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SHORT REPORT

Perinatal infection and hypoxic-ischemic encephalopathy: a pilot study

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Abstract

Recent studies suggest a synergic effect of infection and hypoxia-ischemia in the causation of perinatal brain damage. We conducted a prospective pilot study on the presence of infection in hypoxic-ischemic encephalopathy (HIE), focusing on neurotropic viruses. Sixteen newborns with HIE were included in the study. There were no confirmed cases of viral infection. There was a case of bacterial early onset sepsis and four cases of suspected sepsis due to clinical and/or analytical signs, but with negative cultures. Our results do not support universal screening for viral infection in cases of HIE.

Keywords

Asphyxia, C reactive protein, infection, neurological damage, newborn, virus

History

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Introduction

Neonatal encephalopathy is a neurological syndrome with clinical features consistent with a disorder of the brain [1].

Defining the cause of neurological damage is often challenging. For some, the definitive diagnosis of neonatal encephalopathy of hypoxic-ischemic origin (HIE) should be preceded by the exclusion of other disorders such as infection, genetic anomalies, etc. [2]. Nevertheless, HIE is believed to be the appropriate diagnostic characterization of an infant presenting with neonatal encephalopathy and an arterial cord blood gas indicative of metabolic acidosis, depressed Apgar scores, and cerebral imaging features consistent with hypoxic-ischemic disease [3].

However, the role of many antepartum and intrapartum factors in the causal pathway of neonatal HIE remains unclear. Some observations support the role of intrauterine infection; an exposure to infection contributes to intrapartum hypoxia, and aggravates the secondary neuronal damage after cerebral ischemia [4,5]. Although an infection screening is warranted in cases of HIE, whether this screening should include more infrequent pathogens like neurotropic viruses is controversial. Cytomegalovirus is a major cause of congenital viral infection and brain disease. Other viruses like rubella, varicella-zoster, herpes simplex, enteroviruses and the recently discovered human parechoviruses can also cause brain injury to the newborn [4,6]

We conducted a prospective pilot study to evaluate the importance of perinatal infection in HIE, by searching for bacterial, viral and protozoan infection in all newborns diagnosed of moderate-severe HIE from October 2011 to 2013.

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Methods

This is a prospective study including infants above 35 weeks of gestation diagnosed with moderate or severe HIE in Burgos University Hospital during the period of October 2011–2013. This is the tertiary referral center for neonatal hypothermia treatment to a region of 45.000 km^2 situated in the north of Spain, with an estimate of 8.750 annual deliveries. The study protocol was approved by the Hospital's Ethics Committee.

Inclusion criteria were chosen to detect neonates with HIE. Newborns with both (1) poor condition at birth (arterial cord blood pH <7.1 and/or 5-min Apgar score <5 and/or need for major resuscitation), and (2) the presence of moderate–severe neonatal encephalopathy (defined as a clinical syndrome present from birth and characterized by difficulty initiating and/or maintaining respiration, altered consciousness, and abnormal tone and reflexes, with or without seizures) were selected for the study. Infants were excluded if an identifiable metabolic disorder, severe congenital malformation or genetic abnormality which could predispose to the hypoxic-ischemic insult during labor, was diagnosed. All newborns were treated with whole body hypothermia.

Antenatal and perinatal data, as well as details of the clinical course in the neonatal period were recorded. Gestational complications were defined as multiple pregnancy, thyroid disease, diabetes, hypertension/eclampsia, mental health conditions requiring treatment, ultrasound anomalies or threatened preterm labor. All mothers were screened for HIV, toxoplasmosis, syphilis, rubella and hepatitis. Additionally, mothers

Table 1. Demographic characteristics.

Maternal age, mean ± SD, years	32.62 ± 7.5
Pregnancy complications[a], *n* (%)	4/16 (25%)
Gestational age, mean ± SD, week	39.2 ± 1.8
Birth weight, mean ± SD, g	3276.2 ± 610.1
Male:Female ratio	1:1.6
Cesarean delivery, *n* (%)	11/16 (68.8%)
Eutocic delivery, *n* (%)	1/16 (6.2%)
Instrumental delivery, *n* (%)	4/16 (25%)
Sentinel event[b], *n* (%)	4/16 (25%)
5-min Apgar score ≤5, *n* (%)	14/12 (87.5%)
10-min Apgar score ≤5, *n* (%)	7/10 (70%)
Meconium-stained amniotic fluid, *n* (%)	7/16 (43.8%)
Advanced resuscitation[c], *n* (%)	12/16 (75%)
Cord pH ≤ 7, *n* (%)	10/15 (66.7%)
Seizures, *n* (%)	7/16 (43.8%)
Mechanical ventilation, *n* (%)	11/16 (68.8%)
Inotropic support, *n* (%)	12/16 (75%)

[a]Pregnancy complications: 1 olygoamnios, 1 threatened preterm labour, 1 insuline dependant gestational diabetes, 1 hypothyroidism.
[b]Sentinel event: 3 placental abruptions, 1 uterine rupture.
[c]Advanced resuscitation: tracheal intubation ± chest compressions ± adrenaline.

were asked for infectious processes, including varicella during gestation.

The following microbiological studies were performed to the newborns within the first 24 h after birth: (1) bacterial cultures in blood and cerebrospinal fluid (CSF) before the beginning of antibiotic treatment, (2) viral tests in CSF (polymerase chain reaction for cytomegalovirus, herpes simplex 1 and 2, Epstein-Barr virus, enterovirus and human parechovirus).

Results

Seventeen full-term newborns were diagnosed with moderate–severe HIE. One case was ultimately excluded due to a lack of cerebrospinal fluid samples for the study. There were no cases of congenital anomaly or metabolic disorders. There were no cases of intrauterine growth restriction. Demographic features of the included cases are summarized in Table 1.

Two cases (2/16, 12.5%) died from severe HIE and brain necropsy found major damage of hypoxic-ischemic origin. Cranial MRI in survivors was normal in 9/14 cases; the rest showed injury patterns consistent with hypoxia-ischemia (HI): 2/14 showed mainly cortical damage, 2/14 showed white matter damage, and 1/14 had deep nuclear damage.

The microbiological results are shown in Table 2. There were no cases of viral infection. All maternal serologies during pregnancy were normal. There was a case of early onset sepsis by Group B Streptococcus (case 12). Case 3 was diagnosed of sepsis, with a clinical worsening during the first 72 h of life and a peak C reactive protein (CRP) level of 208 mg/L, but cultures were negative. Further, there were three cases that had elevation of CRP (cases 1, 4 and 13) but all microbiological tests remained negative.

Discussion

To the best of our knowledge, this is the most detailed description of infectious characteristics in a series of HIE cases. In the two-year study period there were no confirmed cases of viral infection. There was a case of bacterial early

Table 2. Maternal and neonatal infection test results.

Case *N*	Infection during pregnancy[a]	Maternal serologies (HIV, HBV, siphilis, toxoplasma, Rubella)	Group B streptococcus vaginal/rectal culture	Membrane rupture time (hours)	Signs of chorio amnionitis[b]	Bacterial cultures (blood/CSF)	Viral tests (CSF)	Max CRP 72 h (mg/L)	Max leukocyte count 72 h ($\times 10^{-6}$L)	Min leukocyte count 72 h ($\times 10^{-6}$L)	Min platelet count 72 h ($\times 10^{-6}$L)	Antimicrobial treatment[c] (days/regimen)
1	–	Normal	–	7	+	–/NA	–	63	13 100	7400	149 000	7 b
2	–	Normal	–	6	–	–/–	–	10	20 500	8500	145 000	10 b
3	3rd termurinary infection	Normal	Unknown	0	–	–/–	–	208	25 000	4700	47 000	14 b
4	NA	Normal	–	NA	–	–/–	–	68	16 500	3900	48 000	8 a
5	–	Normal	NA	NA	–	–/–	–	2	40 800	8800	30 000	4 b
6	–	Normal	–	12	–	–/–	–	7	19 000	9400	144 000	5 a
7	–	Normal	+	1	–	NA/–	–	9	12 200	11500	67 000	3 a
8	–	Normal	+	0	–	–/–	–	29	38 400	6500	75 000	5 a
9	NA	Normal	–	9	–	–/–	–	21	10 200	8100	233 000	5 a
10	–	Normal	–	9	–	–/–	–	11	31 500	10400	128 000	5 a
11	NA	Normal	+	4	–	–/–	–	34	10 500	17200	50 000	6 b
12	–	Normal	–	6	–	+/–	–	86	7200	3500	76 000	8 b
13	–	Normal	–	7	–	–/–	–	86	20 000	5900	230 000	7 a
14	–	Normal	–	0	–	–/–	–	19	20 500	8100	50 000	4 a
15	–	Normal	Unknown	0	–	–/–	–	12	33 400	12600	165 000	7 a
16	–	Normal	–	0	–	–/–	–	1	16 800		200 000	no

NA: not available.
[a]Infection during pregnancy: urinary tract infection, genital infection, fever.
[b]Clinical signs of chorioamnionitis: maternal fever + one of the following: maternal leucocytosis (>15 000/$\times 10^{-6}$L), maternal tachycardia (>100 bpm), fetal tachycardia (>160 bpm), uterine tenderness, foul-smelling amniotic fluid.
[c]Antimicrobial treatment regimen: (a) Ampicillin + Gentamicin, (b) Ampicillin + Gentamicin + Others.

onset sepsis and four cases of suspected sepsis due to clinical and/or analytical signs, but with negative cultures. An elevation of the CRP levels was the sole cause of suspicion in three of these cases but these results have to be interpreted carefully, since CRP levels can be increased in HIE and asphyxia [7].

Infections by different pathogens can damage the developing brain [4,6,8]. Intrauterine infection and HI are independent risk factors for neonatal brain injury. Moreover, recent studies show that exposure of the fetus to a combination of infection and intrapartum HI increases the risk of cerebral palsy, compared to hypoxia alone [5]. It is suggested that both infection and HI could lead to neurological damage via a common cellular and molecular pathway [4,5] and lower the threshold at which HI triggers brain injury. Furthermore, recent experimental studies suggest that hypothermia may not be neuroprotective after infection-sensitized neonatal hypoxic-ischemic brain injury [9]. This could have implications when selecting candidates for hypothermia treatment.

Defining the cause of neonatal brain injury is often challenging. Even when all the criteria for HIE are fulfilled it may still be difficult to attribute an infant's clinical signs as solely due to HI [3]. Viral infections are elusive, can often be nonspecific and pass underdiagnosed. Several viruses have been involved in perinatal brain injury. Recently, human parechovirus has been linked to white matter damage in neonates [6,10]. However, the relationship between perinatal infection and hypoxic ischemic encephalopathy has not yet been precisely defined in clinical studies [11]. Hence the debate on the need for a wider infection screening, including neurotropic viruses, in cases of HIE. Our study was designed to focus on neurotropic viral infection in the perinatal period. Additionally we gathered relevant information about infection in the intrauterine period. The main limitation of this study is the small sample size, therefore, our results have to be interpreted with caution. In addition, data regarding infectious events during pregnancy was not available in three outborn patients (as it is shown in Table 2).

We recommend a screening for bacterial infection in all cases of HIE. Our results suggest that neurotropic viral infections are infrequent in cases of HIE. Thus we cannot support performing a systematic screening for neurotropic viruses in confirmed cases of HIE.

Better understanding of the complex interaction between HI and infection can help in the management of these neonates and ultimately reduce the risk of neurodevelopmental impairment.

Declaration of interest

The authors report no conflict of interest.

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