MRI and Withdrawal of Life Support From Newborn Infants With Hypoxic-Ischemic Encephalopathy

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KEY WORDS

infant, newborn, hypoxia-ischemia, brain, magnetic resonance imaging, prognosis, withholding treatment

ABBREVIATIONS

HIE—hypoxic-ischemic encephalopathy
MR—magnetic resonance
NAA—*N*-acetylaspartate
TOBY—Total Body Hypothermia for Neonatal Encephalopathy
CI—confidence interval

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abstract

The majority of deaths in infants with hypoxic-ischemic encephalopathy (HIE) follow decisions to withdraw life-sustaining treatment. Clinicians use prognostic tests including MRI to help determine prognosis and decide whether to consider treatment withdrawal. A recently published meta-analysis provided valuable information on the prognostic utility of magnetic resonance (MR) biomarkers in HIE and suggested, in particular, that proton MR spectroscopy is the most accurate predictor of neurodevelopmental outcome. How should this evidence influence treatment-limitation decisions? In this article I outline serious limitations in existing prognostic studies of HIE, including small sample size, selection bias, vague and overly inclusive outcome assessment, and potential self-fulfilling prophecies. Such limitations make it difficult to answer the most important prognostic question. Reanalysis of published data reveals that severe abnormalities on conventional MRI in the first week have a sensitivity of 71% (95% confidence interval: 59%–91%) and specificity of 84% (95% confidence interval: 68%–93%) for very adverse outcome in infants with moderate encephalopathy. On current evidence, MR biomarkers alone are not sufficiently accurate to direct treatment-limitation decisions. Although there may be a role for using MRI or MR spectroscopy in combination with other prognostic markers to identify infants with very adverse outcome, it is not possible from meta-analysis to define this group clearly. There is an urgent need for improved prognostic research into HIE. *Pediatrics* 2010;126:e451–e458

Hypoxic-ischemic encephalopathy (HIE) is a major contributor to global child mortality and morbidity.[1] Although therapeutic hypothermia has recently emerged as a means of neuroprotection for infants with HIE, many infants still have an adverse outcome. Almost 50% of infants enrolled in recent trials and treated with hypothermia either died or were found to have severe disability at the 18-month follow-up.[2,3]

In developed countries the majority of deaths of infants with HIE follow decisions to withdraw life-sustaining treatment.[4,5] Two-thirds of the deaths in the recent cooling trials followed treatment withdrawal.[3,6] One important factor that clinicians use in making such decisions is the severity of encephalopathy. In particular, infants with severe (Sarnat stage 3)[7] encephalopathy are generally believed to have a uniformly dire prognosis.[8,9] However, prognostication in infants with moderate encephalopathy is more difficult.[9–11] A variety of clinical, electrophysiological, and radiologic tools have been used to help prognosticate.[9] In particular, MRI has emerged as potentially one of the most useful tools for prognostication in HIE,[8,12–14] and it has been recommended that all infants with HIE have an MRI performed between

days 2 and 8.[15] In a recent survey of neonatologists in Australia and New Zealand, 62% of clinicians indicated that they would attempt to perform an MRI before making a decision about treatment withdrawal.[16]

However, the use of MRI in treatment-limitation decisions raises a number of questions. How reliable is MRI or related technology at predicting outcome for infants with HIE? Which findings on MRI are the most useful? A recently published meta-analysis of magnetic resonance (MR) biomarkers for predicting neurodevelopmental outcome[10] has provided valuable evidence relating to both of these questions.

META-ANALYSIS

Thayyil et al[10] used recently developed Cochrane methodology for performing systematic reviews of diagnostic tests. They carefully reviewed studies that related MR findings in infants with HIE to neurodevelopmental outcome at 12 months or later. The authors included studies that used conventional MRI as well as those that performed spectroscopy, diffusion-weighted imaging, diffusion tensor imaging, or fractional anisotropy. To determine the sensitivity and specificity of different biomarkers, data were extracted from studies in terms of outcome (favorable versus unfavorable) and the presence or absence of abnormality on testing.

Thayyil et al[10] identified 32 studies that included a total of 860 newborn infants with HIE. Their detailed analysis revealed MR spectroscopy to be more specific and sensitive for predicting neurodevelopmental impairment than conventional imaging. In particular, they found that the basal ganglia lactate/*N*-acetylaspartate (NAA) peak/area ratio was the most accurate prognostic marker for predicting adverse neurodevelopmental outcome. Contrary to suggestions from previous studies,[17,18] Thayyil et al found that the brain-water apparent diffusion coefficient and absence of myelin signal in the posterior limb of the internal capsule did not have adequate prognostic utility.

In their review, Thayyil et al argued that an abnormal lactate/NAA peak/area ratio may be useful in helping to identify infants with the most severe brain injury and help clinicians make "objective management decisions."[10] They did not explicitly discuss whether this includes decisions about the continuation or withdrawal of life-sustaining treatment, but this is arguably the most important management decision for infants with HIE. Do the results of the meta-analysis support use of the lactate/NAA peak/area ratio to help decide about treatment withdrawal? Should the results of conventional MRI not be used in decision-making given their low specificity?

LIMITATIONS OF PROGNOSTIC EVIDENCE

The problem with using this evidence in treatment-limitation decisions is that there are a number of serious weaknesses in existing studies of prognostic tests for HIE. Methodologic flaws and poor reporting seriously hamper systematic reviews of diagnostic and prognostic tests.[19] Although the included studies in the Thayyil et al review had moderate-to-high quality on objective criteria,[10] there were a number of important limitations.

Population

First, studies of prognosis of infants with HIE have been mostly small.[9] The reviewed articles reported outcome for a median of 24 infants. Almost half of the infants studied (in those studies that included Sarnat staging) were at either Sarnat stage 1 or 3, groups that are far less prognostically difficult. Furthermore, the inclusion of significant numbers of very mildly or very severely affected infants potentially distorts assessment of the usefulness of prognostic tests. Second, many of the studies had potential selection bias, and few of the authors described in any detail the population from which the studied infants were drawn, which raises questions about representativeness of the samples. In 1 study (for which the source population was actually reported), of 259 patients who met inclusion criteria, only 32 had imaging and completed 12-month follow-up.[20] Entry criteria for the studies were reasonably consistent, although some studies included patients with seizures only, or with low Apgar scores but no encephalopathy.[21–23] Nine of the 32 studies in the meta-analysis included only surviving infants with HIE, which made their results potentially less relevant to questions about withdrawal of intensive care.[24–32]

Timing

Studies included in the meta-analysis varied in the timing of MRI. Some performed scans in the first days of life,[21,33–37] whereas others deferred imaging until after the first week.[24–28,38] However, the timing of imaging may be crucial if it is to be used in treatment-limitation decisions.[39] In infants with moderate or severe encephalopathy in cooling trials, the majority of deaths relating to withdrawal of treatment occurred in the first 3 or 4 days of life.[6,40] Delays in decision-making may mean that infants are no longer ventilator dependent and, consequently, lead to the survival of infants with severe impairment, or to the potential need to contemplate withdrawal of artificial nutrition.[39,41] It is not clear how relevant scans performed in nonventilated infants are to the majority of treatment-limitation decisions.

Self-fulfilling Prophecies

Many of the studies of prognosis in HIE include death as an adverse outcome. However, if treatment-withdrawal decisions are influenced by prognostic tests, then there is the potential for self-fulfilling prophecies.[42] This is a particular problem for assessing prognosis of patients with conditions in which a large proportion of deaths follow decisions to limit treatment.[42] However, in only 1 of the studies included in the systematic review was there discussion of the potential relationship between MRIs and treatment-withdrawal decisions. That study acknowledged that MRI results were available to clinicians making such decisions and potentially influenced withdrawal.[17] Thayyil et al attempted to reduce the problem by considering together outcomes of death or severe impairment, which is only a partial solution because it depends on the assumption that all infants who have treatment withdrawn would have survived with severe impairment. It also obscures a potentially relevant difference to decision-makers between death from multiorgan failure in the newborn period and survival with severe impairment.

Outcome Assessment

Studies of MRI in newborn infants have been criticized for using overly vague and nonstandardized outcome assessments.[43] Only 12 of the 32 studies included in the review reported blinding of outcome assessment to MRI results. For 19 of the studies outcome at 12 months was reported, and assessments were provided at >2 years of age for only 4. However, although severe impairment at this stage predicts later disability,[44,45] milder degrees of impairment on early developmental testing may not correlate well with school-age assessment.[46]

A particularly serious problem is that studies pooled a wide range of different outcomes together as abnormal.[43] In many studies infants were classified as having an unfavorable outcome if they had scores on developmental assessment of >1 SD below the mean.[26,27,37,47–49] Other studies included infants with any neurologic abnormality in this category.[50–54] Infants with mild developmental delay or treatable epilepsy were considered together with infants with spastic quadriplegic cerebral palsy. However, this classification yields information that is of no relevance for treatment-withdrawal decisions. Although there is no clear consensus about the exact severity of impairment that would justify allowing a newborn infant to die,[55] it would be considered universally inappropriate to withdraw intensive care from an infant with mild physical impairment or developmental delay.

QUANTITATIVE OR QUALITATIVE ASSESSMENT?

In initial experience with MRI for infants with HIE, the presence of brain injury was assessed qualitatively, noting the distribution and apparent severity of signal abnormality in different areas of the brain.[31,56,57] However, qualitative changes on MRI or diffusion-weighted imaging are potentially subjective,[10] and it is difficult to distinguish between degrees of signal abnormality or detect changes when they are present symmetrically.[58] This problem has led to considerable interest in developing quantitative markers of brain injury.

Thayyil et al found quantitative markers on spectroscopy more useful than qualitative conventional imaging.[10] Across all the studies included in the review, lactate/NAA peak/area ratios were considerably more specific than conventional MRI (95% vs 51%, respectively) but slightly less sensitive for unfavorable outcome (82% vs 91%, respectively). In the small number of studies from which both were reported and they could be compared directly, the lactate/NAA peak/area ratios again outperformed conventional MRI.

However, there are 2 problems with concluding that quantitative markers are better than qualitative ones for predicting adverse outcome in HIE. The first problem is that many of the studies of quantitative markers used thresholds or cutoff points to categorize patients into low- or high-risk groups. For example, the median cutoff for lactate/NAA peak/area ratio was 0.29, but in many studies (9 of 19 that reported quantitative markers) these thresholds seemed to be determined posthoc by selecting the point that best distinguished between patients with and without an abnormal outcome. This process potentially inflated the sensitivity and specificity of the studied variable.[59] However, Thayyil et al also calculated the threshold-independent measures Q^* and area under the curve for different MR biomarkers (derived from summary receiver operating curves).[60,61] These measures also suggested that quantitative markers were more accurate.

A second reason why qualitative markers may have fared worse in the meta-analysis is that conventional imaging results were categorized as abnormal if they included signal abnormalities in the basal ganglia, white matter, or cortex of any degree. However, the largest studies of conventional MRI have suggested that outcome is radically different between infants with mild basal ganglia or white matter changes compared with those infants with severe or widespread signal abnormality.[18,51,62] It is unsurprising, therefore, that the finding of any abnormality on conventional imaging is nonspecific for infants with HIE.

TABLE 1 Severe Patterns on Conventional MRI and Relationship to Very Adverse Outcome

Study (Year)	Severe Patterns, *n*		Nonsevere Patterns, *n*	
	Very Adverse Outcome	Other Outcome	Very Adverse Outcome	Other Outcome
Barnett et al[51] (2002)	28	4	0	36
Biagioni et al[25] (2001)	15	1	0	9
El Ayouty et al[24] (2007)	10	4	3	8
Gire et al[38] (2000)	8	2	3	5
Jyoti et al[27] (2006)	7	0	0	13
Kuenzle et al[31] (1994)	7	0	1	35
L'Abee et al[34] (2005)	14	0	0	9
Leijser et al[50] (2007)	21	4	0	27
Mercuri et al[26] (2000)	9	3	2	12
Meyer-Witte et al[23] (2008)	3	1	1	9
Robertson et al[48] (2001)	7	0	0	9
Rutherford et al[28] (1996)	32	4	1	35
Rutherford et al[63] (2010)	53	18	5	54
Van Schie et al[30] (2007)	2	4	6	20
Total	216	45	22	281

Published individual patient data are from studies identified by Thayyil et al[10] for which data extraction was possible (see Appendix 1 for details). Severe patterns included at least 1 of the following: nonfocal signal abnormality in basal ganglia, abnormality (not equivocal) in posterior limb of internal capsule, or diffuse or widespread white matter abnormality. Very adverse outcome included death, spastic quadriplegic or dystonic cerebral palsy, or severe developmental delay (>3 SDs from mean on standardized testing). Other outcome included all other outcomes.

A number of the studies of conventional imaging provided individual patient data, so it is possible to calculate the relative usefulness of these more severe patterns of injury for predicting very severe impairment or death. For the following I have also included results from a recently published substudy of the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial, which was not included in the meta-analysis.[63] Table 1 lists the relationship of severe injury to what might be termed "very adverse outcome" in studies from which data extraction was possible. Patterns of moderate or severe basal ganglia injury or severe white matter injury had a sensitivity of 91% (95% confidence interval [CI]: 84%–92%) and a specificity of 86% (95% CI: 82%–89%) for identifying infants who either died or at 12 months appeared to have spastic quadriplegic or dystonic cerebral palsy or severe developmental delay (>3 SDs from the mean) (see Appendix 1 for details of imaging patterns and outcome from the individual studies). (CIs were calculated according to the efficient-score method corrected for continuity.[64])

We can refine this analysis further by including the timing of imaging. In the studies that were performed in the first week of life (Table 2), conventional MRI had a sensitivity of 88% (95% CI: 80%–92%) and specificity of 88% (95% CI: 80%–92%). Although the numbers are small, it is also possible to look at the prognostic efficacy of conventional MRI in the first week of life in infants with moderate encephalopathy (Table 3). In this subgroup, the sensitivity of MRI was 79% (95% CI: 59%–81%) and specificity was 84% (95% CI: 68%–93%). It is not possible from published data to assess the usefulness of quantitative markers such as lactate/NAA peak/area ratio for predicting very adverse outcome as defined above or to look separately at its usefulness for infants with moderate encephalopathy.

IMPLICATIONS FOR PRACTICE

The likelihood ratio of these patterns of conventional MRI changes for very adverse outcome in infants with moderate encephalopathy is 5.0. However, there is a fairly wide CI for this from 2.3 to 10.6, corresponding to a positive predictive value ranging from 59% to 91%. Up to one-third or more of infants with such changes would not, in fact, die or have very severe impairment if treatment were continued. No comparable figure for lactate/NAA peak/area ratios is available.

Does the relatively low specificity mean that conventional MRI changes or elevated basal ganglia lactate should not be used in decisions about withdrawal of life-sustaining treatment? The answer will depend on judgments about how severe impairment needs to be for treatment withdrawal to be an option and the role of uncertainty in such decisions. It is also hard to determine which biomarker we should use. Advantages of MR spectroscopy are that it may be more accurate than conventional MRI and provides early, objective measures of

TABLE 2 Severe Patterns on Conventional MRI in the First Week of Life and Relationship to Very Adverse Outcome (Defined in Table 1)

Study (Year)	Severe Patterns, *n*		Nonsevere Patterns, *n*	
	Very Adverse Outcome	Other Outcome	Very Adverse Outcome	Other Outcome
Kuenzle et al[31] (1994)	2	0	1	26
L'Abee et al[34] (2005)	14	0	0	9
Leijser et al[50] (2007)	9	3	2	12
Meyer-Witte et al[23] (2008)	3	1	1	9
Robertson et al[48] (2001)	24	3	1	32
Rutherford et al[63] (2010)	29	8	1	21
Van Schie et al[30] (2007)	2	2	5	10
Total	83	17	11	119

TABLE 3 Infants With Moderate or Sarnat Stage 2 Encephalopathy: Severe Patterns on Conventional MRI in the First Week of Life and Relationship to Very Adverse Outcome (Defined in Table 1)

Study (Year)	Severe Patterns, *n*		Nonsevere Patterns, *n*	
	Very Adverse Outcome	Other Outcome	Very Adverse Outcome	Other Outcome
Leijser et al[50] (2007)	5	0	0	7
Robertson et al[48] (2001)	2	1	0	6
Rutherford et al[18] (1998)	13	3	1	11
Van Schie et al[30] (2007)	2	2	5	8
Total	22	6	6	32

severity of brain injury.[10,37] On the other hand, there are more available data relating specific patterns on conventional MRI to very adverse outcome.

We might also note that many of the above-mentioned limitations in evidence about prognosis in HIE also apply to other tools often used in practice, including amplitude-integrated electroencephalogram,[65,66] cranial ultrasound,[67,68] and even clinical assessment.[9,69] We should not apply different standards of evidence to MR than we do to other prognostic tools in HIE. One reasonable conclusion is that MRI should not be used in isolation. However, using a Bayesian approach, MR biomarkers might be used in combination with clinical and electrophysiological evidence to identify infants with a high level of certainty of very severe impairment. There is some evidence that MRI improves outcome prediction when added to clinical staging and electroencephalography,[25,50,70] but it is not possible from published studies to define this group clearly.

IMPLICATIONS FOR RESEARCH

The other important conclusion from the discussion above is that if we are to obtain relevant information to inform treatment decisions, there is a need to change the way that prognostic studies of HIE are performed.[71] There is a need for larger prospective studies that assess a number of different prognostic factors in the first days of life and particularly focus on infants with moderate-to-severe clinical encephalopathy. Infants enrolled onto controlled trials of neuroprotective therapies may be ideal for this purpose, because they represent a well-defined and reasonably homogenous cohort with planned and funded follow-up. Such studies would also help determine if neuroprotection influences standard prognostic assessments. One potential concern relating to the widespread adoption of therapeutic hypothermia for infants with HIE has been that it could affect the reliability of prognostic markers, particularly if testing is undertaken while infants are being cooled.[72] For example, MR relaxation times and signal intensity are affected by tissue temperature.[73] (In the TOBY substudy the predictive value of qualitative MRI was not affected by hypothermia, although it should be noted that the median postnatal age at the time of scan was 8 days.[63]) It has been suggested that prognostic studies should be registered,[74] as is now standard for randomized trials. Future meta-analysis would be strengthened by the use of individual patient data from primary studies.[71]

Studies that use continuous variables (such as quantitative biomarkers) should use cutoff points in a data-independent way.[59] The independent value of different prognostic factors should be identified by multiple regression analysis.[59] The problem of self-fulfilling prophecies may be reduced by withholding the results of new prognostic tests from clinicians, reporting and describing treatment-limitation decisions when present, and carefully following up patients from whom treatment withdrawal is contemplated but not undertaken.[42] Follow-up should be performed by using validated measures, blind to prognostic factors, identifying outcome groups in detail. Finally, when study results are reported, they should conform to guidelines for observational cohort studies.[75]

CONCLUSIONS

There are different purposes of prognostication for infants with HIE. One role is to identify infants who might benefit from neuroprotection in the newborn period. At present, given the need to identify infants soon after birth and the practical difficulties in obtaining very early imaging, MRI has little or no role here, although other biomarkers such as amplitude-integrated electroencephalography may be useful.[12,76] Second, prognostication may be used to identify infants with potentially abnormal neurodevelopment to inform parents and potentially provide targeted developmental interventions in early childhood.[77] Test results may also be used as a surrogate outcome measure in trials of interventions in the newborn period.[10] The Thayyil et al meta-analysis provided important evidence on the use of MR biomarkers for both of these purposes.

However prognostication is also critically important in the first days of life for infants with HIE to make decisions about continuation or withdrawal of life-sustaining treatment. There is a need to identify, with a high degree of accuracy, infants who will have very severe impairment if they survive. The analysis discussed above suggests that, on the basis of current evidence, MR biomarkers in isolation are not sufficiently accurate to direct treatment-limitation decisions.

Prognostication for newborn infants will probably always remain challenging because of the influence of neuronal plasticity, the social environment, and the potential for interventions in early childhood to affect outcome.[9] There may be a role for incorporating the results of qualitative or quantitative MRI with the results of other prognostic tests in decisions about treatment withdrawal. However, there is also a need for improved prognostic research in HIE. Better data about the implications of different prognostic factors including MR biomarkers would help parents and clinicians who must grapple with extremely difficult decisions.

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APPENDIX 1 Patterns of MRI Findings and Outcome Descriptions Used in Analysis

Study (Year)	Pattern on MRI Used for Classification	Very Adverse Outcome
Barnett et al[51] (2002)	Moderate or severe BG, severe WM	Death, spastic quadriplegic CP, dystonic/athetoid CP
Biagioni et al[25] (2001)	Moderate or severe BG, severe WM	Quadriplegic or dystonic CP, DQ < 50, CP unable to sit, or death
El-Ayouty et al[24] (2007)	Moderate or severe BG, severe WM	Dystonic or quadriplegic CP
Gire et al[38] (2000)	"Severe": changes involving WM or BG	Profound handicap: CP, blindness, nonaidable deafness
Jyoti et al[27] (2006)	>30% BG or >30% WM or PLIC abnormality	CP not expected to walk, or DQ < 55
Kuenzle et al[31] (1994)	Moderate or severe BG, severe WM	DQ < 55 or spastic quadriplegic CP
Leijser et al[50] (2007)	Moderate or severe BG, severe WM	Spastic quadriplegic CP or death
Mercuri et al[26] (2000)	Moderate or severe BG, severe WM, or WM with hemorrhage	Spastic quadriplegic CP or DQ < 55
Meyer-Witte et al[23] (2008)	Absent (not equivocal) PLIC on T1 or diffusely abnormal gray/white differentiation	"Severe cognitive or motor deficit"
Robertson et al[48] (2001)	Diffuse BG change or abnormal PLIC	DQ < 55 or death
Rutherford et al[28] (1996)	Abnormal BG or multiple areas of WM infarction	Dystonic/quadriplegic CP, "severe developmental delay"
Rutherford et al[18] (1998)	Bilaterally abnormal PLIC	DQ < 50, death
Rutherford et al[63] (2010)	Moderate/severe BG, severe WM, abnormal PLIC	MDI < 70 or GMFCS 3–5 or bilateral cortical visual impairment with no useful vision
van Schie et al[30] (2007)	Abnormal signal in the entire cortex and BG or abnormal PLIC	Dystonic or quadriplegic CP or DQ < 55

Studies were included from those in the meta-analysis by Thayyil et al[10] if they reported patterns of conventional MRI and included individual patient data with indication of the severity of changes in basal ganglia or white matter and outcome in sufficient detail that they could be classified into the following categories: (1) severe pattern: included at least 1 of nonfocal signal abnormality in basal ganglia, abnormality (not equivocal) in posterior limb of internal capsule, or diffuse or widespread white matter abnormality; (2) very adverse outcome: death, spastic quadriplegic or dystonic cerebral palsy, or severe developmental delay (>3 SDs from mean on standardized testing); or (3) other outcome: all other outcomes. In the TOBY study, individual patient data were not available; nevertheless, the definition of severe impairment (Gross Motor Functional Classification System 3–5, cognitive impairment >2 SDs from the mean) was sufficiently close to the one used above to include the results in this analysis. If this article is excluded, the sensitivity and specificity of conventional MRI are 91% and 89%, respectively, if performed at any time and 84% and 92%, respectively, for MRI performed in the first week. BG indicates basal ganglia; WM, white matter; CP, cerebral palsy; PLIC, posterior limb of the internal capsule; DQ, developmental quotient; MDI, Mental Development Index; GMFCS, Gross Motor Functional Classification System.

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