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Brainstem auditory-evoked responses among children afflicted by severely hypoxic CHD

F. Bernardo Pliego-Rivero[1], Keila Isaac-Olivé[2] and Gloria A. Otero[3]

[1]Laboratory of Neurochemistry, Universidad Autonoma del Estado de Mexico, Toluca, Mexico; [2]Laboratory of Theragnostics Research, Universidad Autonoma del Estado de Mexico, Toluca, Mexico and [3]Laboratory of Neurophysiology, Universidad Autonoma del Estado de Mexico, Toluca, Mexico

Original Article

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Author for correspondence:
Dr. Gloria A. Otero, Universidad Autonoma del Estado de Mexico, Toluca, 50000, Mexico.
Tel: + 52 722 350 8866.
Email: oeog45@gmail.com

Abstract

Main aim: To electrophysiologically determine the impact of moderate to severe chronic hypoxia (H) resulting from a wide array of CHD (HCHD) conditions on the integrity of brainstem function. *Materials and methods:* Applying brainstem auditory-evoked response methodology, 30 chronically afflicted HCHD patients, who already had undergone heart surgery, were compared to 28 healthy control children (1–15 yo) matched by age, gender and socioeconomic condition. Blood oxygen saturation was clinically determined and again immediately before brainstem auditory-evoked response testing. *Results:* Among HCHD children, auditory wave latencies (I, III and V) were significantly longer (medians: I, 2.02 ms; III, 4.12 ms, and; V, 6.30 ms) compared to control (medians: I, 1.67ms; III, 3.72 ms, and; V, 5.65 ms), as well as interpeak intervals (HCHD medians: I-V, 4.25 ms, and; III-V, 2.25ms; control medians: I-V, 3.90 ms and, III-V, 1.80 ms) without significant differences in wave amplitudes between groups. A statistically significant and inverse correlation between average blood oxygen saturation of each group (control, 94%; HCHD, 78%) and their respective wave latencies and interpeak intervals was found. *Conclusions:* As determined by brainstem auditory-evoked responses, young HCHD patients manifestly show severely altered neuronal conductivity in the auditory pathway strongly correlated with their hypoxic condition. These observations are strongly supported by different brainstem neurological and image studies showing that alterations, either in microstructure or function, result from the condition of chronic hypoxia in CHD. The non-altered wave amplitudes are indicative of relatively well-preserved neuronal relay nuclei.

Presently, the broadly diverse pathological spectrum of CHD constitutes the most common disorder at birth, estimated at 1% of live parturitions.[1] CHD includes dissimilar types of cardiac and great vessel pathologies. Although in the last decades the survival rate of afflicted children has increased significantly due to improvements in medical knowledge and technical expertise presently, however, the neurological co-morbidities typically associated with moderate and severe CHD conditions remain high.[2–4] Critically, this is due to the prevailing condition of generalised hypoxia among CHD patients (HCHD). In this sense, the low percentage of blood oxygen saturation has been highlighted as a determinant factor leading to developmental brain abnormalities and psychophysiological delays. Diverse neuroimaging studies, regardless of them having been carried out before or after surgical management, demonstrate a high incidence of neurological abnormalities,[4] including alterations in brain function, microstructure, and metabolism. As it is well-known among HCHD patients, the existence of moderate to severe deficiencies in oxygen supply[5–9] is a direct consequence of an altered systemic circulation, present this either along foetal or post-natal development and frequently continuously throughout.

This study was completed applying the electrophysiological technique of brainstem auditory-evoked responses under the hypothesis that the main contributing factor to developmental brain injury under HCHD and long-lasting abnormalities results directly from the major condition of chronically low blood oxygen saturation[5,7,10–20]. In this respect, one of the main features of HCHD is a severe and generalised decrease of metabolic activity[8,18,21–23] among patients well mirrored as an anomalous development of brain structure and function.

Materials and methods

Study subjects

The study included 30 paediatric patients (16 females/14 males) aged 1–15 years (average age, 8 years old) presenting severe HCHD (group HCHD) who attended the Paediatric Cardiology practice of Hospital for the Mother and Child (IMIEM), in Toluca City, State of Mexico. See Table 1 for the listing of cardiovascular pathologies and the number of cases of each. Before their inclusion in this study, all cases were diagnosed by clinical examination, including chest X-ray assessment, electrocardiogram, Doppler echocardiography, and angiotomography.

Table 1. Clinical diagnosis of CHD cases conforming group HCHD

Diagnosis	n
Tetralogy of Fallot	2
Patent ductus arteriosus, ventricular septal defect, overriding aorta	2
Truncus arteriosus	2
Pulmonary atresia, tricuspid atresia	5
Double outlet of right ventricle	4
Ventricular septal defect, pulmonary atresia	5
Pulmonary atresia	2
Hypoplastic right ventricle	3
Pulmonary hypertension, ventricular septal defect	3
Complete atrioventricular canal, unique atrium-ventricle valve	1
Common atrium, pulmonary hypertension, unique atrium-ventricle valve	1

N = number of cases; HCHD=hypoxic CHD.

A peer control group of 28 healthy children (1–15 years old; average age, 9 years old; 14 females /14 males) was collected from the same Hospital for the Mother and Child, matching group HCHD by gender and socioeconomic conditions. The Hospital for the Child, from where the sample of participating children was collected, only receives for attention children of ages between 0 and 17 years old belonging to low-income families without any other kind of social security protection. Social services from this hospital verify and certify that this condition is fulfilled to register any patient. Children participating in the control group were gathered from the Healthy Child Service who regularly attend the hospital for developmental follow-up. The inclusion criteria applied for both groups were born at term, not presenting a peri- or post-natal history of risk or actual damage to the CNS. This latter condition presented neither personally nor in the family clinical history record. Finally, no additional risk was imposed on participating children from attending these studies. All HCHD patients who attended this study had previously undergone palliative surgical treatment.

Electrophysiological procedures

Brainstem auditory-evoked responses were recorded with Ag/AgCl disc electrodes with the active one placed at Cz (+), that is, the vertex and the reference one at the mastoid apophysis. A ground electrode was placed mid-frontally at Fpz. Two channels were used for ipsilateral and contralateral recording with the impedance of all electrodes always kept at <5.0 kOhms. For every participant (control/HCHD), blood oxygen saturation was digitally determined (index finger) immediately before brainstem auditory-evoked response recording.

For those children of age under 4 years, the study was carried out in a state of physiological sleep, and for older children, inattentive wakefulness was required. Auditory stimulation was delivered through earphones under TDH 49 sound specifications which provided air rarefaction "click" sounds at a rate of 11 Hz for a duration of 0.1 ms and an intensity range (high/low) of 100-20 dB (HL). For brainstem auditory-evoked response recording, low (100 Hz) and high (3000 Hz) pass filters were used, each with 12,000X gain. To ensure the replicability of electrophysiological signals, at least 2 trials of 2000 stimuli each were performed.

Table 2. Interpeak latencies significant differences between groups (median test)

	Ctrls			HCDCs			
	25%	(50%) median	75%	25%	(50%) median	75%	P<
I-V	3.70	3.90	4.09	4.01	4.25	4.38	0.003
III-V	1.46	1.80	2.17	2.20	2.25	2.71	0.005

HCHC = hypoxic CHD; Ctrls = Controls.

Table 3. Spearman's correlation coefficient between blood oxygen saturation (SO_2) levels (%) and waves latencies (ms) and interpeak (Ip) intervals (ms) among HCHD cases

	Wave I latency	Wave III latency	Wave V latency	Ip I-V interval	Ip III-V interval
SO_2 correlation	−.847	−.612	−.859	−.593	−.538
p	<0.000	<0.002	<0.000	<0.002	<0.007

HCHD = hypoxic CHD; Ip = interpeak interval.

Statistical analysis

The latencies and amplitudes of the wave components I, III, and V were determined, as well as the length of their interpeak intervals (I-V and III-V). Wave latencies, wave amplitudes, and interpeak intervals were then compared between groups, HCHD versus control, using the median non-parametric test (median test). A Spearman correlation test was further applied to estimate the possible relationship between blood oxygen saturation and the brainstem auditory-evoked response variables determined.

Results

As clinically determined beforehand and as expected prior to brainstem auditory-evoked response recording, the blood oxygen saturation percentage median obtained for group HCHD was significantly lower than that of control participants (control, 94%; HCHD, 78%). Initially, the amplitudes of waves I, III, and V were compared between groups, and no significant differences were found. The latencies of these waves, however, were significantly longer among HCHD children compared to their peers in group control (Fig 1). Likewise, the comparison of interpeak intervals (I-V and III-V) between control and HCHD groups showed highly significant differences with those of HCHD participants substantially longer (see Table 2).

Investigating the possible correlation between the blood oxygen saturation mean of each group and their brainstem auditory-evoked response variables, a very significant and negative correlation was found both with the wave's latencies and their interpeak intervals (Table 3).

Discussion

Current advances in the diagnosis, surgical management, and postoperative care of children with HCHD have allowed the vast majority of them to reach adulthood.[1] Regrettably, however, in parallel to survival HCHD children are at high risk and typically suffer from neurodevelopmental disorders such as inattention, cognitive performance, and executive functions.[5,24,25] Due to the

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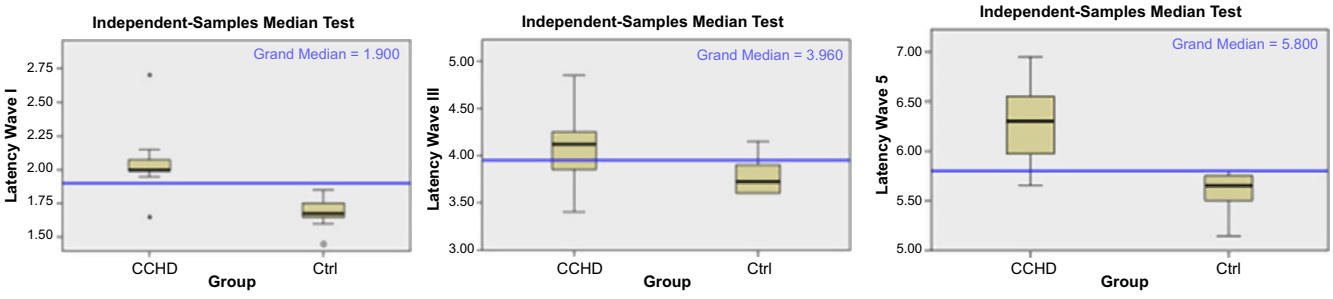

Median	1.900
Test Statistic	18.333
Degrees of Freedom	1
Asymptotic Sig. (2-sided test)	.000
Fisher Exact Sig. (2-sided test)	.000

Median	3.950
Test Statistic	6.600
Degrees of Freedom	1
Asymptotic Sig. (2-sided test)	.010
Fisher Exact Sig. (2-sided test)	.030

Median	5.800
Test Statistic	15.278
Degrees of Freedom	1
Asymptotic Sig. (2-sided test)	.000
Fisher Exact Sig. (2-sided test)	.000

Figure 1. Independent samples median test. Comparison of wave latencies (I, III, V) between groups, hypoxic congenital heart disease (HCHD) and control (Ctrl). The horizontal blue line indicates the grand median while the thick black stripe within each box is indicative of each wave latency's median. Below each graph the stadigraph data are presented.

underlying and pervasive condition of hypoxia, brain injuries continue developing with survival. Another observation made among HCHD newborns is that of a reduction in brain size. Taking the negative neurodevelopmental outcomes altogether, all of them have been strongly correlated to the condition of chronic and persistent hypoxia with this last condition resulting from a wide array of simple and complex cardiovascular pathologies. Among those, the foetal and post-natal systemic alterations are key in this respect.[6,10,14,26] The reduced body tissue oxygenation fundamentally alters basal metabolism concurrently leading to a general reduction of metabolic energy production. Following this argument, myelination as an end result of lipid synthesis is a biochemical event fundamentally dependent on the existence of adequate metabolic energy reserves. Thus, it is highly likely that the neurotransmission defects determined in this work among HCHD children in essence are the consequence of hypoxia[26] and the manifestation of altered myelination. In this respect, white matter injury is a common issue among preterm neonates and children stricken by HCHD. Histopathologically, in both instances, the lesions are strongly reminiscent of periventricular leukomalacia.[17,27] Using brainstem auditory-evoked responses as a clinical evaluation tool among children with hypoxic-ischaemic encephalopathy, Romero[28] assessed their neurodevelopmental status and neurophysiological profile at the ages of 6 months and later at 2 years. The brainstem auditory-evoked responses of those children showed extended latencies and decrements in amplitude indicating the presence of more extended neurological damage when comparing their results to ours. Jiang et al.[29] inform about evident brainstem auditory-evoked response abnormalities in 15 (40.5%) out of 37 children with neurodevelopmental deficits resulting from perinatal asphyxia. Both works[28,29] are in agreement in relation to the usefulness of brainstem auditory-evoked responses as a prognostic instrument of the neurodevelopmental outcome.

In the work presented here, the risk posed to cerebral functional integrity by HCHD was assessed through brainstem auditory-evoked responses. The children studied were compromised by a wide variety of severe cardiovascular conditions with all of them showing in common a severe reduction of blood oxygen saturation. There are different kinds of electrophysiological techniques based on the determination of evoked-response potentials and as brainstem auditory-evoked responses themselves; all of them are non-invasive instruments of great value in the assessment of sensory and neural function under normal or pathological conditions.[30] For instance, brainstem auditory-evoked responses have proved to be a valuable tool in the assessment not only of auditory function integrity but also in the prognosis of neurodevelopmental outcome after perinatal asphyxia,[29] also as a successful diagnostic and prognostic method in medical instances as dissimilar as the study of metabolic anomalies,[31] type-2 diabetes mellitus,[32] multiple sclerosis,[33] and others.

Brain stem myelination disturbances were determined among children who either died at birth or in the course of the first three years of life from severe chronic diseases, including congenital heart failure.[34] Among them, the rate of brain stem myelination indicated a disturbed process of maturation. Among those patients with CHD, it is highly likely that chronic hypoxia led to an altered synthesis of myelin sheaths, an event considered to arise independently of neuronal loss or damage. In the study presented here, the results and our point of view are in coincidence with those observations. That is, brainstem auditory-evoked responses of HCHD children showed significantly longer wave latencies and interpeak intervals compared to the control group indicative of altered electrical conduction in the auditory pathway between relay nuclei. As no significant differences in wave amplitudes were determined, this strongly suggests a considerable degree of neuronal cell body preservation. From an electrophysiological point of view, HCHD children present alterations of nerve conductance but not of signal processing; that is, there are defects along the auditory transmission pathway without evidence of gross damage in nuclei relay points, a fact strongly indicative of myelination defects. It is also well-known that neuronal integrity importantly depends on the trophic relationships between neurons and oligodendroglia, therefore if in parallel there is axonal damage this is highly likely to arise in parallel to myelin-forming cell impairment.[34–37]

Okutan and colleagues[38] investigated through brainstem auditory-evoked responses the impact of HCHD on brainstem

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maturation among 23 hypoxic and 22 non-hypoxic children of ages 2 months to 15 years and determined that neural activity was not altered among hypoxic patients compared to their healthy peers. In contrast, hypoxic patients under one year of age had a prolonged I–V interpeak latency, confirming that adequate oxygenation is critical for optimal development. At no other age did they find differences between groups; this is in contrast to our work. In the study presented here, HCHD children presenting severe hypoxia (median blood oxygen saturation, 76%) showed longer latencies of waves I, III, and V, and also longer intervals I-V and III-V at all ages. Sunaga et al.[39] reported similar findings working with hypoxic children of ages 1 to 4 years old. The works of Okutan et al.,[38] Sunaga et al.,[39] and this one all determined a statistically significant negative correlation between blood oxygen saturation average level with wave intervals and interpeak latencies (Table 3). In conclusion, chronic hypoxaemia among infants is a leading cause of brainstem alterations most likely related to a progressively altered process of myelination. This leads us to hypothesise that under generalised chronic hypoxia, the detrimental conditions may prevail in areas of the brain where an active post-natal development and myelination are taking place, for instance, in the cerebellum.[40]

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Conflicts of interest. None.

Ethical standards. This project was approved in advance by the Bioethics Committees of both the School of Medicine, State of Mexico Autonomous University (UAEMEX) and that of Hospital for the Child (IMIEM). Following the World Medical Association. Declaration of Helsinki, "*Ethical principles for medical research involving human subjects*"[41], the general idea of this study, its aims and procedures were verbally explained to parents and children older than eight years. This explanation included possible benefits, discomforts and risks to the child posed by the technical test procedures. Before starting, the following points were clarified to participants and their parents: 1) the study was absolutely confidential; 2) they could abandon the study at any time without penalties of any kind; 3) the results of the study would be delivered to them free of charge. All information was included in the written consent letter. This was signed by agreeing parents, children older than eight years, principal examiner and one independent witness.

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