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The Relationship between Severe Hyperbilirubinemia and Abnormal Auditory Brainstem Response (ABR) in Children

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Abstract

Introduction:
Hyperbilirubinemia is one of the most common cause of congenital sensory neuronal hearing loss. These patients are screened by auditory brainstem response (ABR) test at bilirubin levels higher than 1% of gestational weight. Aim of this study is to determine whether hyperbilirubinemia less than 1% of gestational weight could induce hearing loss and abnormal auditory brainstem response (ABR).

Materials and Methods:
In this case control study the outcome of ABR test in children younger than 3 years old with a history of term delivery and hyperbilirubinemia (bilirubin level less than 1% of gestational weight) were compared with the control group without hyperbilirubinemia matched for age and gender.

Results:
Mean ABR amplitude (wave I, V) were significantly prolonged in neonates with jaundice compared with controls (P<0.01). Based on receiver-operating characteristic curves, a bilirubin level of 0.6% of gestational weight was the best discriminator with a sensitivity and specificity of 100%. In logistic regression analysis the relative risk of having an abnormal ABR in bilirubin level>0.6% gestational weight was 2.25 with 95% confidence intervals (CI) (1.44-3.89 and p=0.02).

Conclusion:
Our study showed a relevant association between bilirubin levels less than 20 mg/dl and abnormal ABR.

Keywords: Auditory brainstem response, Hearing loss, Hyperbilirubinemia.

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Received date: Jun 23, 2014 ; Accepted date: Jul 22, 2014

Introduction

Hyperbilirubinemia is defined by bilirubin higher than 5 mg/dl at early infant life. Hyperbilirubinemia higher than 1% of gestational weight is one of the most common cause of congenital sensory neuronal hearing loss. It has been shown that pathologic hyperbilirubinemia could have toxic effects on sensory or neuronal pathways of hearing and may affect the speech recognition of neonates (1). Higher levels of bilirubin cause greater impairment in the auditory system, however most of the impairments are reversible (2). Therefore a screening test to diagnose any hearing problems in these patients seems inevitable. Auditory brainstem response (ABR) is an auditory test to diagnose many hearing problems particularly sensory neuronal hearing loss in patients (3). This test produces sensory initiation through a component of auditory stimulus and record of the electrical impulses (4). ABR tests are abnormal in congenital hearing losses particularly hyperbilirubinemia induced hearing loss (5). It is recommended to screen patients for hearing loss at bilirubin level higher than 20 mg/dl or 1% of gestational weight (6). Besides the fact that ABR is an appropriate test in these patients, it is important to choose a serum bilirubin cut-off point to detect the patients before any further developmental sequel Also (7,8), the test should provide a high sensitivity and specificity at the presumed cut-off point. This study aimed to determine whether hyperbilirubinemia less than 1% of gestational weight could induce hearing loss and abnormal auditory brainstem response (ABR).

Materials and Methods

Patient Selection:

This case control study was carried out in Taleghani Hospital, Tehran-Iran, on 126 children younger than 3 years old with a history of term delivery and gestation age ≥37weeks with hyperbilirubinemia (bilirubin higher than 10 mg/dl and less than 20 mg/dl). All patients were referred to our tertiary referral center. Bilirubin was normalized to weight. Control group consisted of patients matched for age and sex without significant hyperbilirubinemia. All patients had neonatal hyperbilirubinemia and referred to our center. Serum bilirubin level was less than 1% of gestational weight in all of our patients (experiment group). The study protocol was approved by ethical committee of Shahid Beheshti University of Medical Sciences and informed written consents were given from the parents of all children.

ABR was performed on these children with severe hyperbilirubinemia. The demographic characteristics were recorded in data sheets and all bilirubin measures were normalized according to the gestational weight of the patients. Data for hyperbilirubinemia and gestational weight were extracted from patients previous admission file during neonatal observation.

Method of Hearing Test:

In current study ABR testing was performed using the hearing screening device (Natus Medical, San Carlos, CA). ABR was performed using non filtered clicks at 100 dB SPL (peak equivalent). Absolute and interpeak latencies of waves I and V were measured and correlated to serum bilirubin levels. The testing device assumes that an infant is deaf until the acquired data fit, with 99.96% likelihood, a template composed of auditory brainstem responses obtained at 35 dB from normal hearing newborns. Failure of an ear to attain this likelihood is reported as a refer result (versus a pass result), which indicates that the infant needs follow-up and further hearing testing. For this study, we separated unilateral abnormal results of left and right ear.

Statistical Analysis

All multiple comparison tests were two-tailed. Direct comparison between case

and control was performed with the indipendent Student t-test or the nonparametric Mann–Whitney test when the data sets were not normally distributed. Pearson's correlation of coefficient was used to analyze correlations between the abnormal ABR waves and serum bilirubin levels. A receiver-operating characteristic curve and area under curve were used to determine the highest sensitivity and specificity of bilirubin to ascribe for abnormal ABR. A p- value of 0.05 or less was considered statistically significant. All statistical analyzes were performed with SPSS18.

Results

126 children include 62(48%) girls and 64 (52%) boys in two groups were evaluated. There was no significant difference regarding age, sex, weight, post-conception age and other demographic and biographic characteristics between case and control groups (Table.1).

Table1: Demographic characteristics in patients with hyperbilirubinemia and controls.

Variables	Cases(n=63)	Control (n=63)	P-value
Gestational Age	39.5±1.4	39.1±1.8	0.45
Gestational weight(kg)	27350±284	2723±334	0.26
Postconceptual age (month)	11.5±11.2	9.2±7.8	0.35
Sex (Female/male)	52%/48%	46%/54%	>0.05
Type of delivery			
NVD	24	20	>0.05
CS	11	8	>0.05

There were significant differences in abnormality of ABR waves between case and control groups using student t-test (Table.2). Mean ABR amplitude (wave I, V), V-I inter-peak latency were significantly prolonged in case compared to control (P<0.01).

Table 2: Auditory brain response (ABR) test results in patients and controls.

	Patients	Control	P-value
I right	2.87±0.55	1.81±0.42	0.02
I left	2.78±0.49	1.89±0.34	0.017
V right	7.91±0.91	5.79±0.94	0.02
V left	8.02±0.87	5.70±0.84	0.01
V-I right	5.04±0.67	2.98±0.29	0.03
V-I left	5.24±0.36	2.81±0.53	0.04

In order to estimate a cut off level for bilirubin in which the highest sensitivity and specificity was recorded we performed a receiver operator characteristics curve (ROC). Based on receiver-operating characteristic curves, a bilirubin level of 0.6% gestational weight was the best discriminator with a sensitivity of 100% (95%confidence interval: 91.96% to 100%) and a specificity of 100% (95% CI: 82.35% to 100%). To determine diagnostic accuracy the area under curve of ROC was determined (Figure1). The area under the curve (AUC) was 0.71 with confidence intervals of 0.56-0.89. We used logistic regression to determine odds ratio (OR) of abnormal ABR in serum bilirubin higher than 0.6% of gestational weight in patients in our study and we used a regression analysis. In logistic regression analysis the

relative risk of having an abnormal ABR in bilirubin level>0.6% of gestational weight was 2.25 with 95% CI (confidence interval): 1.44-3.89 and P=0.02. The impacts of a variety of clinical factors on the regression model were also assessed. Presence of abnormal ABR and hyperbilirubinemia was not associated with age or gestational age (P=0.23 and 0.72 respectively).

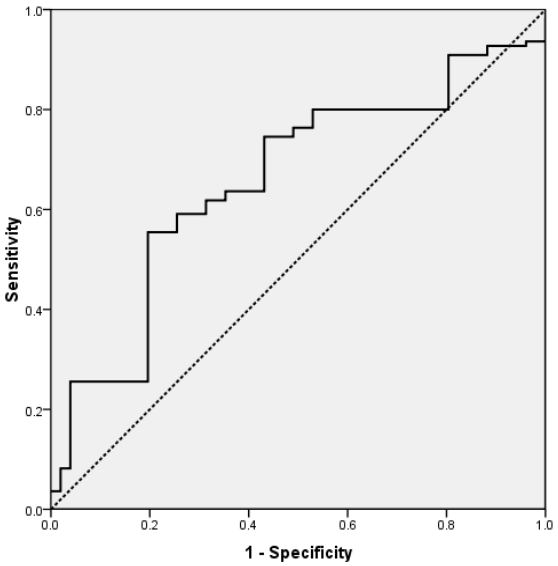

Fig. 1: Area under receiver operator curve (ROC) was 0.71 with 95% confidence intervals of 0.56-0.89 for bilirubin level of 0.6% gestational weight.

Discussion

The serum total bilirubin concentration at any point in time represents the amount of bilirubin being produced minus that being excreted. Hyperbilirubinemia develops when bilirubin production exceeds the body's capability to excrete it, primarily by conjugation (9).

When extreme, hyperbilirubinemia may lead to the development of free bilirubin, the form of bilirubin which may cross the blood-brain barrier and enter and damage the basal nuclei of the brain (10). This rare, though devastating complication may result in irreversible bilirubin induced hearing sensory neuronal damage (11). The debate is in the serum bilirubin level at which phototherapy or exchange should be considered and whether any hearing damage has happened at that bilirubin level. Currently, serum bilirubin level higher than 1% of gestational weight is considered the predicted level at which hearing damage may happen and screening is recommended. Thereby, hyperbilirubinemia is a condition of major importance and a source of concern to all involved in the management of the newborn (12). In this paper, we have embarked on the possibility of hearing damage at lower level of bilirubin in neonates. Understanding the mechanisms and dangers of severe neonatal hyperbilirubinemia (13). Should facilitate recognition of hearing loss situation and optimize the speed with which bilirubin screen testing is performed (14). In children with hyperbilirubinemia the diagnostic value of ABR appears to be more reliable for hearing screening (15). It is suggested that hearing screening for high-risk neonates should be conducted with ABR (16). It was interesting result that all of our patients had normal otoacoustic emissions (OAE) test but abnormal ABR result. Patients with a history of hyperbilirubinemia due to hemolysis having blood exchange were omitted from the study. In fact blood exchange may produce a bias in the study wherein those patients may already have passed the threshold of bilirubin> 1% of gestational weight. Akman et al. (17) also had the same finding in their study which they excluded hemolysis induced hyperbilirubinemia. On the other hand, hemolysis induced hyperbilirubinemia may be treated with blood exchange at a bilirubin level less than 20 mg/dl. Therefore using a 20 mg/dl cut off point for detecting hearing loss by ABR test is debatable. Moreover, other reports showed that neonatal jaundice is associated with significant transient aberrations of ABR, suggestive of a transient toxic brainstem encephalopathy at lower values (18).

Our data suggest that newborn hyperbilirubinemia, particularly less than

1% of gestational weight, may be an unrecognized cause of a refer ABR result. Although this is most likely transient, because the auditory brainstem response usually improves with the resolution of jaundice, the association between bilateral refer ABR results and elevated bilirubin concentrations should not be dismissed as inconsequential (19).

We indicated strong correlation between high bilirubin and abnormal ABR test in patients with bilirubin at levels lower than 1% of gestation weight. Therefore it may be prudent to perform ABR test in patients with bilirubin levels above 0.6% of gestational weight to diminish any future cost for health care system. It is likely to miss many of the patients with a history of high bilirubin if the cut -off point is set at higher values. It is important to note that the sensitivity and specificity of the ABR test in detecting bilirubin induced hearing loss was not tested in our study and we only focused on cut-off value for bilirubin to detect hearing losses.

Additional studies of the relationship between bilirubin concentrations, ABR results, and sensorineural deafness or auditory neuropathy/auditory dyssynchrony (AN/AD) may provide valuable insight into the actual prevalence and role of bilirubin in these disorders (20).

Conclusion

In conclusion, the effect of high serum bilirubin on hearing loss in children is more complex and devastating than what is currently considered. Our study showed a relevant association between bilirubin levels less 1% of gestational weight and abnormal ABR. We believe that screen testing of ABR should be performed at a lower level of bilirubin than the current cut- off level in literature to curb the burden of future hearing loss and developmental or behavioral problems on the children and health care system.

Acknowledgment

The authors would like to express their gratitude and thanks to the staff members of ENT department of Taleghani Hospital-Tehran for their constructive support throughout the study. The results presented here have been abstracted from the thesis with (ID Number: 229 M).

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