Clinical Investigations

SOMATOSENSORY EVOKED POTENTIALS IN FULL-TERM NEONATES
WITH PERINATAL ASPHYXIA

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ABSTRACT

Objective: To explore the capacity of somatosensory evoked potentials (SEP) to assess maturation processes in the development of the nervous system, and the characteristics of SEP in healthy full-term infants and full-term newborns with perinatal asphyxia and their follow up until the age of 14 months.

Materials and methods: SEP were studied in 21 healthy full-term infants and 38 full-term newborns with perinatal asphyxia. The children with asphyxia were studied longitudinally until they were 14 months old. To assess the SEP we measured the latency of the P15, N20 and P25 components, the amplitude ratio N20/ P25 and inter-peak intervals P15-N20 and N20-P25. Results: The component that was most typically always found in the SEP recordings of both healthy infants and those with perinatal asphyxia was N20. The mean latency values of P15, N20 and P25 were higher in the children with perinatal asphyxia (p < 0.001). The SEP amplitude was highly variable (CoV% = 76.6%). The latencies became shorter with age in asphyxia patients aged 0 to 14 months, the shortening being the greatest in the first trimester, while they showed no statistically significant differences in infants aged 6 to 12 months. Conclusions: SEPs in the neonatal period differ considerably from those of adults and older children in the morphology and longer potential latency, which can be accounted for by the incomplete myelination of nerve fibers. The changes in SEP latency in patients with HIE stages I and II follow the same pattern found in healthy children - latency became shorter with increasing age, which was most pronounced in the first 3 months. SEP latency was found to be correlated with height and age. No differences were found in the latency of potentials between healthy infants and infants with brain hemorrhage. Recording SEP is a sensitive method to assess the CNS in children with perinatal asphyxia and to monitor the maturation of the somatosensory pathway.

Key words: somatosensory evoked potentials, perinatal asphyxia, neonate and infants

RESUMEN

Objetivo: Explorar la capacidad de los potenciales evocados somatosensóricos (SEP) para evaluar los procesos de maduración en el desarrollo del sistema nervioso, y las características de los SEP en neonatos sanos y neonatos con asfixia perinatal y su seguimiento hasta la edad de 14 meses.

Materiales y métodos: Los SEP se estudiaron en 21 neonatos sanos y 38 neonatos con asfixia perinatal. Los niños con asfixia se estudiaron longitudinalmente hasta los 14 meses. Para evaluar los SEP se midieron la latencia de los componentes P15, N20 y P25, el cociente de amplitud N20/ P25 y los intervalos interpico P15-N20 y N20-P25. Resultados: El componente más típicamente siempre presente en los grabados SEP de ambos neonatos sanos y aquellos con asfixia perinatal fue N20. Las medias de las latencias de P15, N20 y P25 fueron mayores en los niños con asfixia perinatal (p < 0.001). La amplitud de los SEP varió mucho (CoV% = 76.6%). Las latencias se volvieron más cortas con la edad en los niños con asfixia perinatal de 0 a 14 meses, el acortamiento fue el más grande en el primer trimestre, mientras que no hubo diferencias estadísticamente significativas en los niños de 6 a 12 meses. Conclusiones: Los SEP en el período neonatal difieren en gran medida de los de adultos y niños mayores en la morfología y la mayor latencia potencial, lo que se puede atribuir a la inmadurez de la mielinización de las fibras nerviosas. Los cambios en la latencia de SEP en pacientes con HIE fases I y II siguen el mismo patrón encontrado en neonatos sanos - la latencia se volvió más corta con la edad, lo que fue más pronunciado en los primeros 3 meses. La latencia de SEP se encontró correlacionada con el peso y la edad. No se encontraron diferencias en la latencia de los potenciales entre los neonatos sanos y los neonatos con hemorragia cerebral. Grabar los SEP es un método sensible para evaluar el sistema nervioso central en neonatos con asfixia perinatal y para monitorear la maduración del sistema somatosensorio.

Palabras clave: potenciales evocados somatosensóricos, asfixia perinatal, neonato y niños
INTRODUCTION

Evoked potentials are bioelectric responses of the nervous system to the reception, transmission and processing of information. Somatosensory evoked potentials (SEP) are used to assess the sensory pathway as a projection from the periphery to the parietal cortex.1

Perinatal asphyxia is one of the causes of neonatal lethal outcomes and chronic neurological disorders. Intracranial hemorrhage is the most common cause of acute neurological symptoms in the neonatal period with late complications.

Clinical neurological examination of neonates and young children is difficult and not very reliable. SEP can compensate for this uncertainty by providing objective information about the function of the sensory system that can not be assessed otherwise.

AIM

The aim of this study was to explore the capacity of SEP to assess the maturation processes in the development of the nervous system, and study the characteristics of the SEP in full-term newborns with perinatal asphyxia and ongoing changes in the maturation.

MATERIALS AND METHODS

CLINICAL MATERIAL

Group A: 21 healthy neonates without evidence of perinatal asphyxia and no abnormalities in the somatic and neurological status.

Group B: 38 full-term newborns with perinatal asphyxia.

The group of neonates with perinatal asphyxia included 9 children diagnosed with hypoxic-ischemic encephalopathy (HIE) stage I and 23 diagnosed with HIE stage II - 9 from the latter had intracranial hemorrhage, and 17 had atypical or generalized seizures.

The children in the group with perinatal asphyxia were selected by the following criteria:

- gestational age between 38 and 42 weeks of gestation;
- body mass at birth > 2500g;
- perinatal asphyxia data on the basis of:
  - meconium stained amniotic fluid;
  - 1 min Apgar ≤ 6;
  - need for resuscitation measures in the delivery room;
  - clinical evidence of asphyxia (changes in muscle tone, neonatal reflexes and excitatory events);
  - manifestation of neurological symptoms in the first seven days of birth (or HIE according to Sarnat & Sarnat’s criteria)
  - sonographic criteria of the CNS.

The children in the group met at least three of the criteria for perinatal asphyxia.

For the neonates with perinatal asphyxia, SEP was studied in the neonatal period and they were longitudinally monitored over a period of 3 months, as the result of which 19 children in the age of 3-4 months, 16 children aged 6-7 months and 15 children aged 12-14 months were followed up. Final clinical evaluation of the neurological outcome was performed after 1 year of age. Data on anthropometric indexes were comparable for both groups.

METHODS

The examination was performed with the infants in the supine position, after feeding; no sedatives were used.

SEP were recorded with an active electrode placed on the contralateral sensory cortex C3’ and C4’ (2 cm posterior to C3 and C4) and a reference electrode Fpz. Gold-plated disk electrodes were used and these were attached with adhesive
paste; the attachment site was pre-cleaned with abrasive paste. The strip-like grounding electrode was inserted between the stimulating and the active electrode - under the elbow joint, and the stimulating electrode - in the wrist joint for stimulation of n. medianus. The study was conducted with impedance below 5 kΩ and filters for high frequencies – 1000 Hz, and for low – 10 Hz with automatic artifact control, electric impulse with frequency 3 Hz and analysis time of 50 ms. 200 responses were automatically averaged. The electric current stimulation was gradually increased until the motor threshold and in the neonatal period it reached in some children to 21 mA. With the increase in age the strength of the electrical stimulus for motor response was progressively decreased to reach 5-7 mA. To assess SEP we measured the absolute latency of P15, N20 and P25, the amplitude ratio N20/P25 and inter-peak intervals P15-N20 and N20-P25. The potential area was assessed by measuring the latency of inter-peak distance P15-P25.

A two-channel NeuroScreen (Jaeger-Tonnies) was used to record the evoked potentials. Most parameters of the evoked potentials had Gaussian or normal distribution. In these cases, the standard deviation may be used effectively to describe the normal distribution. To determine the normative limit, at least 2.5 (98.8%) or 3 (99.7%) standard deviations should be used. In our study, we have used 2.5 standard deviations.

ASSESSMENT SCALE

The following SEP components were assessed: morphology of potentials characteristic of healthy children, latency and amplitude of the potential. The evoked responses were defined as:

1. Normal
2. Abnormal – if some of the following criteria were met:
   2.1. Lack of potential;
   2.2. Absence of some of age related manda-
in the infants with perinatal asphyxia ($p < 0.001$). The SEP amplitude was highly variable ($\text{CoV} = 76.6\%$). There was no difference in the amplitude and inter-peak intervals between healthy infants and infants with perinatal asphyxia and between mild HIE infants and moderate HIE infants (Table 2).

No significant differences in the stimulation were found of the right and left hand separately, and of any of the waves, of the inter-peak intervals

Figure 1. Latency of SEP components as assessed by Apgar score < 3 and > 3 in the first minute.

(p > 0.05) and also between the two genders in the studied groups (p > 0.05).

The mean latencies of SEP components were significantly higher in patients born in a more severe depressive condition (APGAR ≤ 3). The differences again reached statistical significance only for the absolute latency of P15, N20, P25, and couldn’t reach significance for inter-peak latencies (IPL) and amplitude ratio of N20 and P25 (Fig. 1).

In the multiple comparison of mean latencies of components using ANOVA with Bonferroni modification we found significant differences between children with HIE stage II and healthy neonates for P15 ($p = 0.004$), N20 ($p < 0.01$) and P25 ($p < 0.01$) (Table 3); there was no significant difference between HIE stage I and P15, N20 and P25 ($p > 0.05$) in healthy infants. No significant difference was found in the inter-peak latencies between the three groups.

In the group with perinatal asphyxia, 9 of the newborns had grade I and II ventricular hemorrhage, in 2 of them the hemorrhage being bilateral; in 2 children (the one with bilateral and the other with unilateral hemorrhage) there was longer latency of N20. The remaining seven infants showed normal latency for the waves, the amplitude on the side of the hemorrhage being lower and the afference more poorly organized.

Using ANOVA with Bonferroni modification we found significant differences in the latencies of N20 and P25 between healthy newborns and infants with asphyxia with and without cerebral hemorrhage. No significant difference was found between children with asphyxia and hemorrhage and those with asphyxia without hemorrhage. We

Table 2. SEP components in newborns with perinatal asphyxia and in the control group

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<tr>
<td>min</td>
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<td>0.7</td>
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<td>41.4</td>
<td>47.7</td>
<td>4.3</td>
<td>14.6</td>
<td>14.0</td>
<td>22.7</td>
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<tr>
<td>2.x</td>
<td>22.3</td>
<td>28.5</td>
<td>35.5</td>
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<td>SD</td>
<td>3.7</td>
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<td>19.6</td>
<td>24.5</td>
<td>0.1</td>
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<td>2.3</td>
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<tr>
<td>max</td>
<td>30.7</td>
<td>38.4</td>
<td>47.5</td>
<td>3.0</td>
<td>11.0</td>
<td>13.4</td>
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| t     | 4.7           | 4.5           | 3.9           | 1.2                  | < 0.001        | < 0.001        | < 0.001        |
| p     | < 0.001       | < 0.001       | < 0.001       | NS                   | NS             | NS             | NS             |

± 2.5 SD are used to determine maximum and minimum values; 1 neonates with asphyxia; 2 healthy newborns.
found a longer latency of N20 (p < 0.05) in infants with asphyxia and seizures as opposed to children with asphyxia without seizures.

**Age-related changes of SEP in children with perinatal asphyxia**

N20 wave is present in all children with asphyxia of all age groups. The characteristic tendency of reducing the area of the potential is maintained, and hence the shape.

The latency time of the waves decreased with age for patients with asphyxia. In multiple comparison by means of ANOVA with Bonferroni modification it was found that the decrease in latency was the greatest in the first trimester, which refers to the latencies of P15, N20 and P25. Between the age of six months and one year no statistically significant differences in latency were found. No difference was found in the latency of inter-peak interval P15-N20 between the groups, which distinguishes it from changes in healthy children identified in a previous study.5

From the results of Table 5, it is seen that there is a strong negative correlation for P15, N20 and P25, and moderate for the inter-peak intervals. The correlation between height and SEP components latencies does not differ from that in healthy children - with the increase of height the latency in children with perinatal asphyxia aged 0 to 14 months decreases. The correlation is the strongest for the absolute values of latencies of SEP both for height and age.

SEP in children with asphyxia proved normal upon examination in the age range 12 - 14 months for all neonates including those who had abnormal potentials and psychomotor retardation at 3 or 6 months of age.

**Discussion**

SEP in the neonatal period are considerably different from those of adults and older children in terms of morphology of the potential, and prolonged latency wave potential. This is due to the anatomy and physiological characteristics of this age – incomplete myelination, synaptogenesis and maturation of the neurotransmitter systems. During the first two years of postnatal life there is a fivefold increase in the amount of myelin in the intracranial structures - the brainstem, thalamus and cortex.

The characteristic shape of cortical SEPs, which is defined by alternating waves of positive and negative polarity in children with perinatal asphyxia did not differ from that of healthy infants in the relevant age groups. Potential depression is characteristic both for healthy children and the sick.

**Table 3.** Age-related changes in SEP components during follow-up of full-term neonates with perinatal asphyxia

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<td>0-1 mos</td>
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<td>31.1</td>
<td>38.0</td>
<td>0.9</td>
<td>6.3</td>
<td>7.2</td>
</tr>
<tr>
<td>SD</td>
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<td>4.0</td>
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<tr>
<td>3-4 mos</td>
<td>x</td>
<td>14.9</td>
<td>21.4</td>
<td>24.8</td>
<td>1.8</td>
<td>5.9</td>
<td>7.0</td>
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<tr>
<td>SD</td>
<td>2.4</td>
<td>3.0</td>
<td>4.6</td>
<td>0.8</td>
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<td>1.8</td>
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<td>6-7 mos</td>
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<td>13.4</td>
<td>21.4</td>
<td>26.2</td>
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<tr>
<td>SD</td>
<td>1.8</td>
<td>2.6</td>
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<td>n = 16</td>
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<td>12-14 mos</td>
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<td>12.2</td>
<td>17.5</td>
<td>23.8</td>
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<tr>
<td>SD</td>
<td>1.3</td>
<td>1.6</td>
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Statistical difference was found in the amplitude between the neonatal period and three months of age (p = 0.004) and between the age of 3 and 6 months (p = 0.001), which was not observed in healthy children (p = 1.000).
The increase of latencies for P15, N20 and P25 in HIE in the neonatal period depends on the severity of the hypoxic-ischemic changes. This fact should be considered when the results of SEP are interpreted in the clinical neurological practice.

George and Taylor found considerable changes in the latency, amplitude, and morphology of SEP in the early neonatal period – a rapid reduction in the latency of the components in the first 3 months of life, particularly in the first three weeks. This regularity was also observed in our patients.

The latency time of waves of the potential is longer in children with asphyxia than in healthy children. There is no difference in the inter-peak intervals of potential in children with asphyxia, which distinguishes it from changes seen in healthy children and described in a previous study. In the reviewed literature, we found no explanation of this fact, but one possible explanation would be that for children having asphyxia the conduction along the afferent pathway is delayed without widening the potential with inter-peak interval P15-P25.

We found no differences in latency of potential waves between healthy neonates and children with asphyxia.
brain hemorrhages - a finding reported also by other researchers.\(^7\) This allows us to assume that it is asphyxia that is responsible for the increase of the latency time, not brain hemorrhage. This is easily explained knowing that asphyxia affects all brain structures, while in cerebral hemorrhage only a certain part of the brain is affected.

Neuro-imaging techniques can be used to diagnose brain hemorrhages, while evoked potentials can be used to assess and monitor the functional status of the affected nerve pathways.\(^8\) A comparative study of latencies between subgroups in infants with asphyxia shows that the cortical N20 potential is most sensitive to hypoxic brain changes and is therefore a better indicator in the complex interpretation of SEP recordings in newborns with perinatal asphyxia.\(^9\)

In the longitudinal study of SEP changes in different periods in infants aged 0 to 14 months it was found that in patients with HIE stage I and II changes in latency time are generally governed by the regularities established for healthy children – shortening of the latency with increasing age. The most significant decrease in latency in the first trimester, which coincides with the period of most rapid growth and development of the infant’s body.\(^9,10\) Development of HIE I and HIE II did not result in violation of the speed of maturation of neural structures.

The statistical difference we found in the amplitude between the neonatal period and 3, and 6 months of age, which is not registered in healthy children, we define as a manifestation of brain dysfunction.\(^11\)

Correlations between the latent time and the amplitude of the SEP with age and height are similar to those in healthy children.\(^4\) The amplitude of cortical potentials is low in infancy, and particularly during the neonatal period and the amplitude of the peripheral and spinal subcortical components increases with age.\(^6,12\)

Jiang monitored age-related changes in brain stem auditory evoked potentials, and found that their maturation does not differ from that of healthy children, despite existent abnormalities.\(^13\) A similar finding on the state of maturation of visual evoked potentials in children with perinatal asphyxia is reported by Hakkinen.\(^14\)

**CONCLUSIONS**

SEP in the neonatal period are significantly different from those of adults and older children in morphology and longer latency of components of the potential, which is due to incomplete myelination of nerve fibers.

Changes in SEP latency in patients with HIE stage I and II comply with the regularities for healthy children – decrease of the latency with increasing age, most pronounced in the first 3 months.

There is a correlation of the latencies of SEP for both height and age.

SEP is a sensitive method for assessing the CNS in children with perinatal asphyxia and for monitoring the maturation of the somatosensory pathway.

**REFERENCES**