Auditory Brain- Stem Responses in Neonatal Hyperbilirubinemia and effect of therapy

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Abstract

Background: Neonatal hyperbilirubinemia is the most common condition that requires medical attention in newborns. 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. Currently, the most sensitive means of assessing neurotoxicity may be auditory brain stem evoked response (ABR), which shows the predictable early effects of bilirubin toxicity.

Aim: This study aims to determine the effect of neonatal hyperbilirubinemia on auditory brainstem response (ABR) and evaluate the effect of treatment of hyperbilirubinemia on ABR findings.

Subjects and Methods: This case-control study was performed on30 neonates with pathologic hyperbilirubinemia as the jaundiced group chosen from Neonatal Intensive Care Unit of AL Zahraa Hospital of Al-Azhar University and 20 healthy neonates as the control group chosen from Maternity department of the same hospital during the period from September, 2011 to August, 2012. ABR was performed on both groups. The evaluated variable factors were latency time, inter peak intervals time.

Results: The mean latencies of waves I, III and V of ABR were significantly higher in the pathologic hyperbilirubinemia group as compared with the controls and the mean interpeak intervals (IPI) of waves I-III, I-V and III-V of ABR were significantly higher in the pathologic hyperbilirubinemia group as compared with the controls. A total reversibility to normal thresholds (normal hearing) was displayed by 23 (77.00%) and 25 (83.30%) of jaundiced neonates in the right and left ears respectively, while the remaining 7 (23.00%) and 5 (16.70%) of jaundiced neonates displayed partial reversibility (mild to moderate hearing loss) in the right and left ears respectively ($p < 0.001$)

Conclusions: About 90% of neonates with pathologic hyperbilirubinemia demonstrate ABR changes. Most of these changes (about 77%) revert to normal early after therapy.

Keywords: Neonates; Bilirubin; Hyperbilirubinemia; Auditory Brain-Stem Response

دراسة استجابة جذع المخ فى حالات ارتفاع نسبة الصفراء فى الاطفال حديثى الولادة وتأثير العلاج

المقدمة: يعد ارتفاع نسبة الصفراء (اليرقان الوليدى) فى الاطفال حديثى الولادة هو من اكثر الأمراض شيوعا ويحتاج الى رعايه طبية. هى ظاهرة انتقالية حميدة ومؤقتة، ولكن ارتفاع نسبة الصفراء التى قد تصل إلى المستويات الخطرة هى التى تشكل تهديدا مباشرا بتلف فى المخ. ان ترسب مادة البيليروبين (المادة المسببة لليرقان الوليدي) فى بعض اجزاء المخ يتسبب فى حالات التأثر المخى الحاد بالبليروبين (كرنيكترس) وكذلك يؤدى الى تاثر الجهاز السمعي. يعتبر جهاز رسم السمع بالجهد المثار لقياس استجابة جذع المخ السمعية من اهم الادوات لتقيم حالات التأثر المخى بالبيليروبين.

الهدف: تهدف هذة الدراسة التى تقيم القدرات السمعيه للاطفال حديثى الولادة والمصابين بارتفاع نسبة الصفراء وتأثير العلاج عليهم.

المنهجيه: تمت هذه الدراسة على ٣٠ طفل يعانون من ارتفاع نسبه الصفراء (اليرقان الوليدي) كمجموعة الدراسة وقد تم اختيارهم من وحده الرعايه المركزة لحديثى الولادة بمستشفى الزهراء الجامعى بجامعة الازهر وأيضا ٢٠ طفل حديثى الولادة لا يعانون من اى مرض كمجموعة مقارنة وقد تم اختيارهم من قسم النساء والولادة بمستشفى الزهراء الجامعى بجامعة الازهر. وخضعت المجموعتين للفحوصات الاكلينيكيه والمعمليه الكاملة وتم اختبارهم لقياس استجابة جذع المخ السمعية قبل وبعد العلاج.

نتائج الدراسه: ٩٠% من حالات الاصابة بالصفراء اظهرت تغير فى نتائج الاختبار حيث اظهرت النتائج ان ١٩(٦٣,٣%) حاله كانوا يعانون من فقدان بسيط لمتوسط للسمع و٥ (٢٠%) حالات يعانون من فقدان شديد للسمع فى الأذن اليمنى و١٥ (٥٠%) حاله و٩ (٣٠%) حالات كانوا يعانون من فقدان بسيط لمتوسط للسمع وفقدان شديد للسمع فى الأذن اليسرى على التوالى قبل العلاج. معظم هذه التغيرات (٧٧%) عادت الى التحسن بعد العلاج مباشرة حيث اصبحت ٧ حالات فقط هى التى تعانى من فقدان بسيط لمتوسط للسمع فقط فى الاذن اليمنى و٥ حالات تعانى فقط من فقدان بسيط لمتوسط للسمع فى الأذن اليسرى. اى ان ضعف السمع نتيجة ارتفاع نسبه الصفراء فى الاطفال حديثة الولادة قابل للتحسن بعد العلاج.

Introduction:

Hyperbilirubinemia is the most common condition that requires medical attention in newborns. The yellow coloration of the skin and sclera in newborns with jaundice is the result of accumulation of unconjugated bilirubin. In most infants, unconjugated hyperbilirubinemia reflects a normal transitional phenomenon. However, in some infants, serum bilirubin levels may excessively raise, which can be cause for concern (Hansen, 2014).

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. Unconjugated bilirubin binds the phospholipids of neuronal plasma membranes as well as the phospholipids of subcellular organelles membrane, which leads to cell oxygen deprivation, energy metabolism impairment, and cell death. 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. Currently, the most sensitive means of assessing neurotoxicity may be auditory brain stem evoked response (ABR), which shows the predictable early effects of bilirubin toxicity (Thilo& Rosenberg, 2011).. Early diagnosis and treatment of hyperbilirubinemia is highly important for preventing hearing loss and all newborns with pathologic hyperbilirubinemia must be screened. ABR abnormalities may be transient in majority of patients (Okhravi et.al., 2015)

Objective:

This study aims to determine the effect of neonatal hyperbilirubinemia on auditory brainstem response (ABR) and evaluate the effect of treatment of hyperbilirubinemia on ABR findings.

Subjects And Methods

Subjects:

This case- control study was performed on 30 neonates with pathologic hyperbilirubinemia as the jaundiced group chosen from Neonatal Intensive Care Unit of AL Zahraa Hospital of Al- Azhar University and 20 healthy neonates as the control group chosen from Maternity department of the same hospital during the period from September, 2011 to August, 2012.

1. Control group or group of healthy neonates: This group included 20 neonates (40 ears were examined), 14 males and 6 females. Birth weight ranged from 2000 to 4000 grams.

   They were delivered normally or by cesarean section (CS) at the Maternity Department in Al Zahraa Hospital. They were not considered at risk of hearing impairment, according to the selected criteria of high risk registers (i.e., normal prenatal history, normal bilirubin level, and no history of craniofacial anomalies, congenital infections (TORCH), bacterial meningitis, prolonged mechanical ventilation for> 10 days or birth weight<1500 grams).

   All the newborns were examined by transcutaneous bilirubin technique and auditory brainstem response (ABR) audiometry between 1st and 7th day of life.
2. Group of neonates with hyperbilirubinemia: It included 30 neonates (60 ears were examined), 13 males and 17 females, selected from the Neonatal Intensive Care Unit (NICU) of Al Zahraa Hospital.
   a. Inclusion Criteria:
      - Full term, appropriate for date neonates (Gestational age> 37weeks) and near term neonates (Gestational age 35- 37weeks) based on New Ballard Score (Ballard et.al., 1991) with uncomplicated birth history.
      - Bilirubin level>13mg/dl.
      - Rh incompatibility and fetomaternal blood group incompatibility.
      - Onset of jaundice before 24 hours of age.
      - History of previous sibling with significant hyperbilirubinemia.
      - Infant of diabetic mother.

   b. Exclusion criteria:
      - Low apgar scores of0- 4 at 1 min. or0- 6 at 5 mins.
      - Birth weight less than 1500 grams.
      - Conjugated Hyperbilirubineamia.
      - Congenital infections such as toxoplasmosis, rubella, cytomegalovirus, syphilis, and herpes simplex (TORCSH).
      - Bacterial Meningitis.
      - Neonatal Sepsis.
      - Birth Asphyxia.
      - Mechanical ventilation lasting>or= 5 days
      - Family history of hereditary childhood sensorineural hearing loss.
      - Craniofacial Abnormalities.
      - Syndromes associated with hearing loss as: Waardenberg Syndrome, Pendred Syndrome, and Usher Syndrome.

Methods:

- All studied newborn infants were subjected to full medical history, through clinical examination and investigations.
- Auditory brain stem responses ABR test measures the electroencephalographic waves generated by the auditory system in response to clicks via three electrodes placed on the infant's scalp.

  Timing of ABR: It will be carried out in two phases:
  1. Phase 1: ABR examination will be carried out within 24 hrs of the diagnosis of hyperbilirubinemia.
  2. Phase 2: repeat examination will be done when total serum bilirubin came down to< 13 mg/dL with treatment.
- Ethical Considerations: according to the Institutions' Ethical Committee.
- Statistical analysis: using spss (statistical package for social science) version12

Results:

Of 50 newborns that met the enrolment criteria and participated in the study, the case group included 30 newborns (13 males and 17 females) and there were 20 newborns (14 males and 6 females) in the control group. In the case group, the mean age of newborns was 3.97± 3.28 days.

- There was no significant statistical difference regarding gender, postnatal age, gestational age, type of delivery, feeding, anthropometric measurements and vital signs between the two groups. The average total serum bilirubin level (TSB) was 22.35± 3.72 and 10.57± 1.55 mg/dL before and after the phototherapy, respectively in the case group.
- The mean latencies of waves I, III and V of ABR were significantly higher in the pathologic hyperbilirubinemia group compared with the control group.
- The mean interpeak intervals (IPI) I- III, I- V and III- V of ABR waves were significantly higher in the pathologic hyperbilirubinemia group compared with the control group.

Table (1) Comparison between jaundiced group and control group regarding absolute and interpeak latencies before treatment

Absolut& Interpeak Latencies		Control Group		Jaundiced Group		Independent T- Test	
		Mean±	SD	Mean±	SD	t	P- Value
Right	I (Ms)	1.54	0.13	1.84	0.30	4.103	0.002
	III (Ms)	3.68	0.28	4.41	0.28	8.245	0.000
	V (Ms)	5.86	0.40	7.01	0.52	7.839	0.000
	I- III (ms)	2.14	0.24	2.57	0.41	4.048	0.002
	III- V (ms)	2.18	0.34	2.46	0.28	2.843	0.007
	I- V (ms)	4.32	0.37	5.03	0.17	7.798	0.000
	V At 40 Db	7.33	0.46	8.06	0.79	3.571	0.001
Left	I (Ms)	1.64	0.15	1.85	0.32	2.657	0.011
	III (Ms)	4.09	0.29	4.41	0.41	2.850	0.007
	V (Ms)	6.32	0.38	6.85	0.67	3.077	0.004
	I- III (ms)	2.45	0.25	3.00	0.43	4.945	0.000
	III- V (ms)	2.23	0.32	2.58	0.39	3.101	0.004
	I- V (ms)	4.68	0.41	5.03	0.50	2.421	0.020
	V At 40 Db	7.61	0.47	8.32	0.23	6.068	0.000

This table shows that there is a highly statistically significant difference between jaundiced group and control group in absolute and interpeak latencies before treatment in the right and left ear.

Table (2) Comparison between jaundiced group and control group regarding wave morphology before treatment

Wave Morphology			Control Group		Jaundiced Group		Chi- Square Test	
			No.	%	No.	%	X^2	P- Value
Right	I	Well Defined	15	75.0%	4	13.3%	24.022	0.000
		Ill Defined	5	25.0%	8	26.7%		
		Absent Wave	0	0.0%	18	60.0%		
	III	Well Defined	15	75.0%	4	13.3%	22.953	0.000
		Ill Defined	5	25.0%	10	33.3%		
		Absent Wave	0	0.0%	16	53.3%		
	V	Well Defined	16	80.0%	3	10.0%	26.316	0.000
		Ill Defined	4	20.0%	15	50.0%		
		Absent Wave	0	0.0%	12	40.0%		
	V At 40 Db	Well Defined	15	75.0%	3	10.0%	31.771	0.000
		Ill Defined	5	25.0%	3	10.0%		
		Absent Wave	0	0.0%	24	80.0%		
Left	I	Well Defined	16	80.0%	4	13.3%	23.704	0.000
		Ill Defined	4	20.0%	14	46.7%		
		Absent Wave	0	0.0%	12	40.0%		
	III	Well Defined	15	75.0%	3	10.0%	25.694	0.000
		Ill Defined	5	25.0%	10	33.3%		
		Absent Wave	0	0.0%	17	56.7%		
	V	Well Defined	16	80.0%	4	13.3%	23.333	0.000
		Ill Defined	4	20.0%	16	53.3%		
		Absent Wave	0	0.0%	10	33.3%		
	V At 40 Db	Well Defined	17	85.0%	3	10.0%	33.125	0.000
		Ill Defined	3	15.0%	3	10.0%		
		Absent Wave	0	0.0%	24	80.0%		

There is a highly statistically significant difference between jaundiced group and control group in all categories of wave morphology in right& left ear before treatment.

Table (3) Comparison between jaundiced group and control group regarding hearing threshold before treatment

Hearing Threshold			Control Group		Patients Group		Chi- Square Test	
			No.	%	No.	%	X^2	P- Value
Before Ttt	RT. Ear	Normal Hearing	20	100.00%	5	16.70%	33.333	0.000
		Mild To Moderate Hearing Loss	0	0.00%	19	63.30%		
		Severe To Profound Hearing Loss	0	0.00%	19	63.30%		
	LT. Ear	Normal Hearing	20	100.00%	6	20.00%	30.769	0.000
		Mild To Moderate Hearing Loss	0	0.00%	19	63.30%		
		Severe To Profound Hearing Loss	0	0.00%	19	63.30%		

There is a highly statistically significant difference between jaundiced group and control group regarding hearing threshold before treatment in both ears.

Table (4) Comparison between jaundiced group before and after treatmentregarding absolute and interpeak latencies

Absolut& Interpeak Latencies Before Treatment		Before		After		Independent T- Test	
		Mean	±Sd	Mean	±Sd	t	P- Value
Right	I (Ms)	1.84	0.30	1.63	0.23	3.043	0.004
	III (Ms)	4.41	0.28	3.81	0.24	8.911	0.000
	V (Ms)	7.01	0.52	6.01	0.35	8.738	0.000
	I- III (ms)	2.57	0.41	2.18	0.29	4.254	0.000
	III- V (ms)	2.46	0.28	2.2	0.34	3.233	0.002
	I- V (ms)	5.03	0.17	4.38	0.40	8.191	0.000
	V At 40 Db	8.06	0.79	7.58	0.34	3.057	0.003
Left	I (Ms)	1.85	0.32	1.55	0.17	4.534	0.000
	III (Ms)	4.41	0.41	4.26	0.29	4.362	0.000
	V (Ms)	6.85	0.67	6.43	0.41	2.929	0.005
	I- III (ms)	2.65	0.43	2.71	0.42	2.643	0.010
	III- V (ms)	2.44	0.39	2.17	0.42	2.962	0.004
	I- V (ms)	5.00	0.50	4.88	0.53	2.847	0.006
	V At 40 Db	8.32	0.23	7.97	0.49	3.542	0.001

This table shows that there is a highly statistically significant difference between jaundiced group before and after treatment in all absolute and interpeak latencies in the right and left ears.

Table (5) Comparison between jaundiced group before and after treatment regarding wave morphology

Wave Morphology			Before		After		Chi- Square Test	
			No.	%	No.	%	X^2	P- Value
Right	I	Well Defined	4	13.3%	21	70.0%	29.619	0.000
		Ill Defined	8	26.7%	9	30.0%		
		Absent Wave	18	60.0%	0	0.0%		
	III	Well Defined	4	13.3%	21	70.0%	22.978	0.000
		Ill Defined	10	33.3%	7	23.3%		
		Absent Wave	16	53.3%	2	6.7%		
	V	Well Defined	3	10.0%	19	63.3%	24.252	0.000
		Ill Defined	15	50.0%	11	36.7%		
		Absent Wave	12	40.0%	0	0.0%		
	V At 40 Db	Well Defined	3	10.0%	14	46.7%	21.687	0.000
		Ill Defined	3	10.0%	10	33.3%		
		Absent Wave	24	80.0%	6	20. %		
Left	I	Well Defined	4	13.3%	21	70.0%	24.647	0.000
		Ill Defined	14	46.7%	9	30.0%		
		Absent Wave	12	40.0%	0	0.0%		
	III	Well Defined	3	10.0%	21	70.0%	27.944	0.000
		Ill Defined	10	33.3%	8	26.7%		
		Absent Wave	17	56.7%	1	3.3%		
	V	Well Defined	4	13.3%	23	76.7%	26.892	0.000

Wave Morphology		Before		After		Chi- Square Test	
		No.	%	No.	%	X^2	P- Value
V At 40 Db	Ill Defined	16	53.3%	7	23.3%	24.218	0.000
	Absent Wave	10	33.3%	0	0.0%		
	Well Defined	3	10.0%	15	50.0%		
	Ill Defined	3	10.0%	10	33.3%		
	Absent Wave	24	80.0%	5	16.7%		

This table shows that there is a highly statistically significant difference between jaundiced group before and after treatment regarding wave morphology (marked improvement is noticed in wave's identifiability).

Table (6) Comparison between jaundiced group before and after treatment regarding hearing threshold

Hearing Threshold		Before		After		Chi- Square Test	
		No.	%	No.	%	X^2	P- Value
RT. Ear	Normal Hearing	5	16.70%	23	76.00%	23.111	<0.001
	Mild To Moderate Hearing Loss	19	63.30%	7	23.00%		
	Severe To Profound Hearing Loss	6	20.00%	0	00.00%		
LT. Ear	Normal Hearing	6	20.0%	25	83.30%	25.645	<0.001
	Mild To Moderate Hearing Loss	15	50.0%	5	16.70%		
	Severe To Profound Hearing Loss	9	30.0%	0	0.00%		

This table shows that there is a highly statistically significant difference between jaundiced group before and after treatment regarding hearing threshold (marked improvement of hearing is noticed).

Discussion:

Hyperbilirubinemia is a common problem and one of the most important problems in newborns (Okhravi et.al., 2015). ABR has been an effective method of assessing the auditory pathway and brainstem function in newborns and infants, recently recognized as a useful diagnostic tool in newborns (Picton et.al., 2012). In the present study, according to the results of ABR, latencies of almost all the waves and intervals were significantly prolonged in jaundiced neonatal group compared with healthy control group, The mean latency time of ABR waves I, III, V and the mean latency time of waves V at 40 dB in right and left ears were significantly higher in the studied group than that of the control group (P< 0.01). Also the mean inter- peak- interval (IPI) time of waves I- III, III- V, I- V in right and left ears of the studied group were significantly higher than that in control group (P<0.01) Table (1). The results of the present study were in agreement with the studies done by Okhravi et.al. (2015), Sobhy et.al. (2015), Liang and Xie (2011), Baradaranfar et.al. (2011), Saluja et.al,. (2010), Jiang et.al., 2007), Sharma et.al. (2006) and EL Meneza et.al. (2005).

Also in the present study a comparison was done between jaundiced neonates group before and after treatment regarding absolute and inter- peak latencies, waves morphology, and hearing threshold Tables (4, 5, 6). The results of this comparison revealed that, most of the ABR tests showed a marked improvement in the mean latency time of waves I, III, V, wave V at 40 dB and the mean inter- peak- intervals (IPI) of waves I- III, III- V, I- V of ABR in right and left ears of the studied jaundiced group after treatment (p< 0.001) Table (4) which indicate an improvement of transmission time in the brainstem. Also a marked improvement in waves identifiability was noticed in waves I, III, V, and wave V at 40 dB in both right and left ears as regarding waves morphology (p= 0.000) Table (5). Also hearing threshold was considered in this comparison as the presence of wave V in ABR with the minimum stimulus intensity which indicate a marked improvement in hearing where, total reversibility to normal thresholds (normal hearing) was displayed by 23 (77.00%) and 25 (83.30%) of jaundiced neonates in the right and left ears respectively, while the remaining 7 (23.00%) and 5 (16.70%) of jaundiced neonates displayed partial reversibility (mild to moderate hearing loss) in the right and left ears respectively (p< 0.001) Table (6). These results of the comparison were in agreement with Sobhy et.al. (2015), Wong et.al. (2006) and Sharma et.al. (2006).

Conclusions:

About 90% of neonates with pathologic hyperbilirubinemia demonstrate ABR changes. Most of these changes (about 77%) revert to normal early after therapy, indicating need for aggressive therapy in this subgroup of neonates.

References:

1. Ballard JK, Khoury JC, Wedig, et.al (1991): New Ballard Score expanded to include extremely premature infants. **J Pediatr**; 119:417.
2. Baradaranfar MH, Atighechi S, Dadgarnia MH, et.al. (2011) Hearing status in neonatal hyperbilirubinemia by auditory brain stem evoked response and transient evoked otoacoustic emission. **Acta Med Iran**. 49 (2):1 09- 12.
3. ElMeneza SA, ElMosely M, Tantawy SM. (2005): Study of Brain- Stem Evoked Responses Among The Newborn Infants Admitted To NICU. **M.Sc. Degree in Pediatrics** (6); 90- 95.
4. Hansen TW, Wagner CL, Carter BS, et.al (2014). **Neonatal Jaundice**. Medscape: Drugs, Diseases& Procedures.
5. Jiang ZD, Chen C, Liu TT, et.al. (2007). Changes in brainstem auditory evoked response latencies in term neonates with hyperbilirubinemia. **Pediatr Neurol**. ; 37 (1):3 5- 41.
6. Liang Y and Xie XM (2011). **Characteristics of auditory brain stem response in neonatal hyperbilirubinemia induced by different causes**. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. ; 46 (3):1 90- 4.
7. Okhravi T, Eslami ST, Ahmadi AH, et.al (2015). Evaluation of Auditory Brain Stems Evoked Response in Newborns with Pathologic Hyperbilirubinemia. **Iran Red Crescent Med J.** 17 (2): e18288.
8. Picton TW, Taylor MJ, Durieux SA (2012). **Brainstem Auditory Evoked Potentials in Infants and Children.** 6 ed. Aminoff MJ editor. Philadelphia: Elsevier.
9. Saluja S, Agarwal A, Kler N, et.al (2010). Auditory neuropathy spectrum disorder in late preterm and term infants with severe jaundice. **Int. J. Pediatr Otorhinolaryngol**. 74 (11):1 292- 7. 10.
10. Sharma P, Chhangani NP, Meena KR, (2006). Brainstem evoked response audiometry (BAER) in neonates with hyperbilirubinemia. **Indian J Pediatr**. 73 (5):4 13- 6. 11.
11. Sobhy OA, Asal S, Ragab F. (2015). Study of reversibility of auditory brainstem abnormalities in infants with high risk for hearing loss. **Egyptian Journal of Ear, Nose, Throat and Allied Sciences** 16, 75- 79.
12. Thilo EH and Rosenberg AA (2011). **The Newborn Infant. 20th ed. Hay** WW, Levin MJ, Sondheimer JM, Deterding RR editors. United States of America: McGraw-Hill Company.