·Clinical Research·

Visual pathways involvement in clinically isolated syndrome in children

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Abstract

• AIM: To investigate extent and nature of visual pathways involvement in children with clinically isolated syndrome (CIS).

• METHODS: Forty-seven patients (age 11-17y) with CIS, which later proved to be multiple sclerosis (MS) onset, and 30 controls underwent visual evoked potentials (VEP) investigation within 12d from the appearance of the first signs of disease. Latency and amplitude of P100 peak were compared with normative data and between groups.

• RESULTS: In 58% patients, including those without signs of retrobulbar neuritis, significant slowing of conduction along the central visual pathways (P100 latency lengthening) is seen. P100 amplitudes drop (signs of axonal damage) are registered less frequently (29% cases).

• CONCLUSION: The results indicate that visual pathways are often affected in the MS onset; mostly demyelination signs are seen. Despite MRI significance for MS diagnostic, VEPs proved to be still effective in early diagnosis of MS in children.

• KEYWORDS: visual evoked potentials; multiple sclerosis; clinically isolated syndrome; children; visual pathway

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INTRODUCTION

Multiple sclerosis (MS) is the inflammatory disease of nervous system, in 5% cases it manifests in patients younger than 18 years old, and in 1% cases in children younger than 10 years old [1]. Adult MS features are investigated quite thoroughly and in great details, but pediatric disease is still less studied.

Sight disturbance considered to be one of the most often occurring symptoms of MS [2]. Inflammation, demyelization and axonal damage of optic pathways neurons are considered to be the main reasons of its occurrence [3,4]. Objective evaluation of the conduction along the visual pathways may be acquired by the use of visual evoked potentials (VEP). Shape, amplitude and latency of main negative peak in pattern-evoked VEP (P100) change significantly in adult MS[5]. In adults with MS in 88% cases of retrobulbar neuritis and 19% of those without this condition VEP abnormalities are seen [6]. P100 latency changes are registered years after retrobulbar neuritis has resolved[5]. VEPs are considered to be one of the most sensitive methods for MS diagnosis on the clinically isolated syndrome (CIS) stage[7].

VEPs in children with MS are rarely studied. One of the most important questions, axonal damage or demyelization prevalence on the early stages of MS, is also debatable[8-10].

Our aim was to investigate degree and nature of visual pathways involvement in children with MS.

SUBJECTS AND METHODS

Subjects Forty-seven children (25 males, 22 females; age 11-17y, mean 13.9) with CIS were enrolled in the study. Inclusion criteria was CIS, established by thorough neurologic examination. CIS neurology symptoms included oculomotor apraxia (12 patients), hemiparesis (8 patients), hemihypestesia (7 patients), central facial palsy (4 patients), vestibular disorders (16 patients). Eye symptoms (pain, visual acuity drop, blurry vision) were evident in 16 patients. Mean expanded disability status scale (EDSS) score in group was 3.5, range 2.5-6.5. All patients were examined by ophthalmologist. There were no severe visual disturbances in the group. Ophthalmologist examination revealed retrobulbar neuritis in 18 patients, in 10 cases at the left side and in 8 cases at the right side. In 2 cases absolute scotoma and in 1 case optic nerve atrophy was diagnosed.

Mean duration of the disease at the moment of examination was 20d, range 1-62d. Thus, in all cases investigation was performed during the MS debut at the height of the clinical symptoms; visual acuity in retrobulbar neuritis drops to its nadir averagely at 2wk from the first complains onset[11].

All patients were conscious. Later in the course of the disease MS diagnosis was established in all cases by thorough

neurologic examination, MRI and oligoclonal antibodies presence in the cerebro-spinal fluid (CSF).

Control group consisted of 30 children (21 males, 9 females; age 10-17 years old, average 12.9), without neurological disorders and any ophthalmological complaints.

Study was approved by the local ethical committee according to the Declaration of Helsinki. The purpose of the study was fully explained to the participants, their parents or legal representatives, written informed consent was obtained from all patients' parents or legal representatives.

Methods All patients underwent VEP procedure, standard checkerboard 30 pattern, reversed every half-second; Neiro-MVP-4 evoked potentials apparatus was used. Investigations were performed in the darkened room. VEP was recorded according to currently accepted standard procedures [12]. IBM monitor was used, model 654741N, size 17 inches. 2 Hz and 100 Hz filters were used, rejection algorithm with upper threshold 300 μV was implemented. Fixation was monitored. Standard cup electrodes (8 mm) were used, 10-20 system modified according to the smaller head size. All equipment and EP software was manufactured by Neurosoft Company (Russia). Amplitude, latency and asymmetry of the main peak P100 were evaluated and compared between groups. At least 2 recordings from each eye were taken and averaged in case of repeatability. Recordings were undertaken through normal pupils and with normal accommodation.

Statistical Analysis Statistical analysis was performed by using statistical analysis software for Windows 7.0, STATISTICA package. For the demographic features of the cohort descriptive statistics were used. For group comparisons Student's *t*-test was used for normally distributed parameters. For not normally distributed values Mann-Whitney *U* test was used. A *P* value <0.05 was considered statistically significant.

RESULTS

Data on average VEP latency, amplitude and asymmetry in groups are presented in Table 1.

VEP parameters in MS group (94 eyes) varied significantly (P<0.05) from controls (60 eyes): P100 latency was longer and its amplitude lower. Amplitude difference between sides in MS group was not significant, but latency difference were (P<0.05).

In individual cases all VEP parameters in controls were normal. In MS group P100 latency lengthening (>110 ms) was seen in 58% of the patients (n=27). Range of P100 latency in MS group was 99-179 ms. Bilateral P100 lengthening was seen in 21% of the children (n=13). Unilateral N75-P100 amplitude lowering (<4 μV) was seen in 29% of the cases (n=14) and bilateral in 8% of the patients (n=4). Range of N75-P100 amplitude was 0.49-17.4 μV. Example of the abnormal VEPs found in MS group is presented on Figure 1.

Table 1 VEP latency, amplitude, latency and amplitude asymmetry in MS group (n=30) and in controls $\bar{x} \pm s$

P100 parameter	MS group	Controls
Mean P100 latency (ms)	[1]111.5±6.3	97.6±3.9
Mean P100 amplitude (μV)	[1]6.8±3.3	11.8±6.3
Mean latency asymmetry (ms)	[1]13.3±15.9	1.05±1.02
Mean amplitude asymmetry (μV)	2.07±2.4	2.9±1.5

[1]Difference is significant between the groups, P<0.05.

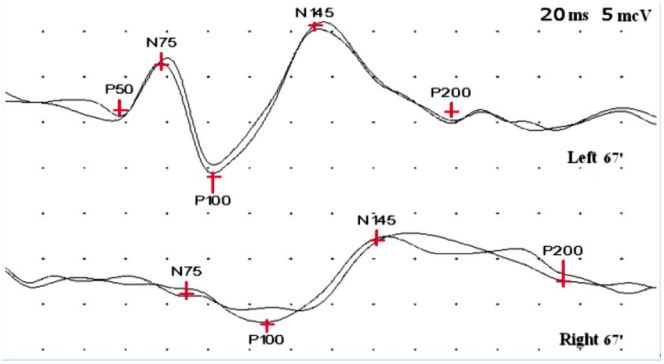

Figure 1 VEP of male patient, age 15y; according to the ophthalmologists investigation retrobulbar neuritis of the left eye is present P100 latency lengthening to 128 ms and amplitude lowering to 3.28 μV are present in the right eye stimulation.

Out of 27 cases, in which P100 latency was more than 110 ms, in 18 patients retrobulbar neuritis was established by previous ophthalmologist examination. Other 9 children were considered disease-free by ophthalmologist, also they did not presented any complain about vision problems.

DISCUSSION

As it can be seen from the data presented, there were significant differences between the MS children and controls. Mostly conduction slowing was seen. Such slowing usually considered to occur due to demyelization [13]. Amplitudes lowering, which reflects axonal damage of the neurons of visual pathways, were more rarely found.

Some authors found that average P100 latency in adults with CIS is 141-146 ms, and amplitude are normal in 100% of the cases, which leads them to conclusion that on MS early stage only demyelization are seen [7,14]. We have found that in 21% of the cases in pediatric MS bilateral damage of the visual pathways are present. This neurophysiologic finding correlates well with clinical reports about frequent bilateral damage of visual pathways in MS[11]. Some authors argue that contralateral eye damage, sometimes seen without any MRI findings, may happen due to acute demyelization of contralateral visual pathways[11,15].

Our data on significant difference between MS patients and controls on amplitudes and latencies of the main peak is partly supporting the report of Steczkowska *et al* [9]. They have found that in 10 patients aged 13-17y latencies changes were significantly different with controls, but amplitude

lowering not. This difference with our data may be explained mainly by the bigger amount of patients enrolled.

Axonal damage and demyelization timeline and extent in the course of MS stay the topic of discussion [8]. We have demonstrated that in children with MS motor pathways on early stage are affected mostly by demyelization[16]. Thus, our finding in present work may be supportive to the hypothesis (considered classic) that MS starts with demyelization and axonal damage appears on later stage[8].

VEP are proved to be easy to implement and easy to interpret tool for additional diagnostic in pediatric MS [17,18]. Despite MRI efficiency in MS diagnostics, implementation of this method in pediatric patients may be challenging. VEP are also quite useful for the MS prognosis: VEP abnormalities and oligoclonal antibodies in CSF may point to the MS relapse in next 2y after the finding[19,20].

One of the limitations of our study is the fact that we have used standard VEP procedure without implementation of more exquisite methods (*e.g.* low-contrast VEP); also we did not used pattern electroretinography (PERG). Such study may be valuable in future research.

In conclusion, VEP in pediatric patients stays useful tool of investigation. In children with CIS it was effective in discovery of hidden visual pathways disorders. Demyelization seems to be seen in more patients on the very early stage of MS, than axonal damage, at least according to the neurophysiological investigation of the visual pathways.

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