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Original Article

Incidence and prediction of outcome in hypoxic–ischemic encephalopathy in Japan

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Abstract ***Background***: Hypoxic–ischemic encephalopathy (HIE) is one of the most critical pathologic conditions in neonatal medicine due to the potential for neurological deficits in later life. We investigated the incidence of term infants with moderate or severe HIE in Japan and identified prognostic risk factors for poor outcome in HIE.

Methods: Data on 227 infants diagnosed with moderate or severe HIE and born between January and December 2008 were collected via nationwide surveys from 263 responding hospitals. Using logistic regression, we examined the relationship between maternal, antepartum, intrapartum, and neonatal risk factors and clinical outcome at 18 months following birth.

Results: In Japan, the incidence of moderate or severe HIE was 0.37 per 1000 term live births. Outborn births, low Apgar score at 5 min, use of epinephrine, and low cord blood pH were intrapartum factors significantly associated with neurodevelopmental delay and death at 18 months. Serum lactate, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase (all, $P < 0.001$) and creatine kinase ($P = 0.002$) were significantly higher in infants with poor outcome compared to those with favorable outcomes. Abnormal brain magnetic resonance imaging (MRI), an important prognostic factor, was significantly associated with poor outcome (odds ratio, 11.57; 95% confidence interval: 5.66–23.64; $P < 0.001$).

Conclusions: Risk factors predicting poor outcome in HIE include outborn birth, low Apgar score at 5 min, use of epinephrine, laboratory abnormalities, and abnormal MRI findings.

Key words hypoxic–ischemic encephalopathy, magnetic resonance imaging, neurodevelopmental outcome, risk factor.

Hypoxic–ischemic encephalopathy (HIE) is one of the most critical pathologic conditions in neonatal medicine. Infants with HIE suffer neurological sequelae in later life.[1–4] Some studies have reported predictive factors for neurodevelopmental outcome in infants with HIE.[5–7] Electroencephalography (EEG), magnetic resonance imaging (MRI), and laboratory data at birth are useful tools for predicting outcome based on neonatal risk factors. Whereas maternal and antenatal factors may foretell the development of HIE, these variables do not predict mortality or neurodevelopmental outcome.[8–10]

Neonatal encephalopathy (NE) refers to neurological abnormalities manifesting in the neonatal period and may be caused by multiple variables, among which, HIE is a key contributing factor. The incidence of NE has been reported in several studies.[8,11,12] The incidence of NE is 1–4 per 1000 live births,[8,11]

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but there are few reports of the incidence of HIE.[12–14] This may be due to the fact that establishing a diagnosis of HIE may be challenging because infants may present with non-specific symptoms and HIE is not always caused by a sentinel event.[4,15] Further, in some cases, an obvious hypoxic–ischemic event may have not been apparent during the intrapartum period or immediately after birth.[15] Because of the diagnostic difficulty, neonatologists and obstetricians are not always able to recognize brain insult in infants who suffer partial asphyxia at birth. Therefore, the incidence of HIE might be underestimated.

Accordingly, the aim of this study was to describe the incidence of HIE in term babies in Japan. Additionally, we investigated the risk factors for neurological sequelae and death.

Methods

This retrospective survey study was approved by the ethics committees of the National Center for Child Health and Development (approval number, 575; date of approval, 5 June 2012). We conducted a nationwide cohort study to retrospectively collect data on term infants with HIE who were born between January and December 2008. The survey was designed to include term infants (≥37 weeks) who had moderate or severe HIE caused by obvious perinatal asphyxia. Term infants without obvious perinatal asphyxia were also included if they demonstrated any of the following during the first 72 h after birth: abnormal consciousness, difficulty maintaining respiration, abnormal tone and reflexes, or neonatal seizures. We excluded infants with acute encephalopathy resulting from causes other than hypoxic–ischemic events, that is, congenital abnormality, chromosomal abnormality, electrolyte abnormality, hypoglycemia, metabolic disease, neuromuscular disease, neurocutaneous syndrome, idiopathic stroke, intracranial hemorrhage, and central nervous infection.

Questionnaires were sent to 290 hospitals associated with the authorized educational facilities of the Japanese Society of Maternal Perinatal Medicine. Of the 290 hospitals, 263 responded, resulting in a response rate of 90.7%. Two hundred and ninety-four infants fulfilled the inclusion criteria. Due to the nature of the survey, patient data were not collected in entirety, and 67 cases had missing outcomes data for the 18 month period following birth. Incidence was estimated based on the total number of eligible subjects ($n = 294$), whereas risk factors were analyzed using data on 227 infants.

The questionnaire consisted of items concerning maternal, ante/intrapartum and neonatal factors. Maternal factors included age (≥35 or <35 years), gravidity, parity, fertility treatment, underlying disease, and medication (with the exception of tocolysis). Ante/intra-partum factors consisted of plurality, hospital of delivery, mode of delivery, induced delivery, instrumental delivery (forceps and/or vacuum delivery), meconium staining, umbilical abnormalities, and placental abnormalities. Fetal heart rate abnormalities included non-reassuring fetal status, bradycardia, deceleration, and loss of or decrease in variability. Fetal heart rate monitoring was evaluated according to the modified definition established by the Japan Society of Obstetrics and Gynecology.

Neonatal factors included gender, gestational age, birthweight, fetal growth, Apgar score (at 1 min and 5 min), and resuscitation. Blood gas analysis of cord blood and the patient's blood as well as the results of blood gas tests performed during admission to the neonatal intensive care unit (NICU) were evaluated.

Brain MRI performed during hospitalization was also reviewed. Decisions regarding whether to perform MRI, technical specifications (such as T1/T2 weighting and image sections), and the timing of imaging were determined by individual clinicians and were based on institutional policy. Abnormal findings included bilateral basal ganglia thalamic lesions, parasagittal injury, subcortical leukomalacia, multicystic encephalomalacia, periventricular leukomalacia, and intracranial hemorrhage.

Neurodevelopmental outcomes were evaluated at age 18 months by the attending physician using neurodevelopmental assessment tools and/or via medical interviews and physical examination. The primary endpoint of this study was outcome at 18 months. Poor outcome was defined as neurodevelopmental delay or death occurring within the first 18 months following birth.

Statistical analysis

In Japan, 1 027 890 term infants were born in 2008; at the time of the survey in 2012, there were a total of 2765 NICU beds. The incidence of HIE among term neonates was calculated based on these data. Statistical analysis was performed using SPSS version 19.0 (SPSS, Chicago, IL, USA) and included the chi-squared test, Fisher's exact test for categorical variables, and logistic regression. The main outcome measures were expressed as odds ratios (OR) and the respective 95% confidence intervals (CI). Continuous variables, such as maternal age, gestational age, birthweight and laboratory data, are reported as median and interquartile range (IQR). $P < 0.05$ was considered to be statistically significant.

Results

The median maternal age was 31 years (IQR, 28–35 years), gestational age was 36.6 weeks (IQR, 38.4–40.6 weeks), and birthweight was 2957 g (IQR, 2640–3253 g). Boys comprised 59.5% (135/227) of the study sample; 72 (24.5%) infants were inborn.

Incidence

In 2012, the number of NICU beds in Japan totaled 2765. Among the 263 hospitals responding to the questionnaire, the total number of NICU beds was 2138, which represented 77.3% (2138/2765) of all NICU beds in Japan. Based on the 294 infants meeting the inclusion criteria, the number of infants with moderate or severe HIE in 2008 was projected to be 380 (294/0.773). In 2008, 1 027 890 term infants were born in Japan. Therefore, the birth incidence of moderate or severe HIE was approximately 0.37 per 1000 term live births.

Risk factors for poor outcome

Table 1 lists the potential maternal risk factors for poor outcome. Of these, maternal age (≥35 years), gravidity, parity, fertility

Table 1 Maternal factors

	Good outcome *n* (%)	Poor outcome *n* (%)	OR (95%CI)	*P*
Maternal age (years)				
<35	61 (68.5)	94 (74.0)	1	
≥35	28 (31.5)	33 (26.0)	0.76 (0.342–1.39)	0.379
Gravida				
0	55 (61.1)	64 (51.2)	1	
≥1	35 (38.9)	61 (48.8)	1.50 (0.86–2.60)	0.149
Parity				
0	64 (72.7)	82 (65.1)	1	
≥1	24 (27.3)	44 (34.9)	1.43 (0.79–2.59)	0.237
Fertility treatment				
No	75 (90.4)	110 (92.4)	1	
Yes	8 (9.4)	9 (7.6)	0.77 (0.28–2.08)	0.601
Underlying diseases				
No	70 (78.7)	111 (86.0)	1	
Yes	19 (21.3)	18 (14.0)	0.60 (0.29–1.22)	0.153
Maternal medications				
No	82 (90.1)	118 (90.8)	1	
Yes	9 (9.9)	12 (9.2)	0.93 (0.37–2.30)	0.869

CI, confidence interval; OR, odds ratio.

treatment, maternal underlying disease, and maternal medication were not associated with poor outcome. Of the potential antepartum risk factors (Table 2), multiple conceptions did not portend an unfavorable outcome, but outborn birth was associated with a twofold increase in the odds of a poor outcome (OR, 2.07; 95%CI: 1.17–3.36). Mode of delivery, induced labor, and instrumental delivery were not associated with poor outcome, nor were umbilical and placental abnormalities. Fetal heart rate patterns were not associated with neurodevelopmental outcome in infants with HIE (Table 3).

Table 2 Intrapartum factors

	Good outcome *n* (%)	Poor outcome *n* (%)	OR (95%CI)	*P*
Plurality				
Singleton	92 (100)	133 (99.3)		
Twins	0 (0)	1 (0.7)	NA	0.406
Hospital of delivery				
Inborn	38 (41.3)	34 (25.4)	1	
Outborn	54 (58.7)	100 (74.6)	2.07 (1.17–3.66)	0.012
Mode of delivery				
Transvaginal	47 (52.2)	70 (56.0)	1	
Caesarean section	43 (47.8)	55 (44.0)	0.85 (0.50–1.48)	0.583
Labor				
Spontaneous	42 (60.9)	63 (63.6)	1	
Induced	27 (39.1)	36 (36.4)	0.89 (0.47–1.67)	0.716
Instrumental delivery				
No	60 (72.3)	82 (73.9)	1	
Yes	23 (27.7)	29 (26.1)	0.92 (0.47–1.75)	0.805
Meconium stain				
No	48 (53.9)	69 (60.5)	1	
Yes	41 (46.1)	45 (39.5)	0.76 (0.44–1.34)	0.346
Umbilical abnormalities				
No	72 (87.8)	88 (80.0)	1	
Yes	10 (12.2)	22 (20.0)	1.80 (0.80–4.05)	0.151
Placental abnormalities				
No	52 (67.5)	72 (69.9)	1	
Yes	25 (32.5)	31 (30.1)	0.90(0.47–1.69)	0.734
Abruptio placentae				
No	54 (70.1)	78 (75.7)	1	
Yes	23 (29.9)	25 (24.3)	0.75 (0.39–1.46)	0.401

CI, confidence interval; NA, not available; OR, odds ratio.

Table 3 Fetal heart rate monitoring

	Good outcome *n* (%)	Poor outcome *n* (%)	OR (95%CI)	*P*
Non-reassuring fetal status				
No	13 (16.3)	11 (10.3)	1	
Yes	67 (83.8)	96 (89.7)	1.69 (0.72–4.01)	0.227
Bradycardia				
No	52 (65.0)	59 (55.1)	1	
Yes	28 (35.0)	48 (44.9)	1.51 (0.83–2.74)	0.714
Deceleration				
No	13 (28.9)	11 (19.6)	1	
Yes	32 (71.1)	45 (80.4)	1.66 (0.66–4.18)	0.278
Loss/decrease in variability				
No	74 (92.5)	99 (92.5)	1	
Yes	6 (7.5)	8 (7.5)	0.99 (0.33–3.00)	0.995

CI, confidence interval; OR, odds ratio.

Female infants had a significantly higher odds for poor outcome compared to male infants (OR, 1.76; 95%CI: 1.01–3.05; $P = 0.004$). Gestational age and birthweight had no association with poor outcome, whereas low Apgar score (<7) at 5 min more than doubled the odds of poor outcome (OR, 2.31; 95%CI: 1.42–5.23; $P = 0.003$). Similarly, use of epinephrine during resuscitation significantly increased the odds of a poor outcome by nearly sevenfold (OR, 6.90; 95%CI: 1.42–33.30; $P = 0.017$; Table 4).

With respect to laboratory indices, pH and base excess (BE) as determined by blood gas analysis at admission were significantly

Table 4 Neonatal factors

	Good outcome *n* (%)	Poor outcome *n* (%)	OR (95%CI)	*P*
Gender				
Male	62 (67.4)	73 (54.1)	1	
Female	30 (32.6)	62 (45.9)	1.76 (1.01–3.05)	0.044
Gestational age (weeks)				
37	16 (17.4)	18 (13.3)	0.87 (0.38–2.02)	0.754
38	15 (16.3)	30 (22.2)	1.56 (0.70–3.44)	0.275
39	20 (21.7)	33 (24.4)	1.28 (0.61–2.70)	0.511
40	28 (30.4)	36 (26.7)	1	
41	10 (10.9)	16 (11.9)	1.24 (0.49–3.15)	0.645
42	3 (3.3)	2 (1.55)	0.52 (0.08–3.32)	0.488
Birthweight (g)				
<2499	12 (13.0)	19 (14.3)	0.97 (0.42–2.24)	0.947
2500–2999	35 (38.0)	57 (42.9)	1	
3000–3499	30 (32.6)	41 (30.8)	0.84 (0.47–1.58)	0.586
3500–3999	13 (14.1)	12 (9.0)	0.57 (0.23–1.38)	0.211
≥4000	2 (2.2)	4 (3.0)	1.23 (0.21–7.04)	0.818
Centile birthweight				
<10th	10 (11.4)	23 (17.6)	1.60 (0.72–3.60)	0.249
10th–90th	67 (76.1)	96 (73.3)	1	
>90th	11 (12.5)	12 (9.2)	0.76 (0.32–1.83)	0.542
Apgar score at 1 min				
<7	80 (39.4)	123 (60.6)	2.31 (0.90–5.89)	0.074
≥7	12 (60.0)	8 (40.0)	1	
Apgar score at 5 min				
<7	63 (36.2)	111 (63.8)	2.80 (1.416–5.529)	0.003
≥7	27 (30.0)	17 (13.35)	1	
Resuscitation				
None	5 (5.4)	4 (3.0)	1	
Oxygen	5 (5.4)	8 (6.0)	2.00 (0.36–11.24)	0.431
Bagging/intubation	72 (78.3)	75 (56.0)	1.30 (0.34–5.05)	0.702
Chest compression	4 (4.4)	14 (10.4)	4.37 (0.78–24.39)	0.093
Epinephrine	6 (6.5)	33 (24.6)	6.90 (1.42–33.30)	0.017

CI, confidence interval; OR, odds ratio.

Table 5 Laboratory data

	Good outcome Median (IQR)	Poor outcome Median (IQR)	*P*
Cord blood			
pH	6.97 (6.87–7.14)	6.88 (6.69–7.17)	0.044
BE (mmol/L)	−16.4 (–20.3 to −10.6)	18.4 (–25.8 to −12.1)	0.057
On admission			
pH	7.24 (7.14–7.33)	7.18 (6.92–7.30)	0.003
BE (mmol/L)	–9.9 (–15.2 to –3.65)	18.4 (–21.6 to –6.95)	<0.001
Lactate (mmol/L)	9.4 (4.7–15.0)	11.9 (5.8–17.6)	0.086
WBC (/mm^3)	20520 (14393–26525)	21500 (16300–29900)	0.030
CRP (mg/dL)	0.01 (0.00–0.15)	0.02 (0.00–0.20)	0.901
LDH (IU/L)	673 (507–1204)	987 (662–1866)	<0.001
AST (IU/L)	68 (45–150)	126 (67–20)	<0.001
ALT (IU/L)	17 (10–40)	34 (14–81)	<0.001
CK (IU/L)	642 (433–1328)	1022 (538–2603)	0.002

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, base excess; CK, creatine kinase; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cells.

lower in infants with poor outcome compared to those with favorable outcomes. Conversely, serum lactate, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatine kinase (CK) were markedly higher in infants with poor outcome compared to infants with good outcome (Table 5).

Infants who had abnormal findings on brain MRI had a significantly higher risk for poor outcome compared to infants with normal MRI findings (Table 6).

Discussion

Incidence

In this study, the incidence of term infants with moderate/severe HIE in Japan was estimated to be approximately 0.37 per 1000 term live births. A few authors have reported the birth incidence of moderate or severe HIE with rates ranging from 0.46 to 1.26 per 1000 live births.[12,14,16] The variation among the reported data may be due primarily to the difficulty in diagnosing HIE. The diagnosis of neonatal HIE is challenging and typically inferred from non-specific signs.[17] Some infants with HIE have failed to exhibit obvious fetal distress, but nevertheless have suffered from neurological abnormalities immediately after birth.[15] In this study, the subjects consisted of infants with neurological abnormalities due to hypoxic–ischemic events, but not other causes, and included all types of HIE.

Neonatal encephalopathy is a heterogeneous syndrome characterized by signs of central nervous system dysfunction in newborn infants. NE occurs as a consequence of intracranial hemorrhage, hypoglycemia, severe hyperbilirubinemia, various metabolic disorders, and intracranial infection, among other disorders. The reported incidence of NE is 3.8 per 1000 term live births in Western Australia[8] and 1.64 per 1000 term live births in France.[12] Because NE may be caused by events other than hypoxic–ischemic events, the incidence of HIE may differ from that of NE.

Risk factors

Whereas several published studies have reported the ante-/intrapartum risk factors for developing NE and/or HIE,[8–10] none has evaluated the relationship between ante-/intrapartum risk factors and outcome in childhood. The present study found that outborn infants had a significantly higher risk of poor outcome. In Japan, approximately 50% of all neonates are delivered in private clinics. Therefore, it is important that medical staff working in facilities lacking organized perinatal centers receive education on neonatal resuscitation.

Fetal heart rate pattern was not associated with neonatal outcome. The reason for this finding may be the poor specificity of cardiotocography.[18] Similarly, fetal heart rate pattern and abnormalities of the placenta and umbilicus were not related with outcome. We speculated that the inability to estimate the severity of placental and umbilical abnormalities due to the retrospective design of the present study may have contributed to this finding.

Low Apgar score is caused by hypoxic–ischemic injury. Apgar scores at 1 min and 5 min reflect the neonate's general condition immediately after birth and are predictive

Table 6 Brain MRI in hospital

	Good outcome *n* (%)	Poor outcome *n* (%)	OR (95%CI)	*P*
Brain MRI				
Normal	54 (63.5)	14 (13.1)	1	
Abnormal	31 (36.5)	93 (86.9)	11.57 (5.66–23.64)	<0.001

CI, confidence interval; OR, odds ratio; MRI, magnetic resonance imaging.

of neurological outcome, respectively. Several authors have reported that low Apgar score at 5 min is a risk factor for serious morbidity and mortality.[19–21] In the present study, Apgar score at 1 min was not associated with poor outcome, but infants with low Apgar score at 5 min had greater risk of poor outcome compared to infants with higher Apgar score at 5 min. This finding was compatible with that reported in previous studies.

In this study, neonatal resuscitation level was predictive of death or neurological sequelae. The incidence of poor outcome in the infants who received epinephrine was significantly higher than in infants who were not given epinephrine. The need for a high level of resuscitation at delivery has been previously cited as a sensitive predictor of subsequent adverse outcome.[13,22] When the need for cardiopulmonary resuscitation coexisted with severe acidemia, an adverse outcome was likely in >90% of cases.[23]

Both cord arterial lactate and pH are measures of acidemia. Fetal arterial lactate measures anaerobic metabolism whereas fetal pH reflects both anaerobic metabolism and acidemia due to increasing fetal carbon dioxide level. LDH is an important biomarker of cellular damage and is commonly designated as an outcome variable in experimental studies of HIE.[24,25] AST, ALT, and CK as well as LDH may reflect cellular damage occurring in conjunction with extensive tissue damage in one or several organs.

Brain MRI is an essential method for establishing prognosis. One systematic review indicated that diffusion weighted and conventional MRI play an important role in prognostic evaluation.[5] MRI findings in HIE infants are heterogeneous.[2,3,15,26,27] In term neonates with brain injury, the specific regional distribution of injury was associated with different durations and severities of ischemia. Partial asphyxia caused cerebral white matter injury,[15,26] whereas acute and profound asphyxia produced basal ganglia and thalamus injury.[27] In this study, abnormal brain MRI findings were associated with poor outcome. We did not, however, evaluate the relationship between outcome and type of brain injury seen on MRI. Further investigation is necessary to confirm the relationship between outcome and type of MRI abnormality.

Limitations and strengths

This study has some limitations. First, the retrospective study design resulted in missing data; 67 cases (22.8%) did not provide outcome data. But whether or not the follow-up rate affected the true incidence of severe disabilities, is unclear.[28,29] A second limitation was the lack of uniformity among techniques for evaluating neurodevelopment. In Japan, methods for assessing neurodevelopment are subject to the individual clinician's practices and institutional policies. Therefore, it is important to establish a standardized protocol for following high-risk infants.

Nevertheless, this study has several strengths. Notably, the response rate was high at 90.7%. In Japan, approximately 50% of neonates are delivered in private clinics. Mothers and newborns suffering from complications are generally transferred to a regional perinatal center, and it is likely that all infants with moderate or severe HIE are treated in NICU. Therefore, the present results accurately describe the current status of infants with HIE in Japan. Additionally, the findings may contribute information that may be useful for prenatal counseling of parents and for cross-national research.

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