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Ganglion cell layer-inner plexiform layer thickness and vision loss in cerebral palsy

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Abstract

Purpose: To determine if measurements of macular ganglion cell layer-inner plexiform layer (GCLIPL) thickness can discriminate between cerebral palsy patients with and without vision loss using spectral domain optical coherence tomography (SDOCT).
Study design: Cross-sectional.
Materials and methods: Participants with cerebral palsy enrolled in a prospective study of SDOCT were included if they were cooperative for visual acuity (VA) testing and macular SDOCT images were acquired. Manual segmentation of the macular GCLIPL was performed using elliptical annuli with diameters of 4.5 mm. Subjects with VA < 6/9 were defined as having abnormal vision. Mann-Whitney U test was used to evaluate the relationship between vision and macular GCLIPL thickness. Data were analysed using SPSS version 22.0 software.
Results: Forty study eyes (normal vision = 17 eyes; abnormal vision = 23 eyes) from 21 participants with spastic cerebral palsy were included. Most subjects were male (61.90%, *n* = 13) and the median age was 13 years (range from 7 to 29 years). The median visual acuity was 0.1 logMAR for subjects with normal vision and 0.3 logMAR for subjects with abnormal vision. Eyes with normal vision had higher average GCLIPL thickness (mean = 106.3 ± 27.85 µm) compared to eyes with abnormal vision (mean = 96.6 ± 36.47 µm). However, a significant association between GCLIPL thickness and visual impairment could not be established in this study.
Conclusion: Our study demonstrated a reduction in macular GCLIPL thickness in

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cerebral palsy patients with visual impairment but did not fully support its use as surrogate marker of cerebral visual impairment due to study limitations. Future longitudinal studies are advised to elucidate the relationship between macular GCLIPL and cerebral visual impairment.

Keywords: cerebral palsy, ganglion cell layer, spectral domain optical coherence tomography, visual impairment

Ketebalan lapisan sel ganglion-pleksifom dalam dan ketajaman penglihtan di kalangan palsi serebrum

Abstrak

Tujuan: Bagi mengenalpasti samada pengukuran ketebalan lapisan sel-ganglion-pleksifom dalam (GCLIPL) menggunakan tomografi koheren optikal spektral domain (SDOCT) dapat mendiskriminasikan kehilangan penglihatan dalam kalangan pesakit cerebral palsi.
Bentuk kajian: Keratan-rentas
Metodologi dan bahan kajian: Pesakit cerebral palsi dipilih sekiranya mereka dapat memberi kerjasama dalam mengukur ketajaman penglihatan dan pengambilan pengukuran GCLIPL pada macula menggunakan SDOCT. Segmentasi GCLIPL dilakukan secara manual menggunakan annuli eliptikal yang bersaiz 4.5mm diameter. Pesakit yang mempunyai ketajaman penglihatan yang kurang dari 6/9 dikenaplasti sebagai pesakit mempunyai penglihatan yang tidak normal. Ujian Mann-Whitney U digunakan bagi memeriksa hubungkait di antara ketajaman penglihatan dan ketebalan GCLIPL pada makula. SPSS versi 22.0 digunakan bagi menganalisa data.
Keputusan: Sebanyak 40 mata (ketajaman penglihatan yang normal: 17, ketajaman penglihtan yang tidak normal: 23) daripada 21 pesakit cerebral palsi jenis spastik terlibat dalam kajian ini. Kebanyakan daripada mereka adalah lelaki (61.9%, n = 13) berumur median 13 tahun (julat umur 7 hingga 29 tahun). Median ketajaman penglihtan adalah 0.1 log MAR bagi penglihatan normal dan 0.3 logMAR bagi penglihatan tidak normal. Mata yang mempunyai ketajaman penglihatan yang normal mempunyai purata ketebalan GCLIPL yang lebih tinggi (106.3 ± 27.85 μm) berbanding dengan mata yang ketajaman penglihtan yang tidak normal (96.6 ± 36.47 μm). Walaubagaimanpun, tiada sebarang hubungkait yang signifikan antara ketebalan GCLIPL dan ketajaman penglihtan.
Rumusan: Berdasarkan kajian ini terdapat penurunan ketebalan GCLIPL pada

makula pesakit cerebral palsi yang mempunyai kecacatan penglihatan tetapi kegunaan GCLIPL sebagai penanda pengurangan tahap penglihatan tidak dapat dibuktikan disebabkan oleh limitasi kajian ini. Kajian secara membujur pada masa akan datang dapat membantu menjelaskan hubungkait antara GCLIPL macula dan kecacatan penglihatan serebrum.

Kata kunci: cerebral palsi, kecacatan penglihatan, lapisan sel-ganglion, tomografi koheren optikal spektral domain

Introduction

Cerebral palsy is defined as a range of nonprogressive syndromes of posture and motor impairment due to a defect or lesion of the developing brain. Worldwide population-based studies have reported a prevalence of 1.5 to more than 4 per 1,000 live births, but the rates vary from country to country and also within countries.[1,2] Cerebral palsy is chronically disabling and is often accompanied by co-occurring developmental disabilities, cognitive deficit, and perception disturbances. Visual disorders in children with cerebral palsy can be ocular or cerebral in origin.[3] Ocular defects associated with cerebral palsy encompass mainly refractive error, squint, squint with amblyopia, nystagmus, and ptosis. Cerebral visual impairment (CVI) is not uncommon in children with cerebral palsy. As the name implies, CVI occurs as a result of injury to the visual association cortices, their interconnecting pathways, and higher visual processing centres in a developing brain of the foetus and the newborn by a set of predisposing antenatal factors, perinatal, and postnatal aggravating events,[1,3,4] Damage to the visual association cortices can impair visual acuity, restrict the visual field, and cause oculomotor incoordination, whereas damage to higher visual processing centres often result in visual, cognitive, and perceptual impairment.[5,6]

The European Cerebral Palsy study has identified several neuropathologies in cerebral palsy.[7] White matter damage of immaturity or cerebral white matter injury, including periventricular leukomalacia and/or intraparenchymal haemorrhage, was the most common finding, followed by other pathologies such as basal ganglia lesions, cortical/subcortical lesions, malformations, and focal infarcts.[6,7] These neuropathologies, caused by various ischaemic and nonischaemic causative factors of cerebral palsy, result in axonal degeneration. Axonal degeneration in the manner of retrograde transynaptic degeneration (RTSD) has been demonstrated in cerebral palsy, which then results in CVI.[7-10]

Cerebral visual dysfunction is difficult to diagnose and is often incorrectly ascribed to apparent developmental disorders. Therefore, identification and measurement of visual dysfunction should be actively sought for early visual rehabilitation in children with cerebral palsy. Early on, the retinal nerve fibre layer thickness has

been widely opted as a biomarker for wide arrays of neurodegenerative disease and cerebral damage. With technological advancement and development of new software, optical coherence tomography now provides rapid, noninvasive, and objective measurement of the inner retinal layers of the macula, the ganglion cell layer, and inner plexiform layer (GCLIPL). Many studies have reported evidence of retinal GCLIPL reduction as a result of RTSD from cortical insult.[11-14] Herro and Lam demonstrated retrograde transynaptic retinal ganglion cell loss in patients with homonymous hemianopsias from ischaemic occipital injury.[15] Choi *et al.* and Garcia-Martin *et al.* have revealed the association between ganglion cell layer reduction with severity of Alzheimer's disease, suggesting that GCLIPL thickness could potentially be an early biomarker of neurodegeneration in Alzheimer's disease.[11,12] Therefore, the aim of this study is to illustrate the reduction of macular GCLIPL thickness in cerebral palsy patients with visual impairment. We hypothesize that said reduction is attributed to RTSD, which can lead to CVI in cerebral palsy patients.

Materials and methods

This cross-sectional study was conducted during an eye screening programme in Johor Cerebral Palsy School in February 2019. All participants underwent basic ocular examination, including visual acuity (VA) assessment, refraction, fundus examination, and spectral domain optical coherence tomography (SDOCT) macular assessment. Only subjects with intellectual and motor prerequisites to cooperate for ocular assessment and the ability to maintain fixation during SDOCT were included in this study via convenience sampling.

As a result of co-occurring developmental disabilities and cognitive impairment in cerebral palsy subjects, VA assessment was carried out using age-appropriate methods as in preverbal and preliterate subjects. Recognition acuity was assessed using Cardiff acuity test, LEA symbols chart, Sheridan Gardiner single letter optotypes, Bock's candy test, and miniature toy test, whereas resolution acuity was assessed with LEA grating paddles. VA assessment was carried out according to established protocol and the results obtained were converted to logarithm of the minimal angle of resolution (LogMAR) units. Subjects with VA < 6/9, LogMAR equivalence > 0.18, were labelled as having abnormal VA.

Retinal scans were obtained using the spectral domain optical coherence tomography from the HOCT-1/1F (HUVITZ Co., Ltd., Dongan-gu, Anyang-si, Gyeonggi-do, Republic of Korea). Macular scanning was conducted using scan protocol 3-D scan, which covers 9 mm x 12 mm of the retina with fovea centred in order to obtain GCLIPL thickness. The thickness maps were divided into six sectors representing the superior, superotemporal, superonasal, inferior, inferotemporal, and inferonasal of the elliptic GCLIPL layer. The outcome report illustrated GCLIPL thickness for each sector and a total average value (mean GCLIPL).

The demographic data and clinical characteristics were summarized by descriptive statistics, *i.e.*, continuous variables such as age and VA of subjects were not normally distributed and therefore were recorded as median and interquartile range; categorical data were recorded as percentages. The total average GCLIPL thickness and GCLIPL thickness by anatomic sectors were checked for Gaussian distribution by using skewness and kurtosis. GCLIPL thickness was normally distributed in subjects with normal and abnormal vision and was presented as mean value and standard deviation. To evaluate the relationship between total average GCLIPL thickness and GCLIPL thickness by anatomic sector with groups of normal and abnormal VA, nonparametric Mann-Whitney U-test was applied due to the small study group, regardless of data being Gaussian distributed. Statistical analyses were performed using the Statistical Package for the Social Sciences version 22 (SPSS, Inc., Chicago, IL, USA). *P*-values of < 0.05 were considered to indicate statistical significance.

Results

Twenty-one subjects met the inclusion criteria. Two subjects contributed only one study eye due to poor cooperation or poor image quality, resulting in a total of 40 study eyes. Demographic data and VA in LogMAR for subjects with normal and abnormal vision are summarized in Table 1. There were 17 eyes with normal vision and 23 eyes with abnormal vision. The eyes with normal vision had VA 0.1 LogMAR, whereas eyes with abnormal vision had VA 0.3 LogMAR. The GCLIPL

Table 1. Demographics and clinical characteristics of subjects with cerebral palsy

Demographics		
Age, *median (IQR)*	13 (7)	
Gender, *n (%)*		
Male	13 (61.90)	
Female	8 (38.10)	
Ethnicity, *n (%)*		
Malay	12 (57.1)	
Indian	5 (23.8)	
Chinese	4 (19.0)	
Clinical characteristics	**Normal vision** *N* = 17	**Abnormal vision** *N* = 23
Visual acuity (logMAR), *median* (IQR)	0.10 (0.10)	0.30 (0.40)
BCVA (logMAR), *mean* (*SD*)	0.04 (0.05)	0.27 (0.08)

BCVA: best-corrected visual acuity; IQR: interquartile range; SD: standard deviation

Table 2. Average macular GCLIPL thickness and GCLIPL thickness by anatomic sectors

GCLIPL (µm)	Vision			
	Normal (*n* = 16) SD (mean)	**Abnormal (*n* = 22) SD (mean)**	***Z***	***p*-value**
Average	106.3 (27.85)	96.6 (36.47)	-1.892	0.058
Superior	99.9 (23.79)	87.0 (22.79)	-1.686	0.092
Superotemporal	97.5 (12.50)	84.1 (18.62)	-2.264	0.024
Superonasal	109.7 (20.76)	94.8 (20.45)	-1.834	0.067
Inferior	107.8 (16.15)	94.0 (20.58)	-1,894	0.058
Inferotemporal	97.9 (17.09)	88.1 (20.10)	-1.790	0.073
Inferonasal	110.4 (21.95)	100.9 (18.89)	-1.272	0.203

GCLIPL: ganglion cell layer inner plexiform layer; SD: standard deviation

thickness measured 106.3 µm in eyes with normal vision, with reduced thickness measuring 96.6 µm in eyes with visual impairment. The analysis showed that there was no significant difference in GCLIPL thickness with VA. Therefore, an association between GCLIPL thickness and visual impairment could not be established.

There was also a reduction in mean GCLIPL thickness in all anatomic sectors in subjects with abnormal vision compared to subjects with normal vision, but the reduction was not significant (Table 2). Table 3 shows the ocular characteristics of cerebral palsy patients with abnormal vision. All eyes in this cohort were diagnosed to have refractive error and they could not be fully corrected to Snellen VA better than 6/9. Refractive errors were classified as follows: low myopia < -3.00 D, -3.00 D < moderate myopia < -6.00 D, and high myopia > -6.00 D; low hypermetropia ≤ +2.00 D, +2.00 D < moderate hypermetropia < +5.00 D, and high hypermetropia > +5.00 D; 0.25 < low astigmatism < 1.5 D, 1.5 D < moderate astigmatism < 3 D, and high astigmatism > 3 D.

Of the 23 eyes with visual impairment, 12 eyes (52.2%) were hypermetropic (10 had low hyperopia and 2 had moderate hyperopia), 7 eyes (30.4%) were myopic (3 with low myopia, 3 with moderate myopia, and 1 with high myopia), and 4 eyes

(17.4%) were emmetropic. Nineteen out of 23 eyes (82.6%) had astigmatism: 11 eyes had low astigmatism, 5 eyes had medium astigmatism, and 3 eyes had high astigmatism. Only one subject in this cohort had strabismus. All subjects had otherwise normal dilated fundus examination.

The gross motor function of subjects was categorized using the Gross Motor Function Classification System (GMFCS). GMFCS is a five-level clinical classification system used to describe the gross motor function of people with cerebral palsy on the basis of self-initiated movement abilities. Lower GMFCS levels correspond to milder forms of cerebral palsy and vice versa.[16,17] All recruited subjects had good gross motor function with GMFCS level III and below as per the study's inclusion criteria, which required subjects able to cooperate and complete the ocular examination and SDOCT assessment. We observed that subjects with GMFCS level IV and V showed difficulty maintaining antigravity head/trunk postures and fixation and dyskinetic movement, which would have rendered ocular assessment and SDOCT capture challenging for this study.

Table 3. Ocular characteristics of eyes with abnormal vision

Patient	Eye	Sphere	Cylinder	BCVA (LogMAR)	Strabismus	Fundus examination
1	1	Emmetropia	Medium	0.30	No	Normal
	2	Emmetropia	Medium	0.30		
2	3	Low hyperopia	Medium	0.30	No	Normal
	4	Low hyperopia	Low	0.30		
3	5	Moderate hyperopia	Low	0.30	No	Normal
	6	Moderate hyperopia	Low	0.30		
4	7	Moderate myopia	Low	0.50	No	Normal
	8	High myopia	Medium	0.40		
5	9	Low hyperopia	Low	0.20	No	Normal
	10	Low hyperopia	No	0.20		
6	11	Low myopia	No	0.30	No	Normal
	12	Low hyperopia	Low	0.30		

Patient	Eye	Sphere	Cylinder	BCVA (LogMAR)	Strabismus	Fundus examination
7	13	Emmetropia	No	0.18	No	Normal
	14	Emmetropia	No	0.18		
8	15	Low hyperopia	Low	0.18	No	Normal
	16	Low hyperopia	Low	0.18		
9	17	Low hyperopia	Low	0.20	Yes	Normal
10	18	Low hyperopia	High	0.18	No	Normal
	19	Low hyperopia	Medium	0.18		
11	20	Moderate myopia	High	0.30	No	Normal
	21	Moderate myopia	High	0.30		
12	22	Low myopia	Low	0.30	No	Normal
	23	Low myopia	Low	0.30		

BCVA: best-corrected visual acuity

Discussion

A wide array of visual problems has been reported in children with cerebral palsy. Children with cerebral palsy often have comorbidities and associated deficits, such as cognitive defects and dyskinesia in athetoid cerebral palsy, which make the identification and evaluation of visual problems difficult. This is even more so in young and noncooperative cerebral palsy subjects. As a result, timely intervention and visual rehabilitation cannot be offered to children with cerebral palsy because of this diagnostic delay.

Accurate assessment of visual function and timely detection of visual problems among cerebral palsy patients will lead to improved patient care, thence quality of life. To date, the most appropriate ophthalmological tools which can be used to delineate ocular deficits of visual decline from cortical blindness in cerebral palsy patients are still unknown. Several studies have demonstrated OCT-verified thinning of GCLIPL in adult subjects with acquired CVI.[18-22] However, such studies are scarce in cerebral palsy subjects since they cannot undergo comprehensive

ocular assessment. A study conducted by Jacobson et. al. recruited a small number of cerebral palsy subjects and found convincing evidence of RTSD by establishing a topographical relationship between GCLIPL and visual field defects that corresponded to the location and extent of the primary brain lesion.[13,21] Therefore, we conducted this study with the aim to identify cerebral palsy patients with CVI by demonstrating a reduction in macular GCLIPL thickness.

Based on the analysis, our study has demonstrated a reduction in macular GCLIPL thickness among eyes with visual impairment compared to eyes with normal vision. We attribute the decrease in VA to CVI secondary to RTSD, as evidenced by the reduction of macular GCLIPL thickness. However, we could not establish a significant relationship between macular GCLIPL thickness and VA. Further analysis on eyes with visual impairment has shown that all eyes in this cohort were structurally normal and had refractive errors with reduced best-corrected Snellen VA of 6/9 or worse.

Several postulations have been made to explain the study outcome. First, we observed that the majority of eyes in visual impairment cohort were structurally normal and had refractive error with reduced best-corrected Snellen VA of ≤ 6/9 (Table 3). This could be attributed to amblyopia. Amblyopia is defined as reduction of BCVA to ≤ 6/9 in Snellen optotype that is not accounted for by other ocular pathologies as a result of abnormal visual stimulation which has occurred during the years of visual development. In our cohort, one subject had strabismus (Eye 17, Table 3), which might have caused amblyopia or a sequela of amblyopia. There were no other signs that could have predisposed our subjects to deprivational or anisometropic amblyopia. Moreover, additional tests such as streoacuity, binocular function, optokinetic nystagmus, visual evoked potential, etc., which can help to ascertain the diagnosis of amblyopia, were not performed in this study. Therefore, we faced a diagnostic dilemma as we were unable to discern CVI from amblyopia in our cohort with abnormal vision. This might explain the lack of significance with the use of macular GCLIPL thickness as a predictor of CVI in our study.

Moreover, we could not establish convincing solid evidence of RTSD in our study as our subjects did not undergo perimetry and neuroimaging with a special focus on the visual pathway, which can help relate GCLIPL topography to brain lesions. Thus, we could not confidently attribute the definite cause of vision impairment in our cohort to CVI and this helps to explain the insignificant reduction of macular GCLIPL thickness in our cohort. Thirdly, some children with cerebral palsy are able to perceive, but have difficulty understanding and organizing visual information. Cerebral palsy is commonly associated with 30% to 50% of intellectual disability and learning difficulties. Our subjects with visual impairment could be experiencing difficulty processing visual information rather than an inability to see. Our study could not have discerned between these two based on VA and refractive assessment alone. This could justify the insignificant reduction of GCLIPL complex in our subjects with visual impairment.

Most of the subjects recruited in our study had GMFCS level III and below. As a result, they were physically and intellectually able to complete our study's eye assessment. We postulate that subjects with low GMFCS levels correspond to milder cerebral insult, which results in minimal or no reduction in GCLIPL thickness as there is lesser degree of RTSD. Thus, the majority of the subjects in this study had comparatively well-preserved GCLIPL thickness. This sampling bias may have resulted in statistically insignificant association between GCLIPL thickness and visual impairment. Last but not least, the small sample size and lack of control group in this study have contributed to the insignificant study outcomes.

This is a pilot study. Our study had a number of other limitations, including its cross-sectional design, which restricts our ability to imply causality. Manual segmentation of the macula is not only time consuming, but also prone to operator error. Future studies may be improved by enrolling larger samples with control cohorts. Randomisation of subjects and recruitment of different subtypes of cerebral palsy will help to improve the generalizability of the study. Assessment of cerebral palsy subjects, especially in those with high GMFCS levels, pose immense challenges. Future studies will therefore be better conducted alongside an optometrist team specialising in CVI assessment for objective assessment of VA in cerebral palsy patients. The use of handheld SDOCT may also be considered to facilitate data collection.

Conclusion

Our study revealed a reduction of macular GCLIPL thickness in cerebral palsy patients with visual impairment but did not fully support the use of macular GCLIPL as a surrogate marker of CVI in cerebral palsy patients due to study limitations. Future longitudinal research with probability sampling could elicit convincing evidence of RTSD, thereby elucidating the topographical relationship between macular GCLIPL thickness and brain lesions in order to promote the use of macular GCLIPL as a potential indicator of CVI impairment in cerebral palsy patients.

Declarations

Ethics approval and consent to participate.
This work adheres to the guidelines and principles of the Declaration of Helsinki and is in accordance with the Malaysian Good Clinical Practice (MGCP) 4th edition 2018. Information sheets and consent forms regarding the screening programme was distributed to the parents/guardians of the students attending Johor Cerebral Palsy School's prior to the study and all subjects recruited in our study had informed consented from their parents/guardians to undergo eye examination. This research

is also registered with the National Medical Research Register (NMRR) and obtained publication/presentation approval granted by the Director General of Health Malaysia.

Competing interests
None to declare.

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