Early Human Development (2007) xx, xxx–xxx

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Newborn oto-acoustic emission hearing screening tests Preliminary evidence for a marker of susceptibility to SIDS

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Accepted 1 June 2007

KEYWORDS
Oto-acoustic emissions;
Hearing;
Hearing screen;
Inner ear;
Vestibular;
SIDS

Abstract

Objective: To evaluate the newborn transient evoked otoacoustic emission (TEOAE) hearing screening tests of infants later diagnosed with the sudden infant death syndrome (SIDS).
Study design: In a case-controlled study, the newborn TEOAE hearing screens of 31 infants who subsequently died of SIDS were retrospectively compared to those of 31 newborn infants that survived the first year of life. SIDS cases were individually matched to surviving controls based on gender, term versus preterm age and NICU versus well baby nursery.
Results: The TEOAE screens of SIDS infants demonstrated significantly decreased signal to noise ratios at 2000, 3000, and 4000 Hz ($p<0.05$) on the right side compared to healthy control infants.
Conclusion: Newborns at risk for SIDS are currently indistinguishable from other newborns and are only identified following a later fatal event. A unilateral difference in cochlear function is a unique finding that may offer the opportunity to identify infants at risk of SIDS during the early postnatal period with a simple non invasive hearing screen test. The ability to implement preventative measures well in advance of a potential critical incident would be an important breakthrough.
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1. Background

Sudden infant death syndrome (SIDS) peaks between the second and fourth month of life [1] and remains the most common cause of death in infancy [2,3]. SIDS occurs during sleep and affects males to females in a ratio of 60:40 [3]. The incidence of SIDS in the United States is approximately 0.55 per thousand, although figures vary widely across socio-economic groups [2,3]. The pathogenesis remains a mystery; however, a disturbance in respiratory control is believed to play a prominent role [4]. The inner ear vestibular apparatus has been demonstrated to play an important role in

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0378-3782/$ – see front matter. Published by Elsevier Ireland Ltd.
doi:10.1016/j.earlhumdev.2007.06.001

Table 1 Summary of demographic characteristics of the SIDS and surviving control group

Study groups	SIDS	Controls
N	31	31
Neonatal intensive care unit	5 (16%)	5 (16%)
Well baby nursery	26 (84%)	26 (84%)
Male gender	21 (68%)	21 (68%)

respiratory control during sleep [1,5-8] and vestibular stimulation has been established to modulate the firing of the respiratory central pattern generator [6,9-14]. We therefore hypothesized that an inner ear insult resulting in disruption of vestibular function might play a critical role in the predisposition for SIDS. Inner ear insults can disrupt cochlear and vestibular function concurrently [15-20] and we hypothesized that such an injury could occur in the perinatal period. Newborn hearing screening is now the standard of care in the United States and 90% of infants are screened annually. The objective of this study was to examine newborn hearing screen results to determine if there was evidence of an inner ear abnormality in SIDS infants compared to matched controls in the early postnatal period.

2. Materials and methods

Newborn transient evoked otoacoustic emissions (TEOAE) hearing screen results of 31 infants born in the state of Rhode Island between the years 1993 and 2005 who subsequently died of SIDS were analyzed. Victims of SIDS were identified by their confirmed autopsy reports of SIDS from the Rhode Island Department of Health Infant Mortality Database. Analyzed SIDS cases were: 1994: 1; 1996: 4; 1997: 5; 1998: 4; 1999: 2; 2000: 3; 2001: 5; 2003: 1; 2004: 3; 2005: 3. SIDS cases were individually matched to surviving controls based on gender and full term versus preterm birth. Matched controls were born within 3 days of the SIDS infants. Almost all were born on the same day ($n=21$).

Index cases were also matched for neonatal intensive care unit (NICU) versus routine nursery admission. NICU admission was used as a proxy for preterm birth when gestational age was not available. Surviving controls were selected with a date of birth as close to matched SIDS cases whenever possible. All SIDS infants expired before 1 year of life and all controls survived the first year of life. Hearing screen results were obtained from the Rhode Island Hearing Assessment data tracking system (RITRACK) data base. The method used for hearing screening during the study period was transient evoked otoacoustic emissions (TEOAE). Evoked OAES are used widely for newborn hearing screening. This method does not require electrode placement and provides cochlea-specific information.

The hearing screen protocol during the study period was the following: A small probe was placed in the ear canal and a click stimulus is administered. Equipment used was the Otodynamics ILO-V5 TEOAE screener. Babies in the well baby nurseries were screened in an isolated pram within the nursery to help block room noise. Babies in the NICU were screened in their own prams. The newborn TEOAE hearing screens were performed on all infants in the well baby nursery during the first week of life and before discharge from hospital for infants in the NICU. The TEOAE hearing screen scores measured as signal to noise ratios (SNRs) were recorded at four frequency levels in each ear. A SNR is the difference between the hearing measurement in decibels and the level of background noise. In order for the screen results to be considered a pass, the following conditions must be met: (1) SNR $\geq$ 4 dB at 2, 3, and 4 kHz; (2) a click stimulus level between 74 dB SPL and 86 dB SPL; and (3) $\geq$ 50 sweeps (or averages) of stimulus delivery in which the detected noise floor falls below the software's predetermined acceptance/rejection level. The study was approved by the Women & Infant's Hospital Institutional

Table 3 Analysis of TEOAE signal to noise ratio difference between matched pairs of SIDS and control infants

Signal/noise dB level at the four tested frequencies	SIDS − Surviving control differences			
	Diff	S.E.M.	*N*	p
1500 dB Left	− 1.4	1.80	27	0.4354
1500 dB Right	− 3.78	2.79	22	0.1895
2000 dB Left	− 0.49	1.58	30	0.7577
2000 dB Right	**− 4.04**	1.61	29	**0.0180**
3000 dB Left	− 1.66	1.81	31	0.3638
3000 dB Right	**− 3.96**	1.14	30	**0.0017**
4000 dB Left	− 1.12	1.44	28	0.4431
4000 dB Right	**− 3.59**	1.62	31	**0.0343**

Signal/noise dB level: measurement of hearing in decibels (dB), determined as the difference between a TEOAE signal and level of background noise. **Diff:** difference in signal to noise ratio score between SIDS cases and matched controls. **S.E.M.:** standard error of the mean. *N*: sample size. *p*: statistical significance, taken at $p<0.05$.
The figures in **bold** highlight the differences that are statistically significant. ($P<0.05$).
This table displays the *difference* in S/N ratios between the SIDS cases and *matched* controls. Table 2 displays the *raw unmatched* S/N ratio scores of both groups.

Table 2 Unmatched analysis of raw TEOAE S/N ratio scores

Group	SIDS		Controls	
Ear	Left	Right	Left	Right
1500 dB	6.3 ± 8.0 (29)	7.3 ± 11.3 (25)	8.3 ± 6.6 (29)	9.5 ± 10.0 (28)
2000 dB	12.7 ± 6.9 (30)	11.3 ± 6.8 (30)	13.5 ± 6.8 (31)	15.2 ± 6.2 (30)
3000 dB	13.6 ± 7.8 (31)	13.0 ± 6.8 (31)	15.3 ± 6.4 (31)	16.6 ± 6.7 (30)
4000 dB	14.3 ± 6.5 (30)	12.4 ± 6.7 (31)	15.0 ± 4.8 (29)	15.9 ± 8.4 (31)

2 control infants and 1 SIDS infant were missing signal to noise ratios between 2000 and 4000 Hz in either the right or left ear.

Please cite this article as: Rubens DD, et al, Newborn oto-acoustic emission hearing screening tests, Early Hum Dev (2007), doi:10.1016/j.earlhumdev.2007.06.001

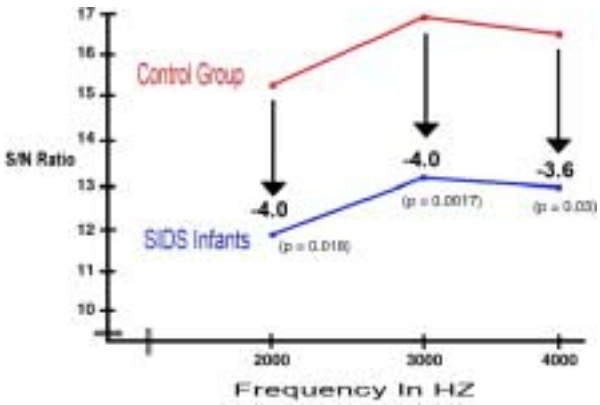

Figure 1 Graph demonstrating the right-sided signal to noise ratio differences in 31 SIDS infants versus matched controls.

Review Board and the Rhode Island Department of Health Institution Review Board. Informed consent was waived.

2.1. Statistical analyses

The screen results were independently evaluated by two audiologists who were unaware of the infant's medical histories. The null hypothesis was applied and the difference in SNR between SIDS cases and matched controls were tested for statistical significance using paired *t*-tests.

3. Results

Sixty-six SIDS cases were identified in the Rhode Island Department of Health Infant Mortality Database during the 12-year period between 1993 and 2005. Of these, 39 were identified in the newborn hearing screening database and 31 had usable TEOAE SNR data with retrievable records. The hearing screen results of the 31 SIDS cases matched with 31 surviving controls were blindly evaluated by two audiologists. Demographic characteristics of the two study groups are shown in Table 1. 16% of both groups were cared for in the NICU and 68% were male. The mean age of death of the infants with SIDS was 3.07 months (S.D. ± 2.33 months). The unmatched mean SNR data at 1500, 2000, 3000, and 4000 Hz of the right and left ears of the 31 SIDS infants and 31 surviving controls are shown in Table 2. The dB response at 2000, 3000, and 4000 Hz trended higher on the right than the left for controls but trended higher on the left than the right for infants with SIDS. The difference between the mean-matched SNRs at 1500, 2000, 3000, and 4000 Hz of matched pairs of SIDS infants and surviving controls are shown in Table 3. The differences for the 3 frequencies that are part of a standard screen pass are shown diagrammatically in Fig. 1. Infants with SIDS had significantly lower SNRs on the right than control infants at 2000, 3000, and 4000 Hz.

4. Discussion

Our results reject the null hypothesis. Significant differences were identified between the TEOAE SNRs on the right at 2000, 3000, and 4000 Hz between infants with SIDS and controls. In addition, infants with SIDS had a reversal of the usual enhanced TEOAE response in newborns on the right. Signal to noise ratios of infants with SIDS consistently trended higher on the left than the right in the 2000–4000 Hz range whereas in the surviving controls the right-sided ratios consistently trended higher than the left. Asymmetries in both ABR and OAE newborn hearing screens have previously been shown by several investigators. Sinninger et al. reported that both male and female infants have greater ABR amplitudes on the right compared to the left and female infants have larger amplitude ABRs than male infants on the right [21,22]. Kei et al. reported greater responses in the right than the left ear using TEOAE in a cohort of 568 infants screened at two months of age [23]. Saitoh et al. identified greater TEOAE signal to noise ratios and response levels in females compared to males, and right-sided responses compared to left in a cohort of 332 infants [24]. The 31 SIDS infants were matched to control infants for gender. The direction of the asymmetry of TEOAE findings in our control group is consistent with prior reports. The direction of the asymmetry among the SIDS infants was reversed and it further supports the potential application of newborn hearing tests for identifying at risk infants.

The important question is what could be a possible mechanism to cause this reversal of TEOAE SNRs in infants with SIDS?

We hypothesize that a perinatal inner ear insult may be associated both with inner ear findings and with other neurological differences associated with SIDS. Placental transfusion differences may play a key role. During delivery of an infant, blood accumulates in the placenta under increasing pressure from the ongoing contractions of labor. Large volumes of placental blood are frequently transfused into the infant's veins at the time of delivery before the umbilical cord is clamped [25,26]. Pressures as high as 115 mm Hg have been recorded in the umbilical vein at this time [26,27]. A possible mechanism is that the inner ear may experience a pressure insult from placental transfusion and that this injury may play an important role in the predisposition for SIDS. Studies have found lower 1-min Apgar scores in newborns with subsequent SIDS versus controls [28–31] lending credence to the proposal that some of these infants may suffer a perinatal insult. The inner ear may be particularly vulnerable to a high venous pressure insult since the veins of the inner ear are supplied directly by large carriageway veins (the internal jugular vein and inferior petrosal sinus) [32,33]. This contrasts with the majority of organs in the body in which the venous supply passes through increasingly smaller tributaries before supplying the organ. As a result, the small end organ veins of the inner ear could rupture and exude blood into the cochlear and vestibular organs when large volumes of placental blood are pulsed under high pressure through an infant's venous system. We propose that the cochlear and vestibular organs may be vulnerable to a high-pressure venous insult since they are mutually encased within the confined space of the temporal bone and share the same venous drainage [32,33]. It is also notable that the cochlear and vestibular hair cells share an extreme sensitivity to pressure changes [15–18] and that vestibular symptoms with high frequency hearing loss are frequently seen following pressure insults [19,20].

Prolonged contractions could consequently create greater pressure in the placenta. This is confirmed by an increased incidence of SIDS with labors lasting longer than 16 h [30] and prima gravida pregnancies [34]. Additionally, a second

delivered twin has more than double the risk of SIDS than a first delivered twin [35].

4.1. Explanation for the right-sided findings

Newborn TEOAE screening tests currently examine hearing only in the 1500–4000 Hz range. The 4000–8000 Hz frequency range is most sensitive to pressure insults [19,20] and therefore a bilateral signal to noise ratio depression in SIDS infants at frequencies above 4000 Hz might be expected. The fact that a difference in signal to noise ratio was only found on the right side in infants with SIDS may be related to the fact that transfused placental blood moving under pressure through a newborn's veins is likely to be preferentially directed to the veins of the right inner ear [36]. The nearly 90° angulation of the left innominate vein away from the line of pressurized blood passing through the superior vena cava (SVC) may afford some protection to the veins of the left inner ear [36]. By contrast, the right innominate vein passes in a straight line from the SVC to the right internal jugular vein allowing pressurized venous blood to impact the right inner ear more directly. This could be associated greater disruption of inner ear hair cells across a wider range of frequencies on the right side.

4.2. Potential relationship between vestibular organ insult and the predisposition for SIDS

Vestibular stimulation has been established to initiate the recommencement of respiration from apnea [1,11,12,37–39] and histological data support apnea as a likely final common pathway in SIDS [40–43]. It is therefore proposed that intact vestibular function may be necessary for maintaining respiration during the vulnerable sleep period in infancy [1,11,12] and that vestibular organ injury may play a critical role in SIDS.

Strengths of this study are that it was based on a conceptual framework, a linkage of data from two statewide databases: hearing screening and infant mortality, was accomplished, and there was a blinded second review by two audiologists of the newborn hearing screen results. Limitations are an observational retrospective design, sample size; the TEOAE SNRs were only available in the 1500–4000 Hz range and there is limited demographic data on the subjects. In this retrospective study of the relationship between TEOAE and SIDS cases, data on sleep position and smoking in the household were not available. Although these variables are known to be associated with SIDS, our study objective was to examine the relationship between TEOAE findings and SIDS. Absence of this information does not affect our findings.

5. Conclusion

A significant decrease in right ear TEOAE signal to noise ratios across three frequencies in 31 infants who died of SIDS is a unique finding that suggests the possibility of a relationship between inner ear findings and SIDS. The utilization of a standard newborn hearing screen to identify susceptibility to SIDS would allow for investigation and preventative measures to be taken in these infants immediately after birth. Including the frequencies above 4000 Hz as a standard for newborn hearing screen tests would be an invaluable step in supporting a large prospective trial and comprehensive analysis of the hearing screens of infants with SIDS. An animal study is planned to investigate a potential association between inner ear vestibular damage and ventilatory control.

Acknowledgements

This study would not have been possible without the support and dedication of the following individuals: Dr. Bruce Beckwith, Dr. Christer Jonmarker, Dr. Anne Lynn, Mr. Don Stephanian., Sam Viner-Brown MS, Mary Catherine Hess MA and the Rhode Island Hearing Assessment Program. A special acknowledgment goes to Ainslie Macleod for his contribution to this paper.

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