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Effect of Perinatal Asphyxia and Body Hypothermia on Hearing Evocated Potentials and Development in the First Two Years of Life

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Abstract

Perinatal asphyxia is associated with a high risk of death as well as neurodevelopmental deterioration both early and late, in addition, severe episodes can have an important effect on auditory function, cochlear damage and retrocochlear neuronal lesions. With the use of body hypothermia therapy as a neuroprotector in the first 72 hours it has been possible to improve the survival of neonates and neurodevelopmental outcomes in cases with moderate to severe Hypoxic Ischemic Encephalopathy (HIE). Objective. To describe the characteristics of Brainstem Auditory Evoked Potentials (BAEP) of infants with moderate and severe HIE treated with body hypothermia, and its connection with the development achieved at one and two years of age. Material and Method. 51 children were studied, who underwent BAEP at 3, 6 and / or 12 months of age, and their development was evaluated at 12 and 24 months of age with the Gesell, Bayley II and Bayley III tests. Results. The BAEP values were similar to those observed in healthy children, and were significantly correlated with development at both ages, especially waves I and III. The Normal / Altered categories in the PEATC showed differences in standard deviation in the developmental score. Conclusions. BAEP showed a relation with later development; the proposed normality / alteration characterization allowed showing the BAEP as an indicator of risk for development, even before frank damage in the auditory pathway.

Keywords: *Perinatal asphyxia, Hypoxic Ischemic Encephalopathy (HIE), hypothermia, child development, BAEP*

Introduction

Perinatal asphyxia is associated with a high risk of death; in Mexico it was reported as the second cause of neonatal mortality between 2008 and 2012 in a tertiary institutional hospital.[1] Survivors have a higher risk of both early and late neurodevelopmental alteration — including functional impairment, cognitive impairment and cerebral palsy —, in addition, serious events can have a significant effect on hearing function, cochlear damage and retrocochlear neuronal lesions.[2,3] With the use of body hypothermia therapy as a neuroprotective in the first 72 hours, it has been possible to improve the survival of neonates, as well as the neurological outcome in cases with moderate to severe Hypoxic-Ischemic Encephalopathy (HIE).[4] Liu et al. followed up for 7 years 325 HIE infants treated with hypothermia and found that at 18 months the risks of cerebral palsy were reduced, and scores on developmental indexes on the Bayley Scales of Infant Development II (BSID-II) and in the Gross Motor Function Classification System were improved.[5] However, although several meta-analyses have analyzed the prognostic capabilities of early clinical tests regarding neurological outcomes between 18 months and 3 years of age, the need for predictive markers has not yet been met.[4, 6]

Regarding auditory function, the brainstem is a region susceptible to damage when events that trigger HIE occur, since it can compromise the function of numerous nuclei, nerve tracts and the reticular formation, with a greater effect being observed in the rostral region of the brainstem.

Romero et al., determined the differences in brainstem auditory evoked potentials (BAEP), between infants with HIE with traditional treatment and healthy children, finding that in the HIE group all the waves showed higher latencies and intervals, moreover, concerning age, they presented faster latency shortening and amplitude increase, probably due to the reorganization process of the nervous system.[7]

Mietzsch conducted a pilot study in HIE newborns treated with hypothermia, and found that peripheral function measured by otoacoustic emissions was disrupted in the first week of life, and normalized by 3 weeks of age; although the BAEP were initially prolonged, especially in waves III and V, over the weeks the central transmission was intact, a behavior comparable to that observed in cardiovascular patients undergoing body hypothermia for surgery.[3]

In the present work, we describe the BAEP of infants with perinatal asphyxia classified with moderate and severe HIE, who received treatment with body hypothermia during the first 72 hours of extrauterine life, and its association with the development achieved at one and two years of age.

Methods

Prospective, descriptive and longitudinal study in which we analyzed the results of BAEP and development of infants with a history of moderate and severe HIE in the neonatal period treated with body hypothermia during the first 72 hours of life in the Neonatal Intensive Care Unit of the Ajusco Medio Hospital. After their discharge they were integrated in the Neurodevelopment Research Center of the National Institute of Pediatrics for follow-up. The BAEP study was performed at 3, 6 or 12 months of age; development was assessed with the Gesell, Bayley II, and Bayley III tests at 12 and 24 months of age. Two children with no measurable response in BAEP were excluded. The final sample included 51 children, from whom 107 BAEP records were obtained (45 at 3 months, 28 at 6 months, and 34 at 12 months of age). In all cases, the parents voluntarily agreed for their children to participate in the study by signing an informed consent letter (INP 075/2014).

The BAEPS were recorded with a Nicolet EDX-Viking equipment at a stimulation rate of 11.5 pulses per second, with a negative polarity click at 80dBHL, surface electrodes were placed according to the international 10-20 technique, with positive in vertex, negative in ipsilateral mastoids and ground in Fpz. The impedance of the electrodes was calibrated to be under 5 kΩ, analysis window of 25ms, and filters of 100-2500 Hz. Monaural stimulation was used, with contralateral masking at 40 dB HL below the stimulation level, averaging 2000 stimulations on two occasions.

All recordings were made during sleep, identifying the latency of waves I, III, and V, as well as interwave intervals I-III, III-V, and I-V, measured in milliseconds (ms); the amplitude of waves I, III and V in microvolts (μV) and the range V/I in percentage (%); the suspected cases presenting central and peripheral deterioration were determined following Pratt's criteria.8 Since there were no significant clinical differences in the side by side comparison, measurements of the right and left ear were averaged, obtaining a single value by indicator for each study. Statistical analysis. For BAEP, measures of central tendency ($\bar{x}$ and SD) were obtained by age group. The z-score was calculated from these measures, to homogenize and categorize the population as Normal —up to $\bar{x}\pm1$SD— or Altered when it was outside that range (prolonged interwave latencies and intervals $\bar{x}+1$SD; decreased amplitude $<\bar{x}$-1SD; and central suspect V/I range $<\bar{x}$-1DS and peripheral suspect $>\bar{x}+1$DS). Subsequently, the components of the BAEP and the scores of the 3 development tests (coefficient for Gesell, developmental index for Bayley II and composite score for Bayley III) were related by correlation and analysis of variance (ANOVA), using the parameters of the BAEP in z-score for the correlations and the categorization of Normality/Alteration for the analysis of variance. The statistical package JMP V.8.0 was used, the level of significance was set at 0.05

Results

The sample was composed of 51 children born at term, 67% of the cases were born vaginally, with the presence of meconium seen in 61%, 48% female and 52% male; the risk events with the highest representation were prolonged expulsive phase and fetal distress (41% and 35%, respectively), distributed by severity degree of asphyxia: 90.7% moderate and 9.3% severe.

The BAEP presented slightly prolonged latencies and interwave intervals in those under 3 months, which showed rapid changes to normal values as age increased, particularly in the most central portions (waves III and V); similarly, the initially small amplitudes had a tendency to increase, normalizing in the older groups. (Table 1)

BAEP and development (correlation). When reviewing the correlation between the components of the BAEP and the areas of development of the three tests at one year of age,

we found that the interval I-III was the indicator that showed the highest correlation with all Gesell and Bayley II areas; amplitudes I and III showed a relationship with all Gesell areas, except with language; wave V amplitude was only related to motor and adaptive. For Bayley III we only found association of the motor component with amplitudes III and V. (Table 2)

For the age cut-off of 2 years, the components of wave III strengthened their correlation with practically all areas of development included in the three tests, proven to be statistically significant. In addition, connections between specific areas of development were added: for Gesell, language was related to amplitude I ($p<0.01$) and, personal-social behavior was associated to interval III-V ($p<0.05$). In the case of Bayley II, the mental area was related to wave I (latency and amplitude) and V/I range, while the psychomotor area was associated to wave V (latency and amplitude) and I-V interval. The Bayley III test, which at the 1-year cut-off only showed a correlation between motor and amplitudes III and V, at 2 years displayed significant associations in its three areas with latencies and amplitudes I and III, intervals I-III and III -V, and with the range V/I; wave V did not showed statistically significant relationships. (Table 2)

Categorization. The indicators with the lowest Normal percentage were range V/I and interwave interval III-V (75.7% and 77.6%, respectively), while amplitude III had the highest percentage (93.5%); the rest of the parameters had at least 80% of normal cases. For the V/I range we present 2 categorizations: 1) the proposal by Pratt,8 from which we obtained a 10.2% with suspected deterioration (6.5% central and 3.7% peripheral), and 2) our proposal based on standardized values, through which we found 24.3% of suspects (15% peripheral and 9.3% central). (Table 3)

Table 1. Distribution of the PEATC components, total population and age groups

		Latency			Interwave Interval			Amplitude			Range
Age groups		I	III	V	I-III	III-V	I-V	I	III	V	V/I
Total	$\bar{x}$	1.66	4.03	6.22	2.38	2.18	4.55	0.25	0.31	0.26	127.23
(107)	ds	0.13	0.26	0.39	0.24	0.26	0.39	0.11	0.12	0.10	77.07
3 months	$\bar{x}$	1.68	4.23	6.52	2.54	2.28	4.82	0.22	0.28	0.23	126.42
(n= 45)	ds	0.13	0.21	0.30	0.21	0.25	0.35	0.09	0.11	0.08	81.08
6 months	$\bar{x}$	1.63	3.96	6.16	2.32	2.20	4.53	0.27	0.32	0.26	116.16
(n=28)	ds	0.12	0.20	0.28	0.17	0.25	0.26	0.11	0.13	0.09	64.86
12 months	$\bar{x}$	1.64	3.84	5.87	2.20	2.02	4.22	0.27	0.34	0.31	137.41
(n=34)	ds	0.15	0.20	0.23	0.17	0.21	0.25	0.13	0.13	0.11	81.60

Table 2. Correlation coefficients between the BAEP standardized parameters and the developmental tests scores by areas at 12 and 24 months of age

		12 months (n=107)										24 months (n=95)									
		Latency			Interval			Amplitude			Rel V/I	Latency			Interval			Amplitude			Rel V/I
		I	III	V	I-III	III-V	I-V	I	III	V		I	III	V	I-III	III-V	I-V	I	III	V	
Gesell	CGD	-0.015	-0.234	-0.115	-0.257 *	0.0786	-0.104	0.1837 *	0.1646 **	0.0386	-0.126	-0.031	-0.294 *	-0.109	-0.314 ***	0.148	-0.102	0.1732	0.1981 +	0.0584	-0.114
	M	-0.077	-0.274	-0.087	-0.262 **	0.1595	-0.052	0.2064 *	0.101 *	0.3096 *	-0.122	-0.026	-0.326 **	-0.121	-0.347 ***	0.158	-0.113	0.1383	0.0757	0.0075	-0.101
	A	-0.051	-0.232	-0.13	-0.239 0.07	0.0588	-0.102	0.2034 *	0.2132 **	0.1771 +	-0.126	-0.003	-0.228	-0.089	-0.262 *	0.1133	-0.087	0.1115	0.158 +	0.0669	-0.093
	L	0.1068	-0.127	-0.12	-0.204 **	-0.043	-0.154	0.0743	0.1074	-0.055	-0.104	-0.053	-0.253 *	-0.144	-0.259 **	0.0481	-0.134	0.2039 **	0.3643 ***	0.1691	-0.063
	PS	-0.007	-0.194 *	-0.099	-0.217 *	0.0614	-0.096	0.1824 ***	0.2016 **	0.0641	-0.119	-0.005	-0.263 +	-0.021	-0.288 **	0.2471 *	-0.03	0.1703	0.1161	-0.042	-0.163
Bayley II	Me	0.0644	-0.142	-0.058	-0.189 *	0.0616	-0.061	0.0816	0.2733 ***	0.0709	-0.042	-0.199 +	-0.307 *	-0.134	-0.238 *	0.1201	-0.071	0.3771 ***	0.3259 **	0.076	-0.222 ***
	Pm	0.0501	-0.194	-0.069	-0.236 **	0.0948	-0.069	0.0331	0.0055	0.056	0.0179	0.0028	-0.343 **	-0.216 *	-0.377 ***	0.0235	-0.21 *	0.1618	0.1511	0.1724 +	-0.063
Bayley III	C	0.0297	0.1334	0.095	0.0466	0.0341	0.1002	-0.077	0.0232	0.013	0.0288	-0.151 *	-0.282 *	-0.052	-0.237 +	0.2245 *	-0.011	0.358 **	0.2959 **	0.0742	-0.247 *
	L	0.1138	0.0152	-0.044	-0.05	-0.072	-0.075	0.0587	0.1229	0.1374	-0.004	-0.148	-0.298	-0.054	-0.259 *	0.2379 +	-0.009	0.4063 **	0.4027 **	0.0847	-0.189 *
	M	-0.068	-0.257	-0.056	-0.187	0.1726	-0.03	0.1847	0.1389 +	0.149 **	-0.0300	-0.149 *	-0.267 *	-0.1	-0.217 +	0.1284	-0.048	0.1931	0.1519	0.0258	-0.142

*p <0.05; **p <0.01; ***p <0.001; +p marginal

GCD: general coefficient of development; M: motor; A: adaptive; L: language; PS: personal-social; me: mental; PM: psychomotor; C: cognitive.

By associating the BAEP categories with the areas of the three development tests, we found that there exist differences between the groups of up to 13.93 points between development mean scores, presenting lower development scores in the groups with some type of alteration. Range V/I, amplitude I, interwave interval I-III and, to a lesser extent, latency III, were the indicators that showed significant differences between groups, both at one and two years. The rest of the BAEP indicators did not show significant differences, although the scores remained higher for those with normal BAEP parameters (Table 4). Similarly, the categorization of Pratt's V/I range did not show significant differences.

Table 3. Population distribution in categories based on the z score normality criterion. (n=107)

	Normal		Prolonged	
Latency	n	%	n	%
I	88	82.2	19	17.8
III	88	82.2	19	17.8
V	88	82.2	19	17.8
IInterwave interval	n	%	n	%
I-III	92	86.0	15	14.0
III-V	83	77.6	24	22.4
I-V	86	80.4	21	19.6
Amplitude	**Normal**		**Decreased**	
	n	%	n	%
I	89	83.2	18	16.8
III	100	93.5	7	6.5
V	89	83.2	18	16.8
Rango V/I	**Normal**		**Suspected impairment**	
			Central	**Peripheral**
	n	%	n %	n %
Pratt	96	89.7	7 6.5	4 3.7
std	81	75.7	10 9.3	16 15.0

Latency and intervals: Normal ≤ $\bar{x}$+1ds; Prolonged >$\bar{x}$+1ds
Amplitude: Normal ≥ $\bar{x}$-1ds; Decreased <$\bar{x}$-1ds
V/I range: Pratt: Normal 50-300%; Central <50%; Peripheral >300%

Discussion

Different studies have addressed the neuroprotective role of treatment with body hypothermia in perinatal asphyxia.[5,6] Its value in the auditory pathway was initially inferred from observations on other populations of patients subject to hypothermia, in which prolongation of conduction times has been described early, as well as the appearance of fast conduction times at older ages, described by some specialists as a compensatory recovery of the maturational pattern.

Although in our population —according to the BAEP records taken at 3 months—, the latencies and interwave intervals showed prolonged values compared to the group of healthy children of a similar age described by Romero, when compared with the group with perinatal asphyxia without hypothermia treatment described in that same study, we found that their means were lower at all times, and even remained close to the values of the healthy group,[7] which supports the use of body hypothermia as a protector of the auditory pathway.

Concerning the neuroprotective role of hypothermia in subsequent neurodevelopment, in our general population the development scores for the three tests at one year of age were within expectations, except for the language (Gesell) and psychomotor areas (Bayley II); however, the mean developmental scores at 2 years of age tended to be lower for the Gesell and Bayley II areas. Bayley III ratings remained relatively similar in both evaluations.

The link between development and functional parameters showed greater importance in the components related to wave III. In this regard, it has been observed that the conduction of the auditory pathway can be delayed in a variety of disorders, including focal damage (demyelination, ischemia, tumors) or diffuse lesions (degenerative disorders, posthypoxic damage, etc.) in any part of the auditory pathway between the generators of wave I (distal VIII nerve) and wave V (superior pons). Amid these alterations, interval I-III — representing the conduction from the cochlear portion of the eighth nerve through the subarachnoid space to the nucleus of the lower pons — has been shown to be susceptible to tumors, inflammation (including inflammation and hemorrhage in the subarachnoid space).[8] Our population had at least one imaging study (CT) during their stay at the Neurodevelopment Research Center and, in cases where it was considered necessary, a transfontanellar ultrasound was performed when they joined the follow-up program, finding that just over half of the cases had presented signs of edema and ischemia at some point.

As we did not have parameters to categorize the PEATC indicators, we resorted to the z-score for the cataloging of our population — setting the cut-off point at the first standard deviation—, in order to achieve a division point that allow us to identify the presence of alterations, from subtle to frank, and to use the BAEP findings as an indicator of risk for subsequent child development. Consequently, it was observed that those patients who had presented some alteration obtained lower scores in their development. Despite this, these results cannot be fully attributed to the presence of functional alterations

Table 4. Analysis of variance of the scores by area of development according to the BAEP components at 12 and 24 months of age.

		Latency III					Interwave interval I - III					Amplitude I					Relation V / I std				
		Normal		Prolonged		p	Normal		Prolonged		p	Normal		Decreased		p	Normal		Suspicion		p
	Gesell	x̄	ds	x̄	ds		x̄	ds	x̄	ds		x̄	ds	x̄	ds		x̄	ds	x̄	ds	
First year of development	CGD	84.0	13.7	76.5	19.6	*	84.2	13.6	73.7	20.8	**	84.4	13.0	74.0	21.4	**	85.4	13.2	74.2	17.7	***
	M	88.5	19.2	77.4	23.3	*	88.3	19.0	75.9	25.6	*	88.9	17.8	74.9	27.7	**	89.9	18.1	76.0	23.5	***
	A	87.4	14.3	81.1	22.6		87.5	13.9	78.9	25.2	*	88.4	13.5	75.8	23.0	**	88.7	14.0	78.8	20.0	**
	L	72.0	13.6	67.2	15.8		72.5	13.5	63.0	15.1	**	72.1	13.4	66.7	16.7		73.9	13.4	62.8	13.0	***
	PS	88.0	14.2	80.7	19.1	+	88.2	14.1	77.6	19.7	**	88.3	13.4	78.4	21.2	**	89.0	13.3	79.3	18.8	**
	Bayley II																				
	Me	81.7	13.4	77.5	14.2		81.6	13.4	76.9	14.0		81.8	13.0	76.6	15.7		82.7	12.5	75.6	15.5	*
	PM	74.1	14.9	71.3	17.5		74.7	14.6	66.8	18.7	+	74.7	15.0	68.2	16.7		75.6	14.4	67.4	16.9	*
	Bayley III																				
	C	99.0	14.0	100.0	18.5		98.9	14.2	100.5	17.4		100.5	12.7	88.4	22.1	*	99.9	13.8	96.4	16.8	
	L	86.7	11.8	80.8	14.1		86.5	12.3	82.7	11.4		86.9	12.1	79.3	11.3	+	87.3	12.4	81.8	10.6	
	M	88.2	12.6	80.7	19.0		88.2	12.6	81.4	18.9		88.3	12.4	80.3	20.2		89.0	12.8	82.0	15.2	+
Second year of development	Gesell																				
	CGD	77.8	12.2	73.1	21.0		78.2	12.1	69.5	22.1	*	78.5	10.9	68.1	24.3	**	78.8	10.8	70.8	20.8	*
	M	84.6	15.9	77.9	25.0		85.2	15.9	73.0	25.2	*	85.4	13.8	72.5	31.0	**	85.8	13.9	76.1	26.1	*
	A	80.5	11.5	76.8	22.5		80.9	11.5	73.1	23.7	+	81.2	10.5	72.1	25.3	*	82.0	10.1	72.8	21.0	**
	L	72.2	17.4	67.0	20.8		72.7	17.0	62.6	22.1	+	73.0	16.7	61.9	22.6	*	73.0	16.5	66.0	21.9	
	PS	73.0	11.0	68.2	18.4		73.3	10.8	65.5	19.6	*	73.5	9.9	64.9	21.6	*	73.7	9.9	67.2	18.3	*
	Bayley II																				
	Me	73.0	15.3	67.3	13.9		72.8	15.2	67.4	14.4		73.5	14.9	63.6	14.4	*	73.5	15.0	67.1	14.8	+
	PM	71.3	10.7	69.2	12.4		72.3	10.3	62.8	11.6	***	72.0	10.3	64.9	12.7	*	72.4	10.4	66.4	11.6	*
	Bayley III																				
	C	93.6	10.7	86.8	15.0	*	93.4	10.6	85.0	17.2	*	93.9	10.3	84.2	15.7	**	94.8	9.7	83.9	14.5	***
	L	86.4	12.1	77.2	15.7	*	86.0	12.6	76.5	14.7	*	86.1	12.5	78.4	15.2	*	86.5	12.4	79.0	14.5	*
	M	89.1	12.4	83.6	18.4		88.9	12.4	82.4	20.5		89.7	12.0	79.5	18.6	**	90.3	11.6	80.2	17.4	***

*p <0.05; **p <0.01; ***p <0.001; +p marginal

GCD: general coefficient of development; M: motor; A: adaptive; L: language; SP: social personnel; me: mental; PM: psychomotor; C: cognitive.

in the BAEP, since it must be considered that part of our population was subject to a double risk condition (biological and psychosocial) as they came from low and medium low socioeconomic strata.

For the V/I range, we initially used the parameter proposed by Pratt[8] to categorize the population; however, this only allowed us to identify subjects with frank alterations; who we anticipated might show developmental problems. With our z-score categorization, we once again extended the range from subtle to frank alteration, which shows it as an important indicator for predicting later developmental delay.

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