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Histologic Chorioamnionitis and Acute Neurologic Impairment in Premature Infants

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Abstract

Objective—To determine if histologic chorioamnionitis is associated with acute neurologic impairment as evaluated by auditory brainstem response in premature infants.

Methods—A prospective study was performed to compare auditory neural function at birth between premature infants with maternal histologic chorioamnionitis and infants without maternal histologic chorioamnionitis. Our inclusion criteria was 28–33 weeks gestational age infants who had maternal placental histopathology performed. Infants with TORCH infections, chromosomal disorders, cranio-facial anomalies, and/or unstable condition were excluded. Bilateral monaural auditory brainstem evoked responses were performed using 80 dB nHL click stimuli at a repetition rate of 29.9/sec within 48 hours after birth.

Results—Of 101 infants who met study criteria, 29 infants were born with history of maternal histologic chorioamnionitis. There were no significant differences between infants with histologic chorioamnionitis and infants without histologic chorioamnionitis in perinatal factors except for gestational age, pregnancy induced hypertension, and exposure to antenatal magnesium sulfate. After controlling for confounders, histologic chorioamnionitis was not associated with prolonged absolute wave latencies I, III, and V and/or decreased frequency of mature auditory waveform compared to infants without histologic chorioamnionitis.

Conclusion—Histologic chorioamnionitis is not associated with neurologic impairment at birth in premature infants.

Keywords

neurologic impairment; histologic chorioamnionitis; premature infants; white matter injury; periventricular leukomalacia

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INTRODUCTION

Neonatal infection, congenital or postnatal, is considered to be one of the major risk factors for cerebral palsy in neonates.[1, 2] Several studies have also reported association between intraamniotic infection (also called chorioamnionitis) and neurodevelopmental delay or cerebral palsy in neonates.[3, 4] There is also growing evidence that suggests that histologic chorioamnionitis, a condition more common than clinical chorioamnionitis among infants born prematurely[5], is associated with cystic periventricular leukomalacia (PVL), white matter injury, and abnormal long-term neurologic outcome in premature infants.[3, 6–9] These adverse neurological effects associated with histologic chorioamnionitis and usually detected a few weeks after birth using neuroimaging studies are thought to be mediated by fetal inflammatory response and elevated fetal cytokine concentration.[8, 9] Although several studies have demonstrated association between histologic chorioamnionitis and adverse neurological effects at a later age, little is known if histologic chorioamnionitis is associated with neurological dysfunction or impairment soon after birth in premature infants.

Auditory brainstem evoked response (ABR) is a non-invasive neurophysiologic assessment of the auditory nervous system and has been used to evaluate the effect of perinatal factors on brain in premature infants.[10, 11] The ABR waveform in term neonates is comprised of 3 waves (I, III, and V). [12] Electrophysiologic data have shown that wave I is generated peripherally in the auditory nerve.[13] Wave III reflects the firing of axons exiting the cochlear nuclear complex in the brainstem, while wave V primarily reflects an action potential generated by axons from the lateral lemniscus at a more rostral brainstem location. [13] The changes in wave I latency reflect the changes in the auditory pathway at auditory nerve level, while the changes in waves III & V latencies reflect the changes in the auditory pathway at the brainstem level.[13] Since waves I, III, & V are not always detectable in premature infants 33 weeks gestational age (GA), the ABR waveform can also be categorized as a Response Type based on the replicability of the response and the presence of wave III or wave V.[12] The categorization of the ABR waveform provides a useful approach and has been previously used to evaluate effects of perinatal factors on the auditory nervous system in extremely premature infants.[10, 11] This study seeks to determine if histologic chorioamnionitis is associated with neurologic impairment in 28–33 weeks GA infants as evaluated by ABR soon after birth. The study was approved by the Institutional Human Subject Review Board.

METHODS

Study Design

This is a prospective observational study performed to evaluate and compare auditory changes during the first 48 hours after birth between premature infants with histologic chorioamnionitis and premature infants without histologic chorioamnionitis. Parental consent was obtained for each subject enrolled in the study.

Study Population

All infants 28–33 weeks GA at birth who were delivered at the University of Rochester Medical Center between July 2007 and November 2008 and participated in the primary ABR study were eligible if placenta was collected at the time of delivery and evaluated for histologic chorioamnionitis by the pathologist. Infants with craniofacial anomalies, chromosomal disorders, TORCH infections (toxoplasmosis, other infections, rubella, cytomegalovirus infection and herpes simplex), or those who were too clinically unstable and on high frequency ventilator for a reliable ABR testing between 24–48 hours after birth were excluded.

GA was assessed by obstetrical dating criteria, or when obstetrical data was inadequate, by Ballard exam. Data were prospectively collected on demographics, maternal diabetes, clinical chorioamnionitis, maternal thyroid disorders, pregnancy induced hypertension, *in utero* exposure to cocaine and other illicit drugs, use of antenatal magnesium sulfate, use of antenatal indomethacin, antenatal steroid exposure, mode of delivery, 5 minute Apgar 3, respiratory distress syndrome, and total serum bilirubin concentrations prior to ABR testing between 24 and 48 hours after birth.

Exposure Variable – Histologic Chorioamnionitis

The institutional policy is to collect placenta on all infants delivered prematurely at the University of Rochester Medical Center for evaluation of placental pathology. Each placenta is then evaluated by an experienced pathologist for any histologic chorioamnionitis as a standard of care. The histologic chorioamnionitis was further graded into those with histologic characteristics of fetal inflammatory response (funisitis and/or chorionic vasculitis) and those without histologic characteristics of fetal inflammatory response.

Outcome Variable - Auditory Brainstem Evoked Response

ABRs were recorded with a Biologic Navigator Evoked Response System with the subjects lying supine in the isolette and skin temperature $> 35.5^{\circ}\text{C}$. Testing was performed by audiologists skilled in the administration of ABR tests to premature infants. Electrode sites were mastoid (reference), midline on high forehead or crown of the head (active), and shoulder (ground). Electrode gel was applied to silver/silver chloride electrodes. Bilateral monaural ABR tests were performed between 24 and 48 hours after birth using 80 dB nHL broadband click stimuli with insert earphones. The clicks were presented at a repetition rate of 29.9/sec, and three runs of 2000 repetitions were recorded for each ear. The 2 most replicable runs for each ear were averaged and used for analysis. The ABRs were analyzed by the audiologists without knowledge of GA, clinical characteristics, or placental pathology. The ABR findings from both ears in each subject were used for the analyses of absolute latencies. In addition, ABR findings from the better ear in each subject were used for the analysis of absolute latencies.

In addition, tympanometry using a 1000 Hz probe was performed in each subject to rule out middle ear disease. Transient otoacoustic emission tests were performed to rule out outer hair cell dysfunction.

Since ABR waves I, III, and V cannot be detected in all premature infants < 33 weeks GA, ABR waveforms were categorized into Response Types based on response replicability and peak identification: Type 1, a waveform with normal morphology and replicable waves III and V (mature response type); Type 2, a replicable response with either a wave III or V; Type 3, a replicable response with neither a wave III or V; Type 4, a waveform with no replicable response.[12] If the waveform was Type 1 or Type 2, latencies for waves I, III, & V were measured. If the Response Type was 1 in both ears, it was considered a mature ABR Response Type for that particular subject.

Sample Size Calculation

An approximate sample size was determined for the number of neonates to be studied based on earlier findings of ABR maturation study.[11, 12] Based on earlier findings, 15 subjects in each group would allow detection of actual difference of 0.7 msec (equal to > 0.75 standard deviation) for absolute latencies for 28–33 weeks' gestational age infants with an α level of 0.05 and a power of 0.80. [11, 12]

Statistical Analyses

Analyses were performed using SAS (version 10, SAS Institute Inc, Cary, NC). The subjects with histologic chorioamnionitis and those without histologic chorioamnionitis were compared using 2-sample t-tests for continuous variables and the Chi-square or Fisher's exact test as appropriate for categorical variables. Repeated measure analysis using linear mixed model was carried out to test the difference in better ear absolute latencies between infants with histologic chorioamnionitis and infants without histologic chorioamnionitis, with I, III, and V absolute latencies as multiple outcomes for each subject. Variables associated with histologic chorioamnionitis or auditory changes on bivariate analysis ($p < 0.1$) were considered potential confounders and included in regression analysis. Unstructured variance covariance matrix was specified. The significance level of the data analysis was set at 0.05.

RESULTS

Demographics

A total of 142 infants, 28–33 weeks GA, were born and admitted to the Neonatal Intensive Care Unit at the University of Rochester Medical Center between July 2007 and November 2008. Of these, 10 infants were excluded (1 infant died within 24 hours after birth, 7 were unstable for ABR evaluation, 1 infant had chromosomal syndrome, and 1 infant had craniofacial anomaly). Of remaining 132 infants, 101 consented and had placental pathology evaluated. Twenty nine infants were born to mothers with histologic chorioamnionitis and 72 premature infants were born to mothers without histologic chorioamnionitis. Among 29 infants with maternal histologic chorioamnionitis, 3 infants were born with maternal history of clinical chorioamnionitis while among 72 infants without histologic chorioamnionitis, one infant was born with maternal history of clinical chorioamnionitis. The diagnosis of clinical chorioamnionitis was at the discretion of the attending obstetrician. Among 29 infants with maternal histologic chorioamnionitis, 9 infants were born to mothers with evidence of placental histologic characteristics of fetal inflammatory response. None of the subjects had

hypoglycemia prior to ABR evaluation. The clinical characteristics of the study subjects as a function of histologic chorioamnionitis are shown in Table I. There were no significant differences between the two groups in clinical characteristics and perinatal factors except for GA at birth, exposure to antenatal magnesium sulfate, and pregnancy-induced hypertension.

ABR Wave Latencies

None of the study subjects had an abnormal oto-acoustic emission test or tympanometry suggesting that none of the infants had middle ear disease or outer hair cell dysfunction that may prolong absolute wave latencies. The stratified analysis for the effect of histologic chorioamnionitis on each of the absolute latencies are provided in Table II. There was a trend for absolute latencies I, III, and V of each ear to be prolonged in infants with histologic chorioamnionitis compared to infants without histologic chorioamnionitis, however the differences in absolute latencies were not statistically significant. Similarly, there was no significant difference in absolute latencies I, III, and V using better ear findings for each infant between the two groups. By fitting the linear mixed effects model with better ear absolute latencies I, III, and V as multiple responses for each subject, there was no significant difference in absolute latencies I, III, and V between the two groups after controlling for GA, pregnancy-induced hypertension, exposure to magnesium sulfate, small for GA, and maternal illicit drug usage ($p = 0.5$). In a subgroup analysis excluding infants born with maternal history of clinical chorioamnionitis ($n = 4$), there was no significant difference in better ear absolute latencies I, III, and V between 26 infants born to mothers with isolated histologic chorioamnionitis and 71 infants born to mothers without histologic chorioamnionitis after controlling for GA, pregnancy-induced hypertension, exposure to antenatal magnesium sulfate, small for GA, and maternal illicit drug usage ($p = 0.63$).

ABR Response Types

There was no statistically significant difference in the frequency of mature ABR Response Type between infants with histologic chorioamnionitis and infants without histologic chorioamnionitis as shown in Table II. Among 72 infants without chorioamnionitis, 19 had a complete ABR waveform (all three absolute waves present), while 10 out of 29 infants with histologic chorioamnionitis had a complete ABR waveform. The difference in the frequency of complete ABR waveform between the two groups was not significant ($p = 0.4$).

DISCUSSION

Compared to term infants, premature infants are at increased risk for abnormal neurodevelopmental outcome, including cerebral palsy.[14–16] With improving survival of premature infants in recent years, improving the neurodevelopmental outcome for these premature infants has been a major challenge. The identification of individual clinical risk factors contributing towards abnormal neurodevelopmental outcome is of paramount importance before any specific interventions can be performed to improve the neurodevelopmental outcome of premature infants. Recently, histologic chorioamnionitis has been associated with subsequent diffuse white matter injury and cystic PVL, neuroimaging findings that usually manifest weeks after premature delivery.[6–9] These late neuroimaging findings account for majority of abnormal neurological outcomes seen in

early childhood, including cerebral palsy in premature infants.[17, 18] However, little is known if histologic chorioamnionitis is associated with neurologic impairment or dysfunction in premature infants soon after birth. A positive association between histologic chorioamnionitis and neurologic impairment at birth will provide a supportive evidence for a likely causal association between histologic chorioamnionitis and later neurological findings. Our findings suggest that histologic chorioamnionitis is not associated with neurologic impairment when evaluated by ABR soon after birth in 28 to 33 weeks GA infants.

Although there is conflicting evidence from several independent observational studies regarding the association between chorioamnionitis and cerebral palsy, the meta-analysis of observational studies found significant association between chorioamnionitis and cerebral palsy in both term and preterm infants.[2–4, 19–23] There are several proposed mechanisms by which chorioamnionitis may cause white matter injury and abnormal neurological outcome among neonates, including premature delivery, perinatal asphyxia, neonatal sepsis, and fetal systemic inflammatory response.[2] Since chorioamnionitis is often associated with preterm delivery and asphyxia, controlling for prematurity and asphyxia often abolishes the association between chorioamnionitis and abnormal neurological outcome.[18, 24] Although a cause and effect relationship has not been established, the available literature suggests that chorioamnionitis may contribute to cerebral palsy by increasing the risk for cystic PVL and diffuse white matter injury in premature infants.[18, 20, 25–29]. We were unable to evaluate the association between clinical chorioamnionitis and acute neurological impairment as there were only 4 infants with clinical chorioamnionitis for a meaningful statistical analysis.

An increasing body of evidence also suggests that not only clinical chorioamnionitis but subclinical or histologic chorioamnionitis may also be associated with PVL, diffuse white matter injury, and subsequent cerebral palsy in neonates.[2, 3, 6–9, 30] Histologic chorioamnionitis, a condition much more common than clinical chorioamnionitis, is characterized by acute polymorphonuclear leukocytic infiltration of the fetal or maternal side of the placenta or both, and in severe cases, the umbilical cord (funisitis) and fetal blood vessels of the chorionic plate (chorionic vasculitis). According to the proposed cytokine theory, fetal systemic inflammatory response to histologic or clinical chorioamnionitis results in elevated levels of blood inflammatory cytokines.[8, 21, 27, 31, 32] The inflammatory cytokines then mediate white matter injury and subsequent cerebral palsy by affecting oligodendrocyte development in fetal brain. [9, 18, 33–35]

We used ABR as an investigational tool because it has been previously used in premature infants to evaluate acute neurophysiologic effects of perinatal factors such as hyperbilirubinemia and antenatal steroids. The three waves that comprise the ABR waveform represent activity at different levels of the auditory pathway.[13] By evaluating the wave latencies, which are influenced by the degree of myelination, axonal growth, dendritic growth, and synaptic function, inferences can be made about the possible effects of perinatal factors on the auditory neural system, a surrogate outcome for central nervous system.[12] We found a pattern of prolonged absolute latencies in infants with histologic chorioamnionitis compared to infants without histological chorioamnionitis. However, the difference in each of the three absolute latencies between the two groups was < 0.5 SD

(~0.25 msec) and was not statistically significant. We have previously shown that absolute latencies III and V decreases by 0.5 msec and 0.75 msec, respectively by the end of the first postnatal week in 28–32 weeks GA infants.[12] Therefore, the small difference noted in absolute latencies III and V between the two groups soon after birth is unlikely to amount to any clinically significant maturational delay in the auditory system.

Whether our findings could have been different in the presence of severe histologic chorioamnionitis or if ABR evaluations were performed at a later chronological age for a possible delayed effect can only be postulated. Firstly, it is possible that the neurologic response may be related to the severity of histologic chorioamnionitis or presence of histologic markers of fetal systematic inflammatory response. This is supported by the findings of several investigators who have reported association between funisitis and/or chorionic vasculitis, histologic markers of fetal inflammatory response, and adverse neurologic outcomes in premature infants. [6, 8, 36–38] In our study, unstable infants who were most likely to have fetal inflammatory response were excluded as it is technically difficult to perform ABR in unstable infants. Moreover, in our study, few subjects with histologic chorioamnionitis had placental findings characteristic of fetal inflammatory response and may explain our findings of no association between histologic chorioamnionitis and acute neurologic impairment. Secondly, it is also possible that neurological response mediated by inflammatory cytokines secondary to chorioamnionitis may not manifest soon after birth unless accompanied by fetal inflammatory response.[39, 40] The few studies that have reported prenatal white matter injury with chorioamnionitis were all characterized by funisitis.[29, 41] Thirdly, it is possible that ABR interpeak latencies, index of myelination, may be more sensitive and specific outcome measures of neurological impairment secondary to histologic chorioamnionitis.

The major strength of our study is the objective assessment of an ABR outcome after confirming absence of middle ear disease and outer hair cell dysfunction. Moreover, Response Type assignments were done by audiologists without knowledge of placental pathology and infants' clinical characteristics. Placental pathology evaluations were done as part of standard of care without knowledge of ABR findings. Because our study was limited to 28 to 33 weeks GA infants, our findings may not be generalizable to premature infants more than 33 weeks GA. We were unable to perform meaningful secondary analysis to evaluate the effect of placental lesions characterized by fetal inflammatory response such as funisitis on auditory nervous system.[42] We were also unable to compare interpeak latencies, a surrogate marker of myelination. Most premature infants < 33 weeks GA do not have a complete ABR waveform with all three absolute wave latencies necessary for measuring interpeak latencies.

In summary, our findings suggest that histologic chorioamnionitis is not associated with neurological impairment at birth as evaluated by ABR in stable premature infants. Whether histologic markers of fetal inflammatory response such as funisitis are associated with neurological impairment at birth needs to be investigated further. In addition, future studies should also address if histologic chorioamnionitis is associated with specific neurodevelopmental processes such as myelination that can be evaluated using ABR in older premature infants.

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Abbreviations

GA	gestational age
ABR	auditory brainstem evoked response
PVL	periventricular leukomalacia.

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Table 1

Clinical Characteristics of Subjects as a Function of Histologic Chorioamnionitis

	Infants without Histologic Chorioamnionitis (N = 72)	Infants with Histologic Chorioamnionitis (N = 29)	P
Birth weight (g) *	1424 ± 360	1430 ± 406	0.9
Gestational age (wks) *	30.5 ± 1.4	29.5 ± 1.4	0.00
Gender (Male/Female) #	37/35	16/13	0.7
Race (% White) #	72	68	0.5
Small for gestational age (%) #	14	3	0.17
Pregnancy-induced hypertension (%) #	26	6	0.03
Exposure to antenatal magnesium sulfate (%) #	63	38	0.02
Exposure to antenatal indomethacin (%) #	6	10	0.4
Maternal diabetes (%)	4	7	0.6
Maternal thyroid disorders (%) #	11	0	0.1
<i>In utero</i> exposure to illicit drugs (%) #	7	20	0.07
Exposure to antenatal steroids (%) #	82	89	0.5
Exposure to antibiotics for GBS prophylaxis #	50	65	0.2
Rate of C-section delivery (%) #	64	45	0.2
Apgar score at 5 minutes *	8 ± 1	8 ± 1	0.9
Respiratory distress syndrome (%) #	66	62	0.7
Peak total serum bilirubin (mg/dl) *	6.4 ± 1.9	6.4 ± 1.4	0.6

* Mean ± SD using t-test,

proportions analyzed using Chi-square test or Fisher exact test

Table II

Absolute Latencies and Mature ABR Response Type as a Function of Histologic Chorioamnionitis in Premature Infants

	Infants without Histologic Chorioamnionitis (N = 72)	Infants with Histologic Chorioamnionitis (N = 29)	<i>P</i>
<u>Right Ear</u>			
Latency I (msec) *	2.45 ± 0.98	2.86 ± 0.88	0.19
Latency III (msec) *	6.24 ± 1.09	6.47 ± 1.01	0.40
Latency V (msec) *	9.52 ± 1.28	9.75 ± 1.06	0.42
Mature ABR Response Type (%)	66	72	0.57 [#]
<u>Left Ear</u>			
Latency I (msec) *	2.24 ± 0.56	2.50 ± 0.67	0.22
Latency III (msec) *	5.95 ± 0.83	6.14 ± 1.02	0.47
Latency V (msec) *	9.13 ± 1.05	9.37 ± 0.81	0.34
Mature ABR Response Type (%)	68	58	0.36 [#]

* Mean (SD) using t test,

[#] using Chi-square test