Detection of sensorineural hearing loss using automated auditory brainstem-evoked response and transient-evoked otoacoustic emission in term neonates with severe hyperbilirubinaemia

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ABSTRACT

Introduction: This study was designed to compare the sensitivity and specificity of detecting sensorineural hearing loss (SNHL) using the transient-evoked otoacoustic emissions (OAE) machine (the Madsen TE Echoscreen) and automated auditory brainstem response (AABR) machine (the Sabre Compac portable AABR) in term neonates exposed to severe hyperbilirubinaemia.

Methods: This was a prospective study carried out over a 30-month period in a neonatal intensive care unit. Term infants (gestation equal to or greater than 37 weeks) with severe hyperbilirubinaemia (peak total serum bilirubin level equal to or greater than 300 umol/L) were recruited. Hearing tests were carried out before discharge.

Results: The median age of the 250 study infants when OAE and AABR were tested, was eight days (IQR four days) and their median age when auditory brainstem-evoked response (ABR) was done was 58 days (IQR 56 days). Based on the findings of ABR, 32 (12.8 percent) infants had unilateral or bilateral SNHL. There was no significant difference in the peak total serum bilirubin levels between infants with SNHL (median 333 umol/L, IQR 57) and those without (median 340 umol/L, IQR: 58) (p-value is 0.3). The sensitivity of OAE for detecting SNHL was 15.9 percent, and its specificity 95.2 percent. The sensitivity of the Sabre Compac portable AABR machine for detecting SNHL was 40.9 percent and its specificity was 63.2 percent.

Conclusion: Both the OAE machine and the Sabre AABR machine were not sensitive enough for mass screening of SNHL in infants exposed to severe hyperbilirubinaemia.

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Keywords: automated auditory brainstem response, hearing loss, otoacoustic emissions, severe hyperbilirubinaemia, transient-evoked otoacoustic emissions

Singapore Med J 2008; 49(3): 209-214

INTRODUCTION

Bilirubin has been recognised as a neurotoxin since the late 19th century.[1] Autopsy findings showed that certain regions (the corpus subthalamicum, hippocampus, striate bodies, globus pallidus, putamen, cerebellar nuclei, cranial nerve nuclei and auditory pathway) of the neonatal brain, when exposed to severe hyperbilirubinaemia, were characteristically stained by bilirubin.[2,3] A recent report on 30 infants with hearing loss, following exposure to severe hyperbilirubinaemia, suggested that impairment of the cochlea hair cells may be common.[4]

The reported incidence of hearing loss in term neonates, following exposure to severe hyperbilirubinaemia, based on auditory brainstem-evoked response (ABR), was as high as 22%.[5] Early detection of hearing loss during the newborn period has been recognised to be beneficial to infants, as early intervention programmes help to promote normal language development.[6-8] Currently, two methods are available for neonatal hearing screen: the transient-evoked otoacoustic emissions (OAEs) and the ABR. OAE is the most commonly-used method, because it is cheap and simple to operate for mass screening. An OAE machine stimulates and detects sounds created by a biomechanical process originating from the outer hair cells within the cochlea. They are, therefore, sensitive enough to detect outer hair cell dysfunction. OAE evaluation does not, however, detect neural (i.e. eighth nerve or auditory brainstem pathway) dysfunction. Thus, using the OAE for hearing screening in a population where sensorineural hearing loss (SNHL) is common due to conditions such as severe hyperbilirubinaemia, may lead to under-detection of hearing loss. However, some investigators reported that the OAE could detect SNHL, because OAEs are acoustic

responses associated with the normal hearing process,[9,10] and that OAEs would be absent when there is hearing loss of greater than 30 decibel hearing level (dBHL).[11-14]

ABR, on the other hand, reflects activity of the cochlea, auditory nerve, and auditory brainstem pathways. It can, therefore, detect auditory neuropathy (AN) or neural conduction disorders in newborns following severe hyperbilirubinaemia.[15,16] However, ABR needs to be carried out in a soundproof room and takes a long time to perform. Furthermore, the interpretation of conventional ABR requires a trained audiologist. The expense, time, and necessity of interpretation of wave V component by trained personnel, negate the use of conventional ABR as a useful mass hearing-screening tool. Since the 1980s, automated detection of ABR has become commercially available.[17] The automated ABR (AABR) objectively assesses the hearing threshold of an infant under testing, with the assistance of in-built computer software which scores and interprets the brainstem response obtained following the clicking stimuli.[18-20] This feature of the AABR provides the advantages of easy machine operability by non-professionals, and a significant reduction in total test time.

Neonatal hyperbilirubinaemia is a common problem in Malaysia, affecting 75% of the infants during the first week of life and 25%–30% of them develop severe hyperbilirubinaemia (total serum bilirubin level ≥ 300 μmol/L).[21] The primary objectives of this study were to compare the sensitivity and specificity of OAEs and AABR in the detection of SNHL in term neonates exposed to severe hyperbilirubinaemia. The ultimate objective was to determine whether the simple OAE could be used as a tool for mass screening of SNHL in term neonates exposed to severe hyperbilirubinaemia, in developing countries with limited resources.

METHODS

This was a prospective study carried out over a 30-month period (between July 1, 2003 and December 30, 2005) in the neonatal intensive care unit (NICU) of the Hospital Universiti Kebangsaan Malaysia. The study protocol was approved by the Institution Research and Ethics Committees. The inclusion criteria were term infants (gestation ≥ 37 weeks) with birth weight ≥ 2,500 g admitted to the NICU for treatment of severe hyperbilirubinaemia (total serum bilirubin level ≥ 300 μmol/L). The exclusion criteria were preterm infants of gestation < 37 weeks, craniofacial malformation, history of exposure to aminoglycosides, family history of hearing loss, and/or perinatal asphyxia.

Hearing tests using ABR, AABR and OAE were carried out on the infants after successful treatment of severe hyperbilirubinaemia, as was indicated by a serial decrease of serum bilirubin level to < 250 μmol/L, and within 48 hours before discharge from hospital. Written parental consent was obtained prior to hearing tests. The tests were conducted in a quiet room within the NICU by one of two trained technicians. Infants were tested in their own cots and at about half an hour after the last feed. If an infant was restless, testing was postponed until after the next feed. Every infant was tested first with the OAE, followed by the AABR.

The OAE screening was performed with the machine Echo Screen TE (Madsen Electronics, Copenhagen, Denmark) that used transient-evoked otoacoustic emissions. Disposable ear tips were used to cover the probes and seal the ear canals snugly during testing. When a test was completed, the results were displayed on the screen as "PASS" when there was OAE response, and "REFER" when there was no response to a stimulus. When a "REFER" result was obtained, the screening test was repeated twice to confirm the result, as conditions such as vernix or debris plugging the ear canals might temporarily prevent the OAE tone from reaching the cochlear.

The Sabre Compac portable AABR machine (SLE Diagnostics, Croydon, Surrey, United Kingdom) was then used. It had a simple on-line computer for detecting and scoring of the wave V component of ABRs using correlation and amplitude analysis.[17] Three disposable electrodes were attached to an infant under testing: two on the mastoid processes and one on the forehead. The brainstem-evoked response was recorded from the ipsilateral mastoids of an infant via silver/silver chloride EEG scalp electrodes. The auditory stimuli were in the form of alternating clicks of 100 millisecond pulse width presented at a rate of 37.3 times per second (or 33 Hz), and with an intensity of 35 dBHL delivered via bilateral ear probes to the infants. The threshold of the response was set at 40 dBHL. On completion of the screening test, the results were presented as either "PASS" when there was response to stimulus at ≥ 35 dBHL, or "REFER" when there was no response to the clicking stimuli at these settings, suggesting possible SNHL.

The ABR hearing test was carried out on infants in the hospital audiology laboratory, preferably within 48 hours of discharge, by one of the audiology technicians who was not aware of the results of the OAE and AABR tests, or the peak serum bilirubin levels of the infants. The machine used during the study was the Amplaid MK10 (Multisensory System Machine, Milan, Italy). An auditory stimulator software version was incorporated into the machine for data processing. A stimulus generator of evoked potential recorder, produced the required stimulus, which was then delivered via earphones to the infants. The electrical responses were recorded via four disposable scalp electrodes attached to the mastoid processes of an

Table I. Comparison of hearing test results in each of the ears of 250 term infants exposed to hyperbilirubinaemia, using an otoacoustic emission machine and an auditory brainstem-evoked response machine at different hearing thresholds.

Hearing threshold based on ABR test	Hearing test results based on OAE					
	Right ear			Left ear		
	PASS	REFER	Total	PASS	REFER	Total
Normal	226	9	235	208	13	221
Mild SNHL	7	2	9	13	3	16
Moderate SNHL	5	0	5	11	1	12
Severe SNHL	1	0	1	0	0	0
Profound SNHL	0	0	0	0	1	1
Total	239	11	250	232	18	250

OAE: otoacoustic emission; ABR: auditory brainstem-evoked response; SNHL: sensorineural hearing loss

infant's ears, its forehead near the anterior fontanelle and at the vertex of its head, respectively. Each infant was tested at multiple hearing thresholds and the results were reported in decibel of sound pressure level (dBSPL). This was then converted to dBHL by deduction of 30 dBSPL from the measured hearing threshold. Infants detected to have abnormal hearing tests were followed-up and managed accordingly in the ENT clinic.

Using the results of the ABR test as gold standard, normal hearing was defined as having response to sound stimuli ≤ 20 dBHL, mild hearing loss at 21–40 dBHL, moderate hearing loss at 41–70 dBHL, severe hearing loss at 71–90 dBHL, and profound hearing loss at > 90 dBHL.[22] Infants were diagnosed to have AN when their OAE test was normal but their ABR test showed a presence of SNHL.[23] The sensitivity of a test was defined as the proportion of infants with SNHL and who were correctly identified by the test. The specificity of the test was defined as the proportion of infants without SNHL and who were correctly identified by the test. The positive predictive value of a test was defined as the proportion of infants with positive test results and had SNHL. The negative predictive value of a test was defined as the proportion of infants with negative test results and did not have SNHL.

Based on the findings of a previous study,[5] the incidence of SNHL in infants exposed to severe hyperbilirubinaemia was 20%. In order to detect a prevalence of SNHL of 20% (within a five percentage point of the true value) among infants with severe hyperbilirubinaemia (with 95% level of confidence), a minimum sample size of 246 infants was required. The Statistical Package for Social Sciences version 10.1 (SPSS Inc, Chicago, IL, USA) was used for analysis of data. The incidences of SNHL detected by OAE and AABR were compared against that detected by ABR. The sensitivity, specificity, positive predictive values and negative predictive values of the OAE and AABR machines in detecting SNHL were calculated against the gold standards set by the ABR machine.

RESULTS

During the study period, 410 infants were admitted with severe hyperbilirubinaemia (total serum bilirubin ≥ 300 μmol/L). 160 of them were excluded from the study for the following reasons: OAE was not tested (n = 12), AABR was not tested (n = 8), both OAE and AABR were not done (n = 18), OAE and ABR tests were not done (n = 3), AABR and ABR were not tested (n = 5), refused ABR (n = 84), defaulted ABR tests (n =13), and missed all three tests because infants were discharged during public holidays (n = 17). The data of the remaining 250 infants are presented here.

The majority (71.6%) of the infants were Malays, and the rest were Chinese (22.0%), Indians (3.6%) or other ethnic groups (2.6%). Males constituted 58.4% of the infants. The median gestation of the infants was 38 weeks (interquartile range [IQR] 1), and their mean birth weight was 3,117 (standard deviation [SD] 402) g. The median age of onset of jaundice was 3 (IQR 2) days, and the median age of admission was 6 (IQR 3) days. After admission, the median peak total serum bilirubin was 339 (IQR 57) μmol/L with a median peak indirect serum bilirubin of 326 (IQR 56) μmol/L, at a median age of 6 (IQR 4) days. The majority (87.6%) of the infants were treated with only phototherapy. 30 (12.0%) infants had one exchange blood transfusion, and one (0.4%) had two exchange blood transfusions, to reduce their levels of hyperbilirubinaemia.

The most common identifiable factors associated with severe hyperbilirubinaemia were glucose-6-phosphate dehydrogenase enzyme (G6PD) deficiency (21.2%), underfeeding with/without associated dehydration (14.4%) and maternal-foetal blood group incompatibility (12.0%). Extravasation of blood (5.6%) and sepsis (0.8%)

Table II. Comparison of hearing test results in each of the ears of 250 term infants exposed to hyperbilirubinaemia, using the automated auditory brainstem response machine and the auditory brainstem-evoked response machine at different hearing thresholds.

Hearing threshold based on ABR test	Hearing test results based on AABR					
	Right ear			Left ear		
	PASS	REFER	Total	PASS	REFER	Total
Normal	156	79	235	132	89	221
Mild SNHL	7	2	9	10	6	16
Moderate SNHL	2	3	5	6	6	12
Severe SNHL	1	0	1	0	0	0
Profound SNHL	0	0	0	0	1	1
Total	166	84	250	148	102	250

AABR: automated auditory brainstem response; ABR: auditory brainstem-evoked response; SNHL: sensorineural hearing loss

were not common. Similar to the national data, no obvious risk factors of severe hyperbilirubinaemia were found in 46% of the infants.[1] No infants recruited during the study period had any history of exposure to loop diuretics, or clinical evidence of intrauterine infection, meningitis, syndromes such as trisomy 21, or persistent hypertension of the newborns. The median age when OAE and AABR were tested was 8 (IQR 4) days, and the median age when ABR was done was 58 (IQR 56) days. Based on the findings of ABR, 32 (12.8%) infants had unilateral or bilateral SNHL. There was no significant difference in the peak total serum bilirubin levels between infants with SNHL (median 333 μmol/L; IQR 57) and those without SNHL (median 340 μmol/L; IQR 58) ($p = 0.3$).

The majority of the infants with SNHL were of mild to moderate severity (Table I). Only two infants had severe (n = 1) or profound (n = 1) hearing loss. OAE response was abnormal in 5.8% (29/500) of all the ears tested. These included 20% (5/25) of the ears with mild SNHL, and 6% (1/17) of ears with moderate SNHL, but none of the ears with severe SNHL. OAE response was also abnormal in a ear with profound SNHL. Among 256 ears tested to be normal by the ABR, 4.8% (n = 22) of them had abnormal OAE response. Overall, OAE detected only 15.9% (7/44) of the ears with SNHL. The sensitivity of OAE for detecting SNHL was 15.9%, and its specificity 95.2%. It had a positive predictive value of 24.1% and a negative predictive value of 92.1%.

Of the 44 infants with SNHL, 37 had normal OAE response. Based on the criteria of Starr et al, 84.1% (37/44) of the ears with SNHL had AN.[23] Table II compares the results of AABR tests versus those by ABR tests at different hearing thresholds in each of the ears of the 250 infants. The AABR machine detected SNHL in only 32% (8/25) of ears with mild hearing loss, 52.9% (9/17) of ears with moderate hearing loss, but none of the ears with severe hearing loss. It detected correctly the ear with profound hearing loss. Overall, the AABR machine detected only 40.9% (18/44) of ears with SNHL hearing loss and falsely diagnosed abnormal hearing in 36.8% (168/456) of ears without hearing loss. It had a sensitivity of 40.9%, a specificity of 63.2%, a positive predictive value of 9.7% and a negative predictive value of 91.7% in detecting SNHL.

DISCUSSION

Based on the ABR results, the present study confirmed that SNHL in infants exposed to severe neonatal hyperbilirubinaemia was not uncommon (12.8%). Although only a small percentage (5.8% or 29/500) of all the ears tested had abnormal OAE results, our findings supported those of Oysu et al, that severe hyperbilirubinaemia could damage outer hair cells of the cochlea in infants with severe hyperbilirubinaemia.[4] Similar to the jaundiced gunn rat model,[24] the prevalence of AN was very high (84.1% of the ears) in infants exposed to severe hyperbilirubinaemia in the present study.

For a universal neonatal screening programme to be effective, a minimum of 95% of newborn infants must be successfully screened. Our study showed that both the Sabre Compac portable AABR and the OAE machines were not optimal tools for mass screening of newborns at high risk of SNHL. Even though the Sabre Compac portable AABR machine had a higher sensitivity than the OAE machine (Table III), its level of sensitivity and specificity were unacceptably low for mass screening of SNHL. Our findings concurred with those of Rhee et al that severe hyperbilirubinaemia caused primarily retrocochlear damage, and the OAE machine was not a sensitive tool for the detection of SNHL in this group of infants.[25] However, the OAE machine was useful in detecting infants with impaired outer hair cell damage and also for the diagnosis of AN.

If left untreated, any of the conditions mentioned could result in delayed speech and language development, as well as emotional, social and academic difficulties in this

Table III. Comparison of the sensitivity, specificity, positive predictive value and negative predictive value of the Sabre Compac portable AABR machine and OAE machine for the detection of sensorineural hearing loss in term infants with severe hyperbilirubinaemia.

	Sabre Compac portable AABR machine (%)	OAE machine (%)
Sensitivity	40.9	15.9
Specificity	63.2	95.2
Positive predictive value	9.7	24.1
Negative predictive value	91.7	92.1

AABR: automated auditory brainstem response; OAE: otoacoustic emission.

group of high-risk infants.[26] The central auditory nervous system starts developing at five months' gestation and reaches maturation at 8–18 months.[6] Hearing-impaired children who received amplification by six months of age showed far greater language development than children receiving amplification later.[8] In a longitudinal study of young children with hearing loss, Yoshinaga-Itano et al showed that hearing-impaired preschool children identified by six months of age had a significantly higher developmental functioning in general development, expressive and receptive language, and personal-social areas.[7] The hearing screening tool must therefore have very high levels of sensitivity to detect hearing loss early, and at the same time, high level of specificity to prevent high referral rates from overwhelming the workload of audiologists.

The low level of sensitivity and specificity of the Sabre Compac portable AABR in detecting hearing loss in the present study was contradictory to those reported by other investigators, who reported a much higher level of sensitivity (> 85%) and specificity using AABR machines produced by different manufacturers.[27,28] Review of the literature at the time of preparation of this manuscript showed that no studies have been reported to compare the sensitivity and specificity of the various AABR machines in the market for the detection of hearing loss in newborn infants. The results of this study showed that the sensitivity and specificity of any AABR machine should not be assumed without scientific evidence. Due to logistic problems, there was a lag time between the testing of AABR and OAE, and that of ABR during the present study. It is not certain how much this could affect the results of our study. Based on the findings of our study, there is a need to compare the sensitivity and specificity of the various AABR machines for the mass screening of newborns at high risk of SNHL. The OAE machine should not be used alone for mass screening of hearing loss in infants exposed to severe hyperbilirubinaemia.

ACKNOWLEDGEMENTS

This study was fully sponsored by a research grant from the Faculty of Medicine, Universiti Kebangasaan Malaysia (Grant no: FF/31/2001). We would like to thank the following technicians from the Departments of Paediatrics and Otorhinolaryngology* for carrying out the AABR, OAE and ABR tests on our patients: Miss Wan Nurliana Azmi, Mr Muhammad Nazrul Hisham Zulkifully, Mr Azmy Sulaiman, Mr Borhan Liyub*, Mr Roslin Said*, Ms Jamilah Abdul Ghani*, and Miss Anne M Thomas*.

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