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Original Article

Effect of Hyperbilirubinemia on Medial Olivocochlear System in Newborns

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OBJECTIVES: To evaluate medial olivocochlear efferent system of babies with hyperbilirubinemia with normal auditory brain stem responses.

MATERIALS AND METHODS: This was a prospective study in a tertiary referral hospital. The study involved 40 hyperbilirubinemic and 44 healthy newborns. Cochlear and auditory activity of participants was evaluated by transient otoacoustic emissions (TOAEs) and brainstem auditory evoked response components (BAER). Medial olivocochlear (MOC) reflex was evoked with contralateral acoustic stimulation and recorded with TOAEs.

RESULTS: A comparison of the MOC reflex activity between two groups with Mann Whitney U test revealed that MOC reflex activity were significantly decreased in the hyberbilirubinemic group for both ears ($p<.05$). This difference was significant for all frequencies in both ears. There was no significant relation between total serum bilirubin level and MOC reflex activity.

CONCLUSION: Hyperbilirubinemic newborns had decreased MOC reflex activity. This may be indicative of future problems in speech discrimination and effective hearing in noisy background. Additional long cohort studies are needed to evaluate the clinical importance of MOC reflex measurements in this group. MOC reflex measurement has the potential to form part of the audiologic evaluation of newborns with hyperbilirubinemia in the future.

KEYWORDS: Medial olivocochlear reflex, newborn, hyperbilirubinemia

INTRODUCTION

After delivery of the fetus, the neonate can experience critical levels of bilirubin. If indirect bilirubin (unbound bilirubin) is increased, it can cross the blood–brain barrier and precipitate into different parts of the nervous system. The term "bilirubin encephalopathy" is used alternatively with "kernicterus" to define the clinical spectrum of a disorder with hearing deterioration, movement problems (athetosis and/or dystonia), ocular movement disorder, and dental enamel dysplasia of the teeth [1]. One of the primary clinical signs of kernicterus is auditory impairment; thus, auditory evaluation is useful and necessary for clinical diagnosis of kernicterus [2].

Several autopsy reports of infants with kernicterus and an animal experiment of Gunn rats with serious hyperbilirubinemia showed that the auditory brain stem, including the superior olivary complex, nuclei of the lateral lemniscus, cochlear nuclei, and inferior colliculi, is more sensitive to bilirubin neurotoxicity than cochlear function [3-5]. Studies of the effects of bilirubin toxicity on cellular metabolism have shown that it alters intracellular calcium regulation through an enzyme called calmodulin-dependent kinase II [6]. This enzyme is crucial for neurotransmitter production and secretion, adjustment of gene expression, ion channel modification, and phosphorylation of structural elements [6-8].

The effects of bilirubin on the auditory system range from elusive problems in auditory and speech processing to total hearing loss. Auditory neuropathy spectrum disorder (ANSD) is usually described by auditory neural dysfunction in the existence of normal cochlear activity. ANSD is associated with progressive hyperbilirubinemia, with at least 50% of children with ANSD with

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a positive history of hyperbilirubinemia and/or hypoxia [9]. It mostly causes symmetric bilateral auditory deterioration. Normal cochlear microphonics and altered or missing brainstem auditory evoked response (BAER) should bring ANSD to mind [10]. It has also been shown that infants with severe hyperbilirubinemia emerged with chronic auditory toxicity despite a normal extensive audiological assessment during the neonatal period, emphasizing the auditory follow-up reevaluation of neonates with severe hyperbilirubinemia [11].

Thick myelinated medial olivocochlear (MOC) fibers arise in the medial portion of the superior olivary complex bilaterally. They innervate the outer hair cells in the cochlea by running through the vestibular nerve [12]. Stimulation of MOC efferent causes suppression of outer hair cell activity, resulting in a decline in the amplitude of otoacoustic emissions (OAEs). OAEs either simultaneously or in response to acoustic stimuli can be measured in the external canal noninvasively. Furthermore, the combination of OAEs and contralateral acoustic stimulation permits the examination of the MOC efferent cochlear innervations. The decline in the amplitude of OAEs in the presence of contralateral acoustic stimuli is known as the "MOC reflex," which is speculated to decrease acoustic trauma and aid in speech perception in a noisy background [13]. It has been investigated in several systemic disorders affecting the auditory pathway to evaluate subclinical cochlear damage, otherwise normal auditory evaluation [14-16]. The aim of the present study was to demonstrate subclinical damage in the MOC efferent system of babies with hyperbilirubinemia with normal auditory brain stem responses.

MATERIALS AND METHODS

The study was approved by the ethics committee of University of Health Sciences Ümraniye Training and Research Hospital (7578-2013). The study design was explained to the parents of all babies. Written informed consent was obtained from the parents of the babies. The study was conducted in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki).

Infants ≥38 weeks gestational age who were referred from the neonatal intensive care unit with a total serum bilirubin level that met the phototherapy or exchange transfusion criteria during the first 2 weeks of life and a control group of age- and gender-matched healthy babies were included in the study [17]. The study included 20 boys and 20 girls in the patient group and 21 boys and 23 girls in the control group.

Exclusion criteria were a family history of hearing loss, ototoxic drug consumption during pregnancy or prescribed to newborns, craniofacial malformations, abnormal otoscopic signs, neonatal asphyxia or hypoxia (assessed as Apgar values <4 in the first minute and 6 in the fifth minute), in utero infection, low birth weight, severe intrauterine growth retardation, and intensive care unit history. The aim of the present study was to determine subclinical changes in the MOC system so patients with hyperbilirubinemia with abnormal otolaryngologic examination results and/or BAER findings were also excluded.

All the babies underwent otoscopic examination and tympanometric measurement (Tympanometer; Capella, Madsen, Denmark) to exclude any middle ear disorder. Participants had extensive auditory evaluation, auditory brainstem response, and OAE without contralateral sound and OAE with contralateral sound executed in both ears at 30-45 days old by a single audiologist blinded to the degree of hyperbilirubinemia.

All infants included in the study underwent BAER (K-500 BDT; Vivosonic Inc., Ontario, Canada) using the monaural method. The test was conducted in a soundproof room reserved for this purpose within the audiology unit of the otolaryngology department, with the child in physiological sleep in a regular bed. The stimulus was introduced by the insertion of headphones (ER3). A bicannal electrode (inverting electrode on the mastoid, non-inverting electrode on the forehead, and ground electrode on the cheek) was used to record

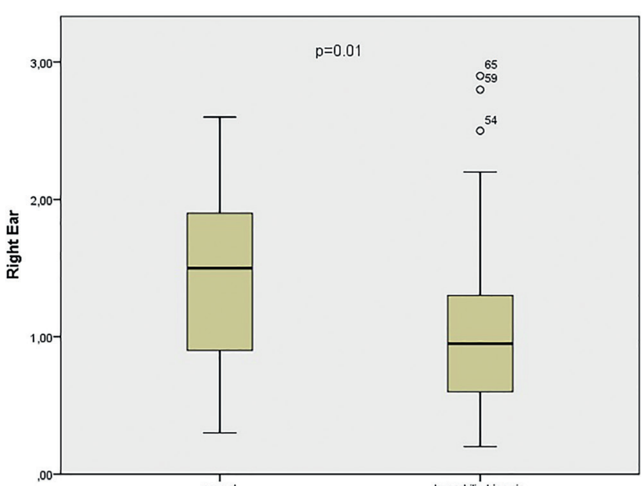

Figure 1. Total suppression levels in dBs for the right ears of the patient and control groups. MOC reflex activity has been evaluated as amplitude difference of the OAE response without and with contralateral acoustic stimuli for the right ear. The amplitude significantly reduced in the patient group showing the reduction of MOC activity.

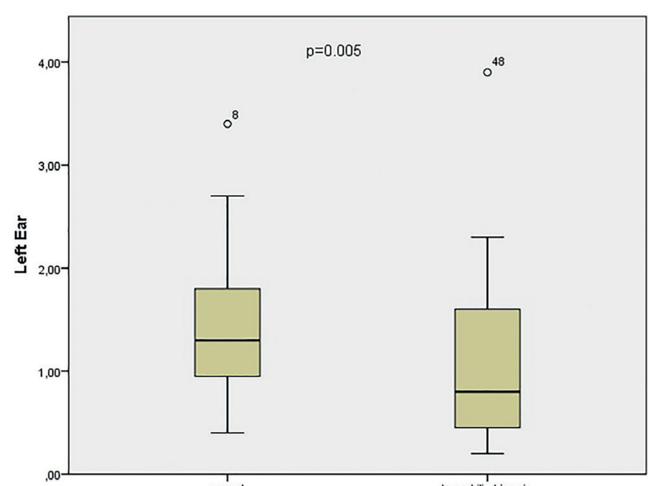

Figure 2. Total suppression levels in dBs for the left ears of the patient and control groups. MOC reflex activity has been evaluated as amplitude difference of the OAE response without and with contralateral acoustic stimuli for the left ear. The amplitude significantly reduced in the patient group showing the reduction of MOC activity.

signals. Test parameters were as follows: clicks with a repetition rate of 29.9/s, average response of 2000 times, and stimulus intensity of 90 dBnHL, with the stimulus intensity lowered to 20 dB intervals to confirm the hearing threshold levels for wave V. The latencies of BAER wave I, III, V, and I-V interpeak intervals were measured. The criterion for normal hearing was the presence of wave V with a stimulus intensity of 20 dBnHL.

Transient-evoked OAEs were documented in linear mode, and test frequencies were at 1, 2, 3, 4, and 5 kHz (Vivosonic Integrity K500; Vivosonic Inc.). Records with >70% wave reproducibility and >80% stimulus stability were included in the study, and each test was terminated with 260 sweeps. Emissions with >6 dB signal-to-noise ratio were considered valid.

For MOC reflex examination, contralateral, a continuous broadband white noise (bandwidth 50-8000 kHz) was delivered at a 70 dB SPL, corresponding to 40 dB HL to avoid stimulation of the stapedial reflex and interaural transmissions. Amplitude reductions for each frequency were calculated by subtracting the data of the emissions with contralateral white noise from the emissions without any contralateral acoustical stimulation.

Statistical Analysis

All analyzes were conducted using Statistical Package for the Social Sciences version 21.0; (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used for data with normal distribution. The Mann-Whitney U test was used for continuous variables. The Spearman correlation test was used for correlation of data. All analyzes were two-tailed. A p<0.05 was considered significant.

RESULTS

A total of 80 ears of 40 patients with hyperbilirubinemia (20 girls and 20 boys) and 88 ears of 44 healthy individuals (23 girls and 21 boys) were included in the present study. The mean test age of babies with hyperbilirubinemia was 34.4 days, whereas it was 34.3 days for the control group. The groups were comparable with regard to age and gender (p>0.05).

There was no difference in BAER measurements between the groups with regard to amplitudes and latencies (Table 1). Amplitudes, wave latencies and inter-peak latencies have been measured as microvolts (μV) and milliseconds (ms), respectively. The latencies for wave I, III, V, and I-V peak intervals were similar for both groups. All the participants had wave V with a stimulus intensity of 20 dBnHL for both ears.

Table 1. Comparison of BAER variables between groups. Amplitudes, wave latencies and inter-peak latencies have been measured as microvolts (μV) and milliseconds (ms), respectively

Variables	Hyperbilirubinemia	Control	p
I amplitude (μV)	0.178±0.057	0.174±0.051	>0.05
III amplitude (μV)	0.210±0.06	0.208±0.059	>0.05
V amplitude (μV)	0.21±0.564	0.208±0.058	>0.05
Wave I (ms)	1.58±0.01	1.54±0.01	>0.05
Wave III (ms)	3.31±0.22	3.38±0.26	>0.05
Wave V (ms)	5.71±0.31	5.76±0.34	>0.05
I-III inter-peak (ms)	2.11±0.32	2.09±0.29	>0.05
I-V inter-peak (ms)	4.46±0.39	4.48±0.4	>0.05

The reduction or suppression of emission levels was observed in the patient group due to contralateral acoustic stimulus (MOC reflex decline). The frequency specific and the total suppression levels for each ear were evaluated. Depression in the MOC reflex amplitude was significant for all frequencies in the patient group. MOC reflex values were significantly lower in the right ear at 1 kHz (p=0.034), 2 kHz (p=0.016), 3 kHz (p=0.021), 4 kHz (p=0.014), and 5 kHz (p=0.02) in the patient group. The values were also significantly lower in the left ear of patients at 1 kHz (p=0.017), 2 kHz (p=0.024), 3 kHz (p=0.004), 4 kHz (p=0.02), and 5 kHz (p=0.006) (Table 2). Total suppression was assessed and significantly lower for the right ear (p=0.012) and for the left ear (p=0.005) of patients (Figures 1 and 2). There was no significant correlation between serum total bilirubin levels and total MOC reflex values of both ears (p=0.278 for the right ear and p=0.236 for the left ear).

DISCUSSION

Bilirubin specifically affects the auditory system. Moreover, auditory pathway damage may arise in the lack of other signs of bilirubin encephalopathy. Nonetheless, the well-known impact of hyperbilirubinemia on the hearing function can be detected by BAER measurements. In fact, it has been shown that BAER waves III and V reduced and V/I and V/III amplitude ratio decreased in term newborns with hyperbilirubinemia [18].

However, the cut-off level of total serum bilirubin level for auditory damage has not been established. A systematic review showed that auditory damage risk is higher when bilirubin levels are >20 mg/dL, with the average occurrence of BAER abnormalities with bilirubin levels >20 mg/dL of 35.1% [19]. Jiang et al. [20] reported that a total serum bilirubin level >10 mg/dL has a negative impact on newborns' hearing status. They found a prevalence of auditory impairment of 28% in term newborns who had a total serum bilirubin level >10 mg/dL [20].

Table 2. MOC reflex activity can be measured numerically as difference in the amplitude of the otoacoustic emission response without and with contralateral acoustic stimuli in dB

Side	1 kHz	2 kHz	3 kHz	4 kHz	5 kHz
Right Ear					
Hyperbilirubinemia	1.96	1.13	0.88	0.9	0.8
Normal	2.87	1.93	1.22	1.26	1.32
p	0.03	0.01	0.02	0.01	0.002
Left Ear					
Hyperbilirubinemia	1.66	1.1	0.88	0.68	0.72
Normal	2.83	1.57	1.47	0.98	1.22
p	0.01	0.02	0.004	0.02	0.006

The decline in difference means the reduction of MOC reflex. The table shows the median values of MOC reflex activity measurements in dB. In the patient group, this difference was significantly decreased in all frequencies demonstrating the reduction of MOC activity.

They also published another study about BAER wave amplitudes in neonates with hyperbilirubinemia [18]. Both studies emphasized that there is no correlation between total serum bilirubin level and severity of hearing impairment. Recent studies showed that unconjugated bilirubin is a more important marker than total serum bilirubin level to evaluate auditory damage in neonates with hyperbilirubinemia [11, 21].

Hearing loss and ANSD due to hyperbilirubinemia are expected to cause speech and language problems, but these capabilities can be difficult to assess in patients with motor deterioration due to bilirubin encephalopathy. These children often have dysarthria, dystonia, and movement problems [2, 5, 9, 10]. Therefore, it is hard to examine their receptive speech structures. However, children who had hyperbilirubinemia in the newborn period with normal hearing level and elusive auditory neural abnormalities have not been fully analyzed for speech and oral communication evolution.

Thick myelinated MOC fibers originate from the medial portion of the superior olivary complex. These fibers run through the vestibular nerve and innervate the outer hair cells in the cochlea. The superior olivary complex is susceptible to the effects of hyperbilirubinemia [12]. The MOC reflex may play a role in auditory processing, particularly in speech recognition in a noisy background [13], but there are studies that oppose this argument [22]. It has been reported that MOC reflex activity-suppression of OAEs in the presence of contralateral acoustic stimuli increased in patients with tinnitus and/or hyperacusis [23, 24]. May et al. [25] showed that an intact MOC reflex decreases the risk of noise-induced auditory neuropathy in laboratory mice. One could argue that MOC reflex has a protective effect on the cochlea among a noisy background. MOC reflex measurements may detect the subclinical effect of systemic disease on the auditory pathway before the routine auditory battery, such as OAE and BAER, can. It can alert the clinician before the auditory impairment due to disease becomes evident. Thus, the focus of this study was to assess the MOC efferent system in neonates with hyperbilirubinemia who had normal routine auditory evaluation (normal OAEs and normal BAER measurements).

Contralateral noise was used to evoke the MOC reflex. Suppression of OAEs in all frequencies significantly decreased after contralateral acoustic stimuli, which was significant in neonates with hyperbilirubinemia for all frequencies. In the present study, MOC reflex changes and total serum bilirubin levels were not correlated, which was in accordance with the recent literature. Unconjugated bilirubin level appears to be a better predictor of auditory damage than total serum bilirubin level [11, 21].

CONCLUSION

To the best of our knowledge, this is the first study showing MOC reflex changes in neonates with hyperbilirubinemia who had passed a routine auditory evaluation. Auditory perception plays a pivotal role in speech and language development in children. Since these children are in the learning period in their early life, these changes may ultimately affect their learning. The present study showed changes in the MOC efferent system in neonates with hyperbilirubinemia. These subtle changes may be indicative of future problems in speech discrimination and effective hearing in a noisy background, but further long-term cohort studies are required to confirm these results. Nonetheless, MOC reflex measurement has the potential to form part of the audiological evaluation of newborns with hyperbilirubinemia in the future.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Ümraniye Training and Research Hospital (7578-2013).

Informed Consent: Written informed consent was obtained from the patients' parents.

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