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Thalamic Auditory Center Activity in Healthy Children and Patients with Acute Bacterial Meningitis

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Abstract—We provide our data on the VI peak of brainstem acoustic evoked potentials (BAEPs) in healthy children and patients in the acute phase of bacterial meningitis (BM). Our aim was to evaluate the functional activity of the thalamic auditory center in children with severe lesion of the central nervous system (acute bacterial inflammation of its meninges). The study involved 120 children: 88 healthy controls and 32 patients in the acute phase of BM, all were aged 3–5 years old (mean age 3.7 ± 1.2 years). BAEPs were registered according to the guidelines, but special attention was paid towards the existence, latency, and amplitude of its VI peak. Statistical analysis was performed using *t*-criteria ($p < 0.05$) as well as ROC-analysis for determination of the threshold value with optimal value of sensitivity and specificity. The VI peak was not present in 2 children out of 88 healthy controls (2.3%) and in 19 patients with BM (60%). Diffuse lengthening of the I–III and III–V intervals were registered, with III and V peaks amplitudes lowering in children with BM. Average latency of the VI peak in controls and BM group were 7.02 ± 0.27 and 7.82 ± 0.63 ms, accordingly (significant difference, $p < 0.001$); amplitudes were 0.223 ± 0.127 and 0.089 ± 0.057 μV (significant difference, $p < 0.001$). Also, with ROC-analysis, it was established that low amplitude of the VI peak (≤0.09 μV) is associated with a bad outcome of the disease with severe neurologic deficit (sensitivity 90% and specificity 60%). Thus, BAEPs VI peak in healthy children aged 3–5 years was registered in 98% of the cases. In the acute period of BM it was registered only in 40% of the cases. Latency and amplitude of this peak in the BM group is significantly different from the healthy controls of the same age. This may reflect the unspecific slowing of the conduction along the brainstem auditory pathways and functional inhibition of the brain structures, supposedly generating a VI peak, a medial geniculate body and probably some other thalamic nuclei. All these nuclei compose the thalamic auditory center. Also, according to ROC-analysis, it was established that a low amplitude of the VI peak (≤0.09 μV) is associated with a bad outcome of the disease with severe neurologic deficit (sensitivity 90% and specificity 60%).

Keywords: brainstem acoustic evoked potentials, VI peak, thalamus, meningitis

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INTRODUCTION

The processing of auditory information in the central nervous system is often viewed as a linear flow of information "upward," from peripheral structures, through the auditory stem nuclei and hierarchically organized control and processing centers to the cortex. Meanwhile, this cascade of information constantly intersects with its downward, reverse movement, with a corresponding change in the activity of the auditory centers [1]. The corticothalamic pathway both under normal and pathological conditions transmits and processes information in two directions; in severe catastrophes, such as, in particular, inflammation of the meninges (in its extreme manifestation, acute purulent meningitis (PM)), the functional activity of both the cortical parts and the thalamus changes significantly [2]. Cortical areas are much easier to examine both under normal and pathological conditions, using the data of multiparametric and functional magnetic resonance imaging and electroencephalography (EEG), while thalamic structures, especially in children, are much more difficult to examine. Under these conditions, clinically proven methods of clinical neurophysiology can provide significant assistance.

Brainstem acoustic evoked potentials (BAEPs) is a neurophysiological technique widely used in clinical practice to assess the function of the auditory nerve and brainstem auditory pathway [3]. Currently, it is most often used in critical conditions of a patient, in intensive care units (ICUs) [4].

The BAEP waves (peaks) recorded during the study are numbered and, according to classical views, each of them reflects the excitation of a certain part of the auditory pathway: peak I corresponds to the response of the auditory nerve, II to the cochlear nucleus, III to the trapezius body, IV to the lateral loop, and V to the lower tubercles of the quadrigemina. Peak VI is believed to reflect the activity of the medial geniculate body [3, 4].

According to established views, peak VI is not assessed in routine clinical practice due to the variability of its parameters (both latency and amplitude) [5]. However, it is reported that in healthy individuals peak VI is recorded in 98% of cases [6]. Some studies have shown that peak VI latency increases in 81% of children with autism spectrum disorders, in 69–72% of children with alalia and speech delay, and in 65% of schoolchildren with learning difficulties [7–9].

Previously, we studied the standard indicators of BAEP in children in the acute period of bacterial purulent meningitis (BPM) [10]. Initially, peak VI was not specially examined, but as part of a further study of the state of the brainstem auditory pathway in children with this severe, life-threatening, and disabling pathology, peak VI in children with BPM was eventually also studied.

Objective—To study the activity of the auditory center of the thalamus in severe lesions of the nervous system (acute purulent inflammation of the meninges) in pediatric patients.

MATERIALS AND METHODS

The study included 120 children, including 88 healthy children and 32 children with BPM (20 girls, 12 boys). According to the severity of the condition, the patients were hospitalized in the ICU of the Pediatric Research and Clinical Center for Infectious Diseasesof (St. Petersburg), in 20 children with BPM, using laboratory methods, meningococcal etiology was confirmed, in 8, hemophilic, and in 4, pneumococcal. The age of the patients was from 11 months to 5 years, averaged 3.7 ± 1.2 years. The study was carried out 2–3 days after admission to the hospital. The comparison group consisted of neurologically healthy children (54 girls and 34 boys) who underwent screening examination, mean age was 3.5 ± 1.6 years.

In patients with BPM, general infectious manifestations were combined with cerebral symptoms, in 60% of cases meningeal symptoms were clearly detected. Disturbances of consciousness were diagnosed in 92.2% of cases from mild obtundation (13–14 points on the Glasgow Coma Scale) to deep coma (6–9 points), in 7.7%, cerebral symptoms were also expressed in psychomotor agitation (all in cases of a mixed form of meningococcal infection complicated by the development of septic shock). In six cases, in patients with meningococcal infection at the time of admission to the clinic, the critical condition was due to the development of septic shock and DIC syndrome. Focal neurological symptoms at the onset of the disease in the form of paresis of varying severity or cranial nerve symptoms were observed in a third of patients, but in most cases they were transient. All patients received therapy in full, depending on the etiology of meningitis and the leading pathological syndrome. In 40% of cases, with the development of cerebral edema, decompensated septic shock, after admission to the ICU, children were transferred to artificial lung ventilation (ALV) until their condition stabilized. Subsequently, a follow-up observation was carried out for 12 months with an assessment of the nature of the recovery period course with the formation of a mild, moderate, or severe neurological deficit. A mild neurological deficit was understood as the persistence of reflex disorders, short-term cephalgia, and asthenoneurotic conditions, the duration of which did not exceed 6 months. Moderate neurological deficit was defined as the presence of ataxia, focal symptoms such as convergent strabismus, tendon areflexia, and cognitive impairment that persisted for 12 months after the acute illness. A severe neurological deficit was understood as persistent pyramidal and extrapyramidal disorders, symptomatic epilepsy, and severe ataxia, persisting for more than a year.

BAEPs were recorded according to the generally accepted method. To eliminate fluctuations in the background activity of the slow components of the electroencephalogram (EEG), the lower frequency band of the device was set to 100 Hz, the upper one to 5 kHz, and the impedance did not exceed 5 kΩ. Sound clicks 0.1 ms long with an intensity of 70 dB above the hearing threshold, or 120 dB in case of impaired consciousness and a stimulation frequency of 11 Hz, were delivered monoaurally through headphones. Active electrodes were placed on the mastoid processes. The reference electrode was located at the *Cz* point according to the International 10–20 Electrode Placement System, the ground electrode at the *Fpz* point. The epoch of analysis is 10 ms, the number of averaging is 2000 [2, 9].

Statistical analysis was performed using the STATISTICA and Excel software packages. Descriptive statistical methods were used to assess the demographic indicators of the groups. The normality of distribution was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov criteria. The significance of differences between groups was assessed using Student's *t*-test ($p < 0.05$). To assess the prognostic significance of the obtained indicators in relation to the prediction of severe neurological deficit in BPM, ROC analysis was performed (MedCalc, Belgium).

RESULTS

Peak VI was not registered in 2 out of 88 children in the comparison group (2.3%) and in 19 patients with

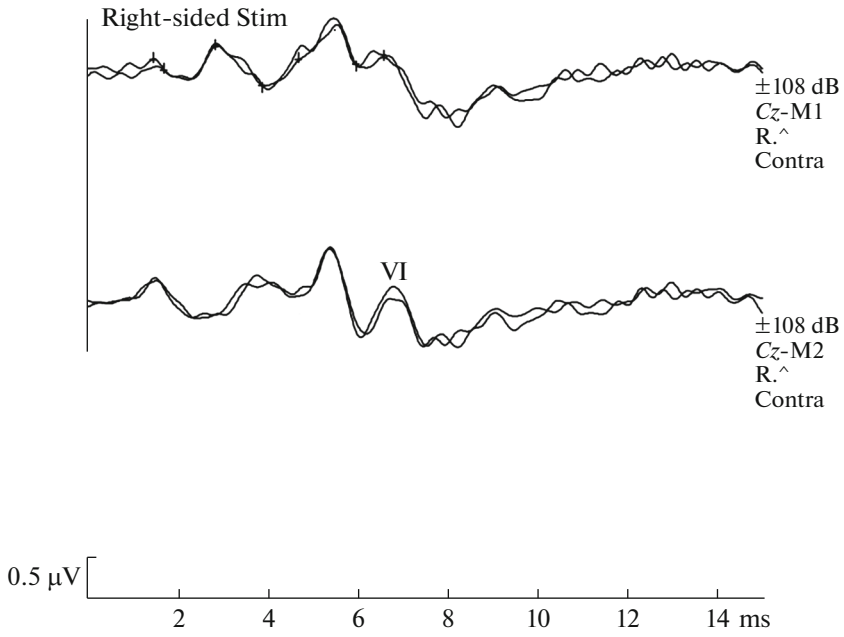

Fig. 1. Brainstem acoustic evoked potentials (BAEPs) of a healthy boy (3 years old). The latency of peak VI is 6.82 ms, the amplitude is 0.528 μV.

BPM (60%). An example of BAEP with a registered VI peak is shown in Fig. 1.

The average parameters of the peak VI of BAEP are presented in Table 1. Other parameters of the main peaks and intervals were close to those observed by us earlier in children with BPM [8] and are not presented here. A diffuse slowing of conduction along the brainstem auditory pathways was recorded due to the lengthening of intervals I–III and III–V and a decrease in the amplitude of peaks III and V.

During ROC analysis, it was found that the peak VI amplitude index in relation to an unfavorable outcome in BPM (outcome with severe neurological deficit) is statistically significant. If the VI peak amplitude is ≤0.09 μV, an unfavorable outcome of BPM is predicted (sensitivity 90.0%, specificity 60%, AUC 0.7) (Fig. 2).

DISCUSSION

We found that, in contrast to adults, peak VI in children under 5 years of age is a stable neurophysiological phenomenon and, apparently, the established normative data can be taken into account for further work with patients of this age group.

There is information that in healthy children, the latency of peak VI is 6.94 ± 0.93 ms, and in children with delayed speech development it is 7.28 ± 0.37 ms; our data on a large sample of healthy children are consistent with those given in the cited paper [11].

It is reported that the absence or deviation from the normal parameters of BAEP peak VI in patients in a coma can correlate with an unfavorable outcome of the coma [7].

The medial geniculate body (*corpus geniculatum medialis*) is an important structure of the thalamus; previously, it was considered a part of a special area of the brain, the metathalamus [12]. It contains the nucleus, in which the lateral loop ends. Together with the lower colliculi of the quadrigemina, the medial geniculate body forms the subcortical auditory center. These structures are associated with the primary associative cortex and are in complex interaction with it, as well as with the underlying stem structures [13, 14].

Taking into account the data that BAEP parameters change when the medial geniculate body is

Table 1. Indicators of peak VI of brainstem acoustic evoked potentials (BAEPs) in healthy children and children in the acute period of bacterial purulent meningitis (BPM)

Peak VI parameter	Latency, ms	Amplitude, μV
Healthy children, $n = 88$	7.02 ± 0.27	0.223 ± 0.127
Children with BPM, $n = 32$	7.82 ± 0.63*	0.089 ± 0.057*

*—significant difference from healthy children, $p < 0.001$.

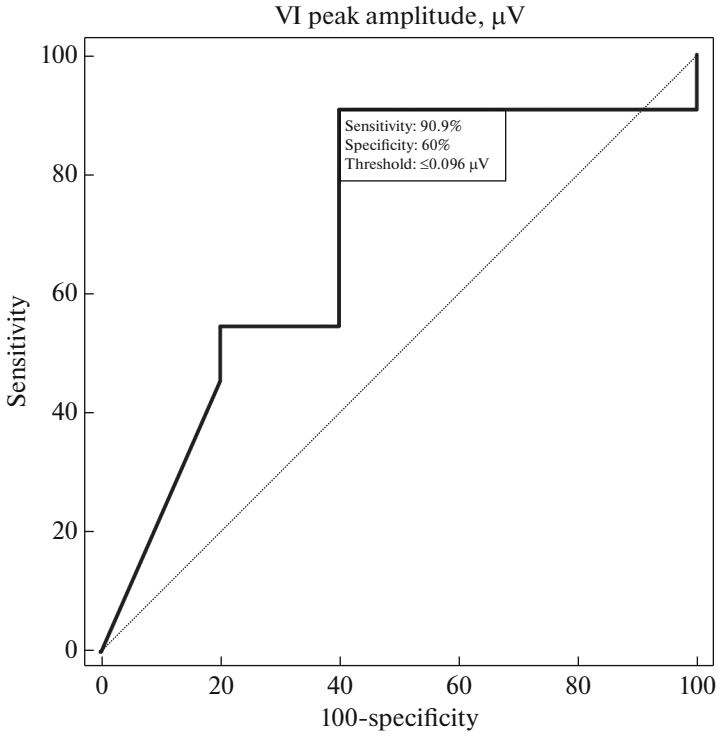

Fig. 2. ROC-analysis of the peak VI amplitude index in relation to an unfavorable outcome (severe neurological deficit) in bacterial purulent meningitis (BPM). If the VI peak amplitude is ≤0.09 μV, an unfavorable outcome of BPM is predicted (sensitivity 90.0%, specificity 60%, AUC 0.7).

affected in humans, in particular, there is a change in the I–V interval and parameters of the V peak, it can be assumed that this anatomical structure is also somehow involved in the generation of the fifth peak. Despite the well-established opinion that BAEP peak VI reflects the activity of the medial geniculate body, there are suggestions that peaks V, VI, and VII may arise due to excitation of sources in the brainstem located much more caudally [15]. Other authors also express doubts about the specific association of late peaks with brainstem structures [16]. Direct clinical observations contradict the categorical assertion that it is the medial geniculate body that generates peak VI of BAEPs; one way or another, it can be assumed that this peak reflects the activity of the *subcortical auditory center of the thalamus* [17–19].

The absence of the peak in most of our observations of children in the acute period of BPM may reflect the suppression of the structures of the posterior part of the thalamus during the ongoing catastrophe, purulent inflammation of the meninges with concomitant disruptions of its parenchyma (vasculitis, etc.), as well as general infectious changes. Previously, we suggested that in the acute period of inflammation of the meninges and brain substance, the activity of the reticular formation of the brain is inhibited; given the large number of its connections with thalamic structures, it can be assumed that there is a combined inhibition of their activity [20].

CONCLUSIONS

It has been established that peak VI of BAEPs in healthy children is recorded in 98% of cases. In children in the acute period of BPM, it is recorded only in 40% of cases. It was also found that both the latency and the amplitude of peak VI in children with BPM significantly differ from those in healthy individuals. This may reflect a general nonspecific slowing of conduction along the brainstem auditory pathways and functional inhibition of the structures responsible for the generation of peak VI; the medial geniculate body and, possibly, other thalamic nuclei that form the subcortical auditory center of the thalamus. The peak VI amplitude indicator in relation to an unfavorable outcome in BPM (outcome with severe neurological deficit) is statistically significant: with a peak VI amplitude value of ≤0.09 μV, an unfavorable outcome of BPM is predicted (sensitivity 90.0%, specificity 60%).

COMPLIANCE WITH ETHICAL STANDARDS

All studies were carried out in accordance with the principles of biomedical ethics formulated in the Declaration of Helsinki of 1964 and its subsequent updates, as well as the "Rules of Clinical Practice in the Russian Federation," approved by the Order of the Ministry of Health of the Russian Federation of June 19, 2003, No. 266, and approved by the local ethical committee of the Children's Scientific and

Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency of Russia (St. Petersburg).

INFORMED CONSENT

Each legal representative of the study participant provided a voluntary written informed consent signed by him after being explained the potential risks and benefits, as well as the nature of the upcoming study.

CONFLICT OF INTERESTS

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

CONTRIBUTIONS

V.B. Voitenkov—the concept of the article, the collection and analysis of the data obtained, the text of the manuscript, and checking the intellectual content of the article; V.N. Komantsev—the concept of the article, collection and analysis of the data obtained, the text of the manuscript, and checking the intellectual content of the article; E.V. Ekusheva—the concept of the article, analysis of the data obtained, the text of the manuscript, and checking the intellectual content of the article; A.V. Klimkin—the concept of the article, the collection and analysis of the data obtained, the text of the manuscript, and checking the intellectual content of the article; M.A. Bedova—collection and analysis of the obtained data, the text of the manuscript, and arranging the manuscript.

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