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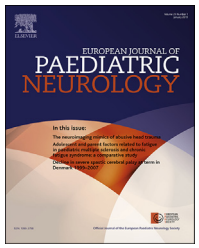

Original article

Hearing impairment and hypoxia ischaemic encephalopathy: Incidence and associated factors

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ABSTRACT

Objective: To establish the local incidence of hearing loss in newborns with Hypoxic Ischaemic Encephalopathy (HIE) and to identify associated risk factors.
Study design: Retrospective Cohort Study. Neonatal Intensive Care Unit (NICU) dual stage hearing screening protocol, including automated otoacoustic emissions (AOAE) and automated auditory brainstem response (AABR) testing.
Results: 57 newborns received therapeutic hypothermia for HIE. Twelve babies (21%) died. Audiology data was incomplete in 3 babies. Complete data was available for 42 babies (male n = 24), 4 (9.5%) of whom had hearing impairment. The development of hearing loss was associated with abnormal blood glucose levels ($p = 0.006$), low Apgar score at 1 min ($p = 0.0219$) and evidence of multi organ dysfunction [high creatinine ($p = 0.0172$ and 0.0198) and raised liver transaminases (aspartate aminotransferase (AST) $p = 0.0012$, alanine aminotransferase (ALT) $p = 0.0037$)]. An association with gentamicin was not found.
Conclusion: This study confirms that hearing impairment is common in term infants who have undergone therapeutic hypothermia for moderate/severe HIE. Blood glucose should be monitored carefully in these infants and developmental surveillance should include formal audiology. Further larger studies are needed to clarify the role, if any, of hypothermia per se in causation of hearing loss and to fully identify risk factors for hearing impairment in this population.
What is new: The current study confirms that hearing impairment is common in term infants who have undergone therapeutic hypothermia for moderate/severe HIE.

No association between gentamicin use and the development of hearing impairment was found however initial blood glucose outside the normal range was of significance.

List of Abbreviations: HIE, Hypoxic Ischaemic Encephalopathy; NICU, Neonatal Intensive Care Unit; AOAE, Automated otoacoustic emissions; AABR, Automated auditory brainstem response; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase.

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Other factors associated with hearing impairment were low Apgar scores, greater need for resuscitation and evidence of multi organ dysfunction (renal and liver failure).

1. Introduction

Therapeutic hypothermia for neonates with moderate to severe HIE has been shown to reduce death and disability without increasing disability in survivors.[1,2] A recent study found hearing impairment to be a common finding among cooled infants.[3] However the risk factors for developing hearing loss in this population are not well established.

Follow up data from the original cooling trials have shown that approximately 4.7% of infants who underwent therapeutic hypothermia for HIE had severe hearing impairment at 18 months of age.[4] A recent study (The NEMO study Treatment of NEonatal seizures with Medication Off-patent) which set out to evaluate the efficacy and safety of bumetanide to treat seizures in this population, closed recruitment early because of concerns regarding hearing impairment.[5] Smit et al., studying 108 babies with moderate to severe encephalopathy who underwent therapeutic hypothermia found a 10.1% incidence of permanent hearing loss.

The objective of this study was to establish the local incidence of hearing loss in newborns with HIE treated with therapeutic hypothermia. A secondary objective was to identify factors associated with hearing loss in this population.

2. Materials and methods

Retrospective case note review was undertaken in a tertiary neonatal intensive care unit in Dublin, Ireland that cares for both inborn and outborn infants. Eligible newborns received therapeutic hypothermia for moderate to severe hypoxic ischaemic encephalopathy in accordance with TOBY criteria. The National Neonatal Transport Programme (Ireland) criteria for therapeutic hypothermia (http://www.nntp.ie/downloads/NNT_Cooling.pdf) were followed in the case of outborn babies who commenced cooling prior to arrival at our institution.

All newborns were also enrolled in the National Universal Newborn Hearing Screening Programme. All infants who fail new born hearing screening (or are contra indicated for new born hearing screening) are offered immediate diagnostic assessments within the HSE Community Audiology services within 4 weeks from screen completion. The diagnostic strategy includes transient oto-acoustic emissions (with a criterion of 3 frequency bands with $\geq$ 6 dB signal to noise ratio). Ear specific tone pip ABR for threshold estimation, utilising the UK NSHP protocols and pass criterion (Ref: 1). Where 4 kHz air conduction thresholds are not present at the pass level (30 dBeHL), bone conduction assessment is performed in order to differentiate conductive or SNHL.

Tympanometry using a high frequency stimulus (1 kHz) is used where clinically appropriate to supplement diagnostic information.

Babies underwent whole body cooling using a servo-controlled machine with a body wrap (Criticool®), to a rectal temperature of 33.0 °C–34.0 °C for 72 h before being gradually rewarmed over a 12 h period.

Anonymised data were collected from medical records and stored in a secure electronic database (Excel, Microsoft ™).

Information collected included delivery details (mode of delivery, Apgar scores, cord blood gases, level of resuscitation required), demographic details (gender, birth weight and head circumference percentiles) and details of initial neonatal course including blood glucose during the initial stabilization period (abnormal blood glucose defined as glucose < 2.6 mmol/L or >10 mmol/L), duration of intubation, seizure history, medications used (inotropes, diuretics, anticonvulsants, antibiotics, nitric oxide) and drug levels as available. An intrapartum sentinel hypoxic event was defined as uterine rupture, placental abruption, umbilical cord prolapse, umbilical cord rupture, amniotic fluid embolus or shoulder dystocia. Measures of renal function (creatinine levels, urine output) and brain magnetic resonance imaging (MRI) findings were also collected.

Baseline characteristics of enrolled babies are shown in Table 1. All babies received empiric antibiotic cover which was discontinued at 36 h in babies with negative cultures and no evidence of sepsis. Gentamicin was administered as a single daily dose of 4 mg/kg every 36 h with trough level routinely checked prior to the second dose if babies were remaining on antibiotics beyond 36 h Some babies due to discontinue antibiotics at 36 h received a second dose of gentamicin but did not have levels checked. If a raised gentamicin level was found, further gentamicin doses were withheld until levels were below 2 mg/L. The National Universal Newborn Screening Programme was introduced in our institution in June 2012.

All enrolled babies underwent the NICU dual stage hearing screening protocol. This included AOAE and AABR testing. Infants who passed the screen were discharged; those who failed the screen were referred for diagnostic Audiological assessment.

Categorical variables were analysed using Fishers exact test and continuous variables were analysed using both the Kruskall Wallis rank and Pearson's r correlation coefficient.

Ethical approval was granted from the local (Rotunda Hospital, Dublin) Research Ethics Committee.

Table 1 – Characteristics of included babies arranged by hearing status (categorical variables).

	Abnormal Hearing (n = 4)	Normal Hearing (n = 38)	P-value[a]
Male	2 (50%)	22 (58%)	0.58
Birth Weight Centile			
<10th	1 (25%)	1 (3%)	0.184
<50th	4 (100%)	16 (42%)	0.04
Emergency Caesarean Delivery	3 (75%)	14 (37%)	0.173
Intrapartum Sentinel Event	1 (25%)	10 (26%)	1
Shoulder Dystocia	1 (25%)	8 (21%)	
Uterine Rupture	0 (0%)	1 (3%)	
Placental Abruption	0 (0%)	1 (3%)	
Umbilical Cord Rupture	0 (0%)	1 (3%)	
Grade of HIE			
2	4 (100%)	35 (92%)	0.74
3	0 (0%)	3 (8%)	
Apgar Score ≤ 3			
1 min	4 (100%)	29 (76%)	0.56
5 min	2 (50%)	7 (18%)	0.196
10 min	1 (25%)	4 (12%)[b]	0.456
Apgar Score 0 at 1 min	2 (50%)	3 (8%)	0.063
Resuscitation at birth			
Nil	0 (0%)	1 (3%)	0.034
Oxygen	0 (0%)	1 (3%)	
Above + IPPV	1 (25%)	9 (24%)	
Above + Intubation	0 (0%)	13 (34%)	
Above + Cardiac Massage	0 (0%)	6 (16%)	
Above + Adrenaline	2 (50%)	1 (3%)	
Above + Fluid Bolus	1 (25%)	7 (18%)	
Adrenaline ± Fluid Bolus	3 (75%)	8 (21%)	0.049
Ventilated	4 (100%)	36 (95%)	0.816
Initial Blood Glucose			
Normal	0 (0%)	29 (76%)	0.006
>10 mmol/L	2 (50%)	6 (16%)	
<2.7 mmol/L	2 (50%)	3 (8%)	
Urine Output – Day 1			
Nil	0 (0%)	1 (3%)	1
<1 ml/kg/h	3 (75%)	29 (78%)	
>1 ml/kg/h	1 (25%)	7 (19%)	
Haematuria/Proteinuria	3 (75%)	9 (30%)	0.115
Positive Septic Screen	0 (0%)	2 (5%)	0.816
Antibiotics			
None	0 (0%)	1 (3%)	0.754
Gent, Normal Dose Pen	3 (75%)	19 (50%)	
Gent, High Dose Pen	1 (25%)	4 (11%)	
Gent, Cef, Normal Dose Pen	0 (0%)	6 (16%)	
Gent, Cef, High Dose Pen	0 (0%)	6 (16%)	
Other	0 (0%)	2 (5%)	
Gentamycin Doses			
0	1	1	
1	1	16	
2	1	13	
3	1	1	
4	0	3	
5	0	2	
6	0	1	
7	0	1	
Gentamicin Levels			
Not Measured	3 (75%)	28 (74%)	1
Normal/Low	1 (25%)	7 (18%)	
Raised	0 (0%)	3 (8%)	
Seizures			
None	1 (25%)	21 (55%)	0.267
Single	2 (50%)	13 (34%)	
Recurrent	1 (25%)	4 (11%)	
Medications Received			
Anticonvulsants	3 (75%)	15 (41%)[c]	0.216
Inotropes	2 (50%)	4 (11%)	0.091
Inhaled Nitric Oxide	1 (25%)	1 (3%)	0.184
Frusemide	1 (25%)	0 (0%)	0.095
Sedation	3 (75%)	35 (92%)	0.341
Abnormal MRI Brain	3 (75%)	11 (30%)[c]	0.07

Gent: Gentamicin, Pen: Benzylpenicillin, Cef: Cefotaxime.
[a] Fisher's exact test.
[b] n = 33.
[c] n = 37.

3. Results

Between June 2012 and March 2016, 57 newborns (27 outborn) received therapeutic hypothermia for HIE. Twelve babies (21%) (9 outborn) died in the initial neonatal period and therefore did not have hearing screening. Data was incomplete in a further 3 babies. In one infant cooling was discontinued early and the baby was transferred for neurosurgical evaluation of an intracranial bleed; the remaining two infants did not have hearing screening [out of jurisdiction (1) and parents declined screening (1)] Complete data was available for 42 babies, 4 (9.5%) of whom had hearing impairment. Diagnostic audiological assessment of babies who failed the newborn hearing test (AOAE and AABR) identified four children with sensorineural hearing loss.

This is classified as a mild unilateral loss in one child. The remaining 3 children have bilateral hearing loss. There is a moderate high frequency sensorineural loss in 2 children who are currently not aided but are being monitored in Audiology. The final child has a bilateral profound sensory neural loss and has amplification provided bilaterally.

Basic characteristics of the babies are outlined in Table 1.

On univariate analysis abnormal glucose recording in the first postnatal hour ($p = 0.006$), Apgar Scores at 1 ($p = 0.0219$) and 10 min ($p = 0.0219$) and degree of resuscitation at birth ($p = 0.034$) were associated with hearing impairment. Birth weight below the 50th percentile was also of significance ($p = 0.043$). Statistically significant higher creatinine levels on the first, second and third days post-delivery were observed in infants who developed hearing loss compared to those who did not ($p = 0.0172$, 0.0198 and 0.0409 respectively). However urinary output and presence of haematuria and proteinuria were not significant. When individual liver function tests were examined AST and ALT were of significance (p values = 0.0012 and 0.0037 respectively) (Fig. 1). Grade of encephalopathy, presence of a sentinel event and seizure history were not of significance. Likewise, medications including anticonvulsants, sedation and diuretics (furosemide) were not associated with hearing impairment (Table 2).

Three of the four infants with hearing impairment received gentamicin. Only 1 baby with hearing impairment had levels

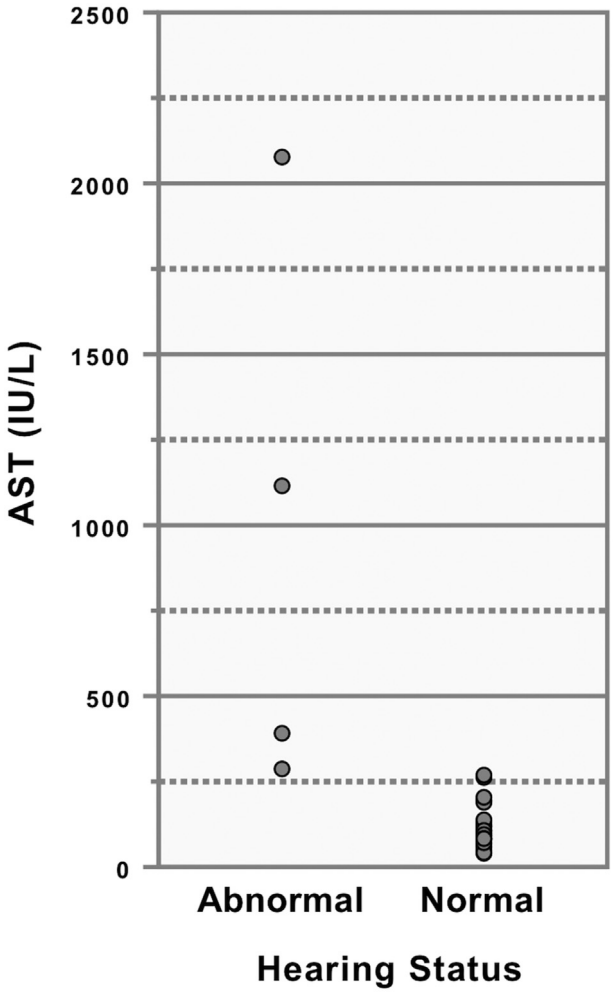

Fig. 1 – Scatterplot of aspartate aminotransferase (AST) measurements arranged by hearing status.

performed and that baby received 3 doses of gentamicin. Gentamicin level in that baby was <2 mg/l. Of the remaining two babies with hearing impairment who received gentamicin, one baby received a single dose and the second baby received two doses. Sixteen babies with normal hearing received a single dose of gentamicin and thirteen babies received two doses. Only 8 babies with normal hearing received more than 2 doses of gentamicin, with only 2 babies receiving greater than 5 doses (Table 1). Four babies who had received two doses of gentamicin also had levels performed. Only three babies had gentamicin levels above 2 mg/l and all with a raised gentamicin level had normal hearing. There was one confirmed case of sepsis in the normal hearing group and none in the hearing loss group.

4. Discussion

This study revealed a high incidence of hearing impairment (9.5%) amongst term infants treated with therapeutic hypothermia for HIE. Hearing impairment was associated with abnormal blood glucose in the first hour after delivery, low Apgar scores, need for resuscitation and raised creatinine and liver function tests in the initial days following birth. These findings are in keeping with the published literature, which report rates of hearing impairment in survivors of HIE treated with therapeutic hypothermia of 3.5–10.1%.[2,3,6,7] Reported rates in survivors not in receipt of therapeutic hypothermia are 5.5–6.4%.[2,6,7] The mortality rate of 21%, is also in keeping with published data of 12.5%–33%.[2,6,7]

Smit et al. found that hearing impairment was associated with a high trough gentamicin level, hypoglycemia and a low cord pH.[3] The current study found similar results in relation to abnormal glucose recordings. Due to small sample sizes hypoglycaemia and hyperglycaemia were not examined independently. Given the time critical period for initiation of therapeutic hypothermia most babies were admitted within 1 h following delivery. Glucose measurement is routinely performed on all babies at the time of admission. Therefore, there was no significant variance in the timing of glucose measurements between inborn and outborn babies. Hypoglycaemia in the immediate newborn period reflects exhausted reserves following prolonged labour and/or resuscitation and is a recognised risk factor for poor neurodevelopmental outcome especially in babies with HIE.[8] Given the known associations between hypoglycaemia and poorer outcomes, hypoglycaemia is very carefully managed in this population. Following stabilization, the glucose infusion rate was adjusted to maintain glucose levels within normal ranges ($\geq$3 mmol/L $\leq$ 10 mmol/L) in all babies. All four infants in the study who developed hearing loss had abnormal initial blood glucose levels, 2 < 2.7 mmol/L and 2 > 10 mmol/L. The mechanisms by which hypoglycaemia and/or hyperglycemia may cause hearing impairment are not well understood, however neuropathy and/or microvasculopathy are potential pathways.

Importantly, hearing impairment was not associated with raised gentamicin levels. Gentamicin has a narrow therapeutic window in neonates and has potential nephrotoxic and ototoxic effects. Our local gentamicin policy reflects this and our dosing regimens are 36 hourly compared to 24 hourly in the study by Smit et al.[3] In addition, given the local unit policy of discontinuing antibiotics at 36 h in newborns with no evidence of sepsis, the majority of babies received only a single dose of gentamicin. All babies who received more than two doses of gentamicin had levels recorded. Only three had levels above 2 mg/l and all with a raised gentamicin level had normal hearing. In contrast, 90% of the infants with hearing impairment in the study by Smit et al.[3] had gentamicin levels greater than 2 mg/l. However, rates of hearing impairment in the current study were only marginally lower than those found by Smit et al. (9.5% vs 10.1%). This raises the question of whether raised gentamicin levels were significant in causation of hearing impairment in that study.[3]

The use of other medications was recorded. However although all babies receive empirical antibiotics the use of other medications is not standard. Larger studies are needed to determine if medications in the setting of hypothermia play a role in the development of hearing impairment. Likewise, due to small number the use of inotropes and an abnormal MRI brain were not of statistical significance but our results would suggest that they should be included as variables of interest in larger studies.

Table 2 – Characteristics of included babies arranged by hearing status (continuous variables).

	n	Median	IQR	Range	P-value[a]
Umbilical Venous pH					
Normal Hearing	33	7.21	7.12 to 7.32	6.65 to 7.39	0.0711
Abnormal Hearing	3	6.8	–	6.49 to 7.21	
Umbilical Venous BE					
Normal Hearing	33	−7.7	−12.3 to −4.7	−23.2 to −1.1	0.4137
Abnormal Hearing	2	−12	–	−17.2 to −6.8	
Umbilical Arterial pH					
Normal Hearing	32	7.13	7.03 to 7.25	6.65 to 7.4	0.51
Abnormal Hearing	2	7.04	–	6.79 to 7.29	
Umbilical Arterial BE					
Normal Hearing	32	−8.25	−12.9 to −6.2	−23.2 to −1.9	0.51
Abnormal Hearing	2	−12.25	–	−17.7 to −6.8	
Creatinine (μmol/L) – Day 1					
Normal Hearing	35	70	55 to 90	31 to 129	0.0172
Abnormal Hearing	3	104	–	99 to 113	
Creatinine (μmol/L) – Day 2					
Normal Hearing	28	52	47 to 75	30 to 119	0.0198
Abnormal Hearing	2	124	–	123 to 125	
Creatinine (μmol/L) – Day 3					
Normal Hearing	22	50	43 to 68	29 to 101	0.0409
Abnormal Hearing	3	84	–	52 to 112	
AST (IU/L)					
Normal Hearing	36	96.5	82 to 123	40 to 269	0.0012
Abnormal Hearing	4	753	313 to 1837	287 to 2077	
ALT (IU/L)					
Normal Hearing	37	31	22 to 46	11 to 185	0.0037
Abnormal Hearing	4	197	134 to 424	117 to 495	
Antibiotic Course Duration (hours)					
Normal Hearing	37	48	36 to 97	1 to 240	0.454
Abnormal Hearing	3	48	–	36 to 48	
Hours of Ventilation					
Normal Hearing	36	101	69 to 116	0 to 147	0.082
Abnormal Hearing	4	129.5	84 to 186	72 to 200	

BE: Base Excess, AST: Aspartate Aminotransferase, ALT: Alanine transaminase, IQR: Interquartile range presented as 25th to 75th centiles (weighted average), Range: Minimum to Maximum.
[a] Kruskal Wallis test.

The association of hearing impairment with low Apgar scores, greater need for resuscitation and evidence of multi organ dysfunction (renal and liver failure) is not surprising. A sentinel event (often associated with greater initial neonatal depression and greater evidence of multiorgan dysfunction) did not appear to be associated with hearing impairment.

The role of therapeutic hypothermia per se in the development of hearing loss is of interest but cannot be addressed by this study. Review of outcome data from a cohort of 75 survivors with moderate or severe HIE born in our institution (2001–2008) prior to the introduction of therapeutic hypothermia shows a rate of hearing impairment of 4.5% (9/75 children lost to follow up; 3/66 with follow up diagnosed with hearing impairment). As universal hearing screening was not in place this may be an under estimate. Interestingly, there is some evidence that mild localized therapeutic hypothermia may be of clinical benefit as a treatment of sudden hearing loss in adults.[9]

While this study is limited by small sample size it does confirm that hearing impairment is common in term infants who have undergone therapeutic hypothermia for moderate/severe HIE. Blood glucose should be monitored carefully in these infants and developmental surveillance should include formal audiology. Further larger studies are needed to clarify the role, if any, of hypothermia per se in causation of hearing loss and to fully identify risk factors for hearing impairment in this population.

Declarations of interest

There is no potential conflict of interest, real or perceived and no funding or sponsor was involved with this study.

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