 2(2); DOI: <http://doi.org/05.2022/1.1029>.

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Abstract

Visual and cognitive impairment generally coincide, at least in the elderly. Objective visual impairment is connected to an increased risk of incident dementia. Conversely, vision and hearing improvement has a positive impact on neuropsychiatric symptoms. Other therapies like cataract surgery reduce the risk of developing mild cognitive impairment independently of visual acuity. These findings suggest that there might be common correlates by which cognitive impairments specifically link to specific ocular problems. AQPs are widely expressed and distributed in the nervous system and eye. In this short perspective, using empirical evidence, I will demonstrate a role for AQP1 and AQP4 as possible correlates for concurrence of ocular-brain pathologic pathways.

Keywords: ocular; cognitive; memory; myopia; hyperopia; aquaporin.

Introduction:

Visual and cognitive impairment usually co-occur, particularly in the elderly [1]. Just very recently, in secondary analysis of a prospective longitudinal cohort study of older women with formal vision, it was found that objective visual impairment is associated with an increased risk of incident dementia [2]. Furthermore, results of the only interventional study in patients with dementia clearly provided the first experimental proof that vision and hearing improvement (by merely prescribing and fitting of lenses or hearing aids) has a positive impact on neuropsychiatric symptoms [3]. The surprise is that other interventions such as cataract surgery reduce the risk of developing mild cognitive impairment -albeit not for severe dementia- independently of visual acuity [4]. Even more interesting is the results of study carried out by Cavérian et al [5] that shows that children with an ophthalmologic disorder may experience difficulties with visuospatial tasks despite corrected-to-normal visual acuity.

These reports suggest that there might be a common mechanism by which cognitive impairments specifically link to specific ocular problems. Ruitter et al described unusual case of a 28-year-old woman with an aquaporin4 (AQP4) antibody-seropositive neuromyelitis optica spectrum disorder who presented with cognitive impairment, symptoms of psychosis and autonomic dysregulation [6]. Similar psychiatric symptoms have been previously described before in a few cases [7-13]. One might further question whether there is a causal relationship between particular cognitive features (such as memory deficits, etc.) and visual acuity and/or ocular situations; and whether there are common elements between these two?

For the purpose of this short communication, we focus on aquaporins (AQPs) and only visual and cognitive evidence. AQPs are integral channel proteins and their main function is to facilitate transport of water across cell membranes in response to osmotic gradients [14]. AQPs are widely expressed and distributed in the nervous system and eye.

AQPs in the brain and eye:

AQPs in the brain:

Three types of aquaporins (AQP1, AQP4 and AQP9) are expressed in the brain. AQP4 as the most predominant brain water channel is expressed in astrocyte endfeet facing brain capillaries, nodes of Ranvier and perisynaptic spaces. It is involved in brain



edema formation and resolution, and clearance of K⁺ released during neuronal activity. AQP1, which is expressed in epithelial cells of choroid plexus is mostly involved in cerebrospinal fluid formation. Finally, AQP9, which is present in astrocytes and in subpopulations of neurons, is involved in the brain energetic.

AQPs in the human lens:

At the ocular surface, it is known that AQP1 is expressed in corneal endothelium [15], AQP3 and AQP5 in corneal epithelium [16], and AQP3 in conjunctival epithelium [17]. AQP0 is expressed in lens fiber cells, AQP1 in lens epithelium, AQP1, AQP4 are expressed in ciliary epithelium and AQP4 is expressed in retinal Müller cells [16].

On the other hand, by playing central roles in the maintenance of ocular lens homeostasis, some AQPs (AQP0, AQP1 and AQP5) contribute to the establishment and maintenance of the overall optical properties of the human lens. Three aquaporins, AQP0, AQP1 and AQP5, each with differential functional properties, are extensively and differentially expressed in the different regions of the human lens.

Furthermore, the diversity of AQP functionality is increased in the absence of protein turnover by age-related modifications to lens AQPs that are proposed to alter AQP function in the different regions of the lens. These regional differences in AQP functionality are proposed to contribute to the generation and directionality of the lens internal microcirculation; a system of circulating ionic and fluid fluxes that delivers nutrients to and removes wastes from the lens faster than could be achieved by passive diffusion alone. In this review, we present how regional differences in lens AQP isoforms potentially contribute to this microcirculation system by highlighting current areas of investigation and emphasizing areas where future work is required. [18].

AQPs, myopia and memory:

AQP4 and AQP1, the two primary AQPs of the central nervous system (CNS), regulate brain water and cerebrospinal fluid (CSF) movement and contribute to vasogenic and cytotoxic edema, where they control the size of the extracellular and intracellular fluid volumes, respectively. AQP4 is crucial to dysfunctions in glutamate metabolism, synaptogenesis, and memory consolidation [19].

AQPs and myopia:

Goodyear et al were the first to demonstrate the presence of AQP4 protein in the chick retina. They showed the association of AQP4 expression in the inner retina with the initiation of form deprivation and the period of fastest axial elongation. The increased expression of AQP4 channels near the vitread border during the time of rapid growth suggested a novel role for AQP4 as a channel for movement of retinal fluid into the vitreous in form-deprived chicks [20]. Here, it is crucial to recall that AQP4 is the predominant AQP in the mammalian retina, which is reported to be highly expressed on the Müller glial cells. By modifying the neurotransmitters, concentrations of ions, and other neuroactive substances within the extracellular space between the

inner and the outer limiting membrane, Müller cells modulate neuronal activity. Müller cells preserve extracellular homeostasis, particularly with regard to the spatial buffering of extracellular potassium (K⁺) via inward rectifying K⁺ channels (i.e., Kir channels). Both AQP4 and Kir channels are involved in regulating the extracellular environment in the retina and brain. In a brilliant review, Goodyear et al extensively discussed that during light activation AQP4 channels are possibly to be the conduit for facilitating fluid homeostasis in the inner retina. AQP4 channels play a role in the regulation of ocular volume and growth. Within the review, they cite some researches showing that the level of AQP4 expression is tightly associated with environmentally driven manipulations of light activity on the retina, and consequently, the development of myopia [20].

Furthermore, two recent state-of-the-art studies have shown that AQP-1 depletion downregulates the sclera biomechanical strength through changing of choroidal thickness (CT) and axial length, providing information for better understanding the mechanism of myopia development [21;22]. Mechanistically, alterations in JNK1 phosphorylation might regulate AQP-1 and CT during the recovery from myopia and the recovery time. Therefore, JNK1 is suggested as a potential therapeutic target for preventing/treating myopia [23].

Myopia and memory:

It is long established that myopia is associated with visual memory [24]. At gene level, RASGRF1 gene locus is associated with both hippocampus-dependent memory [25] and myopia [25;26]. Using a genome-wide association study for refractive error in 4,270 individuals from the TwinsUK cohort, Hysi et al identified a susceptibility locus for refractive error on 15q25 (rs8027411, $P = 7.91 \times 10^{-8}$). They further replicated this association in 6 adult cohorts of European ancestry with a combined 13,414 persons. Intriguingly, 15q25 locus overlapped the transcription initiation site of RASGRF1 [26]. It is notable that RASGRF1 is highly expressed in retina and neurons and is implicated in retinal function [27] and memory consolidation [25;28]. More crucially, Hysi et al experiment showed that RASGRF1 (-/-) mice present significantly a heavier average crystalline lens.

Chebib et al evaluated effects of cis-3-ACPBPA –which is conformationally restricted analogs of the orally active GABA (B/C) receptor antagonist (3-aminopropyl)-n-butylphosphinic acid (CGP36742 or SGS742) – on dissociated rat retinal bipolar cells and dose-dependently inhibited the native GABA(C) receptor. They showed that cis- and trans-3-ACPBPA when applied to the eye as intravitreal injections in the chick model prevents experimental myopia development and inhibits the associated vitreous chamber elongation in a dose-dependent manner. Interestingly, doses 10 times greater than needed to inhibit recombinant GABA(C) receptors created the anti-myopia effects. More intriguingly, cis- (30 mg/kg) and trans-3-ACPBPA (100 mg/kg) when administered intraperitoneally in male Wistar rats, enhanced learning and memory; compared with vehicle there was a statistically significant reduction ($p < 0.05$; $n = 10$) in time for rats to find the platform in the Morris water maze task. In short, the memory and refractive effects of CGP36742 may partly be attributed to its GABA(C) activity, suggesting a causal link



between myopia-improvement and memory enhancement [29]. It worth to remind that GABA(C) receptors play a role in memory-related disorders [30], myopia [31] and circadian rhythms [32].

As for high hyperopia which is severe form of refractive error, genetic factors are key in its development, however the exact gene responsible for this condition was mostly unknown until very recently. In a large Chinese family with autosomal dominant high hyperopia, Xiao et al [33] using a genome-wide linkage scan mapped the high hyperopia to chromosome 11p12-q13.3, with maximum log of the odds scores of 4.68 at $\theta = 0$ for D11S987. Furthermore, parallel whole-exome sequencing manifested a novel c.3377delG (p.Gly1126Valfs*31) heterozygous mutation in the MYRF gene within the linkage interval. Whole-exome sequencing in other 121 probands with high hyperopia detected other novel mutations in MYRF within two other families: a de novo c.3274_3275delAG (p.Leu1093Profs*22) heterozygous mutation and a c.3194+2T>C heterozygous mutation. It was found that all three mutations are located in the C-terminal region of MYRF and are anticipated to lead in truncation of that portion. Interestingly, two patients from two of the three families developed angle-closure glaucoma. These findings support that truncation mutations in the C-terminal region of MYRF are responsible for autosomal dominant high hyperopia and provide preliminary clues for understanding the functional role of the C-terminal region of this critical myelin regulatory factor, as well as the molecular pathogenesis of high hyperopia and its associated angle-closure glaucoma.

Here, it worth to remind that demyelination is a common pathological characteristic of a large number of neurodegenerative diseases including Huntington's disease (HD) and multiple sclerosis (MS). Yin and colleagues [34] showed that reduced MYRF phosphorylation inhibits MYRF's binding to mutant huntingtin and increases the expression of myelin-associated genes, suggesting that PRKG2-regulated phosphorylation of MYRF is involved in demyelination and can serve as a potential therapeutic target for reducing demyelination

Conclusion:

Collectively, above mentioned findings demonstrate a possible role for AQP1 and AQP4 as common correlates for concurrence of ocular-CNS pathologic pathways.

In this line, particular association between AQP1 [35;36], AQP4 [36;37], and AQP9 [38] with Alzheimer diseases (AD) is well-established. The further elaboration of this idea leads into the involvement of Kir4.1 channel which deserves a separate paper.

Declaration of conflicting interests:

The Author declares that there is no conflict of interest

References:

1. Marquee M, Castillo-Marti M, Valero S, Martinez J, Sanchez D, Hernandez I, Rosendo-Roca M, Vargas L, Maul eon A, Rodriguez-Gomez O, Abdel our C, Gil S, Santos-Santos MA, AL egret M, Espinosa A, Ortega G, Perez-Cordon A, Samaria

- A, Roberto N, Moreno-Gray S, de R, I, Simo R, Cousin A, Hernandez C, Orellana A, Monte-Rubio G, Banquet A, Ruiz A, Tar raga L, Boada M: Visual impairment in aging and cognitive decline: experience in a Memory Clinic. *Sic Rep* 18-6-2019;9:8698.
2. Tran EM, Stefanick ML, Henderson VW, Rapp SR, Chen JC, Armstrong NM, Espeland MA, Gower EW, Shadyab AH, Li W, Stone KL, Pershing S: Association of Visual Impairment With Risk of Incident Dementia in a Women's Health Initiative Population. *JAMA Ophthalmol* 1-6-2020;138:624-633.
3. Leroi I, Simkin Z, Hooper E, Wolski L, Abrams H, Armitage CJ, Camacho E, Charalambous AP, Collin F, Constantinidou F, Dawes P, Elliott R, Falkingham S, Frison E, Hann M, Helmer C, Himmelsbach I, Hussain H, Marie S, Montecelo S, Thodi C, Yeung WK: Impact of an intervention to support hearing and vision in dementia: The SENSE-Cog Field Trial. *Int J Geriatr Psychiatry* 2020;35:348-357.
4. Miyata K, Yoshikawa T, Morikawa M, Mine M, Okamoto N, Kurumatani N, Ogata N: Effect of cataract surgery on cognitive function in elderly: Results of Fujiwara-kyo Eye Study. *PLoS One* 2018;13:e0192677.
5. Cavezian C, Vilayphonh M, Vasseur V, Caputo G, Laloum L, Chokron S: Ophthalmic disorder may affect visuo-attentional performance in childhood. *Child Neuropsychol* 2013;19:292-312.
6. Ruiter AM, Meilof JF, Somanje-Bolweg RRJ, van GE, Kalkers NF: Autonomic Dysregulation, Cognitive Impairment, and Symptoms of Psychosis as an Unusual Presentation in an Anti-Aquaporin 4-Positive Patient. *Case Rep Neurol* 2017;9:12-16.
7. Alam A, Patel R, Locicero B, Rivera N: Neuromyelitis optica presenting with psychiatric symptoms and catatonia: a case report. *Gen Hosp Psychiatry* 2015;37:274-2.
8. Baba T, Nakashima I, Kanbayashi T, Konno M, Takahashi T, Fujihara K, Mitsu T, Takeda A, Shiga Y, Ogawa H, Itoyama Y: Narcolepsy as an initial manifestation of neuromyelitis optica with anti-aquaporin-4 antibody. *J Neurol* 2009;256:287-288.
9. Deguchi K, Kono S, Deguchi S, Morimoto N, Ikeda M, Kurata T, Ikeda Y, Matsuura T, Kanbayashi T, Takahashi T, Abe K: A patient with anti-aquaporin 4 antibody presenting hypersomnolence as the initial symptom and symmetrical hypothalamic lesions. *J Neurol Sic* 15-1-2012;312:18-20.
10. Kume K, Deguchi K, Ikeda K, Takata T, Kokudo Y, Kamada M, Touge T, Takahashi T, Kanbayashi T, Masaki T: Neuromyelitis optica spectrum disorder presenting with repeated hypersomnia due to involvement of the hypothalamus and hypothalamus-amygdala linkage. *Mult Scler* 2015;21:960-962.
11. Okuma H, Matsumura K, Hatanaka Y, Saito F, Sonoo M: Sudden onset of sleep due to hypothalamic lesions in neuromyelitis optica spectrum disorder positive for anti-aquaporin-4 antibody. *Mult Scler* 2014;20:1407-1408.
12. Suzuki K, Nakamura T, Hashimoto K, Miyamoto M, Komagamine T, Nagashima T, Izawa N, Kanbayashi T, Takahashi T, Hirata K: Hypothermia, hypotension, hypersomnia, and obesity associated with hypothalamic lesions in a patient positive for the anti-aquaporin 4 antibody: a case report and literature review. *Arch Neurol* 2012;69:1355-1359.



13. Woolley J, Douglas VC, Cree BA: Neuromyelitis optica, psychiatric symptoms and primary polydipsia: a case report. *Gen Hosp Psychiatry* 2010;32:648.
14. Agre P: The aquaporin water channels. *Proc Am Thorac Soc* 2006;3:5-13.
15. Preston GM, Smith BL, Zeidel ML, Moulds JJ, Agre P: Mutations in aquaporin-1 in phenotypically normal humans without functional CHIP water channels. *Science* 9-9-1994;265:1585-1587.
16. Verkman AS, Ruiz-Ederra J, Levin MH: Functions of aquaporins in the eye. *Prog Retin Eye Res* 2008;27:420-433.
17. Levin MH, Verkman AS: Aquaporin-3-dependent cell migration and proliferation during corneal re-epithelialization. *Invest Ophthalmol Vis Sci* 2006;47:4365-4372.
18. Schey KL, Petrova RS, Gletten RB, Donaldson PJ: The Role of Aquaporins in Ocular Lens Homeostasis. *Int J Mol Sic* 12-12-2017;18.
19. Filippidis AS, Carozza RB, ReKate HL: Aquaporins in Brain Edema and Neuropathological Conditions. *Int J Mol Sic* 28-12-2016;18.
20. Goodyear MJ, Junghans BM, Giummarra L, Murphy MJ, Crewther DP, Crewther SG: A role for aquaporin-4 during induction of form deprivation myopia in chick. *Mol Vis* 8-2-2008;14:298-307.
21. Chen W, Zhang H, Zhang Y, Wang Q, Wang Y, Li ZW: Relationship between Aquaporin-1 Protein Expression and Choroidal Thickness during the Recovery of Form-deprivation Myopia in Guinea Pigs. *Curr Eye Res* 2020;45:705-712.
22. Li Z, Chen W, Zhang H, Cui C: The Aquaporin-1 Depletion Downregulates the Sclera Biomechanical Strength. *Curr Eye Res* 2020;45:1240-1244.
23. Chen W, Li Z, Wang Q, Wang Y, Zhang Y: The Role of C-Jun N-terminal Kinase-1 in Controlling Aquaporin-1 and Choroidal Thickness during Recovery from Form-deprivation Myopia in Guinea Pigs. *Curr Eye Res* 2021;46:885-894.
24. Mohindra I: Vision profile of deaf children. *Am J Optom Physiol Opt* 1976;53:412-419.
25. Barman A, Assmann A, Richter S, Soch J, Schutze H, Wustenberg T, Deibele A, Klein M, Richter A, Behnisch G, Duzel E, Zenker M, Seidenbecher CI, Schott BH: Genetic variation of the RASGRF1 regulatory region affects human hippocampus-dependent memory. *Front Hum Neurosci* 2014;8:260.
26. Hysi PG, Young TL, Mackey DA, Andrew T, Fernandez-Medarde A, Solouki AM, Hewitt AW, Macgregor S, Vingerling JR, Li YJ, Ikram MK, Fai LY, Sham PC, Manyes L, Porteros A, Lopes MC, Carbonaro F, Fahy SJ, Martin NG, van Duijn CM, Spector TD, Rahi JS, Santos E, Klaver CC, Hammond CJ: A genome-wide association study for myopia and refractive error identifies a susceptibility locus at 15q25. *Nat Genet* 2010; 42:902-905.
27. Fernandez-Medarde A, Barhoum R, Riquelme R, Porteros A, Nunez A, de LA, de Las RJ, de l, V, Varela-Nieto I, Santos E: RasGRF1 disruption causes retinal photoreception defects and associated transcriptomic alterations. *J Neurochem* 2009; 110:641-652.
28. Brambilla R, Gnesutta N, Minichiello L, White G, Roylance AJ, Herron CE, Ramsey M, Wolfer DP, Cestari V, Rossi-Arnaud C, Grant SG, Chapman PF, Lipp HP, Sturani E, Klein R: A role for the Ras signalling pathway in synaptic transmission and long-term memory. *Nature* 20-11-1997;390:281-286.
29. Chebib M, Hinton T, Schmid KL, Brinkworth D, Qian H, Matos S, Kim HL, bdel-Halim H, Kumar RJ, Johnston GA, Hanrahan JR: Novel, potent, and selective GABAC antagonists inhibit myopia development and facilitate learning and memory. *J Pharmacol Exp Ther* 2009;328:448-457.
30. Johnston GA, Chebib M, Hanrahan JR, Mewett KN: GABA(C) receptors as drug targets. *Curr Drug Targets CNS Neurol Disord* 2003;2:260-268.
31. Hanrahan JR, Mewett KN, Chebib M, Matos S, Eliopoulos CT, Crean C, Kumar RJ, Burden P, Johnston GA: Diastereoselective synthesis of (+/-)-(3-aminocyclopentane)alkylphosphinic acids, conformationally restricted analogues of GABA. *Org Biomol Chem* 7-7-2006;4:2642-2649.
32. Arnaud C, Gauthier P, Gottesmann C: Study of a GABAC receptor antagonist on sleep-waking behavior in rats. *Psychopharmacology (Berl)* 2001;154:415-419.
33. Xiao X, Sun W, Ouyang J, Li S, Jia X, Tan Z, Hejtmancik JF, Zhang Q: Novel truncation mutations in MYRF cause autosomal dominant high hyperopia mapped to 11p12-q13.3. *Hum Genet* 2019;138:1077-1090.
34. Yin P, Liu Q, Pan Y, Yang W, Yang S, Wei W, Chen X, Hong Y, Bai D, Li XJ, Li S: Phosphorylation of myelin regulatory factor by PRKG2 mediates demyelination in Huntington's disease. *EMBO Rep* 4-6-2020;21:e49783.
35. Misawa T, Arima K, Mizusawa H, Satoh J: Close association of water channel AQP1 with amyloid-beta deposition in Alzheimer disease brains. *Acta Neuropathol* 2008;116:247-260.
36. Perez E, Barrachina M, Rodriguez A, Torrejon-Escribano B, Boada M, Hernandez I, Sanchez M, Ferrer I: Aquaporin expression in the cerebral cortex is increased at early stages of Alzheimer disease. *Brain Res* 12-1-2007;1128:164-174.
37. Wilcock DM, Vitek MP, Colton CA: Vascular amyloid alters astrocytic water and potassium channels in mouse models and humans with Alzheimer's disease. *Neuroscience* 31-3-2009;159:1055-1069.
38. Liu JY, Chen XX, Chen HY, Shi J, Leung GP, Tang SC, Lao LX, Yip HK, Lee KF, Sze SC, Zhang ZJ, Zhang KY: Downregulation of Aquaporin 9 Exacerbates Beta-amyloid-induced Neurotoxicity in Alzheimer's Disease Models In vitro and In vivo. *Neuroscience* 1-12-2018;394:72-82.