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Original Article

Automated Auditory Brainstem Response in Neonates with Exchange Transfusion Indirect Hyperbilirubinemia Levels

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Abstract:

Background: Neonatal hyperbilirubinemia maybe complicated by severe neurologic disability including hearing impairment (HI). There is no agreement on the precise bilirubin level that may cause auditory affection.

Aim of the work: to study the frequency of HI in neonates with indirect hyperbilirubinemia threshold for exchange transfusion (ET).

Patients and Methods: This cross-sectional analytical study enrolled full-term neonates whose bilirubin levels were at the ET threshold managed by intensive phototherapy (IP) or ET. Automated auditory brainstem response (AABR) was performed within 24 hours of admission using audiometer among both groups.

Results: This study included 98 full-term neonates. Forty-eight (49 %) were males and 50 (51%) were females. Their mean gestational age was 37.78±0.74 weeks. Forty-six (46.9%) neonates underwent ET while 52 (53%) improved on IP with the rapid decline of their bilirubin levels and did not undergo ET. The mean IP group bilirubin-induced neurologic dysfunction (BIND) score was 0, and reticulocyte count was 7.12±6.49% compared to 1.89±2.16 and 11.47±9.82% of ET group (p=0.001) and (p=0.004) respectively. Abnormal AABR was detected in 23 (23.5%) neonates; 8 had unilateral hearing impairment while 15 had bilateral hearing impairment. IP was associated with less HI in both ears in 3 (5.7%) compared to 12 (26.1%) who underwent ET (p=0.005). Neonates with any HI had higher total serum bilirubin (TSB) levels (p= 0.002) and BIND scores (p= 0.002). IP was associated with less (one or both ears) HI in 8 (15.3%) neonates compared to 15 (32.6%) who underwent ET (p=0.045). A TSB cut-off value of 24.5 mg/dl showed a sensitivity of 60.9% and a specificity of 81.3% while a BIND score cut-off value of ≥ 2 showed a sensitivity of 47.8% and a specificity of 86.7% for detecting any hearing impairment. Males had a higher risk for bilateral hearing impairment (p= 0.040).

Conclusion: Neonates with higher bilirubin levels and BIND scores are at risk for HI. TSB and BIND score have modest sensitivity and specificity in predicting HI. IP is mandatory in all those with ET threshold bilirubin until procurement of blood to prevent HI. HI may occur despite normal BIND scores in the absence of bilirubin encephalopathy. Those who responded to IP for ET level of TSB had less frequency of HI. Males were more at risk for bilateral HI. Screening for HI among neonates who sustain hyperbilirubinemia is a necessity.

Level of Evidence of Study: IV (*1*)**.**

Keywords: Automated auditory brainstem response; AABR; bilirubin-induced neurologic dysfunction; BIND score; exchange transfusion; neonatal hyperbilirubinemia; intensive phototherapy

Abbreviations: AABR: Automated auditory brainstem response; ABE: acute bilirubin encephalopathy; AUC: area under the curve; BIND: bilirubin-induced neurologic dysfunction; CI: confidence interval; ET: exchange transfusion; Hb: hemoglobin; HI: Hearing impairment; IP: intensive phototherapy; NICU: Neonatal intensive care unit; ROC: receiver operating characteristic; SD: standard deviation; TSB: total serum bilirubin

Introduction

Neonatal hyperbilirubinemia is a common clinical condition that occurs during the early newborn period. It is common in 50%-60% of neonates in their first week of life (*2*). Severe hyperbilirubinemia can be harmful to central nervous system development, resulting in

behavioral and neurological dysfunction. Auditory pathways are vulnerable parts of the nervous system to the toxic effects of bilirubin (*3*). Neonatal jaundice is one of the important risk factors of early acquired sensorineural hearing impairment in developing countries. Bilirubin can pass the blood-brain barrier and accumulate in the auditory nuclei (*4*). However, the exact mechanism of bilirubin-induced auditory affection is unclear (*5*). Furthermore, there is no agreement on the precise bilirubin level that may cause auditory affection (*6*). The management plan for neonatal jaundice may include conservative phototherapy or blood exchange transfusion (ET). The choice depends on specific curves related to the total serum bilirubin level, gestational age, and post-natal age (*7*). All neonates with bilirubin levels meeting the criteria for exchange transfusion (ET) should undergo intensive phototherapy (IP) while preparing for ET (*8*).

The automated auditory brainstem response (AABR) is one of the screening tests used to detect hearing loss and is a useful tool in the care of infants with hyperbilirubinemia since it can detect early auditory damage (*9*). This cross-sectional analytical study enrolled full-term neonates whose bilirubin levels were at the ET threshold managed by intensive phototherapy (IP) or ET. AABR was performed within 24 hours of admission using audiometer among both groups.

Subjects and Methods

This cross-sectional analytical study was carried out in the Neonatal intensive care unit (NICU) of Cairo University Children's Hospital. The study was approved by Cairo University's Research Ethics Committee (Approval Number MS-359-2021). The neonates' guardians provided informed consent.

Participants

The study included full-term neonates (≥37 weeks) with indirect hyperbilirubinemia necessitating ET according to the American Academy of Pediatrics guidelines (*7*, *10*). Neonates with major congenital anomalies, craniofacial anomalies, family history of hearing impairment, maternal history of TORCH infection, rash or fever during pregnancy, those who received ototoxic drugs as aminoglycosides, or who have any disease other than jaundice were excluded from the study.

Methods

Maternal and neonatal data were documented including mode of delivery, onset of jaundice, and neonatal anthropometric measurements. They all underwent assessment of serum total and direct bilirubin. Those with ET levels were offered intensive phototherapy until blood group matched blood was procured. If bilirubin declined to non-exchange levels and they had no signs of bilirubin encephalopathy they continued on IP, and if not they underwent ET once the blood was available. BIND scores were assessed to detect signs of acute bilirubin encephalopathy (*11*). It included an assessment of 3 variables: mental status, muscle tone, and cry pattern. Zero score was assigned to normal, and up to a maximum of 3 for maximum abnormality of each variable. Mental status was graded into 1: sleepy, poor feeding, 2: lethargy, irritable, jittery and 3: apnea, unable to feed, seizures, coma. Muscle tone was graded into 1: hypertonia alternating with hypotonia, 2: neck stiffness, flexor spasm, beginning of neck and back arching, hypertonia, and 3: persistent retrocollis and opisthotonos, bicycling, twitching of hands and feet, fisting, severe hypotonia with limp posture. Cry pattern score was coined to: 1) high-pitched cry; 2) shrill cry even if intermittent and 3) weak or absent cry/inconsolable cry.

Laboratory data (CBC, serum bilirubin levels, reticulocyte count, and Coombs test) were documented. The duration of phototherapy and timing of ET were documented. Automated auditory brainstem response (AABR) was performed after ET in the exchange group or 24 hours after the initiation of IP in the phototherapy group using Sera TM version 1.2 Interacoustics A/S, Audiometer (Allé 1, 5500 Middelfart, Denmark). The test was conducted in a quiet environment. After napping, the neonate's skin was cleaned before applying a conductive gel and placing the electrodes on mastoid processes and the front of the face. This was followed by placing a small and lightweight probe with a smooth surface into the ears of the baby and then pressing the test button. Monaural stimuli (35 dBnHL CE-CHIRP filtered at 100-3000Hz). The stimulus frequency was 45.1 chirps per second. To confirm the wave reproduction, 1024 clicks were recorded using a 15 milliseconds analysis time. Results were displayed on the screen in less than 30 seconds with either "refer" or "pass". Neonates with hearing impairment were referred to the audiology

department for follow-up. Audiometry results were compared among those who responded to intensive phototherapy and those who underwent exchange transfusion.

Statistical Analysis

Data were coded and put into SPSS version 28 (IBM Corp., Armonk, NY, USA). Quantitative data was summarized using mean, standard deviation (SD), median, minimum, and maximum, while categorical data was summarized using frequency (count) and relative frequency (%). Quantitative variables were compared using the non-parametric Mann- Whitney test. To compare categorical data, the Chi-square x^2 test was used. When the anticipated frequency is less than 5, we applied the exact test instead. A receiver operating characteristic (ROC) curve was created, and the area under curve analysis was used to determine the optimal cut-off value of serum bilirubin and BIND score for detecting hearing impairment. P-values < 0.05 were considered statistically significant.

Results

This study included 98 full-term neonates. Forty-eight (49 %) were males and 50 (51%) were females. Demographic and laboratory data of the studied neonates are seen in Table 1. Forty-six neonates underwent ET while 52 improved on IP with the rapid decline of their bilirubin levels therefore they did not undergo the procedure. (Table 2). Twenty-three (23.5%) neonates had hearing impairment; 8 had unilateral hearing impairment while 15 had bilateral hearing impairment.

Table 1. Demographic and laboratory data of the studied neonates.

	Mean± Standard deviation	Range
Age at admission (days)	4.56±3.47	(1-25)
Gestational age (weeks)	37.78±0.74	(37-40)
Birth weight (kg)	2.85±0.38	(1.6-3.8)
BIND score on admission	0.89±1.75	(0-8)
Hb (gm/dl)	14.5±2.6	(9.3-20.6)
TSB on admission (mg/dl)	22.4±8.288	(8.7-41.2)
Reticulocyte count (%)	9.16±8.47	(0.1-47)

Hb: hemoglobin, TSB: total serum bilirubin.

Table 2. Clinical Characteristics of the neonates who underwent exchange transfusion and those who improved on intensive phototherapy

		Exchange Transfusion group (N=46)			**Intensive Phototherapy** (N=52)			
		Mean± SD	Median	Range	Mean± SD	Median	Range	P value
Gestational age (weeks)		37.8±0.73	38.00	37-39	37.7±0.76	38.00	37-40	0.724
Birth weight (kg)		2.80±0.38	2.74	2.05-3.8	2.89±0.38	2.90	1.6-3.8	0.054
Age of onset of Jaundice (days)		2.5±3.13	2	1-21	2.65±2.6	2	1-8	0.033
Age on admission (days)		4.35±4.04	4.00	1-25	4.75±2.90	4.00	1-17	0.139
BIND score		1.89±1	1.00	0-8	0	0	0	0.001
Total serum bilirubin (mg/dl)		22.4±8.38	21.60	8.70-49.9	21.2±3.61	20.90	10.4-3	0.613
Reticulocyte count (%)		11.5±9.82	9.50	0.10-47.0	7.12±6.49	5.30	0.10-22	0.004
		Number		%	Number		%	
Sex	Male	19		41	29		56	
	Female	27		59	23		44	0.153
Coomb's test	Positive	6		13	8		15	0.741
	Negative	40		87	44		85	
Hearing loss	None	31		67.4	44		85	
	1 ear	3		6.5	5		9.6	0.005
	2 ears	12		26	3		6	
	Any hearing loss	15		33	8		15	
Affected right Ear		15		33	8		15	0.007
Affected left Ear		12		26	3		6	

BIND: bilirubin-induced neurologic dysfunction.

Neonates who underwent ET were more at risk for one or bilateral hearing impairment (p=0.045 and p= 0.005 respectively). (Tables 2 and 3). Males were more at risk for bilateral but not unilateral hearing impairment (p= 0.04). There was no statistically significant difference between the two groups regarding serum bilirubin levels (p= 0.613). However, the ET group had statistically significantly higher BIND scores (p= 0.001), reticulocyte count (p= 0.004) and statistically significantly younger age at the onset of jaundice (p= 0.033). Neonates with one or bilateral hearing impairment had higher admission bilirubin levels (p= 0.002 and p=0.012 respectively) and BIND scores (p= 0.002 and p=0.001).

Table 3. Comparison between neonates with and without any hearing impairment

		Neonates with hearing impairment (N=23)			**Neonates without any hearing impairment** (N=75)			
		Mean± SD	Median	Range	Mean± SD	Median	Range	P value
Gestational age (weeks)		37.7±0.81	38.00	37.0-39.0	37.79±0.72	38.00	37.0-40.0	0.799
Birth weight (kg)		2.76±0.44	2.76	1.60-3.8	2.87±0.36	2.90	2.0-3.8	0.230
Age on admission (days)		5.61±4.75	5.00	1.0-25.0	4.24±2.94	4.00	1.0-17.0	0.083
BIND score		2.04±2.44	0.00	0.00-8.0	0.53±1.31	0.00	0.0-5.0	0.002
Total serum bilirubin (mg/dl)		25.9±9.02	26.00	10.4-49.9	20.51±4.59	20.40	8.70-34.0	0.002
Reticulocyte count (%)		8.09±5.82	6.60	0.1-20.5	9.49±9.13	7.80	0.10-47.0	0.873
		Count		%	Count		%	
Sex	Male	13		56.5	35		46.7	0.408
	Female	10		43.5	40		53.3	
Coomb's test	Positive	1		4.3	13		17.3	0.177
	Negative	22		95.7	62		82.7	
Treatment	Phototherapy	8		34.8	44		58.7	0.045
	ET	15		65.2	31		41.3	

BIND: bilirubin-induced neurologic dysfunction; ET: exchange transfusion.

Table 4. Comparison between neonates with and without bilateral hearing impairment

		Neonates with bilateral hearing impairment (N=15)			**Neonates without bilateral hearing impairment** (N=83)			
		Mean± SD	Median	Range	Mean± SD	Median	Range	P value
Gestational age (weeks)		37.7± 0.8	38.00	37 -39	37.8±0.73	38.00	37-40	0.597
Age on admission (days)		5.8±5.7	5.00	1-25	4.34±2.89	4.00	1.0-17.0	0.285
Birth weight (kg)		2.74±0.5	2.76	1.60-3.8	2.8±0.35	2.80	2.05-3.8	0.325
BIND score		2.73±2.6	3.00	0.00-8.00	0.55±1.32	0.00	0.00-5.00	0.001
Total serum bilirubin (mg/dl)		25.85±8.	28.50	11.1-37.8	21.04±5.7	20.70	8.70-49.90	0.012
Reticulocyte count (%)		8.55±5.5	6.60	0.1-20.5	9.27±8.9	7.80	0.10-47.0	0.730
		Count		%	Count		%	
Sex	Male	11		73.3	37		44.6	0.040
	Female	4		26.7	46		55.4	
Coomb's test	Positive	0		0.0	14		16.9	0.118
	Negative	15		100.0	69		83.1	
Treatment	Phototherapy	3		20.0	49		59.0	0.005
	ET	12		80.0	34		41.0	

BIND: bilirubin-induced neurologic dysfunction; ET: exchange transfusion.

Using ROC curve analysis for detection of any hearing impairment, a TSB cut-off value of 24.5 mg/dl showed a sensitivity of 60.9% and a specificity of 81.3% area under the curve (AUC): 0.711- p = 0.004- 95% confidence interval (CI): 0.566- 0.857) while a BIND score cut-off value of ≥ 2 showed a sensitivity of 47.8% and a specificity of 86.7% (AUC: 0.666- p= 0.021-95% CI: 0.525-0.806). Using ROC curve analysis for detection of bilateral hearing impairment, a TSB cut-off value of 27.9 mg/dl showed a sensitivity of 53.3% and a specificity of 95.2% (AUC: 0.704- p=0.027-

95% CI: 0.523- 0.884) while a BIND score cut-off value of ≥ 3 showed a sensitivity of 60% and a specificity of 90.4% (AUC: 0.735- p=0.005- 95% CI: 0.573- 0.896). (Figure 1).

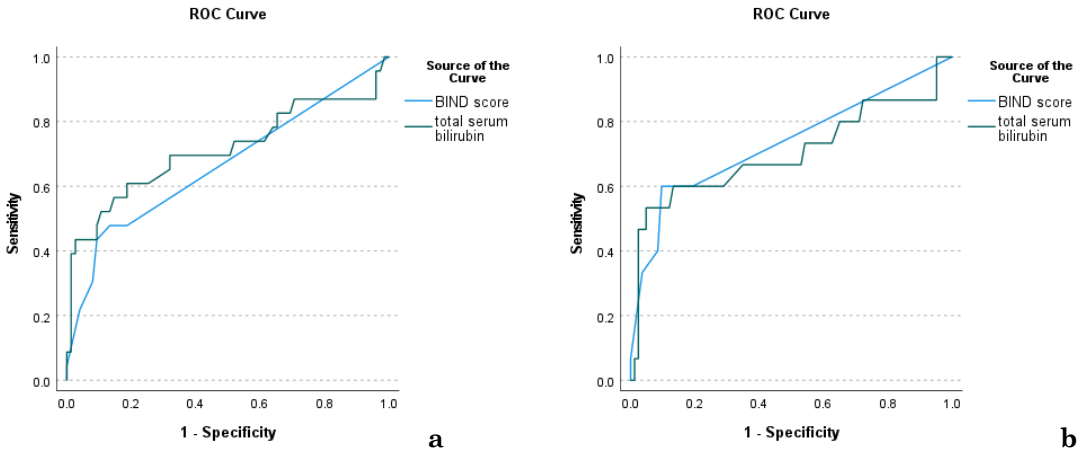

Figure 1. ROC curve for detection of hearing impairment using total serum bilirubin and BIND score. **a**) ROC curve for detection of any hearing impairment. **b**) ROC curve for detection of bilateral hearing impairment.

Discussion

Severe hyperbilirubinemia and its consequences pose a significant high burden in low- and middle-income countries (*12*). Bilirubin neurotoxicity results in a spectrum of disorders depending on the type and severity of the neurological insult that includes motor predominant type, auditory predominant type, classic type (severe motor and auditory affection), and subtle kernicterus that have not yet distinguished and need long-term follow-up for proper care and rehabilitation of affected infants (*13*).

In our study, the mean age at admission was 4.56±3.47 days (range 1-25 days); of them 23.5% had hearing impairment. The auditory pathway is especially vulnerable to the harmful effects of neonatal hyperbilirubinemia. Unconjugated bilirubin can cross the blood-brain barrier, affect brainstem auditory nuclei and the cochlear nerve, as well as central auditory pathways (*14*). It seems that the longer duration of exposure to the elevated TSB contributes to the auditory impairment.

AABR is indispensable for HI detection for neonates admitted to NICU (*15*). There is no agreement on the exact bilirubin level that could induce hearing impairment (*6*, *16*, *17*). The common finding between studies that assess the relationship between TSB and auditory impairment is that bilirubin level has low sensitivity for predicting hearing impairment (*18*, *19*). This reported low sensitivity increases the risk of missing cases below the cut-off value. Bilirubin toxicity to the brain is not related to an absolute level, but to the presence or absence of other risk factors (*20*), as low birth weight, preterm birth, sepsis, blood group incompatibilities and G6PD deficiency (*21*). Our study confirms that neonates with hearing impairment have a higher BIND score (*22*), yet a normal BIND score does not guarantee that the baby has normal hearing (*23*).

Male sex was found to be a risk for bilateral hearing impairment in our study. While it seems unanimous, the underlying etiology remains obscure (*5*, *24–26*). Hence, to date there is no other lab or score that can obviate the need for hearing assessment among neonates (*27*). Once diagnosed, these neonates need intervention an tight follow-up as the HI improvement or reversibility is not a rule (*28*, *29*). Repeated audiometry is necessary even among those with no initial detected abnormality, as AABR though proven to be sensitive, yet it can miss some patients with mild decreased ABR amplitude (*29*, *30*). The right ear affection was more than the left ear in our study, which is not concordant with others (*31*). The cause and implications are not clear, but a follow up study may shed light on the reversibility and causes.

Bilirubin neurotoxicity is affected by the timing of onset of jaundice. The neurotoxicity increases with decreasing post-natal age (*32*), and the risk depends on the rate of decline of bilirubin levels once it reaches the ET threshold. The rate of bilirubin decline in the first few hours after admission is more predictive of adverse neurodevelopmental outcomes at 6 months of age than the type of management or serum bilirubin level (*33*). The timing of ET is crucial to

prevent or alleviate an ongoing insult. Matching the blood with the neonate's and mother's blood and sometimes the initial unavailability of a compatible blood group may result in a delay that could have adversely impacted the outcome of those not improving on IP. However, in our study timing of ET was not significantly associated with either bilateral hearing impairment or any hearing impairment. It seems that the condition that necessitated ET is probably the cause of this association rather than the procedure itself.

IP while awaiting the ET among those with ET bilirubin level proved to be extremely valuable. Those who received IP had less HI. Neonates with high transcutaneous bilirubin measurements should be put on IP while awaiting serum laboratory results. A hearing screen should be done on admission to all neonates with exchange bilirubin levels even if they had no signs of bilirubin encephalopathy with immediate and strict management for younger neonates with high BIND scores and reticulocyte count.

Late presentation is known to contribute to the severity of hyperbilirubinemia in Egypt (*34*). Hyperbilirubinemia induced disabilities are potentially preventable. More investment in early detection and management of neonatal hyperbilirubinemia on the National level is recommended to reduce disabilities burden (*35*). Parents and community awareness of timely bilirubin level assessment in neonates is a necessity. It was reported that when parents sought medical advice, many were not requested to have serum bilirubin measured for timely referrals to healthcare facilities. Moreover, they used home lights and herbal medications for the treatment of hyperbilirubinemia (*34*).

Being a completely preventable disease that could have a long-term effect on the quality of life of the child and his/her family, all efforts should be made to prevent it. National campaigns to raise awareness of family and healthcare workers; about this common yet hearing threatening condition, are essential. We advocate for early screening for hyperbilirubinemia before discharge from maternity hospitals, a proper patient education and a clear follow-up plan. We recommend educating healthcare providers about dealing with severe hyperbilirubinemia as an emergency and being familiar with bilirubin charts to figure out those with exchange levels who need immediate referral. In addition, rapid screening tools such as transcutaneous bilirubinometer should be widely available in hospitals.

Our results are limited by the lack of a follow-up AABR. AABR was performed only within 24 hours of admission (after phototherapy or ET) not necessarily at the peak bilirubin level and the lack of long-term follow-up of the studied neonates as they were out of the scope of this study.

Conclusion

Neonates with higher bilirubin levels and BIND scores are at risk for HI. TSB and BIND score have modest sensitivity and specificity in predicting HI. IP is mandatory in all those with ET threshold bilirubin until procurement of blood to prevent HI. HI may occur despite normal BIND scores in the absence of bilirubin encephalopathy. Those who responded to IP for ET level of TSB had less frequency of HI. Males were more at risk for bilateral HI. Screening for HI among neonates who sustain hyperbilirubinemia is a necessity.

Author Contributions

All shared in design, data curation analysis and drafting of the work. All approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

References

1. S. Tenny, M. Varacallo, *Evidence Based Medicine.* (StatPearls Publishing; Treasure Island (FL), 2020; https://www.ncbi.nlm.nih.gov/books/NBK470182/).
2. S. Ullah, K. Rahman, M. Hedayati, Hyperbilirubinemia in Neonates: Types, Causes, Clinical Examinations, Preventive Measures and Treatments: A Narrative Review Article. *Iran. J. Public Health* **45**, 558–568 (2016).
3. S. Kumbhar, M. Musale, A. Jamsa, Bilirubin metabolism: delving into the cellular and molecular mechanisms to predict complications. *Egypt. J. Intern. Med.* **36**, 34 (2024).

4. H. Boskabadi, M. Zakerihamidi, A. Moradi, M. Bakhshaee, Risk Factors for Sensorineural Hearing Loss in Neonatal Hyperbilirubinemia. *Iran. J. Otorhinolaryngol.* **30**, 195–202 (2018).
5. X. Wu, X. Gao, G. Li, Q. Cao, Y. Guo, H. Deng, Y. Zheng, A prospective observational study to investigate the correlation analysis between neonatal hyperbilirubinemia and deafness gene: Study protocol clinical trial (SPIRIT compliant). *Medicine (Baltimore)* **99**, e19774 (2020).
6. M. H. Teixeira, V. M. S. Borges, R. D. S. Riesgo, P. Sleifer, Hyperbilirubinemia impact on newborn hearing: a literature review. *Rev. Assoc. Médica Bras.* **66**, 1002–1008 (2020).
7. Subcommittee on Hyperbilirubinemia, Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *PEDIATRICS* **114**, 297–316 (2004).
8. A. R. Kemper, T. B. Newman, J. L. Slaughter, M. J. Maisels, J. F. Watchko, S. M. Downs, R. W. Grout, D. G. Bundy, A. R. Stark, D. L. Bogen, A. V. Holmes, L. B. Feldman-Winter, V. K. Bhutani, S. R. Brown, G. M. Maradiaga Panayotti, K. Okechukwu, P. D. Rappo, T. L. Russell, Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics* **150**, e2022058859 (2022).
9. G.-S. Nam, S. H. Kwak, S. H. Bae, S. H. Kim, J. Jung, J. Y. Choi, Hyperbilirubinemia and Follow-up Auditory Brainstem Responses in Preterm Infants. *Clin. Exp. Otorhinolaryngol.* **12**, 163–168 (2019).
10. U. Bhardwaj, V. Kohli, A. Thukral, Management of Hyperbilirubinemia in Newborn Infants 35 or More Weeks of Gestation: American Academy of Pediatrics, 2022. *Indian Pediatr.* **60**, 63–66 (2023).
11. L. Johnson, V. K. Bhutani, K. Karp, E. M. Sivieri, S. M. Shapiro, Clinical report from the pilot USA Kernicterus Registry (1992 to 2004). *J. Perinatol.* **29**, S25–S45 (2009).
12. B. O. Olusanya, M. Kaplan, T. W. R. Hansen, Neonatal hyperbilirubinaemia: a global perspective. *Lancet Child Adolesc. Health* **2**, 610–620 (2018).
13. S. Shapiro, J. B. Le Pichon, S. M. Riordan, J. Watchkoe, The Neurological Sequelae of Neonatal Hyperbilirubinemia: Definitions, Diagnosis and Treatment of the Kernicterus Spectrum Disorders (KSDs). *Curr. Pediatr. Rev.* **13** (2017).
14. S. M. Riordan, S. M. Shapiro, Review of bilirubin neurotoxicity I: molecular biology and neuropathology of disease. *Pediatr. Res.* **87**, 327–331 (2020).
15. H. A. ElGindy, M. Mohamed, M. Kotb, Z. Ezz ElDin, H. Hamdy, M. Elmaghraby, W. Elnaggar, Neonatal Auditory Screening is a Necessity in The Neonatal Intensive Care Unit: Single Center Study. *Pediatr. Sci. J.* **2**, 120–126 (2022).
16. A. Padinharakandy, B. Ramaswamy, D. K, L. Edward, P. G, Prospective Evaluation of Hearing Status in Neonatal Hyperbilirubinemia. *Indian J. Otolaryngol. Head Neck Surg.* **76**, 453–457 (2024).
17. Y. M. Mandour, M. A. El Sayed, A. El Sayed Morgan, R. Bassam, H. Fadl, A. Elrefae, Audiological assessment of neonatal hyperbilirubinemia. *Int. J. Pediatr. Otorhinolaryngol.* **135**, 110126 (2020).
18. Z. M. Ezzeldin, E. Sharaf, H. S. Hamdy, Y. A. Abdelwahab Selim, Hearing screening in neonates with hyperbilirubinemia. *Int. J. Pediatr. Otorhinolaryngol.* **142**, 110591 (2021).
19. O. Oyinwola, M. Mukhtar-Yola, A. Olusesi, T. Oluwasola, Automated ABR Screening for Hearing Loss and its Clinical Determinants among Newborns with Hyperbilirubinemia in National Hospital, Abuja, Nigeria. *Niger. J. Clin. Pract.* **26**, 1249–1256 (2023).
20. I. Iskander, R. Gamaleldin, S. El Houchi, A. El Shenawy, I. Seoud, N. El Gharbawi, H. Abou-Youssef, A. Aravkin, R. P. Wennberg, Serum Bilirubin and Bilirubin/Albumin Ratio as Predictors of Bilirubin Encephalopathy. *Pediatrics* **134**, e1330–e1339 (2014).
21. S. Rauf, B. Salah Ud Din, G. Abbas, Z. Nawaz, Incidence and risk factors of acute bilirubin encephalopathy in neonates with hyperbilirubinemia presenting at secondary care hospital. *Pak. J. Med. Sci.* **39** (2023).
22. S. Z. El Houchi, I. Iskander, R. Gamaleldin, A. El Shenawy, I. Seoud, H. Abou-Youssef, R. P. Wennberg, Prediction of 3- to 5-Month Outcomes from Signs of Acute Bilirubin Toxicity in Newborn Infants. *J. Pediatr.* **183**, 51-55.e1 (2017).
23. D. Sharma, R. Harish, A. Bhatti, R. Uppal, J. Naseem, Early Neurodevelopmental Outcome of Neonates with Gestation 35 Weeks or More with Serum Bilirubin in Exchange Range Without Encephalopathy: A Prospective Observational Study. *Neonatal Netw.* **40**, 66–72 (2021).
24. M. Malhotra, S. Angral, A. Bhardwaj, M. Priya, S. Varshney, A. K. Tyagi, A. Kumar, R. Malhotra, The Clinical-Audiological Cross Sectional Study of Deaf-Mute Patients in a

Tertiary Care Centre of Uttarakhand State and Literature Review. *Indian J. Otolaryngol. Head Neck Surg. Off. Publ. Assoc. Otolaryngol. India* **74**, 106–113 (2022).
25. I. Shuaibu, D. Chitumu, I. Mohammed, N. Shofoluwe, M. Usman, A. Bakari, L. Lawal, Pattern of hearing loss in a tertiary hospital in the North Western Nigeria. *Sahel Med. J.* **21**, 208 (2018).
26. V. Bhat, V. Bhandari, "Sex specificity in neonatal diseases" in *Principles of Gender-Specific Medicine* (Elsevier, 2023; https://linkinghub.elsevier.com/retrieve/pii/B9780323885348000158), pp. 841–867.
27. E. Elmazzahy, I. Iskander, H. Abou-Youssef, H. Madani, S. ElTatawy, Activin A is Not a Reliable Prognostic Biomarker For Bilirubin Induced Neurotoxicity in Neonates. *Pediatr. Sci. J.* **2**, 139–146 (2022).
28. S. S. ElTatawy, E. A. Elmazzahy, A. M. El Shennawy, H. A. Madani, H. Abou Youssef, I. F. Iskander, The spectrum of bilirubin neurotoxicity in term and near-term babies with hyperbilirubinemia: Does outcome improve with time? *Early Hum. Dev.* **140**, 104909 (2019).
29. A. Okumura, Y. Kitai, H. Arai, M. Hayakawa, Y. Maruo, T. Kusaka, T. Kunikata, S. Kumada, I. Morioka, Auditory brainstem response in preterm infants with bilirubin encephalopathy. *Early Hum. Dev.* **154**, 105319 (2021).
30. L. K. Zidan, M. A. Rowisha, M. A. E. Nassar, R. A. Elshafey, T. H. El Mahallawi, H. S. Elmahdy, Magnetic resonance spectroscopy and auditory brain-stem response audiometry as predictors of bilirubin-induced neurologic dysfunction in full-term jaundiced neonates. *Eur. J. Pediatr.* **183**, 727–738 (2023).
31. N. Salehi, F. Bagheri, H. Ramezani Farkhani, Effects of Hyperbilirubinemia on Auditory Brainstem Response of Neonates Treated with Phototherapy. *Iran. J. Otorhinolaryngol.* **28**, 23–29 (2016).
32. R. Cayabyab, R. Ramanathan, High unbound bilirubin for age: a neurotoxin with major effects on the developing brain. *Pediatr. Res.* **85**, 183–190 (2019).
33. E. A. Elmazzahy, Z. E. El Din, M. A. Nessem, S. El Tatawy, Neurodevelopmental outcome at 6 months of age of full-term neonates with hyperbilirubinemia necessitating exchange transfusion. *Early Hum. Dev.* **190**, 105969 (2024).
34. I. Iskander, R. Gamaleldin, M. Kabbani, Root causes for late presentation of severe neonatal hyperbilirubinaemia in Egypt. *East. Mediterr. Health J.* **18**, 882–887 (2012).
35. A. M. Metwally, A. M. Abdallah, E. M. Salah El-Din, Z. Khadr, E. R. A. Raouf, N. A. Elghareeb, R. M. Saleh, M. H. Abuelela, H. A. Amer, H. M. Hasanin, M. A. A. Mawla, S. F. Sallam, I. R. El-Alameey, S. M. Sami, G. A. Abdel-Latif, M. Abdelrahman, M. A. Shehata, A national prevalence and profile of single and multiple developmental delays among children aged from 1 year up to 12 years: an Egyptian community-based study. *Child Adolesc. Psychiatry Ment. Health* **16**, 63 (2022).