[J Tokyo Wom Med Univ
83 (Extra) E131～E136 (2013)]

Original

Outcomes in Term Neonates with Profound Asphyxia Diagnosed by Cranial MR Imaging

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(Accepted December 17, 2012)

Introduction: Profound neonatal asphyxia is an important issue in the fields of neonatology and pediatrics. Developmental progress and outcomes in term infants with profound asphyxia are presented. **Materials and Methods:** Term neonates confirmed to have only radiologically defined perinatal profound asphyxia (RPA) were studied. RPA was defined as findings of high T1 signal intensity of the basal ganglia on cranial magnetic resonance imaging (MRI). All patients were observed for several months perinatally and thereafter. We investigated the perinatal clinical data and development of patients diagnosed of RPA. **Results:** Nine patients presented with RPA. All were born between gestational weeks 37 and 42, with birth weights over 2,500 g. Four of the nine patients were clinically diagnosed with severe birth asphyxia, two others with moderate birth asphyxia. The other three patients were diagnosed with neonatal pneumothorax, hypoglycemia, and/or apnea. MRI showed high T1 signal intensity in the basal ganglia, and two patients also displayed low T2 signal intensity. One patient had mild central hypotonia and motor developmental delays, whereas mental and motor development was normal in the other patients. **Conclusions:** Developmental progress was followed in these patients after the perinatal period, and the outcomes in term neonates with RPA were relatively positive.

Key Words: profound asphyxia, cranial MRI, term infants, gross motor development

Introduction

Profound neonatal asphyxia is an important issue in the fields of neonatology and pediatrics, as it is associated with neurological development, including motor function. Profound asphyxia is characterized by damage to the brainstem and/or the deep gray matter caused by episodes of cardiac arrest or complete asphyxia. It typically results in necrosis of the basal ganglia. To evaluate the extent of damage due to profound asphyxia in early neonatal periods, various neuroradiological examinations are conducted, including cranial ultrasonography, computed tomography (CT) and/or magnetic resonance imaging (MRI), and/or also with neurophysiological devices, such as multichannel electroencephalography (EEG), amplitude integrated EEG, and somatosensory evoked potentials. Assessing brain damage with these examinations is important for treatment management and, furthermore, for predicting outcomes of neonates presenting with birth asphyxia[1)2)]. To date, among these various neuroradiological or neurophysiological examinations, MRI has been performed during adequate periods as is it valuable for assessing brain injuries, including hypoxic-ischemic encephalopathy with profound asphyxia, and for predicting outcomes[3)~6)]. Recently we have on occasion obtained MRI findings indicating profound asphyxia which have raised concerns about poor outcomes and some of those cases had no signs of significant perinatal hypoxic events. So we considered the necessity of the research about the neurological outcomes in infants who had findings of profound asphyxia detected by MRI including cases with no signs of hypoxic events.

Table Patient summary

Patient	Gender	Observation period	Gestational age (weeks and days)	Birth weight (g)	Apgar scores (1/5 minutes)	Umbilical cord arterial pH	Clinical diagnosis	MRI (day)	Other MRI findings besides BG T1W high	Gross motor development
1	B	10 m	38.1	3,087	2/7	7.338	Severe birth asphyxia, HIE, IDM	8	BG T2W low, subdural hemorrhage	No delay
2	B	10 m	37.4	3,294	9/10	No data	Pneumothorax, retinal hemorrhage	10	None	No delay
3	G	10 m	39.4	2,812	8/8	7.43	Apnea, presumptive sepsis, hypoglycemia	15	None	No delay
4	G	11 m	41.2	2,990	4/7	7.01	Moderate birth asphyxia, MAS, pneumothorax, apnea	10	None	No delay
5	B	12 m	41.1	3,092	2/6	7.183	Severe birth asphyxia	12	None	No delay
6	B	12 m	39	3,650	8/9	7.24	Apnea, IDM	7	None	No delay
7	G	15 m	41.4	2,826	2/3	6.67	Severe birth asphyxia, MAS, PPHN, CLD	15	None	Mild delay with hypotonia
8	G	18 m	38.6	3,356	3/7	7.15	Severe birth asphyxia	6	BG T2W low, subtentorial hemorrhage	No delay
9	G	24 m	40.3	3,356	4/9	7.32	Moderate birth asphyxia, MAS	19	None	No delay

Note: B, boy; G, girl; HIE, hypoxic ischemic encephalopathy; IDM, infant of diabetic mother; MAS, meconium aspiration syndrome; PPHN, persistent pulmonary hypertension of the newborn; CLD, chronic lung disease; BG, basal ganglia

In this study, we aimed to investigate the developmental progress and outcomes of term infants with profound asphyxia diagnosed by cranial MRI in a retrospective cohort study.

Materials and Methods

Patients in the present study were admitted to the neonatal intensive care unit of Tokyo Women's Medical University Hospital during the period between June 2008 and June 2011. Inclusion criteria were ① between 37 and 42 weeks gestational age ② perinatal profound asphyxia confirmed only by cranial MRI findings of high T1 signal intensity in the basal ganglia ③ observation and assessment for a minimum of 10 months. We excluded obvious metabolic disorders, congenital malformations, and congenital infections.

Neonates were weighed and given an Apgar score at 1 minute and 5 minutes after birth. Umbilical arterial cord pH was measured when possible. Cranial MRI was performed with a 1.5-T unit. These images included sagittal T1 and axial T1 and T2 views. Cranial MRI results were reviewed and evaluated by pediatric radiologists. The patients were observed at regular intervals by pediatric neurologists who specialized in neurological development and infant outcomes.

Results

Nine patients met the inclusion criteria. The basic information, perinatal data, MRI findings, and gross motor development outcomes of these nine patients are summarized in Table.

Clinical Data

All nine infants were born between gestational weeks 37 and 42, with birth weights over 2,500 g (2,812-3,650 g). Four of the nine were boys, and five girls. Apgar scores ranged between 2 and 10 at 1 minute and between 2 and 10 at 5 minutes after birth. For diagnosing neonatal asphyxia, we adopted the ICD-10 criteria, namely those who had Apgar scores of 0-3 and 4-7 at 1 min were diagnosed as having of severe asphyxia and moderate asphyxia, respectively.

Thus, four of the infants (patients 1, 5, 7, and 8) were diagnosed as having severe birth asphyxia. The umbilical cord blood pH was low in patients 5, 7, and 8 with pH values of 7.183, 6.67, and 7.15, respectively. Additionally, patient 7 presented with persistent pulmonary hypertension of the newborn (PPHN) and chronic lung disease (CLD) associated with severe birth asphyxia and meconium aspiration syndrome (MAS).

Two of the nine infants (patients 4 and 9) were diagnosed as having moderate asphyxia based on the

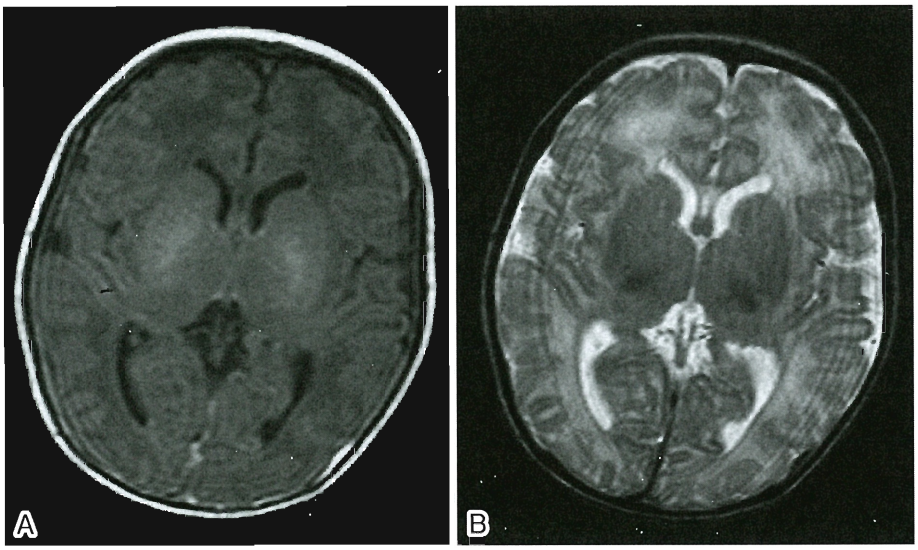

Fig. 1 MR images of Patient 1
A. T1-weighted spin echo (SE) [repetition time (TR) 525/echo time (TE) 17.0].
B. T2-weighted SE [TR 4,000/TE 95.0].
A and B are images obtained at 8 days of age. A shows high T1 signal intensity in the basal ganglia (BG). B shows low T2 signal intensity in the BG.

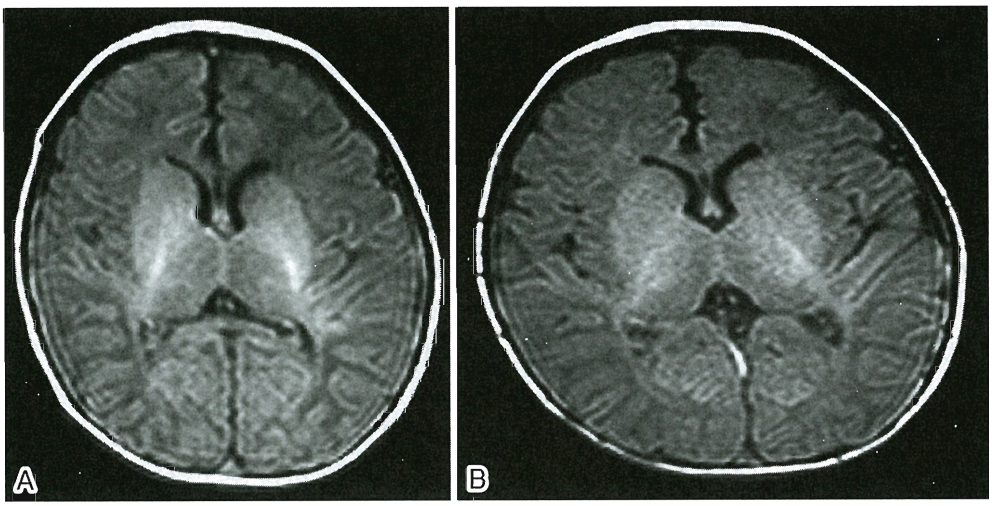

Fig. 2 MR images of Patient 7
A. T1-weighted SE [TR 525/TE 17.0].
B. T1-weighted SE [TR 525/TE 17.0].
A is an image obtained at 15 days of age, and B at 36 days of age. A shows high T1 signal intensity in the BG, while B shows improvement of this abnormal T1 signal intensity.

aforementioned criteria. Patients 4 and 9 also presented with MAS. The other three infants (patients 2, 3, and 6) were not diagnosed with birth asphyxia, because they had high Apgar scores at 1 min. Patient 2 was diagnosed with neonatal pneumothorax with retinal hemorrhage, patient 3 with neonatal hypoglycemia and apnea, and patient 6 also had apnea.

MRI

MRI was performed during the day between 6 and 19 days of age. Patients 1 and 8 displayed low T 2 signal intensity in the basal ganglia in addition to high T1 signal intensity, one of the inclusion criteria for this study (Fig. 1, 3). Additionally, patient 1 had subdural hemorrhage on MRI, and patient 8 displayed subtentorial hemorrhage. Patient 7 under-

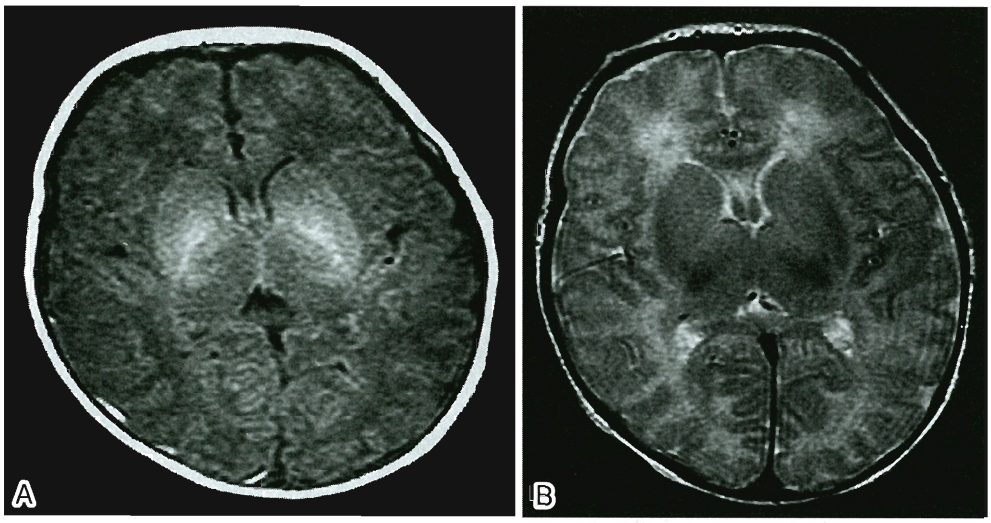

Fig. 3 MR images of Patient 8
A. T1-weighted SE [TR 420/TE 9.0].
B. T2-weighted SE [TR 3,200/TE 115.5].
A and B are images obtained at 6 days of age. A shows high T1 signal intensity in the BG. B shows low T2 signal intensity in the BG.

went MRI scans twice, and the second MRI showed that the high T1 signal intensity had improved as compared with the initial images (Fig. 2).

Follow-up

Four patients were observed for over 10 but less than 12 months, while the other five patient's observation periods exceeded 12 months, and the maximum was 24 months. Eight of the nine infants (all but patient 7) showed normal gross motor development. These patients included two infants with low T2 signal intensity in the basal ganglia. The patients gained appropriate head control at 3-4 months of age, sat without support from 6-8 months of age, and stood and walked by themselves from 9-12 months of age. In regard to psychological development, the patients developed eye contact, smiling, and speech at age-appropriate times. Patient 7 displayed mild delays in gross motor developmental during early infancy due to central hypotonia of the trunk and mildly poor muscle consistency. She could control her head at 7 months of age, sit without support at 10 months of age, and walk while holding onto a wall or a table at 15 months of age.

Discussion

In premature and term newborns, profound asphyxia is characterized by necrosis of the basal ganglia. Interestingly, however, damaged regions of the brain may show plasticity during development.

Diagnostic imaging tools, including cranial ultrasonography, cranial CT, and cranial MRI, can be used to diagnose and assess brain abnormalities. During the acute phase of neonatal asphyxia, the damaged deep gray matter appears as an area of high echogenicity on cranial ultrasonography, a low-density signal on CT, and a high T1 plus abnormal T2 signals on MRI.

The early recognition of CT and MRI abnormalities that involve the thalamus and basal ganglia (putamen) in term newborns is highly predictive of long-term outcomes[7]. Cranial CT is an easier method to use in newborns with birth asphyxia than MRI. The difficulty with a CT diagnosis in this population lies in scan-condition selection. For this reason, MRI is better for evaluating the extent of brain damage in infants with hypoxic-ischemic brain injury during the perinatal period[8]. Furthermore, MRI findings are useful for predicting neurological outcomes in term newborns with asphyxia. Specifically, high T2 and T1 signal intensities in the deep gray matter of the cerebral hemispheres predict poor neurological outcomes with spastic quadriparesis and/or athetosis, epilepsy, and neurological developmental problems[9]. Also, a previous study demonstrated a high correlation between the sever-

ity of basal ganglia and thalamic (BGT) injury and the severity of motor impairment, and concluded that early MRI was of significance for predicting outcomes in term newborns with hypoxic-ischemic encephalopathy and BGT injury[6]. Other studies have also shown a correlation between the outcome and the severity of profound asphyxia or hypoxic-ischemic encephalopathy in premature and term infants to be detectable by MRI[10)11)]. Moreover, diffusion-weighted MRI scans and MR spectroscopy combined with routine MRI improves the precision of diagnostic evaluation and better predicts outcomes in infants with perinatal asphyxia[12)13)].

In the present study, developmental outcomes, specifically gross motor and psychological development, were evaluated during early childhood. We determined that the outcomes in term neonates with profound asphyxia were relatively positive. However, we were unable to predict the relationship between the extent of MRI-detected damage and infant developmental outcomes. Future studies should use diffusion-weighted MRI or MR spectroscopy in combination with routine MRI.

Previous studies have shown that perinatal asphyxia has a long-term influence on cognitive ability, behavioral consequences, academic functioning, and neuropsychological skills or late onset involuntary movement in patients with mild basal ganglia damage following perinatal asphyxia. Therefore, patients without delays in gross motor and psychological development may experience various problems in cognitive ability, behavioral consequences, academic functioning, neuropsychological skills or involuntary movement as they reach school age[14)~18)].

In the present study, focusing on term newborns with profound asphyxia diagnosed radiologically by cranial MRI, patients with nonspecific neonatal complications, such as apnea, pneumothorax, retinal hemorrhage, and hypoglycemia, without remarkable birth asphyxia clinically, were identified. Furthermore, future studies should not only assess gross motor functioning and psychological development during early childhood but also investigate long-term neurological outcomes, including minor neurological signs, cognitive ability, and behavioral consequences in children through school-age and adolescence.

Conclusion

We investigated the outcomes of infants diagnosed with profound asphyxia by cranial MRI. The outcomes in infancy were relatively good, but it appears to be necessary to evaluate long term outcomes, through school age and into the adolescent period.

The authors have no conflicts of interest to declare.

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頭部 MRI で profound asphyxia を認めた正期産児の予後

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〔緒言〕新生児における profound asphyxia は新生児学，小児科学分野において重要な論点となる．今回我々は，頭部 MRI において profound asphyxia の所見を認めた正期産児の精神運動発達と予後に関する検討を行った．〔対象および方法〕新生児期に施行した頭部 MRI の T1 強調画像における基底核高信号所見によって profound asphyxia と診断された症例を対象とした．これらの児で，少なくとも数ヵ月の発達経過を観察した．これらの児における周産期の臨床データと児の発達予後について検討を行った．〔結果〕頭部 MRI で上述した profound asphyxia 所見を認め，乳児期の経過観察が可能だった対象は 9 症例だった．全例が在胎 37～42 週の児で，体重は 2,500 g 以上である．9 症例のうち，臨床的に Apgar score から重症新生児仮死と診断された例が 4 例，中等症新生児仮死例が 2 例だった．他の 3 症例は臨床的には仮死と診断できなかったが，それぞれ，新生児早期に気胸，低血糖または無呼吸を合併したため頭部 MRI が施行されていた．頭部 MRI 所見は profound asphyxia と判断した所見である T1 強調像の基底核の高信号所見以外には，2 例において T2 強調像で低信号を呈していた．乳児，小児期の精神運動発達は，1 例は中枢性筋緊張低下を伴って，運動発達の軽度の遅れを認めたが，他の 8 例は月齢相当の発達を示した．〔結論〕新生児期に頭部 MRI で profound asphyxia 所見を認めた正期産児の発達予後は，概ね良好に経過することが示唆された．