Complement Dysregulation in Glaucoma Patients

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Glaucoma is a progressive neurodegenerative disease characterized by damage to the optic nerve that results in irreversible vision loss. While the exact pathology of glaucoma is not well understood, emerging evidence suggests that dysregulation of the complement system, a key component of innate immunity, plays a crucial role. In glaucoma, dysregulation of the complement cascade and impaired regulation of complement factors contribute to chronic inflammation and neurodegeneration.

Keywords: glaucoma ; complement system ; inflammation

1. Complement Dysregulation in Glaucomatous Retina

Evidence that the complement system is involved in glaucoma comes from studies demonstrating increased expression of complement proteins in glaucomatous donor eyes as compared to age-matched control eyes without glaucoma. For instance, research by Tezel and colleagues in 2010 revealed that CFH, an inhibitor of the alternative complement pathway, is reduced in patients with glaucoma [1]. In addition, there was an increased expression of complement components (C1S, C1R, C1Q, C3, C4B, C7–9, MASP1, MASP2), and complement receptors (CR1, CR2, C5AR) with a concomitant decreased expression of complement regulators (CFH, C4BP, and clusterin) detected in glaucomatous retinas. With immunolabeling, the most significant increase in complement proteins and receptors was observed in the inner retina, specifically in the retinal ganglion cells (RGCs) and inner plexiform layers. Additional studies further confirm the increased expression of the classical components C1Q [2][3] and C3 [2] in human glaucomatous retinas. Increased deposition of C1Q, C3, and MAC (membrane attack complex) is observed in the nerve fiber layer and RGC layer of human eyes with glaucoma and even in eyes with ocular hypertension but no evidence of optic nerve damage [2].

Furthermore, an increased expression of C3 has also been detected in human donor retinas with ocular hypertension, along with decreased expression of complement regulators, C1Q-binding protein (C1QBP), and C1-inhibiting factor (C1-INH) [4]. The similarity of this observation to the glaucomatous human retina suggests its relevance to the early synaptic elimination observed in ocular hypertensive retinas [1][2]. It has been suggested that complement activation plays a role in the early loss of RGC synapses in experimental glaucoma [5][6]. Therefore, it would be intriguing to investigate whether complement-mediated tissue clearance is involved in the elimination of dysfunctional RGC synapses in the ocular hypertensive human retina and whether complement-mediated collateral damage to RGCs precedes the development of glaucoma in humans.

2. Complement Dysregulation in Aqueous Humor and Serum in Glaucoma Patients

Multiple proteomic studies demonstrate significant alterations in complement proteins in the aqueous humor and serum of glaucoma patients, implicating the complement pathway in the pathogenesis of glaucoma [7][8][9][10][11][12][13][14].

2.1. Primary Angle-Closure Glaucoma

A recent study examined the proteome profile of the aqueous humor of glaucoma patients as compared to age-matched control cataract patients [12]. The study especially focused on different types of glaucoma including primary acute angle-closure glaucoma (PAACG), primary chronic angle-closure glaucoma (PCACG), and neovascular glaucoma (NVG). The study, among others, revealed that the activation of the immune response is related to glaucoma. They found a significant increase in the expression of complement proteins (C1R, C2, C4A/C4B, C5, C6, C8A, C9, CFB, CFI, and VTN) in glaucoma patients as compared to the control cataract patients.

Interestingly, in older women (≥60 years) with primary angle-closure glaucoma (PACG), a higher risk of progressive visual field loss was found to be significantly associated with decreased serum levels of C3, C4, and C1Q at baseline [15].

However, the same association was not observed in younger women (<60) or men (<60 and ≥60 years). It was proposed that changes in the sex hormone 17-β-estradiol, which is anti-inflammatory [16] and significantly reduced in older women with PACG and progressive visual field loss [17], may explain the differences in the association of C3, C4, and C1Q with visual field loss between older women as compared to young women and men. However, while C3, C4, and C1Q levels at baseline may serve as biomarkers for predicting visual field loss in older women with PACG, further research is needed to fully elucidate the connection between sex, age, and the complement system.

2.2. Primary Open-Angle Glaucoma

Significant dysregulation of complement proteins was observed in the aqueous humor of individuals with progressive primary open-angle glaucoma (POAG) as compared to control individuals with cataracts [18]. The complement proteins significantly upregulated included C1QB, CFI, C9, VTN, and complement C8 alpha chain (C8A), while C4b binding protein alpha (C4BPA), CFH, C5, C6, and C7 were downregulated. This shift in the expression of complement activators and regulators in the aqueous humor of progressive POAG patients coincides with a shift in complement activity in the retina and the death of RGCs. However, it remains uncertain whether these changes in aqueous humor composition are a cause or an effect of altered complement activity in the retina. Interestingly, a study conducted by Vashishtha et al. detected a downregulation of C6 as well as the MAC component C8G in the aqueous humor of POAG samples compared to control individuals with cataract [14].

Complement components C3, C1Q, C8 beta chain (C8B), and VSIG (V-set and immunoglobulin domain containing protein 4) have also been found to be upregulated in the aqueous humor of POAG patients when compared to control individuals with cataract [11][14][19]. Interestingly, significant alterations in the expression of several complement components in the aqueous humor have not only been found in POAG, PCACG, PAACG, and NVG, but also in NTG (normal tension glaucoma), where Lee et al. reported an upregulation of C7 in aqueous humor NTG patients [20]. Similarly, significant upregulation of the complement components VTN, C3, CFH, ficolin-3 (FCN3), and C4A was also found in the serum of POAG patients [21].

By contrast, another study found a significant decrease in complement C3 levels in the serum of patients with POAG, and this decrease was associated with increased severity of the disease [22]. Others suggest the ratio between complement factors C3a and C3 could serve as a marker for complement activation [13]. The levels of C3a and C3 were measured in the aqueous humor and serum of glaucoma and control (cataract) patients, and a significant increase in the C3a/C3 ratios in the aqueous humor and serum was only found in POAG patients with progressive disease. Moreover, there was a positive correlation between glaucoma progression and the C3a/C3 ratio in both the aqueous humor and serum. In patients with stable POAG, no increase in the C3a/C3 ratio was observed. Together, these results support a strong link between increased complement activation and glaucoma progression. Moreover, glaucoma progression can be linked to both local and systemic changes in complement activation.

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