Early diagnosis and outcome prediction of neonatal hypoxic-ischemic encephalopathy with color Doppler ultrasound

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KEYWORDS
Hypoxic-ischemic encephalopathy; Neonate; Color Doppler ultrasound; Outcome study; Neonatal encephalopathy

Abstract
Purpose: To describe the ultrasound presentation of the brain and cerebral hemodynamics in neonates with hypoxic-ischemic encephalopathy (HIE) by comparison with control subjects.
Material and methods: During June 2012 to April 2013, full term neonates who had clinical evidence of HIE were enrolled. Healthy newborns without HIE were used as a control group. Cerebral parenchyma, size of lateral ventricles and hemodynamic parameters of cerebral arteries were studied using two-dimensional duplex and color Doppler ultrasound. Neonates with moderate and severe HIE were followed-up with ultrasound for at least 3 months.
Results: A total of 158 consecutive neonates (82 boys and 76 girls), including 54 with mild HIE, 60 with moderate HIE and 44 with severe HIE were included. One hundred and twenty healthy newborns were randomly selected as a control group. Abnormal ultrasound findings of brain parenchyma were found in 25/54 (46.3%) neonates with mild HIE whereas they were found in 58/60 (96.7%) neonates with moderate HIE and 44/44 (100%) neonates with severe HIE. Almost all neonates with severe HIE had decreased cerebral artery blood flow velocity and increased resistance index of cerebral arteries. Of the 104 neonates with moderate or severe HIE, follow-up ultrasound examination revealed cystic parenchymal lesions in 12/104 (11.5%), progressive ventricular dilatation and brain atrophy in 12/104 (11.5%), mild ventricular dilatation in 15/104 (14.4%) and leukoencephalomalacia in 2/104 (1.9%) neonates.
Conclusion: Ultrasound features such as the size of lateral ventricles, altered brain parenchymal echogenicity and cerebral blood flow parameters are useful for the early diagnosis of HIE and help predict outcome.

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Neonatal hypoxic-ischemic encephalopathy (HIE) is caused by perinatal hypoxic brain injury. It is the main cause of neonatal mortality and neurological dysfunction [1]. Less severe HIE together with timely intervention could have a better prognosis, while severe HIE will leave permanent neurological sequelae [2]. Therefore, it is of major importance to make an early diagnosis of HIE with a reliable imaging tool. Magnetic resonance imaging (MRI) of the brain is the most trustable imaging examination for the diagnosis of brain injury [3], but it is impossible to perform MRI immediately in acutely asphyxiated neonate.

Two-dimensional transcranial Doppler ultrasound (US) can provide detailed information on brain hemodynamics [4]. US can reflect the changes of cerebral blood flow after newborn asphyxia suffocation [5]. Moreover, US helps detect intracerebral lesions such as hydrocephalus, intraventricular hemorrhage, and infarction of the neonatal brain. The goal of this study was to describe the ultrasound presentation of the brain and cerebral hemodynamics in neonates with hypoxic-ischemic encephalopathy (HIE) by comparison with control subjects.

Materials and methods

Patients

This study was approved by the Institutional Review Board of our institution and written consent was obtained from the parents of each child. During June 2012 to April 2013, full term neonates who met clinical evidence of HIE determined by clinical evaluation of consciousness, neuromuscular control, complex reflexes, autonomic function and presence of seizures were enrolled [6, 7]. The control group consisted of healthy newborns without asphyxia and hypoxia history, who were randomly selected for transcranial US during the same time course at Guangzhou Women and Children Medical Center.

US examination

US examinations were performed with a SSA-660A scanner (Toshiba Medical Systems, Tokyo, Japan) that incorporated a 3.5-MHz curvilinear transducer and a 12-MHz linear array transducer, an EUB-7000HV scanner (Hitachi Medical Corporation, Tokyo, Japan) that incorporated a 2–5-MHz curvilinear transducer and a 6–13-MHz linear array transducer. Initial US examination was performed within 72 hours after birth by one radiologist with an experience of more than 10 years in neonatal cranial US. Neonates were kept in a quiet state with supine position. Firstly, the following items were assessed on sagittal and coronal planes through anterior fontanel:

- morphological structure of brain tissue;
- size and location of US abnormalities;
- size and shape of lateral ventricles;
- anterior cerebral artery (ACA) blood flow parameters using color Doppler flow image (CDFI), color Doppler energy (CDE) and pulsed wave Doppler (PWD).

We then scanned through temporal cross-section to display skull base arterial rings with CDFI and CDE, measured middle cerebral artery (MCA) blood flow parameters, detected bilateral lesions and recorded the focus lesion situation in dynamic images by using high-frequency probe through anterior fontanel and temporal cross-section. The blood flow parameters included resistance index (RI), systolic velocity (Vs) and diastolic velocity (Vd). RI was calculated with the following formula:

\[ RI = \frac{Vs - Vd}{Vs} \]

All US examinations were performed under the same instrument settings, and each Doppler parameter was averaged on 3 to 4 cardiac cycles.

Imaging analysis

The US examinations of each neonate of the study group were reviewed in consensus by two radiologists with more than 10 years of experience in neonatal cranial US to determine the severity of HIE. These two radiologists were not involved in data acquisition. The severity of HIE for every neonate were classified into three categories as follows:

- mild: small hyperechoic foci of brain parenchyma echogenicity were predominantly located in the periventricular areas;
- moderate: more than two lobes of brain were diffusely hyperechoic, with obscure boundary of white-gray matter and narrowing lateral ventricle;
- severe: when diffuse parenchymal hyperechoic areas, and some with no echos, gray and white matter boundaries disappeared, while the lateral ventricle being compressed by intracranial hemorrhage [3–5].

For neonates who were classified into moderate and severe HIE on initial US examination, follow-up US examinations was performed three or four times a week and the follow-up was continued for at least 3 months [8].

Statistical analysis

Statistical analysis was performed with software (SPSS, version 16; SPSS, Chicago, IL, USA). Quantitative variables were expressed as mean ± standard deviation (SD) and ranges. Differences between the two groups were searched using Student t-test for quantitative variables and Chi² (\(\chi^2\)) test for categorical variables. Significance was set at \(P < 0.05\).

Results

Initial brain US

A total of 158 consecutive neonates (82 boys and 76 girls) with HIE, including 54 (54/158; 34.2%) with mild HIE, 60 (60/158; 38.0%) with moderate HIE and 44 (44/158; 27.8%) with severe HIE were enrolled. One hundred and twenty healthy newborns were randomly selected for transcranial US and served as a control group. No significant differences in gestational age, gender and body weight of the newborns were found between the two groups.
The brain parenchyma of normal newborns in the control group showed homogeneous, hypoechoic, clear sulci and gyri, and normal choroid plexus of lateral ventricle (Fig. 1). HIE grades and corresponding results of US examinations in the HIE group are shown in Table 1. Of 54 newborns with mild HIE, there were 23/54 (42.6%) with slightly narrowed lateral ventricle, 2/54 (3.7%) with slightly increasing parenchymal echo limitations, and 29/54 (53.7%) without any US abnormalities of brain parenchyma (Fig. 2). In newborns with moderate HIE, diffuse or focal parenchymal echo was hyperechoic in 56/60 (93.3%) newborns with less clear boundaries of cerebral sulcus, of which 14/56 (25.0%) had periventricular-intraventricular hemorrhage, and their lateral ventricles were generally slightly narrowed (Fig. 3). All 44/44 (100%) neonates with severe HIE showed extensive parenchymal echo with fuzzy brain structure, of which 13/44 (29.5%) showed unclear or slit lateral ventricle and 17/44 (38.6%) had cerebral hemorrhage (Fig. 4). Blood flow parameters of ACA and MCA are reported in Table 2 and Table 3. Among the 44 neonates with severe HIE, only one showed a high perfusion state with faster blood flow velocity and decreased RI, whereas 43/44 (97.7%) showed decreased blood flow velocity and increased RI (Fig. 5).

Figure 1. Normal brain ultrasound examination of full-term newborn without neonatal hypoxic-ischemic encephalopathy.

Figure 2. Newborn with mild neonatal hypoxic-ischemic encephalopathy. Ultrasound examination shows bilateral ventricle narrowing (arrows indicate bilateral choroid plexus).

ACA Vs, MCA Vs, and Vd were lower in the neonates with HIE than in the control group, while RI was higher. There were statistically significant differences for all blood flow parameters between the HIE group and the control group (Tables 2 and 3).

Follow-up brain US

One hundred and four neonates with HIE who had abnormalities on two-dimensional US were followed-up. Of them, 12/104 neonates (11.5%) had formation of cystic lesions of brain parenchyma, 12/104 (11.5%) had progressive ventricular dilatation and brain atrophy (Fig. 6), and 15/104 (14.4%) had mild ventricular dilatation. In addition, there were 2 neonates with leukoencephalomalacia (Fig. 7).

Discussion

HIE mainly occurs in full-term neonates. It is one of the main causes of death by acute and chronic neonatal neurological damage [9]. The incidence of HIE in live births ranges

Table 1. Clinical classification of hypoxic-ischemic encephalopathy and corresponding findings on ultrasound examination.

<table>
<thead>
<tr>
<th>Severity of HIE</th>
<th>n</th>
<th>US findings</th>
<th>Abnormal US findings (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>Mild</td>
</tr>
<tr>
<td>Mild</td>
<td>54</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>Moderate</td>
<td>60</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Severe</td>
<td>44</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>158</td>
<td>31</td>
<td>25</td>
</tr>
</tbody>
</table>

HIE: hypoxic-ischemic encephalopathy.
Figure 3. Newborn with moderate neonatal hypoxic-ischemic encephalopathy. Ultrasound examination shows diffusely hyperechoic periventricular brain parenchyma (arrows) meanwhile the cerebral sulcus boundary is blurry (arrowheads indicate bilateral ventricle).

between 3/1000 and 6/1000, of which 15%–20% of affected neonates die in the neonatal period, and 25%–30% of survivors may have some types of long-term sequelae [10,11].

Figure 4. Newborn with severe neonatal hypoxic-ischemic encephalopathy. Ultrasound examination shows hyperechoic and fuzzy brain parenchyma (arrows) in periventricular areas.

The bad outcome has a tremendous impact on the family and the community [12].

The purpose of imaging examination is to early clarify the range of HIE lesions and to determine if intracranial hemorrhage is present. Further, a follow-up examination plays an important role in assessing the outcomes of HIE. US is

### Table 2
Blood flow parameters of the anterior cerebral artery on duplex Doppler ultrasound in control newborns and newborns with hypoxic-ischemic encephalopathy.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Vs (m/s)</th>
<th>P</th>
<th>Vd (m/s)</th>
<th>P</th>
<th>RI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>120</td>
<td>44.8 ± 9.2</td>
<td></td>
<td>14.2 ± 4.7</td>
<td>&lt;0.001</td>
<td>0.67 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>Mild HIE</td>
<td>54</td>
<td>41.9 ± 8.3</td>
<td>&lt;0.001</td>
<td>12.5 ± 6.6</td>
<td>&lt;0.001</td>
<td>0.70 ± 0.06</td>
<td>0.054</td>
</tr>
<tr>
<td>Moderate HIE</td>
<td>60</td>
<td>38.6 ± 9.1</td>
<td>&lt;0.001</td>
<td>11.3 ± 6.2</td>
<td>0.002</td>
<td>0.74 ± 0.03</td>
<td>0.052</td>
</tr>
<tr>
<td>Severe HIE</td>
<td>44</td>
<td>33.6 ± 10.4</td>
<td>&lt;0.001</td>
<td>10.2 ± 7.5</td>
<td>0.003</td>
<td>0.80 ± 0.11</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are expressed as means ± standard deviation (SD). HIE: hypoxic-ischemic encephalopathy; Vd: diastolic velocity; Vs: systolic velocity; RI: resistance index.

a Comparison was made with the control group.
b Comparison was made with the mild HIE group.
c Comparison was made with the moderate HIE group.

### Table 3
Blood flow parameters of the middle cerebral artery on duplex Doppler ultrasound in control newborns and newborns with hypoxic-ischemic encephalopathy.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Vs (m/s)</th>
<th>P</th>
<th>Vd (m/s)</th>
<th>P</th>
<th>RI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>120</td>
<td>47.2 ± 9.1</td>
<td></td>
<td>18.7 ± 4.8</td>
<td></td>
<td>0.62 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Mild HIE</td>
<td>54</td>
<td>43.5 ± 8.3</td>
<td>&lt;0.001</td>
<td>15.2 ± 6.0</td>
<td>&lt;0.001</td>
<td>0.67 ± 0.02</td>
<td>0.003</td>
</tr>
<tr>
<td>Moderate HIE</td>
<td>60</td>
<td>41.6 ± 9.2</td>
<td>0.002</td>
<td>12.9 ± 6.1</td>
<td>&lt;0.001</td>
<td>0.71 ± 0.03</td>
<td>0.056</td>
</tr>
<tr>
<td>Severe HIE</td>
<td>44</td>
<td>34.7 ± 7.6</td>
<td>&lt;0.001</td>
<td>8.9 ± 7.4</td>
<td>&lt;0.001</td>
<td>0.81 ± 0.12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as means ± standard deviation (SD). HIE: hypoxic-ischemic encephalopathy; Vd: diastolic velocity; Vs: systolic velocity; RI: resistance index.

a Comparison was made with the control group.
b Comparison was made with the mild HIE group.
c Comparison was made with the moderate HIE group.
features can help predict the outcomes of neonate with HIE [13]. These findings are important because an early diagnosis is the cornerstone of early management.

In our study, we found differences between color Doppler US results and clinical classifications in neonates with mild HIE. Only 28/54 neonates (42.6%) with mild HIE had abnormal US findings. On the other hand, 56/60 neonates (93.3%) with moderate HIE and all neonates (100%) with severe HIE had abnormalities on US examinations. Our results indicate that US findings correlate well to the severity of HIE, and that US follow-up is useful for evaluating the extent of brain damage and predicting the outcome [14].

The pathological types of brain damage in HIE depends on the extent, duration and maturity of infants [1]. US helps detect brain edema, periventricular and intraventricular hemorrhage, basal ganglia and thalamic lesions, as well as cerebral artery infarction and other types of lesions [8,14,15]. Depending on the pathological and clinical manifestations, HIE have different US presentations. Early localized or diffuse cerebral edema presents as localized or diffuse hyperechoic parenchyma depending on the degree of damage. Mild HIE may be overlooked whereas with prolonged hypoxia, cerebral edema become more visible, the scope of the hyperechoic parenchyma is expanded, and lateral ventricles are squeezed and narrowed and gray matter boundaries look fuzzy [15]. US is also helpful to detect intracranial hemorrhage, either subchorionic hemorrhage or intraventricular hemorrhage [16,17]. The degree of parenchymal echogenicity is related to the degree of nerve cell damage [17].
In our study, we found that $V_s$, $V_d$ of ACA and MCA of neonates with HIE are lower than those in the control group, especially the end-diastolic velocity. RI of ACA and MCA in neonates with HIE are higher than those in the control group. Some studies pointed out that RI of ACA can directly reflect cerebral blood supply and thus can be used to predict HIE \([8,9,18]\). In this regard, we found that all but one neonate with severe HIE, had elevated RI, which indicates reduced perfusion of brain tissue in HIE. When the cerebral blood flow velocity is decreased and RI is increased in infants with clinical HIE, the blood flow velocity is decreased accordingly, especially the diastolic velocity is decreased significantly, and all of these patients were clinically diagnosed as severe HIE. Drop in blood pressure after asphyxia is one reason of decreased cerebral blood flow, and another reason is that increased cranial pressure can reduce cerebral blood flow, and the regulation of cerebral blood flow in the body is based on change of vascular resistance. RI can reflect the peripheral circulation impedance, positively correlating with loop impedance, which can indirectly reflect blood flow change and local blood supply and oxygen supply. Studies had considered that it was associated with poor prognosis with $RI \leq 0.5$, and $RI \geq 0.9$ may indicate cerebral vasospasm and decreased perfusion of cerebral blood flow, which might have poor prognosis \([9]\).

In our present study, we found that US findings in neonates with mild HIE returned to normal during the follow-up, consistent with clinical course, and most of lesions in those with moderate HIE also returned to normal. Neonates with severe HIE who were followed-up to 12 months had sequelae such as ventricular expansion, brain atrophy, softening of the brain, and nervous system symptoms. This shows that color Doppler US is sensitive when applied for the follow-up of neonates with moderate and severe HIE. Our data are consistent with those of Robertson et al. who found that the onset of the nervous system abnormalities were closely associated with the severity of HIE in 167 neonates with HIE who had a follow-up of 3.5 years \([2]\).

In conclusion, US features such as the size of lateral ventricles, altered brain parenchymal echogenicity and cerebral blood flow parameters are useful for the early diagnosis of HIE and help predict outcome.

**Disclosure of interest**

The authors declare that they have no competing interest.

**References**


