DOI 10.26724/2079-8334-2023-1-83-156-160
UDC 617.751.6-053.5

S.Z. Salmanova
National Center of Ophthalmology, Baku, Azerbaijan

TRANSFORMATIONS OF SENSOMNESTIC DISTURBANCES OF THE VISUAL ANALYZER IN CHILDREN WITH PERINATAL ENCEPHALOPATHY

e-mail: mic_amu@mail.ru

The leading causes of blindness and visual impairment in children is cerebral visual impairment. Perinatal encephalopathy lesions are the main risk factors of this pathology. The purpose of the study was to determine cause-effect relationships of ophthalmic and neurological indices in infants with perinatal encephalopathy. This work is based on the results of a comprehensive dynamic examination of 300 children with perinatal encephalopathy. A complex ophthalmic examination included: assessment of behavioral visual responses, retinoscopy, determination of the angle of deviation, direct ophthalmoscopy, visual evoked potentials and electroretinography. The observation period was 3 years (the first examination-in children aged up to 3 months, and then repeated at 6–12 months. The results showed that in children with perinatal encephalopathy at the age under 3 months, deviations of sensomnestic rates are observed in 35 % of cases. Electrophysiological differential criteria of delayed visual maturation syndrome and visual deficiency syndrome have also been identified, characterized by delayed visual maturation syndrome – lack or instability of clear differentiation of component N2; registration LN2≥155ms; AN2≤AP2 – at 3 months (or later); visual deficiency syndrome – lack or instability of a clear differentiation of component N1; registration LP2≥135ms; AN2≤AP2 – at 6 months (or later). The deficiency of short-latent visual afference is one of the mechanisms of the increasing trend where the threshold for convulsive brain activity in children with perinatal encephalopathy is reduced.

Key words: perinatal encephalopathy, delayed visual maturation syndrome, visual deficiency syndrome, cerebral visual impairment.

С.З. Салманова

ТРАНСФОРМАЦІЇ СЕНСОМНЕСТИЧНИХ ПОРУШЕНЬ ЗОРОВОГО АНАЛІЗАТОРА У ДІТЕЙ З ПЕРИНАТАЛЬНОЮ ЕНЦЕФАЛОПАТІЄЮ

Провідними причинами сліпоти та порушень зору в дітей є церебральні порушення зору. Перинатальна енцефалопатія є головним чинником ризику цієї патології. Метою дослідження було визначити причинно-наслідкові зв'язки офтальмологічних та неврологічних показників у дітей раннього віку з перинатальною енцефалопатією. Робота ґрунтується на результатах комплексного динамічного обстеження 300 дітей з перинатальною енцефалопатією. Комплексне офтальмологічне обстеження включало оцінку зорових реакцій, ретиноскопію, визначення кута відхилення, пряму офтальмоскопію, викликані потенціали та електроретинографію. Термін спостереження склав 3 роки (перше обстеження – у дітей віком до 3 місяців, потім повторне у 6–12 місяців. Результати показали, що у дітей з перинатальною енцефалопатією віком до 3 місяців спостерігаються відхилення сенсомнестичних показників у 35 % випадків. Виявлено також електрофізіологічні диференціальні критерії синдрому затримки зорового дозрівання та синдрому зорової недостатності, що характеризуються: синдром затримки зорового дозрівання – відсутністю або нестабільністю чіткого диференціювання компонента N2, реєстрацією LN2≥155мс, AN2≤AP2 – у 3 міс. (або пізніше); синдром зорової недостатності – відсутністю чи нестабільністю чіткого диференціювання компонента N1; реєстрацією LP2≥135мс; AN2≤AP2 – у 6 міс (або пізніше). Дефіцит коротколатентної зорової аферентації є одним із механізмів наростаючої тенденції зниження порога судомної активності головного мозку у дітей із перинатальною енцефалопатією.

Ключові слова: перинатальна енцефалопатія, синдром затримки зорового дозрівання, синдром дефіциту зору, церебральні порушення зору.

The leading causes of blindness and visual impairment in children in economically developed countries are diseases of the optic tract of various localizations, among which cerebral (or cortical) visual impairment (CVI) accounts for 29.5–36 % of cases [11].

The etiology of CVI in children differs between age groups. Hypoxic-ischemic or hemorrhagic central nervous system (CNS) lesions are the leading causes (57 % of the total number of patients) [12].

The visual system of young children is quite vulnerable to injury, and yet it also responds well to a variety of treatments [5, 13]. Consequently, functional outcomes of rehabilitating infants with CVI depend on quick diagnosis and adequate treatment.

The diagnosis of CVI at an early age is highly complex. According to our research and the broader literature [2, 3, 7], differentiating CVI from other isolated eye conditions, such as congenital-hereditary diseases, cortical blindness, delayed visual maturation as well as associated lesions of the anterior and posterior optic tracts, requires examination of the trans-parent media and the fundus, as well as the identification of characteristic findings in the electroretinogram (ERG) and visual evoked potentials (VEP) [1, 4, 9].

Although clinical manifestations and effective ways to diagnose ophthalmic disorders have been thoroughly described in the literature, there are no reports on the nature of the relationship between

ophthalmic and neurological indices in infants (aged two weeks – 3 years) with lesions of the postgeniculate optic tracts caused by perinatal encephalopathy (PE).

It is, therefore essential to develop an algorithm to investigate the visual system in this group of infants and determine the relevance and theoretical and practical importance of this work.

The purpose of the study was to determine the nature and dynamics of ophthalmic disorders and cause-effect relationships of ophthalmic and neurological indices (or syndromes) in infants with perinatal encephalopathy.

Materials and methods. This work is based on the results of a comprehensive dynamic examination of 300 children with PE at the National Center of Ophthalmology, named after acad. Zarifa Aliyeva referred by neurologists from various children's hospitals in Baku. Perinatal encephalopathy was diagnosed in 150 children aged 2 weeks to 3 months with perinatal cerebral hemorrhage (PCH), another 50 were diagnosed with perinatal toxic and hypoxic encephalopathy (PTHE) born to mothers with toxemia of the last two months of pregnancy, and 100 with perinatal encephalopathy of unspecified genesis (PEUG).

A complex ophthalmic examination included: assessment of behavioral visual responses, retinoscopy, determination of the angle of deviation, direct ophthalmoscopy, as well as electrophysiological studies of the visual system (visual evoked potentials – VEP, and electroretinography – ERG). Both sensomnestic and optokinetic parameters were included in the examination and investigation of ophthalmic problems.

The first examination was conducted in children aged up to 3 months and then repeated at 6–12 months. The observation period was three years.

The adequacy of fixation and visual attention was assessed (at the age of 1–2 months, a child is already capable of fixing to a moving object with both eyes for a prolonged period). Starting from 5 months, visual acuity was assessed based on the preferred eye test as developed by Fantz (1958) and Dobson et al. (1978) in the modification of Good-Lite company (Lea-gratings test). At 18 months, visual acuity was determined using the Single Symbol Book table that does not require a verbal response from the child.

Registration of VEP was carried out on a specialized complex “Neuro-MVP”, produced by “Neuro-Soft”. When registering VEP to a flash of light, a bipolar abduction of O2–Fz, and O1–Fz with active electrodes 2cm to the right and left of the midline was used. Latency and amplitude of P1, N1, P2, N2, P3, and N3 components were measured.

The reaction of “assimilation” of the rhythm of photostimulus (PhS) was in the appearance of rhythmic activity in the occipital regions of the brain that was a characteristic feature of a positive response to photostimulation by registering on the frequency of 2–4–6 Hz.

State of vegetative-vascular reflexes were determined with the use of total estimation of the duration of the white period of local and latent period of reflex dermographism as well as by the severity of the Aschner's phenomenon.

Statistical analysis of the data included: variation analysis, non-parametric criterion – U-criterion of Wilcoxon test (Mann-Whitney U test), discriminant analysis – Pearson fit test – $\chi 2$, correlation analysis – Spearman's rank method.

Results of the study and their discussion. The results revealed three variants for the clinical course of PE which are based on the adequacy of visual attention and a component of visual evoked potentials. The first variant of the progress is characterized by the absence of adequacy of visual attention and the recording of VEP P2 component; the second is characterized by unstable fixation of visual attention and the recording of VEP P2 and N2 components; the third is characterized by stable adequacy of fixation and visual attention and the recording of VEP N1, P2, and N2 components.

There are several findings from the analysis of the sensomnestic indices of children with PE aged up to 3 months. In the 150 children with PCH, all three variants of the clinical course of the disease were observed: PCH1 (70 children), PCH2 (50 children) and PCH3 (30 children). At the same time, the defining value in the treatment plan, dynamics monitoring, and forecasting had the first two of them. According to the study of flash VEP, the component P2 was differentiated and the rhythm assimilation reaction of photostimulus (RAPhS) was absent in the first variant of the course of the disease. In the second variant, both P2 and N2 components were recorded, and the stimuli of frequency of 2Hz were “assimilated” on PhS. In the third variant, the early components N1, P2, and N2 were all present. PhS of 2Hz and 4Hz was clearly “assimilated”. Background features of EEG in the first two variants of the course of the disease were characterized by low-amplitude, low frequency (close to theta rhythm) activity around the Convex. In the third variant, a regular θ-activity with frequency of 5–7Hz was dominant on the EEG.

Among the 50 children with PTHE, 17 children exhibited the second variant of the clinical course of PE, and 33 exhibited the third. In the study of flash VEP, a distinct difference was revealed: in patients with the 2nd variant of the course of the disease, both P2 and N2 components were recorded. In the 3rd, there was a differentiation of all "early" components: P1, N1, P2, and N2. In both cases, low-amplitude θ-activity across the Convex was present on the EEG. RAPhS was absent.

In the 100 children with PEUG, all three variants of the clinical course of the disease were also observed: PEUG1 (35 children), PEUG2 (35 children) and PEUG3 (30 children). In the study of flash VEP in the children with PEUG1, the P2 component was registered. In children with PEUG2, both P2 and N2 components were differentiated. In children with PEUG3, all "early" components were present: P1, N1, P2, N2.

Background characteristics of the EEG during the first two variants of the clinical course of the disease (PEUG1 and PEUG2) are characterized by low-amplitude θ-activity. The assimilation of PhS of 2–4Hz was weak. In the third variant (PEUG3), the frequency of 6–8Hz with the weak presence of α-rhythm was dominant. RAPhS of 2–4Hz was clear.

The analysis of results of the investigation of sensomnestic rates of children aged 6–12 months with PCH (90 patients), PTHE (25 patients) and PEUG (60 patients) revealed the following.

Among the 90 patients with PCH, 15 aged 3 months in the group with PCH1 had unstable adequacy of the fixation and visual attention. The study of flash VEP revealed the differentiation of the missing N2 component at the age of 3 months. Positive dynamics of the presence of α-rhythm of low amplitude were observed on the EEG, and there was no trace of RAPhS as at the age of 3 months.

In the 35 patients with PCH2, the adequacy of fixation and visual attention remained unstable. At flash VEP, P2 and N2 components were registered. EEG revealed quite positive dynamic of presence of α-rhythm (θ) in amplitude and frequency close to θ-rhythm (4–6Hz), and "assimilation" of the rhythm of PhS was not observed.

In the 40 patients with PCH3, the adequacy of fixation and visual attention remained stable. At flash VEP, both P1 and N1 components appeared by 6 months of age, along with the P2 and N2 components. The EEG revealed low-amplitude α-rhythm with frequency of 7–10Hz. RAPhS was unclear.

In all 25 children with PTHE 2 and PTHE that were examined aged 6–12 months, the behavioral visual responses were stable. Flash VEPs were characterized by the presence of all "early" components – P1, N1, P2, and N2. EEG was characterized by the presence of θ-activity across the Convex. By the age of 1-year, α-rhythm of low amplitude with a satisfactory presence in the occipital leads was significantly differentiated. There was a clear RAPhS 2–4Hz.

Among the 60 children with perinatal encephalopathy of unknown origin, 10 with lack of stable adequacy of fixation and visual attention (PEUG1) had instability of behavioral visual responses by the age of 6 months, which is typical for the second variant of the clinical course of the disease. The study of flash VEP in the dynamics revealed, along with P2, the differentiation of the previously missing component N2. Components P1, N1, initially not differentiable by the age of 6 months, were recorded by the age of 1 year. EEG was characterized by low amplitude activity (up to 40mkV) in the range of 6–12Hz. RAPhS was 2–4Hz.

In the 20 children with unstable adequacy of fixation and visual attention (second variant, PEUG2), the behavioral visual responses became stable by the age of 6 months. At flash VEP, P2 and N2 components were recorded at the age of 3 months. Ten of these children who were re-examined at the age of 12 months had component N3. The EEG revealed low-amplitude, low frequency activity; RAPhS 2–4Hz was clear.

In the rest of 30 patients with PEUG3, the adequacy of fixation and visual attention remained stable at 6 months, and the rest of the sensomnestic indices did not differ significantly from the control data (3rd variant of the clinical course). In studies conducted up to the age of 1 year, components P1, N1, P2, and N2 were clearly differentiated. EEG at 6 and 12 months revealed low-amplitude, high frequency activity throughout the Convex; RAPhS 2–4Hz was clear.

Clinical and catamnestic studies conducted in 300 children with PE showed that in 30 (20 %) of 150 children with PCH, 33 (66 %) of 50 with PTHE, and 30 (30 %) of 100 children with PEUG (total 93 children), the clinical progress was relatively favorable for both neurological and ophthalmological findings by the age of three months. By 6 months, the indicators of psychophysical development of these children, as well as sensomnestic criteria, did not significantly differ from those of almost healthy children of corresponding age. Stability and continuing to the age of one-year positive dynamics of psycho-physical development revealed full compensation of the changes. These 93 children were designated as the control group, and their 1-year data of sensomnestic parameters were used for the appropriate statistical analysis as control (Table 1).

Table 1

Control amplitude-latent parameters of VEP of children with PE at the age of 1 year

Parametres	3 months		6–12 months	
	L	A	L	A
P1	55.2±1.2 (44–61)	–	54.3±1.4 (43–60)	–
P2	101.3±2.7 (91–112)	–	99.8±2.4 (90–111)	–
P3	–	–	–	–
N1	64.8±1.6 (53–75)	–	65.1±1.5 (54–75)	–
N2	134.6±2.9 (115–152)	–	135.4±2.7 (118–149)	–
N3	144.9±3.1 (123–165)	–	145.3±3 (126–164)	–

Retrospective analysis of sensomnestic indices revealed quite significant difference in the dynamics of amplitude-time characteristics of flash VEP, especially at the ages of 6–12 months.

Based on our data, lack or instability of the adequacy of the fixation of visual attention, lack or instability of clear differentiation of the component N2, registration LN2≥155ms, and registration AN2≤AP2 diagnosed at the age of 3 months (or later) were classified as delayed visual maturation syndrome. At the same time, lack or instability of the adequacy of the fixation and visual attention, lack or instability of clear differentiation of component N1, registration LP2≥135ms and AN2≤AP2 observed at the age of 6 months (or later) were classified as visual deficiency syndrome, because, by definition, the signs of delayed visual maturation improve without treatment by the age of 6–8 months.

Therefore, the results of the studies of sensomnestic indicators re-veal some additional aspects of the gradual regressive course of sensomnestic disorders in children with PE, providing additional opportunities for early prediction of possible aberrant courses.

Thus, the studies conducted have identified the regularity of pattern matching of behavioral visual responses and EEG manifestations (RAPhS). The latter follows from the interaction of phylogenetic and ontogenetic neurophysiological and neuropsychological mechanisms.

The tracing of the status of spatial adaptation of the gaze, the study of characteristics of refraction and optical-vestibular sensitivity (state of vestibular support) in the dynamics as well as a parallel study of indicators of vasomotor reflexes, indirectly indicating the nature of vasomotor support of the visual system, can serve as a prognostic algorithm of CVI in children with perinatal encephalopathy.

We have also found that in 55 children with PE with undifferentiated short-latent components of flash visual evoked potentials (P1 and N1) by the age of one year, convulsions occur relatively later (at the age of 5–10 or 12–18 months). Under the influence of initiating agents, convulsions are more resistant, still present by the age of 2.5–3 years. The high degree of correlation detected (r=0.7) between the lack of differentiation of the early components of flash VEP and distinct low-frequency high-amplitude EEG trend suggests that the deficiency of short-latent visual afference is one of the mechanisms explaining the gradual increasing rate in the reduction of the threshold for convulsive activity of the brain in children with PE.

PE (especially hypoxic-ischemic encephalopathy) is one of the important risk factors of cerebral visual impairment. This fact was indicated in different studies [6, 11]. Thus, Pehere N, et al with the aim to identify common causes, associated ophthalmological abnormalities, in children with CVI (Andhra Pradesh, India), revealed that the most common causes of CVI were hypoxic-ischemic encephalopathy (HIE) (34.4 %) [12].

Our study revealed that in children with PE visual problems progressed by the time and lead to delayed visual maturation syndrome and visual deficiency syndrome. Using the VEP for prognosis is one of the most informative methods for assess neuro-ophthalmological outcomes. So, Kim J, et al investigated the neurodevelopmental outcomes in children younger than 12 months, 12–23 months, and 24–42 months with developmental disorder according to VEP results. They found out that children with delayed VEP latency showed more developmental delay than children with normal VEP latency. The authors assumed that it is suggested that VEP can be easily applied to children with suspected developmental delay when physicians have concerns about visual impairment. In addition, it is proposed that VEP results could provide an insight into children's development and serve as early indicators for consultation with an ophthalmologist for the existing problem [7].

In the other work (Kooiker MJG, et al) the findings show a substantial risk of visual processing dysfunctions during visual screening (in 38 %) at 1-year corrected year of children born preterm. The data of study suggest that most conventional visual diagnostic methods at this young age are not related to the established visual processing dysfunctions risks. The more informative assessment should be used complimentary to these methods [8, 10]. That is why we used the additional methods (such as VEP etc.) to determine changes in detail. But in our research the results depending on gestation age at birth were not assessed.

Conclusions

1. In children with PE of different etiologies examined at the age under 3 months, deviations of sensomnestic rates are observed in 35 % of cases.

2. Electrophysiological differential criteria of delayed visual maturation syndrome and visual deficiency syndrome have also been identified, characterized by: delayed visual maturation syndrome – lack or instability of clear differentiation of component N2; registration LN2≥155ms; registration AN2≤AP2 – at 3 months (or later); visual deficiency syndrome – lack or instability of a clear differentiation of component N1; registration LP2≥135ms; AN2≤AP2 – at 6 months (or later).

3. The deficiency of short-latent visual afference is one of the mechanisms of the increasing trend where the threshold for convulsive brain activity in children with PE is reduced.

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Стаття надійшла 9.03.2022 р.