Published in final edited form as:
J Child Neurol. 2006 June ; 21(6): 491–495.

Magnetic Resonance Imaging and Electroencephalographic Findings in a Cohort of Normal Children With Newly Diagnosed Seizures

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Abstract

In the initial assessment of children with new-onset seizures, the suggestion that electroencephalography (EEG) should be standard and that magnetic resonance imaging (MRI) should be optional has been questioned. The purposes of this study were to (1) describe the frequency of EEG and MRI abnormalities and (2) explore relationships between MRI and EEG findings to determine their relevance in the assessment of children with new-onset seizures who are otherwise developing normally. As part of an ongoing, prospective study of children with new-onset seizures, we studied 181 children (90 girls and 91 boys). Children were entered into the study within 3 months of their first-recognized seizure. The association between EEG and MRI abnormalities was explored using a chi-square test. Abnormal MRI findings were found in 32.6% (n = 59) of the sample. The EEG and MRI results agreed with respect to classification into normal or abnormal in 37% (n = 67). Of the 50 children with a normal EEG, however, 21 (42%) were found to have an abnormal MRI.

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This research was supported by grant PHS R01 NS22416 from the National Institute of Neurological Disorders and Stroke to J.K.A.

We found an unexpectedly high frequency of imaging abnormalities in our sample of otherwise normal children, although the significance of these findings is not clear. Follow-up of these patients will help us interpret the importance of the abnormalities. Despite our relatively small sample, however, our findings indicate that a normal EEG does not reliably predict a normal MRI in children with first seizures.

The essential diagnostic evaluation for a first unprovoked seizure remains a source of debate. The practice parameter for a first afebrile seizure developed by the Quality Standards Subcommittee of the American Academy of Neurology, Child Neurology Society, and American Epilepsy Society recommends electroencephalography (EEG) as a standard part of diagnostic investigation.[1] Neuroimaging is considered optional. Magnetic resonance imaging (MRI) is the preferred modality and is suggested as an option for children with persistent postictal focal deficit, an abnormal neurologic examination, a focal seizure, or an EEG that shows an abnormality other than patterns characteristic of benign partial epilepsy or idiopathic generalized epilepsy.

Some authors have questioned the need for EEG as a standard part of the initial assessment, suggesting that EEG results do not significantly affect treatment decisions.[2,3] However, experts agree that an EEG is important to help clarify seizure type and to diagnose epilepsy syndrome. Most studies have recommended neuroimaging only in selected cases, but risk factors for abnormal imaging findings cannot always be found. For example, Sharma et al found significant abnormalities on MRI in 26% of the children with focal seizures before 33 months of age or a predisposing condition (eg, sickle cell disease, malignancy, human immunodeficiency virus [HIV] infection) and in 2% of the remainder of the children.[4] In a large pediatric study, Berg et al evaluated 613 children ages 1 month to 15 years with newly diagnosed epilepsy; nearly 80% had neuroimaging, and relevant lesions were found in 12.7% of these children.[5] Such lesions were even found in 2.7% of individuals who had no history suggestive of a central nervous system lesion and no abnormality on neurologic examination. A retrospective review of MRI data in children 1 to 18 years revealed 38% with abnormal results, 25% of whom had normal development.[6] Finally, in a study of adults and children following a first seizure, neuroimaging results indicated symptomatic lesions in nearly 14%.[7] Missing an abnormality in 2% to 3% of children with new-onset seizures might or might not be acceptable. A higher frequency of abnormality might suggest that neuroimaging should be a routine part of the evaluation, with the possible exception of children with idiopathic partial or idiopathic generalized epilepsy.

If relationships between structural abnormalities identified on MRI and physiologic abnormalities identified on the EEG are found, they could provide important information to assist in the assessment of children with new-onset seizures. Only a few studies have explored these relationships. In a study by Berg et al, focal epileptiform discharges were not found to be predictive of MRI lesions; however, focal slowing was a significant predictor.[5] In that study, an abnormal motor examination was the strongest predictor of imaging abnormalities. More research is needed to explore relationships between MRI and EEG findings to determine their relevance in the diagnosis and treatment of children with new-onset seizures. The purposes of this study were to systematically describe the frequency and nature of MRI and EEG abnormalities and to explore relationships between MRI and EEG findings to determine their relevance in the assessment of children with new-onset seizures who were otherwise developing normally.

METHODS

Sample—Children were prospectively recruited from July 2000 through March 2004 as part of a larger ongoing longitudinal study to identify factors that predict child adaptation to

epilepsy. Families were requested to participate at two large, established community medical centers located in Cincinnati, Ohio, and Indianapolis, Indiana. At the Indianapolis site, flyers were also sent to physicians in private practice and to school nurses, requesting them to forward the flyers to appropriate families. Children aged 6 to 14 years who had experienced their first-recognized seizures within the past 3 months were recruited. Children were excluded if the seizure resulted from an acute situational etiology such as toxin, infection, or trauma. They were also excluded if they had a chronic neurologic illness limiting their activities of daily living, such as cerebral palsy, mental retardation, and pervasive developmental disorder. Also excluded were children who scored below 80 on the Kaufman Brief Intelligence Test (K-BIT) [8] or had other abnormalities on neurologic examination. Children were not excluded if it was determined that they had had a seizure that had not been previously recognized as such. This study was approved by the Institutional Review Boards at both participating institutions. Parents signed consent forms and children signed assent forms before participation.

Neurodiagnostic Assessment—Following a detailed clinical and developmental history and physical and neurologic examinations, participants were identified with a predominant seizure type and potential epilepsy syndrome. A neurologic examination was defined as abnormal when there was any focal neurologic abnormality. Children with an IQ composite of less than 80 on the Kaufman Brief Intelligence Test were excluded. The International League Against Epilepsy classifications were used to define seizure types and predict epileptic syndromes.9 Idiopathic syndrome diagnosis required an appropriate clinical presentation, a normal neurologic examination, and typical EEG findings. Idiopathic localization-related syndromes included benign childhood epilepsy with centrotemporal spikes or occipital paroxysms. Symptomatic localization-related epilepsy required a history of focal onset and a cortical lesion on neuroimaging or an abnormal neurologic examination. Cryptogenic focal epilepsy diagnosis was given when children had a history of localization-related events not meeting the criteria for an idiopathic or symptomatic syndrome. Generalized epilepsies were categorized as either idiopathic or cryptogenic/symptomatic. Idiopathic generalized epilepsies included absence, juvenile myoclonic, and generalized tonic-clonic on awakening. The lack of typical EEG findings or an appropriate history resulted in assignment to the cryptogenic/symptomatic syndrome group. Children presenting with a generalized seizure who had unifocal epileptiform activity and/or focal slowing on the EEG were classified as having partial epilepsy syndrome. Individuals who could not be clearly matched were assigned to an unknown group.

EEG Data—EEG reports and medical records were reviewed by two of the authors (T.J.D., D.W.D.) at their respective sites. To ensure consistency in rating, inter-rater reliability was periodically assessed and found to be strong. All EEG reports that were ordered as part of the clinical work-up were reviewed. EEG data were classified as yes or no for three different criteria: abnormal, epileptiform discharges, and slowing. Epileptiform discharges and slowing were separated by distribution into focal or generalized. A hierarchy of positive findings was established to foster group assignment. Focal epileptiform findings had respective priority over generalized epileptiform abnormalities. Slowing was subdivided and prioritized so that focal slowing had higher priority than generalized slowing. Independent focal epileptiform findings were classified as either bilateral or unilateral; unilateral focal findings were further classified as either right or left.

Neuroimaging Data—MRI films that had been ordered as part of the clinical work-up were reviewed. MRI data were coded by three of the authors (A.J.K., J.C.E., V.P.M.). To ensure consistency, they were asked to periodically rate the same films. Agreement among raters was found to be excellent. Neuroradiologists were blind to EEG findings when they coded the MRI. MRI examinations at both sites were performed on 1.5-Tesla (GE Medical Systems, Milwaukee, WI) Signa Horizon platform LX scanners running current system software

(presently version 9.x) and using a standardized pediatric seizure protocol. The standardized protocol consisted of the following scanning sequences: sagittal T_1-weighted spin echo, axial T_2-weighted fast spin echo, coronal oblique fast fluid-attenuated inversion recovery, coronal oblique fast multiplanar inversion recovery, axial diffusion (single-shot, spin echo echoplanar), b = 1000, all directions), and axial three-dimensional spoiled gradient recalled echo.

The total imaging time for all sequences was about 26 minutes. A subset of 34 examinations was performed on MRI units at referring facilities. These were performed on magnet systems varying from 0.5 to 1.5 Tesla and consisted of standard sagittal, axial, and, on most patients, coronal images, using typical clinical sequences. All of these studies were rated as adequate or better in scan quality.

Neuroimaging data were classified into six subgroups: cortical lesions, white-matter lesions, encephalomalacia, enlarged lateral ventricles, volume loss, and a miscellaneous group. Cortical lesions were defined as those involving the neocortex, entorhinal cortex, or hippocampus. These included cortical dysplasias, gray-matter heterotopias, and hippocampal lesions. White-matter lesions included leukomalacia and other lesions specifically involving the white matter. Encephalomalacia was defined as an abnormal MRI signal compatible with chronic injury or other damage to the brain parenchyma not otherwise classified as leukomalacia. Because such signal abnormalities can involve the white matter as well as the cortex, encephalomalacia was considered a separate category. Using normative data from the Cincinnati site, enlarged lateral ventricles were defined as measuring larger than 1.0 cm width at the midbody of the ventricle on axial orientation. Miscellaneous lesions included pathology involving the cerebellum, brain stem, or vascular spaces. Participants with multiple types of neuroimaging lesions were included in all applicable groups. A neuroimaging lesion was described as being ipsilateral if focal epileptic discharges were noted on the same side.

RESULTS

Three hundred fifty-six children met enrollment criteria for this ongoing study. Of these, 291 (81.7%) children had an evaluation including an EEG, 269 (75.6%) had an evaluation including an MRI, and 242 (68.0%) children had both. Of the 242 children who had both, 61 were excluded for the following reasons: 35 did not have baseline neuropsychologic evaluations, 18 had Kaufman Brief Intelligence Test scores less than 80, and 8 had abnormal neurologic examinations. Included in this report are findings for the 181 (50.8% of the total enrollment) children who had an EEG, an MRI, a baseline Kaufman Brief Intelligence Test score greater than 79, and a normal neurologic examination.

This study group was composed of 90 (49.7%) girls and 91 boys. The mean age at onset was 9.4 ± 2.5 years. Parent-reported racial demographics were 18 African-Americans, 157 Caucasians, and 6 other. Right-hand dominance was found in 162 (90%). The mean Kaufman Brief Intelligence Test score was 105 ± 12.9 (range 81-138).

Comparisons of the demographic data and clinical diagnoses of the children excluded from this analysis ($n = 175$) with those included ($n = 181$) were carried out using *t*-tests or chi-square tests as appropriate. The level of significance of .05 was used. No differences in age at onset, gender, or seizure type were found between those excluded and those included.

Clinical Diagnosis—Seizure type and epilepsy syndrome are described in Table 1. The partial seizure group included 12 children with simple partial seizures, 46 with complex partial seizures, and 52 children with partial seizures with secondary generalization. The generalized seizure group included 19 children with absence seizures, 1 child with myoclonic seizures, and 50 children with generalized tonic-clonic seizures. After review of the EEG reports, 15 of these

subjects were classified as having partial epilepsy. The seizure type was undetermined in 1 child, and the epilepsy syndrome was undetermined in 9 children.

The partial epilepsy group included 37 (29.6%) participants with idiopathic, 75 (60%) with cryptogenic, and 13 (10.4%) with symptomatic partial epilepsy. Within the idiopathic partial syndrome group, 34 had the characteristics of benign childhood epilepsy with centrotemporal spikes and 3 had the characteristics of childhood epilepsy with occipital paroxysms. Of the 47 participants with predicted generalized epilepsy, 42 (89.4%) were characterized with an idiopathic etiology.

EEG and MRI Findings—A large majority (*n* = 138; 76.2%) of the EEGs were routine studies, whereas 35 (19.3%) were ordered as sleep deprived. Seven of the children had video-EEG or prolonged EEG done. Epileptiform activity was noted on the EEG of 119 (65.7%) children, with 89 (74.8%) of them showing focal epileptiform abnormalities. Of those with focal abnormalities, 46 were bilateral independent discharges and 43 were unilateral (25 on the left and 18 on the right). Slowing was noted on the EEG in only 25 (13.8%) children; 17 were focal and 8 were generalized.

Abnormal MRI results were present in 59 (32.6%) participants; 13 of these showed multiple abnormalities (Table 2). Cortical abnormalities were found in 8 children (13% of abnormal studies; 4.4% of total group), including 5 with cortical dysplasia/heterotopia and 3 with hippocampal abnormalities. Encephalomalacia was present in 1 child, white-matter lesions were found in 20 children, volume loss was noted in 5 children, and enlarged ventricles were described in 27 children. Miscellaneous abnormalities were noted in 20 participants, consisting of 9 children with structural abnormalities, 3 children with periventricular leukomalacia, 2 children with periventricular white-matter lesions, 2 children with prominence of extra-axial fluid spaces, 2 children with a venous anomaly vascular lesion, 1 child with periventricular heterotopias, 1 child with a cerebellar gray-matter lesion, and 1 child with brainstem white-matter lesions.

The EEG and MRI results were both abnormal in 38 (21%) participants (Table 3). In addition, 29 participants had a normal EEG and a normal MRI. For the other 114 cases, the EEG was classified as abnormal and the MRI as normal in 93 cases and the EEG was classified as normal and the MRI as abnormal in 21 cases. Of the 50 children with a normal EEG, 21 (42%) were found to have an abnormal MRI. Using a chi-square test, the association between EEG and MRI findings was not significant ($P = .0954$).

Tables 4 and 5 show the EEG characteristics of the participants in relation to imaging abnormalities. An MRI abnormality was found in 28% of subjects with focal epileptiform activity and in 47% with focal slowing. Of the 8 children with cortical MRI findings, 6 also had abnormal EEG results. Of the 5 children with cortical MRI findings and focal epileptiform abnormalities, all had EEG abnormalities ipsilateral to the MRI lesion.

Of the 20 children with white-matter lesions noted on MRI, 10 had abnormal EEG results, including 6 with focal epileptiform abnormalities and 4 with generalized epileptiform abnormalities. Of the 6 with focal epileptiform abnormalities, all 6 had focal epileptiform abnormalities ipsilateral to the MRI lesion.

The association of an abnormal EEG with epileptiform discharges and abnormal MRI findings approached significance ($P = .072$). Abnormal MRI findings were not significantly associated with slowing abnormalities on the EEG ($P = .696$). Finally, 21 children with idiopathic epilepsy (9 partial and 12 generalized) had MRI abnormalities (Table 6).

DISCUSSION

This ongoing study is the first study to describe MRI and EEG data in school-aged children with normal intelligence who had new-onset seizures. None of these children had any abnormality in their history or on physical examination indicative of a cerebral abnormality. We found a high rate of MRI abnormalities in the sample (32.6%) and a high rate of MRI abnormalities in the children with a normal EEG (42%). The rate of 4.4% of children with cortical abnormalities, however, is similar to that reported in other studies. Despite the low percentage of abnormalities, these observations might have an impact on both treatment and prognosis. Follow-up of these participants is necessary to demonstrate the possible relevance of any of these abnormal findings. It would be remarkable if these lesions were not related to the seizures and, in fact, were normal variants; however, no study has been published on MRI findings in normal children to date.

In our study, we found results on the frequency of seizure types and epilepsy syndromes to be comparable to those of previous studies. For example, Sillanpaa et al found 62% of a community sample in Finland to have localization-related syndromes.[10] Similar findings also were reported in another community sample by Berg et al showing 59% to have partial epilepsy, with 10% consistent with benign childhood epilepsy with centrotemporal spikes.[11]

We found an unexpectedly high frequency of imaging abnormalities in our sample. Other studies in unselected new-onset populations have found a lower incidence of abnormalities.[4,5] One possible explanation for our high number is that we did a very detailed analysis of the neuroimages. The neuroimaging studies were obtained in a uniform manner, and all were reviewed by one of three pediatric neuroradiologists. Von Oertzen et al showed that neuroradiologists in an epilepsy center found significantly more lesions than radiologists in the community.[12] Because imaging findings were used in the classification of epilepsy syndrome in this study, we did not analyze the relationship between MRI findings and epilepsy syndrome.

We did explore EEG abnormalities and specific findings on the MRI. Although the numbers in this series are small, we found that a normal EEG did not reliably predict a normal MRI. This finding suggests that normal results on EEG should not be used to place a patient in a low-risk group that does not need an MRI for a complete evaluation. Because these studies were obtained at the time of the first seizure, we do not know if lesions on MRI will predict recurrence of seizures in the future. Follow-up is needed to determine the significance of the abnormalities found on neuroimaging.

Our study suggests a need for continuing assessment of the role of neuroimaging in patients with first seizures. Consistent with the recommendations of the practice parameter on evaluation of the first nonfebrile seizure in children, we confirm the recommendation to obtain an MRI study in children with newly diagnosed partial epilepsy. However, we also found that children with apparent generalized idiopathic epilepsy and partial idiopathic epilepsy and children with generalized epileptiform abnormalities on the EEG had abnormal imaging findings. It remains to be determined if the children with apparent generalized epilepsy and those with generalized epileptiform activity on EEG continue to meet diagnostic criteria or if some are subsequently found to have secondary generalized partial seizures. This study provides valuable baseline data for a large cohort of children who can be followed through their developmental maturation and seizure recurrence. Additional evaluation through neuroimaging and EEG might demonstrate progressive change and allow retrospective risk analysis.

CONCLUSION

We found an unexpectedly high frequency of imaging abnormalities in our sample of children with new-onset seizures who were otherwise developing normally. Our findings indicate that EEG results are not good indicators of MRI results and that they should not be used as the only criterion for ordering an MRI.

Acknowledgments

We acknowledge assistance from the epilepsy and pediatric neurology clinics at Children's Hospital Medical Center, Cincinnati, OH, and Riley Hospital, Indiana University Medical Center, as well as from B. Hale, MD. We thank D. Doescher and A. McNelis for help with data collection, P. Dexter for editorial comments, and C. Benson for editorial assistance.

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Table 1

Seizure Type and Epilepsy Syndrome

Seizure Type	Predicted Epilepsy Syndrome			Total
	Partial	Generalized	Undetermined	
Partial	110	0	0	110
Simple	12			
Complex	46			
Secondary generalization	52			
Generalized	15	47	8	70
Absence	0	18	1	19
Tonic-clonic	14	29	7	50
Myoclonic	1	0	0	1
Undetermined	0	0	1	1
Total,*n*(%)	125(69)	47(26)	9(5)	181

Table 2

Participants with Multiple Magnetic Resonance Imaging Abnormalities

Participant	Number of Abnormalities	*Cortical Lesions*[*]	*Encephalomalacia*[*]	*White-Matter Lesions*[*]	*Volume Loss*[*]	*Enlarged Ventricles*[*]	Miscellaneous Lesions
1	3	-	R	R	R	-	-
2	3	L	-	R	R	-	-
3	3	-	-	R	R	R = L	-
4	4	-	-	B	B	R = L	+
5	2	L	-	L	-	-	-
6	2	-	-	-	-	R = L	+
7	2	-	-	B	-	L>R	-
8	2	-	-	B	-	-	+
9	2	-	-	B	-	-	+
10	2	-	-	B	-	-	+
11	3	B	-	-	-	R >L	+
12	2	-	-	B	-	-	+
13	5	R	-	B	B	R>L	+

[*] B = bilateral; L = left; R = right.

J Child Neurol. Author manuscript; available in PMC 2006 September 6.

Table 3

Comparison of Electroencephalographic and Magnetic Resonance Imaging Findings

	MRI		
EEG	**Normal**	**Abnormal**	**Total**
Normal	29	21	50
Abnormal	93	38	131
Total	122	59	181

EEG = electroencephalography; MRI = magnetic resonance imaging.

Table 4

Comparison of Epileptiform Activity on Electroencephalographic and Magnetic Resonance Imaging Findings

	MRI		*MRI-Specific Abnormalities*[*]					
EEG Epileptiform Activity	**Normal**	**Abnormal,n (%)**	**Cortical Lesions**	**Encephalo-malacia**	**White-Matter Lesions**	**Volume Loss**	**Enlarged Ventricles**	**Miscellaneous Lesions**
Focal	64	25 (28.1)	5	0	6	1	12	5
Generalized	22	8(26.7)	1	0	4	1	3	2
None	36	26(41.9)	2	1	10	3	12	13
Total	122	59 (32.6)	8	1	20	5	27	20

EEG = electroencephalographic; MRI = magnetic resonance imaging.

[*] Children can have multiple MRI abnormalities.

Table 5

Comparison of Slowing of the Background on Electroencephalographic and Magnetic Resonance Imaging Findings

	MRI		*MRI-Specific Abnormalities*[*]					
EEG Epileptiform Activity	**Normal**	**Abnormal,n (%)**	**Cortical Lesions**	**Encephalo-malacia**	**White-Matter Lesions**	**Volume Loss**	**Enlarged Ventricles**	**Miscellaneous Lesions**
Focal	9	8 (47.1)	1	0	3	2	4	4
Generalized	7	1 (12.5)	0	0	0	0	1	0
None	106	50 (32.1)	7	1	17	3	22	16
Total	122	59 (32.6)	8	1	20	5	27	20

EEG = electroencephalographic; MRI = magnetic resonance imaging.

[*] Children can have multiple MRI abnormalities.

Table 6

Magnetic Resonance Imaging Findings in Relation to Epilepsy Syndrome

	Epilepsy Syndrome						
	Partial, n (%)			Generalized, n (%)			
MRI	Idiopathic	Cryptogenic	Symptomatic	Idiopathic	Cryptogenic or Symptomatic	Undetermined	Total
Abnormal	9 (24)	23 (31)	11 (85)	12 (29)	1 (20)	3 (33)	59 (33)
Normal	28 (76)	52 (69)	2 (15)	30 (71)	4 (80)	6 (67)	122 (67)
Total	37	75	13	42	5	9	181

MRI = magnetic resonance imaging.