Positioning value of objective analysis of macular ganglion cell complex (mGCC) in optic pathway-related neuro-ophthalmology

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Research article

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Abstract

Background: This study aimed to explore the positioning value of objective analysis of macular ganglion cell complex (mGCC) in optic pathway-related neuro-ophthalmology diseases.

Methods: This retrospective study included 32 patients with optic pathway-related neuro-ophthalmology diseases. A swept-source optical coherence tomography (SS-OCT) was used to scan and analyze the morphological characteristics of mGCC thickness and peripapillary retinal nerve fiber layer (pRNFL) thickness in these patients, and then they were compared with the visual field changes at the corresponding phase to analyze their relationship.

Results: In optic pathway-related neuro-ophthalmologic diseases, the morphological characteristics of mGCC thickness demonstrated similar characteristic changes to that of visual field, and mGCC analysis remained to be objective.

Conclusion: The application of SS-OCT to examine the morphological changes of mGCC thickness has position value of objective analysis in the diagnosis and treatment of optic pathway-related neuro-ophthalmologic diseases.

Background

With the development of ophthalmic diagnostic techniques, swept-source optical coherence tomography (SS-OCT) is widely used in the diagnosis and treatment of neuro-ophthalmologic diseases due to its rapid process, high-resolution and non-invasiveness.1-3 This technique provides favorable conditions for observing the retinal ganglion cells in the optic nerve and macular area.4,5 Most of the previous OCT studies focused on observing the thickness of the optic nerve fiber layer present around the optic disc and the thickness of the retinal ganglion cells in the macular area,6-9 while studies describing the morphological characteristics of the ganglion cells in the macular area are lacking. Hence, in the present study, SS-OCT was used to examine the topographical map of macular ganglion cell complex (mGCC) thickness as well as the nerve fiber thickness around the optic disc. The probability graph of atrophied disappear changes of mGCC combined with visual field examination was adopted to analyze the changes in imaging of the optic pathway-related neuro-ophthalmologic diseases. We aimed to observe the changes in the optic nerve of the above diseases from a new imaging perspective, thereby deepening the understanding of the pathological and physiological changes of these diseases.

Methods

General data: Thirty-two patients with optic pathway-related neuro-ophthalmology diseases who visited our ophthalmology center were collected (Table 1), which included 15 males and 17 females, aged 5-77 years, and with a range of visual acuity of 20/800-20/16. Among them,12 cases had pituitary tumors, 3 had craniopharyngioma, 2 had transparent septum deficiency, 3 had hemangioma, 2 had vascular
malformation, 6 had ischemia, 1 had meningioma, 1 had schwannoma, 1 had chordoma or metastatic carcinoma and 1 had other tumors.

Methods

Routine examinations including distance visual acuity, near visual acuity, intraocular pressure, slit lamp microscope, and mydriasis funduscopy were performed. In terms of visual field examination (model750i, Carl Zeiss Meditec, Inc., Dublin, CA), an automatic visual field analyzer was used for central 30°, 60° and 90° examinations.

SS-OCT examination (Deep Range Imaging OCT, Topcon2000, Tokyo, Japan) and image analysis: SS-OCT was used to analyze the morphological features in mGCC thickness map, and the peripapillary retinal nerve fiber layer (pRNFL) thickness as well as its clinically significant probability graph of the lesions. These features were compared with the changes in the visual field at the corresponding phase to analyze their relationship.

Results

The visual field, mGCC atrophied disappear and lesion positioning of the 32 patients with optic pathway-related neuro-ophthalmology mainly showed (1) superior visual field hemianopia based on monocular horizontal demarcation, mGCC showed inferior atrophied disappear, and the lesion could be diagnosed as optic neuropathy at the anterior lamina cribrosa (for cases 31 and 32). In case of monocular complete blindness, the mGCC was manifested as complete atrophied disappear, and the lesion could be considered as optic neuropathy between the lamina cribrosa and the optic chiasm (such as unilateral postocular neuritis, optic canal fracture). (2) For bitemporal hemianopia, the bilateral mGCC rings showed nasal atrophied disappear by taking midperpendicular bisector as demarcation, and the lesion was located at the optic chiasm (in cases 1, 2, 6, 7, 18, 22, and 23). In terms of bitemporal hemianopia and one eye crossing the midperpendicular bisector, the bilateral mGCC rings were manifested as nasal atrophied disappear by taking the midperpendicular bisector as demarcation and one eye crossed the midperpendicular bisector, and the lesion was considered as optic chiasm lesion that is biased towards one eye (in cases 4, 5, 8, 19, 20, 21, 24, 26, and 28). (3) For homonymous hemianopia without macular sparing, mGCC was manifested as nasal atrophied disappear in one eye and temporal atrophied disappear in another eye by taking the midperpendicular bisector as demarcation, and the patients were diagnosed with lesion of between the posterior optic chiasm and the middle of the optic radiation (in cases 3, 9, 14 and 25). For cases with both eyes of hemianopia towards 1/4 upper or lower quadrant, without the macula sparing, the mGCC ring was manifested as atrophied disappear at 1/4 of the lower nasal side in one eye and atrophied disappear at 1/4 of the lower temporal side in the other eye, and the lesion was located at the anterior optic radiation (such as in case 12). In terms of homonymous hemianopia with macular sparing, mGCC was manifested as nasal atrophied disappear in one eye and temporal atrophied disappear in another eye by taking the midperpendicular bisector as demarcation, and the lesion was located at the posterior optic radiation and further (in cases 10, 13, 15). For homonymous
hemianopia with macular sparing and retain of contralateral 30-degree crescent, mGCC was manifested as nasal atrophied disappear in one eye and temporal atrophied disappear in another eye by taking the midperpendicular bisector as demarcation, with macular sparing, and the lesion was located in the middle of the calcarine fissure (such as in case 17). If the visual field was symmetric and ipsilateral central hemianopia, then the mGCC appeared as nasal atrophied disappear in one eye and temporal atrophied disappear in another eye by taking the midperpendicular bisector as demarcation, with macular sparing, and the lesion was positioned at the occipital pole. Meanwhile, if the visual field was symmetric and ipsilateral hemianopia, with the meniscal defects at the contralateral eye, then the mGCC appeared as nasal atrophied disappear in one eye and temporal atrophied disappear in another eye by taking the midperpendicular bisector as demarcation, with macular sparing, and the lesion was positioned at the anterior calcarine fissure. (4) Altered visual field and normal mGCC ring were found in patients with short onset time, either in the latent period or during the early onset (such as in cases 27, 29, and 30), and with descending optic neuropathy of trans-neuronal lesion after optic radiation that did not induce mGCC injury, wherein the lesion positioning relied on the visual field and MRI (in cases 11 and 16), (Figure 1).

Discussion

Optic pathway-related neuro-ophthalmologic diseases mainly included diseases of optic nerve, optic chiasm, optic tracts, optic radiation, central nervous system. The cause could be tumor, trauma, degeneration and congenital dysplasia and others. Ganglion cell complex-optic nerve is a pivotal pathway that connects the retina and the brain. The nerve conduction begins in the ganglion cell complex (dendrites-inner plexiform layer, ganglion cell layer, axon-neural fiber layer) and nerve fiber bundle, converging at the lamina cribrosa till the optic nerve. The bilateral optic nerves form an optic chiasm in the suprasellar region, and then divide into bilateral optic tracts, exchanging the neurons at the lateral geniculate nucleus (LGN). These in turn form optic radiation that projects towards the fissura calcarina, and finally the visual information is completed by the visual center in the occipital region. As the optic nerve fibers travel in clear regularity, then the nasal retinal nerve fibers (including the nasal part of the macula) of each eye intersect at the optic chiasm till the contralateral tract, while those at the temporal side do not intersect. The inferior retinal nerve fibers are located in the medial optic tract after passing through the optic nerve and the optic chiasm. Hence, the optic nerve fibers rotate to 90° when they enter the optic tract from the optic nerve and optic chiasm. The subnasal retinal nerve fibers pass through the optic chiasm, but travel forward in the contralateral optic nerve (Wilbrand's knee) before merging with the contralateral inferotemporal non-crossing-fibers and entering the optic tract. Therefore, the diseases at different parts of optic pathway-related neuro-ophthalmology have regularity, and manifest as visual field changes with different regularities. Meanwhile, the visual field examination remains subjective, and is largely influenced by the visual function, psychological factors and cognitive coordination ability of the patients. The macular region accounts for 50% of ganglion cells, and are arranged regularly. The normal mGCC manifests as a ring structure, which is an yellow ring, while the mGCC in the subnormal status or in the swelling period was manifested as a red ring. The common atrophic forms of mGCC included: 1/4 quadrant atrophied disappear, upper and lower atrophied
disappear based on horizontal demarcation, binasal or concurrent homonymous atrophied disappear or complete atrophied disappear by taking the midperpendicular bisector as demarcation (Figure 2).

Through clinical diagnosis and treatment, we found that the ganglion cells were distributed in the macular region also and were precisely presented in horizontal, vertical and quadrant regularity. Specifically, they manifest as unilateral mGCC ring atrophied disappear or mGCC atrophied disappear at the upper and lower half side based on horizontal demarcation for the lesion at anterior optic chiasm, the mGCC atrophied disappear at half of the bilateral nasal sides based on midperpendicular demarcation for the lesion at optic chiasm, and the mGCC atrophied disappear with or without macular sparing at homonymous side or 1/4 quadrant based on midperpendicular demarcation for lesion at posterior optic chiasm. The combination of MRI and 90-degree visual field should be performed to analyze the accurate positioning of the visual pathological lesions at the posterior optic chiasm. The results showed that the visual tract lesions as well as lesions at the anterior and the middle of the optic tract were not accompanied by macular sharing, while the lesions at the posterior optic radiation and the subsequent calcarine fissure were accompanied by macular sparing. The mGCC showed atrophied disappear at 1/4 quadrant below the same name for lesions at the anterior ring of optic radiation, while showed atrophied disappear at 1/4 quadrant above the same name for lesions present in the medial optic radiation. In calcarine fissure lesions, the mGCC showed semi-asymmetric atrophied disappear in the same name with macular sparing based on midperpendicular demarcation, while appeared as symmetric ipsilateral hemianopia under 90-degree visual field for lesions in the middle of calcarine fissure, with macular sparing and contralateral crescent sparing. The mGCC showed a crescent defect in the contralateral eye under the 90-degree visual field for lesions in the anterior calcarine fissure, while manifested as symmetric and ipsilateral central hemianopia (Figure 3) under 90-degree visual field for lesions at the occipital pole.

In the diseases of between the optic nerve and the optic tracts, the visual field, the mGCC and the pRNFL damage evolution are divided into three stages: (1) subnormal eyes at the preclinical or latent period showed normal visual acuity and visual field, with swelling of mGCC and pRNFL; (2) subnormal eyes at the beginning of the disease that lasted for 2-3 weeks, with abnormal visual acuity and visual field, and swelling of mGCC and pRNFL. The visual field changes and mGCC swelling do not coincide during this period; and (3) mid-term progression and separation period that lasted for 2-3 weeks after the onset, with the occurrence of mGCC atrophied thinning, but swollen pRNFL. The visual acuity as well as the visual field showed improvement when compared with those during the early stage of the disease. The change of visual field in this period was basically consistent with the changes of mGCC atrophied thinning. Stabilization and atrophy period showed pRNFL atrophied disappear, which usually lasted for more than 6-8 weeks after the onset. Generally, the disease discontinued to progress and tended to stabilize after 3 months, and then showed improvement in the visual acuity and stabilized the visual field. These changes are better than those at the initial stage, but generally do not recover to the original normal levels. At this stage, the change in the visual field coincides with those in mGCC and pRNFL atrophied disappear. Functional changes of ganglion cells (visual field changes) occur (in the early stage) before the organic changes of ganglion cells (middle stage). The ganglion cell body showed atrophied thinning initially
(appeared after 2-3 weeks of onset), and the corresponding ganglion cell axon fiber (mRNFL) also showed atrophied thinning, followed by the atrophied disappear of pRNFL (6-8 weeks after onset). Generally, the disease becomes stable after 3 months. The time difference between atrophy of ganglion cell bodies and axons (mRNFL, pRNFL) might be related to the apoptosis of astrocytic-vascular sheath in the periphery of nerve fibers that occurs after the atrophy of ganglion cell axons.

The concept and essence of subnormal eye: The latent state of the onset (clinically cured) or the non-onset optic nerve disease or the clinically cured fundus diseases are accompanied by optic nerve damage. Both types of diseases involve optic nerve damage - mGCC swelling and pRNFL swelling. Also the optic disk was stained at the later FFA stage. Therefore, the subnormal eye is essentially considered to be in the latent state (most of the cases) or early (very few) manifestation of the eye diseases, which showed association with mGCC swelling and atrophy (fundus diseases, optic neuropathy, and glaucoma). The latent sub-normal eye refers to no clinical symptoms, except for mGCC and pRNFL swelling and stained FFA optic disc during this period, with normal visual acuity and visual field. Therefore, it is considered as the latent period or preclinical period, which might last longer or for the whole life. Only few cases had the onset based on this.

The visual field of trans-neuronal descending lesions at the posterior optic tracts changes from hours to weeks, and the mGCC atrophy might take several months to years to occur. Nevertheless, the evolution and the characteristics of visual field, mGCC and RNFL in patients with trans-neuronal descending lesions at the posterior optic radiation require further investigation.

**Conclusion**

The distribution of ganglion cells is closely related to the visual field. Evaluation of morphological characteristics of the ganglion cells in the macular region of the eyes by SS-OCT can be used to locate the diseases of different parts of optic pathway-related neuro-ophthalmology. The morphological analysis of the ganglion cells remained objective, and has the same value as the subjective positioning diagnosis of the visual field, but is superior over the visual field inspection. Since mGCC provides only 50% of neural visual information, accurate visual field examination is still needed to improve the necessary supplement. The authors hypothesized that mGCC cannot completely replace the visual field examination at present, and further research on mGCC is warranted. Meanwhile, the positioning of optic pathway-related neuro-ophthalmologic diseases without changes in mGCC ring in the preclinical or latent stage relies on the visual field and the MRI, and the precise positioning of the optic lesion at the posterior optic chiasm requires combination of MRI and 90-degree visual field.

Therefore, application of SS-OCT examination to analyze the morphological changes in mGCC thickness probability graph, and close combination of it with visual field and MRI examination assists in mutual verification and brings out the best in each other, thus achieving the objective localization value in diagnosing and treating optic pathway-related neuro-ophthalmic diseases.
Abbreviations
mGCC: macular ganglion cell complex  SS-OCT: swept-source optical coherence tomography  pRNFL: peripapillary retinal nerve fiber layer  LGN: lateral geniculate nucleus  MRI: magnetic resonance imaging  FFA: fundus fluorescein angiography

Declarations

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Authors’ contributions
WZ data collection, data analysis, literature search, manuscript preparation, and manuscript editing. XS conceived of the study. XP data collection, manuscript preparation, manuscript editing, and research supervision. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Research ethics approval was obtained from Beijing Tongren Eye Hospital Ethics Board. All participants have given written informed consent for the collection and analysis of patient data. Written informed consent was obtained from a parent or guardian for participants under 16 years old.

Consent for publication
The study received consent for publication as per the research ethics board at the Beijing Tongren Eye Hospital. All of the study patients have agreed with the completion and publication of this study as per the guidelines of the Beijing Tongren Eye Hospital board at the Capital Medical University. All patients described within the study gave informed, written consent for their personal or clinical details along with any identifying images to be published in this study.

Competing interests
The authors declare that there is no competing interest.
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References


**Table**

Table 1 Baseline patient characteristics
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<th>diagnosis</th>
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<tr>
<td>272</td>
<td>20/25</td>
<td>Hemianopia</td>
<td>Bitemporal hemianopia, left eye crossing midperpendicular line</td>
<td>Slightly to the left of optic chiasm</td>
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<td></td>
<td>50-59 20/800</td>
<td>Pituitary tumor</td>
<td>Bilateral mGCC ring swelling, no atrophy (mGCC ring did not occur atrophy in subnormal eye after 1 week of onset)</td>
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<tr>
<td>282</td>
<td>20/200, 20/800</td>
<td>Chordoma or metastatic cancer</td>
<td>Bitemporal hemianopia, right eye crossing midperpendicular line</td>
<td>Right side of optic chiasm</td>
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<tr>
<td>282</td>
<td>70-79 20/40</td>
<td>Pituitary adenoma in the saddle</td>
<td>Normal visual field in both eyes</td>
<td>Pituitary adenoma in the saddle was located by postoperative MRI</td>
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<tr>
<td>302</td>
<td>40-49 20/25</td>
<td>Schwannoma beside the right saddle</td>
<td>Irregular reduced visual field sensitivity in the right eye and normal visual field in the left eye</td>
<td>Beside the right saddle (positioning by MRI)</td>
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<tr>
<td>312</td>
<td>50-59 20/400</td>
<td>Ischemia optic neuropathy in anterior left eye</td>
<td>Lower hemianopia in the left eye based mGCC ring based on horizontal demarcation</td>
<td>Left optic nerve</td>
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<tr>
<td>322</td>
<td>50-59 20/400</td>
<td>Ischemia optic neuropathy in anterior left eye</td>
<td>Lower hemianopia in the left eye based mGCC ring based on horizontal demarcation</td>
<td>Left optic nerve</td>
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*The number 1 means male and the number 2 means female in the gender.*

**Figures**
In optic pathway-related neuro-ophthalmologic diseases, the morphological characteristics of mGCC thickness demonstrated similar characteristic changes to that of visual field.

a. Left papillitis optica: In case of monocular complete blindness, the mGCC was manifested as complete atrophied disappear. Left eye visual field showing total blindness.

b. Ischemia at the posterior segment of the left optic radiation or in the center of the calcarine fissure. The mGCC was manifested as nasal atrophy in the right eye and temporal atrophy in the left eye in mGCC ring based on midperpendicular demarcation. The visual field showing that Homonymous hemianopia of right side.

Figure 1
Figure 2

The common morphological characteristics of mGCC thickness graph and the change of the visual field a. The normal mGCC ring appeared yellow in shape and normal visual field b-f. The common atrophy forms of mGCC included 1/4 quadrant atrophy, complete atrophy, upper atrophy based on horizontal demarcation, temporal atrophy based on midperpendicular demarcation, and nasal atrophy based on midperpendicular demarcation g. The subnormal or swelling period of mGCC appeared red in shape and normal visual field.
Figure 3