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Perinatal inflammation/infection and its association with correction of metabolic acidosis in hypoxic-ischemic encephalopathy

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Abstract

OBJECTIVE—To investigate the decreased response to hypothermia in neonates with hypoxic-ischemic encephalopathy (HIE) and infection, we sought to determine the association of fetal inflammation/infection with perinatal metabolic acidosis.

STUDY DESIGN—We performed a retrospective cohort study of neonates with suspected HIE started on whole-body hypothermia within 6 h of birth that had a cord gas at delivery and placental pathology performed. Neonates were compared based on the presence of clinical and histologic chorioamnionitis. The cord gas at delivery was compared with the initial arterial gas after birth.

RESULTS—In all, 50 out of 67 (74.6%) neonates admitted for therapeutic hypothermia met inclusion criteria. Chorioamnionitis did not affect the cord gas at delivery, but both clinical and histologic chorioamnionitis were associated with a significantly increased metabolic acidosis on the initial neonatal arterial gas.

CONCLUSION—Chorioamnionitis, diagnosed both clinically and histologically, is associated with a persistent state of acidosis in neonates with HIE that may contribute to worse neurologic outcomes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

INTRODUCTION

Chorioamnionitis is an independent risk factor for cerebral palsy in term infants, associated with a 4.1-fold increased risk of cerebral palsy after 36 weeks gestation.[1] The wide prevalence but relatively low absolute frequency of poor long-term outcomes associated with chorioamnionitis have challenged establishing a link between chorioamnionitis and brain injury. Perinatal hypoxic-ischemic injury with an umbilical arterial pH<7.0 is consistent with a peripartum event that may lead to cerebral palsy.[2,3] Despite this, a majority of neonates with perinatal acidemia, as with chorioamnionitis, will have normal long-term neurologic outcomes.[1,2,4] We suspect that among neonates with encephalopathy, chorioamnionitis may contribute to increased morbidity and mortality.

Chorioamnionitis is diagnosed using a variety of criteria: clinical, histopathologic or microbial.[5] The diagnosis of clinical chorioamnionitis is made before delivery allowing the immediate institution of antibiotics. Not all cases of clinical chorioamnionitis will demonstrate histologic chorioamnionitis.[6] Laboratory values, such as amniotic fluid white blood cell count, culture or maternal serum C-reactive protein levels, each has its own limitation in making the diagnosis of clinical chorioamnionitis.[7] Despite imprecise diagnosis before delivery, antibiotic therapy significantly improves neonatal outcomes in cases of clinical chorioamnionitis.[8] Challenges exist in making the diagnosis of clinical chorioamnionitis, however, it remains important given its significant attributable burden to neonatal disease.

Previous studies evaluating the effect of both clinical and histologic chorioamnionitis on umbilical cord gases at birth have found no significant difference on the cord pH or base deficit,[9,10] although these studies did not focus specifically on neonates with encephalopathy at birth. There is evidence to show that increased acidosis following delivery is associated with increased neonatal morbidity.[11] Chorioamnionitis and intrapartum hypoxia-ischemia are independently, and synergistically, associated with brain injury[1,3] but may not follow the same pathway to injury. As chorioamnionitis is not associated with a more severe metabolic acidosis at the time of birth,[9,10] it is unclear how chorioamnionitis and perinatal hypoxia-ischemia may act together to increase the risk of long-term neurologic sequelae.

Whole-body hypothermia has emerged as an effective treatment for the neonate with hypoxic-ischemic encephalopathy (HIE).[12] We sought to study a population of neonates with moderate to severe encephalopathy that qualify for whole-body hypothermia, examining the effect of intrauterine inflammation and infection on perinatal acidemia after delivery. Elucidation of this relationship is necessary to gain insight into how perinatal inflammation and infection may compound the effect of hypoxicischemia on neonatal brain injury.

METHODS

This is a retrospective cohort study of all neonates admitted to the Johns Hopkins Neonatal Intensive Care Unit with suspected HIE treated with whole-body hypothermia initiated within 6 h of birth from two hospitals within our system from January 2007 to June 2015.

This study was approved by our institutional review board, IRB# 00026068. Diagnostic criteria to initiate whole-body hypothermia for neonates in our unit have been previously published.[13] Exclusion criteria for whole-body hypothermia treatment included greater than 6 h of life before initiation, gestational age <35 weeks, severe growth restriction (birth weight <1800 g), major congenital anomaly, severe persistent pulmonary hypertension with anticipated need for extracorporeal membrane oxygenation, coagulopathy with active bleeding and suspected sepsis with severe hemodynamic compromise requiring large doses of pressors.[13] Whole-body hypothermia was initiated within 6 h of birth and continued for 72 h with a goal temperature of 33.5 °C. Infants enrolled in the hypothermia protocol were evaluated by a pediatric neurologist within 12 h of life.

Maternal antepartum and intrapartum as well as neonatal clinical variables were obtained for each case of suspected HIE treated with whole-body hypothermia. Intrauterine growth restriction was defined as an estimated fetal weight less than the 10th percentile for gestational age.[14] Preeclampsia was diagnosed as the presence of proteinuria, edema and new onset hypertension. A sentinel event was defined as a ruptured uterus, abruption, umbilical cord prolapse, amniotic fluid embolism, maternal cardiopulmonary arrest, ruptured vasa previa or significant feto-maternal hemorrhage.[3] Within our institution it is routine practice to attempt to obtain umbilical arterial gases at birth for all deliveries. The initial neonatal arterial blood gas was obtained during the resuscitation of these infants in the delivery room and compared with the cord gas at delivery.

All neonates treated with whole-body hypothermia were independently stratified for comparison by the presence of clinical chorioamnionitis and histologic chorioamnionitis. The clinical diagnosis of chorioamnionitis was made in the presence of maternal fever, with the presence of at least one other finding of fetal tachycardia, uterine tenderness or purulent vaginal discharge as determined by the obstetric team. Patients diagnosed with clinical chorioamnionitis were immediately started on intravenous antibiotics. Placental histopathology was performed by an attending pathologist from our institution. Histologic chorioamnionitis was diagnosed when polymorphonuclear leukocytes were seen in either the chorion or the amnion, or in significant amounts in the subchorionic space. Histologic funisitis was diagnosed when polymorphonuclear leukocytes were seen in the umbilical cord.

Stata version 13 (StataCorp LP, College Station, TX, USA) was used for statistical analysis. Normality for the continuous variables of cord pH and first neonatal cord gas was confirmed using the Kruskal–Wallis rank test. Bivariate analysis of continuous variables was performed using Student's *t*-test. χ^2 or Fisher's exact test was employed to compare categorical variables. Statistical significance was determined by a *P*-value <0.05.

RESULTS

During this 8 and a half year period, 183 neonates were admitted to our neonatal intensive care unit for whole-body hypothermia, of which 67 (36.61%) were born at two hospitals within our health system. Placental histopathology results were available for 50 out of 67 (74.63%) of neonates with an umbilical arterial cord gas at delivery that were treated with

therapeutic hypothermia. An initial neonatal arterial gas was available for all neonates with available placental pathology reports. Clinical chorioamnionitis was present in 10 out of 50 (20%), histologic chorioamnionitis in 16 out of 50 (32%), histologic funisitis in 10 out of 50 (20%) and neonatal bacteremia in 4 out of 50 (8%). Of the 10 patients with clinical chorioamnionitis who had placental histopathology performed, 8 (80.0%) had histologic chorioamnionitis. Of the 15 patients with histologic chorioamnionitis, 8 (53.3%) had clinical chorioamnionitis and 10 (62.5%) had histologic funisitis. Of the four neonates with neonatal bacteremia, three had both clinical and histologic chorioamnionitis.

Maternal and neonatal clinical variables were compared between neonates with HIE treated with hypothermia based on the presence of clinical chorioamnionitis (Table 1). There was a significant increase in oxytocin use during labor in cases of clinical chorioamnionitis. In the presence of clinical chorioamnionitis, neonates were significantly more likely to have neonatal bacteremia.

Histologic chorioamnionitis was associated with a statistically significant difference in race (Table 2); however, race was not associated with significant changes in umbilical arterial ($P = 0.97$) or initial neonatal ($P = 0.28$) pH results. Factors significantly associated with either histologic or clinical chorioamnionitis in Tables 1 and 2 were found not to be independently significantly associated with the pH values or base deficit values in a way that might confound the relationship. Histologic funisitis was present in 62.5% of cases with histologic chorioamnionitis, and histologic chorioamnionitis was also associated with a significant increase in neonatal bacteremia.

The presence of clinical chorioamnionitis did not have a significant effect on either the umbilical arterial gas pH or base deficit at the time of delivery (Table 3). On the initial neonatal arterial gas there was a significant increase in base deficit, and when comparing the umbilical arterial gas at delivery to the initial neonatal arterial gas, the increase in base deficit was statistically significant. There was a trend toward a smaller increase in pH between birth and the time of the initial neonatal gas in the presence of clinical chorioamnionitis. Neonates who received whole-body hypothermia for suspected HIE with histologic chorioamnionitis also had no difference in the pH or base deficit in the cord gas at birth, but had a significantly lower pH after delivery (Table 4). In the absence of histologic chorioamnionitis, there was a significant increase in arterial pH after birth, but in the presence of histologic chorioamnionitis this improvement in pH failed to occur (Table 4). We did not find a statistically significant difference in pH or base deficit in either the cord gas at delivery, the initial neonatal arterial gas after birth, or the change between the two in either the 10 neonates with histologic funisitis or the 4 neonates with neonatal bacteremia.

DISCUSSION

The presence of chorioamnionitis correlates with a deficiency in correcting a severe metabolic acidosis following delivery leading to a prolonged acidotic state in the neonate. This association involving pH is seen with histologic chorioamnionitis. Although this relationship was not significant with clinical chorioamnionitis, there was a trend to suggest this relationship, and the fact that the base deficit increases significantly after birth in the

presence of clinical chorioamnionitis appears to support this relationship. Recent research examining the independent effect of umbilical arterial base deficit and pH at delivery with neonatal neurologic morbidity suggest that worse outcomes with greater base deficit simply reflect a relationship with a decreased pH such that the prognostic significance attached independently to base deficit among acidemic neonates may be questionable.[15] At the same time, it would support the thesis that either clinical or histologic chorioamnionitis appear to impair correction of metabolic acidosis.

We found significant racial differences among patients with histologic chorioamninonitis in our population. Although this may reflect an underlying relationship regarding race/ethnicity and perinatal infection in severe hypoxia, this study was not designed or powered to study this relationship. Regarding the impact on our analysis, we performed analysis of the relationship between racial groups and both umbilical artery gas and neonatal gas, finding that race did not associate with the gas results. Therefore race would not confound the association between infection and acidosis or correction of acidosis.

Higher cesarean rates in the absence of chorioamnionitis likely reflects the wide variety of indications for cesarean delivery among patients who have been in labor for different lengths of time. Chorioamnonitis is more likely to be associated with a pregnancy that undergoes labor with rupture of membranes for a prolonged time before delivery. In our study, non-reassuring fetal heart rate tracing was significantly more common in patients without clinical chorioamnionitis. In the setting of non-reassuring fetal status remote from delivery before the rupture of membranes or labor, when the risk of chorioamnionitis is low, the cesarean delivery rate may be higher.

The association between 5 min APGAR scores and chorioamnionitis likely demonstrates the impact of perinatal infection can have on a neonate independent of specific acidemia at birth. Given that chorio is not associated with pH at delivery, we feel that the relationship between APGAR scores and pH at delivery is independent. The idea that low APGAR scores correlate with correction of acidemia and chorioamnionitis, rather than being a confounder, would seem to work through a similar mechanism.

Hypothermia has become the standard treatment for term and near-term neonates after perinatal hypoxic-ischemic injury as it has been shown to significantly reduce mortality and neurodevelopmental disability in survivors.[12] Unfortunately, around 50% of cooled asphyxiated newborns still suffer poor outcomes, some of which may be related to infection.[16] Perinatal infection increases the vulnerability of the newborn brain to hypoxia-ischemia,[17] and newborns who have been exposed to both chorioamnionitis and perinatal asphyxia may not benefit from hypothermia.

Although a single catastrophic event can be sufficient to cause cerebral palsy, much more often multiple concurrent risk factors precede the injury, and as the number of risk factors increase, the risk for brain injury increases.[18] In a review of 168 neonates born at >34 weeks with cerebral palsy because of antenatal and/or intrapartum conditions reviewed by the Japan Council for Quality Health Care, among all cases delivered for an abnormal fetal heart rate pattern, brain injury occurred in the presence of chorioamnionitis at a higher umbilical

arterial pH, which supports the idea that the fetal brain is susceptible to injury following a lesser degree of metabolic acidosis in the presence of infection.[18] Neonates not affected by chorioamnionitis may have acidemia at birth, but appear to better correct this acidemia. Previous study has demonstrated the significant morbidities associated with prolonged acidosis following delivery.[11] Depending on the duration of the acidemia before delivery, neonatal correction potentially has a significant impact on decreasing neonatal neurologic morbidity and mortality. This suggests that neonatal injury relies not only on degree of acidemia at delivery, but also the duration of acidemia in the neonatal period, and based on this data may explain how histologic inflammation is related to an increase in long-term neonatal neurologic morbidity.

It has been shown in rat pups that sensitizing a neonatal brain injury model with lipopolysaccharide (LPS) injection before the hypoxic-ischemic injury increases the injury to about threefold at normothermia, and that hypothermia is not neuroprotective after LPS-sensitized hypoxic-ischemic injury.[17] In the two hit model of LPS-sensitized HIE, it has been shown that although a single injection of LPS did not induce brain injury, the combination of a single LPS injection and mild hypoxia-ischemia dramatically increases brain injury.[19] Systemic inflammation weakens the blood–brain barrier as shown by an increase in blood–brain barrier permeability to endogenous albumin following intravenous injections of LPS in fetal sheep.[20] These models suggest a lower ability to tolerate a hypoxic insult to the brain in fetuses with severe inflammation or infection.

Perinatal inflammation/infection may affect neurologic injury through the production of fever. There is overwhelming evidence that temperature at the time of or following a hypoxic-ischemic insult can modulate the extent of subsequent brain injury.[21] In the presence of fever, an increase in metabolic demand is associated with a simultaneous increase in cerebral blood flow, which exacerbates the extent of reperfusion injury following hypoxiaischemia.[21] Hypothermia is thought to work by decreasing the cellular metabolic rate as well as reducing excitotoxic products such as free radical or excessive glutamate accumulation among other mechanisms.[22] Hypothermia also has a large suppressive effect on neuro-inflammation, which might be its major mechanism of neuroprotection for neonatal brain injury.[23] Neonatal outcomes following delivery with chorioamnionitis are improved with the intrapartum administration of antibiotics suggesting that *in utero* therapy my alleviate some of this risk. Meanwhile, if histologic findings correlate to an impaired correction of acidemia after delivery, this may support a potential role for placental pathology in guiding neonatal management.

Limitations of this study include that it was a collection of retrospective data, with incomplete availability of cord gas and placental pathology results on all neonates with suspected HIE admitted for therapeutic hypothermia. All neonates had a neonatal arterial gas soon after birth, but the timing was variable with respect to the course of neonatal resuscitation. Strengths of the study include that these high-risk neonates with a rare condition were all managed in the same institution providing uniformity in their care. Whole-body hypothermia is currently administered by a single protocol for all neonates suspected to have HIE, but as more information becomes available on how the presence of other risk factors such as inflammation and infection affect the response to treatment, these

neonates could potentially be triaged to other therapies such as different cooling regimens, erythropoietin, xenon gas, new anti-epileptic drugs and stem cell therapy.[13]

In conclusion, we found that neither clinical chorioamnionitis nor histologic chorioamnionitis were significantly associated with either the cord gas or base deficit at delivery, but that histologic chorioamnionitis was significantly associated with worsening acidosis after birth, whereas clinical chorioamnionits was associated with a worsening base deficit. An inability to correct their metabolic acidemia after birth may lead to a more prolonged metabolic acidosis, which may directly or indirectly explain the decreased response to hypothermia in the presence of inflammation and infection. Better means to identify neonates with inflammation or infection at the time of birth, and interventions to potentially prevent the morbidity associated with inflammation and infection are needed. Ultimately, diagnostic and therapeutic tools to identify and treat the fetus and neonate with inflammation and infection may reduce the duration of acidemia and lead to improved neurologic outcomes in this high-risk population.

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Table 1

Bivariate analysis of neonates with moderate-severe hypoxic-ischemic encephalopathy treated with whole-body hypothermia within 6 h of birth comparing demographics based on the presence of antenatally diagnosed clinical chorioamnionitis

	With clinical chorioamnionitis (n = 10)	*Without clinical chorioamnionitis (n = 40)*	*P-value*
Maternal age, years[a]	22.8 ± 6.2	29.2 ± 7.4	0.01
Nulliparous	3 (30.0%)	23 (57.5%)	0.12
Race			0.51
Caucasian	1 (10%)	10 (25%)	
African-American	8 (80%)	18 (45%)	
Hispanic	1 (10%)	8 (20%)	
Other	0	3 (7.5%)	
Cesarean delivery	4 (40%)	33 (82.5%)	0.01[b]
Oxytocin use during labor	8 (80%)	12 (30%)	< 0.01[b]
Preeclampsia	1(10%)	6 (15%)	0.68
Meconium stained fluid	6 (60%)	14 (35%)	0.15
Intrauterine growth restriction	1 (10%)	3 (7.5%)	0.79
Placental abruption	0	7 (17.5%)	0.15
Sentinel event	4 (40%)	17 (42.5%)	0.59
Nonreassuring FHR tracing	4 (40%)	31 (77.5%)	0.02[b]
Male gender	3 (30%)	14 (35%)	0.76
5 Min APGAR < 7	10 (100%)	27 (67.5%)	0.04[b]
Length of NICU stay (days)[a]	14.5 ± 7.5	13.5 ± 9.0	0.73
Neonatal demise	1 (10%)	1 (2.5%)	0.30
Intraventricular hemorrhage	2 (20%)	2 (5%)	0.17
Seizure activity	4 (40%)	7 (17.5%)	0.12
Neonatal bacteremia	3 (30%)	1 (2.5%)	< 0.01
Histologic chorioamnionitis	8 (80.0%)	8 (20%)	0.01[b]

Abbreviations: FHR, fetal heart rate; NICU, neonatal intensive care unit.

[a] Mean ± standard deviation.

[b] Indicates $P < 0.05$.

Table 2

Bivariate analysis of neonates with moderate-severe encephalopathy treated with whole-body hypothermia within 6 h of birth comparing demographics based on the presence of histologic chorioamnionitis

	With histologic chorioamnionitis (n = *16*)	*Without histologic chorioamnionitis* (n = *34*)	P-*value*
Clinical chorioamnionitis	8 (50%)	2 (5.9%)	0.01[a]
Maternal age, years[b]	28.8 ± 7.8	25.9 ± 6.9	0.20
Nulliparous	9 (56.25%)	17 (50%)	0.68
Race			0.03[a]
Caucasian	0	11 (32.5%)	
African-American	12 (75%)	14 (41.2%)	
Hispanic	3 (18.8%)	6 (17.7%)	
Other	1 (6.3%)	3 (8.8%)	
Cesarean delivery	10 (62.5%)	27 (79.4%)	0.20
Oxytocin use during labor	7 (43.8%)	13 (38.2%)	0.71
Preeclampsia	3 (18.8%)	4 (11.8%)	0.50
Meconium stained fluid	9 (56.3%)	11 (32.4%)	0.11
Intrauterine growth restriction	2 (12.5%)	2 (5.9%)	0.42
Placental abruption	1 (6.7%)	4 (13.3%)	0.28
Sentinel event	5 (33.3%)	16 (47.1%)	0.29
Nonreassuring FHR tracing	9 (56.3%)	26 (76.5%)	0.15
Male gender	12 (75%)	21 (61.8%)	0.36
5 Min APGAR < 7	12 (75%)	25 (73.5%)	0.91
Length of NICU stay (days)[b]	14.6 ± 7.6	13.20 ± 9.3	0.59
Neonatal demise	1 (6.3%)	1 (2.9%)	0.58
Intraventricular hemorrhage	2 (13.3%)	2 (6.7%)	0.59
Seizure activity	5 (31.3%)	6 (17.7%)	0.28
Histologic placental infarcts	1 (6.3%)	5 (14.7%)	0.39
Histologic funisitis	10 (62.5%)	0	< 0.01[a]
Neonatal bacteremia	3 (18.8%)	1 (2.9%)	0.05[a]

Abbreviations: FHR, fetal heart rate; NICU, neonatal intensive care unit.

[a] $P < 0.05$.

[b] Mean ± standard deviation.

Table 3

A comparison of pH and base deficit between umbilical arterial blood at delivery and the initial neonatal arterial gas after delivery in neonates with hypoxic-ischemic encephalopathy treated with whole-body hypothermia based on the presence of clinical chorioamnionitis

	With clinical chorioamnionitis (n = 10)	*Without clinical chorioamnionitis (n = 40)*	*P-value*
Cord blood			
pH	6.97 ± 0.14	7.01 ± 0.12	0.33
Base Deficit (mM)	13.4 ± 6.9	14.4 ± 8.1	0.73
1st Neonatal gas			
pH	7.14 ± 0.16	7.20 ± 0.10	0.18
Base Deficit (mM)	19.4 ± 8.2	12.95 ± 7.3	0.02[a]
Difference			
pH	0.14 ± 0.20	0.24 ± 0.16	0.09
Base Deficit (mM)	5.9 ± 9.8	−1.5 ± 9.5	0.03[a]

Data are presented as mean ± standard deviation.

[a] $P < 0.05$.

Table 4

A comparison of pH and base deficit between umbilical arterial blood at delivery and the initial neonatal arterial gas after delivery in neonates with hypoxic-ischemic encephalopathy treated with whole-body hypothermia based on the presence of histologic chorioamnionitis

	With clinical chorioamnionitis (n = 16)	*Without histologic chorioamnionitis (n = 34)*	**P-*value***
Cord blood			
pH	6.99 ± 0.12	6.96 ± 0.15	0.41
Base Deficit (mM)	13.9 ± 6.5	14.4 ± 8.4	0.84
1st Neonatal			
pH	7.13 ± 0.13	7.20 ± 0.10	0.03[a]
Base Deficit (mM)	15.4 ± 12.2	13.7 ± 4.8	0.45
Difference			
pH	0.14 ± 0.17	0.25 ± 0.16	0.03[a]
Base Deficit (mM)	−1.6 ± 14.2	0.7 ± 7.2	0.45

Data are presented as mean ± standard deviation.

[a] $P < 0.05$.