Pharmacologically intractable epilepsy in children: diagnosis and preoperative evaluation

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It is important to correctly diagnose medically intractable epilepsy in children and to identify those children whose medically refractory, localization-related seizures may be surgically remediable as soon as possible to optimize the surgical outcome. In this paper the authors review the definition of medically intractable seizures and discuss the various causes and risk factors for this disorder in children. They also outline the presurgical diagnostic evaluation process for pharmacologically intractable epilepsy in children who may be candidates for surgical treatment of localization-related seizures. The treatment of children with medically intractable epilepsy is both challenging and rewarding. Surgery has the potential of altering the natural history of epilepsy by improving or eliminating seizures in carefully selected patients. (DOI: 10.3171/FOC/2008/25/9/E2)

Key Words • epilepsy surgery • medically intractable epilepsy • presurgical evaluation

Definition of Pharmacological Intractability

Medical management with AEDs remains the first-line treatment in patients with epilepsy. (Note that the term, “AED,” although commonly used, is a misnomer because none of these drugs affect the natural history of epilepsy but instead are effective to one degree or another in the symptomatic control of seizures.) In 1857 Sir Charles Locock reported the efficacy of bromides in the treatment of epilepsy, thus heralding the beginning of epilepsy’s pharmacological treatment. In 1912 phenobarbital was shown to be effective. There was a desultory release of a few drugs (for example, phenytoin, carbamazepine, and valproic acid) until the past 12 years when 10 new anticonvulsion drugs were approved for use by the US Food and Drug Administration. These newer drugs differ from the older ones in terms of pharmacokinetics and side-effect profiles, but there is no evidence that any are more efficacious in the treatment of epilepsy than the older AEDs.

Children who are good candidates for surgery generally have medically refractory epilepsy, which can be defined as inadequate seizure control despite appropriate medical therapy with at least 2 AEDs in maximally tolerated doses for 18 months–2 years, or adequate seizure control with unacceptable drug-related side effects. There are several factors to be considered in a definition of medical intractability (Table 1), including the number of AED failures, minimum frequency at which seizures must occur to be considered intractable (daily, monthly, and so forth), duration of unresponsiveness to medication, epilepsy syndrome involved, cause of seizures in the absence of a clear-cut epilepsy syndrome, and patient age at the onset of seizures.
Antiepilepsy Drug Failures

When 2 AEDs for the correct seizure type and in adequate doses fail, there is only a 5–10% probability of achieving seizure control with a third drug. Kwan and Brodie and Dlugos et al. have suggested that the failure of seizures to respond to a single AED is a strong predictor of medically refractory epilepsy. Hence, the general consensus among the tertiary and quaternary care centers that minister to children with medically refractory seizures is that the number of failed AEDs needed to define seizures as intractable is ≥ 2. Note, however, that the majority of children referred to a comprehensive epilepsy center for presurgical evaluation have already taken more than 2 AEDs that have failed by the time a referral is made. Moreover, the development of pharmacokinetic (metabolic) and pharmacodynamic (functional) tolerances may explain the loss of efficacy of almost all first-, second-, and third-generation AEDs with prolonged use. This phenomenon may be a significant reason for medication failure in some patients.

Minimum Seizure Frequency

Is there a minimum frequency at which seizures must occur to be considered intractable? The answer to this question varies across the different studies. Berg and colleagues and Camfield et al. used a minimum seizure frequency of 1/month in their definition of intractability. Other authors have used a range from any seizure in the past 6 months to any seizure in the past 3–5 years. Minimum seizure frequency is a critical issue in the impact of seizures on the quality of life for the pediatric patient with epilepsy. For example, a few seizures a year in adolescence can limit independence and impede social interaction because of the social stigma attendant to seizures in this age group, whereas a similar frequency may be better tolerated in a child younger than 6 years of age. From a practical point of view, seizure frequency can determine surgical candidacy, particularly if extraoperative intracranial video–EEG monitoring from subdural and/or depth electrodes is being used, because frequent seizures within a short time frame, typically a week or so, are required to decide on surgery in these children. Thus, the definition of inadequate seizure control varies for each patient, depending on epilepsy type, patient age, lifestyle, quality of life issues, personal objectives, and patient expectations of the therapeutic success.

Duration of Unresponsiveness to Medication

How long does it take for a child’s epilepsy to reveal itself as intractable? Different physicians have raised this question over the years. Based on retrospectively collected cohort data from 120 children followed up for at least 2 years, Dlugos et al. concluded that the failure of a first AED trial accurately predicts refractory temporal lobe epilepsy at 2 years. Based on a prospective study involving more than 300 patients, Berg et al. asserted that a substantial proportion of epilepsy cases with an onset in childhood or adolescence might not become clearly intractable for many years. Most comprehensive epilepsy centers use a failure of seizures to respond to AEDs for 18 months–2 years as a working definition of refractory epilepsy. However, it rarely takes 2 years to determine refractoriness, and most children referred to tertiary and quaternary care epilepsy centers for consideration for surgery have had uncontrollable seizures far longer than 2 years.

Epilepsy Type or Specific Epilepsy Syndromes

It is well known that a number of age-specific childhood epilepsy syndromes, such as idiopathic generalized epilepsy–absence type, benign Rolandic epilepsy, and febrile convulsions, are associated with a good prognosis for remission. Certain epilepsy syndromes are associated with a higher risk of medical intractability in children: Rasmussen syndrome, West syndrome, Ohtahara syndrome, Dravet syndrome, Lennox–Gastaut syndrome, juvenile myoclonic epilepsy, progressive myoclonic epilepsy, Sturge–Weber syndrome, and Landau–Kleffner syndrome.

Etiology of Epilepsy

Certain epilepsy origins more commonly seen in the pediatric population have been recognized as contributing to the disease’s medical intractability, including cortical malformation due to abnormal neuronal and glial proliferation or apoptosis (for example, congenital microcephalies and megalencephaly, cortical hamartomas of tuberous sclerosis, cortical dysplasia with balloon cells, or dysembryoplastic neuroepithelial tumor), abnormal neuronal migration (lissencephalies, cobblestone complex syndromes, or heterotopias), abnormal cortical organization (polymicrogyrias or schizencephalies), and malformations of cortical development not otherwise specified, even those caused by an inborn error of metabolism (mitochondrial, pyruvate...
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FIG. 1. Schematic showing an algorithm for the presurgical evaluation and treatment of patients with medically intractable epilepsy. CC = corpus callosotomy; fMRI = functional MRI; KD = ketogenic diet; VNS = vagus nerve stimulation.

metabolic, and peroxisomal disorders). Other causes associated with medical intractability include mesial temporal sclerosis, a variety of metabolic or genetic conditions, infections, trauma, and tumors.

Patient Age at Seizure Onset

The influence of patient age at seizure onset on the intractability of epilepsy is unclear. A patient's age at the onset of seizures appeared to be the predominant predictor of intractability in a case-control study by Berg et al involving 76 children with intractable epilepsy compared with 96 controls: patients younger than 1 year of age had the highest risk for intractability even after the authors controlled for infantile spasms and was evident in both cryptogenic and remote symptomatic groups. These authors also noted that the prognosis for remission appeared to be progressively better as the age at seizure onset increased during childhood and adolescence. In a subsequent population study, however, the same authors observed that the apparent effect of an age < 1 year was explained by syndromic grouping in a multivariable analysis. In contrast, an early age at seizure onset was not seen as a predictor of intractability in a prospective cohort described by Arts et al or in a case series of localization-related epilepsy.

Presurgical Evaluation

Some have divided epilepsy surgery for children into curative and palliative types. Examples of palliative epilepsy surgery are multiple subpial resections when the epileptogenic zone is localized to eloquent cortex and corpus callosotomy for drop attacks in children with multiple seizure types. Extratemporal cortical resection is the most common curative epilepsy surgery in infants and children, whereas temporal lobectomy is the most common in adults. Children with intractable epilepsy may benefit from early surgical intervention to avoid the potential negative effects of continued seizures and prolonged use of AEDs on cognitive and psychosocial development and to increase the chances of postoperative neurodevelopmental reorganization due to the inherent functional plasticity of a child’s brain. Regardless, surgery is a radical and costly approach to the treatment of epilepsy and is not without risk.

The definitive successful outcome of epilepsy surgery is a seizure-free state without significant neurological impairments. In focal cortical resection, complete resection of the epileptogenic zone correlates with a better seizure outcome; therefore, precise localization of the epileptogenic zone is crucial. Equally important is the localization of eloquent cortex to spare these areas during any planned resection of the epileptogenic region. Although localization of the epileptogenic zone and eloquent cortex can be achieved through invasive intracranial EEG monitoring by using subdural and depth electrodes, there is no single noninvasive diagnostic test that can be used to reliably achieve these goals. Rather, concordance from multiple tests is needed to lateralize and localize the epileptogenic zone and function in the brain and thus ascertain the candidacy of a

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child with medically refractory seizures for surgery. The following diagnostic tests are performed in comprehensive epilepsy centers as part of the presurgical evaluation for potential epilepsy surgery candidates (Fig. 1). At our center, the presurgical studies are designed to go from the least (patient history, physical, and video-EEG monitoring) to the most (Wada testing) invasive, and the data are discussed by a multidisciplinary epilepsy surgery team on a regular basis to formulate a decision of whether to proceed to the next stage of testing. Note that in young children routine imaging, such as MR imaging or MEG, may not be all that noninvasive if it requires general anesthesia.

History and Physical Examination

A detailed history, including seizure onset and evolution over time, description of seizure semiological features, and the AEDs used as well as a comprehensive neurological examination help in determining whether a child’s seizures are indeed medically intractable. It is also important to obtain a family history to rule on the possibility of genetic syndromes. The importance of a history cannot be overstated; consider, for example, that medical intractability may in fact be due to pharmacokinetic anomalies, the wrong drug, non epileptic events, or poor compliance—all of which can be determined by carefully obtaining a history.

Scalp EEG

Video-EEG monitoring is important in documenting ictal events, lateralizing and localizing the electrographic onset of seizures, and defining the seizure semiological factors. Admission to an epilepsy monitoring unit for prolonged video-EEG monitoring also has the advantage of allowing prolonged evaluation of interictal EEG activity during wakefulness and sleep, adjustment of AEDs to obtain adequate seizures, and monitoring the effects of medications if new ones are added. Newer methods of EEG analysis, such as EEG dipole analysis and EEG source imaging, provide excellent localizing information in pediatric patients, especially in cases of extratemporal lobe epilepsy.51,59

Neuroimaging Procedures

In patients undergoing presurgical evaluation, the goals of neuroimaging studies include the identification of structural abnormalities in the possible epileptogenic region; eloquent regions of the brain including language, memory, and sensorimotor functions; and the relation of these regions to the potential epileptogenic zone by using noninvasive techniques.

Structural Neuroimaging. Magnetic resonance imaging with a specified epilepsy protocol is the imaging study of choice and is mandatory as the primary imaging modality according to the International League Against Epilepsy guidelines.36,37 Subtle structural abnormalities are better visualized on MR imaging compared with CT, although CT may be indicated in special circumstances, such as when looking for intracranial calcifications. Newer MR imaging techniques, such as diffusion tensor imaging, enable visualization of the white matter fibers in the brain and are helpful in looking for subtle changes in the white matter that can be seen in cases of suspected cortical dysplasia, cases in which regular MR imaging fails to pick up the abnormality.68 In children with localization-related epilepsy but nonlesional or nonfocal MR images, surgery may still be an option provided that other testing modalities, including interictal and ictal scalp and invasive EEG studies as well as other functional imaging procedures, provide concordant localizing findings.38

Magnetoencephalography. An innovative noninvasive technique, MEG measures activity-related magnetic dipoles produced by electric currents in the brain. It has the advantage of high-spatial- and temporal-resolution recordings not hampered by the skull or other intervening tissues between the scalp and brain, which can be a limitation of scalp EEG. The localization of MEG spike clusters has up to a 90% concordance with that of the epileptogenic zone as defined by ictal invasive monitoring with subdural electrodes.40,47,53 In some cases, MEG-localized epileptiform areas (MEG cluster) can help in detecting epileptogenic neocortical lesions on high-spatial-resolution MR imaging that otherwise would have been missed or hidden on conventional MR imaging.48 Magnetoencephalography is also used in functional mapping of language and somatosensory cortex. The combination of MEG and MR imaging data creates magnetic source imaging data that has proved most useful in the localization of extratemporal foci and when there is more than one potential epileptogenic focus. The results of MEG can aid in ensuring adequate coverage of the cortex during invasive EEG monitoring with subdural electrodes.

Other Neuroimaging Procedures. Fluorine-18-labeled fluorodeoxyglucose-PET is a nuclear medicine scanning procedure that measures regional glucose metabolic rates. It is performed during the interictal period and measures relative glucose utilization in suspected epileptogenic regions compared with the contralateral areas. Alpha-methyl-tryptophan PET scans can be useful in identifying the epileptogenic region especially if there are multiple structural lesions on MR imaging, as in cases of tuberous sclerosis.21 Ictal SPECT scans showing ictal hyperperfusion in the epileptogenic zone are useful in cases of MR imaging-negative partial epilepsies and focal cortical dysplasia. Subtraction ictal SPECT scans coregistered with MR images can further increase the yield of the study. It is important to ensure early ictal SPECT injections to avoid problems with seizure propagation and nonlocalization due to an early switch from ictal hyperperfusion to postictal hypoperfusion.63

Lateralization of Language Function

The lateralization of language function is crucial in the presurgical evaluation of children with intractable frontal or temporal lobe epilepsy to prevent postoperative language deficits. Atypical language dominance can be seen especially in children whose seizure onset occurred at an early age, because of the influence of seizures on brain development. Functional MR imaging using different language paradigms can be performed to lateralize language in cooperative patients. It may be used in lieu of the more invasive intracarotid amytal or amobarbital procedure or Wada testing.3 As mentioned previously, MEG also proves useful in the localization and lateralization of language function in children who are candidates for epilepsy surgery.
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Neuropsychological Testing

Neuropsychological testing plays an important role in assessing preoperative overall cognitive function and the potential impact of surgery and helps in lateralizing the cerebral hemisphere dominant for verbal and nonverbal function in older children.22,58 In younger children, a neurodevelopmental assessment can be done preoperatively to serve as a baseline for future follow-up of surgical outcome. Neuropsychological data are critical in interpreting semiological, electroencephalographic, and radiological data in terms of lateralizing and localizing the seizure focus.

Wada Testing

The Wada test is an invasive procedure utilizing amobarbital injected into each internal carotid artery to determine language dominance and can be used to assess the risk of postoperative amnestic syndromes in temporal lobe epilepsy.69 Selective middle cerebral artery Wada tests can also be done to assess the risk of postsurgical motor deficits before functional hemispherectomies.62 Note, however, that the test carries with it an increased risk of morbidity because of its invasiveness and has major shortcomings given its lack of standardization and absence of spatial resolution.46 Therefore, noninvasive tests like functional MR imaging, MEG, and neuropsychological testing are used initially, although there may be a role for the Wada test if the above tests are equivocal or patients have contraindications to MR imaging studies.

Intracranial EEG

Some patients scheduled for resection need to undergo further precise localization of the epileptogenic zone and functional mapping of eloquent cortex with invasive EEG monitoring via intracranial subdural grid and/or depth electrodes. The need for these additional studies is especially true in cases of extratemporal lobe epilepsy, which is common in the pediatric population, and in cases of temporal lobe epilepsy when lateralization cannot be adequately done by scalp EEG.8,10,23,38,75 In children with medically intractable, localization-related lesional epilepsy who are candidates for focal cortical excision, either temporal or extratemporal, and whose clinical, neuropsychological, electroencephalographic, and radiological data are all concordant and point to the same area of epileptogenicity in the brain, cortical excision of the suspected epileptogenic zone is undertaken. However, if the medically intractable localization-related epilepsy is nonlesional, if the epilepsy is lesional but the data are discordant for localization of the epileptogenic zone, or if the epileptogenic zone appears to reside wholly or partially in eloquent cortex, then invasive intracranial monitoring from depth and/or subdural electrodes during a seizure is required to map out areas of epileptogenicity in the brain prior to epilepsy surgery.

Conclusions

Medically refractory epilepsy refers to either inadequate seizure control despite appropriate medical therapy with at least 2 AEDs in maximally tolerated doses for 18 months–2 years or adequate seizure control accompanied by unacceptable drug-related side effects. Up to 30% of children with epilepsy fit this definition. The treatment of children with medically intractable epilepsy is both challenging and rewarding. With the exception of the successful resolution of infantile spasms with adrenocorticotropic hormone and possibly vigabatrin,42,64 there is no evidence that AEDs alter the natural history of epilepsy in children. In contrast, surgery does have the potential to alter the natural history of epilepsy by improving or eliminating seizures in carefully selected patients.30 There are many factors associated with and affecting pharmacological intractability, and such factors should be taken into consideration when a patient is being evaluated as a potential candidate for epilepsy surgery.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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