International Journal of Pediatric Otorhinolaryngology 135 (2020) 110126

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Review Article

Audiological assessment of neonatal hyperbilirubinemia☆

Yasser Mohammad Mandour[a,*], Mohamed Aly El Sayed[a], Ashraf El sayed Morgan[b], Rehab Bassam[a], Hamada Fadl[a], Ahmed elrefae[a]

[a] Faculty of Medicine, Department of Otorhinolaryngology, Benha University, Benha Faculty of Medicine, Egypt
[b] Faculty of Medicine, Department of Audio Vestibular Medicine, Mansoura University, Mansoura Faculty of Medicine, Egypt

ARTICLE INFO

Keywords:
ABR
Hyperbilirubinemia
Neonate
Hearing loss

ABSTRACT

Object: To evaluate the hearing of infants with history of neonatal hyperbilirubinemia using ABR.
Methods: A prospective randomized study carried on 100 infants whose hearing was assessed by ABR. Infants were allocated into two groups; case group which involve 60 infants with history of neonatal hyperbilirubinemia (bilirubin more than17 mg/dl and less than 30 mg/dl) and control group involve 40 healthy infants. Each group was divided into 3 groups based on their age **i.e.** ≤ 6 months, > 6–9 months & > 9–12 months. The evaluated variables were latency time & inter peak latency time.
Results: The mean latencies of wave III&V of ABR were significantly higher in the case group compared with the controls ($P < 0.001$) while the mean latencies of wave I did not show a significant difference between the two study groups ($P > 0.05$). The mean inter wave latencies I-III, I–V& III-V of ABR were significantly higher in the case group compared with the controls. There was a negative correlation between age and the studied variables.
Conclusion: Hyperbilirubinemia have an adverse effect on neonatal hearing which was reflected by ABR parameters of this study.

1. Introduction

Hyperbilirubinemia is a common problem in newborns. It was manifested by yellowish discoloration of sclera, skin and mucous membrane. As bilirubin is lipid soluble, it could pass across the blood brain barrier and distribute in the brain [1] (see Table 3).

The indirect bilirubin, the main cause of neonatal jaundice, is strongly neurotoxic for underdevelopment neural system, especially when the indirect bilirubin concentration exceeds the albumin binding capacity. The phenomenon of deposited indirect bilirubin in basal ganglia as well as in the vestibule-cochlear nucleus causes a neurological syndrome called kernicterus as well as sensorineural hearing loss [2].

Up to 40% of neonates with jaundice are at risk of hearing loss [3].The most common causes of pathologic indirect hyperbilirubinemia are increased bilirubin production due to hemolytic diseases which includes immune-mediated hemolysis (ABO or Rh incompatibility), inherited red cell membrane defects (spherocytosis), erythrocyte enzymatic defects (G6PD) deficiency) and sepsis.Also hyperbilirubinemia can caused by decreased clearance (Crigler-Najjar and Gilbert's syndromes) and increased enterohepatic circulation such as breast feeding jaundice [4].

Auditory Brainstem Response **(ABR)** is a reliable and objective electrophysiological method for evaluating ascending auditory systems.It relies on recording the electrical activity of the auditory system that occurs in response to an appropriate acoustic stimulus [5].

In ABR, diagnosis is based on the evaluation of latencies of waves I, III & V and interwave latencies of I-III, I–V& III-V. ABR is the most sensitive test for detecting retrocochlear hearing loss [6].

ABR evaluates the important waves of the auditory pathways which include: wave I related to the primary part of the auditory nerve, near the cochlea, wave II related to the intracranial part of the eight nerves near the brain stem and cochlear nucleus and pons, wave III related to the superior olivary complex, wave IV related to the middle and superior parts of pons, wave V related to the lateral lemniscus above the pons and inferior lemniscus of the midbrain [7].

☆ We certify that we are the author of this article and all the data in this article not published elsewhere, We would like to publish this work in your respectable journal and transfer the copy write of this work to your respectable journal, We hope to accept this work to be published in your journal, We will work as corresponding author for this work and We will grantee to answer all your questions.

* Corresponding author.
E-mail addresses: ghader_massoud@yahoo.com (Y.M. Mandour), drmohamedalyelsayed@yahoo.com (M.A. El Sayed), ashraf_morgan75@yahool.com (A. El sayed Morgan), ghadeer_masoud@yahoo.com (R. Bassam), fadl_hamada@yahoo.com (H. Fadl), refae_ahmed@yahoo.com (A. elrefae).

https://doi.org/10.1016/j.ijporl.2020.110126
Received 10 March 2020; Received in revised form 15 May 2020; Accepted 15 May 2020
Available online 20 May 2020

1.1. Patients and methods

This study was carried out in Benha University Hospitals, Egypt, on 100 infants, from October 2018 to October 2019, Local ethical committee approval and Informed consent had been obtained before the onset of this study.

The inclusion criteria were; a history of healthy term delivery (more than 37 weeks old) or near term delivery (35–37 weeks old), average weight and with hyperbilirubinemia (bilirubin more than 17 mg/dl and less than 30 mg/dl).

Presences of neonatal hypoxia, intrauterine infections, sepsis or meningitis were not included in this study. In addition infant with a family history of hearing loss, low birth weight, ototoxic medication as aminoglycosides or congenital malformations were not included.

Totally, 100 infants (200 ears) were enrolled in the study. The case group included 60 healthy infants with history neonatal hyperbilirubinemia and the control group included 40 infants without history of neonatal hyperbilirubinemia.

A Routine otoscopic examination was performed to exclude conductive causes of hearing loss as wax impaction, chronic supportive otitis media or otitis media with effusion.

Both groups were referred to auditory outpatient clinic where tympanometry was done to exclude otitis media with effusion (type B) then ABR was done after preparation of each case. The baby was given Chloral hydrate syrup (50–100 mg/kg).

ABR was performed by one channel, Biologic pro-navigator machine. Both ears are tested in all infants. Three disk electrodes were placed at ipsilateral mastoid process (negative), contralateral mastoid process (positive) &middle forehead (ground).

The ABR parameters were taken into consideration at 90 dBnHL Intensityinclude absolute latency of wave I, III&V and interpeak intervals of waves (I-III), (I–V) & (III–V).

1.2. Statistical analysis

Categorical data were presented as number and percentages; Chi Square ($\chi 2$) was used to analyze them. Quantitative data were tested for normality using Shapiro-Wilks test assuming normality at $P > 0.05$. They proved to be normally distributed, so they were expressed as mean ± standard deviation and analyzed by one way analysis of variance (ANOVA), for 3 independent groups or Student "t" test for 2 independent groups. Correlations were assessed by Person's correlation coefficient (r). $P \leq 0.05$ was considered significant.

1.3. Results

100 infants in two groups were evaluated, the case group included 60 infants and there were 40 infants in the control group. Each group was divided into 3 groups based on their age **i.e.** ≤ 6 months, > 6–9 months & > 9–12 months. There was no significant statistical difference regarding age (Table 1).

The absolute latencies and inter peak intervals of different waves in cases and control groups (both right and left ear separately) are measured among group ≤ 6 months, 6–9 months & > 9–12.

There was no significant difference in mean values of absolute latency of wave I between control and case groups in right ear & left ear among different age groups ($P > 0.05$) {Table (2, 3&4)}.

Table 1
Comparing the studied groups regarding age.

			Groups		Total	χ^2& p value
			Cases	Controls		
Age	≤6 m	Count	19	15	34	50 &
		% within Groups	31.7%	37.5%	34.0%	0.78 (NS)
	> 6-9	Count	20	11	31	
		% within Groups	33.3%	27.5%	31.0%	
	> 9-12	Count	21	14	35	
		% within Groups	35.0%	35.0%	35.0%	
Total		Count	60	40	100	
		% within Groups	100.0%	100.0%	100.0%	

Table 2
Absolute Latency of wave I at 90 dBHL among age group ≤6 months.

	Ear	Group	Mean ± SD		P Value
I	R	Case	1.64	0.09	0.24
		Cont.	1.61	0.06	
	L	Case	1.65	0.08	0.41
		Cont.	1.63	0.04	

Table 3
Absolute Latency of wave I at 90 dBHL among age group > 6–9 months.

	Ear	Group	Mean ± SD		P Value
I	R	Case	1.57	0.048	0.066
		Cont.	1.61	0.071	
	L	Case	1.59	0.048	0.58
		Cont.	1.60	0.062	

1.4. Among age group ≤6 months (Table 5)

The mean latencies of wave III in right ears of the case groups (4.49 ± 0.22) was significantly higher than that of the control group (4.17 ± 0.16) ($P < 0.001$). The mean latencies of wave III in left ears of the case groups (4.48 ± 0.24) was significantly higher than that of the control group (4.16 ± 0.18) ($P < 0.001$).

The mean latencies of wave V in right ears of the case groups (7.04 ± 0.17) was significantly higher than that of the control group (6.34 ± 0.12) ($P < 0.001$). The mean latencies of wave V in left ears of the case groups (6.97 ± 0.28) was significantly higher than that of the control group (6.33 ± 0.11) ($P < 0.001$).

The mean inter peak intervals (IPI) of waves I-III of right ears of the case groups was (2.85 ± 0.216) and in control groups was (2.56 ± 0.137) ($P < 0001$), and the IPI of I-III of left ears of the case groups was(2.84 ± 0.184)and in control groups was (2.56 ± 0.134) ($P < 0.001$).

The mean inter peak intervals (IPI) of waves I–V of right ears of the case groups was (5.40 ± 0.206) and in control groups was (4.73 ± 0.113) ($P < 0001$), and the IPI of I–V of left ears of the case groups was(5.31 ± 0.250)and in control groups was (4.56 ± 0.531) ($P < 0.001$).

The mean inter peak intervals (IPI) of waves III-V of right ears of the case groups was (2.65 ± 0.461) and in control groups was (2.37 ± 0.113) ($P < 0001$), and the IPI of III-V of left ears of the case groups was(2.47 ± 0.198)and in control groups was (2.15 ± 0.131) ($P < 0.001$).

1.5. Among age group > 6–9 months (Table 6)

The mean latencies of wave III in right ears of the case groups (4.29 ± 0.063) was significantly higher than that of the control group

Table 4
Absolute Latency of wave I at 90 dBHL among age group > 9–12 months.

	Ear	Group	Mean ± SD		P Value
I	R	Case	1.58	0.07	0.88
		Cont.	1.57	0.07	
	L	Case	1.60	0.05	0.52
		Cont.	1.58	0.052	

Table 5
Latencies and inter peak intervals of various waves and inter wave latencies at 90 dBHL among age group ≤6 months.

	Ear	Group	Mean ± SD		P Value
III	R	Case	4.49	0.22	< 0.001
		Cont.	4.17	0.16	
	L	Case	4.48	0.24	< 0.001
		Cont.	4.16	0.18	
V	R	Case	7.04	0.17	< 0.001
		Cont.	6.34	0.12	
	L	Case	6.97	0.28	< 0.001
		Cont.	6.33	0.11	
I-III	R	Case	2.85	0.216	< 0.001
		Cont.	2.56	0.137	
	L	Case	2.84	0.184	< 0.001
		Cont.	2.56	0.134	
I–V	R	Case	5.40	0.206	< 0.001
		Cont.	4.73	0.113	
	L	Case	5.31	0.250	< 0.001
		Cont.	4.56	0.531	
III-V	R	Case	2.65	0.461	< 0.001
		Cont.	4.73	0.113	
	L	Case	2.47	0.198	< 0.001
		Cont.	2.15	0.131	

Table 6
Latencies and inter peak intervals of various waves and inter wave latencies at 90 dBHL among age group > 6–9 months.

	Ear	Group	Mean ± SD		P Value
III	R	Case	4.29	0.063	< 0.001
		Cont.	3.94	0.107	
	L	Case	4.31	0.068	< 0.001
		Cont.	4.03	0.192	
V	R	Case	6.81	0.095	< 0.001
		Cont.	5.98	0.094	
	L	Case	6.68	0.100	< 0.001
		Cont.	5.99	0.111	
I-III	R	Case	2.71	0.046	< 0.001
		Cont.	2.32	0.108	
	L	Case	2.73	0.059	< 0.001
		Cont.	2.36	0.120	
I–V	R	Case	5.24	0.071	< 0.001
		Cont.	4.33	0.127	
	L	Case	5.09	0.098	< 0.001
		Cont.	4.36	0.127	
III-V	R	Case	2.52	0.078	< 0.001
		Cont.	2.06	0.132	
	L	Case	2.36	0.077	< 0.001
		Cont.	2.04	0.151	

(3.94 ± 0.107) (P < 0.001). The mean latencies of wave III in left ears of the case groups (4.31 ± 0.068) was significantly higher than that of the control group (4.03 ± 0.192) (P < 0.001).

The mean latencies of wave V in right ears of the case groups (6.81 ± 0.095) was significantly higher than that of the control group (5.98 ± 0. 094) (P < 0.001). The mean latencies of wave V in left ears of the case groups (6.68 ± 0.100) was significantly higher than that of the control group (5.99 ± 0.111) (P < 0.001).

The mean inter peak intervals (IPI) of waves I-III of right ears of the case groups was (2.71 ± 0.046) and in control groups was (2.32 ± 0.108) (P < 0001), and the IPI of I-III of left ears of the case groups was(2.73 ± 0.059)and in control groups was (2.36 ± 0.120) (P < 0.001).

The mean inter peak intervals (IPI) of waves I–V of right ears of the case groups was (5.24 ± 0.071) and in control groups was (4.33 ± 0.127) (P < 0001), and the IPI of I–V of left ears of the case groups was(5.09 ± 0.098)and in control groups was (4.36 ± 0.127) (P < 0.001).

The mean inter peak intervals (IPI) of waves III-V of right ears of the case groups was (2.52 ± 0.078) and in control groups was (2.06 ± 0.132) (P < 0001), and the IPI of III-V of left ears of the case groups was(2.36 ± 0.077)and in control groups was (2.04 ± 0.151) (P < 0.001).

Table 7
Latencies and inter peak intervals of various waves and inter wave latencies at 90 dBHL among age group > 9–12 months.

	Ear	Group	Mean ± SD		P Value
III	R	Case	4.04	0.108	< 0.001
		Cont.	3.82	0.128	< 0.001
	L	Case	4.10	0.14	< 0.001
		Cont.	3.85	0.11	
V	R	Case	6.26	0.90	0.032
		Cont.	5.71	0.18	
	L	Case	6.35	0.14	< 0.001
		Cont.	5.79	0.18	
I-III	R	Case	2.48	0.144	< 0.001
		Cont.	2.24	0.142	
	L	Case	2.50	0.148	< 0.001
		Cont.	2.26	0.131	
I–V	R	Case	4.88	0.180	< 0.001
		Cont.	4.24	0.150	
	L	Case	4.75	0.154	< 0.001
		Cont.	4.27	0.177	
III-V	R	Case	2.38	0.098	< 0.001
		Cont.	2.01	0.149	
	L	Case	2.24	0.123	< 0.001
		Cont.	1.94	0.170	

1.6. Among age group > 9–12 months (Table 7)

The mean latencies of wave III in right ears of the case groups (4.04 ± 0.108) was significantly higher than that of the control group (3.82 ± 0.128) (P < 0.001). The mean latencies of wave III in left ears of the case groups (4.10 ± 0.14) was significantly higher than that of the control group (3.85 ± 0.11) (P < 0.001).

The mean latencies of wave V in right ears of the case groups (6.26 ± 0.90) was significantly higher than that of the control group (5.71 ± 0. 18) (P < 0.001). The mean latencies of wave V in left ears of the case groups (6.35 ± 0.14) was significantly higher than that of the control group (5.79 ± 0.18) (P < 0.001).

The mean inter peak intervals (IPI) of waves I-III of right ears of the case groups was (2.48 ± 0.144) and in control groups was (2.24 ± 0.142) (P < 0001), and the IPI of I-III of left ears of the case groups was(2.50 ± 0.148)and in control groups was (2.26 ± 0.131) (P < 0.001).

The mean inter peak intervals (IPI) of waves I–V of right ears of the case groups was (4.88 ± 0.180) and in control groups was (4.24 ± 0.150) (P < 0001), and the IPI of I–V of left ears of the case groups was(4.75 ± 0.154)and in control groups was (4.27 ± 0.177) (P < 0.001).

The mean inter peak intervals (IPI) of waves III-V of right ears of the case groups was (2.38 ± 0.098) and in control groups was (2.01 ± 0.149) (P < 0001), and the IPI of III-V of left ears of the case groups was(2.24 ± 0.13)and in control groups was (1.94 ± 0.170) (P < 0.001).

1.7. Among different study group

There was no significant correlation between bilirubin level and the studied variables (Table 8) and There was a negative correlation between age and the studied variables among cases group (P < 0.001) (Table 9).

Table 8
Correlation between total bilirubin and the studied variables among the cases group.

With		Total bilirubin			
		Right ear		Left ear	
		R	P	r	P
Wave I		−0.132	0.31	−0.176	0.17
Wave III		−0.093	0.47	−0.116	0.38
Wave V		−0.052	0.69	−0.069	0.60
I-III		−0.083	0.53	−0.058	0.66
III-V	0.07	0.59	0.052	0.69	
I–V	−0.03	0.82	−0.02	0.87	

Table 9
Correlation between age and the studied variables among the cases group.

With	Age (months)			
	Right ear		Left ear	
	R	P	R	P
Wave I	−0.354	0.006 (S)	−0.330	0.01 (S)
Wave III	−0.813	1. < 0.001 (HS)	−0.707	< 0.001 (HS)
Wave V	−0.513	< 0.001 (HS)	−0.836	< 0.001 (HS)
I-III	−0.710	< 0.001 (HS)	−0.705	< 0.001 (HS)
III-V	−0.389	0.002 (S)	−0.594	< 0.001 (HS)
I–V	−0.747	< 0.001 (HS)	−0.820	< 0.001 (HS)

2. Discussion

In spite of large developments of medicine in recent years, hyperbilirubinemia and its effects on sensory and motor systems is still a major problem [8].

Significant increase in unconjugated bilirubin in neonates makes bilirubin cross the blood brain barrier and induce acute encephalopathy [9].

The neonatal auditory system is very sensitive to high levels of bilirubin and can be affected in hyperbilirubinemia [9].

ABR has been an effective method of assessing the auditory pathway and brainstem function in newborns and infants [6].

It is well known that ABR have three waves I, III&V with latency values that have physiological and clinical importance, because change in latency values is indicative for disturbances in the auditory brainstem function [9].

Wave Iorginates from spiral ganglion cells of the auditory nerve that connected to the cochlea. Wave III and V are attributed to lower and upper brainstem areas, respectively [10].

In our study, absolute latencies of waves III & V are significantly prolonged in infants with hyperbilirubinemia than normal controls and there was not any significant difference in wave I absolute latency between both study groups.

These results coincide with **salehi et al., 2016** [9]who demonstrated that there was a significant increase in the absolute latencies of waves III and V, and nosignificant difference in wave I absolute latency.

On the other hand, **InSharma et al. 2006** [11]reported that the mean latencies including wave I absolute latency are prolonged.

Biochemical and physiological evidences introduce the synapses as the primary target for bilirubin effect. Synapses along the auditory brain stem pathway can be disturbed severely [9].This is supported by an increasing in I-III, I–V &III-V interpeak latencies which are found in this study.

In our study, the studied variables were seen progressively reduced as the age increased which is consistent with studies conducted by **Singhal et al., 2014** [12].

In accordance with previous studies [13] and based on our work, There was no association between serum total bilirubin concentrations and ABR results. In other words serum total bilirubin can't be used as a valid criterion for early predication of bilirubin induced encephalopathy.

However some studies such as those **singhal et al., 2014** [12]demonstrated thatthere is an effective relationship between the bilirubin level and ABR finding.

It must be noted that in this study, the infant didn't have any history of pathological process that could have affected ABR responses and the reversibility of auditory pathway damage following the treatment of hyperbilirubinemia couldn't be established.

3. Conclusion

Hyperbilirubinemia have an adverse effect on neonatal hearing, which was reflected on auditory brainstem response parameters of our study.

Results of this study underline the importance of ABR in evaluating the auditory system. ABR can be an efficient tool for monitoring the auditory brainstem pathway in infants who are at risk of neurotoxicity.

Ethics approval and consent to participate

Local ethical committee approval and Informed consent had been obtained before the onset of this study.

Consent for publication

Not applicable.

Availability of data and material

Data are available on request.

Funding

No external source of funding.

Declaration of competing interest

No conflict of interest and nothing to disclose.

References

[1] A. Maheshwari, W.A. Carlo, R.M. Kleigman, B.F. Stanton, N.F. Schor, J.W. Geme, IIIR.E. Behraman (Eds.), Digestive System Disorders, Saunders, Philadelphia, 2011.
[2] J.R. Gowen, W. Clarence, K.J. Marcdante, R.M. Kleigman, H.B. Jenson, R.E. Behraman (Eds.), Anemia and Hyperbilirubinemia, Saunders, Philadelphia, 2011.
[3] N.Y. Boo, M. Oakes, M.S. Lye, H. Said, Risk factors associated with hearing loss in term neonates with hyperbilirubinemia, J. Trop. Pediatr. 40 (1994) 194–197.
[4] K.S. Najib, F. Saki, F. Hemmati, S. Inaloo, Incidence, risk factors and causes of severe neonatal hyperbilirubinemia in the South of Iran (fars province), Iran. Red Crescent Med. J. 15 (3) (2013) 260–263.
[5] J.W. Hall, New Handbook of Auditory Evoked Responses: (1), Pearson, Boston, Mass, 2007.
[6] T. Okhravi, S.T. Eslami, A.H. Ahmadi, H. Nassirian, Najibpour, Evaluation of auditory brain stems evoked response in newborns with pathologic hyperbilirubinemia, Iran. Red Crescent Med. J. 17 (2) (2015) e18288.
[7] T.W. Picton, M.J. Taylor, S.A. Durieux, M.J. Aminoff (Ed.), Brainstem Auditory Evoked Potentials in Infants and Children, 6 ed., Elsevier, Philadelphia, 2012.
[8] S.A. Fakhim, M. Naderpoor, N. Shahidi, F. Basharhashemi, N. Nejati, S.H. Sakha, Study of prevalence and causes of hearing loss in high risk neonates admitted to neonatal ward and neonatal intensive care unit, IntAdv Otol 6 (2010) 365–370.
[9] N. Salehi, F. Bagheri, H. RamezaniFarkhani, Effects of hyperbilirubinemia on auditory brainstem response of neonates treated with phototherapy, Iranian journal of otorhinolaryngology 28 (84) (2016) 23–29.
[10] F. Rattay, S.M. Danner, Peak I of the human auditory brainstem response results from the somatic regions of type I spiral ganglion cells: evidence from computer modeling, Hear. Res. 315 (2014) 67–79.
[11] P. Sharma, N.P. Chhangani, K.R. Meena, R. Jora, N. Sharma, Gupta BD. Brainstem evoked response audiometry (BAER) in neonates with hyperbilirubinemia, Indian J.

Pediatr. 73 (5) (2006) 413–416.
[12] A. Singhal, T. Ojha, S. Kumar, P. Vyas, I. Goel, M. Chaudhary, N.S. Rathore, Exploration of early auditory effects of hyperbilirubinemia in neonates using BERA, International journal of medical science and education 1 (2014).
[13] M. Mohammadi, M.R. Ashrafi, R. Shabanian, Auditory brain stem response in hyperbilirubinemic newborns, Med. J. Islam. Repub. Iran 16 (2) (2002).