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MRI and Ultrasound Injury in Preterm Infants with Seizures

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Abstract

The utility of magnetic resonance imaging (MRI) as a universal screening tool in preterm infants has been contested; however, MR is increasingly used in investigation of neonatal seizures. We evaluated 236 infants <34 weeks gestation at birth. Seizures were documented according to clinical standard of care. Infants were imaged using MRI and head ultrasound during the neonatal period. A neuroradiologist and ultrasonologist performed detailed reviews of the images. Nine infants (3.8%) had clinical suspicion of seizures during the hospital course. MRI was abnormal in each case (three with intraventricular hemorrhage (IVH) and periventricular hemorrhagic infarct, two with findings of hypoxia-ischemia, three with white matter injury (WMI) and one each with schizencephaly and dysplasia –one infant had two lesions). Periventricular hemorrhagic infarct was more common in infants with seizures (33% vs 6% of those without seizures, OR 8.23, 95% CI 1.8-36.7). Infants with seizures were more likely to have WMI, though the difference was not significant (RR 2.4, 95% CI 0.54-11.1, P=0.3). Head ultrasound failed to detect the extent of brain abnormality in eight (89%) of the infants. In this large cohort, infants with clinical suspicion of seizures had a high rate of MRI abnormalities that were not as well characterized by head ultrasound. MRI may be the study of choice for evaluating preterm infants with seizures. Further studies using better seizure monitoring are necessary to evaluate electrographic seizures and their relationship to brain injury on MRI.

Keywords (MeSH)

Infant, premature; Seizures; Magnetic resonance imaging

INTRODUCTION

According to the Centers for Disease Control, the rate of preterm delivery has increased steadily over the last decade and now accounts for 12.5% of births in the United States.¹ Although advances in medical care have resulted in decreased mortality of infants born preterm, survivors remain at risk for a broad range of neurodevelopmental disabilities

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including cerebral palsy, mental retardation, visual and hearing impairment, as well as more subtle impairments in attention, learning and coordination.²

Seizures are an important risk factor for adverse outcome in preterm newborns, likely as a result of the high rate of underlying brain injury. Past studies have used ultrasound, computed tomography (CT), and post-mortem pathology to show that intraventricular hemorrhage, hypoxic-ischemic injury and stroke are the most common brain lesions seen in preterm infants with seizures.³⁻⁷ However, up to 30% of preterm infants with seizures in these series have no pathology detected by these modalities.^{6,8,9}

Although magnetic resonance imaging (MRI) has increased sensitivity for brain injury when compared with head ultrasound,^{10,11} its utility as a universal screening tool has been contested.¹² The purpose of this study was to compare the incidence and type of brain abnormality detected by MRI and ultrasound in a large cohort of prematurely born neonates with seizures.

METHODS

The study subjects were infants <34 weeks gestation at birth who were admitted to the intensive care unit at the University of California, San Francisco Medical Center and enrolled into a cohort study examining MRI predictors of neurodevelopmental outcome. Exclusion criteria were (1) clinical evidence of a congenital malformation or syndrome and (2) ultrasound evidence of a large (> 2cm) parenchymal hemorrhagic infarction. Infants were studied only after informed parental consent. The Committee for Human Research at UCSF approved the study protocol.

Two hundred and fifty-seven infants were enrolled between April 1998 and June 2008. Twenty-one infants were withdrawn or not adequately imaged and, therefore, 236 were evaluated for this study. Medical management of the infants including clinical investigations (e.g. electroencephalogram) and treatment (e.g. anti-seizure medication) was at the discretion of the treating physician.

Clinical Data Collection

Trained neonatal research nurses prospectively extracted clinical data from the medical records. Perinatal variables included gestational age at birth, birth weight and type of gestation (single versus multiple). Gestational age was calculated based on the last menstrual period or early ultrasound (< 24 weeks). In cases where the difference between the two methods exceeded seven days, the ultrasound date was used.

Electroencephalogram

Video-EEG was recorded using a NicoletOne video-EEG monitoring system capable of capturing synchronized video images and digital EEG data according to the international 10-20 system, modified for neonates. Tracings were recorded at 15 mm/s with a sensitivity of 7 microvolts/mm. Archived electroencephalograms recorded after 2004 (six of nine) were examined for continuity, synchrony, symmetry and presence of electrographic seizures¹³ by a pediatric neurophysiologist with special interest in neonatal EEG (JS). For studies recorded prior to 2004, the initial report was reviewed and reinterpreted.

Ultrasound

Ultrasound was performed according to standard clinical protocol on day of life three or seven and weekly for infants with significant hemorrhage or at one month of life for those without abnormality. In all but two cases, ultrasound was performed within 72 hours of

MRI. Images were acquired in the sagittal, parasagittal and coronal planes via the anterior fontanel and postero-lateral fontanel using a multifrequency transducer (5-8.5 MHz) as previously described.¹¹ Images from the studies prior to and after the MRI for infants with seizures were reviewed by a single ultrasonologist (RG).

Magnetic Resonance Imaging

MR images were acquired using a 1.5 Tesla scanner (General Electric Signa or Siemens Avanto) and a specialized, high-sensitivity neonatal head coil, built into an MR compatible incubator (a General Electric prototype or Lammers Medical Technologies). Image sequences included axial spin-echo T2-weighted and coronal volumetric 3D spoiled gradient echo T1-weighted images, acquired as previously reported.¹⁴ If necessary, infants were sedated according to institutional guidelines.

Two neuroradiologists, masked to the subjects' clinical condition, evaluated the MR images at the time of enrollment. A neuroradiologist (AJB) reviewed imaging for infants with seizures in detail for the purpose of this study. Each of the scans was evaluated for focal and diffuse white matter injury, intraventricular and parenchymal hemorrhage, ventriculomegaly and cortical or deep grey matter injury or abnormality. Focal white matter injury was graded using a validated four-point scale.¹⁵ White matter was considered "normal" if there were no white matter abnormalities. The scan was graded as "minimal" white matter injury if there were three or fewer areas of T1 signal abnormality each less than two millimeters. Injury was considered "moderate" if there were more than three areas of T1 signal abnormality or if these areas measured more than two millimeters but less than five percent of the hemisphere was involved, and "severe" if more than five percent of the hemisphere was affected. Newborns were diagnosed with mild ventriculomegaly if the largest atrial ventricular diameter (at the level of the glomus of the choroid plexus) measured 8-10mm and moderate/severe if it measured greater than 10mm. Intraventricular hemorrhage was graded according to standard criteria.^{16,17}

Neurodevelopmental Follow-Up

All infants enrolled in the study were evaluated periodically in the High Risk Infant Follow-up Clinic and/or Pediatric Neurology clinic at UCSF.

A developmental psychologist who was blinded to the neonatal course examined the children using the Bayley Infant Neurodevelopmental Screener for children younger than 11.5 months, the Bayley Scales of Infant and Toddler Development (3rd edition) for children 11.5 months to 3.5 years of age and the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI) for children 3.5 to 6 years, or Wechsler Intelligence Scale for Children III-IV (WISC) for children older than 6.

A neuromotor score was assigned by a neurologist or developmental pediatrician as follows: (0) normal exam, (1) abnormal tone or reflexes or persistent primitive reflexes, (2) abnormal tone and reflexes, (3) decreased power in addition to tone/reflex abnormality, (4) cranial nerve involvement plus any motor abnormality and (5) cranial nerve involvement plus spastic quadriparesis.¹⁸ A score of 2 reflects an abnormal neurological examination without functional impairment whereas a score of 3 or higher suggests functional impairment and/or cerebral palsy.

Statistical Analysis

Statistical analysis was performed using Stata 9.2 software (Stata Corp., College Station, Texas). Differences between clinical predictors were assessed using two-tailed student's *t*-test for continuous variables and Chi Square or Fisher exact for categorical variables. The

association between seizures and brain injury was assessed using logistic regression. $P \leq 0.05$ was considered significant.

RESULTS

Clinical Characteristics

Of the 236 infants enrolled and imaged according to protocol during the study period, nine (3.8%) had clinical seizures. Among infants with seizures, the average gestational age at birth was 27.5 (± 2.9) weeks, the average birth weight was 1124.9 (± 469.6) grams and 56% were male (Table 1A). There were no apparent differences in these clinical characteristics when comparing infants with and without seizures ($P \geq 0.4$).

Seizures and Electroencephalogram

Nine newborns (3.8%) had clinical seizures documented during the hospital admission. Median timing of onset was day of life four (range 0-30)(Table 1B). All but one infant was treated with phenobarbital. Seizure semiology was most commonly myoclonic (three infants), focal clonic (two infants) or tonic (one infant). In two infants, seizure was suspected on the basis of unexplained autonomic signs. In one infant, the description was not adequate to classify the semiology. All subjects were evaluated using EEG (with prolonged EEG greater than two hours or multiple recordings in five infants). EEG was excessively discontinuous for gestational age in five (with myoclonic jerks and uncertain electrographic correlate in one), confirmed electrographic seizure in one and normal in three. None of the infants without clinical suspicion of seizures were evaluated using EEG.

Magnetic Resonance Imaging

The MRI was abnormal in all infants with seizures (Figure 1, Table 1C). Three infants had intraventricular hemorrhage with periventricular hemorrhagic infarct, one of whom also had clear evidence of increased T1 and decreased T2 signal intensity in the ventrolateral thalamus and basal ganglia in keeping with hypoxic ischemic injury and another who had questionable edema in the basal ganglia and thalami bilaterally. One infant had severe basal ganglia and thalamic signal change on T1 and T2 consistent with hypoxic-ischemic injury, which was consistent with the clinical perinatal history. Two subjects had severe white matter injury and a history of infection. One child with a history of *Candida* infection had multifocal enhancing cerebral white matter injury consistent with *Candida* encephalitis. The second child had diffuse plus focal white matter injury and culture positive *Staphylococcus aureus* sepsis. One child had severe diffuse posterior predominant white matter and cortical injury felt to be consistent with intrauterine infection (evaluation non-diagnostic). Finally, there were two developmental abnormalities: one infant had a left frontal cortical dysplasia and another had a right occipital schizencephaly.

Of the 13 infants with periventricular hemorrhagic infarct, three (19%) had clinical seizures. Intraventricular hemorrhage with periventricular hemorrhagic infarct was common in infants with seizures (33% vs 6% of those without seizures, OR 8.23, 95% CI 1.8-36.7).

The T1-weighted imaging was of high enough quality to assess for areas of focal white matter abnormality in 231 infants (including seven with seizures). Of the 56 infants with moderate/severe focal white matter injury, three (5%) had seizures. Infants with seizures were more likely to have focal white matter injury graded as moderate or severe (43% vs 24%), though the difference was not significant (OR 2.4, 95% CI 0.54-11.1, $P=0.3$).

Ultrasound Findings

The ultrasound was performed within 72 hours of the MRI in all but two cases (neither with evidence of acute injury on MRI or US). The head ultrasound was abnormal in all infants, however identified the full extent of injury present on MRI in only one case (subject E, IVH with periventricular hemorrhagic infarct with ventriculomegaly and bilateral subdural hemorrhages). Ultrasound was accurate for detecting IVH and periventricular hemorrhagic infarct; however, it failed to adequately identify and characterize white matter injury, basal ganglia/thalamic injury and malformations (cortical dysplasia and schizencephaly). In one case, white matter increased echogenicity detected on ultrasound was not seen on MRI.

Outcome

One infant with IVH plus periventricular hemorrhagic infarct and hypoxic ischemic brain injury died following transition to comfort care. The remainder survived to hospital discharge. Of the eight surviving patients, six have been evaluated in the UCSF High Risk Infant Follow-Up Program. The two remaining patients, who are not yet old enough to be evaluated with formal developmental testing, were assessed in the Pediatric Neurology clinic at UCSF.

The mean age of follow up for the eight patients was 24 months (range 2-60 months). Overall 62.5% had an abnormal neurologic examination. Three had a neuromotor score (NMS) of 0 (i.e. normal neurologic exam) at time of follow up, two had mild neurologic abnormality without functional impairment (NMS 1 or 2), and three had moderate motor impairment and/or cerebral palsy (NMS 3). Formal developmental evaluation was performed in four children at a mean age of 33 months (range 22-42 months). The developmental scores were all within the normal range, with a mean of 101.5 (range 91-110). Two additional children without formal developmental testing had abnormal cognitive evaluations, one with a high risk BINS screening at 9 months and another who was unable to be formally evaluated due to autistic features who has severe cognitive impairment in kindergarten.

DISCUSSION

Four percent of infants enrolled in our study of MR imaging in preterm newborns <34 weeks gestation at birth had clinical seizures. The etiology in this population was heterogeneous, and all infants had abnormal neuroimaging by MRI and ultrasound. Periventricular hemorrhagic infarct with intraventricular hemorrhage and hypoxia-ischemia were the most common etiologies. Two infants with infection had only focal or multifocal white matter injury and no obvious cortical injuries.

Our findings are in keeping with past studies showing that preterm and low birth weight infants have a high risk of seizures. The rate of seizures is at the lower end of the 4-27% range that has been detected in past single-center studies.³⁻⁷ This lower incidence may be related to the fact that infants with large periventricular hemorrhagic infarcts detected by ultrasound were excluded from the study. Past studies have also found that seizures frequently reflect significant underlying brain injury. Hypoxic-ischemic injury, intracranial infection, malformation and intraventricular and intraparenchymal hemorrhage were also the most common causes of seizures in preterm infants in prior case series.³⁻⁷

In this small series, the full extent of brain abnormalities was not well characterized by head ultrasound in eight of nine cases. Past studies comparing head ultrasound with MRI have found that ultrasound often fails to detect white matter injury.^{10,11,19} We also found that ultrasound was similarly insensitive to injury to in the basal ganglia, thalamic and cerebral cortex. The clinical implications of the differences in sensitivity are not known, though

white matter injury, as characterized using MRI, has been associated with increased risk for adverse neurodevelopmental outcome.^{14,20} In this series of infants with clinical seizures, a neurologist (HCG) and neonatologist (SLB) judged the difference between MRI and ultrasound findings significant enough to suggest a change in parent counseling in seven of nine cases, though this may be related to our clinicians' familiarity with MRI over ultrasound.

This study includes a large cohort of preterm infants with high-quality imaging using MRI and ultrasound in the newborn period. However, the data are limited significantly by the fact that seizures were detected clinically and there was a lack of standardized EEG monitoring. In newborns, almost any abnormal movement can be due to seizure, and electrographic seizures frequently do not have a clinical correlate.^{21,22} It is therefore likely that some infants in our cohort had seizures that went undetected and/or some of the events we recorded as clinical seizures were without electrographic correlate. In spite of this limitation, clinical seizures were associated with a high rate of MRI abnormality beyond what was detected by ultrasound, and therefore are important even in the absence of confirmed EEG correlates.

MRI can be performed safely in the newborn period and has increased sensitivity for brain injury when compared with head ultrasound.^{10,11} However, its use involves increased cost, as well as specialized equipment and personnel to ensure safety during transport and imaging. Furthermore, some have argued that the results may not change parent counseling or recommendations for interventions.¹² De Vries and Cowan have suggested that head ultrasound and MRI are complementary modalities, with ultrasound as an especially useful tool in the early days, when the infant is unstable for transport and ultrasound findings may be sufficient for major clinical decisions. They recommend MRI at term equivalent age for infants with white matter injury on ultrasound, poor brain growth, abnormal cerebellum, severe clinical course or abnormal symptomatology.²³ Others have suggested specific indications for MRI including IVH grade III and periventricular hemorrhagic infarction, cystic periventricular white matter damage, cerebellar hemorrhage, suspected white matter abnormalities, post-hemorrhagic hydrocephalus, abnormal neurologic examination, or suspected structural abnormality or inborn error of metabolism.²⁴ Given the results from this study, we propose that a clinical suspicion of seizures is an additional important indication for MRI in infants born preterm. Our study was not designed to assess the optimal timing for imaging in preterm infants with seizures.

Preterm infants with seizures have high rates of cerebral palsy, mental retardation and learning disorders.^{9,25-27} While, in many cases, the underlying brain injury likely accounts for the adverse outcome, there is accumulating evidence from animal models the seizures themselves may also be harmful to the developing brain (reviewed in²⁸⁻³⁰). Further studies using MRI with standardized EEG monitoring in preterm infants will be necessary to better characterize the types of brain lesions associated with electrographic and confirmed clinical seizures, as well as the indications and optimal timing for performing MRI.

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Figure 1. Neonatal magnetic resonance imaging in nine preterm infants with clinical seizures

- A) 24-week male with seizures in the first week of life. Axial T2-weighted image at 25 weeks postmenstrual age (PMA) shows bilateral intraventricular hemorrhage (IVH) with parenchymal hemorrhage involving the basal ganglia and periventricular white matter on the left and caudate on the right with ventriculomegaly. Signal change in the thalami and basal ganglia in keeping with edema and possible hypoxic-ischemic injury.
- B) 24-week male with seizures in the 3rd week of life. Axial T2-weighted image at 36 weeks PMA shows right occipital schizencephaly.
- C) 24-week male with seizures on the first day of life. Axial T1-weighted image at 29 weeks PMA shows extensive posterior white matter and cortical injury with reduced gyrification suggestive of congenital infection or intrauterine toxin exposure.
- D) 25-week male with seizures on the day of birth. Axial T2-weighted image at 27 weeks PMA shows left IVH with parenchymal hemorrhagic infarct involving the peritrigonal area, plus right intraventricular hemorrhage with ventriculomegaly. Signal change in basal ganglia in keeping with hypoxic-ischemic injury.
- E) 28-week male with seizures on the 4th day of life. Axial T2-weighted image at 29 weeks PMA shows right IVH with hemorrhagic infarct and ventriculomegaly. Additional smaller left-sided intraventricular and parenchymal hemorrhages were also present.
- F) 28-week male with seizures and *Candida* sepsis during the 3rd week of life. Axial T1-weighted image at 33 weeks PMA shows numerous focal areas of white matter hyperintensity, many of which were enhancing.
- G) 29-week female with birth asphyxia and seizures on the 4th day of life. Axial T2-weighted image at 30 weeks PMA shows diffuse white matter injury with reduced signal in the ventrolateral thalami and basal ganglia, in keeping with hypoxic-ischemic injury.
- H) 31-week female with seizure and *Staphylococcus aureus* sepsis during the 4th week of life. Axial T2-weighted image at 36 weeks PMA shows diffuse and focal (arrow) white matter injury.
- I) 31-week male with seizures on the first day of life. Axial T1-weighted image at 32 weeks PMA shows left frontal dysplasia (arrow).

Table 1A

General clinical characteristics and outcome for nine preterm infants with seizures.

Subject	General Characteristics	Outcome
A	GA: 24 1/7 wk; singleton; BW 680 g	NMS 1 Not testable due to autistic behaviors and cortical visual impairment; severe cognitive impairment (5yr)
B	GA: 24 3/7; singleton; BW 690 g	NMS 0 BSID III cognitive score: 105 (3yr 3mo)
C	GA: 24 6/7; singleton; BW 603 g	NMS 2 (2 mo)
D	GA: 25 wk; singleton; BW 841 g	Died at 3 wk following transition to comfort care
E	GA: 28 2/7 wk; singleton; BW 1190 g	NMS 3 BSID III cognitive score: 100 (2yr 6mo)
F	GA: 28 3/7; singleton; BW 1050 g	NMS 0 FSIQ: 91 (3yr 6mo)
G	GA: 29 6/7; singleton; BW 1560 g	NMS 3 BINS: high risk (9mo)
H	GA: 31 1/7; twin; BW 1630 g	NMS 3 BSID III cognitive score: 110 (1yr, 10mo)
I	GA: 31 2/7; singleton; BW 1880 g	NMS 0 (2mo)

GA indicates gestational age; **BW**, birth weight; **NMS** Neuromotor score, where 0 indicates normal examination, 1 abnormal tone or reflexes, 2 abnormal tone and reflexes, and 3 abnormal tone, reflexes and power; **BSID III** Bayley Scales of Infant Development, 3rd edition; **MDI**, Mental Developmental Index; **FSIQ** Wechsler Intelligence Scale for Children full-scale IQ; **BINS** Bayley Infant Neurodevelopmental Screen.

Table 1B

Seizure characteristics and electroencephalogram (EEG) findings for nine preterm infants with seizures.

Subject	Seizure Onset (days)	Seizure Semiology	EEG
A	7	• Episodic blood pressure instability	• Normal
B	24	• Focal clonic (hemiconvulsive)	• Electrographic seizures
C	1	• Myoclonic (multifocal)	• Normal
D	0	• Myoclonic (generalized)	• Excessively discontinuous for gestational age • Myoclonic jerks with uncertain electrographic correlate
E	4	• Apnea	• Excessively discontinuous for gestational age • Asymmetry suggesting right hemisphere dysfunction
F	26	• Unknown	• Normal
G	4	• Focal clonic (multifocal) and motor automatisms (oral-buccal-lingual movements)	• Excessively discontinuous for gestational age
H	30	• Myoclonic (multifocal)	• Excessively discontinuous for gestational age
I	1	• Generalized tonic	• Normal

Table 1C

Magnetic resonance imaging (MRI) and head ultrasound (US) findings for nine preterm infants with seizures.

Subject	MRI Findings	US findings
A	<ul style="list-style-type: none"> Bilateral IVH + periventricular hemorrhagic infarct (left > right) Ventriculomegaly Edema of the basal ganglia and thalami bilaterally 	<ul style="list-style-type: none"> Bilateral IVH + periventricular hemorrhagic infarct (left > right) Ventriculomegaly
B	<ul style="list-style-type: none"> Occipital schizencephaly 	<ul style="list-style-type: none"> Diffuse, mild increased echogenicity of periventricular white matter
C	<ul style="list-style-type: none"> Severe, symmetric white and grey matter injury of bilateral posterior temporal/parietal/occipital white and grey matter Ventriculomegaly Severely delayed sulcation 	<ul style="list-style-type: none"> Poorly defined periventricular and cortical abnormalities Ventriculomegaly
D	<ul style="list-style-type: none"> Bilateral IVH + right periventricular hemorrhagic infarct Ventriculomegaly Increased T1 signal in the ventrolateral thalami in keeping with hypoxic-ischemic injury 	<ul style="list-style-type: none"> Bilateral IVH with echogenicity suggesting hemorrhagic infarct on the right and possibly the left Ventriculomegaly
E	<ul style="list-style-type: none"> Bilateral IVH + periventricular hemorrhagic infarct (right > left) Bilateral subdural hemorrhage Ventriculomegaly 	<ul style="list-style-type: none"> Bilateral IVH + periventricular hemorrhagic infarct (right > left) Bilateral subdural hemorrhage Ventriculomegaly
F	<ul style="list-style-type: none"> Bilateral subependymal hemorrhage Mild ventriculomegaly Numerous bilateral multifocal punctate enhancing T1 hyperintense white matter lesions in keeping with <i>Candida</i> microabscess 	<ul style="list-style-type: none"> Resolving subependymal hemorrhages Borderline left ventriculomegaly Few parenchymal echogenic foci, non-specific in appearance
G	<ul style="list-style-type: none"> Bilateral subependymal hemorrhages Increased T1 and decreased T2 signal in the ventrolateral thalami and basal ganglia in keeping with hypoxic-ischemic injury Diffuse white matter injury 	<ul style="list-style-type: none"> Bilateral subependymal hemorrhages Echogenic thalami, non-specific in appearance
H	<ul style="list-style-type: none"> Extensive diffuse and focal white matter injury 	<ul style="list-style-type: none"> Heterogeneity of the white matter
I	<ul style="list-style-type: none"> Left IVH grade II Left frontal dysplasia 	<ul style="list-style-type: none"> Left IVH grade II Increased echogenicity of periventricular white matter bilaterally left >right

IVH indicates intraventricular hemorrhage (grade I, subependymal hemorrhage; grade II intraventricular hemorrhage; grade III intraventricular hemorrhage with dilatation of the ventricles).