Predictive Value of Clinical and EEG Features in the Diagnosis of Stroke and Hypoxic Ischemic Encephalopathy in Neonates With Seizures

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Background and Purpose—In neonates, the differentiation of stroke and hypoxic ischemic encephalopathy (HIE) is important. Neuroimaging presents technical challenges in unstable neonates, resulting in frequently delayed or missed diagnosis of stroke. Differentiating clinical and electroencephalographic (EEG) features would assist physicians in the timely diagnosis. We sought to determine, in neonates with seizures, clinical and EEG features that differentiate stroke and HIE.

Methods—Retrospective cohort study comparing clinical, seizure, and EEG features in term neonates with ischemic stroke or HIE and seizures within 7 days after birth, admitted at The Hospital for Sick Children. Putative clinical and EEG predictors of stroke were analyzed with univariate and multivariate methods.

Results—Sixty-two newborns with stroke (n=27) or HIE (n=35) were studied. With univariate analysis, predictors of stroke included delayed seizure onset (≥12-hours after birth) (P<0.0001; OR, 26.4; 95% CI, 6.8, 102.5), focal motor seizures (P=0.001; OR, 7.2; 95% CI, 2.0, 26.0) and pattern of neurological abnormalities (P<0.0001). With multivariate analysis, delayed seizure onset (P<0.0001; OR 39.7; 95% CI, 7.3, 217.0) and focal motor seizures (P=0.007; OR, 13.4; 95% CI, 2.1, 87.9) predicted stroke. Presence of both predictors had 100% positive predictive value and specificity, 61% negative predictive value and 37% sensitivity.

Conclusions—In neonates, onset of seizures beyond 12 hours of birth and clinically observed focal seizures are predictive of stroke. These preinvestigation indicators of stroke may facilitate earlier diagnosis and institution of specific management strategies. (Stroke. 2009;40:2402-2407.)

Key Words: acute care ■ EEG ■ hypoxic ischemic encephalopathy ■ predictors of diagnosis ■ cerebral infarction ■ neonates

Seizures occurring in the neonatal period may be the manifestation of a serious underlying brain insult. The etiologic diagnosis of neonatal seizures is necessary to permit accurate decisions regarding management and prognosis. The incidence of seizures in neonates ranges from 0.15% to 3.5%, with most occurring within the first week of life.1–3 Although neonatal seizures can result from transient metabolic derangements such as hypoglycemia or hypocalcaemia, hypoxic ischemic encephalopathy (HIE) accounts for as many as 60% to 65% and ischemic stroke for 12% to 20%.4,5,11,12

Stroke is frequently misdiagnosed as HIE because of overlapping clinical features.9,10 In neonates with stroke, seizures are the only manifestation in 70% to 91%1–5 and hemiparesis is uncommon (20%).13 Generalized neurological abnormalities including encephalopathy can be present in both HIE and stroke. The prognosis and clinical management of neonatal stroke and HIE are very different.6–12 Early identification of these conditions maximizes opportunities for disease specific management strategies. The current approach for differentiating neonatal stroke and HIE relies on neuroimaging. Neuroimaging, however, is not straightforward in neonates who, when unstable, can be difficult to safely transport and image with CT (computed tomogram) and preferably MRI.13,19 In neonates, cranial ultrasound is a useful noninvasive easily accessible intervention for the evaluation of both HIE and focal brain lesions such as stroke. However, it may not accurately diagnose stroke.15,16 In addition, an early CT and MRI without diffusion may be normal in neonates with ischemic injury.20 Electroencephalograph (EEG) is often the first diagnostic tool used to evaluate seizures, however, the utility of clinical seizure and EEG features in ascertaining the cause for neonatal seizures is not well established. Few studies have
systematically examined the association between EEG findings, clinical features, and specific brain lesions in neonates.\textsuperscript{18,19} Therefore, we conducted the current study to determine which clinical and EEG features differentiate HIE and stroke in neonates.

**Study Design and Methods**

Term neonates with clinical seizures and a diagnosis of neonatal stroke (January 1992 to December 2003) or HIE (from January 1996 to December 2001) admitted to The Hospital for Sick Children comprised the study population. All infants were born in peripheral hospitals in and around Toronto (total number of live births approximately 65,000 per year).

**Patient Identification**

Neonates with the diagnosis of ischemic stroke and seizures were identified from the Canadian Pediatric Ischemic Stroke Registry database, which has enrolled patients since January 1992. Registry identifies patients based on the referral to the hospital’s Stroke service supplemented by the International Classification of Diseases, 9th revision (ICD-9) discharge codes searches of the medical records. Neonates with the diagnosis of HIE and seizures were identified by the hospital’s neonatal intensive care unit database and the ICD-9 medical records discharge codes searches. Neonates with HIE were studied from January 1994 (because of the poor availability of both EEG and neuroimaging for review before that period). All cases with ICD-9 diagnostic codes for neonatal seizures, neonatal stroke, neonatal HIE, and birth asphyxia were evaluated, so that all potential cases were included. The health records of study patients were reviewed and inclusion determined based on the criteria below.

**Inclusion Criteria**

Inclusion criteria consisted of: (1) gestational age \( \geq 36\)-weeks to 42-weeks, (2) seizure onset within 7-days of birth, (3) diagnosis of ischemic stroke or HIE during the neonatal period (\( <28\)-days age), and (4) availability of EEG and neuroimaging (CT or MRI) during the neonatal period. The diagnosis of AIS required neuroimaging findings of focal infarction confined to an established arterial territory. Neonatal HIE is defined as an abnormal neurological state occurring in the newborn after a significant perinatal hypoxic ischemic insult.\textsuperscript{4} For this study, the diagnosis of neonatal HIE was based on the criteria proposed by the American College of Obstetrics and Gynecology (ACOG) 2003 Task Force Report for intrapartum asphyxia.\textsuperscript{25} Diagnosis of HIE required 3 or more of the following: (1) evidence of metabolic acidosis on cord gas (pH < 7 and base deficit \( \geq 12\)-mmol per liter), (2) early onset neonatal encephalopathy, (3) fetal bradycardia or absence of fetal heart rate variability in the presence of persistent, late, or variable fetal heart rate decelerations, (4) Appgar Scores of 0 to 3 by 5 minutes of age, (5) evidence of multisystem involvement within 72 hours of birth, and in all cases no evidence of acute focal cerebral abnormality on CT or MRI.\textsuperscript{20} All neuroimaging features were ascertained from radiology reports, or when unclear, by review of neuroimaging films by the study neurologists.

**Exclusion Criteria**

Infants with cerebral sinovenous thrombosis (CSVT) were excluded, as most had associated venous infarction. Newborns with cerebral hemorrhage not associated with stroke, other structural central nervous system disorders, or other identifiable causes for encephalopathy such as genetic disorders, infections, and inborn errors of metabolism were also excluded.

**Data Collection**

**Clinical Features**

Clinical features assessed included: time of seizure onset, number, duration, and type of seizure (unifocal or hemifocal versus other seizure types such as generalized, multifocal, and subtle seizures) according to the seizure classification proposed by Volpe.\textsuperscript{4} Other clinical features included neurological examination (diffuse or asymmetrical neurological abnormalities), and requirement for antiepileptic agents (single or multiple agents). Diffuse neurological abnormalities included decreased responsiveness, diffuse tone abnormalities, and diminished or absent primitive reflexes. Asymmetrical neurological abnormalities included asymmetry in tone, limb, facial, or eye movements.

**EEG Features**

EEG features were obtained from the EEG reports. All EEGs were performed with neonatal montage with 16 channels for EEG and 5 additional channels for polygraphic recording for eye movements, muscle activity, respirations, and ECG. The EEG features included: background abnormalities, presence of unilateral or bilateral rolandic sharp waves, lateralized and midline EEG findings, and electrographic seizures. Background abnormalities were categorized into background type (normal or abnormal) and background asymmetry. The background activity was considered abnormal if the EEG demonstrated low voltage, discontinuity, or immaturity of background for the conceptional age. The background asymmetry was defined as more than 50% difference in amplitude between each hemisphere. Lateralized EEG findings were defined as the presence of positive or negative sharp or slow waves originating from one hemisphere. The laterality of EEG features (right or left) was also recorded. Midline EEG findings were defined as rhythmic or nonrhythmic, high, low, or normal amplitude theta or delta activity originating form midline hemispheric regions lasting for > 5 but < 10 seconds. The electrographic seizures were defined as rhythmic activity in the alpha, theta, delta range or sharp waves lasting > 10 seconds with or without clinical signs.

**Radiographic Features**

The radiographic diagnosis of stroke on CT or MRI was the study outcome. We also collected data in the neonates with stroke regarding the parenchymal infant characteristics. These were classified by the presence or absence of hemorrhagic conversion of the infarct, infect location (unilateral or bilateral), and infarct number (single or multiple). One third of the HIE infants had basal ganglia injury, one third had watershed injury, and one third had combined basal ganglia/watershed lesions.

**Statistical Analysis**

Both clinical and EEG putative predictors of stroke or no stroke were selected a priori. For categorical and nominal variables, the \( \chi^2 \) test or Fisher exact test (when at least 1 cell had an expected value of less than 5) were used. When there was a 0 cell in a \( \times 2 \) table, 0.5 was added to that cell. The significance level was set at \( p < 0.05 \). Standard deviations of the mean and odds ratios (OR) and 95% confidence interval (CI) were noted. With respect to the number of tests applied, Bonferroni correction was performed. After univariate analysis, multivariate models of association between the significant predictors and the outcome (stroke/no stroke) were constructed using a binary logistic regression analysis. All statistical analyses were performed using the statistical software package SAS version 8.2 (SAS Institute Inc).

**Results**

During the study period, 102 neonates with seizures and the clinical diagnosis of either AIS (n=49) or HIE (n=53) were screened. We excluded 22 neonates with AIS and 18 with HIE as study inclusion criteria were not met, primarily as EEG and neuroimaging were unavailable (Figures 1 and 2). The remaining 62 neonates formed the study cohort, 27 with AIS and 35 with HIE.

The mean gestational age of the enrolled cohort was 39.4 weeks (range 36 to 42 weeks). There were 38 males (18 in stroke, 20 in HIE) and 24 females (9 in stroke, 15 in HIE). The mean seizure onset was 15.0 hours (27.8 hours \( \pm 23.3 \) hours in stroke and 5.1 hours \( \pm 5.2 \) hours in HIE). The mean

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time from seizure onset to the initial EEG recording was 2.2±2.5 days (median day 1 for HIE and day 2 for stroke). The EEG was abnormal in all patients with HIE and 20 patients with AIS. The clinical and EEG features are compared between neonates with stroke and HIE in Tables 1 and 2.

In neonates with stroke, 6 had Apgar scores of <3 at 1 minute, including 3 neonates with persistently low Apgar scores at 5 and 10 minutes. Diffuse neurological abnormalities were present in nearly one third and an asymmetrical motor examination in 3 neonates (2 unilateral AIS and 1 bilateral AIS). All neonates with HIE had diffuse neurological abnormalities and none had an asymmetrical neurological examination. Focal motor seizures were observed in 11 of 22 neonates with unilateral AIS infarcts and 2 of 5 with bilateral AIS infarcts. In neonates with unilateral infarcts, focal motor seizures were contralateral and lateralized EEG findings were ipsilateral to the infarct in all except 1 patient.

In univariate analysis the predictors significant for the diagnosis of stroke were: seizure onset 12 hours or more after birth (P<0.0001; OR, 26.4; 95% CI, 6.8, 102.5), focal motor seizures (P=0.001; OR, 7.2; 95% CI, 2.0, 26.0), and pattern of neurological abnormalities (P<0.0001; Table 1). Differences were also identified in the duration of seizures (P=0.020; OR, 0.91; 95% CI, 0.84, 0.99), frequency of response to single antiepileptic drug (P=0.03; OR, 12.1; 95% CI, 0.7, 225.4), and lateralized EEG findings (P=0.02; OR, 5.7; 95% CI, 1.1, 28.7; Table 2). Other EEG features, including background asymmetry, presence of rolandic sharp waves (either unilateral or bilateral), midline EEG findings, and electrographic seizures, were not significantly different between AIS or HIE group (Table 2).

Using multivariate binary logistic regression analysis, significant predictors for stroke included delayed seizure onset (12 hours or more after birth; P<0.0001; OR 39.7; 95% CI, 7.3, 217) and focal motor seizures (P=0.007; OR, 13.4; 95% CI, 2.1, 87.9). The presence of both later onset and focal motor seizures had a positive predictive value and specificity of 100%, negative predictive value and sensitivity of 61% and 37%, respectively, and conferred a 2.6 times increased likelihood of stroke (95% CI, 1.8 to 3.5).

**Discussion**

Our study is the first to assess in a well-defined cohort of term neonates the clinical and EEG characteristics differentiating stroke from HIE. We found that delayed seizure onset and
clinically observed focal seizures are predictors of stroke in neonates with seizures. The differentiation of stroke and HIE in neonates is important as management approaches differ in the two conditions. These predictors will be helpful to prioritize neonates who require rapid neuroimaging useful for the diagnosis of stroke or the initiation of neuroprotective therapies for HIE.

Asymmetrical neurological examination cannot differentiate stroke from HIE, because with an immature brain hemiparesis is only seen in the minority of neonates with stroke. In our study, an asymmetrical neurological examination was present in only 3 neonates with stroke. If stroke is suspected additional vascular imaging including MR or CT angiogram or venogram or DWI (diffusion weighted imaging) is indicated. Once stroke is diagnosed, investigations to identify cardiac sources for embolism underlying stroke and prothrombotic disorders are performed. Recommended treatments for neonatal stroke include anticoagulant therapy in specific stroke subtypes such as CSVT and cardiogenic AIS. 

For HIE, early hypothermia (starting within 6 hours of delivery) has been proven to be effective, and this and other neuroprotective strategies are increasingly being recognized as standard treatment options. For clinically suspected neonatal HIE, neuroimaging, preferably MRI, is recommended at or more than 48 hours after birth, however if other conditions such as birth trauma are suspected, an earlier CT or MRI may be required. The prompt differentiation of stroke and HIE is therefore crucial because these interventions are maximally effective if instituted early or within a narrow therapeutic window. Early diagnosis also assists in early and specific prognostication. Death and severe neurological deficits are frequent in neonates with HIE compared to stroke. The nature of neurological deficits typically also differs, with hemiparesis in stroke and cognitive and bilateral motor deficits in HIE.

In our study the seizure onset in neonates with stroke was significantly delayed beyond 12 hours of life compared to neonates with HIE. Traditional teaching has associated neonatal stroke with seizures occurring between 24 and 72 hours and neonatal HIE with seizures occurring within 12 to 24 hours after birth. Although in neonates with stroke, studies have also reported early seizures, our findings show that in neonates with stroke, seizure onset after 12 hours is 5 times more frequent than in neonates with HIE.

The second predictor of stroke was the occurrence of clinically apparent focal seizures, which were present in half of the neonates with stroke and only 11% of neonates with HIE. Focal seizures are uncommon among neonatal seizures, and have been previously associated with focal structural abnormalities including stroke. In these studies, focal seizures were contralateral to the stroke in the majority, as we observed in our patients. Other seizure types, including automatisms and generalized seizures, were also seen which have been previously reported in unilateral neonatal stroke. In our study, focal motor seizures, combined with later seizure onset, reliably predicted stroke (all neonates with both features had AIS). This combination when present can be used to confidently predict stroke in the first few days

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Stroke (n=27)</th>
<th>HIE (n=35)</th>
<th>OR (95% CI)</th>
<th>χ² Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological abnormalities*</td>
<td>Normal 15 (56) 0 (0)</td>
<td>26.4 (6.8, 102.5) 28.00</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diffuse 9 (33) 35 (100)</td>
<td>0 (0)</td>
<td>5.09 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asymmetric 3 (11) 0 (0)</td>
<td>0 (0)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sz. onset ≥12 hours after birth</td>
<td>22 (81) 5 (14)</td>
<td>28.00 0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Sz (minutes ± SD)</td>
<td>6.3 ± 5.0 13.3 ± 11.7</td>
<td>0.91 (0.84, 0.99) 5.09 0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal motor Sz</td>
<td>13 (48) 4 (11)</td>
<td>7.2 (2.0, 26.0) 10.32 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to single AED*</td>
<td>27 (100) 29 (83)</td>
<td>12.1 (0.7, 225.4) 0.03</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| n indicates number of patients; SD, standard deviation; AED, antiepileptic drug; Sz, seizure; OR, odds ratio; CI, confidence interval.

*Fisher exact test reported. All P values and OR represent univariate analysis, †P value 0.08, OR: 0.1 (0.0, 2.0).

Table 2. Comparison of EEG Characteristics of Neonates With Stroke and HIE

<table>
<thead>
<tr>
<th>EEG Characteristics</th>
<th>Stroke (n=27)</th>
<th>HIE (n=35)</th>
<th>OR (95% CI)</th>
<th>χ² Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal background</td>
<td>14 (52) 12 (34)</td>
<td>2.1 (0.74, 5.8) 1.93 0.16</td>
<td></td>
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</tr>
<tr>
<td>Background asymmetry</td>
<td>10 (37) 7 (20)</td>
<td>2.4 (0.8, 7.3) 2.22 0.14</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unilateral rolandic PSW</td>
<td>2 (10) 9 (32)</td>
<td>0.23 (0.02, 1.4) 0.23 0.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateralized EEG findings</td>
<td>9 (33) 2 (6)</td>
<td>8.25 (1.4, 83.6) 0.007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midline EEG findings*</td>
<td>3 (11) 1 (3)</td>
<td>4.3 (0.31, 229.5) 0.31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrographic seizures</td>
<td>7 (26) 13 (37)</td>
<td>0.59 (0.2, 1.8) 0.88 0.35</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n indicates number of patients; PSW, positive sharp waves; OR, odds ratio; CI, confidence interval.

*Fisher exact test reported. All P values and OR represent univariate analysis.
of life, however the absence of this combination cannot rule out stroke, and neuroimaging is still necessary.

In our study EEG features were not significantly different between neonates with stroke or HIE. We observed electrographic seizures in approximately one third of neonates at similar frequencies in both groups, emphasizing that clinical observation alone underestimates seizure frequency in neonates. A normal EEG background and lateralized EEG findings tended to be more frequent in neonates with stroke. A normal EEG background in neonates with stroke may reflect a smaller localized distribution of cerebral damage compared with the diffuse injury in HIE, and corresponds with the observation that neonates with stroke are less likely to be encephalopathic or obtunded between seizures.5,6,38 In one study, diffuse background abnormalities were frequently seen with multifocal lesions as compared to unifocal lesions.39 EEG background provides prognostic information for both neonatal stroke and HIE. Moderate to markedly abnormal background has been correlated with poor outcome in both conditions.3,8,12,13,15,16,40–42 Our study may have been underpowered to detect normal background as a predictor of stroke. This may also be related to the coexistence of hypoxic insult in some neonates with stroke in our cohort.

We observed asymmetrical EEG abnormalities in one third of neonates with stroke and infrequently in neonates with HIE. None of our neonates had periodic lateralized epileptiform discharges. The presence of asymmetrical EEG abnormalities has been associated with focal structural brain lesions such as stroke in children.5,6,23,24,43–45 However, asymmetrical EEG abnormalities with HIE23,44 and transient asymmetries of the background in healthy term neonates45,46 have also been reported.

Our study had several limitations related to the retrospective design including potential patient selection bias consisting of inclusion of patients admitted to our tertiary care hospital (may have resulted in studying more severely affected neonates), small sample size with resultant wide 95% confidence intervals, requirement of EEG and neuroimaging (may have biased our inclusion to those with most severe seizures requiring these investigations or exclusion of those who did not have these tests performed in the time frame), and reliance on reports for radiographic and EEG findings. Because the description of clinical seizures was obtained by retrospective chart review, the seizure occurrence and characteristics were potentially subject to both under- and over-reporting. In some children, considerable delay in EEG recording and use of antiseizure medications before EEG may have affected the EEG findings. Individual reader differences in reporting EEG features and also may have been a potential source of error.4,47 However, these limitations would likely have applied equally to both groups and therefore should not account for the differences we observed.

Summary
In conclusion, in neonates with seizures, clinical features including delayed seizure onset (12 hours or more after birth) and focal motor seizures reliably differentiate stroke from HIE among neonatal seizure etiologies, especially when both features are present. These findings are highly relevant to clinicians caring for neonates, because application of these predictors can assist in the diagnosis of stroke even before EEG, CT, or MRI. Earlier diagnosis will be helpful in allowing more specific management strategies and prognosis which are geared to reducing adverse outcomes in neonates with stroke and HIE.

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Disclosures
None.

References


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