Prognostic Tests in Term Neonates With Hypoxic-Ischemic Encephalopathy: A Systematic Review

abstract

BACKGROUND AND OBJECTIVE: Hypoxic-ischemic encephalopathy (HIE) after perinatal asphyxia in term neonates causes long-term neurologic sequelae or death. A reliable evidence-based prognosis is essential. The study goal was to investigate the prognostic value of currently used clinical tests in neonatal patients with perinatal asphyxia and HIE.

METHODS: Searches were made on MEDLINE, Embase, Central, and CINAHL for studies occurring between January 1980 and November 2011. Studies were included if they (1) evaluated outcome in term infants with perinatal asphyxia and HIE, (2) evaluated prognostic tests, and (3) reported outcome at a minimal follow-up age of 18 months. Study selection, assessment of methodologic quality, and data extraction were performed by 3 independent reviewers. Pooled sensitivities and specificities of investigated tests were calculated when possible.

RESULTS: Of the 259 relevant studies, 29 were included describing 13 prognostic tests conducted 1631 times in 1306 term neonates. A considerable heterogeneity was noted in test performance, cut-off values, and outcome measures. The most promising tests were amplitude-integrated electroencephalography (sensitivity 0.93, [95% confidence interval 0.78–0.98]; specificity 0.90 [0.86–0.98]), EEG (sensitivity 0.92 [0.66–0.99]; specificity 0.83 [0.64–0.93]), and visual evoked potentials (sensitivity 0.90 [0.74–0.97]; specificity 0.92 [0.68–0.98]). In imaging, diffusion weighted MRI performed best on specificity (0.89 [0.62–0.98]) and T1/T2-weighted MRI performed best on sensitivity (0.98 [0.80–1.00]). Magnetic resonance spectroscopy demonstrated a sensitivity of 0.75 (0.26–0.96) with poor specificity (0.58 [0.23–0.87]).

CONCLUSIONS: This evidence suggests an important role for amplitude-integrated electroencephalography, EEG, visual evoked potentials, and diffusion weighted and conventional MRI. Given the heterogeneity in the tests’ performance and outcomes studied, well-designed large prospective studies are needed. Pediatrics 2013;131:88–98

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KEY WORDS perinatal asphyxia, hypoxic-ischemic encephalopathy, prognosis, clinical test, systematic review

ABBREVIATIONS aEEG—amplitude-integrated electroencephalography
CI—confidence interval
HIE—hypoxic-ischemic encephalopathy
MRS—magnetic resonance spectroscopy
SEP—sensory evoked potential
VEP—visual evoked potential

Drs van Laerhoven, de Haan, and Post all had full access to the meta-analysis data and take responsibility for the integrity and accuracy of all data and subsequent analysis; Drs Post and Offringa are responsible for the original design and concept of the study, Drs van Laerhoven, de Haan, van der Lee, and Post acquired the data; and Drs van Laerhoven, de Haan, and van der Lee analyzed and interpreted the data. Statistical analyses were performed by Drs van der Lee, de Haan, and Offringa. Drafting and revision of the manuscript were performed by Drs van Laerhoven, de Haan, van der Lee, Offringa, and Post. Drs de Haan, van der Lee, and Offringa supervised the study.

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Perinatal asphyxia is an important cause of acquired neonatal brain injury in term neonates leading to hypoxic-ischemic encephalopathy (HIE). It may lead to long-term neurologic sequelae or death. In these critically ill neonates, a reliable evidence-based prognosis is of key importance to correctly inform parents and caretakers regarding the possible long-term neurodevelopmental consequences.

Clinical neurologic dysfunction immediately after HIE has long been regarded to be the best predictor of long-term neurodevelopmental outcome or death.

Because neurophysiologic tests as EEG, amplitude-integrated electroencephalography (aEEG), and advanced neuro-imaging modalities such as MRIs have become widely available, these tests have attained a significant role in the process of prognostication.

Nevertheless, uncertainty remains regarding the accuracy of these tests to predict long-term neurodevelopmental outcome or death. Most studies concerning prognostic tests are based on small case series or retrospective data or evaluate short-term follow-up (≤18 months). In the era before the use of controlled hypothermia, 3 meta-analyses evaluated the prognostic value of biochemical tests, aEEG, and MRI or magnetic resonance spectroscopy (MRS) in the neurodevelopmental outcome in term neonates with severe HIE. Most studies concerning prognostic tests are based on small case series or retrospective data or evaluate short-term follow-up (≤18 months).

To investigate the prognostic value of currently used clinical tests for long-term neurodevelopmental outcome of neonatal patients suffering from perinatal asphyxia and HIE we performed a systematic review of the literature. If possible, results from studies concerning patients treated with controlled hypothermia were compared with normothermic patients.

METHODS

Information Sources

We followed the guidance from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements. A comprehensive electronic literature search was conducted in the MEDLINE (Pubmed), Embase, CENTRAL, and CINAHL databases for studies published between January 1980 and November 2011. Only studies including humans and reported in the English or Dutch language were eligible. We checked the citations of eligible studies for additional articles that might be included. In addition, experts were contacted for relevant articles concerning prognosis after HIE. The search strategies from the meta-analyses of Spitzmiller et al, Ramaswamy et al, and Thayyil et al were used as examples of literature searches for studies on the use of aEEG, biomarkers, and MRI as prognostic tests. The Medical Subject Heading terms and keywords used for the search are included in the online-only material (see Supplemental Information eMethods 1).

Eligibility Criteria and Definitions

Three reviewers independently selected studies based on the following inclusion criteria: (1) observational prognostic studies that included neonates with a gestational age of 36 weeks or greater who had perinatal asphyxia and HIE (both perinatal asphyxia and HIE had to be clearly defined in the study methods section); (2) neurodevelopmental follow-up available for at least 18 months postnatal age; and (3) neurodevelopmental outcome clearly defined as good or adverse. Adverse neurodevelopmental outcome was defined by either 1 or more of the following criteria: (1) cerebral palsy, either described by standardized clinical neurologic examination or defined by the Global Motor Functioning Scale; (2) an abnormal test result on developmental test scores using the Bailey States of Infant Development test or the Griffith Mental Developmental Index (a test score of ≥2 SDs below mean was defined as adverse outcome); and (3) death during admission or during the specified follow-up period. Disagreements were resolved by discussion until consensus.

Data Extraction

A standardized data extraction form was used to record study information (see Supplemental Information eMethods 2). Disagreements were resolved by discussion until consensus was reached. If the required data could not be extracted from the publication, the corresponding author was contacted and additional information was requested. If core data remained missing the study was excluded from the analyses.

Methodologic Quality

Appraisal of the methodologic quality of the included studies was performed by 3 reviewers (H.v.L., T.R.d.H., and B.P.) with the use of a checklist (see Supplemental Information eMethods 3 and 4). Criteria were adapted from instruments developed by Kwakkel et al and Borghouts et al and general recommendations for prognostic studies. A set of 14 items was obtained to evaluate the methodologic quality of studies. All 14 items were assumed to be of equal importance and were not weighed.

Summary Measures and Synthesis of Results

The prognostic accuracy of each test was assessed on the basis of 2 × 2 tables for both normothermic and hypothermic neonates if available. Neurodevelopmental
outcome at the age of 18 months or older at follow-up was recorded as either “good” (ie, normal or mild disability) or “adverse” (moderate/severe disability or death) as defined by each individual study. In case of continuous variables, cut-off values for normal or abnormal test results were used as defined by the authors of the original studies and were stated as either positive or negative. Because the results of diagnostic tests predictive of cerebral damage can change over time after perinatal asphyxia, we documented the prognostic value of each test per time window of test performance if the published data allowed us to do so.

We calculated the sensitivity and specificity for each prognostic test in relation to good or adverse outcome. A meta-analysis of the results of included studies on the same prognostic test among either normothermic or hypothermic neonates was carried out by using Review Manager Version 5.0 (The Cochrane Collaboration 2008, The Nordic Cochrane Centre, Copenhagen, Denmark) in combination with the SAS (SAS Institute, Cary, NC) macro METADAS v 1.3 developed by Yemisi Takwoingi. Meta-analyses using the bivariate approach in which pairs of sensitivity and specificity are jointly analyzed, incorporating any correlation that might exist between these 2 measures using a random effects approach, were carried out when multiple studies addressed the same prognostic relation. In accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Version 1.0; 2010, http://srdta.cochrane.org), random effects analyses were performed and no indicator of heterogeneity was calculated.

RESULTS

Our literature search yielded 3469 article abstracts, and 259 were selected for review of the full-text articles. Inclusion criteria were met by 46 studies. Checking citations and consulting experts yielded 6 additional studies, for a total of 52 inclusions. Despite contacting corresponding authors, adequate data for 2 × 2 tables could be retrieved only from 29 of 52 studies. Of these final 29 studies, 28 had included normothermic patients and 1 included both normothermic and hypothermic patients. A flow diagram of the search and selection process is shown in Fig 1; Table 1 summarizes the characteristics of all included studies.

In 29 studies, 1411 term infants with HIE after perinatal asphyxia were investigated. Follow-up was available for 1306 (93%) infants. The degree of HIE (mild, moderate, or severe) was clearly described in 23 (79%) of 29 studies. The included studies contained 201 infants with mild HIE (grade 1), 469 patients with moderate HIE (grade 2), and 186 patients with severe HIE (grade 3). The remaining 450 patients were less clearly qualified as having either moderate or severe HIE.

In 19 (66%) of 29 studies, the outcome assessor was blinded for the test result. In 6 (21%) of 29 studies, the number of included patients was larger than 50, and 25 of 29 studies had 15% or less loss to follow-up. Five (17%) studies reported on the method or extent of the provided intensive care treatment or on end-of-life decisions. Twenty-one (72%) studies were of a prospective design.

The 29 included studies described 13 different clinically used diagnostic tests. These tests included different cerebral imaging modalities, neurophysiologic tests, and clinical neurologic examination. The age at test performance ranged from 1 to 30 days after birth. The age at neurodevelopmental outcome testing ranged from 18 months to 7 years. Table 2 reports the classification for positive or negative test as reported per study.

Results of the meta-analysis are reported in Table 3 (pooled sensitivities and specificities with confidence intervals) and Fig 2 (forest plots of sensitivity and specificity as calculated from the original reports). Figure 2 A and B reports the forest plots for neurophysiologic tests and clinical physical examination, and Fig 2C reports the forest plots for imaging tests.

The most promising neurophysiologic tests (performed in the first week) were aEEG (sensitivity 0.93, 95% confidence interval [CI] 0.78–0.98; specificity 0.90 [95% CI 0.60–0.98]), EEG (sensitivity 0.92 [95% CI 0.66–0.99]; specificity 0.83 [95% CI 0.64–0.93]), and visual evoked
<table>
<thead>
<tr>
<th>Year of Publication</th>
<th>First Author</th>
<th>Prospective/ Retrospective Study Design</th>
<th>Blinded Y/N</th>
<th>Female/ Male Ratio</th>
<th>HE Stage 1/ 2/3 (n)</th>
<th>ni/N</th>
<th>Timing of Testing</th>
<th>Test Follow-up</th>
<th>Outcome Studied</th>
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<tbody>
<tr>
<td>2011</td>
<td>Alderliesten</td>
<td>R</td>
<td>N</td>
<td>31/50</td>
<td>2/73/4</td>
<td>81 (122)</td>
<td>Days 1–8</td>
<td>MRI, ADC and MRS</td>
<td>18–46 mo</td>
</tr>
<tr>
<td>2011</td>
<td>Ferrari</td>
<td>P</td>
<td>Y</td>
<td>14/20</td>
<td>9/11/14</td>
<td>34 (43)</td>
<td>Days 1–42</td>
<td>MRI, T1/T2 and GM</td>
<td>2 y</td>
</tr>
<tr>
<td>2010</td>
<td>Twomey</td>
<td>P</td>
<td>N</td>
<td>3/15/8</td>
<td>2/73/4</td>
<td>81 (122)</td>
<td>Days 1–8</td>
<td>MRI, ADC, DWI and mCUS</td>
<td>2 y</td>
</tr>
<tr>
<td>2010</td>
<td>Rutherford</td>
<td>P</td>
<td>NA</td>
<td>32/55</td>
<td>150 (121)</td>
<td>Days 2–30</td>
<td>MRI, T1/T2</td>
<td>18 mo</td>
<td>MDI, Bayley and GMFCS</td>
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<tr>
<td>2010</td>
<td>Ancora</td>
<td>P</td>
<td>Y</td>
<td>8/24</td>
<td>17/13/2</td>
<td>32 (33)</td>
<td>Days 1–8</td>
<td>MRI, T1/T2 and aEEG</td>
<td>2 y</td>
</tr>
<tr>
<td>2009</td>
<td>Liau</td>
<td>Y</td>
<td>11/13</td>
<td>3/18/3</td>
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<td>Days 1–8</td>
<td>MRI, ADC</td>
<td>2 y</td>
<td>van Wijchen examination</td>
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<td>2009</td>
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<td>P</td>
<td>N</td>
<td>NA</td>
<td>18/17/9</td>
<td>44 (54)</td>
<td>Days 1–2</td>
<td>EEG</td>
<td>2 y</td>
</tr>
<tr>
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<td>Vermeulen</td>
<td>P</td>
<td>Y</td>
<td>18/26</td>
<td>18/17/9</td>
<td>44 (54)</td>
<td>Days 1–2</td>
<td>aEEG</td>
<td>2 y</td>
</tr>
<tr>
<td>2008</td>
<td>Toet</td>
<td>P</td>
<td>N</td>
<td>0/8/8</td>
<td>18 (21)</td>
<td>Days 1–2</td>
<td>aEEG</td>
<td>2 y</td>
<td>Griffiths and Movement ABC</td>
</tr>
<tr>
<td>2005</td>
<td>L’Abee</td>
<td>P</td>
<td>Y</td>
<td>6/14</td>
<td>4/7/11</td>
<td>11 (11)</td>
<td>Days 1–2</td>
<td>MRI, T1/T2, DWI and MRS</td>
<td>2 y</td>
</tr>
<tr>
<td>2005</td>
<td>van Rooij</td>
<td>R</td>
<td>Y</td>
<td>NA</td>
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<td>Day 2</td>
<td>aEEG</td>
<td>2 y</td>
<td>Griffiths and neurologic examination</td>
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<tr>
<td>2004</td>
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<td>P</td>
<td>Y</td>
<td>7/17</td>
<td>2/16/6</td>
<td>24 (24)</td>
<td>Days 5–14</td>
<td>MRI, T1/T2</td>
<td>3.5–4 y</td>
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<tr>
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<td>Khong</td>
<td>P</td>
<td>Y</td>
<td>6/14</td>
<td>0/15/5</td>
<td>20 (20)</td>
<td>Days 2–14</td>
<td>MRI, T1/T2, DWI and MRS</td>
<td>18–24 mo</td>
</tr>
<tr>
<td>2004</td>
<td>ter Horst</td>
<td>R</td>
<td>Y</td>
<td>15/15</td>
<td>4/18/5</td>
<td>26 (30)</td>
<td>Days 1–3</td>
<td>aEEG</td>
<td>2 y</td>
</tr>
<tr>
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<td>P</td>
<td>Y</td>
<td>12/13</td>
<td>8/16/1</td>
<td>25 (25)</td>
<td>Days 1–8</td>
<td>MRI, T1/T2 and EEG</td>
<td>2 y</td>
</tr>
<tr>
<td>1999</td>
<td>Mercurt</td>
<td>R</td>
<td>Y</td>
<td>18/17/5</td>
<td>19 (21)</td>
<td>Days 1–30</td>
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<td>2 y</td>
<td>Griffiths and neurologic examination</td>
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<tr>
<td>1999</td>
<td>Toet</td>
<td>P</td>
<td>N</td>
<td>27/17/20</td>
<td>68 (73)</td>
<td>Day 1</td>
<td>aEEG</td>
<td>5 y</td>
<td>Griffiths and neurologic examination</td>
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<tr>
<td>1998</td>
<td>Scalais</td>
<td>P</td>
<td>Y</td>
<td>5/24/1</td>
<td>40 (40)</td>
<td>Days 1–7</td>
<td>VEP, SEP and BAEP</td>
<td>2 y</td>
<td>Griffiths and items from Brunet-Lezine and neurologic examination</td>
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<tr>
<td>1996</td>
<td>Groenendaal</td>
<td>P</td>
<td>N</td>
<td>5/20/7</td>
<td>31 (32)</td>
<td>Day 1–14</td>
<td>MRI, CUS, SEP, VEP and aEEG</td>
<td>18 mo</td>
<td>Griffiths and neurologic examination</td>
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<tr>
<td>1995</td>
<td>Eken</td>
<td>P</td>
<td>Y</td>
<td>19/18</td>
<td>11/17/6</td>
<td>34 (34)</td>
<td>Days 1–8</td>
<td>CUS, SEP, VEP</td>
<td>2 y</td>
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<td>Y</td>
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<td>NA</td>
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<td>Day 3</td>
<td>EEG</td>
<td>7 y</td>
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<td>1994</td>
<td>Thornber</td>
<td>P</td>
<td>N</td>
<td>24/14</td>
<td>NA</td>
<td>38 (38)</td>
<td>Days 1–3</td>
<td>aEEG</td>
<td>18 mo</td>
</tr>
<tr>
<td>1993</td>
<td>Bad</td>
<td>P</td>
<td>NA</td>
<td>52/33</td>
<td>49/57/8</td>
<td>133 (145)</td>
<td>Days 3–14</td>
<td>NBNA</td>
<td>2 y</td>
</tr>
<tr>
<td>1993</td>
<td>Prechtt</td>
<td>P</td>
<td>Y</td>
<td>8/18</td>
<td>0/13/13</td>
<td>26 (26)</td>
<td>Days 1–8</td>
<td>GM and EEG</td>
<td>17–24 mo</td>
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<tr>
<td>1992</td>
<td>Taylor</td>
<td>R</td>
<td>Y</td>
<td>NA</td>
<td>57 (57)</td>
<td>Day 1–8</td>
<td>SEP and VEP</td>
<td>2 y</td>
<td>Bayley II and neurologic, audiometric and visual examination</td>
</tr>
<tr>
<td>1991</td>
<td>de Vries</td>
<td>P</td>
<td>Y</td>
<td>8/26</td>
<td>4/12/18</td>
<td>34 (34)</td>
<td>Days 1–14</td>
<td>SEP</td>
<td>18 mo</td>
</tr>
<tr>
<td>1991</td>
<td>Muttitt</td>
<td>P</td>
<td>Y</td>
<td>12/24</td>
<td>2/20/13</td>
<td>35 (30)</td>
<td>Days 1–7</td>
<td>VEP</td>
<td>2 y</td>
</tr>
<tr>
<td>1991</td>
<td>McCulloch</td>
<td>R</td>
<td>N</td>
<td>NA</td>
<td>NA</td>
<td>25 (25)</td>
<td>Days 1–7</td>
<td>VEP</td>
<td>2.5–4.5 y</td>
</tr>
</tbody>
</table>

DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; CUS, cerebral ultrasound; GM, general movements; GMFCS, Gross Motor Function Classification System; MDI, Motor Development Index; NA, not available; WHO, World Health Organization.

* Blinded Y/N, outcome assessment blinded yes or no.
* n/N, number of cases with complete follow-up/total number of cases in study.
* Wechsler Preschool and Primary Scale of Intelligence.
<table>
<thead>
<tr>
<th>Year of Publication</th>
<th>First Author</th>
<th>Normal Findings</th>
<th>Abnormal Findings</th>
</tr>
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<tbody>
<tr>
<td>2011</td>
<td>Alderliesten</td>
<td>MRI: basal ganglia ADC $&gt;1031 \times 10^{-6}$ mm²/s</td>
<td>MRI: basal ganglia ADC $=1031 \times 10^{-6}$ mm²/s</td>
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<tr>
<td></td>
<td></td>
<td>MRS: basal ganglia lactate/NA $&lt;0.08$</td>
<td>MRS: basal ganglia lactate/NA $&gt;0.08$</td>
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<tr>
<td>2011</td>
<td>Ferrari</td>
<td>Normal T1/T2-weighted MRI or</td>
<td>Abnormal T1/T2-weighted MRI in basal ganglia; white matter; cortex or PLIC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mild abnormalities cortex, no abnormalities in basal ganglia or PLIC</td>
<td>GM: poor repertoire; abnormal movements for age.</td>
</tr>
<tr>
<td>2010</td>
<td>Twomey</td>
<td>Normal T1/T2-weighted MRI</td>
<td>Abnormalities T1/T2-weighted or DW-MRI (diffuse, watershed, central, atypical)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal DW-MRI</td>
<td>Abnormal CUS (abnormal cortex/isolated gray matter hyperechogenicity, central hyperechogenicity)</td>
</tr>
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<td>2010</td>
<td>Rutherford</td>
<td>Normal T1/T2-weighted MRI</td>
<td>Abnormalities on T1/T2-weighted MRI (basal ganglia; PLIC; white matter; cortical).</td>
</tr>
<tr>
<td>2010</td>
<td>Ancora</td>
<td>Normal background aEEG</td>
<td>Abnormal background aEEG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No Lactate</td>
<td>Ratio MRS lactate/Cr &gt;0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ratio MRS NAA/Cr &gt;0.5</td>
<td>Ratio MRS NAA/Cr &lt;0.5</td>
</tr>
<tr>
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<td>Twomey</td>
<td>MRI: ADC Basal ganglia $&gt;1018.5 \times 10^{-6}$ mm²/s</td>
<td>MRI: ADC Basal ganglia $&lt;1018.5 \times 10^{-6}$ mm²/s</td>
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<td>2008</td>
<td>Murray</td>
<td>EEG normal background for age</td>
<td>Moderate, major abnormalities EEG background, seizures or inactive EEG</td>
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<td></td>
<td>No seizures</td>
<td>Normal ADC</td>
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<td>Normal ADC</td>
<td>Normal ADC cortex; basal ganglia; brainstem; PLIC or cerebellum</td>
</tr>
<tr>
<td>2006</td>
<td>Toet</td>
<td>Normal aEEG pattern</td>
<td>Abnormal aEEG pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(continuous normal voltage, discontinuous normal voltage $&gt;5 \mu$V)</td>
<td>(flat trace, continuous low voltage, burst suppression; seizures)</td>
</tr>
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<td>2005</td>
<td>L’Abee</td>
<td>Normal T1/T2-weighted or DW-MRI</td>
<td>Abnormalities T1/T2-weighted or DW-MRI (cortex, basal ganglia or white matter)</td>
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<td></td>
<td>Normal ADC</td>
<td>Abnormal ADC (basal ganglia; white matter)</td>
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<td></td>
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<td>basal ganglia/white matter</td>
<td>Elevated lactate/N-acetyl aspartate (basal ganglia)</td>
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<td>Normal MRS of basal ganglia.</td>
<td>MRS Lactate peak present in basal ganglia</td>
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<td>van Rooij</td>
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<td>Abnormal aEEG pattern</td>
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<td></td>
<td></td>
<td>(continuous normal voltage, discontinuous normal voltage $&gt;5 \mu$V)</td>
<td>(flat trace; continuous low voltage; burst suppression)</td>
</tr>
<tr>
<td>2004</td>
<td>Belet</td>
<td>Normal T1/T2-weighted MRIs</td>
<td>Abnormalities T1/T2-weighted MRI (White matter lesions/deep gray matter lesions/encephalomalacia-atrophy)</td>
</tr>
<tr>
<td>2004</td>
<td>Khong</td>
<td>Normal T1/T2-weighted or DW-MRIs</td>
<td>Abnormal T1/T2-weighted or DW-MRIs (Diffuse white matter lesions, abnormalities in deep gray nuclei, lesions in brainstem)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal ADC</td>
<td>Abnormal ADC basal ganglia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>basal ganglia</td>
<td>MRS Lactate peak present in basal ganglia</td>
</tr>
<tr>
<td>2001</td>
<td>Biagioni</td>
<td>Normal aEEG pattern</td>
<td>Abnormal aEEG pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(continuous normal voltage, discontinuous normal voltage $&gt;5 \mu$V)</td>
<td>(flat trace; continuous low voltage; burst suppression), Seizures, status epilepticus</td>
</tr>
<tr>
<td>2001</td>
<td>Biagioni</td>
<td>Normal EEG background for age,</td>
<td>Abnormal EEG (low voltage; constant discontinuity, abnormal for age)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No seizures</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal T1/T2-weighted MRIs</td>
<td>Abnormal T1/T2-weighted MRI (abnormalities in basal ganglia, thalamus, PLIC, white matter).</td>
</tr>
<tr>
<td>2001</td>
<td>Roelants-van Rijn</td>
<td>Normal T1/T2-weighted MRIs</td>
<td>Abnormalities T1/T2-weighted MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRS: lactate/NA ratio $&lt;0.09$</td>
<td>(Moderate to severe Abnormalities in basal ganglia/thalamus/PLIC/cortex)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRS: NAA/Cho ratio $&gt;0.62$</td>
<td>MRS: Lactate/NA ratio $&gt;0.09$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRS: NAA/Cho ratio $&lt;0.62$</td>
<td>MRS: NAA/Cho ratio $&lt;0.09$</td>
</tr>
<tr>
<td>1999</td>
<td>Mercuri</td>
<td>Normal T1/T2-weighted MRIs</td>
<td>Abnormalities T1/T2-weighted MRI (moderate to severe abnormalities in basal ganglia/thalamus/white matter)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurologic exam: normal</td>
<td>Neurologic exam: abnormal</td>
</tr>
<tr>
<td>1999</td>
<td>Toet</td>
<td>Normal aEEG pattern</td>
<td>Abnormal aEEG pattern (flat trace; continuous low voltage; burst suppression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(continuous normal voltage, discontinuous normal voltage $&gt;5 \mu$V)</td>
<td></td>
</tr>
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</table>
potential (VEP) (sensitivity 0.90 [95% CI 0.68–0.96]) and T1/T2-weighted MRI (first 2 weeks) performed best on sensitivity (0.98 [95% CI 0.80–1.00]). Early MRS demonstrated a sensitivity of 0.75 [95% CI 0.26–0.96] with poor specificity (0.58 [95% CI 0.23–0.87]). Clinical neurologic examination and cerebral ultrasound both performed poorly.

### DISCUSSION

To our knowledge, this is the first review to systematically evaluate currently used clinical tests for the prediction of outcome in term neonates with perinatal asphyxia and HIE. Although the literature contains a wide variety of studies on outcome in these patients evaluating a host of mostly new and relatively unknown test modalities, we have focused on tests used in everyday medical practice. Knowledge on the prognostic value of these tests is most helpful for the clinician. This review is, therefore, not an effort to provide a comprehensive overview of all available tests. Although the initial search yielded 259 potentially relevant studies, we could only use the information on 13 different prognostic tests reported in 29 studies These 13 prognostic tests consisted of...
a wide array of tests such as imaging modalities, neurophysiologic tests, and clinical neurologic examinations. According to our findings, the most promising neurophysiologic tests in the first week of life in neonatal patients with HIE after perinatal asphyxia are aEEG, EEG, and VEP. The 95% CIs are wide, due to small numbers. As far as we...
know, both sensory evoked potentials (SEP) and VEP are not used routinely in most NICUs, but both may provide important prognostic information. We did, however, find considerable heterogeneity in specificity, especially for SEP as can be seen in Fig 2A. This may be caused by differences in cut-off values used for positive or negative test results. In a meta-analysis by Zandbergen et al., the investigators concluded that in these patients the SEP is the most accurate early predictor of poor neurologic outcome or death. Additional investigation into the prognostic value of evoked potential tests after perinatal asphyxia is warranted.

Imaging studies of the brain in patients with HIE after perinatal asphyxia are essential in the process of prognostication nowadays. Although the original studies concerning imaging and outcome were heterogeneous and based on small numbers, we decided to perform meta-analyses. Of the imaging modalities, diffusion weighted MRI (performed in the first week) had the highest specificity and T1/T2-weighted MRI (performed in the first 2 weeks) had the highest sensitivity. An abnormal DW image is therefore highly predictive of adverse outcome (SPIN), and a normal T1/T2-weighted MRI is highly predictive of normal outcome (SNOUT). Outcome may, however, still be favorable in cases with early abnormal DW imaging. Cerebral ultrasound and clinical neurologic examination, both frequently used bedside screening methods, had a reasonable sensitivity but a poor specificity. Abnormalities on cerebral ultrasound or clinical neurologic examination may therefore lead to unnecessary apprehension due to the relatively large number of false positives.

Comparison With Earlier Reviews

Three earlier meta-analyses, each focusing on a single prognostic test, have reported on the prediction of neurodevelopmental outcome or death in term neonates with HIE. The meta-analysis by Spitzmiller et al. on aEEG included 8 studies, of which 5 fulfilled our inclusion criteria. Spitzmiller et al. reported pooled specificity is in line with our findings (0.88 vs 0.90). The meta-analysis by Ramaswamy et al. on biochemical markers in serum, urine and cerebrospinal fluid is, in our opinion, inconclusive as the included studies are highly heterogeneous with regard to the type of biochemical test methods used and clinical outcome measures reported. Although biomarkers of cerebral cellular damage comprise a very interesting field of research, their value in the process of prognostication in daily practice needs to be evaluated.

Finally, the meta-analysis by Thayyil et al. evaluating the prognostic value of MRI and MRS concluded that basal ganglia or thalamic lactate/N-acetyl aspartate is a highly accurate marker for the prediction of adverse long-term neurodevelopmental outcome or death. We included 2 additional studies in our meta-analysis. Spitzmiller et al. reported pooled specificity in line with our findings (0.88 vs 0.90). The meta-analysis by Ramaswamy et al. on biochemical markers in serum, urine and cerebrospinal fluid is, in our opinion, inconclusive as the included studies are highly heterogeneous with regard to the type of biochemical test methods used and clinical outcome measures reported. Although biomarkers of cerebral cellular damage comprise a very interesting field of research, their value in the process of prognostication in daily practice needs to be evaluated.

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lactate MRS complied with our inclusion criteria\textsuperscript{17,26,29,32,35} of which 3 were also included in Thayyil et al’s review. Based on our analysis and pooled sensitivities and specificities, taking into account the very wide 95% CIs, we conclude that there is insufficient evidence so far to advise either positively or negatively about the use of MRS. More prospective studies need to be done.

**Strengths and Weaknesses**

The evidence from the studies we included seems applicable to the care and treatment policies for infants with HIE after perinatal asphyxia. A countereffect of our strict inclusion criteria is that our review includes only 1306 patients studied over 50 years. The major cause of the relatively small number of included patients is our inclusion criterion of a neurodevelopmental follow-up period of at least 18 months; many studies did not follow children beyond 12 months of age. In our opinion the relevance of the assessment of neurodevelopmental outcome at ages before 18 months is at least questionable as neurodevelopmental sequelae can become manifest at ages beyond 12 months, and mental and behavioral disabilities may appear at even later ages.\textsuperscript{49}

The presence of bias is almost unavoidable in systematic reviews and meta-analyses of observational studies. Selection bias and information bias may be present in the original studies under review (by flaws in study design) or arise from the way studies were selected for inclusion. Several forms of bias may have influenced our results regarding the tests’ accuracies. Language bias by restriction to the English and Dutch language sources may have led to an overestimation or underestimation of both sensitivity and specificity. However, the incremental value of searching for studies in other languages than English has not been fully investigated.\textsuperscript{50} An overestimation of test accuracy may have occurred as it was not always clear if eligible patients in the included studies were entered in the cohort nonrandomly or consecutively. Overestimation of test result accuracy may also have occurred due to information bias as in a number of studies tests were analyzed in retrospect with knowledge of the clinical outcome. Selection bias by the possible exclusion of deceased patients in included studies may also have led to overestimation of the prognostic value of the tests. Publication bias, the selective publication of studies based on the magnitude and direction of their findings, represents a particular threat to the validity of meta-analysis of observational studies that may very well have inflated our results.

Last but not least, our results were most often based on small sample sizes; the CIs of our pooled data are therefore wide. Unfortunately, we could only retrieve useful data from 29 of the 52 selected studies due to poor reporting. A subgroup analysis of the prognostic value of the investigated tests in neonates with different grades of HIE after perinatal asphyxia was not possible with these limited data. This is of importance as tests may behave differently in different sub populations.

**Validity of Results in Patients Under Hypothermic Treatment**

Controlled hypothermia has proved to be a major improvement in the care of newborns with HIE as it improves neurodevelopmental outcome and survival.\textsuperscript{51,52} Studies incorporated in this review were mainly performed in the era before controlled hypothermia. Studies on EEG and aEEG during controlled hypothermia have reported an optimal time window of 48 hours after the hypoxic-ischemic event for optimal prognosis of outcome.\textsuperscript{53,54} So far, there is no evidence that the optimal time window for MRI is essentially different due to this new hypothermia treatment protocol.\textsuperscript{20,55} Therefore, based on the current state of knowledge, we believe that the results of this review concerning EEG, aEEG, and MRI can be used in infants treated with controlled hypothermia. It is not known whether VEPs are influenced by hypothermia and it is thus not certain if our results on VEP can be extrapolated to neonates undergoing controlled hypothermia.

**CONCLUSIONS**

EEG and aEEG both perform well in predicting outcome for neonates with perinatal asphyxia and HIE even when performed in the first week of life. MRI is generally advised between the fourth and the eighth day after HIE. This time window is clinically essential to evaluate brain damage.\textsuperscript{56} Our analysis shows considerable variation in the accuracy of MRI, either conventional, diffusion weighted, or spectroscopy. The clinician should be aware of the essence of test timing and the variability in sensitivity and specificity per time window of test performance. Cerebral ultrasound may be a quick and noninvasive bedside tool, but its specificity in children with HIE is unacceptably low. The prognostic value of SEP and VEP is promising but should be investigated in well-designed prospective studies before standardized clinical use is advocated. In general, we found large variability in the timing and cut-off values of the tests and in outcome assessment at follow-up, stressing the importance of clear definitions and harmonization of test methods and outcome measures in this field.

Finally, it seems clinically sensible that a combination of prognostic test results in individual patients, although correlated, will perform better than individual tests. From the available data we could not evaluate the accuracy of any combination of prognostic tests and therefore we cannot advise on the optimal test combination. A well-designed
prospective study is needed to test the joint accuracy of several complementary tests in prognostication. Results from such a study will not only aid in the clinical care of these patients but may also be used for the inclusion and stratification of patients in neuroprotective intervention trials that need to include patients at high risk of adverse outcome after HIE.

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