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CASE REPORT

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The role of visual evoked potentials in ophthalmological evaluation of a patient with optic nerve hypoplasia in septo-optic dysplasia

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ABSTRACT

Optic nerve hypoplasia (ONH) is a congenital malformation which results in various degrees of visual impairment. Together, optic nerve hypoplasia, midline brain defects and dysfunction of the pituitary gland represent the characteristic triad of symptoms of septo-optic dysplasia (SOD).

We describe a case of a severely intellectually disabled child with optic nerve hypoplasia, as one of the manifestations of septo-optic dysplasia syndrome. At 1 month of age, head ultrasound detected agenesis of the septum pellucidum and the corpus callosum. Magnetic resonance imaging also showed hypoplasia of the optic nerves. In ophthalmologic examination, high-intensity nystagmus was noted. Visual tracking was not observed. At 6 months of age, a visual evoked potentials (VEP) examination was performed. The results suggested the possibility of developing functional vision and led to the patient's referral for visual rehabilitation. The VEP examination was repeated at 20 months and 5 years of age with the results showing progressive improvement of the function of the visual pathway.

We aimed to depict related ophthalmic disorders of SOD and present the role of visual evoked potentials (VEP) as a useful tool for regular evaluation of patients with optic nerve hypoplasia, especially with accompanying severe developmental delay.

KEY WORDS: visual evoked potentials, optic nerve hypoplasia, septo-optic dysplasia, visual rehabilitation, case report.

INTRODUCTION

Optic nerve hypoplasia (ONH) is a congenital malformation characterized by underdevelopment of the optic nerves [1]. As the incidence of ONH increases, it becomes a common cause of varying degrees of visual impairment, from moderate vision loss to blindness [1, 2].

Although the aetiology of this disease is not clearly identified and remain unknown in many cases, dozens of aetiological factors have been suggested, predominantly young maternal age and primiparity, and also prenatal exposure to alcohol, drugs, smoking or viral infections is considered [2]. In some cases, mutations in genes such as *HESX1*, *OTHX2*, *SOX2*, *SOX3*, *PROKR2* have been associated with ONH [1].

The condition can be bilateral or less often unilateral. The first presented sign of ONH is often poor visual behaviour. Visual acuity ranges from no light perception to near normal [1]. Ocular manifestations of ONH include strabismus and nystagmus. Strabismus is the main feature in unilateral cases, in comparison to bilateral ONH, which is more often associated with nystagmus [1, 2].

Optic nerve hypoplasia may be an isolated defect or occur with endocrinopathies or central nervous system abnormalities [1]. In septo-optic dysplasia syndrome, ONH occurs as a feature of the classical triad linked to pituitary hormone dysfunction and midline brain defects including agenesis of the septum pellucidum and corpus callosum [3].

We report case of a patient with optic nerve hypoplasia in septo-optic dysplasia, describing related ophthalmic disorders and presenting the role of visual evoked potentials (VEP) in evaluation of the patient.

CASE REPORT

The 10-year-old boy, born at 39 weeks of gestation, with an Apgar score of 10, birth weight 2550 g, length 49 cm, head circumferences 30 cm, with congenital *human papillomavirus* infection, was exposed to tobacco smoke during pregnancy. At 1 month of age, head ultrasound revealed agenesis of the septum pellucidum and corpus callosum, which was confirmed in magnetic resonance imaging (MRI) examination at 5 months of age. MRI also showed pachygyria/

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polymicrogyria of the cerebral cortex in the right fronto-parietal area. Underdevelopment of the optic nerves as well as septo-optic dysplasia (SOD) was suspected. In ophthalmologic examination, high-intensity horizontal/rotatory nystagmus was noted. The nystagmus was decreasing in intensity in down gaze. Visual tracking was not observed. At 6 months of age, flash and pattern visual evoked potentials (FVEP, PVEP) testing was performed using an EP-1000 device (Tomey), skin gold-cup electrodes (active electrodes were placed at O_1 and O_2, a reference electrode at Fz). Other examination conditions followed the standards of the International Society for Clinical Electrophysiology of Vision [4]. In standard visual evoked potentials (VEP) examination, one active electrode placed at O_z (about 3 cm above the inion) is used. In patients with various pathologies of the brain, multichannel VEP (O_1, O_2, O_z) provide more information about crossed and uncrossed visual pathways. In our modification for examination of babies and children, we placed two instead of three electrodes (at O_1 and O_2). It makes the procedure shorter and avoids crowding of electrodes on a small head. On the other hand, electrodes which are placed too close to each other may interact and give additional noises.

During the examination the child was not interested in pattern and flash. A response to the flash was observed, while no response to pattern (transient pattern reversal, checkerboard size 4 degrees) was found. Based on the result, the boy was referred for visual rehabilitation. A funduscopic examination, performed at 11 months of age, demonstrated small optic discs with asymmetrical outlines. A visual refractive error was diagnosed after cycloplegia (0.5% atropine twice daily, 4 days): right eye +3.0 D, left eye +2.0 D. Corrective lenses were prescribed. The boy was not able to fixate.

The flash and pattern VEP were performed for a second time at 20 months of age. The visual response to the pattern VEP appeared and the visual response to the flash VEP improved (shorter latencies and higher amplitudes). PVEP responses were very small, but after stimulation magnitudes of 4.0, 2.5 and 1.5 degrees were observed. Improvement of visual responses was the only sign that the maturation of patient's vision progressed. Visual rehabilitation was

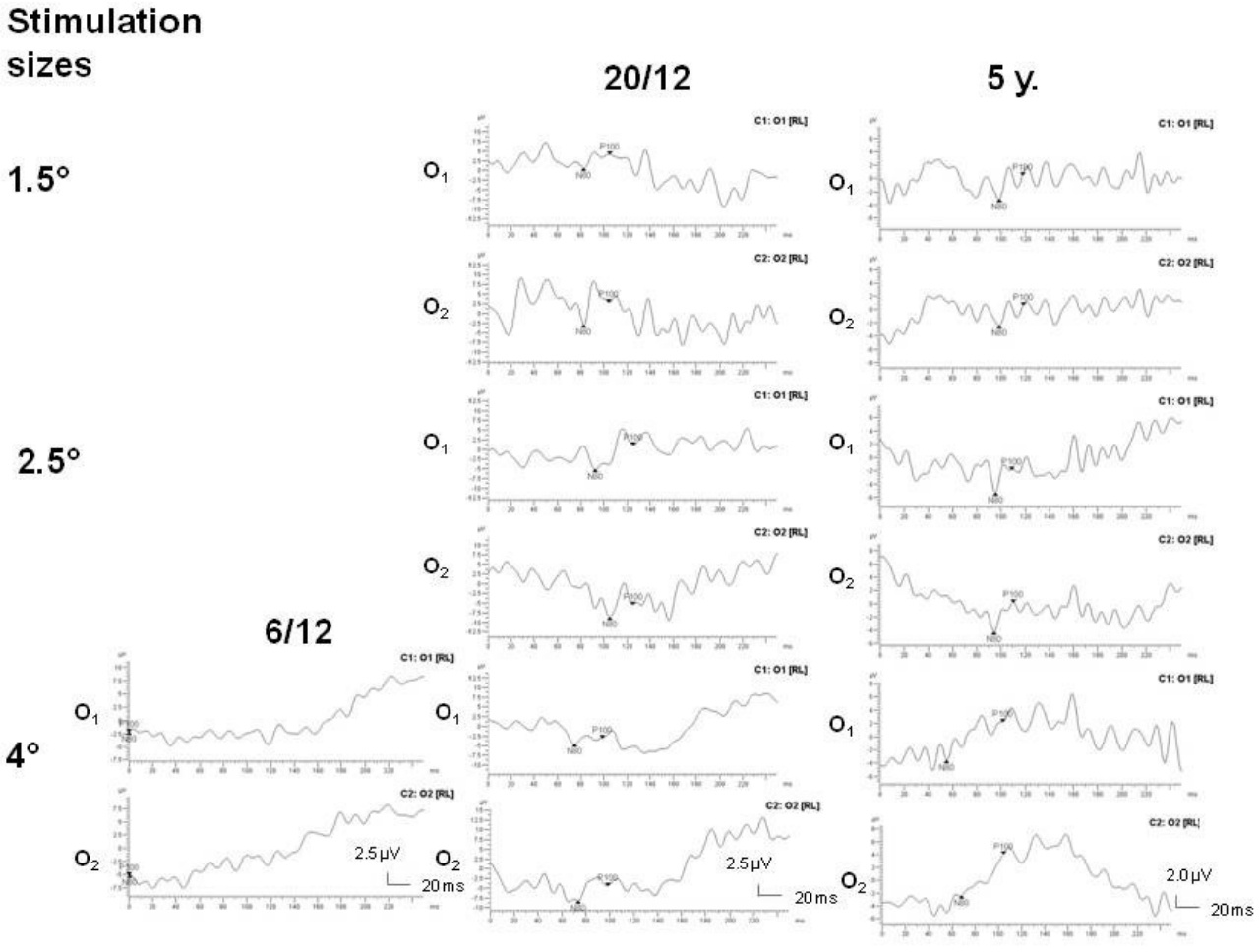

Figure 1. Pattern visual evoked potentials obtained binocularly after various magnitudes of stimulation at 6 months (no response), 20 months (low amplitudes of P100 waves) and 5 years (slightly higher P100 wave amplitude after the biggest stimulation, no improvement after smaller stimulations). Differences in scale among examinations are caused by default settings of EP-1000 and adjustment of examination results to the screen. Cursors indicate N80 and P100 waves

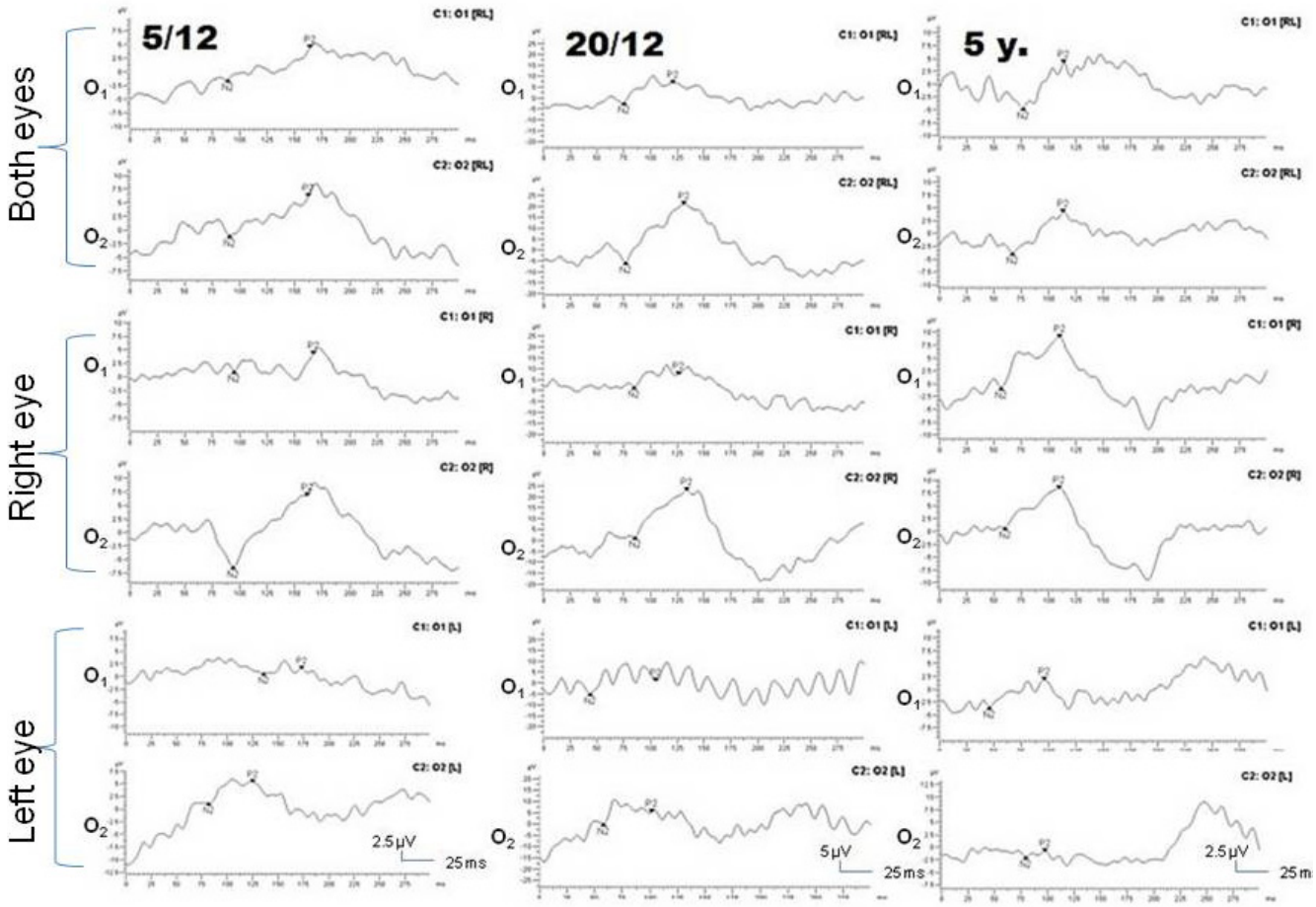

Figure 2. Flash visual evoked potentials obtained at 6 months, 20 months and 5 years. The general shape of VEP is stable. The latency of waves is shorter in consecutive examinations. The differences in amplitude should be regarded as inter measurements fluctuations, more expressed in a case of nystagmus. Differences in scale among examinations are caused by default settings of EP 1000 and adjustment of examination results to the screen. Cortical responses after right eye stimulation are higher than after left eye stimulation. Visual evoked potentials after left eye stimulation is very low or absent with a markedly abnormal shape. Generally responses from O_2 (right occipital region) have better shape and higher amplitudes of P2 wave. [RL] – binocular result, [R] – right eye result, [L] – left eye result. Cursors indicate N2 and P2 waves

continued then. The rehabilitation methods which were used integrated exercises into the child's daily play. Initially, these were simple commands, such as guiding eyes behind a moving light, outlining the contours of objects with light, illuminating an object on command, and recognizing simple pictures. The exercises also involved the child in locating scattered toys in the field of his vision. The improvement of basic visual functions was also carried out by playing with interactive toys for 20-30 minutes a day and participation in three camps containing in their schedule play in sensory rooms, equipped, among other equipment, with special illuminated tables with geometric figures. Rehabilitation classes were also organized in light experience rooms.

At 3 years of age MRI examination demonstrated optic nerve and optic chiasm hypoplasia, confirming the diagnosis of SOD. The patient was also diagnosed with diabetes insipidus. Treatment with desmopressin was implemented.

During an ophthalmology consultation at 4 years of age, it was observed that the horizontal, jerk nystagmus was less intense. Visual fixation with fixation nystagmus in the right eye occurred. The patient began to follow a moving object with his eyes and reach the object with his hands. He presented asymmetric nystagmus with associated head nodding called spasmus nutans-like nystagmus.

At 5 years of age, the flash and pattern VEP were performed for the third time. The FVEP response was stable, confirming a developmental brain disorder. In the PVEP, an improvement of response after stimulation of 4 degrees only was observed. It indicated the little development of vision, but visual acuity based on PVEP response was estimated below 0.1. Changes of VEP are presented in Figures 1 and 2. PVEP were examined with both eyes open, without patching eyes. In the FVEP response after left eye stimulation (L) is significantly lower than the other responses. Based on this the left eye is probably practically blind. A fundus image showed small optic discs in both eyes. The patient presented fine horizontal nystagmus and positioned his eyes downward and to the left. After less than 2 years, the eye alignment changed. The patient began to align the right eye downward and to the right.

According to neurological assessment, the boy is a child with psychomotor retardation (sitting – 2 years old, walking – 3 years old), severe intellectual disability, and manifestations of autism spectrum disorder. The boy does not speak. He has functional vision in the small visual field, but visual acuity assessment is not possible because of very limited cooperation. He requires multidisciplinary care, including vision therapy exercises and motor rehabilitation.

The cytogenetic examination revealed a normal male karyotype. Genetic tests did not detect specific mutations in *HESX1*, *OTX2*, *SOX3* genes, but mutations of undetermined pathogenicity in the *ACOT7* (homozygous deletion of exon 1) gene and in the *PTCH1* (heterozygous mutation c.4delG) gene were detected.

DISCUSSION

VEP are of great value due to their wide clinical application in both ophthalmology and paediatric neurology. The examination is used to locate abnormalities at each level of the visual pathway. Visual evoked potentials are used to assess the visual function of children with ONH and for the early diagnosis of this condition [5, 6]. Visual evoked potentials are an example of a safe, non-invasive test, suitable for infants or non-verbal and intellectually impaired patients. In such patients, reliable behavioural assessment of visual acuity is often not possible and consequently VEP is the only diagnostic tool enabling an objective assessment of vision [6, 7]. Visual evoked potentials may be particularly useful in the case of patients with septo-optic dysplasia, such as the described boy, in whom cooperation during ophthalmological examination is particularly difficult due to accompanying intellectual disability and autism spectrum disorders, including speech disturbances.

The flash VEP response of patients with optic nerve hypoplasia is characterized by decreased wave amplitude and increased latencies. Visual evoked potentials may be useful to predict the severity of ONH in children. In severe cases of ONH, it may be impossible to obtain VEP activity both in flash and pattern stimulation. The FVEP may be abnormal with attenuated changes in infants with less severe optic nerve hypoplasia and even with normal latency in some cases. Children with mild optic nerve hypoplasia may present normal results of both FVEP and PVEP, although mild reduction of visual acuity or subtle visual field defects may be observed. However, it should be mentioned that despite normal FVEP results in some patients with mild ONH, the pattern-reversal VEP test may reveal abnormalities [8, 9]. The described patient was diagnosed with nystagmus, which is often also one of the first visible features of septo-optic dysplasia. The VEP examination may be used in the screening of infants with congenital nystagmus. Combined ERG/VEP as a non-invasive test may allow one to determine whether retinal and postretinal pathway dysfunction is involved [9]. The presence of nystagmus makes it difficult to assess vision in young children with ONH during the VEP examination [10]. Nystagmus correlates with poor visual acuity [3]. Although the most reliable results are shown by monocular stimulation, studies have shown that in patients with nystagmus, there is a significant improvement in the quality of VEP recording when it is replaced with binocular stimulation [6].

Nevertheless, in patients with ONH and nystagmus the onset/offset pattern VEP may be particularly effective. In this examination the checkboard pattern is suddenly changed into a diffuse grey background. The benefits of using this technique in patients with nystagmus result from lower sensitivity of pattern onset/offset stimulation to confounding factors such as poor fixation and eye movements [11]. Establishing clinical prediction of visual potential in young children with ONH can be challenging. Patients with similar visual function in the initial examination may develop varied range of visual acuity. Children with initial poor visual function may present features of functional vision at the age of 5 [12]. However, FVEP can be a useful prediction tool enabling estimation of the further visual outcome. It has been proved that a large FVEP amplitude (> 6 μV) at the initial examination (before the age of 36 months) was associated with good visual acuity at 5 years of age. The final visual outcome ranged from acuity of 6/60 or better to steady fixation and good pursuit of a small target in patients with learning disability. Conversely, small FVEP amplitude (< 6 μV) and non-recordable FVEP examination were correlated with a poorer final result with variable visual outcome from acuity of 6/24 to non-perception of light. The negative predictive value of FVEP amplitude was 59%. Another proposed prognostic indicator for vision outcome at 5 years of age was VEP threshold category, with positive prognostic value of 93%, stated as achievement of any recordable pattern VEP for VA better than 6/240. However, it should be mentioned that young children, especially with nystagmus and visual impairment, may have difficulties with attention to pattern stimulation, so FVEP may be the only useful option [12]. Recent studies suggest occurrence of a relationship between reduced VEP response and visual acuity with smaller optic disc diameter. However, it is highlighted that there is a group of patients with visual acuity and VEP amplitude in the normal range despite presenting a small optic disc [10, 12].

However, with the example of the patient described, we can emphasize the role of regular VEP testing as a tool for evaluating the development of vision in paediatric patients. Based on the physical and the funduscopic examination it was predicted that the patient would remain blind. However, a VEP test was performed and a response from the occipital cortex to light stimulation in FVEP was obtained, which led us to assume that the patient has a chance of developing functional vision and supported implementation of visual revalidation. Repeating the VEP in the 20th month made it possible to obtain a response in the PVEP test, which indicated the progressive development of the patient's vision, and allowed for continuation of the visual rehabilitation. Moreover, in the repeated VEP test at 5 years of age, the persistence of a constant response in the FVEP test confirmed the inborn nature of the disorder, excluding

the diagnosis of a degenerative process. Obtaining an improvement in the response in the PVEP test also indicated a progressive improvement in visual acuity. Careful monitoring of vision development may result in the implementation of visual therapy and revalidation appropriate to the degree of visual functioning of the child, which may be particularly important for children with neurodevelopmental disorders.

It should be emphasized that the results of electrophysiological tests must be interpreted in the context of the suspected clinical problem [13]. Deviations from the correct VEP record are not specific to particular disease entities [11]. Additionally, in children, differences resulting from the development of the visual pathway and vision should be considered. Further development of the VEP testing method is also necessary to improve the course of the test, that is, to minimize the test duration and connect with artificial intelligence technology.

From the age of 6 months, the patient was under the constant supervision of a vision therapy specialist and performed various visual exercises to stimulate the brain intensively. Vervloed *et al.* report that visual rehabilitation seems to be effective if ecologically valid social skills (behaviours that are naturally exhibited by socially accepted children, adolescents or adults) are exercised, taking the individual needs of the child into account. On the other hand, there is not enough empirical evidence to support this hypothesis unequivocally [14]. We can therefore assume that thanks to the use of extended diagnostics and the implementation of appropriate visual rehabilitation, the patient is now a partially sighted child, instead of a blind child.

Optic nerve hypoplasia (ONH) may present as an isolated defect or may be accompanied by other neurological disorders [1]. Agenesis of the corpus callosum is often found in patients with ONH [15]. Moreover, ONH is detected in 25% of patients with agenesis of the septum pellucidum [3]. Optic nerve hypoplasia, midline brain defects, i.e. agenesis of the septum pellucidum and/or corpus callosum, and dysfunction of the pituitary gland constitute the characteristic triad of symptoms of septo-optic dysplasia (SOD) [3]. Therefore, it suggests the necessity of careful ophthalmological evaluation of patients with the above characteristic CNS abnormalities in imaging tests. In addition, it also makes it necessary to perform MRI on patients diagnosed with ONH, in order to extend the diagnosis to congenital defects of the CNS and endocrine disorders, which together with ONH constitute the characteristic symptoms of SOD.

About 30% of patients with SOD and/or ONH have autism spectrum disorders (ASD) [16], which was also revealed in the described patient. Due to the increased risk of ASD diagnosis in such patients, it is necessary to provide them with psychological care. Apart from the bilateral hypoplasia of the optic nerves, the boy also had disorders of the cerebral cortex organization in the form of pachygyria/polymicrogyria, which suggests the diagnosis of septo-optic dysplasia plus (the term proposed by Miller *et al.* [17] to distinguish patients with SOD in whom, apart from the classic triad of symptoms, there are also malformations of the cerebral cortex). These cerebral cortex malformations may be associated with the presence of significant developmental delay and/or movement disorders [18, 19], which was also reported in the described patient. The current scientific reports suggest a higher risk of developmental delay in patients with neurological disorders and accompanying hypoplasia of the optic nerves [1, 20].

The genetic basis of SOD remains identified in less than 1% of patients [21]. Mutations of the *HESX1*, *SOX2*, *SOX3* genes described in the literature as characteristic of SOD were excluded in the described patient [22]. However, a homozygous deletion of the *ACOT7* gene was detected. A deletion of the *ACOT7* gene has been previously described in a patient with intellectual disability, epilepsy and abnormal behaviour [23]. Moreover, in the described patient a mutation of the *PTCH1* gene was also found. The same heterozygous gene mutation has been detected in a patient with microphthalmos, cataracts and sclerocornea [24]. Further studies are required to determine the pathogenicity of these mutations and their link to septo-optic dysplasia.

In conclusion, this case study aims to draw attention to the value of VEP as a tool that can be used for regular evaluation of vision development in patients with ONH, which may lead to implementation of visual therapy appropriate to the degree of visual functioning of the child. This may lead to improvement of vision, which is especially important in supporting the development of children with neurological disorders and developmental delay.

DISCLOSURE

The authors declare no conflict of interest.

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