PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B, Vol. 69 (2015), No. 5 (698), pp. 232–236.
DOI: 10.1515/prolas-2015-0035

FUNCTIONAL AND STRUCTURAL EVALUATION OF AFFERENT VISUAL SYSTEM IN MULTIPLE SCLEROSIS PATIENTS

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Communicated by Igors Aksiks

There is insufficient information about the progress and variability of multiple sclerosis (MS). Afferent visual pathways are an appropriate MS clinical model. Optical coherence tomography (OCT) allows to perform precise measurements of axonal tissue in the retinal nerve fibre layer (RNFL). Visual evoked potentials (VEP) provide information about the functional status of visual pathways. The aim of our study was to use OCT and VEP to evaluate MS patients with and without optic neuritis (ON) history and to determine relationships between functional and structural changes. The cross-sectional study included 76 relapsing-remitting MS patients and 28 healthy controls. The lowest mean VEP N75/P100 amplitude was found in ON affected eyes (8.16 mkV, SD = 4.60). However, it was observed that the mean amplitude in patients without ON (M = 9.86; SD = 4.63) was by 4.64 mkV lower than in controls ($p < 0.001$*). Similarly, the mean P 100 latency in ON eyes was 9.26 ms longer than in eyes of patients without ON history (*$p < 0.01$*). RNFL in the temporal segment (RNFLT) was the thinnest in ON eyes, and even in patient eyes without ON, it was thinner than in controls. We found a significant positive correlation between RNFLT and mean N75/P100 amplitude in patients without ON (*$r_s = 0.43$; $p < 0.001$*), and after ON (*$r_s = 0.45$; $p < 0.001$*). Both in patients without ON (*$r_s = –0.40$; $p < 0.001$*) and in ON eyes we found a significant negative correlation (*$r_s = –0.55$; $p > 0.001$*) between RNFLT and mean P100 latency. In summary, we found that deterioration in the visual system was not associated with the clinical ON episode. Regardless of ON symptoms in history, there exists correlation between functional and structural changes.*

Key words: *multiple sclerosis, optic nerve, axonal damage, visual evoked potentials, optical coherence tomography.*

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative central nervous system disorder that is characterised by inflammation, demyelination and primary or secondary axonal degeneration (Trapp *et al*., 1998). MS is the most common reason of non-traumatic disability in young adults and there are more than 2.3 million MS patients in the world (Browne *et al*., 2014).

The pathogenesis of MS is not entirely clear. For a long time it was considered to be a primarily demyelinating disease, but there is increasing evidence that neurodegeneration and axonal damage begins early and plays a more important role (Bruck, 2005; Zipp and Aktas, 2006; Fisniku *et al*., 2008; Siffrin *et al*., 2010).

There are no identified factors that cause expressed MS variability and transformation to the progressive and treatment-resistant stage. MS cannot be completely cured and available treatment is mainly based on inflammation decrease, which barely impacts neurodegeneration (Costello, 2013). There is increased need for neuroprotective treatment and biological markers to follow the course of the disease and treatment effectiveness (Fernandez, 2013).

Afferent visual pathways are an appropriate MS clinical model. MS often affects visual pathways, as almost 70% of MS patients will experience an optic neuritis (ON) episode in their lifetime (Di Maggio *et al*. 2014). Afferent visual pathways represent an acute demyelination episode through acute ON, while in the case of chronic, subclinical retinopathy and optic neuropathy — diffuse, chronic central nervous system damage. For better understanding of MS, recently a new biological marker was proposed — optical coherence tomography (OCT), which allows to perform precise measurements of retinal axonal tissue in the retinal nerve fiber layer (RNFL). Visually evoked potentials (VEP) provide information about functional status of visual pathways.

The aim of our study was to use VEP and OCT to evaluate MS patients with and without ON history and to determine relationships between functional and structural changes.

MATERIALS AND METHODS

The cross-sectional study included 76 relapsing-remitting MS patients who were divided into two groups:

- MS patients without ON symptoms in history;

- MS patients with ON history.

In the MS patient group with ON history, ON-affected eyes (ON+) and contralateral, ON-unaffected eyes (ON–) were analysed separately

The control group included 28 age-matched and sex-matched healthy individuals.

MS patients were selected from the Pauls Stradiņš Clinical University Hospital Multiple Sclerosis Centre during the period from October 2011 to April 2014. The study was approved by the local research ethics committee. Part of the MS patients continued their immunomodulatory therapy. Inclusion criteria were:

- relapsing remitting MS diagnosis, based on the 2010 McDonald criteria;

- for MS patients with a history of ON > 6 months after unilateral ON episode;

- ≥ 30 days after corticosteroid therapy.

Exclusion criteria:

- acute ON clinical signs;

- refraction disorders exceeding ± 6 diopters;

- other neurological and ophthalmic diseases, which could affect the afferent visual system;

- inability to participate in visual system examinations.

A history of ON was determined on the basis of symptoms and clinical signs (Voss *et al*., 2011). Neurological examination of patients with disability was assessed using the Kurzke Expanded Disability Status Scale (EDSS). In clinical assessment of the ophthalmological condition, the following functional and structural visual system tests were made separately for each eye.

Visual acuity was tested with the Snellen chart. For all participants, the pattern–reversal VEP record was performed using hardware "RETI port 21 ROLAND CONSULT". Individuals were placed 70 cm away from the screen, fixing their view on the red dot in the centre of the screen. When required, a full refractive correction was made. For establishing of potential, vision was repeatedly stimulated in a monocular way with a black-white video monitor at 1.6 Hz frequency. Record of the potential was made with disc electrodes, placing them in the brain visual cortical projection areas of the International 10–20 system; the active and reference electrodes were placed according to Oz and Fz areas (Odom *et al*. 2010). The average potentials of action were filtered and analysed, repeatedly performing 100 re-stimulations twice for each eye. N75/P100 amplitude measurements in microvolts (mkV), as well as P 100 latency measurements in milliseconds (ms) were made. Based on recommendations of the International Federation of Clinical Neurophysiology on the limits for evaluation of measurements made using the VEP hardware, N75/P100 amplitude below 10.52 mkV was considered to be reduced, and P100 latency longer than 110.25 ms was considered to be extended.

Using the OCT method (Heidelberg Engineering SPECTRALIS), RNFL thickness was measured in six standard sectors (temporal, temporal upper, temporal lower, nasal, nasal upper and nasal lower) with measurements expressed in micrometers (mkm). For all study participants, active Tru Track eye tracking technology was used. RNFL thickness results were evaluated using the OCT normative database, where green marked areas were classified as normal, and the red marked areas were considered abnormally reduced. OCT images of unsatisfactory quality were rejected.

For statistical analysis, the IBM SPSS v.22. software was used. Data were presented as mean (M) and standard deviation (SD) or median (Me) and interquartile range (IQR) for continuous variables, and counts for categorical variables. Logistic regression modelling techniques were used to determine patient factors that were associated with the binary outcome. Significant differences of quantitative variables between groups were tested using the Student's t test. Correlation between variables was assessed using the Spearman's correlation test. All tests were two-sided and statistical significance was considered at $p < 0.05$.

RESULTS

The study included 76 MS patients with minimum age 17 years and maximum age 65 years. The control group included 28 healthy subjects aged 19 to 65 years. It was found that age of MS patients and the control group did not significantly differ (t-test; $p > 0.05$). The mean disease dura-

tion in MS patients was 39.56 months (6 to 384 months). In both MS patient groups, the modal EDSS step was 1.5 and the maximum was 6. The medians of EDSS in the MS patient groups did not significantly differ (Mann-Whitney test; $p > 0.05$). The mean corrected visual acuity in MS patients was 0.94 (SD = 0.25), and lowest value of the corrected visual acuity was 0.02. Demographic and clinical details of MS patients and controls are reproduced in Table 1.

The N75/P100 VEP amplitude was lower in the MS patient group with ON history, particularly in the ON+ eyes (8.16 mkV (SD = 4.60)). The mean amplitude was 2.87 mkV lower than in ON– eyes ($p = 0.01$). Furthermore, a lower N75/P100 amplitude was observed in MS patients without any ON history, compared to that in the control group. The independent samples t test showed that that the mean amplitude in MS patients without ON (M = 9.86; SD = 4.63) was significantly lower (by 4.64 mkV, $p < 0.001$), than in the control group (M = 14.51; SD = 3.35). Similarly, mean P 100 latency in ON+ eyes was 9.26 ms longer than in eyes of MS patients without any ON history ($p < 0.01$). Also, the mean P 100 latency was 11.25 ms longer in ON+ eyes compared with that in ON– eyes ($p < 0.01$) in the MS patient group with ON clinical signs in their history.

Comparing the control group and MS patients using OCT measurements, the RNFL set significantly different in all quadrants ($p < 0.05$). ROC curve analysis showed that the biggest RNFL difference was in the temporal quadrant (RNFLT) (accordingly AUC = 0.72; 95% CI: 0.64 to 0.79; $p < 0.01$). RNFLT was thinner in ON+ eyes, but even in MS patient eyes without ON symptoms history, this layer was 8.45 μm thinner than in the control group. The mean RNFLT differed between the three study groups ($p < 0.001$). Furthermore, age of individuals did not have a significant effect on these differences (ANCOVA; $p > 0.05$). Mean VEP amplitudes, latencies and RNFLT measurements are shown in Table 2.

Spearman's correlation coefficient analysis showed a positive correlation ($r_s = 0.43$; $p < 0.001$) in MS patients without ON history between RNFLT and mean N75/P100 amplitude, and in ON+ eyes ($r_s = 0.45$; $p < 0.001$). There was negative correlation ($r_s = –0.55$; $p < 0.001$) between RNFLT and P100 latency in patients without an ON history ($r_s = –0.40$; $p < 0.001$) and ON + eyes (Figs. 1 and 2).

Table 1

CLINICAL AND DEMOGRAPHICAL CHARACTERISTICS OF SUBJECTS

Subjects	MS patients with ON	MS patients without ON	Controls
n	33	43	28
Age (years)	37.57 (SD = 12.04)	38.94 (SD = 12.31)	35.78 (SD = 12.14)
Disease duration (months)	39.56 (6 – 384)	72.03 (0–400)	-
EDSS Me (IQR)	1.5 (1)	1.5 (2)	-
Visual acuity (corrected)	0.92 (SD = 0.25)	1.02 (SD = 0.21)	1.00 (SD = 0.12)

MS, multiple sclerosis; ON, optic neuritis; EDSS, Expanded Disability Status Scale; IQR, interquartile range; SD, standard deviation

DISCUSSION

In our study the thinnest RNFL was observed in ON+ eyes, but also in eyes without previous ON this layer was significantly thinner than in the control group. This finding confirms the observed subclinical ongoing axonal tissue damage in numerous previous studies (Parisi *et al*., 1999; Pueyo *et al*., 2008; Zaveri *et al*., 2008; Garcia-Martin *et al*., 2010,

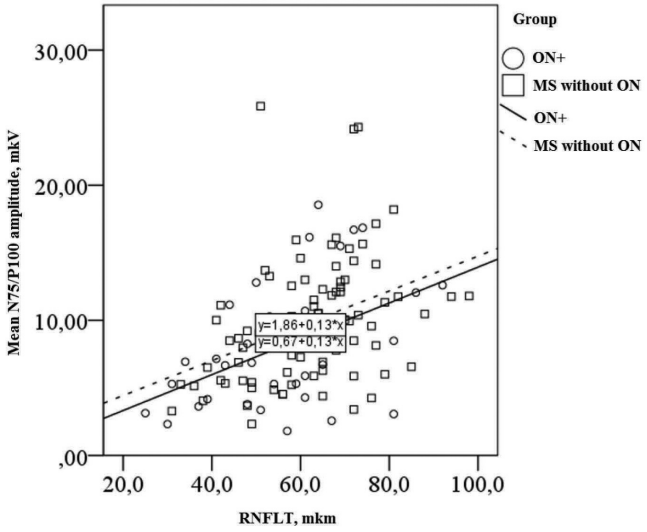

Fig. 1. Relationship of RNFLT (retinal nerve fiber layer in the temporal segment) with mean N75/P100 amplitude. MS, multiple sclerosis; ON, optic neuritis

Table 2

MEAN VISUAL EVOKED POTENTIAL AMPLITUDE, LATENCY AND RETINAL NERVE FIBRE THICKNESS IN THE TEMPORAL SEGMENT

	MS with ON, eyes		MS without ON, eyes (n = 86)	Controls, eyes (n = 56)
	ON+ (n = 33)	ON- (n = 33)		
Mean N75/P100 amplitude, mkV, (SD)	8.16 (4.6)	11.03 (5.40)	9.86 (4.63)	14.15 (3.35)
Mean P100 latency, ms, (SD)	126.0 (18.26)	114.75 (11.94)	116.73 (16.00)	101.81 (5.66)
Mean RNFLT, mkm (SD)	56.44 (16.51)	62.12 (13.92)	62.47 (11.18)	70.92 (7.12)

For abbreviations see Table 1. RNFLT, retinal nerve fiber layer in the temporal segment

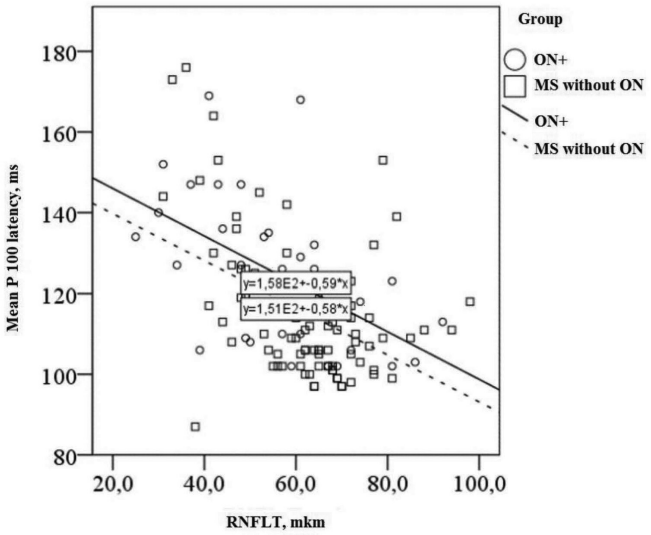

Fig. 2. Relationship of RNFLT with mean P100 latency. (For abbreviations see Fig. 1).

Quelly *et al*., 2010; Fjeldstad *et al*., 2011). In a large meta-analysis it was estimated that RNFL is about 20 μm thinner in ON+ eyes than in controls (Petzold *et al*., 2010). According to our results, the mean difference was not as pronounced (14 μm), which might indicate transaxonal degeneration after an acute demyelinating event.

Less understandable is the decrease of the axonal tissue layer thickness in patients without any ON clinical signs in their history. These changes may suggest chronical axonal tissue involvement during progress of the disease. Furthermore, this may be considered as a biological marker that can be monitored in different clinical situations. Subclinical decline in parameters of VEP also may indicate dynamically deteriorating functional status of the nervous system. The literature on usefulness of VEP and OCT in subclinical ON diagnostics are controversial. There are studies that find both of these methods to be helpful for subclinical involvement detection (Trip *et al*., 2005; Fisher *et al*., 2006; Klistorner *et al*., 2008; Naismith *et al*., 2009; Talman *et al*., 2010). Our study showed significant correlation between RNFLT with mean VEP amplitude and latency, as previously observed (Naismith *et al*., 2009; Di Maggio *et al*., 2014). However, a few authors have described a relationship between RNFLT and P 100 latency, (Fatehi *et al*., 2012), and with N75/P 100 latency (Trip *et al*., 2005). Taking into account that these methods assess different damage aspects (structural and functional), it may be advised to perform both of them for patients without specific complaints about vision. Furthermore, RNFLT charcterises only the anterior part of visual pathways, while VEP shows integrity of the whole visual system from retina to visual cortex. To improve the sensitivity of OCT, recently it was suggested to perform inner plexiform layer and ganglionic layer measurements (Davies *et al*., 2011; Seigo *et al*., 2012; Walter *et al*., 2012), which could more precisely quantify axonal tissue, as these structures do not contain glia cells and blood vessels (Hood *et al*., 2010).

In conclusion, there are functional and structural changes in afferent visual system that are not associated with the clinical optic nerve inflammation episode. Regardless of ON clinical presence, there exists a correlation between functional and structural changes in the afferent visual system.

ACKNOWLEDGEMENTS

The authors state no conflict of interest.

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Received 30 April 2015

FUNKCIONĀLAS UN STRUKTURĀLAS REDZES SISTĒMAS IZMAIŅAS MULTIPLĀS SKLEROZES PACIENTIEM

Multiplās sklerozes (MS) gaita ir mainīga un grūti prognozējama. Redzes sistēma var tikt analizēta kā MS klīniskais modelis. Ar optiskās koherences tomogrāfijas (OCT) metodi iespējams veikt precīzus aksonālo audu mērījumus, mērot tīklenes nervu šķiedru slāni (RNFL). Izmantojot redzes izsaukto potenciālu metodi (VEP), iespējams analizēt redzes sistēmas funkcionālo stāvokli. Pētījuma mērķis bija veikt redzes sistēmas izmeklējumus ar OCT un VEP metodēm MS pacientiem ar un bez redzes nerva neirīta (ON) epizodes anamnēzē, kā arī noskaidrot strukturālo un funkcionālo izmaiņu savstarpējās saistības. Šķērsgriezuma pētījumā tika iekļauti 76 recidivējoši remitējošas MS pacienti, kā arī 28 kontroles grupas indivīdi. Zemākā vidējā VEP N75/P100 amplitūda tika konstatēta acīs pēc ON epizodes (8,16 mkV, SD = 4,60), taču arī pacientiem bez ON anamnēzē vidējā VEP amplitūda bija par 4,64 mkV zemāka, salīdzinot ar kontroles grupu ($p < 0.001$). Līdzīgi vidējā VEP P100 latence ON skartajās acīs bija par 9,26 ms garāka, salīdzinot ar pacientiem, kuriem ON klīnisko pazīmju anamnēzē nav bijis ($p < 0,01$). Analizējot RNFL temporālajā segmentā (RNFLT), visplānākais tas bija acīs pēc ON epizodes, tomēr arī MS pacientiem bez ON pazīmēm tas bija plānāks nekā kontroles grupai. Tika konstatēta pozitīva korelācija starp RNFLT un vidējo N75/P100 amplitūdu gan pacientiem pēc ON epizodes ($r_s = 0,43$; $p < 0,001$), gan pacientiem bez ON klīniskajām pazīmēm anamnēzē ($r_s = 0,45$; $p < 0,001$). Arī vidējai P100 latencei tika konstatēta saistība ar RNFLT gan pacientu grupā pēc ON ($r_s = -0,55$; $p < 0.001$), gan arī pacientiem bez iepriekš pārciesta ON ($r_s = -0,40$; $p < 0,001$). MS pacientiem vērojamas subklīniskas funkcionālas un strukturālas izmaiņas redzes sistēmā, kas nav saistītas ar klīnisku ON epizodi. Neatkarīgi no ON klīniskajām pazīmēm anamnēzē vērojamas korelācija starp strukturālām un funkcionālām izmaiņām redzes sistēmā.