영아의 체성감각유발전위 N20 잠시의 결정인자

박재은, 이용현, 박혜린, 김승기, 박은숙, 나동욱

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The Determinant for N20 Latency of Somatosensory Evoked Potentials in Infants

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Objective: To obtain the reference value of N20 latency of median and ulnar nerve somatosensory-evoked potentials (SEPs) in infants.

Method: Medical data from infants diagnosed with lumbosacral lipomyelomeningocele who underwent SEP analysis were reviewed retrospectively. Multiple regression analyses were performed to determine the factors that affect N20 latency of median and ulnar nerves ($N20_{median}$ and $N20_{ulnar}$) considering age, weight, total arm length, upper arm length, and forearm length. Pearson's correlation analysis was performed between N20 latencies and upper arm length.

Results: Total arm length ($p < 0.01$; $p < 0.01$), upper arm length ($p < 0.001$; $p < 0.01$), and forearm length ($p < 0.01$; $p < 0.01$) contributed to $N20_{median}$ and $N20_{ulnar}$ in simple regression analyses. Upper arm length ($p < 0.001$; $p < 0.01$) was the only contributing factor for $N20_{median}$ and $N20_{ulnar}$ following multiple regression analyses. The regression equations for estimating N20 latencies in infants from upper arm length were $N20_{median} = -0.47 \times \text{upper arm length} + 22.53$ ($R^2 = 0.21$) and $N20_{ulnar} = -0.46 \times \text{upper arm length} + 22.66$ ($R^2 = 0.19$).

Conclusion: Upper arm length was negatively correlated with N20 latency of upper extremity SEPs in infants. The equations derived from the medical data can be clinically applied as references for infant SEPs.

Key Words: infant, median nerve, ulnar nerve, somatosensory-evoked potentials, reference values

Introduction

Somatosensory-evoked potentials (SEPs) are electro-

physiological parameters that continuously measure changes in potentials in the sensory pathway until they reach the cerebrum, with temporary stimulation of the peripheral sensory nervous system. The sensory and motor pathways lie nearby in regions of the brain,¹ and they are useful for diagnosing central nervous system diseases such as movement disorders. SEP analysis is an objective and noninvasive method for assessing the functional integrity of the somatosensory

Received October 5, 2019

Revised October 25, 2019

Accepted October 29, 2019

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pathway.² In infants, SEPs can be used to determine neurodevelopmental prognosis.³ SEP analysis is also a method for evaluating the functional involvement of somatosensory pathways. Furthermore, SEPs in children have high sensitivity and specificity for predicting prognosis of perinatal brain injury.³ In the case of upper limb SEPs, they are useful for prognostic judgment by confirming the preservation of sensory nerves from the peripheral nerve to the central nerve in the brachial plexus with birth injuries.^{4,5} Upper limb SEPs are also used for prognosis of childhood hydrocephalus.⁶

The latency of SEP in adults has a proportional relationship that increases with height, and the reference range of somatosensory induction potential is determined according to the height of the subject. However, in infants, although heights are short, SEP does not decrease proportionally with height for some time. The rate of infant nerve conduction is lower than that of adults because nerve myelination does not occur completely until later in development. However, it is difficult to interpret the test's results because few data have been reported on SEPs of children in Korea.

The purpose of this study was to analyze the factors that affect the temporal implications of upper limb SEPs and derive an equation that can be used to determine a reference range in infants.

Materials and Methods

1) Subjects

This is a retrospective study using medical data from patients with lumbosacral lipomyelomeningocele (LMMC) who underwent a preoperative SEP study between August 2014 and November 2016 at a university-affiliated hospital. The patients who were admitted for lumbosacral LMMC surgery were referred to the Department of Rehabilitation Medicine for the preoperative SEP study for electrophysiologic functional assessment. The upper and lower extremity SEP studies were performed for baseline evaluation before

surgery. Among these data, only the upper limb SEPs were analyzed because lower limb SEP study could be affected by lumbosacral LMMC. The inclusion criteria were as follows: age < 12 months corrected age and patients with LMMC who underwent SEP study of the upper limb. Exclusion criteria included: patients with reported neurological deficit in any side of the upper limb, patients with disease or lesion in the central nervous system, such as combined hydrocephalus or cervical syringomyelia, patients who did not fall asleep during the SEP study, or patients who could not comply with the complete averaging process of SEPs.

The medical data used for analysis included records of the upper limb SEP study, several demographic parameters, including age, sex, and weight, and several measurements of the upper limb, including total arm length, upper arm length, and forearm length.

2) Methods

Infants (younger than 12 months corrected age) are usually unable to stand independently, so obtaining accurate standing height measurements is difficult. Previously, Mohanty et al. reported that arm span is the most reliable body parameter for predicting the height of an individual.⁷ Therefore, we measured the length of the upper limb to identify any correlations with the latency of upper limb SEPs. Upper arm lengths were measured by referencing surface bony eminences from the acromion of the scapula to the olecranon of the ulnar bone; forearm length was measured from the olecranon to the distal end of the thumb. Total arm length was calculated as the sum of the upper arm length and forearm length.

Patients underwent SEP studies while sleeping after sedative (midazolam) administration to ensure the reliability of the test. This sedative was administered not only for the current study, but also for usual preoperative SEP evaluations because infants typically cannot comply with the electrodiagnostic test in an awake state. Electrodiagnostic equipment (Medelec Synergy; Oxford Instruments Medical Ltd., Surrey,

UK) was used for the SEP studies. Recordings were performed via subdermal needle electrodes from the scalp at C3 (right median nerve stimulation), C4 (left median nerve stimulation), and Cz (right and left tibial nerve stimulation) positions, and a reference electrode at Fz according to the 10~20 International Electroencephalography System (Jasper 1958). The ambient temperature of the room was kept between 25 and 28°C. The following settings were used for stimulating the median and ulnar nerves at the volar side of the wrist: minimal stimulating intensity to produce thumb twitching, 0.05 ms stimulation duration, 2 Hz repetition rate, 250 repetitions, and 20~2000 Hz band filter width.

3) Statistical analysis

Statistical analysis was performed using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA). To determine the factors that affect the N20 latency of median and ulnar nerves ($N20_{\text{median}}$ and $N20_{\text{ulnar}}$), including age, weight, total arm length, upper arm length, and forearm length, multiple regression analyses were performed. Pearson's correlation analyses were performed of N20 latencies and several arm measurements, including total arm length, upper arm length, and forearm length. $p < 0.05$ was considered statistically significant.

Table 1. Basic Characteristics of the Patients

Variables	Values
Age (month)	6.16 ± 2.03 (2~12)
Sex (n, %)	
Male	29 (52.73)
Female	26 (47.27)
Body weight (kg)	7.90 ± 1.18
Total arm length (cm)	26.78 ± 4.56
Upper arm length (cm)	12.35 ± 2.67
Forearm length (cm)	14.43 ± 2.03
Median N20 latency (ms)	16.7 ± 2.74
Ulnar N20 latency (ms)	16.93 ± 2.86

Values are expressed as mean $\pm$ standard deviation (range) or number of patients (%)

Results

Following the inclusion criteria, 76 infants were enrolled in this study, and their medical records were reviewed. Among these, six patients (two with combined hydrocephalus and four with cervical syringomyelia) were excluded for medical diseases that may affect the results of the upper limb SEPs. An additional 15 patients were excluded because of movement artifacts due to an awake state during examination. Finally, the data of 55 patients (26 females and 29 males) were analyzed. The demographic and baseline characteristics of the study population are listed in Table 1. The age distribution of participants is shown in Fig. 1. The mean age at the time of electrodiagnostic study was 6.16 months (range 2~12 months). The mean $N20_{\text{median}}$ was 16.71 ± 2.74 ms and the mean $N20_{\text{ulnar}}$ was 16.93 ± 2.86 ms (Table 2).

Simple linear regression analysis indicated that total arm length ($p < 0.01$), upper arm length ($p < 0.001$), and forearm length ($p < 0.01$) were negatively correlated with the $N20_{\text{median}}$. Total arm length ($p < 0.01$), upper arm length ($p < 0.01$), and forearm length ($p <$

Fig. 1. Age distribution of participants.

Table 2. The N20 Latency of SEPs of Median and Ulnar Nerves in Infants

N20 latency	Mean $\pm$ standard deviation (ms)	Median value (ms)	Range (ms)
Median nerve	16.71 ± 2.74	17.10	12.05~23.80
Ulnar nerve	16.93 ± 2.86	17.40	12.30~24.45

Table 3. A Simple Linear Regression Analysis for N20 Latencies of the Median and Ulnar Nerve SEPs

	N20 latency							
	Median nerve				Ulnar nerve			
	β	RS	R ²	p value	β	RS	R ²	p value
Age	-0.13	17.50	0.01	0.491	-0.05	19.88	0.07	0.059
Weight	-0.47	20.40	0.04	0.140	-0.59	21.61	0.06	0.071
Total arm length	-0.27	24.00	0.21	< 0.05*	-0.27	24.08	0.18	< 0.01*
Upper arm length	-0.47	22.53	0.21	< 0.001*	-0.46	22.66	0.19	< 0.01*
Forearm length	-0.55	24.71	0.17	< 0.01*	-0.54	24.71	0.15	< 0.01*

RS: regression constant

*p < 0.05

Table 4. A Multiple Regression Analysis for N20 Latencies of the Median and Ulnar Nerve SEPs

	N20 latency			
	Median nerve		Ulnar nerve	
	β	p value	β	p value
Age	0.35	0.408	0.19	0.814
Weight	0.52	0.756	0.64	0.829
Upper arm length	-0.47	< 0.001*	-0.46	< 0.01*

*p < 0.05

Table 5. SEP Latency Value for Median and Ulnar Nerve According to Upper Arm Length

Upper arm length (cm)	N20 _{median} (ms)	N20 _{ulnar} (ms)
8~10	14.00~23.80	13.90~24.45
11~13	12.15~20.65	12.30~21.05
14~16	12.25~19.85	12.85~19.05
17~19	12.05~16.35	12.70~17.80

Values are minimum-maximum

0.01) were also negatively correlated with the N20_{ulnar} (Table 3).

Considering these contributing factors, multiple regression analyses were performed. Simple regression analysis indicated that upper arm length had the largest R² value and the smallest p-value compared to forearm length and total arm length. Upper arm length was analyzed as a representative in multiple regression analysis. Upper arm length (p < 0.001; p < 0.01) was revealed as the only contributing factor for N20_{median} and N20_{ulnar}, respectively, following multiple regression analysis (Table 4). Upper arm length was negatively correlated with N20 latency of SEPs in the upper extremities in infants. Table 5 shows SEP latency values for median and ulnar nerves according to upper arm

Fig. 2. Correlation between the upper arm length and the N20 latency of median nerve SEPs (N20_{median}). N20_{median} = -0.47 × upper arm length + 22.53. **Fig. 3.** Correlation between the upper arm length and the N20 latency of median nerve SEPs (N20_{ulnar}). N20_{ulnar} = -0.46 × upper arm length + 22.66.

length.

In all of those infants enrolled in this study, the regression equation for estimating the N20_{median} from upper arm length was N20_{median} = -0.47 × upper arm length + 22.53 (R² = 0.21) and that for estimating the

$N20_{\text{ulnar}}$ from the upper arm length was $N20_{\text{ulnar}} = -0.46 \times \text{upper arm length} + 22.66$ ($R^2 = 0.19$) (Figs. 2, 3). These analyses indicate that upper arm length has a negative correlation with N20 latency of each nerve. In turn, N20 latency was shorter in infants with longer upper arms.

Discussion

Willis J et al.³ reported that SEP analysis is a process that has high sensitivity and specificity for predicting the prognosis of perinatal brain injury in children. In a follow-up study, median nerve SEP latency was determined every 2 months from 2 months of the corrected age in preterm infants with periventricular hemorrhage. Infants who showed absent or prolonged latency had motor abnormalities identified in the follow-up study.³ The SEPs are also used for diagnosis of obstetric brachial plexus injuries.^{4,5} Furthermore, several studies have used SEPs to find spinal cord lesions, such as tethered cord syndrome.^{8,9} Therefore, it is important to establish normal reference values for SEP latency in infants and children.

Although many studies have shown that the central nervous system is myelinated during early childhood, the maturation of the nervous system for complete communication of motor functions occurs throughout childhood and approaching adulthood.¹⁰ Childhood development of the somatosensory system is remarkably complex because of coinciding non-parallel changes in parameters of maturation, such as pathway lengths, various rates of myelination of portions of the pathway, and increasing numbers of synapses in the pathway. Peripheral nerves and spinal cords lengthen and myelinate at different rates. The maturation of the peripheral nerve precedes that of the spinal cord. However, both of these developmental progressions are relatively simple compared to the maturation of the brain, which includes the process of synaptogenesis, as well as lengthening and myelination of complex polysynaptic pathways.¹¹

Previously, central somatosensory conduction times have been calculated for adults¹²⁻¹⁴ and children.¹⁵ Conduction delays in the peripheral components of both motor and somatosensory pathways also decrease initially but then progressively increase from the age of 5 years in proportion to arm length.¹⁶ The conduction delays in the central nervous segments of both somatosensory and motor pathways to the upper extremities fall within a narrow and consistent range from the age of approximately 2 years through adulthood despite a more than 2-fold increase in height and a 60% increase in pathway length. In contrast, conduction delays of the peripheral components of somatosensory and motor pathways increase gradually with age, starting at 5 years in proportion to body height and limb length. Therefore, different mechanisms must underlie the maturation of conduction velocities during development of central and peripheral nervous pathways.¹⁶

The central and peripheral nervous systems consist of the afferent pathway and the efferent pathway. Electrophysiologically, the afferent pathway has been studied through various evoked potentials, such as SEPs, and the efferent pathway through motor-evoked potential.¹⁷ A previous study reported childhood delayed maturation patterns compared to those of adults for both afferent and efferent central pathways; the developmental speeds of the afferent and efferent pathways were reported as different. It takes 5~7 years for the central afferent pathway to reach adult values, while the efferent pathway takes approximately 10 years. In contrast, maturation of the peripheral afferent and efferent pathways occurs at similar rates, reaching a relatively consistent conduction velocity around 3 years of age. The maturation of both pathways in the peripheral nervous system is earlier than in the central nervous system and there were no central conduction delays in afferent and efferent central pathways after the age of 2 years. The maturation of both pathways in the peripheral nervous system is earlier than in the central nervous system, and there

were no central conduction delays in afferent and efferent central pathways after the age of 2 years. The authors concluded that the prolonged maturation of central conduction time precludes the use of a predetermined temporal timing patterns in adaptive processes in the developing human nervous system.¹⁸

Eyre J et al.¹⁶ reported that threshold stimulus intensities for exciting somatosensory nerves are reduced through the age of 5 years and plateau. There is a robust decline in overall somatosensory conduction delay from birth to 2 years. From the age of 4 years, a progressive increase in overall delay occurs, which contributes to increased peripheral conduction delay and is correlated to arm length. The central somatosensory conduction delay reaches adult values at approximately 2 years of age. In the central visual and auditory pathways, the conduction delay to the brain stem and to the cortex shows adult values within approximately 2 years of life.^{19,20}

The myelination of somatosensory fibers is complete within 2~5 years after birth²¹ and is likely to be responsible for the rapid reduction in conduction delay over this period. In previous studies on childhood SEPs, the SEP latencies tend to decrease until approximately 3~5 years of age.²²⁻²⁴ However, the relationship between limb length or height and SEP latency is uncharacterized.

In this study, the length of the upper arm was the most useful indicator for predicting latency of SEPs in infants, showing a negative correlation between upper arm length and N20 latencies of the median and ulnar nerves. These results are consistent with previous studies that indicated that nerve myelination progresses and conduction delays occur in children prior to 2 years of age. Follow-up studies with children aged 12 to 24 months would be helpful for determining the rate of latency increase that occurs after 1 year of age.

Interestingly, our cross-sectional results showed that latency was shorter as the infants' arms became longer. In general, the longer the distance, the longer the expected latency. In other words, in adults, the longer

the height, the longer the SEP latency. Considering that myelination maturation of the peripheral nervous system begins during the last 4 months of fetal life and is completed at approximately 5 years of age, the different correlating patterns of latency and height or arm length can be attributed to the fact that development is ongoing.²⁵

Data analysis indicated that the age and arm lengths of the patients both had an inverse correlation to latency in infants. There was a significant relationship with arm length, rather than with age itself. However, the small study sample size limits the reliability of our regression equations. In future studies, a larger number of infants will be needed to be classified into more defined age groups to overcome problems with scattered data points. Although we derived the equations from infant arm lengths, there is an inevitable limitation to predicting the normal range of latency because there are variable differences between individuals in the progression of myelination and the accumulated data showed severe scattering. In addition, although we analyzed the data from only infants under 12 months of age, performing further studies in children over 12 months of age is necessary to understand developmental changes of the neuronal conduction rate on myelination. In our study, the SEP studies were performed while the patients slept after midazolam administration. Other studies have shown that midazolam can reduce amplitude but does not cause clinically significant changes in latency.^{26,27} Therefore, the effect of midazolam on our results may not be clinically significant. However, when studying brain function during sleep, the sleep stage needs to be carefully monitored because base neural activity changes between each sleep stage.²⁸ These limitations should be addressed in future studies.

Conclusion

This study investigated the factors that may affect SEP latencies of the upper limb in 55 infants. Among

the measured factors, the length of the upper extremity, especially the upper arm length, was most relevant to SEP latency, showing a negative correlation. To understand the changes that occur during the maturation process of the somatosensory tract, the results from children over the age of 1 year is required in a future study.

Acknowledgements

This study is supported by a research grant from the Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine for 2019.

References

1. Klimach VJ, Cooke RW: Maturation of the neonatal somatosensory evoked response preterm infants. *Dev Med Chil Neurol* 1988; 30: 208-14
2. Trollmann R, Nüsken E, Wenzel D: Neonatal somatosensory evoked potentials: maturational aspects and prognostic value. *Pediatr Neurol* 2010; 42: 427-33
3. Willis J, Duncan MC, Bell R, Pappas F, Moniz M: Somatosensory evoked potentials predict neuromotor outcome after periventricular hemorrhage. *Dev Med Chil Neurol* 1989; 31: 435-9
4. Waters PM: Obstetric brachial plexus injuries: evaluation and management. *J Am Acad Orthop Surg* 1997; 5: 205-14
5. Zafeiriou DI, Psychogiou K: Obstetrical brachial plexus palsy. *Pediatr Neurol* 2008; 38: 235-42
6. Koršič M, Denišlić M, Jugović D: Somatosensory evoked potentials in children with brain ventricular dilatation. *Croat Med J* 2006; 47: 279-84
7. Mohanty S, Babu SS, Nair NS: The use of arm span as a predictor of height: A study of South Indian women. *J Orthop Surg* 2001; 9: 19-23
8. Maurya VP, Rajappa M, Wadwekar V, Narayan SK, Barathi D, Madhugiri VS: Tethered Cord Syndrome-A Study of the Short-Term Effects of Surgical Detethering on Markers of Neuronal Injury and Electrophysiologic Parameters. *World Neurosurg* 2016; 94: 239-47
9. Thomas DT, Yener S, Kalyoncu A, Uluc K, Bayri Y, Dagainar A, et al: Somatosensory evoked potentials as a screening tool for diagnosis of spinal pathologies in children with treatment refractory overactive bladder. *Childs Nerv Syst* 2017; 33: 1327-33
10. Brody BA, Kinney HC, Kloman AS, Gilles FH: Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. *J Neuropathol Exp Neurol* 1987; 46: 283-301
11. Gilmore RL, Bass NH, Wright EA, Greathouse D, Stanback K, Norvell E: Developmental assessment of spinal cord and cortical evoked potentials after tibial nerve stimulation: effects of age and stature on normative data during childhood. *Electroencephalogr Clin Neurophysiol* 1985; 62: 241-51
12. Desmedt JE, Cheron G: Somatosensory evoked potentials to finger stimulation in healthy octogenarians and in young adults: wave forms, scalp topography and transit times of parietal and frontal components. *Electroencephalogr Clin Neurophysiol* 1980; 50: 404-25
13. Ganes T: A study of peripheral, cervical and cortical evoked potentials and afferent conduction times in the somatosensory pathway. *Electroencephalogr Clin Neurophysiol* 1980; 49: 446-51
14. Matthews W, Beauchamp M, Small D: Cervical somatosensory evoked responses in man. *Nature* 1974; 252: 230
15. Lauffer H, Wenzel D: Maturation of central somatosensory conduction time in infancy and childhood. *Neuropediatrics* 1986; 17: 72-4
16. Eyre J, Miller S, Ramesh V: Constancy of central conduction delays during development in man: investigation of motor and somatosensory pathways. *J Physiol* 1991; 434: 441-52
17. Matsumoto H, Hanajima R, Terao Y, Hamada M, Yugeta A, Shirota Y, et al: Efferent and afferent evoked potentials in patients with adrenomyeloneuropathy. *Clin Neurol Neurosurg* 2010; 112: 131-6
18. Müller K, Ebner B, Hömberg V: Maturation of fastest afferent and efferent central and peripheral pathways: no evidence for a constancy of central conduction delays. *Neurosci Lett* 1994; 166: 9-12
19. Barnet A, Friedman S, Weiss I, Ohlrich E, Shanks B, Lodge A: VEP development in infancy and early childhood. A longitudinal study. *Electroencephalogr Clin Neurophysiol* 1980; 49: 476-89
20. Allison T, Wood CC, Goff WR: Brain stem auditory, pattern-reversal visual, and short-latency somatosensory evoked potentials: latencies in relation to age, sex, and brain and body size. *Electroencephalogr Clin Neurophysiol* 1983; 55: 619-36

21. Yakovlev P, Lecours A-R, Minkowski A, Davis F: Regional development of the brain in early life. 1967:
22. Boor R, Goebel B: Maturation of near-field and far-field somatosensory evoked potentials after median nerve stimulation in children under 4 years of age. *Clin Neurophysiol* 2000; 111: 1070-81
23. Doria-Lamba L, Montaldi L, Grosso P, Veneselli E, Gribaldi G: Short latency evoked somatosensory potentials after stimulation of the median nerve in children: normative data. *J Clin Neurophysiol* 2009; 26: 176-82
24. Lauronen L, Nevalainen P, Pihko E: Magnetoencephalography in neonatology. *Neurophysiol Clin* 2012; 42: 27-34
25. Favilla JT, Frail DE, Palkovits CG, Stoner GL, Braun PE, Webster Hd: Myelin-associated glycoprotein (MAG) distribution in human central nervous tissue studied immunocytochemically with monoclonal antibody. *J Neuroimmunol* 1984; 6: 19-30
26. Sloan TB, Fugina ML, Toleikis JR: Effects of midazolam on median nerve somatosensory evoked potentials. *Br J Anaesth* 1990; 64: 590-3
27. Laureau E, Marciniak B, Hebrard A, Herbaux B, Guieu JD: Comparative study of propofol and midazolam effects on somatosensory evoked potentials during surgical treatment of scoliosis. *Neurosurgery* 1999; 45: 69-74; discussion 5
28. Nevalainen P, Lauronen L, Pihko E: Development of human somatosensory cortical functions-what have we learned from magnetoencephalography: a review. *Front Hum Neurosci* 2014; 8: 158