Table 3 Fontan candidate characteristics ($n = 16$)

Case	CVM	Side of CDH	Complication	Treatment strategy	ECMO	Operation for CDH	Operation for CVM	90 day survival	2 year survival
1	HLHS	L	–	Palliative	–	–	–	No	No
2	HLHS	L	–	Positive	–	–	–	No	No
3	HLHS	L	–	Positive	–	–	–	No	No
4	HLHS	L	–	Positive	+	+	–	No	No
5	HLHS	L	Agenesis of the corpus callosum	Positive	–	–	–	No	No
6	HLHS, PA, DORV	L	–	Palliative	–	–	–	No	No
7	HLHS, TAPVC	L	–	Positive	+	–	–	No	No
8	SA, VSD, PS	R	–	Positive	–	–	–	No	No
9	SV, CoA	L	Agenesis of the corpus callosum	Positive	–	–	–	No	No
10	SV, IAA	L	–	Positive	–	–	–	No	No
11	SA, SV	L	Fryns syndrome	Palliative	–	–	–	No	No
12	SV, DORV	R	Trisomy 18	Positive	–	+	–	Yes	No
13	PA	L		Positive	–	+	+	Yes	No
14	TA	L		Positive	–	+	+	Yes	No
15	SA, SV, TAPVC, PS	R	Situs inversus	Positive	–	+	+	Yes	Yes
16	SV	L		Positive	–	+	+	Yes	Yes

ASD, atrial septal defect; CDH, congenital diaphragmatic hernia; CoA, coarctation of aorta; CVM, cardiovascular malformations; DORV, double outlet right ventricle; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; IAA, interruption of aortic arch; SA, single atrium; SV, single ventricle; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; VSD, ventricular septal defect.

The therapeutic strategy (palliative or radical), presence of malformations other than CVM and the type of cardiac deformity according to 90 day survival of the 16 FC patients are listed in Table 4. Neither the rate of palliative approach nor the presence of complications other than CVM differed significantly between the five and 11 patients who did and did not survive >90 days. All of the nine patients with LVOTO had PDA-dependent disease, and the absence of LVOTO was significantly associated with 90 day survival. Neither RVOTO nor PVO was significantly associated with 90 day survival.

Discussion

In the present study 2.6% (16/614) of the CDH patients were potentially candidates for the Fontan procedure. In this study, many physicians hesitated to offer the Fontan procedure to these patients, and consequently none of the patients underwent the Fontan procedure. In addition, all of the nine patients with LVOTO died within 90 days of life.

CDH is rare, present in only 2.4–2.5 of 10 000 births,[6,7] while CVM are relatively common, present in nine of 1000 births.[8] The overall prevalence of CVM was 17.6% (108/614) in the present subjects with CDH,[4] and the prevalence of CVM other than PDA, ASD, pulmonary valvular stenosis or a right-sided aortic arch was 12.4%, consistent with previous studies.[9,10] According to Pober *et al.*, CVM including ASD were present in 11.3% (23/203) of their study patients with CDH, while ASD and/or VSD and SV accounted for 56% (13/23) and 4% (1/23) of the CVM observed, respectively.[11] According to Calzolari *et al.*, ASD and/or VSD and SV accounted for 48% (634/1328) and 3% (43/1328) of their study patients with CDH complicated by CVM, respectively.[12] In the present 108 CDH

Table 4 Fontan candidate characteristics vs 90 day survival

	90 day survival		*P*
	Yes ($n = 5$)	No ($n = 11$)	
Palliative strategy	0	3	0.1100
Presence of other anomalies	2	3	0.6100
PDA-dependent disease	1	9	0.0160
LVOTO and PDA-dependent disease	0	9	0.0007
PDA-dependent disease without LVOTO	1	0	0.1155
Neither LVOTO nor PDA-dependent disease	4	2	0.0166
Absence of LVOTO	5	2	0.0007
RVOTO	2	2	0.3600
PVO	1	1	0.5500

Other anomalies included Fryns syndrome, trisomy 18, situs inversus and agenesis of the corpus callosum. CoA, coarctation of aorta; HLHS, hypoplastic left heart syndrome; IAA, interruption of aortic arch; LVOTO, left ventricular outflow tract obstruction including HLHS, CoA, and IAA; PA, pulmonary atresia; PDA-dependent disease, patent ductus arteriosus-dependent disease including HLHS, CoA, IAA and PA; PS, pulmonary stenosis; PVO, pulmonary venous obstruction including TAPVC; RVOTO, right ventricular outflow tract obstruction including PA and PS; TAPVC, total anomalous pulmonary venous connection.

patients with CVM, including the 32 patients excluded from the present analysis, ASD and/or VSD and SV accounted for 36% (39/108) and 5.6% (6/108) of all CVM, respectively. Therefore, patients with CDH are consistently more likely to have CVM compared with neonates without CDH. This study is the first to demonstrate the prevalence of indications for the Fontan procedure among patients with CDH. Among the 614 CDH patients, 16 (2.6%) had CVM that were considered to be potential indications for the Fontan procedure. In contrast, the frequency of Fontan candidates is 0.045% among the general population, in which the frequency of CVM is 0.96%.[13] Thus, patients with CDH have a >10-fold higher risk of CVM that are potential indications for the Fontan procedure compared with the general population. In addition, the frequency of Fontan candidates was several fold higher in patients with CDH and CVM than in patients with CVM but not with CDH: 16 (14.8%) per 108 patients including 32 excluded from the present study versus 4.7% in the general population with CVM.[13]

Although the clinical outcomes, including the 90 day and 2 year survival and intact discharge rates, did not differ statistically between the 16 and 60 patients with and without indications for the Fontan procedure, respectively, these indices were consistently better among the 60 patients without indications for the Fontan procedure than among the 16 patients with indications for the Fontan procedure despite the fact that as many as one-third of these 60 patients had chromosomal abnormalities and/or genetic abnormalities or syndromes. After excluding 22 patients with these abnormalities, the surgical rate of CDH increased and the 90 day and 2 year survival rates improved considerably in the non-FC group, resulting in significantly better outcome with respect to 90 day survival in the non-FC group than in the FC-group. Therefore, better outcome can be expected in patients with both CDH and CVM without indication for the Fontan procedure when chromosomal and/or genetic abnormalities or syndromes are absent. The highest PaO_2 was significantly lower and the lowest $PaCO_2$ and OI were more severe in the patients with CVM with indications for the Fontan procedure in this study. It is possible that these factors were responsible for the poor outcome observed in this group. These factors, however, generally do not serve as indices of survival, perhaps because blood gas data do not reflect the state of respiration, but rather the volume of the pulmonary blood flow, in patients with cyanotic heart disease.

The surgical rate of CDH was found to be significantly lower in the FC group than in the non-FC group after excluding the 22 patients with chromosomal and/or genetic abnormalities or syndromes. We anticipated that a certain type of CVM in patients with indications for the Fontan procedure would predict poor outcome. Indeed, outcome was poorer in the nine patients with LVOTO (patients 1–7, 9, 10): none had a 90 day survival. Although therapeutic strategy was positive in seven of the patients with LVOTO, no patients were able to undergo radical treatment for CDH or palliative surgery for CVM in this study. This suggests that a positive therapeutic strategy is not indicated at present in patients with CDH and LVOTO.

The left heart system is small in fetuses and neonates with left-sided CDH.[14–25] Direct compression of the lungs and left atrium by abdominal organs prolapsing into the thoracic cavity, disturbance of the blood flow passing through the foramen ovale and a decreased pulmonary blood flow are considered to be complex factors causing a decrease in the amount of blood flowing into the LV.[23] The LV mass index is significantly lower in fetuses with CDH than in those without CDH.[21] When the LV is too small to output sufficient volume in neonates, the RV successfully compensates for the low output by directing blood through the ductus arteriosus, which is kept patent by nitric oxide and prostaglandin E1.[22] The poor outcomes observed in the present patients with LVOTO may be explained by insufficient maintenance of hemodynamics due to the small size of the LV. In addition to the heart disease itself, changes in hemodynamics due to CDH in the fetal period may have further worsened LV function. These factors may have hindered repair of CDH and CVM in the patients with LVOTO. In contrast, among the four patients with RVOTO (patients 6, 8,13,15), both radical treatment for CDH and palliative surgery for CVM were possible in two patients (patients 13, 15). Because the LV function was nearly normal, it was relatively easy to maintain hemodynamics in the patients with RVOTO. The positive therapeutic strategy was undertaken in seven of the nine patients with LVOTO

Surgical treatment for CVM may have led to the longer 90 day survival observed in some patients, although none of the 16 patients underwent the Fontan procedure due to the severity of their disease. Pulmonary function is an important factor determining the feasibility of the Fontan procedure.[1] Preventing the persistence of chronic lung disease and chylothorax, the occurrence of gastroesophageal reflux and the persistence of pulmonary hypertension, however, was often difficult, even after surgical treatment for CDH. Patient 14 died early from chronic lung problems following the Glenn procedure.

Many patients with heart disease complicated by CDH are diagnosed prenatally. Radical treatment may be initiated promptly after birth in such patients, but the outcome of patients with heart disease with indications for the Fontan procedure remained poor in this study, and only a few such patients are able to survive until palliative surgery for heart disease (I. Adatia, unpubl. data, 2004), as confirmed in the present study. The outcomes were especially poor in the patients with LVOTO. The present results have revealed a problem in how to determine how extensively patients with indications for the Fontan procedure should be treated. Systematic large studies are therefore needed to address this issue.

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Original article

Diffusion-weighted MRI for early diagnosis of neonatal herpes simplex encephalitis

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Abstract

Aim: To determine the early changes and evolutions of brain diffusion-weighted imaging (DWI), and analyze prognostic factors of the early changes among patients with neonatal herpes simplex encephalitis (NHSE).

Method: We selected patients who developed encephalitis by 28 d after birth; had herpes simplex infection; and who underwent magnetic resonance imaging, including DWI, ⩽7 d of symptom onset. Thirty-two DWI scans between 0 and 28 d after onset in 13 patients and the clinical data were recruited. The distribution, evolution of the lesions, and neurological outcome were analyzed.

Results: DWI frequently showed multiple cortical lesions in both hemispheres in the early period and both hemispheres on DWI (8/9 scans at ⩽48 h, 7/7 patients). As time from onset increased, the cortical lesions tended to coincide with subcortical white matter lesions beneath the initial cortical lesions ($p < 0.01$). Lesions from the cortex extended to the subcortical white matter in 7 patients.

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Deep cerebral lesions, involving basal ganglia, internal capsules, thalamus, were also found in 9 patients ⩽7 d of onset. The distributions of deep cerebral lesions (none/unilateral/bilateral) ⩽7 d of onset showed significant correlations with neurological prognoses (gross motor functions: $p < 0.01$; developmental or intellectual quotient scores: $p < 0.01$).

Interpretation: Cortical lesions were main findings of DWI in NHSE in the early period. Bilateral deep cerebral lesions ⩽7 d were highly indicative of poor motor and cognitive outcomes.

Keywords: Magnetic resonance imaging; Cortical lesions; Diffusion weighted imaging; Herpes simplex encephalitis; Early diagnosis; Neonate

1. Introduction

Neonatal herpes simplex encephalitis (NHSE) is a rapidly progressive, rare infectious disease (mortality rate, approximately 50% in untreated newborns) [1,2]. Although antiviral therapy decreases mortality, 56–70% of survivors experience significant neurological sequelae [1–5]. Early diagnosis is difficult because initial symptoms are usually nonspecific. Herpes simplex virus (HSV) DNA polymerase chain reaction is essential for NHSE diagnosis [1–3]. However, due to the lack of rapidly available diagnostic results (i.e., within hours) and the possibility of false-negative results [6], these viral infections are difficult to correctly diagnose in a timely manner; another method for the early diagnosis of NHSE needs to be established [7].

Magnetic resonance imaging (MRI) of infants with NHSE in acute and subacute stages reveals lesions in the cerebral cortex, white matter, basal ganglia, brainstem, and cerebellum [8–15]. Lesions detected with diffusion-weighted imaging (DWI) show up more clearly than lesions detected with conventional MRI [11,15]. Only 3 cases were reported wherein DWI were demonstrated within 48 h of onset [14,15]. Kubota et al., using DWI, reported a case with progression of lesions from the cerebral cortex to subcortical white matter during 72 h of onset [14]. The correlations between early DWI lesion patterns and time point of the scans have not been reported.

DWI has been applied to predict patient prognosis in neonatal hypoxic ischemic injury [16]. DWI lesions in bilateral posterior limbs of the internal capsule were correlated with poor outcome of motor functions in infants. For NHSE, the correlation between DWI lesion patterns and patient prognosis has not been established.

We analyzed DWI data and the time point of scan. We hypothesize (1) DWI is most sensitive at the early stage, (2) the lesion distribution changes over a period of time, and (3) early DWI findings can correlate with the outcome of motor and cognitive function. We tested these hypotheses by conducting a retrospective, multicenter study of DWI findings in patients with NHSE.

2. Method

2.1. Patients and clinical data

The inclusion criteria were acute symptoms including seizure, lethargy, and feeding impairment, which appeared within 28 d of birth; HSV infection confirmed by virological examinations, including antibody/polymerase chain reaction (PCR) in serum/cerebrospinal fluid or viral culture; and MRI, including DWI, performed within 7 d of onset. The study covered newborns diagnosed with NHSE between September 2001 and August 2011. A questionnaire was sent to 214 neonatal intensive care units throughout Japan and, from the responses, 13 patients who met the criteria (from 12 hospitals) were identified. HSV type 1 infection was detected in one patient (8%), and HSV type 2 infection in 5 patients (38%). Seven patients were tested by antibody or PCR examinations without specifying the subtypes. The ages at symptom onset ranged from 13 to 26 d of birth (mean: 17 d). The age at the last follow-up ranged from 2 to 76 months (30 months).

A structured research questionnaire was used to collect the following information regarding each identified patient: gestational age at birth, birth weight, age at onset and at the last follow-up visit, clinical signs and symptoms, maternal genital lesions present at the time of delivery, virological examinations, time course of neuroimaging, treatment, and outcome. The symptom onset was defined as the timing of initial manifestations including seizures, lethargy, poor feeding, fever, skin or mouth vesicles, conjunctivitis, keratitis, hepatopathy, coagulopathy and pneumonia. The ethics committee of Seirei-Hamamatsu General Hospital approved the study.

2.2. MRI studies

The following 4 time points from symptom onset were chosen for DWI and conventional MRI scans:

(1) Within 48 h of onset (⩽48 h).
(2) During 3–7 d after onset (during 3–7 d).
(3) During 8–28 d after onset (during 8–28 d).

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(4) At 29 d or later (only for conventional MRI; ⩾29 d).

Observed high-signal DWI abnormalities were classified as:

Type 1. Superficial cerebral lesions
- 1a. Cortical lesions: Only cortical lesions, not extending to the subcortical white matter (Fig. 1A and B).
- 1b. Cortical lesions + subcortical white matter lesions: Cortical lesions extending to the subcortical white matter lesions (Fig. 1C).

Type 2. Deep cerebral lesions including basal ganglia, internal capsule, and thalamus (Fig. 1D).

We analyzed a total of 32 DWI scans consisting of 9 scans in 7 patients <48 h, 11 scans in 9 patients during 3–7 d, and 12 scans in 10 patients during 8–28 d.

Apparent diffusion coefficient (ADC) maps were applied for 24 MRI scans in 10 patients. The low ADCs were available to confirm restricted diffusion in DWI (Fig. 1E and F). Unless ADC mapping was performed on the scans, we reviewed the possible effect of T2 shine though effects using T2-weighted and/or fluid-attenuated inversion recovery (FLAIR) images.

Conventional MRI scans were also collected, including T1-weighted, T2-weighted, and FLAIR images. We analyzed 9 scans for 7 patients ⩽48 h, 11 scans for 9 patients during 3–7 d, 12 scans for 10 patients during 8–28 d, and 11 scans for 10 patients ⩾29 d. We reviewed the abnormal signals in conventional MRI, including gray/white matter differentiation and hemorrhage, as well as atrophic and cystic changes. Conventional MRI data were compared to the changes observed using DWI.

We reviewed the location and size of the superficial cerebral lesions and the location of the deep cerebral lesion. We classified distributions of superficial cerebral lesions at ⩽7 d of onset into unilateral or bilateral lesions. We classified distributions of the deep cerebral lesions at ⩽7 d of onset into none, unilateral or bilateral lesions. DWI and conventional MRI scans were initially reviewed by one board certified pediatric neurologist (T. Okanishi). Thereafter, three other board certified pediatric neurologists (H. Yamamoto, J. Takanashi, A. Okumura) reviewed the images, and if necessary, they corrected the initial reports with their consensus. The three authors were unaware of the clinical information or scan time points of the patients.

Because this study was undertaken retrospectively at multiple institutions, the MRI protocols varied. The MRI field strength was 1.5 T for all scans. For each neonate, the acquisition parameters used with an FOV of 160–230 mm were as follows: DWI, TR = 2440–5200 ms and TE = 65–107 ms; T1-weighted imaging, TR = 442–3110 ms and TE = 10–15 ms; T2-weighted imaging, TR = 3800–43000 ms and TE = 85–115 ms; and FLAIR, TR = 9000–43000 ms, TE 95–102 ms, and TI = 200–2500 ms. The imaging matrix on DWI was 90–128 × 128. The slice thickness of DWI was 3–6 mm. The *b*-value was 0 and 1000, or 0 and 1200 s/mm^2.

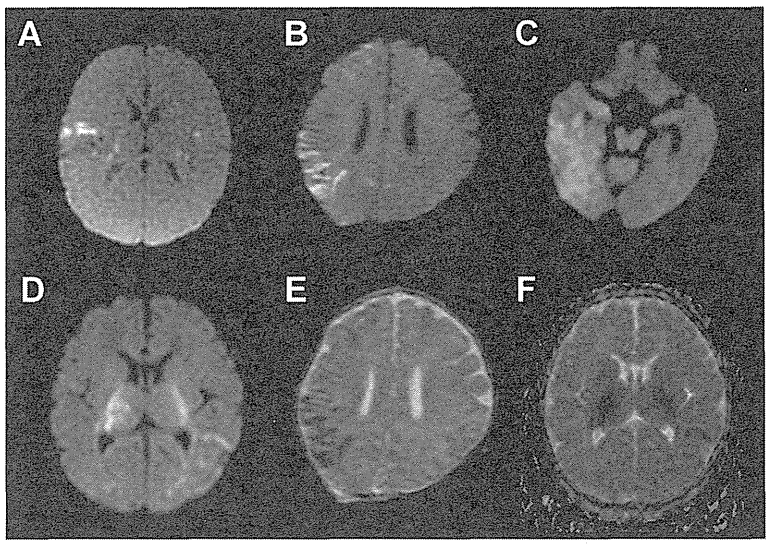

Fig. 1. Lesions on diffusion-weighted imaging. (A) (patient #4) and (B) (#5), cortical lesions; (C) (#12), cortical lesions + subcortical white matter lesions; (D) deep cerebral lesions (#10) in the internal capsules and thalamus. The distribution of high-signal lesions seen on (B) and (D) corresponded to the low diffusion area in apparent diffusion coefficient (ADC) maps ((E) and (F), respectively).

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2.3. Clinical outcomes

Twelve patients were monitored for more than 6 months and we evaluated the motor and cognitive outcomes. Gross motor function was evaluated and described as: "normal," if milestone of the highest functions, including rolling (5 months old), sitting (7 months old), crawling (8 months old) and walking (12 months old), were >70% of those expected for the child's chronological age; "delayed," if the milestone behaviors were 31–70% of those expected for their chronological age; and as "severely delayed," if the milestones were <30% of those expected. Developmental quotient or intellectual quotient (DQ/IQ) score was evaluated, and described as follows: "normal," if >70% of the expected value for the child's chronological age; "delayed," if 31–70% of the expected value; and "severely delayed," if ⩽30% of the expected value. The DQ or IQ was measured using the Tsumori-Inage Developmental Assessment Test, Enjoji Analytical Development Test, Kyoto Scale of Psychological Development, and Tanaka-Binet Intelligence Scales according to the age of the patient and preference of each hospital.

2.4. Statistical analyses

We analyzed the correlation between the incidence of cortical lesions/cortical lesions + subcortical white matter lesions and the 3 time periods (⩽48 h, during 3–7 d, and 8–28 d). We analyzed the correlations of the distributions of the superficial cerebral lesions and the deep cerebral lesions at ⩽7 d of onset with the outcomes of gross motor function and DQ/IQ score. In patients with 2 or more DWI scans at ⩽7 d of onset, the most abnormal results were used. We analyzed the correlations of the timing of acyclovir therapy (⩽6 h, during 6–24 h, and over 24 h) with the outcomes. For these analyses, we used Spearman's rank correlation test. A value of $p < 0.05$ was considered significant. The statistical analyses were performed using Excel 2010 (Microsoft, Redmond, WA, USA) with a Statcel 3 add-in (OMS, Tokyo, Japan).

3. Results

3.1. Patient and clinical data

We present the clinical data in Supplementary Table. The records of 8 girls and 5 boys, born between October 2004 and June 2011, were reviewed. The patients had a mean gestational age of 40 weeks (range, 36–41 weeks) and a mean birth weight of 3216 g (2670–4196 g); and a mean age at symptom onset of 17 d (13–26 d).

The initial clinical symptoms included fever in 7 patients (54%), seizures in 5 (38%), lethargy in 3 (23%), and feeding impairment in 1 (8%). All patients presented with isolated encephalitis. Patient #3 presented with skin vesicles.

Throughout the acute clinical phase of the disease, 11 patients had experienced seizures by day 4. The remaining 2 patients had no seizure history. None of the patients demonstrated asphyxia, shock, cardiac arrest, or other serious complications.

HSV infection was confirmed by cerebrospinal fluid (CSF)-PCR in all patients, serum-PCR in 3 (14%), CSF-antibody in 2 (15%), serum-antibody in 4 (31%), and viral isolation from skin vesicles in 1 (8%). All the patients were treated with intravenous acyclovir (20–60 mg kg^{-1} day^{-1}).

3.2. Clinical outcomes

The ages range at the last follow-up ranged from 2 to 76 months (mean: 30 months). We excluded one patient (#2) after 2 months follow-up from the outcome evaluations. At the last follow-up assessment, motor function was "normal" in 6 patients (#3–5, 9, 11, and 13), "delayed" in 1 (#1), and "severely delayed" in 5 (#6–8, 10, and 12). DQ/IQ scores were "normal" in 3 patients (#4, 5 and 13), "delayed" in 5 (#1, 3, 8, 9, and 11), and "severely delayed" in 4 (#6, 7, 10, and 12).

The timing of acyclovir therapy did not show any significant correlations with motor functions ($p = 0.11$) or DQ/IQ scores ($p = 0.17$).

3.3. DWI studies

Table 1 describes DWI findings in each scan time point.

3.3.1. Superficial cerebral lesions

All scans obtained at ⩽7 d showed superficial cerebral lesions. Cortical lesions were evident on 8 scans (89%) of all 7 patients (#1–7) at ⩽48 h, 3 scans (27%) of 3 patients (#9, 11, and 13) during 3–7 d, and no scans during 8–28 d. Cortical lesions + subcortical white matter lesions were evident on 1 scan (11%, #1) at ⩽48 h, 8 scans (83%) of 6 patients (#3, 4, 7, 8, 10, and 12) during 3–7 d, of 9 scans (75%) on 9 patients (#1–4, 7, and 10–13) during 8–28 d. Multiple cortical lesions, ranging in size from <1 gyrus to ⩾3 gyri, were scattered throughout the cerebral cortices of both hemispheres of the patients. Within 48 h of onset, the lesions were distributed over 2–6 cerebral lobes The lesions were distributed unilaterally on 2 scans (22%) of 2 patients (#3 and 4) and bilaterally on 7 scans (78%) of 5 patients (#1, 2, and 5–7). During 3–7 d of onset, the lesions were distributed over 1–8 cerebral lobes. The lesions were distributed unilaterally of 2 scans (18%) in 2 patients (#9 and 11) and bilaterally on 9 scans (82%) of 7 patients (#3, 4, 7, 8, 10, 12, and 13). The lesions were asymmetrically distributed and not related to the arterial

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Table 1
DWI findings within 7 d after onset.

Patient	≤ 48 hours of onset					3-7 d after onset				
	Hours	Types	Number of locations	Laterality	Locations	Days	Types	Number of locations	Laterality	Details
1	17	C	3	Bil.	R. F, T; L. F				NA	
		D	3	Bil.	R. IC; Bil. Thalami					
	40	C+WM	3	Bil.	R. F, T; L. F					
		D	3	Bil.	R. IC; Bil. Thalami					
2	19	C	2	Bil.	Bil. F				NA	
		D	1	Uni.	R. Thalamus					
3	20	C	2	Uni.	L. F, T	3	C+WM	3	Bil.	R. T; L. F, T
		D	1	Uni.	L. IC		D	1	Uni.	L. IC
4	23	C	2	Uni.	R. F, T	5	C+WM	3	Bil.	R. F, T; L. T
		D	2	Uni.	R. IC, Putamen		D	2	Uni.	R. IC, Putamen
5	26	C	6	Bil.	R. F, T, P, O; L. F, O				NA	
6	27	C	3	Bil.	R. F, T; L. F				NA	
		D	4	Bil.	Bil. IC, Thalami					
	42	C	3	Bil.	R. F, T; L. F					
		D	4	Bil.	Bil. IC, Thalami					
7	30	C	3	Bil.	R. F, T; L. T	6	C+WM	3	Bil.	R. F, T; L. T
		D	4	Bil.	Bil. IC, Thalami		D	4	Bil.	Bil. IC, Thalami
8			NA			3	C+WM	7	Bil.	R. F; Bil. T, P, O (MCA areas)
							D	4	Bil.	Bil. IC, Thalami
						5	C+WM	7	Bil.	R. F; Bil. T, P, O (MCA areas)
							D	2	Bil.	Bil. IC
9			NA			4	C	1	Uni.	L. T
10			NA			4	C+WM	6	Bil.	Bil. F, P, O (parasagittal)
							D	4	Bil.	Bil. IC, Thalami
						6	C+WM	8	Bil.	Bil. F, T, P, O (parasagittal)
							D	4	Bil.	Bil. IC, Thalami
11			NA			4	C	2	Uni.	R. F, T
12			NA			4	C+WM	5	Bil.	R. F, T, P, O; L. O
							D	4	Bil.	Bil. IC, Thalami
13			NA			5	C	3	Bil.	R. T; L. F, T

C, cortical lesions; C + WM, cortical + subcortical white matter lesions; D, deep cerebral lesions; R., right; L., left; Bil, bilateral; F, frontal lobe; T, temporal lobe; P, parietal lobe; O, occipital lobe; IC, internal capsule; NA, not available.

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territories (Fig. 1A and B). In 7 patients, we confirmed consecutive changes of lesions extending from the cortex into the subcortical white matter (Fig. 2A and B). Such changes were found in 1 patient (#1) at ⩽48 h, 3 patients (#3, 4, 7) ⩽7 d, 1 patient (#2) at ⩽28 d, and 2 patients (#11 and 13) during 3–28 d. The cortical lesions + subcortical white matter lesions were also distributed asymmetrically in most patients. Exceptional findings were observed in 2 patients and consisted of symmetrical, diffuse cortical and white matter lesions. The lesions were distributed in the regions of the posterior middle cerebral arteries on 2 scans (#8), and in the parasagittal area on 2 scans (#10). The signal intensities and the margins of the superficial cerebral lesions at ⩽7 d became fainter and blurred during 8–28 d. Finally, the incidences of cortical or cortical + subcortical lesions were significantly correlated with the time point of DWI scans ($p < 0.01$).

Table 2 presents the distributions of DWI lesions at ⩽7 d. Eleven patients (#1–8, 10, 12, and 13) showed bilateral superficial cerebral lesions. Two patients (#9 and 11) showed unilateral superficial cerebral lesions. Six patients (#2, 5, 6, 9, 11, and 13) showed cortical lesions at ⩽7 d. Seven patients (#1, 3, 4, 7, 8, 10, and 12) showed cortical lesions + subcortical white matter lesions. The distributions of superficial cerebral lesions (unilateral or bilateral) did not correlate with outcomes of gross motor function or DQ/IQ scores.

3.3.2. Deep cerebral lesions

Deep cerebral lesions were found on 8 scans (89%) of 6 patients (#1–4, 6, and 7) at ⩽48 h, in 8 scans (73%) of 6 patients (#3, 4, 7, 8, 10, and 12) during 3–7 d, and on 5 scans (45%) of 5 patients (#1, 2, 7, 10, and 12) during 8–28 d. All deep cerebral lesions coincided with the superficial cerebral lesions. Within 48 h of onset, the deep cerebral lesions distributed over 0–4 locations. The lesions were distributed unilaterally on 3 scans (33%) of 3 patients (#2–4) and bilaterally on 5 scans (56%) in 3 patients (#1, 6, and 7). During 3–7 d of onset, the deep cerebral lesions were distributed over 0–4 locations during 3–7 d. The lesions were distributed unilaterally on 2 scans (18%) of 2 patients (#3 and 4) and bilaterally on 6 scans (55%) of 4 patients (#7, 8, 10, and 12). The deep cerebral lesions in the internal capsules were found on 7 scans at ⩽48 h, 8 scans during 3–7 d, and 5 scans during 8–28 d. Lesions in the thalamus were found on 6 scans at ⩽48 h, 5 scans during 3–7 d, and in 5 scans during 8–28 d. Lesions in the putamen were found on 1 scan ⩽48 h, 1 scan during 3–7 d, and were not found during 8–28 d.

Seven (#1, 2, 6–8, 10, and 12) patients showed bilateral deep cerebral lesions (Table 2). Two (#3 and 4) patients showed unilateral deep cerebral lesions. Four patients (#5, 9, 11, and 13) showed no deep cerebral lesions. All the patients with severely delayed outcomes of gross motor function and DQ/IQ scores displayed the bilateral deep cerebral lesions. The distributions of deep cerebral lesions (none, unilateral, bilateral) at ⩽7 d were significantly correlated with poor outcomes of gross motor function ($p < 0.01$) and DQ/IQ scores ($p < 0.01$; Supplementary Figure). In this study, we found no patients with DWI lesions in either the brainstem or cerebellum.

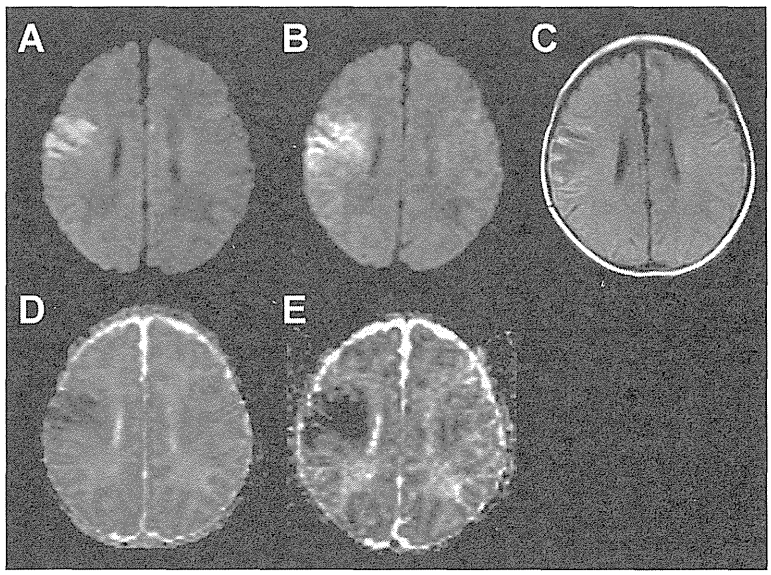

Fig. 2. Diffusion-weighted imaging (A and B) and T1-weighted imaging (C) in patient #1. (A) Cortical lesion in the right front temporal lobe, 17 h after onset; (B) extending to the subcortical white matter in the same area at 40 h after onset; (C) the lesion evolved into areas of encephalomalacia by day 14. The distribution of high-signal lesions on (A) and (B) corresponded to the low diffusion area in apparent diffusion coefficient maps (ADC) ((D) and (E), respectively).

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Table 2
Distributions of diffusion-weighted imaging lesions within 7 d of onset relating with outcomes.

Patient	Cortical, subcortical white matter lesions		Deep lesions	Follow-up months	Gross motor function	DQ/IQ scores
	Bil./Uni.	C/C + WM	Bil./Uni./None			
1	Bil.	C + WM	Bil.	17	Delayed	Delayed
2	Bil.	C	Bil.	2	NA	NA
3	Bil.	C + WM	L.	76	Normal	Delayed
4	Bil.	C + WM	R.	43	Normal	Normal
5	Bil.	C	None	35	Normal	Normal
6	Bil.	C	Bil.	15	Severely delayed	Severely delayed
7	Bil.	C + WM	Bil.	13	Severely delayed	Severely delayed
8	Bil.	C + WM	Bil.	9	Severely delayed	Delayed
9	L.	C	None	60	Normal	Delayed
10	Bil.	C + WM	Bil.	25	Severely delayed	Severely delayed
11	R.	C	None	34	Normal	Delayed
12	Bil.	C + WM	Bil.	38	Severely delayed	Severely delayed
13	Bil.	C	None	26	Normal	Normal

Bil., bilateral; Uni., unilateral; R., right; L., left; C, cortical lesions; C + WM, cortical lesions + subcortical white matter lesions; DQ/IQ, developmental quotient or intellectual quotient; NA, not applicable.

3.3.3. ADC maps

Restricted diffusions upon DWI was confirmed on all 24 scans as low signals on ADC maps (Figs. 1E, F and 2D, E). The remaining 8 DWI images were analyzed for the presence of the T2 shine-through effect. Two scans of patient #12 showed high-signal regions on T2-weighted images corresponding to the DWI lesions. These lesions were small and did not affect the result of the analyses in this study.

3.3.4. Conventional MRI studies

T1- and T2-weighted images were obtained in all scans. FLAIR images were obtained in 27 scans.

Among the 20 total scans obtained at ⩽7 d, conventional MRI scans showed signal changes in 11 patients: loss of gray/white matter differentiation (5 scans [25%]) and high-intensity signals in the cerebral cortex (10 scans [50%]), white matter (4 scans [20%]), or thalamus (1 study [5%]). These lesions were blurred or small compared to those observed on DWI. Conventional MRI did not detect any small (<1 gyrus) cortical lesions.

After 8 d of onset (⩾8 d), 23 total conventional MRI scans from 11 patients were analyzed. In all cases, the cortical lesions eventually evolved into encephalomalacia and/or atrophic changes (Fig. 2C). The thalamus and putamen lesions, visible on DWI in 9 patients at ⩽7 d, changed to atrophy with high-intensity signals on T1-weighted or FLAIR images. Apart from 1 scan (#13, 14 d of onset), the lesions on conventional MRI were more distinct than those of DWI at ⩾8 d.

Five patients (#2, 6, 7, 10, and 12) showed diffuse (>1 lobe) encephalomalacia with atrophic changes in both hemispheres at ⩾8 d. MRI showed focal (<3 gyri) encephalomalacia in 1 hemisphere in 1 patient (#4) and both hemispheres in 5 patients (#1, 3, 8, 11, and 13). One patient (#1) demonstrated growing cysts in the left hemisphere at 3 months of age.

We did not find lesions in any of the patients at any time point in either the cerebellum or brainstem.

4. Discussion

As the time from symptom onset increased, the cortical lesions extended to subcortical white matter. The lesion progressions strongly indicate herpes encephalitis in newborns. Deep cerebral DWI lesions at ⩽7 d of symptom onset in NHSE are prognostic factors for neurological outcomes.

The cortical lesions were characteristically evident as multiple, scattered lesions, asymmetrically distributed and not related to the major arterial territories. This cortical lesion pattern was previously reported in three cases with the scan time points of 20 h to 5 d from onsets [12,14,15]. Our study revealed that DWI is the most sensitive brain imaging technique available to reveal cortical lesion patterns in the early period (⩽48 h) of the onset of NHSE.

The early DWI patterns of NHSE are different from those of ischemia and other central nervous system infections. The DWI patterns of thrombotic brain infarction involved the cerebral cortex and correlated with the territories of the large- or medium-sized arteries, with the lesions being distinct in the white matter rather than in the cortices [17–19]. Neonatal bacterial brain infections show DWI patterns typical of watershed or major arterial infarctions, or brain abscesses in the white matter [15,20]. In 2 cases with parechovirus or coxsackie B2 virus, MRI showed symmetrical lesions in both cortices and white matter [21,22]. Depending on their size and distribution, the scattered and asymmetrical cortical lesions can suggest an NHSE diagnosis. Because virological examinations regularly yield false-negative results and the results that are also slow to obtain [6], brain DWI can facilitate a rapid

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and early diagnosis of NHSE. Although early acyclovir therapy did not show any correlation with the neurological outcomes in this study, the presence of the cortical lesions on brain DWI can strongly indicate starting or continuing acyclovir therapy in neonates.

HSV has a high affinity for neurons and may initially infect the cortical neurons of NHSE patients [23]. In adult HSE, HSV initially disseminates to one or both mesial temporal lobes by retrograde transmission via the olfactory nerves [24]. The multiple and scattered cortical abnormalities in DWI that appear to be associated with NHSE are specific to newborns. Gutierrez et al. hypothesized that in infants with isolated HSE, maternally derived transplacental neutralizing antibodies in the infants' serum prevent hematogenous transmission; thus, the retrograde transmission causes isolated encephalitis [25]. The multiple scattered neocortical lesions observed at $\leqslant$7 d in the present study suggest that hematogenous transmission is the main route of infection in NHSE.

Kubota et al. previously reported the progression of lesions from cerebral cortex to subcortical white matter in 1 (#3) of the current patients [14]. We confirmed this phenomenon in 6 additional patients (#1, 2, 4, 7, 11, and 13) within 4 weeks of symptom onset. HSV shows a specific cell-to-cell infection pattern via nectin binding on cell surface [23]. This form of transmission may account for the phenomenon of lesions spreading from the cortex to the subcortical white matter.

The bilateral deep cerebral lesions at $\leqslant$7 d correlated with poor neurological outcomes. The patients with severely delayed development showed extended encephalomalacia in the cerebrums. In newborns with hypoxic-ischemic encephalopathy, DWI lesions in bilateral posterior limb of the internal capsule predict poor neurological outcomes [16]. Here, 5 of 6 patients with NHSE had bilateral deep cerebral lesions including the internal capsule lesions in our cases. Similar to hypoxic–ischemic encephalopathy, the damaged posterior limb of the internal capsules by NHSE might precipitate poor neurological outcomes.

This study has some limitations. The imaging techniques varied in each hospital, and these differences might have affected the sensitivity of DWI. It is difficult to differentiate between the cortex and white matter in neonates has difficulties. Therefore the selected cortical lesions are more likely to be located in the superficial cortex. In 2 data, the high-signal DWI lesions might actually be T2 shine through effect. The time point of DWI scans depended on each physician's decision. Although there was one case report of cerebellar and brainstem lesion [13] and fatal cases of disseminated herpes infection [11], we had no such cases in this study. Early and consecutive changes in DWI of neonatal brain infections other than HSV also have not been sufficiently documented. Thus, DWI investigations of other infections are necessary to evaluate the specificity of the changes we found in the present study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.braindev.2014.07.006.

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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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