The Clinical Spectrum and Prediction of Outcome in Hypoxic–Ischemic Encephalopathy

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**Objectives**

After completing this article, readers should be able to:

1. List the signs related to problems in labor and immediately following birth used to diagnose hypoxic–ischemic encephalopathy (HIE).
2. Compare and contrast the grade of HIE and Apgar score for predicting outcome.
3. Describe the role of likelihood ratios in altering diagnostic and prognostic probabilities.
4. Compare and contrast the electroencephalogram and newer technologies in assessing outcome early in the course of HIE.

**Introduction**

The major problem that confronts those caring for infants who have hypoxic-ischemic encephalopathy (HIE) is how to provide families with reliable information about outcome. These infants present few diagnostic problems, and treatments are mostly supportive. The difficulty lies in how long to pursue treatment in infants who may have a very poor prognosis.

This review presents a scheme for predicting outcome based on information gathered over the past three decades using a combination of clinical assessment and routine neonatal electroencephalography (EEG). This approach is contrasted with more recent methods of assessing prognosis using evoked potentials, near-infrared spectroscopy, and imaging (see *NeoReviews*, January 2001), including manipulations of magnetic resonance imaging. After determining whether the newer technologies simply complement or actually improve outcome prediction based on the simpler investigations, the use of higher-tech, and less available, tests can be assessed for specific clinical situations.

**Incidence and Severity Grading of HIE**

Birth asphyxia, defined as an Apgar score of less than 7 at 5 minutes, with exclusion of congenital infection, malformation, or opioid-induced respiratory depression, occurred in 5.4 per 1,000 liveborn infants born between 1985 and 1991 in Goteborg, Sweden. Of these “asphyxiated” infants, HIE occurred in one third for an incidence of 1.8 per 1,000. HIE occurred at a rate of 6 per 1,000 in a 4-year English study published in 1985. Thus, the compromised infant who has a significant encephalopathy is seen regularly in active obstetric services.

There have been multiple reports of neurodevelopmental outcome following asphyxia over the past three decades. One particularly helpful review appeared in the Danish literature authored by Bohr and Greisen in 1998. They collected outcome information from 16 studies performed in Europe, Japan, and the United States that included well-defined criteria for asphyxia. Of the 1,042 infants for whom outcome information was available, 25% died or had multiple handicaps, 4% had mild-to-moderate forms of cerebral palsy, and 10% had developmental delay. Interestingly, the authors pointed out that the rate of developmental delay did not differ between cases and controls in the studies. Thus, as has been emphasized in the classic literature on asphyxia, hypoxic-ischemic injury results in some form of cerebral palsy with or without cognitive...
problems and not in cognitive problems alone. Thus, short-term outcome studies that include assessment before school age are legitimate because cerebral palsy, especially when it is severe, manifests by the end of the first year after birth.

Most of the outcome studies used to develop estimates of risk in this review are short-term studies, and the severe adverse outcomes reported are usually spastic quadriplegia with severe developmental retardation. Milder forms of cerebral palsy (diplegic, dyskinetic, or hemiplegic cerebral palsy) are grouped with the moderate-to-good outcomes.

Inclusion and exclusion criteria for perinatal asphyxia in the articles reviewed by Bohr and Greisen are similar to those in Table 1. Findings that suggest a neurologic syndrome present immediately after birth are likely to result from a hypoxic-ischemic insult to the brain. Assessing the degree of HIE sets the stage for attempts to predict outcome.

Sarnat and Sarnat described a grading system for HIE in 1976 that they believed helped to estimate the risk of adverse outcome. Their grading, with some modifications, is the approach adopted by most authors; 11 of 16 studies reviewed by Bohr and Greisen used a system modified from that of Sarnat and Sarnat. Thus, they were able to classify the outcome by the initial stage of HIE in 488 infants. With mild HIE, 98% of infants had a normal outcome compared with death or severe neurologic sequelae among 96% of those who had severe HIE. About 25% of infants who had moderate HIE died or had poor outcomes. These data support the general belief that infants who have mild (stage 1) encephalopathy have a universally good outcome, and those who have severe (stage 3) encephalopathy have a universally poor outcome. The problem lies in predicting which infants who have moderate (stage 2) encephalopathy will recover and which will not.

### Assessing Risk for Death or Severe Disability in HIE

Levene and associates evaluated the ability of the HIE grade to predict the outcome of infants who had low Apgar scores born over a 4-year period at one regional obstetric unit in Leicester, England. Their object was to compare this method of predicting outcome with various Apgar score cutoffs. Ascertainment of both the neonatal data and outcomes for children who had handicaps was excellent. In this study, HIE grading performed better than did Apgar scores. Overall, 122 term infants had HIE and follow-up information, and 23 died or had severe adverse outcome (adverse outcome prevalence of 19% among infants who had HIE). The degree of encephalopathy was categorized as mild, moderate, and severe by a system similar to that of Sarnat and Sarnat. Death or severe adverse outcome was documented in 76% of infants who had severe encephalopathy, 26% who had moderate encephalopathy, and less than 1% who had mild encephalopathy. These percentages are similar to those found among the multiple studies reviewed by Bohr and Greisen. In addition, the prevalence of adverse outcome or death among infants who had HIE was 23% in the studies reviewed by Bohr and Greisen, which also was very similar. Thus, it appears that assigning a grade of HIE results in similar outcome predictions among many different centers, and the prevalence of adverse outcome in infants who have HIE is similar. These two facts support the use of HIE grading as a starting point for providing reliable outcome information. By applying further tests, possibly infants who will have adverse outcomes can be identified in the group who has moderate HIE and confirmed in those who have severe HIE.

A description of findings that are characteristic of the various grades of encephalopathy along with an estimated probability of death or adverse outcome is shown in Table 2. Four grades of encephalopathy are used rather than three grades to improve prediction in moderate encephalopathy. The major distinction between the system shown in the table and descriptions in the literature involves the group labeled moderate-to-severe encephalopathy. Infants in this group have a need for respiratory assistance, but are not comatose and flaccid. Because coma is difficult to distinguish from lethargy in infants, most neurologists and neonatologists rely on the flaccid paralysis found in severe encephalopathy to assign

### Table 1. Findings Suggesting a Relationship Between Neonatal Neurologic Syndrome and Hypoxic-Ischemic Encephalopathy

- Abnormal fetal heart rate pattern (especially after a previously normal pattern)
- Metabolic acidosis present at birth (severe = pH ≤7.0, base excess ≥12 mmol/L)
- Apgar score 0 to 6 for ≥5 min
- Multiple organ dysfunction (cardiac, pulmonary, renal, gastrointestinal, hematologic, hepatic)
- Absence of infection, congenital central nervous system malformation

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this grade. However, if the need for mechanical ventilation is the reason for assigning an infant to the severe encephalopathy category, it may not be as predictive of poor outcome. Some infants who have increased tone and abnormal alertness require respiratory assistance, and they are not as likely to have a bad prognosis as the flaccid infant. The probability of adverse outcome is approximated as 50% for this grade of encephalopathy. Other than this new group, the probability of adverse outcome shown in Table 2 follows that found by Levene and associates. These estimates are relatively optimistic, based on the 96% probability of death or adverse outcome with severe encephalopathy reported by Bohr and Greisen.

After using the information in Tables 1 and 2 to recognize and grade HIE, the next step is to evaluate the probable outcome using EEG.

### Outcome Assessment for HIE

#### EEG

In 1982, Holmes and colleagues published an assessment of neonatal EEG in asphyxiated infants. They examined paroxysmal activity as well as the background patterns and used these findings to predict outcome at a mean age of 24 months in a blinded fashion. As in the outcome studies mentioned previously, severe abnormalities represented severe mental and motor retardation that required total nursing care. The timing of the EEG varied, with a mean of 4.8 days and a maximum of 2 weeks. Thus, the EEG was performed at a time when some infants who had mild asphyxia would have recovered and those who still had signs of encephalopathy were likely to have significant insults. The EEG abnormalities were graded, with the severe abnormalities consisting of low-voltage tracings, electrocerebral inactivity, or burst-suppression patterns. These patterns are easily distinguished from marginal abnormalities and normal records. Most authors have adopted these patterns when labeling the EEG of a term infant as severely abnormal (Fig. 1). Seizure activity independent of a severely abnormal background tracing was less useful in predicting outcome. To apply the EEG result in the clinical setting, the calculations shown in Table 3 are used. Table 3 is a 2×2 table assessing the severely abnormal EEG in Holmes’ study. The detection rate (sensitivity), false-positive rate (1-specificity), and likelihood ratio are calculated for predicting death or severe disability.

Use of the likelihood ratio (and what is termed the “unlikelihood ratio” in Table 3) to improve prediction in infants who have HIE is shown in Table 4. The likelihood ratio of 9.5 calculated in Table 3 has been adjusted to 8, and the unlikelihood ratio has been adjusted to 0.1. These more conservative ratios are based on an analysis of multiple studies of EEG shown in Table 5. These studies, which used criteria similar to those of Holmes and associates, included single-channel continuous EEG and routine EEG in the first 48 hours. When the EEG is performed early, it may reflect dysfunction that can resolve rather than permanent injury. The ratios from the pooled studies are used in Table 4 because they represent the likely result of performing the EEG around 48 hours—a time when families are facing decisions about continued support.

Table 4 shows how the odds of adverse outcome are adjusted for each of the grades of HIE. Using the probability of death or severe encephalopathy based on the grade of HIE as the pretest odds, the posttest odds are calculated according to whether the EEG is severely abnormal. Thus, in infants who have moderate (Sarnat grade 2) HIE, recording of a severely abnormal EEG changes the probability of death or severe disability from 25% to 73%. This raises the possibility significantly, but there is still about a 1 in 4 chance that the child will make a good recovery. A marginally abnormal or normal EEG is very reassuring because the posttest probability be-
Table 3. Calculating A Likelihood Ratio for Outcome After Severely Abnormal Electroencephalography (EEG) Results

<table>
<thead>
<tr>
<th>Abnormal EEG*</th>
<th>Death or severe disability at age 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Abnormal</td>
<td>18</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>DR = 18/19 = 0.95</td>
</tr>
</tbody>
</table>

*Abnormal EEG—low amplitude, electrocerebral silence, burst-suppression
DR=detection rate or sensitivity (those who had poor outcome and positive test/total who had positive test)
FPR=false-positive rate or 1-specificity (those who did not have poor outcome and had positive test/total who did not have poor outcome)

If the EEG is severely abnormal, the risk of death or severe disability is estimated by the Likelihood Ratio:

\[ \text{Likelihood Ratio (LR)} = \frac{\text{DR}}{1-\text{FPR}} = 9.5 \]

If the EEG is not severely abnormal, the risk of death or severe disability is reduced and can be estimated by the “negative” likelihood ratio, which is termed the “unlikelihood” ratio. This is the likelihood of adverse outcome if the EEG is normal or marginally abnormal:

\[ \text{Unlikelihood Ratio (UR)} = \frac{1}{\text{LR}} = 0.05 \]

Information about using likelihood ratios can be found online at the Centre for Evidence-Based Medicine in Toronto, Canada at http://www.cebm.utoronto.ca/glossary/lrs.htm.


comes about 3% that the child will have a severe disability or die. The other stages of HIE are evaluated similarly. As can be seen, the EEG is most helpful in infants who have moderate-to-severe encephalopathy. In this setting, the probability of adverse outcome changes from 50% before the EEG to 89% after a severely abnormal EEG or to 9% after a normal or marginally abnormal EEG. Overall, the usefulness of EEG in infants who have HIE has been confirmed by multiple studies (Table 5).

Evoked Potentials and Near-infrared Spectroscopy

Fewer studies have examined evoked potentials and near-infrared spectroscopy in assessing infants who have HIE. Further, these modalities are not as available as EEG to neonatologists. Evoked potentials can be used to assess multiple anatomic levels of the central nervous system, suggesting that they may be more sensitive and specific than EEG alone. The major disadvantage is the difficulty in obtaining reliable studies at the bedside and the lack of experience among pediatric neurologists with these studies in neonates. As in older children and adults who have comas, the somatosensory evoked potentials are the most sensitive and specific, with visual and brainstem evoked potentials less so. Likelihood ratios for somatosensory evoked potentials are as good as for severely abnormal EEGs (not better) and range from 6 to 8. Majnemer and Rosenblatt reviewed several outcome studies using evoked potentials in 1996 from which likelihood ratios could be calculated.

Near-infrared spectroscopy assesses cerebral hemodynamics, which are altered by hypoxia-ischemia, especially early in the injury process. If significant abnormalities that correlated with outcome could be recognized within the first 24 hours after birth, it might help to identify infants who would benefit from neuroprotective interventions. In a recent study of outcome by Meek and associates, 27 term infants were studied on the first day after birth. Cerebral blood volume was increased in infants who had adverse outcomes. However, the sensitivity of 86% was associated with a high false-positive rate (5 of 8 normal or moderately affected infants had increased cerebral blood volume), making the likelihood ratio only 1.3.

Imaging Studies

Imaging studies offer the potential advantage of showing the neuropathology that results from birth asphyxia. This should produce better correlation with outcome, but abnormalities may take days to weeks to develop. Cranial ultrasonography is the easiest study to perform and because it is used nearly universally in preterm infants, it is readily available (see NeoReviews, January 2001). In addition to producing an image, ultrasonography can measure cerebral blood velocity by Doppler. In an interesting prospective study of asphyxiated infants, ultrasonography and Doppler measurements were compared with EEG and evoked potentials by Eken and colleagues. Ultrasonography was a poor predictor of outcome, with a likelihood ratio of close to 1 because of a high false-positive rate. With Doppler measurements, the false-positive rate was 0 in this study of 32 infants, but the detection rate (sensitivity) was only 23.5%.

Outcome studies based on computed tomography (CT) are rare and anecdotal. CT results do not become abnormal for several days following birth, as is true with cranial ultrasonography, and the modality is only slightly
more sensitive. Recent authors have used magnetic resonance imaging (MRI) in place of CT because sick neonates must be transported for either modality, and MRI is known to be superior in children and adults. The advantage of any imaging modality is its ability to show probable neuropathology. Roland and associates and Pasternak and Gorey noted a pattern of low attenuation of the thalamus and basal ganglia on CT that was associated with a syndrome of “acute total asphyxia” in term infants. The name of this syndrome derives from animal studies of hypoxia-ischemia. It is believed to be the result of intrauterine events such as cord prolapse and is recognized by terminal bradycardia on fetal heart rate monitoring. Pasternak and Gorey noted that the outcome was devastating when there were both severe HIE and abnormal CT findings, but CT did not show good sensitivity and specificity in the presence of moderate encephalopathy.

MRI is more sensitive in children and adults than CT, and with newer imaging protocols, it may show infarctions within hours of the insult in adult studies. A case report describing the time course of diffusion-weighted imaging (DWI) abnormalities in infants is available. The study reported that DWI may be misleading early, show abnormalities that are transient, and potentially miss significant insults. Outcome studies are also disappointing for MRI in that likelihood ratios are not significantly better than for EEG or evoked potentials. Rutherford and colleagues studied 73 infants who had HIE in whom MRI was obtained during the first week. When bilateral loss of signal in the posterior limb of the internal capsule was used to predict severe adverse outcome at 1 year, it pro-

<table>
<thead>
<tr>
<th>Investigation</th>
<th>No. of infants</th>
<th>DR</th>
<th>FPR</th>
<th>LR</th>
<th>UR</th>
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<tr>
<td>Holmes G, 1982</td>
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<td>0.95</td>
<td>0.10</td>
<td>9.5</td>
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<tr>
<td>Rowe J, 1985</td>
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<td>0</td>
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<td>0</td>
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<td>Hellstrom-Westas L, 1995</td>
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<td>1.0</td>
<td>0.13</td>
<td>7.5</td>
<td>0</td>
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<td>van Lieshout H, 1995</td>
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<td>0.13</td>
<td>7.5</td>
<td>0</td>
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<td>Sinclair D, 1999</td>
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<td>0.81</td>
<td>0.28</td>
<td>2.8</td>
<td>0.26</td>
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<tr>
<td>Toet M, 1999</td>
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<td>0.91</td>
<td>0.14</td>
<td>6.5</td>
<td>0.1</td>
</tr>
<tr>
<td>McBride M, 2000</td>
<td>68</td>
<td>0.85</td>
<td>0.07</td>
<td>11.6</td>
<td>0.16</td>
</tr>
<tr>
<td>Biagini E, 2001</td>
<td>25</td>
<td>0.94</td>
<td>0.11</td>
<td>8.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Zeinstra E, 2001</td>
<td>36</td>
<td>0.6</td>
<td>0.26</td>
<td>2.3</td>
<td>0.54</td>
</tr>
<tr>
<td>OVERALL</td>
<td>411</td>
<td>0.92</td>
<td>0.11</td>
<td>8.3</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Severely abnormal EEG in these studies meant low voltage, electrocerebral inactivity, or burst suppression, as defined in Holmes, et al. Contact the author for a complete list of references (allan@fbr.org).
duced a detection rate of 100%, a false-positive rate of 10%, and a likelihood ratio of 10. Recently, Biagioni and coworkers compared MRI and EEG in the same infants. Although the study only involved 25 infants, the correlation was good between results of the EEG within the first 3 days and the MRI after 1 week (7 to 28 d) and outcome prediction. The major advantage to MRI after 1 week was its ability to predict the severity of outcome if interpretations were divided into eight different patterns, ranging from normal to severe injury of basal ganglia and thalami.

Suggested Approach to Outcome Prediction in HIE

Studies of outcome prediction show that clinical assessment and the EEG provide the best guidance and are readily available. The newer technologies complement this approach but do not significantly improve on it. The author’s approach is to obtain an EEG and cranial ultrasonography on all infants who have HIE. Although ultrasonography does not predict outcome as well as EEG, it excludes significant central nervous system malformations and can show unexpected hemorrhage or infarction. Once these other problems are excluded, the EEG result can be related to the grade of HIE using the four grades as outlined in Table 2.

In infants who have moderate encephalopathy, a severely abnormal EEG reading does suggest a poor prognosis. However, it can be helpful to emphasize that there is a 1 in 4 chance of escaping a severely abnormal outcome when speaking to parents because these infants usually do not require significant supportive care and are likely to survive. A marginal or normal EEG reading in this setting is very reassuring, with only a 3% chance of severe disability. Most families do not have trouble being optimistic in this situation.

Among infants who have moderate-to-severe encephalopathy, respiratory support is required, and a severely abnormal EEG finding suggests an 89% probability of a severe disability. Accordingly, withdrawing support should be considered. If the EEG is not severely abnormal, cautious optimism may be expressed. If the infant is not showing signs of improvement over the next few days, cranial ultrasonography could be performed to look for severe basal ganglia or thalamic echo densities that would suggest that the prognosis is poor (Fig. 2). If no obvious ultrasonographic abnormalities are seen, clinical signs of improvement should guide the discussions with the family. Improvement in encephalopathy often is accompanied by the infant beginning to seek the nipple before the end of the second week of life. When this occurs, optimism likely is justified.

Among infants who have severe HIE, a marginal or normal EEG finding suggests reconsideration of the diagnosis. Cranial ultrasonography may show some structural reason to disregard the EEG result, but if

Figure 2. Cranial ultrasonographic images from a term infant born by emergency cesarean section after a partial abruption. The infant had a severe encephalopathy with a burst-suppression EEG at 24 hours. The family did not wish to have the child removed from supportive care, and imaging was obtained to assess the degree of central nervous system injury. A. Coronal scan at the level of the third ventricle performed at 24 hours of age. The lateral and third ventricles are indistinct, and the parenchyma is echo-dense, suggesting generalized cerebral edema. B. Coronal scan at the level of the third ventricle performed at 2 weeks of age. Basal ganglia infarctions are indicated (arrows) by the increased echo-density of these structures. C. Sagittal scan performed at the same time as B. Note the distinct area of increased echo-density involving the entire basal ganglia (globus pallidus and putamen) indicated by the arrow. The infant survived for 2 years with intractable seizures, lack of development, and spastic quadriplegia.
it does not, metabolic causes of encephalopathy (NeoReviews, August 2001) or even neuromuscular disease should be considered. When the EEG is severely abnormal, withdrawal of support is appropriate because the probability of severe disability is 96%.

In this author’s opinion, MRI is not superior to EEG in separating severely abnormal outcomes from moderate-to-good outcomes at the early stages when decisions about withdrawing support are being made. Attempting to detail the type of disability the child possibly will suffer is especially important in the neonatal period once the decision is made that the child will be fully supported. There are exceptions to this philosophy, but I have relied on ultrasonography rather than MRI in the neonatal period. MRI always can be used for this purpose after the neonatal period.

Suggested Reading


Figure 1. Comparison of normal and severely abnormal EEG patterns. By clicking on the movie icon, the reader can view a brief video of digital electroencephalographic tracings from a normal infant during active sleep, from an infant who has moderate-to-severe HIE and a burst-suppression pattern, and from an infant who has severe HIE and a tracing showing electrocerebral inactivity. The tracings are distinctly different and easy to differentiate in the term infant.
NeoReviews Quiz

4. The severity of hypoxic-ischemic encephalopathy (HIE) can be graded as mild, moderate, or severe, using a classification proposed by Sarnat and Sarnat. Of the following, the criterion most consistent with the diagnosis of mild HIE is:

A. Absence of seizures.
B. Low Apgar scores.
C. Need for assisted ventilation.
D. Proximal muscle weakness.
E. Obtunded state of consciousness.

5. Several ancillary tests have been proposed to improve the prediction of long-term outcome of infants who have suffered from HIE. Of the following, the most useful and practical test for determining the prognosis in HIE is:

A. Cranial ultrasonography.
B. Magnetic resonance imaging.
C. Electroencephalography.
D. Near-infrared spectroscopy.
E. Somatosensory evoked potentials.