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ORIGINAL ARTICLE

Association of perinatal risk factors with neurological outcome in neonates with hypoxic ischemic encephalopathy

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ABSTRACT

Objective: Neonates exposed to perinatal insults typically present with hypoxic ischemic encephalopathy (HIE). The aim of our study was to analyze the association between known risk factors for HIE and the severity of encephalopathy after birth and neurological outcome in neonates during the first 4 d of life.

Methods: Retrospective cohort study including 174 neonates registered between 2011 and 2013 in the National Asphyxia and Cooling Register of Switzerland.

Results: None of the studied perinatal risk factors is associated with the severity of encephalopathy after birth. Fetal distress during labor (OR, 2.06; 95% CI, 1.02–4.25, $p = .049$) and neonatal head circumference (HC) above 10th percentile (p10) at birth (OR, 1.33; 95% CI, 1.05–1.69, $p = .02$) were associated with neurological benefit in the univariate analysis. Fetal distress on maternal admission for delivery was the only risk factor for neurological harm in the univariate (OR, 0.26; 95% CI, 0.12–0.57, $p < .01$) and the multivariate analysis (OR, 0.15; 95% CI, 0.04–0.67, $p = .013$). We identified two different patient scenarios: the probability for neurological benefit during the first 4 d of life was only 20% in neonates with the combination of all the following risk factors (gestational age >41 weeks, chorioamnionitis, fetal distress on maternal admission for delivery, fetal distress during labor, sentinel events during labor, HC below 10th percentile), whereas in the absence of these risk factors the probability for neurological benefit increased to 80%.

Conclusions: We identified a constellation of risk factors that influence neurological outcome in neonates with HIE during the first 4 d of life. These findings may help clinicians to counsel parents during the early neonatal period. (ClinicalTrials.gov NCT02800018).

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Introduction

Perinatal insults are a leading cause of infant mortality and for survivors, they are frequently associated with neurocognitive impairment, cerebral palsy (CP), and seizure disorders [1]. Neonates exposed to perinatal insults typically present with hypoxic ischemic encephalopathy (HIE). The reported incidence of HIE ranges from about 1 to 8/1000 life-births [2,3]. HIE is a syndrome with nonspecific features characterized by a disorder of neurological function occurring in the first days of life in term and near-term neonates and is defined by difficulty initiating and maintaining respiration, abnormal level of consciousness, depression of tone and reflex responses, and often seizures [4]. Based on such neurological symptoms, HIE is graded into three categories: mild, moderate, and severe [4]. The degree of HIE closely correlates with the risk of future neurological impairment. Importantly, neonates with HIE constitute an inhomogeneous patient group with different etiologies leading to HIE. Previous clinical studies have identified a number of peripartal and socioeconomic risk factors for HIE. The most commonly reported ones in the literature are older maternal age, higher parity, lower socioeconomic status (SES), preeclampsia, bleeding during pregnancy, shoulder dystocia, placental abruption, uterine rupture, abnormal cardiotocography (CTG) on maternal admission or during labor, older gestational age, mode of delivery, abnormal placenta histology or meconium aspiration syndrome [3,5–12]. There is now growing evidence that there is a strong association between prenatal sensitization such as inflammation for example and HIE [1].

A better understanding of the risk factors, hence, the underlying sensitizing events, may be an

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important step toward the design of new and/or adjunct therapies to further reduce the burden of disability in neonates suffering HIE [1,13]. However, therapeutic hypothermia reduces the burden of disability by only 11%.

The aim of our study was to analyze the association of the previously identified risk factors for HIE and the severity of encephalopathy after birth and the neurological outcome in neonates during the first 4 d of life.

Materials and methods

Register centers and data collection

This is a retrospective cohort study including 174 term and near-term neonates born between 2011 and 2013 (≥35 0/7 weeks of gestation at birth). Data of these neonates were extracted from the National Asphyxia and Cooling Register of Switzerland. Eight tertiary level neonatal intensive care units and two pediatric intensive care units take part in the Swiss National Asphyxia and Cooling Registry. Data from pregnancy were collected in the chart notes and data from the neonates were collected prospectively with an electronic case report form (eCRF). Data collection, evaluation, and publication for this study were approved by the Swiss ethical committee and the Swiss Federal Commission for Privacy Protection in Medical Research. The study is registered in ClinicalTrials.gov (NCT02800018).

Patients

The following inclusion criteria had to be fulfilled for cooling: Apgar score of ≤5 at (5)10 min after birth, continued need for resuscitation at 10 min after birth, acidosis within 60 min of birth defined as any occurrence of umbilical cord, arterial or capillary pH ≤7.00, base deficit ≥16 mmol/L, or lactate ≥12 mmol/L and encephalopathy. All included neonates had neurological examinations classified according to Sarnat staging by a senior neonatal consultant performed on days 1, 2, 3, and 4 after birth [4]. According to our register protocol, neonates with Sarnat staging 2 or 3 after birth were cooled [14,15]. Some neonates with encephalopathy staged Sarnat 1 were cooled at the discretion of the clinician in charge because the perinatal history fulfilled the inclusion criteria. Target temperature range of 33–34 °C was reached by whole body cooling and maintained for 72 h. After the maintaining phase the neonates were rewarmed 0.2 °C/h to normothermia (36.5 ± 0.5 °C). Hourly temperature point measures of core temperature by rectal probe were recorded in the registry. All neonates with congenital malformations or syndromes were excluded.

Risk factors

The analyzed risk factors are presented in Table 1. They were categorized into antepartum, intrapartum, and postnatal risk factors.

Antepartum risk factors

SES was calculated according to the recommendations of Largo et al. [16]: SES of the mother plus SES of the father or one of them doubled if one was unknown. In the mother's notes data of drug consumption as alcohol, nicotine, any medication, cannabis, methadone, or cocaine were collected. Neurological diseases of the mother include epilepsy, seizures, migraine, polyneuropathy, multiple sclerosis, depression, anxiety-/panic disorder, post-traumatic stress disorder, burnout syndrome, postnatal depression or psychosis, borderline personality disorder, and mental retardation. Endocrine diseases encompassed obesity (body mass index >30), hypo- or hyperthyroidism and diabetes mellitus. Sarcoidosis, celiac disease, autoimmune-thyroiditis, and lupus erythematodes were summarized as autoimmune diseases. Maternal infection during pregnancy was defined as any of the following infections: urinary tract infection, pyelonephritis, vaginal candidiasis, vaginal chlamydia, Gardnerella or *Escherichia coli* infection, genital herpes, parasitize, upper airway infection, or gastroenteritis. Toxoplasmosis, rubella, cytomegalovirus, herpes virus, hepatitis B, parvovirus B19, varicella zoster virus, and listeria (TORCH) infections were noted. Placenta previa, preeclampsia, anemia, coagulopathy, high blood pressure (only if medically treated), and hemorrhage during pregnancy were defined as antepartum risk factors for hypoxia. Fetal distress on maternal admission for delivery was described by pathological/silent/sinusoidal CTG, decreased fetal movements or fetal tachy- or bradycardia on admission. Microcephaly was specified according to Voigt et al. (head circumference (HC) below 10th percentile) [17].

Intrapartum risk factors

Risk factors for fetal infection include maternal pyrexia (>38.0 °C), premature rupture of membranes and chorioamnionitis. Chorioamnionitis was diagnosed by histopathological findings. Sentinel events were

Table 1. Frequency of the analyzed perinatal risk factors.

Perinatal risk factors	Mean	SD	*n*	%
Demographic data				
Maternal age (years)	31.75	4.99	–	–
Maternal race				
Europe	–	–	150	86.2
South America	–	–	2	1.1
Asia	–	–	4	2.3
Africa	–	–	12	6.9
Socioeconomic status[a]	5.55	2.17	–	–
Women with regular pregnancy checkups	–	–	167	96.0
Maternal conditions and obstetric history				
Drugs[b]	–	–	50	28.7
Neurological disease[c]	–	–	15	8.6
Endocrinological disease[d]	–	–	33	19.0
Autoimmune diseases[e]	–	–	5	2.9
Previous life birth	–	–	70	40.2
Previous cesarean section	–	–	30	17.2
Previous miscarriage	–	–	48	27.6
Infertility treatment	–	–	10	5.7
Antepartum risk factors				
Trauma during pregnancy	–	–	2	1.1
Maternal infection in pregnancy[f]	–	–	26	14.9
Poly-/oligo- or anhydramnios	–	–	12	6.9
Intrauterine infection[g]	–	–	1	0.6
Risk factors for hypoxia[h]	–	–	21	12.1
Twins	–	–	2	1.1
Neonates with malformations or genetic disorders	–	–	12	6.9
Fetal distress on maternal admission[i]	–	–	36	20.7
Head circumference below 10th percentile[j]	–	–	73	41.9
Intrapartum risk factors				
Mode of delivery	–	–	–	–
Cephalic delivery	–	–	44	25.3
Breech delivery	–	–	1	0.6
Instrumental	–	–	36	20.7
Elective cesarean	–	–	5	2.9
Emergency cesarean	–	–	88	50.6
Fetal distress during labor	–	–	120	69.0
Risk factors for fetal infection[k]	–	–	31	17.8
Sentinel events[l]	–	–	61	35.1
Shoulder dystocia	–	–	10	5.7
Labor induction	–	–	41	23.6
Anesthesia	–	–	–	–
PDA	–	–	72	41.3
general anesthesia	–	–	27	15.5
none	–	–	22	12.6
missing data	–	–	53	30.5
Meconium aspiration	–	–	21	12.1
Postnatal risk factors				
Hypoglycemia[m]	–	–	30	17.2
Sepsis	–	–	12	6.9
Necrotizing enterocolitis	–	–	4	2.3
Pneumonia	–	–	9	5.2

SD: standard deviation; CTG: cardiotocograph; PDA: peridural anesthesia.
[a]SES of the mother plus SES of the father or one of them doubled, if unknown.
[b]Alcohol, nicotine, any medication, other drugs (cannabis and methadone).
[c]Epilepsy, seizures, migraine, polyneuropathy, multiple sclerosis, depression, anxiety/panic disorder, post-traumatic stress disorder, burnout, postnatal depression or psychosis, borderline personality disorder, and mental retardation.
[d]Obesity (BMI $>$ 30), hypothyroidism, hyperthyroidism, and diabetes.
[e]Sarcoidosis, celiac disease, autoimmune-thyroiditis, and lupus.
[f]Pyelonephritis, vaginal candidiasis, vaginal chlamydia, *gardnerella* or *E. coli* infection, urinary tract infection, genital herpes, parasitize, upper airway infection, and gastroenteritis.
[g]TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes virus, hepatitis B, Parvovirus B19, varicella zoster virus, and listeria).
[h]Placenta praevia, preeclampsia, anemia, coagulopathy, hypertension (only if medically treated), and hemorrhage during pregnancy.
[i]Pathological CTG on admission or decreased fetal movements.
[j]According to Ref. [17].
[k]Fever, PROM (=premature rupture of membranes), and chorioamnionitis.
[l]Abruptio placentae, uterine rupture, maternal hemorrhage/shock, cord prolapse, and amniotic embolism.
[m]At least once blood glucose $<$ 2.5 mmol/L.

defined as abruption placentae, uterine rupture, maternal hemorrhage/shock, cord prolapse, and amniotic embolism. Fetal distress during labor was defined by pathological/silent/sinusoidal CTG during labor. If a mother was already in labor on admission and there were signs of fetal distress, fetal distress was included in both categories "fetal distress on maternal admission" and "fetal distress during labor."

Postnatal risk factors

Hypoglycemia (blood glucose <2.5 mmol/l), sepsis with positive blood cultures, necrotizing enterocolitis (pneumatosis intestinalis on x-ray and bloody stool) and pneumonia were defined as postnatal risk factors.

Additionally, we defined two different patient scenarios, either with or without the most well-known risk factors for HIE in the literature combined with the risk factors that were statistically significant for neurological outcome in our univariate analysis: gestational age >41 weeks, chorioamnionitis, fetal distress on maternal admission for delivery, sentinel events during labor, fetal distress during labor, HC below 10th percentile (p10). We assessed the association of all these risk factors together with neurological outcome over the first 4 d of life.

Outcome definitions

Primary outcome was neurological benefit defined as improvement of Sarnat stage from admission to day 4 of life. Neurological harm was defined as lack of improvement of Sarnat stage during the same time period. All neonates who were examined neurologically at least on two different days during the first 4 d of life, were included in this analysis. Secondary outcome was defined as death or seizures (=need for anticonvulsive therapy) during the first 4 d of life.

Statistics

Descriptive statistics include mean and standard deviation for continuous outcomes. Apgar scores were reported as median and range. Categorical variables are shown as counts and percentages of total. Univariate logistic regression analysis is used to quantify the association between independent variables and the binary outcomes. The multiple logistic regression model is used to account for the interdependencies between predictors and outcomes. The model includes the statistically significant risk factors for HIE reported in the literature and those risk factors with evidence of a univariate association in our analysis (HC, fetal distress during labor and fetal distress on maternal admission for delivery). Analyses were conducted with R for windows [18] and SPSS for Windows version 20.0 (IBM, Armonk, NY).

Results

Perinatal risk factors for HIE and demographic data

The analyzed perinatal risk factors for HIE and their frequency are depicted in Table 1. Fetal distress on maternal admission for delivery occurred in 20.7% of cases, whereas 69% showed fetal distress during labor. Half of all neonates were born by emergency cesarean. The demographic data of all 174 included neonates are depicted in Table 2.

Association between perinatal risk factors and the severity of HIE after birth

None of the analyzed perinatal risk factors (Table 1) was associated with Sarnat stage on admission.

Primary outcome: neurological outcome during the first 4 d of life

Improvement of Sarnat stage during the first 4 d of life occurred in 66% of the neonates, while 28% did not neurologically improve and in 6% no information was available.

We analyzed the association of the perinatal risk factors with neurological outcome during the first 4 d. In the univariate analysis fetal distress during labor (OR, 2.06; 95% CI, 1.02–4.25, $p = .049$) and neonatal HC above 10th percentile at birth (OR, 1.33; 95% CI, 1.05–1.69, $p = .02$) were associated with neurological benefit. Fetal distress on maternal admission for delivery is the only statistically significant risk factor for neurological harm during this time period (OR, 0.26; 95% CI, 0.12–0.57, $p < .01$) in the univariate analysis. There was no association of the remaining investigated risk factors.

For the multiple regression analysis we included the significant perinatal risk factors for HIE reported in the literature (gestational age >41 weeks, chorioamnionitis, and sentinel events) and those risk factors with evidence of a univariate association in our analysis (HC, fetal distress during labor and fetal distress on maternal admission for delivery). Fetal distress on maternal admission for delivery was independently associated with neurological harm (OR, 0.15; 95% CI, 0.04–0.67, $p = .013$). None of the included risk factors were significantly associated with neurological benefit during the first 4 d of life.

Table 2. Demographic characteristics of the study population (n= 174).

Variable	Mean	SD	n	%	Median	Range
Place of birth						
Outborn	–	–	143	82.2	–	–
Inborn	–	–	31	17.8	–	–
Parity						
0	–	–	69	39.7	–	–
1	–	–	52	29.9	–	–
2	–	–	38	21.8	–	–
3	–	–	10	5.7	–	–
Missing data	–	–	5	2.9	–	–
Sex						
Male	–	–	104	59.8	–	–
Female	–	–	70	40.2	–	–
Gestational age in days	275.68	12.37	–	–	–	–
Birth weight in grams	3319.8	552.21	–	–	–	–
Head circumference in cm	34.49	1.67	–	–	–	–
Cesarean						
None	–	–	81	46.6	–	–
Elective cesarean	–	–	5	2.9	–	–
Emergency cesarean	–	–	88	50.6	–	–
Resuscitation[a]						
Required >10 min	–	–	100	57.5	–	–
Required <10 min	–	–	72	41.4	–	
Missing data	–	–	2	1.1	–	–
Apgar score at 5 min	–	–	–	–	3.6	0–10
Apgar score at 10 min	–	–	–	–	5	0–10
Umbilical artery pH	6.92	0.28	–	–	–	–
Lowest pH within 60 min of birth	6.88	0.18	–	–	–	–
Lowest BE (mmol/L) within 60 min of birth	−18.78	6.95	–	–	–	–
Highest lactate (mmol/L) within 60 min of birth	14.9	5.07	–	–	–	–
Sarnat stage at birth						
Sarnat stage 1	–	–	16	9.2	–	–
Sarnat stage 2	–	–	126	72.4	–	–
Sarnat stage 3	–	–	32	18.4	–	–
Seizures on day 1–4	–	–	56	32.2	–	–
Death on day 1–4	–	–	18	10.3	–	–
Seizures at discharge						
Yes	–	–	24	13.8	–	–
No	–	–	143	82.2	–	–
Missing data	–	–	7	4	–	–
Death to discharge	–	–	30	17.2	–	–

SD: standard deviation.
[a]min: minutes; all neonates are resuscitated.

Further, we identified two different patient scenarios: the probability for neurological benefit during the first 4 d of life was only 20% in neonates with the combination of all the following risk factors (gestational age >41 weeks, chorioamnionitis, fetal distress on maternal admission for delivery, sentinel events during labor, HC below 10th percentile at birth), whereas in the absence of these risk factors the probability to neurological benefit increased to 80%.

Secondary outcome: death or seizures during the first 4 d of life

Death occurred in 18/174 (10.3%) neonates and 56/174 (32.2%) developed seizures during the first 4 d of life. The univariate analysis showed a 2.19-fold increased odds for seizures/death in the neonates with fetal distress on maternal admission for delivery (OR, 2.19; 95%CI 1.04–4.62, $p = .04$). HC above 10th percentile at birth was associated with a lower risk of seizures/death (OR, 0.80; 95% CI, 0.65–0.99, p.045).

Discussion

In our cohort, we report the association of perinatal risk factors with the severity of HIE after birth and with neurological outcome during the first 4 d of life. None of the investigated risk factors showed an association with the Sarnat stage on admission in our study population. This finding is astonishing and needs further investigation. At our knowledge, the previously published studies identified risk factors for the development of HIE, but not their association with the severity of HIE.

Neurological benefit during the first 4 d of life was associated with fetal distress during labor and HC above 10th percentile at birth in the univariate analysis, however, in the multivariate analysis these risk factors lost their association. Fetal distress on maternal

admission was the only risk factor associated with neurological harm during the first 4 d of life in the univariate and multivariate analysis.

Fetal distress on maternal admission, indicating fetal impairment of unknown duration, might be a consequence from major preceding hypoxic–ischemic events [1,19] and is associated with neurological harm during the first 4 d of life in our study population. Fetal distress during labor with no prior signs of fetal distress might reflect a presumed short period of hypoxia-ischemia and is associated with neurological benefit in our study population. This finding probably reflects the temporal relation of several risk factors for HIE. Thus, monitoring fetal heart trace during labor gives the obstetrician the chance to intervene whereas fetal distress on maternal admission is probably a sign of a long-lasting distressed fetus [20,21].

The analysis of the two patient scenarios showed that the probability for neurological benefit during the first 4 d of life was only 20% in neonates with the combination of all of the following risk factors: gestational age >41 weeks, chorioamnionitis, fetal distress on admission, sentinel events, fetal distress during labor, HC below 10th percentile, whereas in the absence of these risk factors the probability for neurological benefit increased to 80%. These findings support the results of previous studies showing that not a single event but several events/insults during pregnancy on different time points lead to HIE [1,3,22,23]. Several studies investigated ante- and intrapartum risk factors for HIE [5–9,19,21]. They analyzed if antepartum risk factors alone, intrapartum risk factors alone or both in combination are associated with the incidence of HIE in term and near-term neonates [5–9,19,21]. Badawi et al. concluded that the causes of HIE were predominately related to antepartum risk factors while intrapartum risk factors accounted only for a small number of HIE cases [5,6]. However, they used a quite variable definition of HIE. Locatelli et al. used a more strict definition of HIE as in our study [7]. Their analysis confirmed that in most neonates with HIE antepartum in combination with intrapartum risk factors could be identified. These study results are consistent with more recently published cohort studies [3,8,19] confirming that the combination of ante- and intrapartum risk factors increase the risk of developing HIE. Fleiss et al. describe a multiple hit hypothesis [1]. In this model, different antenatal factors not severe enough by themselves to induce significant brain damage make the developing brain more susceptible to a second insult [1]. These antenatal sensitizing factors include inflammation, gestational chronic mild maternal stress, and gestational hypoxia on perinatal excitotoxic or hypoxic–ischemic lesions [24–29]. Chorioamnionitis (diagnosed histologically or clinically) as a contributing factor for the development of neonatal HIE is discussed controversially in the literature [6,20,30–32]. In our cohort, chorioamnionitis was not a statistically significant risk factor for the severity of encephalopathy after birth or for neurological harm. This is in-line with other recently published studies [19,20,33], although, Harteman et al. describe a higher incidence of histological chorioamnionitis across all patterns of brain injury when compared with healthy term neonates [34]. In the study by Tann et al., funisitis but not chorioamnionitis was an independent risk factor for HIE [35]. A high incidence of funisitis with HIE was also reported in other studies [34,36]. The difference between the association of chorioamnionitis and funisitis with HIE may be explained by the duration or the proximity of inflammation or the fetal response to inflammation [35]. Parker et al. describe an association of clinical chorioamnionitis with the incidence of HIE [32], but clinically it is not possible to distinguish between chorioamnionitis and funisitis. In the Swiss National Asphyxia and Cooling Register histopathological information of chorioamnionitis is mentioned, but the histological data of funisitis is not collected. Although not a significant risk factor in the univariate and multivariate analysis, chorioamnionitis included in the analysis of the two patient scenarios seems to play a role by influencing the other included risk factors, supporting the hypothesis of Fleiss et al.

The finding that HC above 10th percentile is associated with neurological benefit during the first 4 d of life in our analysis supports the hypothesis of Fleiss et al. as well. Acute insults and chronic conditions may result in decreased rate of head growth and eventual development of microcephaly [37]. Thus, microcephaly might be a consequence of events during pregnancy predisposing the brain for further hypoxic damage. The relationship of head growth and neurological outcome is well known in the literature [37,38]. Microcephaly correlates closely with major neurologic sequelae as CP and intellectual impairment [37]. In contrast, neonates who are normocephalic at birth and maintained normal postnatal rate of head growth have normal neurological outcome [37].

Our study has some limitations worth mentioning. The study population is small and the analysis may be underpowered to detect the association between certain risk factors and the severity of HIE after birth and neurological outcome in neonates during the first 4 d of life. Antenatal risk factors (especially the mother's

characteristics) were collected retrospectively from the chart notes with some missing data, although they are quite well documented (missing data 2–3%).

The results of our study reveal that certain perinatal risk factors and constellations of risk factors are associated with neurological outcome during the first 4 d of life. In the future, we will analyze the association of the different risk factors with the long-term neurodevelopmental outcome of our study population. To understand the different risk factors, their association with HIE and the pathways leading to HIE might be an approach for further improvement of neuroprotective therapy for neonates with HIE.

Conclusion

None of the investigated risk factors for HIE is associated with the severity of encephalopathy on admission. However, some ante- and intrapartum risk factors such as fetal distress on maternal admission or during labor and HC and certain constellations of risk factors are associated with neurological outcome during the first 4 d of life. These findings may increase the awareness of the clinicians on the evolution of HIE and might help them to counsel parents during the early neonatal period.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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