

SPECIAL REPORT

Guidelines for imaging infants and children with recent-onset epilepsy

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SUMMARY

The International League Against Epilepsy (ILAE) Subcommittee for Pediatric Neuroimaging examined the usefulness of, and indications for, neuroimaging in the evaluation of children with newly diagnosed epilepsy. The retrospective and prospective published series with $n \geq 30$ utilizing computed tomography (CT) and magnetic resonance imaging (MRI) (1.5 T) that evaluated children with new-onset seizure(s) were reviewed. Nearly 50% of individual imaging studies in children with localization-related new-onset seizure(s) were reported to be abnormal; 15–20% of imaging studies provided useful information on etiology or and seizure focus, and 2–4% provided information that potentially altered immediate medical management. A significant imaging abnormality in the absence of a history of a locali-

zation-related seizure, abnormal neurologic examination, or focal electroencephalography (EEG) is rare. Imaging studies in childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and benign childhood epilepsy with centrotemporal spikes (BECTS) do not identify significant structural abnormalities. Imaging provides important contributions to establishing etiology, providing prognostic information, and directing treatment in children with recently diagnosed epilepsy. Imaging is recommended when localization-related epilepsy is known or suspected, when the epilepsy classification is in doubt, or when an epilepsy syndrome with remote symptomatic cause is suspected. When available, MRI is preferred to CT because of its superior resolution, versatility, and lack of radiation.

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For the purposes of this discussion, localization-related epilepsy refers to simple partial, complex partial, and secondarily generalized epilepsy, and is often alternately called focal or partial epilepsy. The etiology for the localization-related epilepsies may be "remote" symptomatic (e.g., a past historical event, such as ischemia or encephalitis, or an underlying structural abnormality, such as a brain tumor), idiopathic (genetic), or cryptogenic (nonlesional, symptomatic cause is suspected but not confirmed). The idiopathic (genetic) epilepsies may be primary generalized (e.g., juvenile absence) or localization related [e.g., benign childhood epilepsy with centrotemporal spikes (BECTS)]. Some of the catastrophic pediatric epilepsy syndromes in which generalized seizures are prominent such as infantile spasms and Lennox-Gastaut syndrome, may have a symptomatic cause.

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Here we propose guidelines for imaging children with newly diagnosed epilepsy. We confine our discussion to children with afebrile seizures and those in whom acute symptomatic causes have been excluded (such as hyponatremia, meningitis). We also exclude evaluation of children with neonatal seizures. We presume that electroencephalography (EEG) will be obtained to assist in establishing the diagnosis of seizures, characterizing syndromes, and providing prognosis (King et al., 1998; Hirtz et al., 2000; Jallon et al., 2001). The role of advanced imaging techniques—including specialized structural magnetic resonance (MR) imaging, high-field magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), functional MRI (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT)—for the evaluation of the child with catastrophic (recent, abrupt onset, frequent, associated with developmental arrest, and difficult to control) or medically refractory epilepsy for whom epilepsy surgery is a consideration will be the topic of a later document. Prior guidelines have primarily focused on adults with epilepsy and the evaluation of patients considered for epilepsy surgery (Recommendations for neuroimaging of patients with epilepsy, 1997; Guidelines for neuroimaging evaluation of patients with uncontrolled epilepsy considered for surgery, 1998). The role of imaging in the setting of the first unprovoked afebrile seizure has recently been reviewed (Hirtz et al., 2000); here we update that discussion based on MEDLINE search and focus on recent-onset epilepsy, but also include imaging data on children with new-onset seizures (Bernal & Altman, 2003). We provide guidelines for optimal care, but acknowledge that these may not be practicable or readily available especially when resources are scarce.

It is important to stress that few studies have prospectively examined substantial pediatric epilepsy populations with a primary view to evaluate imaging (Wang et al., 1997; King et al., 1998; Berg et al., 2000; Shinnar et al., 2001; Chang et al., 2002). Aside from studies in emergency departments where CT is the imaging modality of choice (McAbee et al., 1989; Warden et al., 1997; Garvey et al., 1998; Maytal et al., 2000; Chang et al., 2002; Sharma et al., 2003), none have sought to define indications for MRI and thus are uncontrolled studies and do not meet criteria for class 1 studies (Landfish et al., 1992; Gibbs et al., 1993; Bronen et al., 1996; Caraballo et al., 1997; Harvey et al., 1997; Garvey et al., 1998; Guidelines for neuroimaging evaluation of patients with uncontrolled epilepsy considered for surgery, 1998; King et al., 1998; Kramer et al., 1998; Berg et al., 2000; Hirtz et al., 2000; Jallon et al., 2001; Chang et al., 2002; Kuzniecky & Knowlton, 2002; Bernal & Altman, 2003; Gelisse et al., 2003; Eltze et al., 2005; Korff & Nordli, 2005). Table 1 lists prospective and retrospective studies since 1989 that incorporate some form of imaging using CT and/or MRI

that involve more than 30 children. Studies that include patients evaluated before 1989 do not include current MRI technology with 1.5 Tesla. It is uncertain at present to what extent 3 Tesla MRI or higher strength magnets will affect clinical imaging practices and standards. Important for childhood epilepsies is recognition of the high incidence of “idiopathic” epilepsies in contrast to localization-related epilepsy and epilepsy syndromes that may have a remote symptomatic cause (Stroink et al., 1998; Shinnar et al., 1999; Berg et al., 2000, 2001a; Jallon et al., 2001; Arts et al., 2004).

Most published pediatric imaging studies are directed toward evaluation of the first seizure and are targeted to identify an acute symptomatic cause such as febrile illness (encephalitis, meningitis), trauma, or central nervous system (CNS) hemorrhage that will influence immediate treatment. These studies principally assess the utility of CT; MRI, when performed, is typically obtained on a selected subset of these children. These studies are instructive, as children with recently diagnosed epilepsy are likely to have a similar spectrum of static findings indicating remote cause, and some will have subacute etiologies, such as tumor, vascular malformation, or vasculitis that warrant change in medical/surgical management. Approximately one-third of children in studies from emergency departments who are evaluated for a “first” seizure will be recognized as having epilepsy. These studies show that CT identifies clinically relevant abnormalities in 7–24% of children but alters immediate medical management in only a minority. These studies also suggest that it is possible to identify children who are unlikely to benefit from CT imaging: older than 2 years, generalized seizures, normal examination, and either generalized EEG abnormalities or normal EEG (McAbee et al., 1989; Warden et al., 1997; Garvey et al., 1998; Maytal et al., 2000; Chang et al., 2002; Sharma et al., 2003).

Imaging is most often abnormal in children with localization-related or remote symptomatic epilepsy. In contrast, imaging in the typical idiopathic generalized epilepsies is normal (see subsequent text). Close to 50% of imaging studies in children with localization-related new-onset seizures/epilepsy will be abnormal; 15–20% will provide useful information on etiology and focus, and 2–4% will alter immediate medical management (King et al., 1998; Berg et al., 2000; Shinnar et al., 2001; Chang et al., 2002). It is rare to find a significant imaging abnormality in the absence of a history of a localization-related seizure, abnormal neurologic examination, or focal EEG. Infants may be a higher risk population, as it is unusual for infants to have a primary generalized epilepsy; rather they are more likely to have a localization-related epilepsy, an epileptic syndrome with remote symptomatic cause, or metabolic disorder (Korff & Nordli, 2005). Furthermore, infants are more likely to have focal malformation of

Table 1. Summary of imaging studies involving substantial children and adolescents, for evaluation of first seizure and epilepsy; listed by year, and whether prospective or retrospective studies; only King and Wang set out to systematically evaluate MRI as a primary aim

Study	Age	Design	Epilepsy	Location	Number	CT (abnormal)	MRI (abnormal)
Sztriha et al., 2002	c	Prospective	TLE	Community	30	NA	30 (13/10*)
Chang et al., 2002	c/t	Prospective	1st seizure	ED	712	653 (156/77*)	390 (191 /108*)
Shinnar et al., 2001	c/t	Prospective	1st seizure	Community	412	159 (35)	59 (20)
Berg et al., 2000	c/t	Prospective	All seizures	Community	613	197 (NA)	388 (80/62*)
King et al., 1998	c/t/a	Prospective	All seizures	Clinic	300	>42 (NA)	263 (35*)
Wang et al., 1997	c	Prospective	Partial epilepsy	Clinic	300	128 (NA)	300 (125)
Harvey et al., 1997	c	Prospective	TLE	Community	63	48 (11/10*)	58 (23 /22 *)
Sharma et al., 2003	c/t	Retrospective	1st seizure	ED	500	475 (38*)	NA
Maytal et al., 2000	c/t	Retrospective	1st seizure	ED	66	66 (14)	NA
Al-Sulaiman & Ismail, 1999	c	Retrospective	New dx epilepsy	Community	263	162 (64/23*)	NA
Kramer et al., 1998	c/t	Retrospective	Partial epilepsy	Clinic	143	101 (NA)	42 (NA)
Stroink et al., 1998	c/t	Prospective	1st seizure	Clinic	156	112 (12)	NA
Garvey et al., 1998	c/t	Retrospective	1st seizure	ED	107	107 (19)	NA
Warden et al., 1997	c/t	Retrospective	1st seizure	ED	203	203 (25)	NA
Resta et al., 1994	c/t	Retrospective	Partial epilepsy	Clinic	111	98 (20)	111 (57)
Gibbs et al., 1993	c/t	Retrospective	1st seizure	Clinic	157	121 (26/19*)	NA
Landfish et al., 1992	c/t	Retrospective	1st seizure	ED	56	23 (0)	2(0)
McAbee et al., 1989	c/t	Retrospective	1st seizure	ED	101	101 (7)	NA

c, child; t, teen (adolescent); a, adult; ED, emergency department; dx, diagnosis; TLE, temporal lobe epilepsy; NA, not available.

* clinically significant (for those that note clinical significance).

Comments:

King: 59 children (20%) sample; of the total, 35 were clinically significant. 26/154 (17%) partial, 9/59 unclassified (CT with no MRI) added two more; CT missed 12 of 28 abnormal MRIs; 19 had tumor or vascular malformation and so changed medical management.

Warden: 30% of patients were febrile.

Garvey: Eight ultimately not seizures, 49 provoked (including fever), 50 unprovoked.

McAbee: 80 afebrile, 21 complicated febrile (one with abnormal imaging study had fever).

Resta: 30 with normal CT had abnormal MRI.

Wang: >30 children treatable disease: tumor, vascular malformation, vasculitis; another 35 focal cortical dysplasia/mesial temporal sclerosis (MTS).

Chang: 38 patients with abnormal MRI had normal CT.

Stroink: CT abnormalities mostly nonspecific (e.g., atrophy).

Gibbs: Identified 964 children and teens who had EEG, 182 had a single seizure, 530 had epilepsy; they report on 157 with (persistent) focal EEG.

Harvey: CT and MRI both identified tumors and dysplasia, CT did not identify any MTS, but did identify calcification not seen on MRI presumed to be hamartoma in one child.

cortical development (MCD) as a cause of seizures than are older pediatric populations (Vanderver et al., 2003).

REASONS FOR STRUCTURAL NEUROIMAGING

Structural neuroimaging plays an important role in the evaluation, management, and treatment of the child with epilepsy. The role of neuroimaging is to detect an underlying cerebral lesion(s) that may be causally related to the child's seizure disorder or associated neurodevelopmental impairment. Imaging is obtained to establish etiology, to provide prognosis, and to plan appropriate clinical care. For example, children with remote symptomatic localization-related epilepsy have a poorer prognosis than children with idiopathic or cryptogenic epilepsy (Shinnar et al., 1994; Sillanpaa et al., 1998;

Berg et al., 2001b; Arts et al., 2004). However, which patients require neuroimaging, when imaging should be obtained, and the optimal imaging modality are often debated.

Imaging early in the course of epilepsy is directed at identifying an etiology for seizures that requires other medical or surgical attention. It is important to bear in mind the distinction between:

- 1 Identifying an abnormality on an imaging study that is nonspecific (e.g., periventricular leukomalacia, atrophy).
- 2 Identifying (or confirming) static remote lesions (e.g., porencephaly, MCD).
- 3 Finding a focal lesion responsible for the seizures that does not require immediate intervention but would be potentially amenable to epilepsy surgery (e.g., focal cortical dysplasia or mesial temporal sclerosis).

- 4 Finding a subacute or chronic process that has therapeutic implications [e.g., requires more immediate intervention (brain tumor), or that has important diagnostic or prognostic implications (e.g., leukodystrophies, metabolic disorder)].
 - 5 Identifying an acute process that requires urgent intervention (e.g., hydrocephalus, acute stroke or hemorrhage, encephalitis, metabolic cytopathy) or need for additional urgent diagnostic evaluation and counseling.
- The last two of these reasons provide the impetus for imaging after the first seizure; the others may be reserved for once the diagnosis of epilepsy is established.
- 4 Children with characteristics of a symptomatic generalized epilepsy syndrome, including infantile spasms or early Lennox-Gastaut syndrome (e.g., tonic, atonic, mixed seizures), as focal MRI findings may be found in a substantial proportion of these children.
 - 5 Failure to control seizures, worsening seizures, changes in seizure manifestations, or developmental regression also merit neuroimaging if not previously performed.
 - 6 Finally, new-onset seizures/epilepsy presenting with evidence for a medical emergency such as increased intracranial pressure or status epilepticus always merit emergency imaging.

INDICATIONS FOR STRUCTURAL NEUROIMAGING

Imaging is most useful for children with a suspected or confirmed localization-related or remote symptomatic generalized epilepsy. Early in the course of epilepsy it may be difficult to decide whether a child has a localization-related epilepsy. Therefore, it is proposed that children with epilepsy undergo neuroimaging if one or more of the following are present (Table 2):

- 1 If there is any evidence to suggest the epilepsy is localization related (e.g., focal), with the exception of typical benign idiopathic partial epilepsy (see subsequent text). The basis for establishing localization-related seizures includes the characteristics of the seizure, abnormalities on EEG, focal examination (including Todd's paralysis), and history or examination to suggest remote symptomatic cause (such as extreme prematurity, meningitis, encephalitis, complicated febrile convulsion, or significant head injury).
- 2 Abnormal neurologic examination, including focal deficits, stigmata of neurocutaneous, cerebral malformation syndrome, or a history of significant developmental delay, arrest, or regression.
- 3 Children younger than 2 years, excluding those with simple febrile seizures.

SITUATIONS WHERE IMAGING MAY NOT BE NECESSARY

A substantial proportion of children with newly diagnosed epilepsy have an idiopathic focal or generalized epilepsy (King et al., 1998; Stroink et al., 1998; Shinnar et al., 1999; Berg et al., 2000; Jallon et al., 2001). The natural history of these syndromes has resulted in their "benign" designation: they are outgrown, readily treated, and not associated with neurologic deterioration, and imaging is unremarkable (Loiseau et al., 1983, 1988; Shinnar et al., 1994; Sillanpaa et al., 1998). Recent imaging data at 1.5 T supports the absence of significant imaging abnormalities when the clinical presentation is typical, the neurologic examination is normal, and characteristic electrographic features are present (King et al., 1998; Berg et al., 2000) (Table 2). These include BECTS, childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME). Although approximately 15% of the patients with BECTS exhibit abnormal MRI, the structural abnormalities found do not influence the favorable prognosis of the epilepsy (Gelisse et al., 2003). Similarly, a study using statistical MRI maps of gray matter provides evidence for the existence of structural abnormalities in idiopathic generalized epilepsy (Woermann et al., 1998), especially in JME (Woermann et al., 1999). However, MRI is normal in all of the patients with IGE in whom routine visual analysis of MRI has been performed (King et al., 1998; Berg et al., 2001a; Wiesmann, 2003), provided patients have not experienced focal seizures or focal spikes on EEG (Berg et al., 2000). There is a cautionary note: Because some nonidiopathic epilepsies may sometimes mimic these idiopathic epilepsy syndromes, MRI is recommended in these patients if they present any atypical features such as abnormal neurologic or intellectual development, difficult-to-treat seizures, or unusual course. There is insufficient evidence to comment on the role of not imaging in other less common "benign" or generalized epilepsies and which may be difficult to differentiate from symptomatic epilepsies [e.g., other idiopathic focal epilepsies (childhood epilepsy with occipital paroxysms), primary reading epilepsy, and

Table 2. Summary of populations who do and do not warrant imaging

Imaging indicated	Imaging not indicated
Localization related seizures ^a	Childhood absence epilepsy
Focal history, abnormal exam, focal EEG abnormalities ^a	Juvenile absence epilepsy
Developmental regression <2 years old	Juvenile myoclonic epilepsy
Symptomatic generalized epilepsy syndrome	BECTS
Increased intracranial pressure	
History of status epilepticus	
Atypical course for BECTS/IGE	
^a Except for BECTS.	

idiopathic generalized epilepsies (benign neonatal convulsions, benign myoclonic epilepsies of infancy and epilepsy with seizures precipitated by specific modes of activation)] (Caraballo et al., 1997).

RECOMMENDATIONS FOR IMAGING

MRI is considered the imaging modality of choice because of superior anatomic resolution and characterization of pathologic processes (Table 1). CT confers some advantages with regard to identifying blood and calcification (as found in congenital infection). Studies in adults with childhood-onset epilepsy and in children in both recent-onset and chronic epilepsy find that MRI identifies more abnormalities than CT. Furthermore CT does not identify abnormalities found on MRI (Resta et al., 1994; Bronen et al., 1996; Wang et al., 1997; Berg et al., 2000; Shinnar et al., 2001; Chang et al., 2002; Kuzniecky & Knowlton, 2002). MRI will identify focal cortical dysplasia, mesial temporal sclerosis, small tumors (such as oligodendrogliomas and gangliogliomas), and vascular malformations (AVM, cavernous angioma); CT will not or may not identify these. However, CT is more widely available than MRI, is less expensive, and is less likely to require sedation for younger children.

Therefore, a minimum standard is to use history, examination, and EEG to characterize the epilepsy in order to identify patients with BECTS or IGE in whom imaging is not useful versus those with a localization-related epilepsy for whom imaging is likely to be abnormal and contribute to establishing cause and identify the seizure focus. CT with and without contrast can be performed on these patients if MRI is not available, recognizing that some symptomatic causes for epilepsy—such as MTS, small tumors, small or subtle focal cortical dysplasia—will not be identified. When resources are very limited an argument can be made to obtain imaging when a trial of one or two medications has been ineffective. There are no data, however, upon which to base this supposition. Identifying a static lesion will not affect immediate medical therapy. In this setting, imaging is pursued to identify children in need of surgical intervention, such as tumor or vascular malformation, and to identify children with other medical conditions that require intervention or evaluation of other organ systems (e.g., tuberous sclerosis), although here the diagnosis can often be established by other clinical features and laboratory examination. Here MRI remains superior to CT, but CT serves as a screening modality. MRI would be performed if there were persistent seizures, a deteriorating neurological examination to define abnormalities found on CT, or, if resources are available, when there is clinical suspicion of a focal process.

There is no agreement on specific imaging protocols or specifics of the MRI sequences proposed, but

there is general agreement that the following be performed (Bronen et al., 1996): An anatomic, thin-slice volumetric T_1 -weighted gradient-recalled-echo sequence, axial and coronal T_2 -weighted sequence, fluid attenuated inversion recovery (FLAIR) sequence (axial, and coronal if possible), and high resolution oblique coronal T_2 -weighted imaging of the hippocampus (fast or turbo spin echo weighted sequence). Maximal slice thickness should not exceed 4–5 mm. In cases of focal epilepsy, thinner slices (2 or 3 mm) or else three-dimensional (3D) volume acquisitions (with thickness of 1–2 mm) may be necessary to identify or characterize subtle cortical malformations. There is debate, and there are limited data, about the utility of newer sequences such as magnetization transfer imaging and diffusion tensor imaging. When metabolic disorders are suspected MRS may be helpful.

Children younger than 2 years require special sequences, as immature myelination affects the ability to identify common causes of epilepsy. Lesions may “appear” or “disappear” with the changing pattern of myelination, they may be seen as “enhanced myelination” indicative of areas of possible cortical malformation, and may not appear on scans acquired at an older age (Sankar et al., 1995; Takanashi & Barkovich, 2003; Eltze et al., 2005). In addition to a 3D dataset, imaging in children younger than 2 years should include sagittal, axial, and coronal T_1 -weighted sequences. Volumetric T_1 -weighted sequences are less useful before age one year due to incomplete myelination on T_1 sequences. MR imaging (especially high-resolution T_2 images) performed early in the first year of life in infants with epilepsy is important to identify areas of cortical or subcortical dysplasia, which can become difficult to identify after myelination. Conversely, if MR imaging before the age of 2 years is normal, and seizures persist, then MRI may be repeated at 6-month intervals, and certainly after age 24–30 months when more mature myelination can reveal otherwise unsuspected cortical dysplasia. Repeat imaging in older children is a topic for the evaluation of chronic epilepsy and is not considered here.

Gadolinium contrast is reserved for circumstances where tumor, vascular malformations, inflammation, and infectious concerns arise or are suspected based on review of noncontrast studies. Routine administration of Gadolinium contrast provides little advantage in children with epilepsy. For younger children (generally <7 years) sedation requires a dedicated pediatric sedation team and/or skilled pediatric anesthesia. Infants, especially those younger than 3 months, may not need sedation if the infant is fed just before imaging. It is preferable, especially for younger children, that studies be interpreted by professionals skilled in interpreting pediatric imaging studies.

SUMMARY AND CONCLUSION

Structural neuroimaging is recommended for all children with recently diagnosed localization-related or generalized epilepsy who do not have the clinical and EEG features characteristic of classical idiopathic focal or generalized epilepsy (BECTS, CAE, JAE, or JME) and for any child younger than 2 years of age. These children have the highest likelihood of identifying a symptomatic etiology for their seizures. The imaging modality of choice is MRI because of its superior resolution compared to CT. However when scarce resources may preclude MRI, CT can be used in its place. Children younger than the age of 2 years require different MR imaging sequences because of the affect of developmental myelination on the ability to detect certain lesions such as cortical dysplasia. Imaging is performed to establish etiology, assist in determining prognosis, and identifying patients in whom alteration in medical or surgical management would ensue.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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