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ARTICLE

The Current Etiologic Profile and Neurodevelopmental Outcome of Seizures in Term Newborn Infants

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ABSTRACT

OBJECTIVES. The objectives of this study were to delineate the etiologic profile and neurodevelopmental outcome of neonatal seizures in the current era of neonatal intensive care and to identify predictors of neurodevelopmental outcome in survivors.

METHODS. Eighty-nine term infants with clinical neonatal seizures underwent neurologic examination, electroencephalography (EEG), neuroimaging, and extensive diagnostic tests in the newborn period. After discharge, all infants underwent regular neurologic evaluations and, at 12 to 18 months, formal neurodevelopmental testing. We tested the prognostic value of seizure etiology, neurologic examination, EEG, and neuroimaging.

RESULTS. Etiology was found in 77 infants. Global cerebral hypoxia-ischemia, focal cerebral hypoxia-ischemia, and intracranial hemorrhage were most common. Neonatal mortality was 7%; 28% of the survivors had poor long-term outcome. Association between seizure etiology and outcome was strong, with cerebral dysgenesis and global hypoxia-ischemia associated with poor outcome. Normal neonatal period/early infancy neurologic examination was associated with uniformly favorable outcome at 12 to 18 months; abnormal examination lacked specificity. Normal/mildly abnormal neonatal EEG had favorable outcome, particularly if neonatal neuroimaging was normal. Moderate/severely abnormal EEG, and multifocal/diffuse cortical or primarily deep gray matter lesions, had a worse outcome.

CONCLUSIONS. Mortality associated with neonatal seizures has declined although long-term neurodevelopmental morbidity remains unchanged. Seizure etiology and background EEG patterns remain powerful prognostic factors. Diagnostic advances have changed the etiologic distribution for neonatal seizures and improved accuracy of outcome prediction. Global cerebral hypoxia-ischemia, the most common etiology, is responsible for the large majority of infants with poor long-term outcome.

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Key Words
neonatal seizures, outcome, developmental delay, cerebral palsy, postneonatal seizures

Abbreviations
EEG— electroencephalography
CT— computed tomography
HI— hypoxia-ischemia
ADC—apparent diffusion coefficient
BSID-II—Bayley Scales of Infant Development II
MDI—Mental Development Index
ECMO— extracorporeal membrane oxygenation

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SEIZURES ARE THE most common and distinctive clinical manifestation of neurologic dysfunction in the newborn infant.[1] Newborn infants with seizures are at risk for neonatal death and survivors at risk for neurologic impairment, developmental delay, and later epilepsy.[1–5] Despite increasingly sophisticated neonatal intensive care, clinicians managing seizures remain challenged by difficult prognostic and therapeutic questions.[1,6]

The changing etiologic profile of neonatal seizures over the years[7–10] can be ascribed to advances in several areas. Among these are significant developments in obstetric and neonatal management that have changed the spectrum of insults to which the immature brain is exposed. In addition, more accurate etiologic diagnosis has been facilitated by advances in neurodiagnostic technology, particularly brain imaging.[11–14]

The mortality of infants developing seizures during the neonatal period has shown a decreasing trend over time. In earlier studies, the mortality was as high as 40% but decreased in subsequent reports to ~20%.[1,2,15–18] As opposed to this increase in survival, the prevalence of long-term neurodevelopmental sequelae in survivors has remained unchanged at ~30%.[1,15,19]

Previous studies have sought to define predictors of long-term outcome in newborn infants developing seizures.[20–24] The most reliable early predictors of later neurologic outcome have been the underlying etiology of the seizures and specific electroencephalography (EEG) background patterns.[4,5,7,20–22,25,26]

The aims of the current study were to describe the etiologic profile of neonatal seizures, the neurodevelopmental outcome, and reliable prognostic indicators of outcome for infants surviving neonatal seizures in the modern era.

MATERIALS AND METHODS

Patients

Our study population included all newborn infants admitted to the NICUs of Children's Hospital and Brigham and Women's Hospital in Boston, between January 1, 1997, and March 1, 2000. Eligibility criteria were a birth gestational age ≥37 weeks, clinical seizures in the neonatal period diagnosed by a child neurologist, EEG and neuroimaging (computed tomography [CT] and/or magnetic resonance imaging [MRI]) studies in the neonatal period, and at least 12 months of follow-up in our Neonatal Neurology Program. The diagnosis of neonatal seizures by the child neurologist is based either on direct observation of the clinical and/or EEG events in question or on the review of observations made by the neonatologists. Because we have a neurology consultation service dedicated to the NICU, the neurologists are called at the first suspicion of seizures. We identified cases through the careful review of our neonatology and neurology databases. During the clinical evaluation of suspected seizures, it is standard practice for the child neurologist to exclude phenomena that mimic seizures in the newborn using widely accepted criteria.[1] For example, in cases in which myoclonic events were confined to sleep, benign neonatal sleep myoclonus was specifically excluded by clinical and EEG criteria[1] before infants were considered eligible for the study. We obtained prenatal, perinatal, and neonatal data by detailed review of the maternal and infant's medical charts. This study was approved by the Institutional Review Boards of Brigham and Women's Hospital and Children's Hospital Boston.

At our center, neurologists with special expertise in neonatal neurologic conditions are involved from the outset in the diagnosis and acute management of all infants with seizures. Diagnosis of clinical neonatal seizures is based on observations by the NICU staff and confirmed by the neurologist. Clinical seizures are classified according to Volpe[1] as subtle, clonic, tonic, and myoclonic. Although many infants had more than 1 seizure type, we assigned the single most prominent seizure type to the infant in each case. In cases in which myoclonic seizures occurred only during sleep, benign neonatal sleep myoclonus was excluded by widely accepted criteria.[1] The attending neurologist performs daily neurologic examinations during the newborn period. For this study, we documented the most abnormal neurologic examination during the neonatal period.

A consistent institutional management protocol was used for neonatal seizures based on published guidelines.[1] Specifically, the first-line agent was intravenous phenobarbital, increased as needed to a maximum cumulative loading dose of 40 to 50 mg/kg. For refractory seizures, defined as persistent seizures despite a phenobarbital blood level of 40 to 50 mg/dL, we used intravenous phenytoin to a maximum of 20 mg/kg. As a third-line agent for persistent seizures, we used doses of 0.05 mg/kg lorazepam. When these measures failed to control seizure activity, 100 mg intravenous pyridoxine was administered with EEG monitoring.[1]

Etiologic Classification

We made an etiologic diagnosis based on the clinical history and examination and a uniform protocol of special laboratory tests and imaging studies. All infants with neonatal seizures undergo early EEG and neuroimaging studies (mostly MRI). We use a consistent protocol of MRI techniques for all neonatal studies, which include conventional T1/T2-weighted studies as well as diffusion-weighted sequences. These imaging studies not only enhance the accuracy of the etiologic diagnosis, but also allow inferences about the timing of the insults. Laboratory studies included serum glucose and electrolyte levels, cerebrospinal fluid studies, and arterial blood gas and acid-base analysis. When indicated, we also measured serum ammonia, urine and serum organic and

amino acid analysis, lactate and pyruvate levels. Infants with thromboembolic or hemorrhagic lesions were evaluated by a battery of coagulation studies, and if thromboembolic lesions remained unexplained, these infants underwent echocardiography.

We assigned each infant to 1 of the following 9 etiologic categories: global cerebral hypoxia-ischemia (HI), focal cerebral HI, trauma/hemorrhage, cerebral dysgenesis, transient metabolic disturbances, infection/inflammation, inborn errors of metabolism, toxins, and familial/genetic syndromes. In cases in which this comprehensive diagnostic evaluation revealed no etiology, infants were assigned to an "etiology unknown" category.

In the global cerebral HI group, we included infants with evidence for a diffuse cerebral HI insult occurring in the neonatal, intrapartum, or antepartum periods. Infants were assigned to the neonatal cerebral HI group if seizures developed after an identified postnatal acute hypoperfusion insult. The diagnosis of intrapartum cerebral HI required that 4 specific criteria be met: (1) severe metabolic acidemia (pH $\leq$ 7.0) on the umbilical cord or first neonatal blood sample, (2) 5-minute Apgar score of $\leq$6, (3) fetal distress (abnormal fetal heart rate and/or meconium-stained amniotic fluid), and (4) neonatal seizures within the first 24 hours after delivery. Fetal heart rate patterns considered abnormal were loss of variability with late decelerations and/or prolonged bradycardia. For the purposes of this study, we diagnosed antepartum cerebral HI when infants had MRI patterns typical for cerebral HI,[27–30] failed to meet our criteria for intrapartum asphyxia or neonatal HI, and had other etiologies excluded. For infants with the diagnosis of global cerebral HI, the associated encephalopathy was graded as mild, moderate, or severe.[31] In the focal cerebral HI group, we included infants with evidence on neuroimaging studies of vascular territory infarction(s).

The intracranial hemorrhage group included infants with extra-axial (epidural, subdural, and subarachnoid) hemorrhage or intraparenchymal hemorrhage. We did not distinguish in this classification between the various causes of hemorrhage (eg, coagulopathic, parturitional, traumatic, or idiopathic).

EEG Studies

All EEG studies were recorded at the bedside using a digital portable EEG machine (Nicolet Voyageur, Nicolet Biomedical Inc, Madison, WI). All studies used the 10/20 international system of electrode placement both bipolar and referential electrode montages, recording through 17 to 21 channels for a minimum duration of 30 minutes. Infants with abnormal EEG recordings on initial studies underwent at least 1 follow-up EEG examination during the neonatal period.

All initial and follow-up EEG recordings were reviewed by 2 child neurologists (H.T. and B.B.) without knowledge of the neonatal and subsequent long-term outcome data. We graded the interictal EEG background into 4 categories of abnormality using previously published criteria[22,32]: Normal studies had preserved sleep state modulation and transitions; voltage, synchrony, and symmetry appropriate for age; and age-appropriate patterns (eg, δ brushes and frontal sharp transients). Mildly abnormal recordings had preserved sleep state modulation and transitions but excessive sharp wave activity and decrease or absence of normal patterns. Moderately abnormal recordings had low voltage background activity; "dysmaturity" of more than 2 weeks for conceptional age; asymmetric voltage or frequency; excessive asynchrony for postconceptional age; and/or markedly excessive discontinuity for age. Severely abnormal recordings included those with low-voltage undifferentiated patterns; markedly discontinuous and nonreactive tracings; burst-suppression pattern, or electrocerebral inactivity. Single recordings with elements of more than 1 grade of abnormality were assigned the highest grade. Not all patients underwent prolonged recordings; therefore, to avoid bias, we did not consider electrographic seizures in our analysis.

We examined the prognostic use of the EEG background patterns by comparing long-term outcome with the worst neonatal EEG background, with the EEG background during the first 3 days (early EEG), and with the EEG background between 5 and 9 days after the onset of seizures (later EEG).

Neuroimaging Studies

All MRI was performed on either a GE 1.5-Tesla 5X or LX (GE Medical Systems, Milwaukee, WI) magnetic resonance scanner using a standard quadrature head coil. Anatomic magnetic resonance was performed using sagittal and/or axial conventional spin echo T1-weighted imaging (TR/TE = 300/14; 4-mm slice thickness/1-mm gap) and axial fast spin echo T2-weighted imaging (TR/TE/etl = 3000/126/16; 4-mm slice thickness/1-mm gap) in all neonates. Axial line scan diffusion imaging (LSDI) (TR/TE/b factor = 1258/63/750; nominal 7-mm slice thickness/0-mm gap) was also obtained. Isotropic diffusion-weighted images and apparent diffusion coefficient (ADC) maps were generated for each examination.

MRI studies were obtained using a departmental protocol of conventional T1/T2 techniques, proton density, and diffusion-weighted imaging. At our center, neonatal CT scan is used only when the critical clinical condition of the infant demands more rapid scanning or when MRI is not available. If the seizure etiology was identified by standard CT scan, infants did not always undergo MRI studies. All neuroimaging studies were interpreted by a single pediatric neuroradiologist (R.R.) without knowledge of the neonatal and subsequent long-term outcome data. We categorized CT and/or MRI examinations as normal or abnormal, and if abnormal, into extra- and/or intraparenchymal lesions. The MRI findings were also

classified according to the predominant pattern of abnormality, as follows: normal, extra-axial hemorrhage only, focal cortical abnormality, multifocal or diffuse cortical abnormality, and primarily deep gray matter abnormality with or without white matter abnormality.

Outcome Measures

At our center, all infants with a history of neonatal seizures are followed for at least the first year of life in the Neonatal Neurology Program where they are evaluated by a multidisciplinary team of experienced child neurologists, developmental psychologists, and physical therapists. In this study, we evaluated outcome by neurologic examination, developmental progress, and the presence of seizures after NICU discharge. All infants with neonatal seizures were evaluated on at least 3 occasions (ie, around 2 months, between 6 and 9 months, and between 12 and 18 months of age) in the Neonatal Neurology Program at Children's Hospital. At each visit, infants underwent a full neurologic examination by 1 of 2 child neurologists (A.d.P., J.S.) as well as a developmental assessment.

Neurologic Examination

During each of the neurologic examinations, we measured the head circumference, cranial nerve function, motor function, auditory function, and visual function.[33] Motor function was assessed by testing muscle strength, tone, posture, coordination, and reflexes (deep tendon, primitive, and postural). Motor skills were compared with those expected for age. In cases of suspected visual dysfunction, formal ophthalmology consultation was obtained. Visual impairment was diagnosed only if confirmed by ophthalmologic consultation. Neurologic function was categorized as follows: normal, if no abnormalities were identified; mild deficit, if abnormalities were present on examination but had little or no functional significance; moderate deficit, if abnormalities caused functional impairment; or severe deficit, if full-time special assistance was required.

Developmental Testing

After the first year of life, all infants underwent formal testing by an experienced developmental psychologist using the Bayley Scales of Infant Development II (BSID-II). Specifically, we used the Mental Developmental Index (MDI) of the BSID-II to measure cognitive development. We categorized MDI scores below 85 on BSID-II as indicative of delayed cognitive development.[34]

Postneonatal seizures were diagnosed if >1 afebrile and unprovoked seizures occurred after the neonatal period.

Statistical Analysis

The primary outcome variable for this study was overall outcome defined as "poor" if an infant had at least 1 of the following: moderate to severe motor deficit and/or visual impairment at the 12- to 18-month visit, significantly delayed mental performance (BSID MDI score <70), or postneonatal seizures. All other infants were considered to have a "favorable" outcome.

Patient characteristics, including EEG background activity, CT, and MRI, were compared for infants experiencing poor versus favorable outcome by using Fisher's exact test.

RESULTS

Patient Population

Over the 38-month study period, 116 infants developed neonatal seizures. Of these, we excluded 16 preterm infants from the study based on our entry criteria. Seven of the remaining 100 term infants died during the acute neonatal illness. Four infants left the Boston area and were lost to follow-up, precluding reliable long-term evaluation. The study therefore focused on the 89 surviving term infants (41 girls and 48 boys), ranging in gestational age from 37 to 42 weeks (median: 40 weeks), with a history of clinical seizures in the newborn period, followed in our Neonatal Neurology Program for at least 12 months. Birth weight in these infants ranged from 2050 to 4536 g (median: 3400 g). Although all infants were ≥37 weeks in gestation at birth, 5 infants met criteria for intrauterine growth retardation. Sixty-three infants (71%) were in-born at the Brigham and Women's Hospital; of the remaining 26 infants, who were referred from surrounding centers to Children's Hospital, 7 underwent extracorporeal membrane oxygenation (ECMO) for meconium aspiration and/or persistent pulmonary hypertension.

The onset of seizures was the first day of life in 57 infants (64%), the second or third day in 18 (20%), and after 3 days in 14 (16%). Distribution of the predominant clinical seizure type was as follows: clonic (54 [61%]), tonic (17 [19%]), subtle (12 [13%]), and myoclonic (6 [7%]). Eighty-five neonates (96%) were treated with anticonvulsant medications; all 85 infants received phenobarbital, whereas 20 infants (22%) with refractory seizures received additional phenytoin or lorazepam. Anticonvulsant medication was started before the onset of EEG recording in 67 infants and after the initial EEG in 18 cases. In our NICUs, the standard protocol is to follow a loading dose of phenobarbital with maintenance doses of 3 to 5 mg/kg per day; both the onset and dosing of maintenance phenobarbital therapy are based on measured blood levels. In addition, infants are discharged on maintenance phenobarbital with decisions for ongoing therapy based on the clinical findings at 6- to 12-week neurology follow-up.

Etiologic Classification

The distribution of etiologies for the neonatal seizures in our 89 term infants is presented in Table 1. The most

TABLE 1 **Etiologic Distribution of Clinical Neonatal Seizures (n = 89)**

	n (%)
Global cerebral HI	36 (40)
Intrapartum cerebral HI	23
Antepartum cerebral HI	10
Postnatal cerebral HI	3
Focal cerebral HI	16 (18)
Arterial infarct	13
Venous infarct	3
Intracranial hemorrhage	15 (17)
Extraparenchymal hemorrhage	11
Intraparenchymal hemorrhage	2
Combined intraparenchymal hemorrhage/extraparenchymal hemorrhage	2
Cerebral dysgenesis	4 (5)
Cortical dysplasia + agenesis of corpus callosum	2
Congenital hydrocephalus	2
Transient metabolic disturbance	3 (3)
Hypoglycemia	2
Hypocalcemia + hypomagnesemia	1
Infection	3 (3)
Bacterial meningitis	1
Herpes simplex encephalitis	1
Enterovirus encephalitis	1
Inborn error of metabolism	1 (1)
Pyridoxine dependency	1
Etiology unknown	11 (12)

common etiologies for neonatal seizures were global cerebral HI, cerebral vaso-occlusive lesions, and intracranial hemorrhage. Of note, none of our infants had toxin exposure; drug withdrawal; or familial, genetic, or syndromic causes for their seizures.

Among the 23 infants with intrapartum asphyxia, 10 had moderate and 13 had severe encephalopathy. By definition, no infant had mild encephalopathy because seizures placed infants in at least the moderate level of encephalopathy. The median 5-minute Apgar score was 5 (range: 0–6). Seventeen neonates had an umbilical cord blood pH ≤ 7.00. Neonatal cerebral HI occurred in 3 infants after circulatory insufficiency secondary to severe congenital heart disease, severe respiratory failure, or cardiac arrest.

Infants with vaso-occlusive lesions or unexplained hemorrhage were evaluated for coagulopathy. The only case of suspected thrombophilia (ie, protein C deficiency) occurred in an infant with arterial stroke. Diagnoses of extraparenchymal hemorrhage included subdural (4), subarachnoid (3), and combined (4). Among infants with no identified etiology, 6 infants had seizures around the third day, whereas in the remaining 5 infants, seizures occurred after the fifth day of life. None of these infants had a known family history of neonatal seizures, and chromosomal studies for benign familial neonatal seizures were not performed.

Overall Neurologic Outcome

By definition, the overall outcome was considered poor at the ≥12-month follow-up evaluation if significant abnormalities were present on neurologic examination or cognitive testing, or if seizures recurred after NICU discharge. Table 2 summarizes the neurologic outcome of our overall group. Among the infants with a favorable outcome, 41 (64%) infants were considered normal in all areas evaluated, whereas 23 (36%) had neurologic abnormalities on examination without apparent functional impact. Among the infants with overall poor neurologic outcome, 20 had severe and 5 had moderate neurologic impairment. Details of the neurologic findings are shown in Table 2.

Factors Associated With Outcome

Etiologic Classification and Outcome

Table 3 summarizes the neurologic impairment by seizure etiology. The statistical relationship between neonatal seizure etiology and poor outcome was highly significant ($P < .001$).

Seizure Classification and Outcome

The relationship between the type of neonatal seizure and overall outcome did not achieve statistical significance ($P = .12$). Poor outcome occurred in 8 of 17 infants (47%) with predominantly tonic seizures, 15 of

TABLE 2 **Summary of Neurologic Outcome at 1 Year of Age (n = 89)**

	n (%)
Overall outcome	
Favorable (normal/mild abnormality)	64 (72)
Poor (moderate/marked abnormality)	25 (28)
Abnormal neurologic examination	48 (54)
Mild	23 (26)
Moderate	5 (6)
Severe	20 (22)
Features of neurologic abnormality	
Abnormal head growth	22 (25)
Macrocephaly	1 (1)
Microcephaly	19 (21)
Failing head growth	2 (2)
Motor impairment	47 (53)
Abnormal motor examination	41 (46)
Spastic quadriparesis	14 (16)
Dystonic quadriparesis	6 (7)
Hypotonic quadriparesis	5 (6)
Spastic hemiparesis	8 (9)
Spastic diparesis	8 (9)
Gross motor delay (normal examination)	6 (7)
Visual impairment	8 (9)
Mild	6 (7)
Severe	2 (2)
Cognitive function, MDI in BSID-II (median: 88; range: 49–115)	
Mental impairment (MDI < 85)	34 (48)
Mild mental impairment (MDI 70–84)	15 (21)
Marked mental impairment (MDI < 70)	19 (27)
Seizures after NICU discharge	19 (21)

TABLE 3 **Outcome by Etiology of Neonatal Seizures**

Etiology (*n*)	Neurologic Impairment, *n* (%)		Cognitive Impairment (MDI), n (%)		Seizures After Intensive Care Unit Discharge, *n* (%)	Overall Outcome, *n* (%)	
	Mild–Moderate	Severe	Mild MDI 70–84	Severe MDI < 70		Favorable	Poor[a]
Global HI (36)	15 (42)	13 (36)	6 (20)	13 (43)	11 (31)	18 (50)	18 (50)
Focal HI (16)	6 (37)	0	3 (19)	0	0	16 (100)	0
Hemorrhage (15)	4 (27)	2 (13)	5 (50)	1 (10)	3 (20)	13 (87)	2 (13)
Cerebral dysgenesis (4)	0	4	0	4	3	0	4 (100)
Transient metabolic disturbance (3)	1	0	1	0	1	2	1
Infection (3)	0	1	0	1	0	2	1
Inborn error of metabolism (1)	0	0	0	0	0	1	0
Unknown etiology (11)	2	0	0	0	9	11 (100)	0

[a] The proportion of infants with poor outcome differs by etiologic subgroup ($P < .001$).

54 infants (28%) with clonic seizures, and 2 of 12 infants (17%) with predominantly subtle seizures. None of the 6 infants with predominantly myoclonic seizures had poor outcome.

Neurologic Examination and Outcome

Next we assessed the ability of the neurologic examination performed at different ages (ie, neonatal, 2 months, and 6–9 months) to predict long-term outcome at 12 to 18 months. We found the neurologic examination to have 100% sensitivity and negative predictive value at each of these time points. Specifically, any infant with a normal neurologic examination performed by a child neurologist at these times had a favorable long-term outcome. However, the converse was not true, ie, the specificity and positive predictive values of the neurologic examination in the newborn period (39% and 39%), at 2 months age (61% and 51%), and at 6 to 9 months (62% and 52%) were all low.

Neonatal EEG Studies and Outcome

The relationship between the most abnormal neonatal EEG studies and neurologic outcome is summarized in Tables 4 and 5. All infants with clinical neonatal seizures underwent EEG recordings between 1 and 14 days of age (median: 2 days). Of the 89 infants, 55 (62%) had at least 1 follow-up EEG during the neonatal period. Seventy-three patients (82%) had at least 1 abnormal EEG recording. Twenty-nine infants (33%) had electrographic seizures on at least 1 EEG.

The EEG background activity on the most abnormal neonatal study was a powerful predictor of overall outcome ($P < .001$). Normal or mildly abnormal EEG background was associated with a favorable outcome in 42 of 47 infants (89%), whereas 36% of infants with a moderately abnormal background and 82% with severely abnormal EEG background had a poor outcome. Interestingly, 18% of infants with severely abnormal EEG background had favorable outcomes. Conversely, in 3 of

TABLE 4 **Relationship Among Neonatal EEG, Neuroimaging (CT, MRI), and Overall Outcome at 1 Year of Age**

	Total, *n* (%)	Favorable Outcome, *n*	Poor Outcome, *n*	*P*
EEG background activity ($n = 89$)				<.001
Normal	21 (24)	17	4	
Mildly abnormal	26 (29)	25	1	
Moderately abnormal	31 (35)	20	11	
Severely abnormal	11 (12)	2	9	
Neuroimaging (CT/MRI) ($n = 89$)				<.001
Normal	19 (21)	18	1	
Extraparenchymal	11 (12)	10	1	
Parenchymal	59 (66)	35	24	
MRI alone ($n = 73$)				<.001
Normal	16 (23)	16	0	
Extraparenchymal lesion	5 (7)	4	1	
Parenchymal: cerebral cortex				
Focal cortical	14 (19)	14	0	
Multifocal/diffuse cortical	19 (26)	7	12	
Parenchymal: deep gray matter nuclei	19 (26)	8	11	

CT indicates computed tomography; MRI: magnetic resonance imaging.

TABLE 5 **Outcome After Global Cerebral HI ($n = 36$): Predictive Value of EEG Background (Most Abnormal EEG and After 1 Week) and MRI Findings**

EEG Background Activity	*n* (%)	Favorable Outcome	Poor Outcome	*P*
Most abnormal EEG ($n = 36$)				.02
Normal/mildly abnormal	14 (39)	11	3	
Moderate/severe abnormality	22 (61)	7	15	
1-week EEG ($n = 27$)				.12
Normal/mildly abnormal	14 (52)	8	6	
Moderate/severe abnormality	13 (48)	3	10	
MRI findings ($n = 32$)				.06
Normal	4 (13)	4	0	
Extraparenchymal lesion	0	—	—	
Focal cortical lesion	0	—	—	
Multifocal/diffuse cortical lesion	13 (41)	6	7	
Deep gray matter nuclei	15 (47)	5	10	

4 infants with normal EEG background patterns but poor outcome, MRI studies showed injury confined to the deep gray matter. When comparing normal/mildly abnormal versus moderate/severe EEG background abnormality, we found that EEG predicted outcome with a sensitivity of 80% and specificity of 66%.

Next we performed stratified analyses by etiologic classification to determine the added prognostic value of EEG background for each etiologic subgroup. The relationship between EEG background activity on the most abnormal neonatal study and outcome was examined for each etiologic class separately and was statistically significant for global HI only (83% poor outcome if moderate/severe background vs 17% if normal/mild; $P = .02$). Within the focal HI, intracranial hemorrhage, and unknown categories, the prognosis was good regardless of EEG background; other categories contained few infants.

Within the global HI group, we also compared the prognostic use of background EEG activity on early (days 1–3) EEG studies ($n = 33$); later (5–9 days) studies ($n = 27$); and the study with the most abnormal neonatal EEG background ($n = 36$). We found the most abnormal EEG recording to be predictive of the overall outcome in these infants ($P = .02$); we found no difference in prognostic value between the early and later EEG studies.

Neonatal Neuroimaging and Outcome

The relationship between the neonatal neuroimaging studies and neurologic outcome is summarized in Tables 4 and 5. All 89 infants underwent brain imaging studies (CT and/or MRI) in the acute period (median age: 5 days). Seventy-three (82%) had at least 1 MRI, whereas 16 (18%) required only CT scans. Imaging studies were normal in 19 infants (21%), 2 of whom had only CT scans. Eleven infants (12%) had extraparenchymal lesions only, whereas 59 infants (66%) had parenchymal lesions.

Not unexpectedly, infants with abnormal neuroradiologic studies (CT/MRI) were more likely to have a poor outcome than those with normal studies (36% vs 1%; $P = .001$). Only 1 infant with normal brain imaging had a poor outcome. Furthermore, infants with parenchymal brain injury were more likely to have poor outcome than those with normal studies or those with extraparenchymal injury (41% vs 0% and 9%; $P < .001$). The predictive value of MRI abnormalities was evaluated in the 73 infants with such studies. Multifocal/diffuse cortical lesions or primarily deep gray matter involvement on MRI were strongly associated with poor outcome. Outcome was favorable in infants with MRI studies that either were normal or showed extraparenchymal or focal cortical lesions.

DISCUSSION

Important diagnostic and therapeutic advances have entered the practice of neonatal intensive care in recent years. The principal aim of this study was to assess the impact of these advances on the etiology and outcome of neonatal seizures. We found certain striking differences between our population and those from previous studies, whereas in other respects, there was little if any change. The mortality associated with neonatal seizures in our infants was substantially lower than in earlier studies; in fact, the 7% mortality in our study is less than half that reported 2 decades ago.[1,3,18] The improved survival of infants with neonatal seizures in our study likely reflects advances in neonatal critical care over time, including the advent of life-support techniques such as ECMO, a rescue technique used in 7 (7.8%) of our infants. Conversely, the 28% prevalence of adverse long-term outcome and the 20% rate of later seizure recurrence[35] in our survivors are essentially unchanged from earlier studies.[1,3,18]

The large majority of seizures in our population was symptomatic of an identifiable cause from a broad spectrum of etiologies. In fact, the number of infants without identified etiologies was significantly lower than in previous studies.[8,24] In addition, there were clear differences in the relative distribution of seizures in the various etiologic categories.[7,10,24]

Cerebral HI has been the leading cause for neonatal seizures in most previous studies, although the incidence has varied, likely as a result of the inconsistent diagnostic criteria used. Although global cerebral HI remains the most common etiology for seizures in our study, there are distinct differences from previous reports.[1,8,9,36,37] First, intrapartum asphyxia was less frequently implicated in our study,[1,3,14,18,38,39] possibly because of improved obstetric management and the relatively more stringent diagnostic criteria for intrapartum asphyxia in our study.[31] Second, we diagnosed antepartum HI in a number of our infants, a diagnosis facilitated by the superior tissue resolution of MRI that allowed detection

of topographic patterns of injury[14,27,28,40–46] typical for global cerebral HI insults in animals[47,48] and at autopsy.[49] Infants were diagnosed with antepartum HI if they had these characteristic MRI patterns but failed to meet our criteria for intrapartum asphyxia, and no other cause was identified. In these infants, it is assumed that a transient global cerebral HI insult in the late antepartum period had resolved with sufficient time for recovery of, for example, metabolic acidosis before delivery.

The increased sensitivity of recent neuroimaging techniques has had other important repercussions.[50,51] In addition to reducing the frequency of seizures with unknown etiology, techniques such as diffusion-weighted MRI have enhanced the diagnosis of focal cerebral HI, particularly during the early stages of infarction when techniques such as CT scan, and even conventional MRI, may fail to identify the lesion. As experience accrues with other in vivo techniques such as proton magnetic resonance spectroscopy (^{1}H-MRS), the accuracy of diagnosis for cerebral HI and certain metabolic diseases is likely to be enhanced further.[12,52–54]

In our study, acute transient metabolic disturbances and central nervous system infections were less commonly implicated as the cause of neonatal seizures than in earlier studies.[8,55–57] In fact, seizures caused by transient metabolic disturbances (eg, hypoglycemia and electrolyte disturbances) show a 10-fold decrease compared with other reports over the past 30 years.[55–57] It is likely that improved neonatal intensive care is at least partly responsible for this trend, just as improved maternal and neonatal antimicrobial strategies are likely a reason for the marked decrease in seizures resulting from central nervous system infections.

As in earlier reports, the strongest early predictors of long-term outcome in our study were the underlying seizure etiology and EEG background patterns.[1,10,24,58] Etiologies associated with poor outcome included cerebral dysgenesis, global cerebral HI, and central nervous system infection. Conversely, infants with focal cerebral HI, transient metabolic disturbances, or idiopathic seizures had an almost universally favorable outcome. The more favorable outcome in our infants with posthemorrhagic seizures may reflect the exclusion of premature infants from our study. We found no significant relationship between the predominant clinical seizure type and outcome. This finding differs from other reports in which generalized tonic[19,59] and subtle seizures[9] have been associated with a worse outcome. The reasons for this are not certain, but one important difference between our study and these others is the fact that our study was confined to term infants, whereas these others included both preterm and term infants. Not only are generalized tonic seizures more common in the preterm infant, but they are also associated with major structural lesions such as severe intraventricular hemorrhage and hence with a worse outcome.

The prognostic value of the neurologic examination in infants is difficult to evaluate across studies because of inconsistencies in examiner expertise, diagnostic criteria, and timing of the examinations.[4,5,18,20,35,60–62] In our study, all neonatal examinations were performed daily by the attending neurologist. After ICU discharge, a consistent team of neurologists, physical therapists, and developmental psychologists in our Neonatal Neurology Program performed comprehensive evaluations at regular intervals. With this approach, we found that a normal neurologic examination during the neonatal period and early infancy predicted a uniformly favorable outcome between 12 and 18 months; conversely, an abnormal examination at these times was an unreliable predictor. Background EEG abnormalities of moderate to severe grades were strong predictors of poor outcome, as in earlier reports.[20,22,32] However, in our study, these background EEG patterns provided significant added value to prognostic power over etiology only in the global HI group, in which the most abnormal EEG background regardless of its postnatal timing was the best predictor. In fact, unlike previous reports, we found no use in considering rate of EEG recovery in infants with seizures after global HI; specifically, there was no difference in prognostic value between the early and late studies. All but 1 infant with normal neonatal brain imaging and all infants with focal cortical infarcts had a favorable long-term outcome, whereas infants with deep gray matter lesions or multifocal/diffuse cortical lesions invariably had a poor outcome.

Our findings raise several important questions. First, although our data suggest that recent advances in neonatal care are associated with a promising decrease in the mortality of infants with neonatal seizures, the long-term neurologic morbidity in survivors remains substantial and unchanged from earlier studies. Potentially, this trend is the result of sicker infants with previously lethal insults now surviving the acute illness only to manifest adverse neurologic sequelae later. Another possibility is that seizures themselves are causing brain injury despite improved overall life-support measures. Whether seizures cause additional injury to the immature brain over that attributable to the underlying etiology remains controversial.[63–71] Some studies have suggested that the immature brain is remarkably resistant to injury by even prolonged seizures.[63–68,72] Conversely, others have shown that when cerebral energy metabolism has previously been compromised by, for example, cerebral HI, ongoing seizures may contribute directly to the ultimate brain injury.[73–78] The enormous importance of this latter finding relates to our findings not only that cerebral HI insults are the leading cause of neonatal seizures, but also that 70% of infants with adverse long-term outcome had cerebral HI as the cause of neonatal seizures. This would suggest that particular urgency is warranted in controlling seizures after global HI insults. Unfortu-

nately, it is well known that post-HI seizures in the newborn are particularly refractory to conventional anticonvulsant agents,[6] even at high doses.[79] Recent data suggest that induced moderate hypothermia[80] may provide effective neuroprotection against cerebral HI injury. However, in animal studies, this neuroprotection depends on the initiation of hypothermia before the onset of seizures, which may herald closure of the therapeutic window.[81] For all of these reasons, the future reduction of long-term neurologic deficits in this population will require rapid and accurate diagnostic evaluation to identify the asphyxiated fetus and newborn followed by urgent treatment with agents that demonstrate neuroprotective efficacy in clinical trials.

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REFERENCES

1. Volpe JJ. Neonatal seizures. In: *Neurology of the Newborn*. Philadelphia, PA: WB Saunders; 2001:178–214
2. Andre M, Matisse N, Vert P. Prognosis of neonatal seizures. In: Wasterlain C, Vert P, eds. *Neonatal Seizures*. New York, NY: Raven Press; 1990:61–67
3. Scher MS, Aso K, Beggarly ME, Hamid MY, Steppe DA, Painter MJ. Electrographic seizures in preterm and full-term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. *Pediatrics.* 1993;91:128–134
4. Bye AM, Cunningham CA, Chee KY, Flanagan D. Outcome of neonates with electrographically identified seizures, or at risk of seizures. *Pediatr Neurol.* 1997;16:225–231
5. Legido A, Clancy RR, Berman PH. Neurologic outcome after electroencephalographically proven neonatal seizures. *Pediatrics.* 1991;88:583–596
6. Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med.* 1999;341:485–489
7. Rose AL, Lombroso CT. A study of clinical, pathological, and electroencephalographic features in 137 full-term babies with a long-term follow-up. *Pediatrics.* 1970;45:404–425
8. Kellaway P, Hrachovy RA. Status epilepticus in newborns: a perspective on neonatal seizures. *Adv Neurol.* 1983;34:93–99
9. Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. *Neurology.* 1987;37:1837–1844
10. Mizrahi EM, Plouin P, Kellaway P. Neonatal seizures. In: Engel JJ, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. Philadelphia, PA: Lippincott-Raven; 1997:647–663
11. Mercuri E, Cowan F, Rutherford M, Acolet D, Pennock J, Dubowitz L. Ischaemic and haemorrhagic brain lesions in newborns with seizures and normal Apgar scores. *Arch Dis Child Fetal Neonatal Ed.* 1995;73:F67–F74
12. Barkovich AJ, Westmark KD, Bedi HS, Partridge JC, Ferriero DM, Vigneron DB. Proton spectroscopy and diffusion imaging on the first day of life after perinatal asphyxia: preliminary report. *AJNR Am J Neuroradiol.* 2001;22:1786–1794
13. Barkovich AJ, Chuang SH, Norman D. MR of neuronal migration anomalies. *AJR Am J Roentgenol.* 1988;150:179–187
14. Leth H, Toft PB, Herning M, Peitersen B, Lou HC. Neonatal seizures associated with cerebral lesions shown by magnetic resonance imaging. *Arch Dis Child Fetal Neonatal Ed.* 1997;77:F105–F110
15. Lombroso CT. Prognosis in neonatal seizures. *Adv Neurol.* 1983;34:101–113
16. Dennis J. Neonatal convulsions: aetiology, late neonatal status and long-term outcome. *Dev Med Child Neurol.* 1978;20:143–148
17. Keith HM. Convulsions in children under three years of age: a study of prognosis. *Mayo Clin Proc.* 1964;39:895–907
18. Andre M, Matisse N, Vert P, Debruille C. Neonatal seizures: recent aspects. *Neuropediatrics.* 1988;19:201–207
19. Bergman I, Painter M, Hirsch R, Crumrine P, David R. Outcome in neonates with convulsions treated in an intensive care unit. *Ann Neurol.* 1983;14:642–647
20. Rowe JC, Holmes GL, Hafford J, et al. Prognostic value of the electroencephalogram in term and preterm infants following neonatal seizures. *Electroencephalogr Clin Neurophysiol.* 1985;60:183–196
21. Holmes G, Rowe J, Hafford J, Schmidt R, Testa M, Zimmerman A. Prognostic value of the electroencephalogram in neonatal asphyxia. *Electroencephalogr Clin Neurophysiol.* 1982;53:60–72
22. Holmes GL, Lombroso CT. Prognostic value of background patterns in the neonatal EEG. *J Clin Neurophysiol.* 1993;10:323–352
23. Wical BS. Neonatal seizures and electrographic analysis: evaluation and outcomes. *Pediatr Neurol.* 1994;10:271–275
24. Lombroso CT. Neonatal seizures: a clinician's overview. *Brain Dev.* 1996;18:1–28
25. Holden KR, Mellits ED, Freeman JM. Neonatal seizures. I. Correlation of prenatal and perinatal events with outcomes. *Pediatrics.* 1982;70:165–176
26. Mellits ED, Holden KR, Freeman JM. Neonatal seizures. II. A multivariate analysis of factors associated with outcome. *Pediatrics.* 1982;70:177–185
27. Barkovich AJ, Westmark K, Partridge C, Sola A, Ferriero DM. Perinatal asphyxia: MR findings in the first 10 days. *AJNR Am J Neuroradiol.* 1995;16:427–438
28. Barkovich AJ, Hajnal BL, Vigneron D, et al. Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MR scoring systems. *AJNR Am J Neuroradiol.* 1998;19:143–149
29. Barkovich AJ. Brain and spine injuries in infancy and childhood: diffuse ischemic brain injury. In: *Pediatric Neuroimaging*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:203–244
30. Martin E, Barkovich AJ. Magnetic resonance imaging in perinatal asphyxia. *Arch Dis Child Fetal Neonatal Ed.* 1995;72:F62–F70
31. Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. In: *Neurology of the Newborn.* Philadelphia, PA: WB Saunders; 2001:331–394
32. Laroia N, Guillet R, Burchfiel J, McBride MC. EEG background as predictor of electrographic seizures in high-risk neonates. *Epilepsia.* 1998;39:545–551
33. Nellhaus G. Head circumference from birth to eighteen years: practical composite international and interracial graphs. *Pediatrics.* 1968;41:106–114
34. Bayley N. *Bayley Scales of Infant Development*. 2nd ed. San Antonio, TX: Psychological Corp; 1993
35. Clancy RR, Legido A. Postnatal epilepsy after EEG-confirmed neonatal seizures. *Epilepsia.* 1991;32:69–76
36. Kellaway P, Mizrahi EM. Clinical, electroencephalographic, therapeutic, and pathophysiologic studies of neonatal seizures. In: Wasterlain CG, Vert P, eds. *Neonatal Seizures: Pathophysiology and Pharmacologic Management*. New York, NY: Raven; 1990:1–13
37. Mizrahi EM, Kellaway P. Etiology. In: *Diagnosis and Manage-*

ment of Neonatal Seizures. Philadelphia, PA: Lippincott-Raven; 1997:47–60
38. Calciolari G, Perlman JM, Volpe JJ. Seizures in the neonatal intensive care unit of the 1980s: types, etiologies, timing. *Clin Pediatr (Phila).* 1988;27:119–123
39. Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. *J Pediatr.* 1999;134:71–75
40. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet.* 2003;361:736–742
41. Biagioni E, Mercuri E, Rutherford M, et al. Combined use of electroencephalogram and magnetic resonance imaging in full-term neonates with acute encephalopathy. *Pediatrics.* 2001; 107:461–468
42. Rutherford MA, Pennock JM, Schwieso JE, Cowan FM, Dubowitz LM. Hypoxic ischaemic encephalopathy: early magnetic resonance imaging findings and their evolution. *Neuropediatrics.* 1995;26:183–191
43. Barkovich AJ. MR and CT evaluation of profound neonatal and infantile asphyxia. *AJNR Am J Neuroradiol.* 1992;13:959–972; discussion 973–975
44. Roland EH, Poskitt K, Rodriguez E, Lupton BA, Hill A. Perinatal hypoxic-ischemic thalamic injury: clinical features and neuroimaging. *Ann Neurol.* 1998;44:161–166
45. Barkovich AJ, Truwit CL. Brain damage from perinatal asphyxia: correlation of MR findings with gestational age. *AJNR Am J Neuroradiol.* 1990;11:1087–1096
46. Pasternak JF, Gorey MT. The syndrome of acute near-total intrauterine asphyxia in the term infant. *Pediatr Neurol.* 1998; 18:391–398
47. Myers RE. Two patterns of perinatal brain damage and their conditions of occurrence. *Am J Obstet Gynecol.* 1972;112: 246–276
48. Myers RE. Four patterns of perinatal brain damage and their conditions of occurrence in primates. *Adv Neurol.* 1975;10: 223–234
49. Leech R, Alvord E. Anoxic-ischemic encephalopathy in the human neonatal period: the significance of brain stem involvement. *Arch Neurol.* 1977;34:109–113
50. Bangert BA. Magnetic resonance techniques in the evaluation of the fetal and neonatal brain. *Semin Pediatr Neurol.* 2001;8: 74–88
51. Cowan FM, Pennock JM, Hanrahan JD, Manji KP, Edwards AD. Early detection of cerebral infarction and hypoxic ischemic encephalopathy in neonates using diffusion-weighted magnetic resonance imaging. *Neuropediatrics.* 1994;25:172–175
52. Zarifi MK, Astrakas LG, Poussaint TY, Plessis Ad A, Zurakowski D, Tzika AA. Prediction of adverse outcome with cerebral lactate level and apparent diffusion coefficient in infants with perinatal asphyxia. *Radiology.* 2002;225:859–870
53. Soul JS, Robertson RL, Tzika AA, du Plessis AJ, Volpe JJ. Time course of changes in diffusion-weighted magnetic resonance imaging in a case of neonatal encephalopathy with defined onset and duration of hypoxic-ischemic insult. *Pediatrics.* 2001; 108:1211–1214
54. Pavlakis SG, Kingsley PB, Harper R, et al. Correlation of basal ganglia magnetic resonance spectroscopy with Apgar score in perinatal asphyxia. *Arch Neurol.* 1999;56:1476–1481
55. Keen JH. Significance of hypocalcaemia in neonatal convulsions. *Arch Dis Child.* 1969;44:356–361
56. Friedman M, Hatcher G, Watson L. Primary hypomagnesaemia with secondary hypocalcaemia in an infant. *Lancet.* 1967; 1(7492):703–705
57. Griffiths AD. Association of hypoglycaemia with symptoms in the newborn. *Arch Dis Child.* 1968;43:688–694
58. Scher MS. Neonatal seizures. In: Wyllie E, ed. *The Treatment of Epilepsy*. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:577–599
59. Brunquell PJ, Glennon CM, DiMario FJ Jr, Lerer T, Eisenfeld L. Prediction of outcome based on clinical seizure type in newborn infants. *J Pediatr.* 2002;140:707–712
60. Ellison PH, Largent JA, Bahr JP. A scoring system to predict outcome following neonatal seizures. *J Pediatr.* 1981;99: 455–459
61. Ortibus EL, Sum JM, Hahn JS. Predictive value of EEG for outcome and epilepsy following neonatal seizures. *Electroencephalogr Clin Neurophysiol.* 1996;98:175–185
62. Mizrahi EM, Clancy RR, Dunn JK, et al. Neurological impairment, developmental delay, and postneonatal seizures 2 years after EEG-video documented seizures in near-term and term neonates: report of Clinical Research Centers for Neonatal Seizures [abstract]. *Epilepsia.* 2001;42(suppl 7):102–103
63. Albala BJ, Moshe SL, Okada R. Kainic-acid-induced seizures: a developmental study. *Brain Res.* 1984;315:139–148
64. Nitecka L, Tremblay E, Charton G, Bouillot JP, Berger ML, Ben-Ari Y. Maturation of kainic acid seizure-brain damage syndrome in the rat. II. Histopathological sequelae. *Neuroscience.* 1984;13:1073–1094
65. Stafstrom CE, Chronopoulos A, Thurber S, Thompson JL, Holmes GL. Age-dependent cognitive and behavioral deficits after kainic acid seizures. *Epilepsia.* 1993;34:420–432
66. Stafstrom CE, Thompson JL, Holmes GL. Kainic acid seizures in the developing brain: status epilepticus and spontaneous recurrent seizures. *Brain Res Dev Brain Res.* 1992;65:227–236
67. Hirsch E, Baram TZ, Snead OC 3rd. Ontogenic study of lithium-pilocarpine-induced status epilepticus in rats. *Brain Res.* 1992; 583:120–126
68. Liu Z, Gatt A, Werner SJ, Mikati MA, Holmes GL. Long-term behavioral deficits following pilocarpine seizures in immature rats. *Epilepsy Res.* 1994;19:191–204
69. Cataltepe O, Vannucci R, Heitjan D, Towfighi J. Effect of status epilepticus on hypoxic-ischemic brain damage in the immature rat. *Pediatr Res.* 1995;38:251–257
70. Franck JE, Schwartzkroin PA. Immature rabbit hippocampus is damaged by systemic but not intraventricular kainic acid. *Brain Res.* 1984;315:219–227
71. Wasterlain CG. Recurrent seizures in the developing brain are harmful. *Epilepsia.* 1997;38:728–734
72. Camfield PR. Recurrent seizures in the developing brain are not harmful. *Epilepsia.* 1997;38:735–737
73. Wirrell EC, Armstrong EA, Osman LD, Yager JY. Prolonged seizures exacerbate perinatal hypoxic-ischemic brain damage. *Pediatr Res.* 2001;50:445–454
74. Young RS, Osbakken MD, Briggs RW, Yagel SK, Rice DW, Goldberg S. 31P NMR study of cerebral metabolism during prolonged seizures in the neonatal dog. *Ann Neurol.* 1985;18: 14–20
75. Young RS, Petroff OA, Chen B, Gore JC, Aquila WJ. Brain energy state and lactate metabolism during status epilepticus in the neonatal dog: in vivo 31P and 1H nuclear magnetic resonance study. *Pediatr Res.* 1991;29:191–195
76. Chapman AG, Meldrum BS, Siesjo BK. Cerebral metabolic changes during prolonged epileptic seizures in rats. *J Neurochem.* 1977;28:1025–1035
77. Yager JY, Brucklacher RM, Vannucci RC. Cerebral energy metabolism during hypoxia-ischemia and early recovery in immature rats. *Am J Physiol.* 1992;262:H672–H677
78. Palmer C, Brucklacher RM, Christensen MA, Vannucci RC. Carbohydrate and energy metabolism during the evolution of hypoxic-ischemic brain damage in the immature rat. *J Cereb Blood Flow Metab.* 1990;10:227–235
79. Mizrahi E. Consensus and controversy in the clinical management of neonatal seizures. *Clin Perinatol.* 1989;16:485–500

80. Battin MR, Dezoete JA, Gunn TR, Gluckman PD, Gunn AJ. Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. *Pediatrics.* 2001;107:480–484

81. Gunn AJ, Bennet L, Gunning MI, Gluckman PD, Gunn TR. Cerebral hypothermia is not neuroprotective when started after postischemic seizures in fetal sheep. *Pediatr Res.* 1999;46:274–280

PRE-IMPLANTATION GENETIC DIAGNOSIS

"According to a 2004 survey by the Genetics and Public Policy Center at Johns Hopkins University, about two-thirds of the respondents approved of the use of pre-implantation genetic diagnosis (PGD) to prevent a fatal childhood disease and for tissue matching to save a sibling, said Kathy Hudson, the center's director. The procedure was first successfully performed in humans in 1989 in London, after years of animal testing. It is currently performed in about 10 percent of in vitro fertilization (IVF) procedures annually in the United States. (Some 100,000 IVF cycles were performed as of 2002, the most recent year to have complete statistics.) The test adds an estimated $2,000 or more to the already high cost of IVF, which can range from $7,000 to $10,000 for each attempt. A majority of women turning to PGD are those over 35 and have a high risk of having offspring with chromosomal abnormalities, like Down syndrome. Without PGD, many women over 35 get an amniocentesis around the 15th week of pregnancy to test for disabling genetic disease. If a disease is found, the couple then faces the choice of having an abortion or bearing the child. Andrew R. LaBarbera, scientific director of the American Society of Reproductive Medicine, said, 'That's very distasteful for many people who don't have a problem undergoing PGD to avoid this situation.' Also using the procedure are couples who are carriers of single-gene disorders like cystic fibrosis, fragile X, and Tay-Sachs disease. These couples have an extremely high risk of passing the disease on to their children and may have already given birth to a child with the disease. Tests can be given for more than 100 single-gene disorders. PGD is performed when an embryo has only six to eight cells, called blastomeres." [Editor's Note: This does not kill the embryo.]

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The Current Etiologic Profile and Neurodevelopmental Outcome of Seizures in Term Newborn Infants

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