Retinal ganglion cell topography predicts visual field function in spastic cerebral palsy

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This article is commented on by Williams on page 1012 of this issue.

The aim of this study was to evaluate the use of optical coherence tomography (OCT) to identify and assess visual field defects caused by primary damage to the optic radiation in individuals with spastic cerebral palsy (CP). Ten individuals with spastic CP (six females, four males, with a median age of 21 years [range 17–38y]) had their brain lesions documented with conventional magnetic resonance imaging (MRI) and diffusion-weighted MRI fibre tractography. Their macular ganglion cell layer (GCL) and inner plexiform layer (IPL) were examined with OCT and their visual fields were plotted. All participants had good visual acuity and were able to cooperate with the MRI and OCT examinations, as well as undergoing reliable perimetry. We found focal thinning of the GCL+IPL and corresponding homonymous visual field defects in individuals with brain damage affecting the optic radiation. We used GCL+IPL sector asymmetry as a sensitive OCT parameter to identify focal visual field defects. We observed no such sector asymmetry in GCL+IPL, or focal visual field defects, in individuals with normal MRI optic radiation imaging. Lesions affecting the optic radiation cause retrograde trans-synaptic degeneration of retinal ganglion cells. OCT examination of the GCL in the macula identified corresponding focal damage to the optic radiation in individuals with spastic CP and can be used to predict focal visual field defects.

Various patterns of brain damage can cause cerebral palsy (CP) in children. Bax et al.1 analysed the magnetic resonance imaging (MRI) scans of 351 children diagnosed with CP as part of a European multicentre study and found that white matter damage of immaturity (WMDI), including periventricular leukomalacia, was the most common finding (42.5%), followed by basal ganglia lesions (12.8%), cortical/subcortical lesions (9.4%), malformations (9.1%), focal infarcts (7.4%), and miscellaneous lesions (7.1%).

All these different patterns of brain damage may affect not only the motor pathways but also the retro-geniculate visual pathways, causing cerebral visual impairment (CVI). Many children with prenatal and perinatal brain damage have CP and CVI.2 If the lesion affects the motor pathways but the retro-geniculate visual pathways are spared, the child will be diagnosed with CP but may yet develop normal visual acuity and normal visual field function. If the motor pathways are spared but the visual pathways are injured, the child will be spared CP but will suffer from CVI.

In fact, CVI has become the most common cause of paediatric visual impairment in the UK3 and in other parts of the industrialized world4 because of improved survival of critically ill neonates, infants, and children. In CVI, visual acuity and visual field function may be affected; ocular motility problems and cognitive visual dysfunction may also be present.5 The term ‘retrograde trans-synaptic degeneration’ (RTSD) describes the secondary death of neurons after injury, which affects the target neurons they synapse with. This phenomenon was described in the 1900s in animal studies,6 case reports,7,8 and studies of optic disc appearance in children with brain damage.9 RTSD affecting the human visual system was described in a review article by Dinkin,10 which highlighted the importance of combining MRI and optical coherence tomography (OCT) to prove the occurrence of RTSD in those affected. With diffusion-weighted MRI (dMRI) and fibre tractography, it has become possible to describe the location and extent of primary lesions in the posterior visual system.11–13 By adding information from OCT, secondary changes in the retina can be mapped and related to the consequent visual dysfunction. Evidence of RTSD identified using OCT was described by Jindahra et al.14 in both immature and mature visual systems. The study analysed the peripapillary retinal nerve fibre layer. Since then, OCT measurements of the ganglion cell complex in the macula have shown a more direct correlation between retinal structure and function after RTSD.15 Our group used dMRI and fibre tractography to map out primary lesions in the optic radiation in individuals with WMDI13 and in adolescents with brain
damage acquired prenatally and postnatally, demonstrating corresponding local thinning of the ganglion cell layer (GCL) and inner plexiform layer (IPL) topography. Thinning of the GCL+IPL complex was a predictor of visual field loss.

The purpose of this multi-case study was to evaluate the possibility of using OCT and GCL+IPL topography as targeted assessment tools to identify visual field defects caused by primary damage to the retro-geniculate visual system in a group of individuals with spastic CP.

**METHOD**

**Participants**

From a large cohort of individuals presenting with spastic CP collected by one of the authors (LJ) during paediatric ophthalmology clinical practice, 12 reached adolescence/adulthood, were successfully examined with MRI, and were invited to participate. Five were selected from a group of participants with known WMDI, three were selected from a group of participants with homonymous hemianopia, and four were selected because of unilateral spastic CP with documented brain injury. Only individuals with the intellectual and motor prerequisites to maintain fixation during OCT and capacity to carry out standardized perimetry were invited. Two of the invited individuals could not complete all the examinations and were excluded. The final study group consisted of 10 individuals (six females, four males) with a median age of 21 years (range 17–38y). None of the participants had any known ocular disease besides possible axonal loss related to brain injury.

The study was approved by the local ethics committee (EPN Stockholm Nord, registration number 2013/1114-31/2) and followed in accordance with the Declaration of Helsinki. All participants were given verbal and written information and written approval was obtained.

**Motor function**

All individuals were diagnosed with spastic CP as children and were followed in the Department of Neuropaediatrics at Astrid Lindgren Children’s Hospital, Karolinska University Hospital, Stockholm. Information about the type and severity of CP, graded according to the Gross Motor Function Classification System (GMFCS), was retrieved from their records and is shown in Table S1 (online supporting information).

**Neuroimaging**

Conventional MRI and dMRI images were collected using the scanning protocols from two previous studies: cases 1, 2, 9, and 10 and cases 3 to 8. Conventional MRI scans were visually assessed for lesion type, location, and extent with a special focus on the visual pathways. The dMRI data were used to reconstruct the optic radiation with probabilistic constrained spherical deconvolution-based fibre tractography by seeding streamlines in a 4mm sphere encapsulating the lateral geniculate nucleus and using a 30mm radius sphere centred in the occipital pole (covering the calcarine sulcus) as an inclusion target. The fibre-tracking algorithm was run until 10⁴ accepted streamlines were generated. To exclude connections of (very-)low probability (typically false-positives), streamlines that entered voxels with a visitation count of less than 10 (i.e. voxels through which less than 0.1% of the streamlines passed) were rejected; the remaining streamlines represented the desired optic radiation tract. The optic radiation tracts were assessed in relation to their expected topography and with regard to lesions identified on conventional MRI. Cases where the number of streamlines (streamline density) in the optic radiation tracts were clearly fewer (lower) then expected were considered abnormal (Fig. 1). All radiological assessments were carried out by an experienced neuroradiologist (FL).

**Visual field and ocular examination**

All participants underwent an eye examination including cover-uncover test, ocular motility, best-corrected visual acuity, perimetry, fundus photography, and OCT examination. Cognitive visual problems were identified using structured history taking. All individuals were questioned regarding problems with visual guidance of movements, recognition, and route finding. The severity of the cognitive visual problems was graded by an experienced paediatric neuro-ophthalmologist (LJ) as mild, moderate, and severe.

**OCT**

Retinal scans were obtained using a spectral-domain OCT system (CIRRUS HD-OCT 5000 v8.0 [Carl Zeiss Meditec, Dublin, CA, USA]). A macular cube 512×128 scanning protocol, covering 6×6mm of the retina with the fovea centred, was used to measure the thickness of the GCL+IPL. The thickness of the GCL+IPL was calculated by using the ganglion cell analysis software tool. Thickness maps were divided into six sectors representing the superior, superonasal, inferior, inferonasal, inferotemporal, and superotemporal portions of the elliptic GCL+IPL. The OCT output provided the mean values for each sector, and the total average (mean GCL+IPL) and minimum thickness value (minimum GCL+IPL). The software automatically compares the outcome against a built-in normative database based on the estimated 1%, 5%, 95%, and 99% normal limits of an age-matched group of unaffected individuals. Normal values are typically marked in green, borderline values are marked in yellow, and values below the normal limits are marked in red. In addition, GCL+IPL
Figure 1: Magnetic resonance imaging (MRI), optical coherence tomography (OCT), and visual field maps for case number 1. (a) Axial MRI showing right-sided, closed-lip schizencephaly with perisylvian polymicrogyria (left). A coronal MRI with overlaid fibre tractography of the optic radiations (right) shows the lesion extending into the superior portion of the right optic radiation, which has reduced fibres/fibre density (red arrow). Visual field sensitivity is given as the percentage of the intact visual field (Visual Field Index [VFI]). (b) Homonymous lower quadrantanopia in the left visual field (top row). The OCT measurements show the corresponding thinning of the ganglion cell layer (GCL) in the corresponding superotemporal (right eye) and supernoasal (left eye) quadrants. (Note the GCL-inner plexiform layer [IPL] topography projected on the fundus with red indicating focal thinning). The coloured stars show the correlation between structure and function. The lower row shows the GCL-IPL sector thicknesses. (c) Topographical correlation between the primary postgeniculate lesion, affecting the superior portion of the optic radiation (purple fibres), and the associated visual field defects (lower left quadrant, purple).
symmetry was investigated by calculating the maximal difference in GCL-IPL thickness between sectors within the macula in each eye. The rationale behind this asymmetry ratio has been described previously.\textsuperscript{16}

High-quality images from the OCT measurements were defined as images with little or negligible influence from eye movements and/or blinking and with a signal strength of six or higher.

**Perimetry**

The visual field was tested using the Humphrey\textsuperscript{®} Field Analyzer HFA\textsuperscript{™} (models HFA IIi and HFA3; Carl Zeiss Meditec) and the SITA Fast 24-2 test. All participants unfamiliar with perimetry testing were offered a training session. If the result was considered unreliable, that is, more than 30\% fixation losses and more than 15\% false positives, this individual was retested. Results were expressed as the Visual Field Index (VFI), that is, the percentage of intact visual field function. The VFI is a global metric that represents the entire visual field based on the deviation pattern, with central points accorded a greater weighting than more peripheral ones. The VFI is calculated from a pattern deviation probability plot in the eyes, with a mean deviation better than $-20$ dB, and from the total deviation probability plot in the eyes with a mean deviation worse than $-20$ dB. The VFI can range from 100\% (normal visual field) to 0\% (perimetrically blind field).\textsuperscript{23}

**Statistical analysis**

Data used for the statistical analysis were tested for normal distribution using the Shapiro–Wilk test. VFI and GCL-IPL asymmetry values did not follow a normal distribution. Therefore, data are presented as the median and range. The correlations between GCL and IPL thickness and VFI were evaluated using the Spearman’s $\rho$ correlation coefficient. Both eyes were evaluated in the correlation analysis, resulting in within-participant association. All statistical analyses were performed using JASP v0.11.0 (JASP Team, University of Amsterdam, Amsterdam, the Netherlands).

**RESULTS**

The data on visual acuity, ocular alignment, and cognitive visual dysfunction are shown in Table S1.

**Neuroimaging**

The MRI showed injuries with different lesion patterns including malformations, WMDI, and focal infarcts (Table S1). By comparing the lesion pattern on the MRI scan with gestational age, two of the cases (cases 1 and 2) had lesion patterns consistent with prenatal injuries. In six of the cases (cases 1–6), fibre tractography revealed different degrees of lesional involvement of the optic radiation, whereas in the other four cases (cases 7–10), the optic radiation showed normal appearance on fibre tractography (Table S1).

**OCT and visual field outcome**

The median average GCL-IPL thickness of all cases was 68\,$\mu m$ (range 50–86\,$\mu m$), the minimum GCL thickness was 65\,$\mu m$ (range 50–83\,$\mu m$), and the VFI was 90\% (range 23–100\%). The median asymmetry, that is, the difference between the thinnest and thickest sector in the eye, was 12\,$\mu m$ (range 3–37\,$\mu m$).

Greater GCL-IPL asymmetry was associated with lower VFI (Spearman’s $\rho=0.83$, $p<0.001$). GCL-IPL minimum thickness was also associated with lower VFI (Spearman’s $\rho=0.85$, $p<0.001$). The correlation between GCL-IPL asymmetry and minimum GCL thickness was highly significant (Spearman’s $\rho=0.82$, $p<0.001$).

Seven out of the 10 cases (cases 1–7) showed reduced minimum GCL-IPL thickness; the software reported ‘red’ values in relation to the built-in normative database (Figs 1 and 2). We found high GCL-IPL thickness asymmetry in six of these cases (cases 1–6), that is, the difference between the thinnest and thickest sector ranged between 11\,$\mu m$ and 37\,$\mu m$. In cases 7 to 10, the asymmetry ranged between 3\,$\mu m$ and 5\,$\mu m$ (Fig. 2).

Cases 1 to 6, who presented with minimum GCL-IPL thinning and high asymmetry, had a VFI outside the normative database and reduced visual field sensitivity. In cases with GCL asymmetry (cases 1–6), focal thinning correlated with homonymous visual field defects, either hemifield defects or unilateral or bilateral quadrantanopia (Figs 1 and 2). We found a general reduction in visual field sensitivity but no focal defect with reduced GCL thickness and no asymmetry in case 7. Case 8 showed a similar reduction in VFI sensitivity but had normal minimum GCL-IPL thickness and low asymmetry. Two cases presented with normal GCL topography and normal visual field sensitivity (cases 9 and 10).

**DISCUSSION**

In this multi-case study that included individuals with spastic CP, OCT enabled the identification of individuals with focal visual field defects by analysing the GCL-IPL. There was a correlation between brain lesions affecting the optic radiation, as demonstrated by dMRI fibre tractography, focal GCL-IPL thinning in the macula due to RTSD, and corresponding homonymous visual field defects. In individuals without brain lesions affecting the optic radiation, no signs of retinal RTSD nor focal visual defects were found.

All participants who had homonymous visual defects had cognitive visual dysfunction and ocular motor problems (strabismus and/or nystagmus). Four cases, all with CP and classified in GMFCS level I, with no signs of brain lesions affecting the optic radiation, focal GCL-IPL thinning, or focal visual field defects, had either cognitive visual problems (three cases) or strabismus (one case). Therefore, an unaffected optic radiation does not rule out the risk that other parts of the visual brain may be affected by lesions and cause, for example, ocular motor or cognitive visual impairment as observed in this study.
Figure 2: Ganglion cell topography based on optical coherence tomography measurements and visual field maps. Visual fields are shown in greyscale with black indicating the defects. Visual field sensitivity is presented as a Visual Field Index (VFI), that is, the percentage of intact visual field function. The ganglion cell layer (GCL)-inner plexiform layer (IPL) topography is shown below each visual field (red indicates thinning). The circles represent the GCL-IPL sector thicknesses. In all cases with magnetic resonance imaging-verified damage to the optic radiance (cases 2–6), asymmetry values were high in both eyes and ganglion cell thinning correlated with focal, homonymous visual field defects. In cases without optic radiation damage (cases 7–10), no GCL asymmetry and no focal visual field defects were found.
On conventional MRI, it can be difficult to assess the extent of brain lesions. In fact, in individuals with CP, 11.7% have normal conventional MRI findings. dMRI can increase both sensitivity and specificity when detecting and determining the extent of injuries to the white matter pathways in CP. The lesional involvement of the immature optic radiation can be assessed with fibre tractography. The superiority of dMRI was clearly demonstrated in this study, for example, when comparing case 3 to case 9. Both cases suffered with extensive WMDI with similar timings (Table S1 and Fig. 2); however, in case 3 the injuries involved the optic radiation and the patient had congruent thinning of the GCL+IPL on OCT as well as homonymous visual field defects. Nonetheless, both individuals had cognitive visual problems; this was not an unexpected finding since the peritrigonal white matter is a known site of WMDI. A recent dMRI study showed an association between diffusion parametric changes in the superior longitudinal fascicles and cognitive visual dysfunction in children with CP, highlighting the potential of studying white matter pathways involved in higher-order visual processing in this patient group.

In one case (case 7) we found generally thin GCL+IPL, combined with minor reduced visual field sensitivity. Neither visual field nor GCL+IPL pattern indicated any focal defects and the MRI examinations demonstrated WMDI lesions not affecting the optic radiation. Thus, there are other factors during development that may influence the organization of the retinal GCL. In this specific case, we speculate that intrauterine growth restriction may have contributed to the subnormal number of ganglion cells.

In this study, we aimed to evaluate the potential of OCT as a targeted assessment tool to identify possible visual field defects. Our results indicate that OCT can be valuable in this respect given its high-resolution three-dimensional scans and accompanying software, which can be used to analyse the GCL+IPL. For optimal sensitivity and specificity during clinical examination, the clinician can use colour grading for interpretation purposes; however, to detect visual field defects based on GCL+IPL thickness, we suggest that they should also consider asymmetry and the difference between the average sector GCL thickness compared to minimum GCL+IPL thickness. Large differences are more likely to predict visual field defects. Reliable automated standardized perimetry is quite demanding for the patient and impossible to perform on small children. OCT requires shorter concentration and less compliance (a measurement takes a few seconds). Therefore, OCT might enable the examination of younger children compared to standardized perimetry. However, loss of retinal nerve fibres is delayed compared to the timing of brain damage. Jindahra et al. studied the time course of retinal RTSD after occipital lobe damage in adults. Reduction of retinal nerve fibre layer thickness ranged from 0.9µm to 6.3µm for every 100 days of elapsed time. Comparable studies on infants and children are awaited.

This study is not representative of all children with spastic CP since we recruited individuals with sufficient intellectual ability and attention to be able to participate in MRI and OCT imaging and visual field testing. Of the 10 individuals, seven were classified in GMFCS level I. However, in children with severe spastic CP due to extensive brain damage, where neither standardized perimetry nor OCT can be performed, we suspect even more pronounced overall loss of retinal ganglion cells with less evident asymmetry and more severe loss of visual function. It is likely, from other studies and our own experience, that the structure-function relationship between OCT and visual field defects tends to be weaker in cases with severe axonal loss. For example, it seems to have an offset below 20µm and nerve fibre layer thickness is never 0 even in patients who are blind.

CONCLUSION

When the brain damage that causes CP also affects the optic radiation, OCT can detect the RTSD of retinal ganglion cells and predict focal visual field defects. We recommend that all young children with CP who can cooperate with an OCT examination should be examined for the early identification of possible visual field defects and CVI. Identification of CVI facilitates prompt and salient education and habilitation.

Notwithstanding, individuals with spastic CP who present with normal retinal ganglion cell topography and normal visual field function may still have ocular motor and/or cognitive visual dysfunction.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Characteristics of study cohort

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