

**Ophthalmological examination and VEPs in preterm children
with perinatal CNS involvement**

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KEY WORDS

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ABSTRACT

Five children with a history of preterm birth (mean gestational age of 27 weeks; birth weight 870 - 1,380 grams) and perinatal post-hemorrhagic hydrocephalus were examined ophthalmologically at ages ranging from 4 - 11 years. An extended visual evoked potentials (VEPs) examination was simultaneously performed, using pattern-reversal, motion-onset and cognitive visual stimuli. Although three of the ten eyes displayed about normal visual acuity (≥ 0.9), all of the examined eyes were abnormal for at least one variant of the tested VEPs. Pathological changes in VEPs (missing responses, shape abnormalities due to delayed VEPs maturation, prolonged peak latencies and reduced amplitudes) were roughly proportional to both gestational age and reduction in visual acuity. A more severe pathology was found in the motion-onset VEPs (in all 5 subjects - 9 eyes) when compared to the pattern-reversal VEPs (in 4 subjects - 8 eyes). These observations suggest that the magnocellular system/dorsal stream of the visual pathway (which is particularly activated in response to motion stimuli) may be more frequently affected in preterm children than the parvocellular system/ventral stream (tested mostly by the standard pattern-reversal VEPs). This pilot study may encourage further testing of the combined pattern and motion-related VEPs examinations in preterm children as a way of detecting hidden cortical/cerebral visual impairment (CVI).

ABBREVIATIONS

CNS - central nervous system; CVI - cortical/cerebral visual impairment;

VEPs - visual evoked potentials

INTRODUCTION

Due to advances in perinatal intensive care, there has been a distinct decrease in the mortality of newborns with low birth weight and neurological morbidity [1]. While the number of live newborns in the lowest weight categories has only slightly increased, the number of these newborns that survive the neonatal period has significantly increased. In the Czech Republic, the number of newborns with a birth weight below 1,000 grams that survived the neonatal period more than doubled between 1993 and 2002 [2].

However, due to the distinct immaturity of such newborns, there is a higher probability of perinatal organ impairment with possible long-lasting or irreversible functional consequences in infants with birth-weights below 1,000 g. The development of alterations in visual functions is dependent not only on retinal dysfunction due to retinopathy, but also on impairments of the central nervous system (CNS). The immature visual pathway is very sensitive to various perinatal insults. Asphyxia, CNS hypoperfusion, and CNS infarctions can all cause “White matter injury of prematurity”, previously known as periventricular leukomalacia, which is quite common in preterm infants [1, 3]. The parieto-occipital cortex is one of the areas most sensitive to hypoxia, and impairment of this area may be associated with visual defects of varying severity. These defects may manifest as decreased visual acuity, visual field defects, nystagmus, strabismus, optic nerve hypoplasia, severe cupping of the optic disc, and visual cognitive deficits [4]. Ophthalmological disorders may be combined with mental retardation or central paresis [5]. CNS immaturity is quite frequently complicated by periventricular and/or intraventricular hemorrhage, and strabismus develops in 50% of these patients [6]. Intraventricular hemorrhage can cause post-hemorrhagic hydrocephalus and appears in 30 - 40% of newborns with a gestational age of 32 weeks or less [3]. The extent of

hemorrhage influences the severity of neurological disorders and visual dysfunction in children [7, 8, 9]. The term “cortical or cerebral visual impairment” (CVI) has been previously used to describe the etiological factors of such visual impairment [10]. CVI became the leading cause of bilateral visual impairment in children in western countries [11,12]. Children with CVI comprise 36% of all visually-impaired children in the population, and visual deficits in these children can be present even when other ophthalmological findings are normal [6].

Although preterm children (mainly those displaying some perinatal CNS complications) are frequently the subjects of long-lasting ophthalmologic monitoring, it has not been precisely specified which examinations should be included during these studies. In this pilot study, we explored the possibility of an objective verification of visual pathway impairment in preterm children (ages 4 - 11 years) with the use of visual evoked potentials (VEPs). We extended the examination, and in addition to the standard pattern-reversal stimuli, motion-onset and visual cognitive stimuli were also used. The results of this set of VEPs were compared with routine ophthalmological examinations to assess the sensitivity of the VEPs for detecting potential CVI cases.

Motion-onset VEPs were included to provide a more specific examination of possible magnocellular pathway/dorsal stream dysfunctions, which may selectively appear in some brain pathologies (For an overview, see [13, 14]).

SUBJECTS AND METHODS

Five children with an average gestational age of 27 weeks (26 - 29 weeks) and average birth weight of 1,106 grams (870 - 1,380 grams) were examined at the Dept. of Ophthalmology, University Hospital in Hradec Králové, at the ages of 4 - 11 years. All these children had suffered post-hemorrhagic hydrocephalus with subsequent

neurosurgery. This group represents only a fraction of the registered cases, since only a few children's parents were willing to participate in all parts of the study and signed a written consent form, in accordance with the Declaration of Helsinki, 2004.

An age-matched group of 20 healthy children (ages of 4 - 11 years; with a median of 7 years) born at term, with normal perinatal development and normal visual functions provided the control data. (For detailed information about the age related changes of the used VEPs see [15].)

The ophthalmological examination included:

- *Visual acuity* was evaluated under cycloplegia with the best possible dioptric correction at a distance of 5 meters with the use of Snellen, Pflüger, or picture optotypes. The method used was dependent on the subject's age and on the cooperation of the particular child.
- *Refraction* was examined with the use of Nidek AR – 800 and Powerref (EriLens) autorefractors.
- *Strabismus and binocular vision* were examined with an Oculus 58 100 synoptophore. We examined subjective and objective deviations and fusion. Spatial binocular vision was examined using the Bagolini test.

Visual evoked potentials (VEPs) were recorded within two weeks of the ophthalmological examinations. The following variants of VEPs were used for objective testing of visual functions in CVI:

1. **Pattern-reversal VEPs** (2 Hz reversal rate) of high contrast (96% according to Michelson's formula), consisting of a checkerboard with three pattern element sizes (in the range of 160' – 20,' according to the visual acuity of subjects), were used to test the function of the parvocellular system/ventral stream.

2. Motion-onset VEPs were examined to verify magnocellular system/dorsal stream activity. Two variants of moving visual stimuli were used:

a) Unidirectional linear motion, which consisted of “translation” (velocity = 10 deg/s) of isolated checks with randomized directions of motion. Motion was randomized to reduce adaptation of direction-specific cortical neurons. Check size was 40', and check-to-check distance on both the vertical and horizontal axes was 120'.

b) Radial motion, which consisted of randomly changing expanding/contracting (centrifugal/centripetal) motion of a concentric pattern (rings). Rings showed decreasing spatial frequency (1 – 0.2 c/deg) in the periphery of the visual field to account for cortical magnification, and increasing motion velocity (5 – 25 deg/s) in the periphery to account for different motion sensitivities in the center versus the periphery of the visual field [16, 17]. Thus, a temporal frequency of 5 c/s was kept constant over the entire stimulus field.

In both variants of the motion-onset VEPs, a low contrast (10%) pattern was used for more selective activation of the magnocellular pathway [18]. The circular pattern (rings) for the radial motion had sinusoid modulation of luminance to eliminate high spatial frequencies. The same timing for both moving stimuli was used to avoid adaptation to motion, and this consisted of a 200 ms moving phase with 1 s inter-stimulus interval during which a stationary pattern was presented [19, 20].

3. Cognitive VEPs, which monitored *wave P300* during an oddball paradigm with recognition of the letter X (frequent) and digits (rare, target stimuli). This part of the study was included to assess whether upper cognitive visual processes can be evaluated in this way in premature children at this age.

All stimuli were generated using our own software on a 21" Iiyama monitor (stimulus field $37^\circ \times 28^\circ$) with a 105 Hz frame frequency and a mean luminance of 17 cd/m^2 [21]. Forty single sweeps (440 ms epochs 20,000 times amplified in the frequency band of 0.1 – 45 Hz with sampling frequency of 500 Hz) were averaged, and each condition was repeated at least twice to verify the reliability of the recorded potentials.

Recordings

We recorded monocular VEPs from six unipolar derivations using the right ear lobe as a reference. Four derivations were from the midline (O_z , P_z , C_z , and F_z), and two were from lateral leads (O_L and O_R , 5 cm to the left and right of the O_z position, respectively). For a review of our extended VEP examination, see [13]. Parameters of the pattern-reversal VEPs (latencies and inter-peak amplitudes of the P100 peak) were always evaluated in the O_z derivation. In contrast, parameters of motion-onset VEPs (latencies and inter-peak amplitudes of the P-N-P potential complex occurring around the dominant N2 motion-onset specific peak) were read from one of the lateral derivations, providing larger amplitude. This procedure was chosen because the N2 motion-onset specific peak is mostly lateralized towards the temporo-occipital cortex, irrespective of the dominant hemisphere [22]. Attempts to evaluate cognitive VEPs (P300 parameters) were focused on the C_z , P_z , and F_z derivations.

RESULTS

An overview of results of the ophthalmological examinations, together with a summary of neuro-psychiatric complications and current MRI examination is provided in Table I.

Insert Table I about here

An approximately normal visual acuity of 1.0-0.9 was found in only three out of the ten eyes examined. In one child who provided limited cooperation (Subject 3), acuity could not be measured. All of the children were hypermetropic. Strabismus was recognized in three children; two were esotropic and one exotropic. One child had a history of mild retinopathy of prematurity and all were judged to have optic atrophy. One had excavation of the optic nerve head, as has been previously reported in children with white matter injury of prematurity [23]. All five children had cerebral palsy, hemiparesis or quadriparesis. The side of the hemiparesis did not correlate with the dominant monocular VEP changes.

Results of VEPs examination

All five preterm children displayed significant VEP abnormalities, which may be consistent with the pathology of the visual pathway functions (see Tab. II).

Insert Table II about here

Pattern-reversal VEPs were influenced less when compared to the motion-onset VEPs. These VEPs displayed prolonged latencies and/or reduced amplitudes, but they were detectable in all of the eyes examined. The pattern-reversal VEPs latencies were good for three eyes that had roughly normal visual acuity (see Fig. 1), however they were significantly delayed in four eyes where the visual acuity was reduced to 0.5. The child with visual acuity of 0.3 in one eye (Subject 4) exhibited the worst VEPs results.

Insert Fig. 1 about here

Motion-onset VEPs were not detectable in two subjects (Subject 2, with missing response to radial motion, and Subject 5, with no reaction to translation motion). Both cases represent the worst VEPs results. In the remaining children, at least one variant of the motion-onset VEPs was significantly delayed (see Tab. II and Fig. 1). Although the visual acuity of one child (Subject 3) could not be examined due to poor cooperation, this child displayed normal responses to radial motion stimuli. This finding supports the view that neuropsychiatric development of preterm children does not necessarily correlate with certain visual functions [3].

There were differences between the results of the two variants (translational or radial motion) of the motion-onset VEP, which suggests that the origins of these VEP variants are probably at least partially distinct. This result supports the hypothesis that separate cortical regions are dedicated to the processing of more complex forms of motion [24, 25], and these regions may be selectively involved in different subjects. Subject 3 in Tab II exhibited pathological changes in the pattern-reversal VEPs and motion-onset VEPs to translational motion, but they also had completely normal parameters for the motion-onset VEPs to radial motion. This result may be interpreted as a sign of persisting normal function of one part of the motion-processing system, accompanied by severe impairment of other parts of the system. In Subject 5, the opposite changes in VEPs were observed.

Visual cognitive VEPs were not recordable in the youngest children (ages 4 - 5 years) due to poor cooperation. In two older subjects (No. 1 and 5), the interpretation of cognitive VEPs was difficult because single target reactions showed higher variability in these subjects than in normal children of this age. According to our recent study (in preparation

for publication), 10 year old children display approximately adult-like P300 waves with latencies of about 350 ms.

DISCUSSION

The influence of brain perinatal lesions in preterm children on visual functions has been analyzed by many authors. Although a reduction of visual acuity dominates those reports, some residual vision is preserved in the majority of cases [26, 27]. In our group of five children with preterm birth and perinatal brain lesions, about normal visual acuity was seen only in one child who also displayed the best VEPs results. The observed hypermetropia and strabismus in our preterm children is in agreement with earlier reports [e.g. 28, 29, 30].

Atrophy of the optic papilla and a correlated prolongation in VEP latencies have been formerly explained as a consequence of optic nerve compression or stretching around dilated ventricles due to hydrocephalus, but more recently, these problems have been attributed to neural trauma or diffuse brain edema [31]. According to the literature, the observed papilla excavation (cupping) is mainly related to trans-synaptic degeneration that appears in the 29 – 34th week of gestation in subjects with periventricular leukomalacia [32].

All of the children in our group had severe movement disorders. The simultaneous appearance of visual and motor impairments due to brain perinatal lesions has been previously reported by many authors. For example, Huo et al. [33] described such defects in 75% of children with CVI.

The pathological changes of VEPs found in all of our preterm children show that latent (subclinical) impairment of the visual pathway may be present even in those subjects where there was no significant impairment of visual functions, as assessed by

standard ophthalmologic examinations. Similar observations in CVI were recently reported by Lowery et al. [34]. Although VEPs findings in children with CVI are quite variable [31, 35], and changes in parameters over a longitudinal period may not precisely represent development of visual functions in children with CVI [36], VEPs represent a method for the objective quantitative definition of vision in CVI [37].

In contrast to the studies cited above which used either flash or pattern VEPs in CVI, we tested the combination of pattern- and motion-related VEPs. As previously mentioned, the pattern-reversal VEPs test the parvocellular system/ventral/WHAT stream and the motion-onset VEPs test the magnocellular system/dorsal/WHERE stream in a relatively selective manner [13,14]. The two main parallel visual subsystems may be independently involved in various pathological processes in the CNS including CVI [13,38] although some overlapping activity in both systems is known to be evoked by pattern-reversal or motion-onset stimulation. Our subjects with CVI had post hemorrhagic hydrocephalus that is associated with injury to the periventricular white matter and hypoxic-ischemic injury [e.g. 39, 27]. Behavioral studies have concluded that dorsal stream involvement is a characteristic consequence of such brain injury [40]. Our objective VEP results are in accord with the dorsal stream hypothesis.

Despite the low number of subjects with CVI examined in this pilot study, comparison with the larger control group shows that the N2 peak latency of the motion-onset VEPs seems to be the most sensitive VEP parameter for the diagnosis of CVI. However, motion-onset VEPs can be indistinct, even in some children without CVI due to immaturity of the magnocellular system [15]. Motion-onset VEPs to radial motion may not be distinct in early childhood, and this might represent a problem at the level of more complex visual motion information processing in the parietal associate visual cortex [21].

Possible compensatory processes in altered CNS development could influence VEP topography. Topographical abnormalities were not, however, apparent in our VEP data.

The observed discrepancy between subjective vision and VEP parameters in some subjects with CVI (Subject 1 in Tables I and II) is quite common, and Lim et al. have reported similar findings [36]. For example, discrepancies of this sort are seen in adult patients with demyelination processes [38,41]. These discrepancies may be dependent on the spectrum of the involved channels (fibers) within the visual pathway.

The failure of our attempt to assess higher cognitive visual functions in the tested children with CVI was not surprising, since existing studies examining P300 in five year old children have described similar problems with variability. The main reason for this variability is probably a lack of cooperation [42]. Therefore, other methods to obtain objective information regarding cognitive processes in this age group with CVI should be tested further.

CONCLUSIONS

Our results provide new knowledge about visual dysfunction in former preterm children with a history of post-hemorrhagic hydrocephalus. Both symptomatic and asymptomatic children display abnormal VEPs. Despite the small number of subjects examined in this pilot study, it seems that the combined examination of pattern-reversal and motion-onset VEPs improves definition of the visual deficits in these children.

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Tab. I: Subjects characteristics

Subject	Eye	Visual acuity	Refraction	ROP	Optic atrophy	Strabismus	Brain hem. (age)	Neurosurg. (age)	Mult. shunts	Plegia	P-Mretard.	Seizures	Antiepilept.
1. 11 years 29 weeks 1,380 grams MRI: Periventric. atrophy, enlarged IVth ventricle	RE LE	1.0 0.9	+ 0.75 + 3.25	No No	Yes Yes	esotropic	subdural (10 days)	VP-drain (1 month)	Yes	Hemipar. left-sided	No	No	No
2. 5 years 27 weeks 1,150 grams MRI: status post Periventricular Leukomalacia VL, Porencephalic cyst., white matter atrophy in Corpus callosum	RE LE	0.5 0.5	+ 0.50 + 0.25	1 st deg. 1 st deg.	Yes Yes	--	IIIrd ventricle (3 days)	VP-drain (15 month)	Yes	Hemipar. right-sided	No	No	No
3. 5 years 27 weeks 1,100 grams MRI: pseudocystic structure in occipital and parieto-occipital areas of the left hemisphere without brain parenchyma	RE LE	? ?	+ 1.00 + 1.25	No No	Yes Yes	--	IVth ventricle (10 days)	VP-drain (2 months)	No	Hemipar. right-sided	Yes	Yes	Topiramate Valproate
4. 10 years 26 weeks 1,030 grams MRI: Diffuse brain atrophy	RE LE	0.5 1.0	+ 0.50 + 1.00	No No	Yes Yes	exotropic	IIIrd - IVth v. (4 months)	ventriculostomy (4 months)	No	Quadripar.	Yes	Yes	Phenobarbital
5. 4 years 26 weeks 870 grams MRI: status post Periventricular Leukomalacia; status post Purulent Meningitis	RE LE	0.3 0.5	+ 2.75 + 2.00	No No	Yes Yes	esotropic	IVth ventricle (2 days)	VP-drain, fenestr. (3 years)	Yes	Hemipar. left-sided	Yes	Yes	Valproate

Abbreviations: **Antiepilept.** - antiepileptic medication; **Brain hem.** - brain hemorrhage; **fenestr.** - fenestration; **Hemipar** - hemiparesis; **MRI** - MRI examination; **P-M retard.** - psychomotor retardation; **Quadripar** - quadripareisis; **ROP** - retinopathy of prematurity; **VP-drain** - ventriculoperitoneal drain (shunt);

Tab. II: Results of VEPs examination

Subject	Eye	Visual acuity	Pattern-reversal A [μ V]	Pattern-reversal L [ms]	Translat. motion A [μ V]	Translat. motion L [ms]	Radial motion A [μ V]	Radial motion L [ms]
1.	RE	1.0	8.9	106	4.1	250	3.3	288
11 years	LE	0.9	9.0	106	5.2	274	2.1	300
29 weeks		<i>(Norm: 18.0\pm5.9</i>		<i>109\pm5</i>	<i>7.0\pm2.4</i>	<i>185\pm33</i>	<i>10.0\pm3.5</i>	<i>189\pm28)</i>
2.	RE	0.5	5.1	158	4.9	270	0	--
5 years	LE	0.5	6.0	142	3.4	290	0	--
27 weeks		<i>(Norm: 21.0\pm6.0</i>		<i>116\pm4</i>	<i>9.8\pm1.9</i>	<i>209\pm21</i>	<i>11.0\pm5.4</i>	<i>231\pm31)</i>
3.	RE	?	4.4	168	4.1	262	12.1	252
5 years	LE	?	3.8	158	2.4	270	15.1	250
27 weeks		<i>(Norm: 21.0\pm6.0</i>		<i>116\pm4</i>	<i>9.8\pm1.9</i>	<i>209\pm21</i>	<i>11.0\pm5.4</i>	<i>231\pm31)</i>
4.	RE	0.5	5.1	162	4.4	186	7.3	316
10 years	LE	1.0	3.5	128	3.2	216	6.3	256
26 weeks		<i>(Norm: 18.0\pm5.9</i>		<i>109\pm5</i>	<i>7.0\pm2.4</i>	<i>185\pm33</i>	<i>10.0\pm3.5</i>	<i>189\pm28)</i>
5.	RE	0.3	6.1	164	0	--	9.9	332
4 years	LE	0.5	8.1	154	0	--	8.5	346
26 weeks		<i>(Norm: 23.0\pm6.2</i>		<i>111\pm3</i>	<i>10.0\pm2.0</i>	<i>220\pm22</i>	<i>11.4\pm5.6</i>	<i>244\pm32)</i>

Legend: **A** - inter-peak amplitude; **L** - P100 latency of pattern-reversal VEPs or N2 peak latency of motion-onset VEPs
The bold values represent pathological changes of VEP (out of $M \pm 2.5$ SD of the specified age related norm).

Figure legend:**Fig. 1:**

Example of pathological pattern-reversal and motion-onset VEPs in an 11-year-old preterm child (birth weight of 1,200 g); subject No. 1 in Table I and Table II.

Reduced and split pattern-reversal VEPs, as well as delayed motion-onset VEPs (bold underlined latency values), are consistent with the observed atrophy of the optic nerves. These results suggest that the magnocellular system impairment is possibly predominant.

