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Subcortical visual pathway may be a new way for early diagnosis of glaucoma

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A B S T R A C T

Glaucoma is the leading cause of irreversible blindness worldwide, which is now viewed as a disease of brain with pathogenesis not fully understood. The main diagnostic methods are examining the retinal nerve fiber layer through optical coherence tomography and investigating visual field defect, but these methods present disadvantages in clinical practice. Studies have shown that patients with glaucoma often suffer negative emotion like anxiety and depression which is related to abnormal or reduced amygdala. Moreover, selective reduction of fMRI responses to transient achromatic stimuli in the superficial layer of the superior colliculus was found in the early glaucoma patients. By summarizing previous studies, we developed a hypothesis: superior colliculus-pulvinar-amygdala subcortical visual pathway may be involved in the incidence or progression of glaucoma. Validating this hypothesis would further clarify the mechanism of glaucoma and lead to the development of a more sensitive method for making an early diagnosis of glaucoma.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide. The global population of individuals with glaucoma between 40 and 80 years old is predicted to increase to 76 million by 2020 and 111.8 million by 2040 [1]. However, the pathogenesis of glaucoma is not yet fully clear. Moreover, finding a method for the early diagnosis of glaucoma is a huge challenge.

Currently, glaucoma diagnoses are often based on identifying structural damage to the optic nerve and deficit of visual function. Visual field (VF) examination is considered to be the gold standard for evaluating functional visual loss in glaucoma and for detecting disease progression [2]. VF examination is necessary in tracking functional loss and especially informative in moderate to advanced glaucoma [3], but VF testing is subjective and has low reproducibility [4]. The data have shown that glaucomatous optic neuropathy cannot be detected by standard automated perimetry in 54% of glaucoma patients [5]. Moreover, retinal ganglion cell (RGC) apoptosis, which has been recognized as the earliest form of cell death in glaucoma, is responsible for visual field loss [6], but about 40% of RGCs will be lost before signs of damage can be perceived through perimetry [7]. On the other hand, determining the retinal nerve fiber layer (RNFL) thickness through optical coherence tomography (OCT) is another important measurement for the diagnosis of glaucoma. The results from previous studies found that RNFL tended to be more sensitive than VF in early detection of glaucoma. The RNFL has been found to become thin before VF impairment [8,9]. However, measurement by OCT can only provide structural information. And, several factors affect OCT accuracy, such as image quality, opacities, scan alignment and centration, and segmentation errors, which cause it can't replace VF as gold standard for glaucoma diagnosis. Thus, it is imperative to improve or find new methods for the early diagnosis of glaucoma.

Previous studies have shown that glaucoma is associated with the degeneration of brain [10]. Patients with glaucoma often suffer negative emotion like anxiety and depression which is related to abnormal or reduced amygdala. In addition, superior colliculus (SC) is also possibly linked to the pathogenesis of glaucoma. Selective stimuli reduction of fMRI in the superficial layer of the SC was found in the early

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glaucoma patients. Recently, subcortical visual pathway was found proceeding from the retina to SC, pulvinar, and amygdala, which was mainly responsible for processing unaware, coarse and early visual information [11]. Thus, we hypothesize that the subcortical visual pathway may be involved in glaucoma and technique targeting the pathway may be a new and effective way to detect glaucoma early.

Hypothesis

By summarizing the results of the previous studies, we came up with the following hypothesis: the dysfunction of the subcortical visual pathway might be involved in glaucoma and further serve as a new method for diagnosing glaucoma early. Deficits in the pathway may play an important part in the incidence or progression of glaucoma.

Evaluation of the hypothesis

It was reported that anxiety and depression was more prevalent in glaucoma patients [12–16]. Statistically significant association between glaucoma and anxiety/depression was also found in a large population [17]. Patients with more severe glaucoma may suffer depression more easily [18]. Pseudoexfoliative glaucoma patients were more depressed than controls [19]. Patients with primary angle closer glaucoma (PACG) presented a higher level of depression than patients with primary open angle glaucoma (POAG) [20]. Glaucoma patients had higher Hospital Anxiety and Depression Scale score than cataract patients [21].

Studies suggested that amygdala played an important role in regulating emotion [22]. MRI studies found reduced amygdala volumes in depressed patients [23,24]. Moreover, a 3T MRI study demonstrated the left amygdala volume of POAG patients significantly decreased compared to the normal control [25]. Therefore, we speculate that the abnormal amygdala is probably involved in the incidence of glaucoma and depression. In addition, SC is also possibly linked to the pathogenesis of glaucoma. fMRI study showed that 'large cells' in the human SC suffered selective loss of response to transient achromatic stimuli at the early stage of POAG [26]. Experimental model of glaucoma suggested a retinotopic misconnection between retina and SC followed by early apoptotic events and oligodendrocyte and microglial response in the lateral SC at the early stage of ocular hypertension [27].

In conclusion, there is evidence that patients with glaucoma are often afflicted by anxiety and depression which is associated with abnormal or reduced amygdala. Changes in SC is also observed among glaucoma subjects. It seems reasonable to speculate that deficits in SC-pulvinar-amygdala subcortical visual pathway may be associated with glaucoma. Techniques targeting the pathway might be a more sensitive and effective way to detect glaucoma early.

Consequences of the hypothesis and discussion

Currently, it is believed that glaucoma is not only an ocular disease but also a brain neurodegenerative disorder characterized by progressive damage of the optic nerve head and different visual brain centers [28,29]. Proving the hypothesis may need a significant reconsideration of methods to treat glaucoma.

The subcortical visual system is divided into magnocellular and parvocellular pathway [30]. Studies have shown that the magnocellular pathway may contribute to cognitive abilities like reading, working memory, executive functioning, and attention [31–33]. It has been reported that glaucoma is related to a decline of cognitive abilities [34]. Therefore, diagnosing glaucoma early by examining the subcortical visual pathway will also be helpful for preventing glaucoma patients' decline in cognitive performance in advance. In addition, fMRI studies suggested that subcortical visual pathway might be involved in coding the hole feature, which could be detected by measuring the topological properties of the visual system [35,36]. Thus, it is meaningful to conduct a study investigating the early-stage glaucoma diagnostic efficacy via the strategy targeting abnormal subcortical visual pathway by measuring the topological properties.

By summarizing evidence from previous studies, we hypothesize that the subcortical visual pathway may be involved in the pathogenesis of glaucoma. Validating this hypothesis would further clarify the mechanism behind glaucoma and may lead to the development of a more sensitive method for early glaucoma diagnosis.

Conflict of interest

The authors declare that there is no conflict of interest.

Sources of support

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