Magnetic resonance imaging versus transcranial ultrasound in early identification of cerebral injuries in neonatal encephalopathy

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Abstract  Objective: Neonatal encephalopathy (NE) is a condition that causes significant morbidity and mortality to the infant. The diagnosis and severity of NE rely heavily on clinical presentation and imaging findings.

The present study was planned to assess the role of MRI and Transcranial ultrasound (TCUS) in the early identification of cerebral injuries in NE.

Patients and methods: Our study enrolled 38 newborns presented with NE. Brain MRI and TCUS were carried out for each case and their results were compared.

Results: MRI was positive in 33 cases. Findings at MRI supported hypoxic-ischemic encephalopathy as an etiology in 25 neonates, and other etiologies included metabolic disorders in 2, congenital neonatal infection in 1, 2 cases of neonatal stroke, congenital brain anomalies in 2 neonates and cerebral venous sinus thrombosis in 1. The overall diagnostic accuracy of TCUS compared to MRI was 78.9%, while the overall sensitivity and specificity were 81.8% and 60% respectively.

Conclusion: TCUS is an effective screening tool in detecting the etiology of NE in suspected cases; it is sometimes crucial in critically sick neonates; however, early MRI is mandatory as it can detect precisely the extent of brain injury compared with TCUS alone.

1. Introduction

Neonatal encephalopathy (NE) is a heterogeneous, clinically defined syndrome characterized by disturbed neurological function in the earliest days of life, manifested by feeding difficulties, irritability, abnormality of tone, seizures, and reduced level of consciousness, and often accompanied by difficulty with initiating and maintaining respiration (1). The terminology NE is preferred to Hypoxic Ischemic Encephalopathy...
(HIE) because it does not imply a specific underlying etiology or pathophysiology. Neonatal encephalopathy can result from a wide variety of conditions and often remains unexplained. Perinatal HIE (by far the most common cause) is one subset of neonatal encephalopathy; other subsets include those resulting from metabolic disorder, congenital infection, drug exposure, nervous system malformation, birth trauma and neonatal stroke (2,3).

A clinical history that includes a perinatal insult, low Apgar score, need for resuscitation, decreased cord arterial pH level, other organ failure, respiratory failure, or some combination of these factors increases the level of confidence in a diagnosis of HIE (4).

Neonatal encephalopathy incidence is estimated as 3.0 per 1000 live births (5). Estimates in developing countries range from 2.3 to 26.5 per 1000 live births (6,7). The risk factors for NE vary between developed and developing countries with growth restriction the strongest in the former and twin pregnancy in the latter. It is estimated that 30% of cases of NE in developed populations and 60% in developing populations have some evidence of intrapartum hypoxic-ischemia (5).

Although term infants with mild encephalopathy generally make a full recovery, 20% of affected infants die in the neonatal period and another 25% develop significant neurological sequelae. For preterm infants, compared with term infants, the overall prognosis is worse (8).

Neonatal encephalopathy or HIE has been graded by Sarnat and Sarnat (9) into mild (stage 1), moderate (stage 2) and severe (stage 3). Moderate and severe encephalopathy is attributable to asphyxia in 60% of cases, most of which evolve during labor (10). Early identification of infants at risk.

**Table 1** TCUS findings correlated with Brain MRI findings in our 38 patients.

<table>
<thead>
<tr>
<th></th>
<th>Positive MRI</th>
<th>Negative MRI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive TCUS</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Negative TCUS</td>
<td>2</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>33</td>
<td>38</td>
</tr>
</tbody>
</table>

**Fig. 1** Preterm neonate delivered at 32 weeks with uncomplicated delivery. Presented by CL, seizures and low Apgar score at day 1 after delivery. TCUS revealed bilateral ventricular dilatation (arrows) (a) and caudothalamic groove echogenicity representing germinal matrix hematoma (arrow). (b) Duplex interrogation revealed reduced RI in the ACA, indicating hyperemia (c & d). A diagnosis of Grade II–III intraventricular hemorrhage was suggested. MRI confirmed the above mentioned findings and hemorrhage was evident in gradient weighted image (arrows) (e).
risk of developing moderate-severe encephalopathy is crucial to determine the appropriate supportive treatment methods (11,12).

Early diagnosis of brain injury in neonates due to perinatal hypoxic-ischemic brain insult is important for both neuroprotective interventions and prognosis. Therapeutic hypothermia (cooling) appears to be the most reliable intervention available at the moment for reducing the risk of death or disability in infants with brain injury (13). Cooling decreases mortality and long-term neurological morbidity rates by 15% and reduces the risk of cerebral palsy by 12% (14).

Imaging plays an essential role in the assessment of brain injury in patients with NE by helping establish the timing, severity and likely the nature of injury and the expected neurological outcome (15).

Different imaging modalities are available to detect neonatal brain injury, including transcranial ultrasonography (TCUS), computer tomography (CT), and magnetic resonance imaging (MRI). TCUS can be performed at the bedside, which is an advantage in unstable and/or preterm newborn. It is suitable for screening and follow-up examinations. CT is the least sensitive modality for evaluation of NE because of poor parenchymal contrast resolution in neonatal brain and unnecessary ionizing radiation. MR imaging has the advantage of superbly displaying soft tissue contrast differentiation and moreover displaying the exact extent and site of brain injury better than TCUS (16).

We designed this study to assess the role of MRI versus TCUS in the early identification of cerebral injuries in neonatal encephalopathy.

2. Patients and methods

2.1. Patients

This study was carried out in Ain Shams University Hospitals during the period from February to July 2015. We included 38 neonates (25 full terms and 13 preterms; 23 males and 15 females) in whom we succeeded performing Brain MRI and TCUS examinations on the same day. Their gestational ages ranged from 31 to 41 weeks (mean = 38.4 weeks). All neonates were presented at time of examination by variable clinical picture of neonatal encephalopathy; disturbed conscious level (DCL) and low Apgar scoring (5 min score of 0–3) were common features. The degree of encephalopathy was graded as mild, moderate and severe based on the staging system of Sarnat and Sarnat (9). All neonates were subjected to full clinical, neurological assessment and Apgar scoring by a consultant pediatrician, full history taking of any perinatal
Fig. 3  Full term neonate delivered at 38 weeks by prolonged delivery and at birth had DCL and low Apgar score. TCUS was negative in this case. MRI revealed subtle increased intensity at the subcortical white matter in T1WIs (arrows) (a & b) which was not clear in T2WIs (c & d). DWIs and ADC (e & f) (g & h) were the most informative, and they revealed peripheral pattern of hypoxic/ischemic injury, involving the watershed zones, sparing the cortex and deep gray matter, appearing as restricted diffusion lesions on DWI (arrows) and corresponding low signal on ADC maps signifying acute white matter injury.
insult, full laboratory investigations including blood glucose and bilirubin, umbilical cord arterial blood sampling.

MRI was clinically indicated for all neonates with NE as part of the management protocol. In our institution, TCUS is routinely requested for all patients as a bedside screening tool which provides preliminary knowledge of the etiology of NE prior to performing the Brain MRI given the technical and logistical difficulties in transporting and imaging critically ill neonates. In our patients, we ensured that TCUS studies were to be performed within few hours interval of the MRI exams in order to have accurate correlation between both modalities’ findings. Neonates were transported to MRI unit in company of trained nurses via dedicated MR-compatible incubators with built-in coils.

TCUS and MRI exams were performed at the same day of clinical presentation of NE at which patients’ age ranged from 1 to 24 days: mean = 4.8 days.

Fig. 4 Full term neonate delivered at 39 weeks with uncomplicated delivery. Presented by DCL and seizures 3 days after birth. TCUS (a & b) revealed enlargement of the left cerebral hemispheres (arrow) with enlarged left lateral ventricle sparing the frontal horn, associated with abnormal cortical arrangement. MRI T2 (c) and T1WI (d & e) documented the aforementioned findings. A case of left hemimegalencephaly.
2.2. Transcranial ultrasound

Transcranial ultrasound was done at the NICU by a consultant radiologist within 3–4 h prior to MRI exams. The TCUS examinations were performed using Hitachi EUB 8500 Logos equipment (Hitachi Medical Systems, Tokyo, Japan). Imaging was performed using a high-frequency phased array transducer (5–8 MHz) with a small footprint probe. Multiple acoustic windows were used to visualize as much of the central and peripheral structures of the brain as possible by using, the anterior and posterior fontanels, as well as views through the temporal, mastoid and occipital areas. The transducer frequency was set at 8.2–11 MHz for detection of cortical and/or subcortical abnormalities. We independently evaluated deep gray-matter structures, including basal ganglia, thalami and the brainstem. The angle of the transducer was varied in an attempt to evaluate the periphery of the brain with particular attention to the subcortical white matter and the gray-white matter differentiation in both of cerebral hemispheres.

Spectral Doppler tracings were obtained from the anterior cerebral arteries, and resistive indices (RI) [peak systolic velocity (PSV)—end diastolic velocity (EDV)/peak systolic velocity] were recorded.

2.3. MRI

MRI examinations were all performed with a 1.5 T Achieva; Philips Medical Systems, Eindhoven, The Netherland, with a neonatal head coil. Neonates were swaddled in a blanket for keeping warmth and limiting movement. If necessary, neonates were sedated (with 75 mg oral chloral hydrate/kg body weight) just before imaging. Six neonates needed sedation in our study. Spin echo sequences yielding T1 and T2 weighted images (repetition time msec/echo time msec, 550–560/14–20 and 5406–6883/100–120 respectively), and diffusion-weighted images (DWI) (using single-shot spin-echo echo-planar sequences with a b value of 1000 s/mm² and a section thickness of 6 mm) including apparent diffusion coefficient (ADC) maps were performed in all patients. MRA and T2* were acquired in suspected cases of stroke and hemorrhage. MRV was done in whom venous thrombosis was suspected based on the SE sequences or clinical findings.

MRI exams were reviewed by another consultant radiologist who was unaware of the ultrasound or clinical results. Both Radiologists were blinded to the clinical condition and progression in all cases.

2.4. TCUS and MRI findings correlation

Brain findings at TCUS and MRI exams were interpreted as regards their imaging appearances and distribution, thus reporting the likely etiology of NE and the extent of brain lesions. Findings at TCUS were prospectively compared to those of MRI for the same case.

2.5. Statistical analysis

Statistical analysis (sensitivity, specificity and diagnostic accuracy) was performed with statistical software SPSS, version 11.0; SPSS, Chicago, Ill.

3. Results

In our cases series, an MRI or a TCUS exam was considered positive if it depicted at least one lesion and was considered negative if failed to detect any lesion. In many cases, TCUS did not detect as many lesions as Brain MRI, so a TCUS exam was considered true positive if it detected at least one MRI finding in the same case.

In comparison with MRI, the number of positive and negative cases by TCUS was determined (Table 1) and thus the overall sensitivity, specificity and overall diagnostic accuracy were calculated.

Our study included 38 neonates, and MRI exams were positive in 33 cases and negative in 5. TCUS was regarded as positive in 29 out of 38 neonates and negative in the remaining 9 (Table 1). Compared to MRI, 27 TCUS exams were true positive while 2 were false positive, and 3 cases were true negatives while 6 cases were false negatives. The overall sensitivity and specificity of TCUS in detecting imaging findings in our 38 neonates with NE compared to MRI were 81.8% and 60% respectively, yielding overall diagnostic accuracy of 78.9%. The positive predictive value was 93.1 (95% confidence interval = 0.7803–0.9808), while the negative predictive value was 33.3 (95% confidence interval = 0.1205–0.6457).

According to MRI positive exams (33 neonates), the etiology of NE in our patients’ series included 25 cases consistent with HIE (Figs. 1–3) (of whom 21 had highly suspicious perinatal history), and TCUS agreed with MRI in 22. MRI
showed congenital brain abnormalities in 2: 1 hemimegalencephaly (Fig. 4) and 1 holoprosencephaly which were both diagnosed by TCUS. One case of basal ganglia increased signal proved kernicterus (Fig. 5) and 1 case proved Maple syrup urine disease which were both missed by TCUS. One neonate showed periventricular calcifications diagnosed clinically as cytomegalovirus infection and 1 neonate had cerebral venous sinus thrombosis, in both cases findings were detected by TCUS. Lastly, 2 cases of neonatal stroke in whom TCUS was negative in 1 (Table 2).

Table 2 Etiology of NE in our patients’ series according to MRI with comparison to TCUS.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. by MRI</th>
<th>No. by TCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIE:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Full term neonate:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild form</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Severe form</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>– Preterm neonate:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild form (PVL)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Severe form</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Germinal matrix hemorrhage</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Congenital infection (CMV)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Kernicterus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>– Maple syrup urine disease</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3 Comparison between Brain MRI and TCUS imaging findings outcome in 38 patients of our study.

<table>
<thead>
<tr>
<th>Imaging findings of brain lesions</th>
<th>No. of +ve MRI</th>
<th>No. of –ve MRI</th>
<th>No. by TCUS</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Altered parenchymal Signal/echogenicity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a- Central:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Basal ganglia</td>
<td>16</td>
<td>22</td>
<td>13</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>– Thalamus</td>
<td>17</td>
<td>21</td>
<td>15</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>– Periventricular white matter</td>
<td>5</td>
<td>33</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>– Corpus callosum</td>
<td>8</td>
<td>30</td>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>– Brain stem</td>
<td>9</td>
<td>36</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>– Cerebellar white matter</td>
<td>6</td>
<td>32</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>b- Peripheral:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Cortex</td>
<td>7</td>
<td>31</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>– Subcortical white matter</td>
<td>3</td>
<td>35</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2- Germinal matrix hemorrhage</td>
<td>2</td>
<td>36</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3- Congenital brain anomaly</td>
<td>3</td>
<td>35</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4- Venous sinus thrombosis</td>
<td>1</td>
<td>37</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

4. Discussion

Neonatal Encephalopathy is one of the most important causes of neurological disabilities during childhood. Transcranial ultrasound is an operator dependent, bedside, easily available, cheap and quick method for imaging NE. MR imaging is an established tool to detect the timing, severity and extent of neonatal brain injury and it plays an important role in the prediction of neurological outcome (17).

The aim of our study was to investigate the value of TCUS versus MRI in the early detection of brain injuries in newborns with neonatal encephalopathy. We resulted that the overall sensitivity and specificity of TCUS in detecting brain changes compared to MRI were 81.8% and 60% respectively, yielding overall diagnostic accuracy of 78.9%. The overall sensitivity of TCUS in our study agreed with other records from previous studies (18,19) that compared TCUS and MRI in this age group and concluded that sonography remains a valuable modality for evaluation; however, early MRI will provide important information on the presence and extent of brain injuries. Epelman et al. (20) stated that their study had 100% sensitivity for TCUS and that it was much higher than recorded in relevant studies, specificity 33.3% and accuracy 95.7%.

In our study, TCUS accurately diagnosed all cases of germinal matrix hemorrhage, congenital brain anomalies and venous sinus thrombosis. In correlation with MRI, TCUS had better sensitivity for detecting thalamic, basal ganglia and periventricular white matter lesions (88.2%, 81.2% and 80% respectively) rather than lesions in the corpus callosum, brain stem, cerebellar white matter, cerebral cortex and subcortical white matter (37.5%, 33.3%, 33.3%, 28.6% and 50% respectively) (Table 3). However, TCUS had high specificity in most of the lesions reaching 100% sparingly lesions at the periventricular and subcortical white matter and cortical lesions which had lower specificity (94%, 94.4% and 96.8% respectively) (Table 3). Epelman et al. (20) deduced in their study that TCUS had relatively higher sensitivities in lesions at the periventricular white matter (79.5%), subcortical white matter (71.9%) and deep gray matter (71.1%) rather than lesions at the cortex (58.8%), corpus callosum (50%) and the brainstem (26.7%). Our results agreed with those of Steggerda.
et al. (21,22) who concluded that TCUS can depict central abnormalities better than peripheral lesions. Blankenberg et al. (23) also stated in their study that TCUS is less sensitive to structural abnormalities in the cerebral convexity and in the brain stem. However, Epelman et al. concluded in their study that both peripheral and central brain findings were equally detected by Ultrasound.

TCUS is a useful screening modality which can also offer a much more convenient method for follow-up of patients in a setting of acute and critical care. However, TCUS might not detect as many lesions as MRI. Therefore, TCUS might severely underestimate the degree of injury.

MRI is the reference standard for infant brain imaging (18). It is needed in most neonates with suspected parenchymal brain injury or neurological manifestations (24). MRI is an indispensible and conclusive evaluation modality on account of its superior sensitivity and pathology discriminating techniques. Diffusion-weighted imaging (DWI) often reveals ischemic brain injury at an earlier stage than conventional MR imaging (25). In our study, DWI was the only positive sequence that detected mild to moderate HIE pattern in a full term, while other conventional MR sequences and TCUS were negative (Fig. 3). Moreover, GRE (T2*) MR sequences are extremely sensitive to hemorrhage. Both MRI- GRE (T2*) and TCUS accurately diagnosed all cases of germinal matrix hemorrhage in our work.

MRI can be used to gain insight into the neurological effects of brain injuries in encephalopathic neonates. Therefore, we recommend that the ultimate radiodiagnostic protocol for cases of NE is a combination of both TCUS and MR imaging.

We experienced some limitations throughout this work. First, it was sometimes challenging dealing with critically ill neonates specifically in terms of transportation from the NICU to the MRI unit as regards the specialized equipments for transport to the MR scanner, as well as trained personnel to provide ongoing clinical care during MR scanning. Second, the relative small number of patients in our study owing to the inability to collect concurrent MRI and TCUS studies for many patients. This was because of their rapid death or the presence of obstacles in their transfer to the MRI scanner due to their critically unstable medical conditions or technical factors regarding the transportation equipments.

In conclusion, TCUS is an effective screening tool in detecting the etiology of NE in suspected cases; it is sometimes crucial in critically sick neonates; however, early MRI is mandatory as it can detect precisely the extent of brain injury compared with TCUS alone.

Conflicts of interest and source of funding

None declared.

References


