Multiple Sclerosis and Related Disorders 5 (2016) 66–69

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Clinical trial

Ganglion cell analysis in acute optic neuritis

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ARTICLE INFO

Article history:
Received 4 May 2015
Received in revised form
16 October 2015
Accepted 21 October 2015

Keywords:
Optic Neuritis
Multiple Sclerosis
Optical Coherence Tomography
Ganglion Cell and Inner Plexiform Layer

ABSTRACT

Background: Optic neuritis has a diagnostic and prognostic significance in predicting the development of multiple sclerosis. Optical coherence tomography is being increasingly used to detect and monitor axonal damage in MS by measuring the retinal nerve fiber layer (RNFL). However, RNFL can be affected by edema and inflammation and obscure early axonal damage.
Objective: To study the pattern of change in the ganglion cell and inner plexiform layer compared to retinal nerve fibber layer in acute optic neuritis using spectral domain OCT.
Methods: Ten patients with acute optic neuritis were followed prospectively for 6 months with spectral domain optical coherence tomography. A group of 40 of eyes of 20 healthy controls was used for baseline comparison.
Results: The ganglion cell and inner plexiform layer (GCIPL) was significantly lower (thinner) at onset in patients' affected ($p=0.009$) eyes. Both RNFL and GCIPL were significantly lower in affected eyes at 6 months ($p=0.012$ and $p=0.007$) respectively compared to baseline.
Conclusion: The GCIPL is probably more sensitive index of axonal loss than the RNFL in acute optic neuritis and could be a better index to detect neurodegeneration in multiple sclerosis. This can helpful in estimating early axonal loss and can potentially be used in therapeutic trials of neuroprotective drugs.

1. Introduction

Optic neuritis (ON) is a common clinical presentation of multiple sclerosis (MS). It is highly predictive of future development of MS if associated with magnetic resonance imaging (MRI) brain lesions (Miller et al., 2012). Optical coherence tomography (OCT) is a non-invasive tool, which allows quantitative and qualitative assessment of the retinal layers. Measurement of the retinal nerve fiber layer (RNFL) has been used to assess the degree of axonal loss in MS (Trip et al., 2006). Recent algorithms using spectral domain OCT (SDOCT) allow segmentation of retinal layers and measurement of the thickness of ganglion cell layer complex and inner plexiform (GCIPL). RNFL thickness has been studied extensively using time-domain OCT (TDOCT) in patients with clinically isolated syndrome (CIS) or MS (Costello et al., 2006). However, there are few studies on ON using the new spectral domain OCT (SDOCT) that longitudinally examined changes the GCIPL (Garas et al., 2011). Unlike the RNFL, the GCIPLis less affected by axonal swelling due to inflammation and edema in acute optic neuritis. Accurate assessment of the extent of axonal loss early in the disease can be important from both a diagnostic and therapeutic aspects. We have prospectively evaluated a cohort of patients with acute ON with SDOCT using a segmentation protocol to determine whether GCIPL thinning is seen earlier in patients with CIS with ON at onset and to longitudinally follow the changes of the peripiapillary and macular RNFL, and GCIPL and central macular thickness during a 6-month period.

2. Methods

We have prospectivley recruited 10 patients with acute ON within 5 weeks of onset of visual symptoms Mean $\pm$SD; 13.7 ± 10.7 (range 4–35 days) in the MS clinic at Dasman Institute. All subjects had an neuro-ophthalmologic assessment and spectral domain OCT using the Cirrus HD-OCT 5000 (Cirrhus HDOCT 5000; Carl Zeiss Meditec) was used to obtain perpipapillary and macular data (RNFL, and GCIPL and central macular thickness) using the protocol of optic disc cube scan of 200x200 and macular cube scan of 512x128 centered on the fovea. The built-in algorithm in the ganglion cell analysis measures the combined thickness of the ganglion cell and inner plexiform layer. Because of the similar

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http://dx.doi.org/10.1016/j.msard.2015.10.008
2211-0348/

Table 1
Summary of the demographics of the studied cohort and control group.

	Patients	Control	*P* value
Subjects	10	20	
Age Mean (SD)	26.8 (1.7)	28.6 (4.9)	0.015
Gender			
Male (%)	4 (40.0)	5 (55.6)	0.403
Female (%)	6 (60.0)	15 (44.4)	
Time from symptom onset Mean (SD)	13.7 (10.7) range 4–35 days		

tissue reflectivity of these two layers, current segmentation algorithms cannot discern the two layers apart and they are measured as one layer (GCIPL). This value has been used as a surrogate to denote ganglion cell layer similar publications. 6 OCT scanning was performed at onset, 3, and 6 months follow up period. We have excluded patients with high refractive errors (± 6 diopters), those with prior history of ON, or patients with other neurological diseases and/or disease of the retina and optic nerve. Furthermore, OCT on 40 eyes of 20 healthy controls was performed for baseline comparison with our cohort. This study was approved by the local ethical committee and was conducted in accordance with the declaration of Helsinki for biomedical research.

2.1. Statistical analysis

All statistical analyses were completed using JMP® (SAS Institute Inc., Cary, NC). An Independent *t*-test was used to determine the difference in RNFL, central macular thickness (CMT) and GCIPL between patients and healthy controls. Paired *t*-test was used to determine the difference between the onset, 3 months and 6 months follow-up period to evaluate the difference in RNFL, CMT and GCIPL. Data were represented in mean and standard deviation for both the *t*-tests. Statistical significance was defined as $P < 0.05$.

3. Results

The study subjects comprised 6 females and 4 males with the mean age (standard deviation) of 26.8 years (1.7) Six patients had MRI brain lesions consistent with demyelination while 4 had normal brain MRI. Of the six patients who had MRI brain lesions, only 1 satisfied the 2010 McDonald criteria for MS. (Polman et al., 2011) Data of three patients were not available for the 3 month OCT follow up. All patients received IV Methylprednisolone (one gram once daily for 3–5 days) for treatment of acute ON. Patients' affected ($n=10$) and unaffected ($n=10$) eyes were included in final analysis. The clinical characteristics of study subjects are summarized in Table 1. Using the independent *t*-test at baseline, the mean GCIPL was significantly lower at onset in patient with affected eyes compared to healthy control ($p=0.009$), while RNFLT and CMT were not (Table 2, Fig. 1). Paired *t*-test was done to compare the difference between onset, 3 months and 6 months follow-up period and both RNFLT ($p=0.012$; Fig. 2A) and GCIPL ($p=0.007$; Fig. 2B) were significantly lower in affected eyes at 6 months compared to onset (Table 3a). There was a trend for GCIPL to be thinner in the patients' unaffected eyes compared to controls ($p=0.068$) but that did not reach statistical significance. Similarly, RNFL and CMT were not significantly thinner at onset in patients' with unaffected eyes compared to healthy controls at onset, 3 months and 6 month follow up (Table 3b).

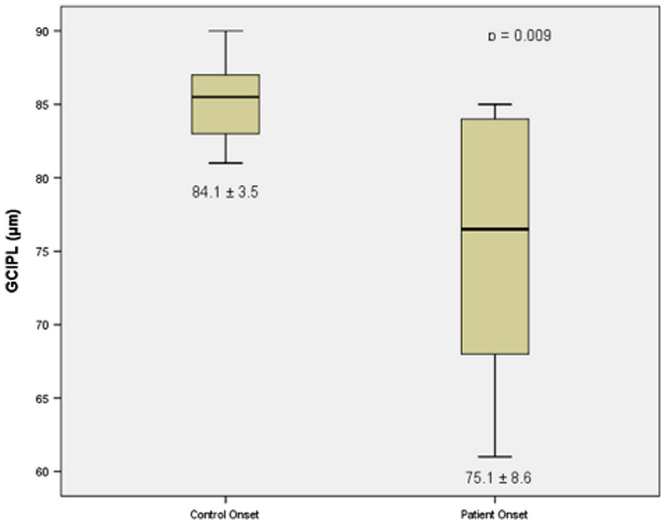

Fig. 1. A box-plot showing ganglion cell and inner plexiform layer (GCIPL) thickness in micrometer between control onset and patient onset ($p=0.009$).

4. Discussion

We have found that GCIPL was significantly thinner at onset of optic neuritis in the involved with a trend to significance in the non-involved eye when compared to healthy controls. Peripapillary RNFL and CMT were not significantly different at onset in either the affected eyes or unaffected eyes compared to healthy controls.This suggests that GCIPL is a more sensitive index for early axonal loss in acute optic neuritis . Both GCIPL and RNFL were significantly thinner at 6 months compared to baseline. Although we cannot determine the exact time at which GCIPL thinning starts because of the variable points in the time window in which SDOCT was obtained, we speculate that most of the thinning of GCIPL takes place between onset and 3 months while RNFLT thinning progressed over the follow-up period. (Fig. 2A and B) Previous studies have shown that RNFL thinning progresses up to 6 months. (Costello et al., 2006, 2011). While GCIPL thinning starts around 3 months in other studies, we have found that in some

Table 2
Independent *t*-test shows the measurements of the RNFLT, CMT and GCIPL in the affected and unaffected eyes between studied control and patients.

	Affected eyes			Unaffected eyes		
	Control Onset Mean ± SD	Patient Onset Mean ± SD	*P* value	Control Onset Mean ± SD	Patient Onset Mean ± SD	*P* value
RNFLT (µm)	94.9 ± 6.0	90.9 ± 13.5	0.385	94.9 ± 6.0	89.6 ± 15.0	0.302
CMT (µm)	244.3 ± 20.0	241.5 ± 19.4	0.686	244.3 ± 20.0	242.4 ± 14.9	0.735
GCIPL (µm)	84.1 ± 3.5	75.1 ± 8.6	0.009	84.1 ± 3.5	77.0 ± 10.8	0.068

SD=Standard deviation; RNFLT=Peripapillary Retinal Nerve Fiber Layer Thickness; CMT=Central Macular Thickness; GCIPL=Ganglion cell and Inner Plexiform Layer; µm=micrometer.