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Diagnostic test utilization in evaluation for resective epilepsy surgery in children

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SUMMARY

Epilepsy surgery is highly successful in achieving seizure freedom in carefully selected children with drug-resistant focal epilepsy. Advances in technology have aided presurgical evaluation and increased the number of possible candidates. Many of the tests employed are resource intense, and in specific cases they may be unhelpful or have adverse effects. Some standardization of the evaluation process is thus considered timely. Given the lack of class I or 2 evidence defining the relative utility of each test in specific clinicopathologic cohorts, a set of expert recommendations was attempted using consensus among members of the Pediatric Epilepsy Surgery Task Force of the International League Against Epilepsy (ILAE) Commissions of Pediatrics and Diagnostics. These recommendations aim to limit fringe over or underutilization of use while retaining substantial flexibility in the use of various tests, in keeping with most standard practices at established pediatric epilepsy centers.

KEY WORDS: Children, Epilepsy surgery, EEG, MRI, PET, MEG, SPECT.

Epilepsy surgery is now an accepted practice of management in carefully selected children with drug-resistant focal epilepsy. Recommendations published in 2006 defined the principles that differentiate epilepsy surgery in children from that in adults, including the role of brain development and plasticity. These recommendations further emphasized the need for specialty expertise in caring for the complex

issues related to a wide range of clinical cohorts and epilepsy syndromes unique to childhood.¹ Data at that time were limited with regard to the more complex technologies; with time, increasing advances in technology and practice mean the spectrum of possible candidates is ever widening. Much of the data available are in adults, however, and such technologies are not only resource intense but carry risk of adverse effects. Consequently, standardization to guide utilization and care in children is needed. The Pediatric Epilepsy Surgery Task Force of the International League Against Epilepsy (ILAE) Commissions of Pediatrics and Diagnostics undertook the task of formulating recommendations for diagnostic evaluation in localizing the epileptogenic region (ER) or critical cortex (CC) and to guide clinical care in children. Recognizing that a unified optimal evaluation strategy acceptable to all pediatric centers is unachievable, the recommendations were devised to minimize overutilization and underutilization, especially those that could potentially jeopardize patient care.

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METHODOLOGY

A panel formed from the respective ILAE Task Forces and Commissions (Table 1) began developing the recommendations in September 2011. Following a conceptual discussion at the 29th ILAE meeting in Rome, a dedicated Pediatric Epilepsy Surgery group met for a two-day workshop in Florence, Italy. At this venue, there were 30 members from 26 centers, representing 16 countries from 6 continents.

The panel reviewed literature using the American Academy of Neurology criteria (tools.aan.com/globals/axon/assets/9023.pdf) on the utility of diagnostic tests in presurgical evaluation of various clinicopathologic cohorts, including many unique to childhood. The review revealed that there is no class 1 evidence and little class 2 evidence for

children. Data interpretation was compounded by several factors. Most studies combine adult and pediatric age groups. The sensitivity and specificity of a test is often not etiologically specific, but rather tested in heterogeneous cohorts. Access and use vary considerably across centers. Comparison of test utility is problematic, as there is usually a bias in skill with the specific technology at any given center.² Furthermore, nonmedical factors including family dynamics and fiscal incentives may influence test utilization.

Given the lack of class 1 and class 2 evidence, a broad-based global panel of experts was used to create consensus rather than systematic review. Special consideration was given to the known strengths and limitations, risk, clinical benefit, and incremental cost-effectiveness, as well as access to various tests. In evaluating specific clinical cohorts, the panel assumed that each epilepsy center has a multidisciplinary team with appropriate standard of proficiency and the minimal diagnostic capabilities required. The panel recognized, however, that resource-poor regions of the world face unique challenges with limited access to certain more costly technologies or expertise. A guarded approach with due consideration of the potential risks may allow local teams to offer surgeries to specific patients or patient groups with substantial benefit.

Within this framework of understanding, the panel addressed the scalp electroencephalography (EEG) and magnetic resonance imaging (MRI) that are used by almost all centers and a select group of ancillary tests including three-dimensional (3D) magnetoencephalography (MEG) or EEG source imaging, fluorodeoxyglucose–positron emission tomography (FDG-PET), hexamethylpropylene amine oxime (HMPAO)/ethylcysteinate dimer (ECD) SPECT, electrocorticography (ECoG), and extraoperative invasive EEG monitoring (IEM). The panel refrained from addressing several other tests that have potential utility, but have few data or general use experience in pediatrics. These include MR spectroscopy, EEG triggered functional MRI (fMRI), MRI post-processing techniques, newer PET ligands, diffusion-weighted imaging with tractography, transcranial magnetic stimulation, and intraoperative ultrasound. These tests are not addressed further in this document.

Following review of the literature and discussion, the panel voted on the utility of each test with the assumption that the case under consideration represented a fairly standard presentation of the respective clinical cohort. Utility of each test was categorized as follows:

1. **Mandatory [M].** Mandatory testing capability was required of all designated epilepsy surgery centers that offer surgery for that specific group. It was recommended, however, that surgery not be denied to patients in resource-deficient areas because of lack of availability of a specific test if the treating team is otherwise proficient and able to address all possible risks.

Table 1. ILAE Task force and commission panel

(A) Pediatric Epilepsy Surgery Sub-commission members contributing to Florence	
J. Helen Cross	London, England
William D. Gaillard	Washington, DC, U.S.A.
Prasanna Jayakar	Miami, Florida, U.S.A.
Renzo Guerrini	Florence, Italy
A. Simon Harvey	Melbourne, Australia
Hans Holthausen	Vogtareuth, Germany
Philippe Kahane	Grenoble, France
Gary Mathern	Los Angeles, California, U.S.A.
Brian Neville	London, England
Alexis Arzimanoglu	Lyon, France
Carmen Barba	Florence, Italy
Eduardo Barragan	Ciudad de, Mexico
Christine Bulteau	Paris, France
Sarat Chandra	New Delhi, India
Arthur Cukiert	Sao Paolo, Brazil
Deepak Gill	Sydney, Australia
Adam Hartman	Baltimore, Maryland, U.S.A.
Nathalie Jette	Calgary, Canada
Jack Kerrigan	Phoenix, Arizona, U.S.A.
Pavel Krsek	Prague, Czech Republic
Mark Libenson	Boston, Massachusetts, U.S.A.
Guoming Luan	Beijing, China
Liisa Metsahonkala	Helsinki, Finland
Taisuke Otsuki	Tokyo, Japan
Bertil Rydenhag	Gothenburg, Sweden
Manjari Tripathi	New Delhi, India
Angus Wilfong	Houston, Texas, U.S.A.
Jo Wilmshurst	Cape Town, South Africa
Nandan Yardi	Pune, India
Flavio Giordano	Florence, Italy
Yu-Tze Ng	Oklahoma City, U.S.A.
(B) Diagnostic Commission members participating in Rome	
Prasanna Jayakar	Miami, Florida, U.S.A.
William D. Gaillard	Washington, DC, U.S.A.
Fernando Cendes	São Paulo, Brazil
Hermann Stefan	Erlangen, Germany
Catherine Chiron	Paris, France
Czaba Juhasz	Detroit, Michigan, U.S.A.

2. Highly recommended [H]. These tests are considered very useful for either localizing the ER or assessing overall surgical candidacy, including ascertaining the baseline seizure frequency, prognostic factors, and so on.
3. Optional [O]. These ancillary tests may help define convergence of data and add to the confidence level for localizing the ER. As such, the choice of ancillary tests is guided by access and experience at each center. When faced with tests of comparable utility and access, consideration of the cost–benefit ratio is recommended in establishing priority.
4. Little use [L]. These tests are not believed to add useful information and are unlikely to affect the final surgical plan.
5. Unwarranted [U]. These tests may potentially provide confusing findings, distracting from correct management, and incur unnecessary costs or risk.

The results of the consensus categorizations were then compiled within the framework of a flow chart to prioritize test utility for various cohorts but retain flexibility to account for variations in standard practices.

OVERVIEW OF ER LOCALIZATION TESTS

The utility of various diagnostic tests is amply documented in a large number of class 3 or class 4 studies. Addressing all of these studies is beyond the scope of this document.

The commentary below highlights known limitations of each test that often lead to overutilization by prompting additional unnecessary testing, or occasionally may put the patient at risk.

Interictal EEG

Scalp EEG recording has limited spatial resolution, but the relatively low cost and global accessibility enhance its utility, especially in the patients who have a single discrete focus. Dense array EEG has been reported to have a higher localization value than conventional electrode placement.³

In general, the reliability of localization is likely to be higher for convexity foci as compared to basal, mesial temporal, or interhemispheric foci, which are more prone to false localization/lateralization. False lateralization deserves special consideration in hemispheric syndromes, especially encephalomalacia and Sturge-Weber syndrome, in which the amplitudes of activity over the involved hemisphere may be lower than those over the intact hemisphere,⁴ but may also occur in temporal lobe epilepsy in presence of large focal lesions^{5,6} or with profound unilateral hippocampal sclerosis.⁷

Infrequently, patients with localized lesions may demonstrate interictal discharges multifocally at remote/

contralateral sites or bilaterally, or in an apparently generalized distribution, but considered in isolation should not influence candidacy or the extent of resections.^{8,9,10} Attention to features such as focal attenuation or bursts of fast activity or analyses of subtle time leads and dipolar field distributions helps increase the sensitivity and reliability of localization in these cases.¹¹ Specific interictal EEG findings unique to childhood deserve due consideration. Some of these interictal abnormalities can be linked to maturation (“benign” spikes) and can give the false impression of “multifocality.”¹²

Ictal EEG with video

Ictal EEG shares some of the same limitations as the interictal discharges.⁵ The initial low amplitude fast activity at seizure onset or deep foci may not be evident on the scalp, with the subsequent propagated discharges appearing non-focal.

Although video-EEG ictal recordings in children may not always provide localizing information, they may be useful in confirming seizure semiology, as well as identification of multiple seizure types or nonepileptic events that are a concern, since parental reports may not always be reliable. Specific patterns unique to children, such as asymmetric spasms or electrical status epilepticus during sleep,¹³ are additional features that may help define the epileptogenic region.

Magnetic resonance imaging

In general, a focal cortical lesion is a reliable marker of the location of the ER,¹⁴ but it may not be concurrent with its extent, being either smaller or rarely larger than the ER. Furthermore, there are documented cases, albeit rare, where the detected lesion was unrelated to the ER. The presence of multiple lesions (e.g., tuberous sclerosis or nodular heterotopias) does not necessarily mean that seizures are multifocal in onset.

Reliable detection of abnormalities requires a standardized high resolution MRI acquisition protocol; the complex evolution with maturation in early childhood warrants specific expertise with a neuroradiologist skilled with interpreting cases of pediatric epilepsy.¹⁵ Reasons for imaging failures include also an “unfavorable time window,” typically between the age of 6 months to 2 years at which time a lesion, especially focal cortical dysplasia (FCD), can be masked because of increasing but yet incomplete myelination, and where repeat imaging would be recommended every 3–6 months, and if tolerated after 2 years age. Detection of the lesion may help restrict the extent of resection.

There is general impression that the yield of a 3T MRI is superior,¹⁶ to 1.5T, although there are no studies with direct comparison of the two, and none in children. Proton density sequences such as magnetization transfer may be helpful in some circumstances, (e.g., transmental dysplasias), but

there are insufficient data to recommend them as part of a standard protocol.

3D EEG/MEG

These techniques help locate the 3D source of interictal spikes; ictal source analyses are usually feasible only with EEG. In general, EEG source imaging and MEG have been shown to be complementary, with MEG being more sensitive to tangential sources and EEG to radially oriented sources.^{17,18} MEG is able to define smaller foci (4–8 cm²) compared to EEG (10–15 cm²). Furthermore, MEG is not influenced by inhomogeneity of conductivity and thus allows for easier source analysis. In patients with lesions, skull defects, asymmetries, malformations, and so on, taking these structural changes into account is a critical, albeit cumbersome, prerequisite for EEG. MEG is thus particularly suited for foci in neocortical areas oriented tangentially, such as basal or interhemispheric region, or in postoperative cases. Access and cost differential are, however, the major limitation of MEG compared to EEG source imaging.

PET and SPECT

Both interictal FDG-PET and ictal SPECT appear comparable in utility.¹⁹ Both are prone to effects of seizure propagation and thus areas of abnormality be more extensive than the ER. FDGPET is most useful for defining ER lateralization, and to a lesser extent localization, but not necessarily its extent.

For ictal SPECT, the timing of injection is critical; late injections may provide false localizing or even lateralizing data in patients with complex seizure propagation patterns.^{20,21} Subtraction of ictal and interictal SPECT may help localization, but imposes the need for an additional SPECT test and computational expertise.

Electrocorticography

ECoG requires an a priori definition of the origin of seizures, influencing the type of surgical approach and of the explored cortical regions. ECoG is influenced by anesthesia and generally provides only interictal data, which limits its usefulness.^{22,23} In the presence of discrete lesions, ECoG has been reported to be useful to define the ER extent beyond the anatomic boundaries of a lesion.^{24–27}

In a subset of patients with FCD, the ECoG may reveal continuous focal ictal/interictal discharges,²⁸ a marker considered reliable for the ER that may alleviate the need for ictal capture through extraoperative IEM.

Extraoperative invasive EEG monitoring

IEM is considered the gold standard for ER localization, but it has its own limitations, including the potential for adverse events.^{29–31} The optimal choice of subdural, depth, or a combination of electrodes needs further study in children; stereotactic depth placement (SEEG) is

generally feasible only above the age of 3 years. High frequency oscillations are gaining increased attention as potential reliable markers of the ER. Rates of explantation without resection vary considerably across centers, and given the added risk and costs, added caution is recommended in patient selection and the use of IEM as an exploratory procedure.³²

OVERVIEW OF CRITICAL CORTEX LOCALIZATION TESTS

Functional mapping tests used to lateralize or localize eloquent function(s) deemed at risk are essentially of two categories:

Noninvasive

Either fMRI or MEG may help in demonstrating preserved function, especially in the very young where clinical evaluation may be difficult, although the significance of positive findings obtained under sedation or general anesthesia is unclear.

In older children, both tests are reliably used to lateralize language function, although partial discordance can occur. There are also known circumstances in which fMRI is less reliable, such as in post ictal states and situations with critical carotid stenosis, vascular malformations with vascular steal, and large mass lesions with edema.^{33–36} There is comparable but limited evidence in children for motor mapping with fMRI and MEG^{37,38} but none for memory function. Current practice for a growing number of pediatric centers is to use fMRI or MEG to determine the need for invasive testing, either Wada or cortical stimulation.

Invasive

Wada test (intracarotid sodium amobarbital) is generally reliable for lateralization of language dominance.^{39–42} Memory functions may also be tested, but since the mesial temporal structures subserving this function are primarily perfused via the posterior circulation, the reliability of Wada testing for this purpose is less clear. The need for patient cooperation limits use in younger children.

Electrocortical stimulation mapping is considered the “gold standard” for functional localization, but it often requires adaptation of stimulation paradigms to elicit reliable responses in young children.⁴³ It can be used in either the intraoperative or extraoperative setting; the latter is done via subdural or stereotactic depth electrodes and allows more thorough testing and is specifically required for language mapping in the younger patients who cannot cooperate for awake surgery. Intraoperative mapping has the added advantage of allowing subcortical white matter tract mapping during the course of the resection.

THE ROLE OF NEUROPSYCHOLOGY/ NEUROPSYCHIATRY

Neuropsychology/neurodevelopmental testing is a requirement for all children being assessed for epilepsy surgery.^{44,45} This serves multiple purposes including the following: (1) the provision of baseline data for later comparison to quantify surgical impact and outcome, (2) the characterization of cognitive strengths and deficits sometimes not previously detected, (3) informing the risk of postoperative deficits, (4) contribution to the localization/lateralization of function, and (5) the provision of information pertinent for educational and, in older children, rehabilitation planning. Serial comparative testing, however, remains problematic in view of the lack of standardized tests that cover all age groups. In addition, many children presenting for assessment will have a psychiatric diagnosis or diagnoses, which also require assessment (e.g., autistic

spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD)) and evaluation of possible likely benefit or deterioration.^{46,47} Consequent neuropsychiatric evaluation may also be useful in the delineation of specific aims of surgery of the family, and whether such can be matched following overall delineation of the ER and functional ability.^{1,48}

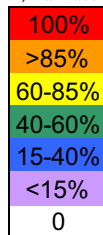
TEST UTILITY FOR ER LOCALIZATION IN SPECIFIC CLINICAL SETTINGS

Table 2 represents the categorization of the utility of all tests in each clinical cohort derived through consensus voting. Interictal EEG and MRI were the only tests unanimously agreed to be mandatory across many clinical cohorts. Most ancillary tests mostly achieved a majority consensus across all clinical groups, although a 50/50 split vote was recorded for a few categories.

Table 2. Diagnostic test utility voting results in major clinical cohorts

Etiology	II EEG					Video EEG					MRI					3D EEG/MEG					FDG-PET					SPECT					ECoG					IEM				
	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U
Single Lesion																																								
<i>Dev. Tumors</i>																																								
<i>FCD I</i>																																								
<i>FCD II</i>																																								
<i>Hipp. Sclerosis</i>																																								
<i>Hypo.Hamar.</i>																																								
<i>Vascular</i>																																								
<i>Cavernoma</i>																																								
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<i>PMG</i>																																								
<i>Rasmussen</i>																																								
<i>Sturge-Weber</i>																																								
Other																																								
<i>Tuberous Scl.</i>																																								
<i>Sturge Weber Focal</i>																																								
<i>Post infectious</i>																																								
MRI negative																																								

M, mandatory; H, highly recommended; ,O optional; L, little use; U, unwarranted.



The color scale represents the proportion of votes for categorizing each test in each clinical cohort.

Single discrete MRI lesion

The rationale for use of ancillary tests in children with discrete lesions is mainly empiric and guided by the observation that the ER may extend variably beyond the anatomic boundaries or less commonly be smaller than the lesion. The comparative utility of each ancillary test may be greater in some epileptogenic substrates than others.

Developmental tumors

If the lesion location is concordant with semiology and interictal or ictal scalp EEG, resection without any additional testing could be justified. Some centers may, however, optionally use ancillary tests to extend resection beyond the MRI-identifiable lesion that may harbor occult dysplasia.^{49–51}

FCD type I and minimal change

FCD type I is probably considerably underdiagnosed, since many children present with no or subtle changes on MRI as well as nonlocalizing/nonlateralizing EEG findings/seizure semiology. Extension of the ER beyond the MRI lesion when present is common, and ancillary testing including invasive EEG recordings is highly recommended.^{52–55}

FCD type II

Type II FCD often presents with a discrete ER. Ancillary testing was thus considered optional with the exception of ECoG, a technique that was considered highly recommended or mandatory given the likelihood of recording continuous discharges that help guide the resection.

Hippocampal sclerosis

This pathology as a cause of surgically remediable epilepsy is uncommon in childhood and when seen has to be recognized as possibly secondary to another coexisting pathology. Older children generally have a clinical-electrographic picture similar to the adult temporal lobe epilepsy (TLE) syndrome^{56–58} and are more likely not to require additional testing. By contrast, younger children may have a more ambiguous clinical pattern or harbor dual pathology justifying additional investigations. Ancillary tests including IEM may help differentiate mesial versus neocortical epileptogenesis and allow tailored resections in some cases.

Sturge-Weber syndrome

MRI with contrast (to highlight the extent of the leptomeningeal angioma) is recommended. MR venography may be helpful, as there may be sinus venous occlusion, which could lead to surgical complications. Ancillary tests may be used to further define the ER, but ECoG is likely to be attenuated and therefore not useful. IEM is likewise difficult to justify.

Hypothalamic hamartoma

High-resolution MR imaging (especially coronal T2 fast spin echo sequences in multiple planes) is the single most important test, both with respect to definitive diagnosis and presurgical planning. Abnormalities elsewhere in the brain are rare but should be excluded. Serial imaging of these lesions is not required in otherwise typical cases. Video-EEG monitoring may confirm the child has seizures but may falsely localize ictal onset; the interictal and ictal EEG is typically nonlocalizing in children with only gelastic seizures and should not prompt consideration for neocortical resection.⁵⁹ Ictal SPECT may likewise have substantial false-positive or false-negative results. IEM is not required in the absence of atypical findings (such as other MRI abnormalities). Perioperative memory, endocrine, and sometimes visual evaluations are necessary.

Vascular lesions/cavernomas

As with some of the other diagnostic groups, no additional testing may be necessary if the lesion location is in agreement with seizure semiology and scalp EEG. Hemosiderin staining and/or FCD type III changes around the lesion may contribute to seizures; the extent of surgery may be guided by ancillary testing such as ECoG.

Postinfectious pathologies

Surgical outcomes are generally unfavorable, other than patients revealing unilateral temporal lobe epilepsy related to hippocampal sclerosis.⁶⁰ Herpes simplex virus 1 encephalitis warrants special mention as viral reactivation may occur following resective surgery. Neurocysticercosis and tuberculomas can sometimes present with refractory partial epilepsy, particularly in endemic areas,⁶¹ and may not require any additional testing if the lesion is concordant with seizure semiology and EEG. However, ECoG is recommended to tailor surgical resection, as the ER may extend beyond the lesion.

Perinatal brain injury

Perinatal hypoxia, ischemia, and hypoglycemia can result in focal ulegyria and gliosis with resultant drug-resistant seizures, often with occipital and/or rolandic features. As it is not uncommon to find bilateral pathology in the parietal, occipital, and central cortex, ictal SPECT may be of help, although interpretation may be difficult. It should be noted that in some children, drug-resistant seizures are age limited and resolve with appropriate drug therapy and time.⁶²

Hemispheric lesions

Detailed neurologic evaluation of motor, visual function, and developmental level are critical in guiding the decision to perform hemispheric disconnection versus tailored focal resection. Physiotherapeutic and occupational therapeutic evaluation are desirable.

Preexisting hemispheric functional deficit

In children with hemimegalencephaly, advanced Rasmussen's encephalitis, extensive Sturge-Weber syndrome, and hemispheric stroke/encephalomalacia who have hemiplegia, demonstrable hemianopia, and cognitive deficits, no additional tests are generally required. The scalp EEG abnormalities may appear more prominent over the contralateral healthy hemisphere and need only prompt scrutiny of MRI for occult pathology. Recognition of such "false lateralization," especially in the context of lateralized clinical semiology consistent with the MRI lesion, may help reduce aggressive pursuit of additional unnecessary testing.

Preserved hemispheric functionality

In children with hemispheric or multilobar cortical dysplasia or polymicrogyria, or localized stroke, further localization using ancillary tests is required to localize the seizure onset and allow a tailored resection preserving motor, visual, or temporal lobe functions. This may include ictal SPECT and/or FDG-PET, although the former may be more helpful by identifying the ictal-onset region in the context of a large lesion. 3D EEG source or MEG may likewise be helpful for localizing focal clusters of spikes, and invasive EEG recordings may allow tailored resections, thereby sparing critical functions.

Polymicrogyria: It is important to note that polymicrogyric cortex may still retain eloquent function and the entire lesion may not necessarily be epileptogenic. Ancillary tests including functional imaging and IEM may be required dependent on location and size.⁶³

Rasmussen's encephalitis presents unique challenges when the dominant hemisphere is involved. Partial resections are not effective. Serial MRI helps demonstrate progressive hemispheric atrophy. Contralateral independent interictal EEG discharges on the "normal" side may herald cognitive decline and therefore aid in decision making with regard to the need for surgery.⁶⁴ fMRI may help assess transfer of function to the contralateral hemisphere, but its role for surgical timing is unclear. Other ancillary tests such as 3D EEG/MEG/PET/SPECT are of little use.

Tuberous sclerosis

Identifying the epileptogenic tuber or tubers and defining the extent of the ER, that is, tuber versus perituberal cortex, represent the main challenges in the surgical treatment of epilepsy in tuberous sclerosis. Young children with infantile spasms, evolving multifocal epilepsy, developmental slowing, and immature neuroimaging pose greater challenges than older children with unifocal seizures. Interictal alpha methyl tryptophan (AMT) PET⁶⁵ and MEG^{66,67} are reported to provide additional localizing information, as is ictal SPECT. Certain features of a tuber on MRI such as size,⁶⁸ cystic change,^{69,70} calcification,^{70,71} and diffusion characteristics⁷² have been reported as potential markers of tuber

epileptogenicity. IEM is required in many patients and may lead to multiple staged resections in some children.

MRI-negative cases

It is recommended that pending MRI guidelines specifically for FCD detection, the ILAE guidelines for imaging children (including sequences for those under 2 years of age) be used¹⁵. Use of 3T MRI scans is advocated when available.¹⁶ To be classified as MRI negative, all MRI studies should have been reported blind as normal, and should undergo a post hoc review by a suitably skilled neuroradiologist after other functional localization data are available, in an effort to identify occult FCD.^{14,73,74} However, there is concern that focusing attention on only a specific suspect location might lead to elevated sensitivity (detection of "lesion") at the cost of diminished specificity. It is recommended that attempts should be made to exclude any other lesion elsewhere at similar sensitivity thresholds. If the suspect lesion is the only one identified (high specificity), an official addendum to the radiology reports should be entered in patient records and the case excluded from the nonlesional category.

MRI-negative patients should undergo serial assessment to document temporal consistency of localization and have a greater emphasis on exclusionary etiologies such as genetic/idiopathic (e.g., *SCN1A* epilepsies, atypical benign epilepsy with centrotemporal spikes (BECTS)) autoimmune (e.g. N-methyl-D-aspartate (NMDA), voltage gated potassium channel (VGKC), α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), gamma-Aminobutyric acid B (GABA_B) receptor antibodies), and neurodegenerative syndromes as compared to "true" lesional cases. The MRI should be repeated after completion of "maturation" especially in infancy (up to the age of 2 years), since FCD may appear and occasionally vanish with increasing myelination.⁷⁵ Video-EEG should be performed serially to document consistency of clinical characteristics and EEG localization. The time frame over which consistency is preferred depends on the degree of acuity of presentation (catastrophic epilepsies, behavioral deterioration, etc.) and is left to the judgment of the treating multidisciplinary team.

In nonlesional cases, one or more ancillary tests are required to allow a hypothesis for ER location that can then be confirmed by either ECoG or IEM.

"FLOW CHART" PROTOCOL

To optimize the practical applicability of diagnostic utility proposed in Table 2, the recommendations for various cohorts are prioritized within the framework of a flow chart protocol (Fig. 1). The recommendations assume that the index case is a standard representation of the specific clinical cohort. Atypical case scenarios as well as logistics of implementation such as concern for repeated sedation in the very young may warrant alternate strategies.

Evaluation Protocol

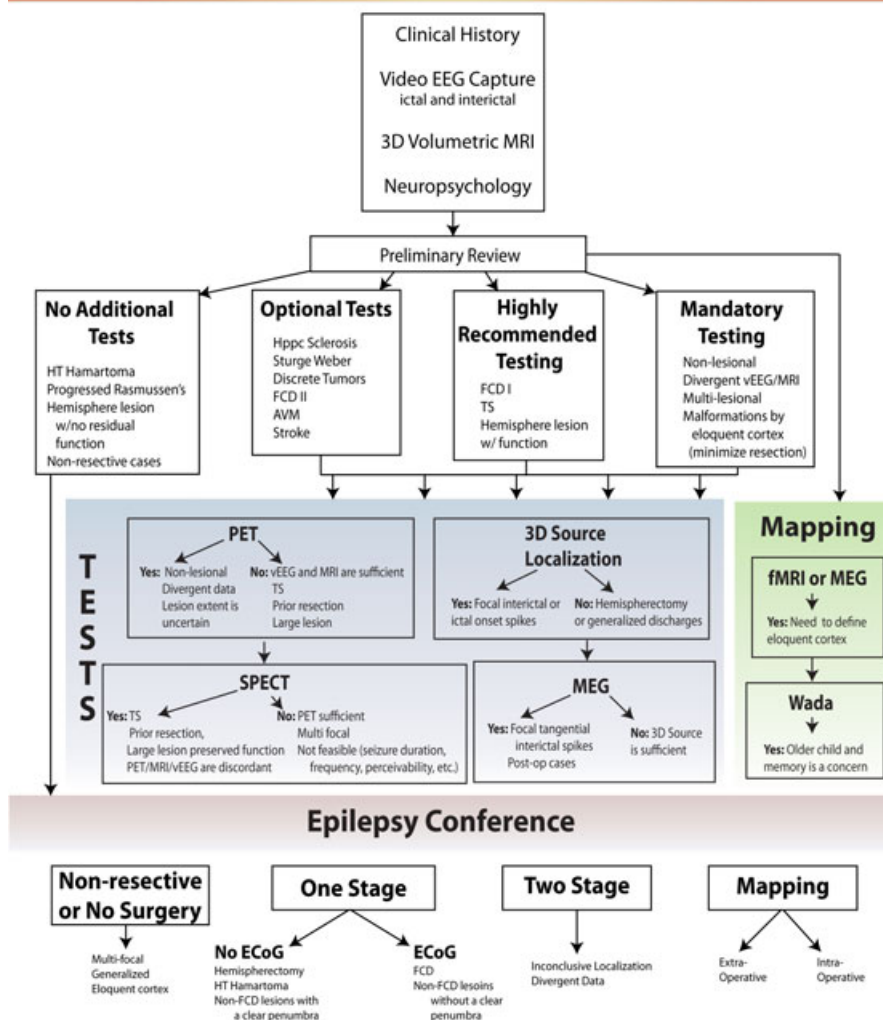


Figure 1.
Evaluation protocol.
Epilepsia © ILAE

Along with clinical and neuropsychological assessment, the interictal EEG and high resolution epilepsy protocol MRI form the mainstay of the initial assessment and are mandatory for all patient groups. The ictal EEG with video was highly recommended across all cohorts, not only for the important localizing information it provides but also for documenting seizure types, and to exclude nonepileptic events, the latter being considered particularly relevant in pediatric cases where parental history alone may not be accurate. All epilepsy surgery centers are expected to have these minimal capabilities, although resource-deficient regions of the world may consider surgery under specific circumstances.

Although there is no agreement on the specifics of MRI sequences, the following are recommended for children older than 2 years: An anatomic, thin-slice T1-weighted gradient-recalled-echo sequence, axial and coronal

T2-weighted sequence, fluid-attenuated inversion recovery sequence (FLAIR) axial (and coronal if possible), and high resolution oblique coronal T2-weighted imaging of the hippocampus (fast or turbo spin echo weighted sequence). Image thickness should be 3–4 mm—with thinner slices 2 mm T2-weighted for subtle FCD—and with 1–1.5 mm slice thickness for 3D T1 sequences. Different sequences are necessary for children younger than age 1 year: high resolution thin (2 mm or less) T2-weighted (or 3D) in three planes; 3D T1-weighted (less useful <1 year), FLAIR (axial), and oblique coronal high resolution T2-weighted perpendicular to the hippocampus.

Preliminary conference

A preliminary hypothesis is generated based on a discussion and review of the initial “mandatory” data collected regarding the specifics of the epileptic substrate, including

its location, extent, data convergence, proximity to eloquent regions, and impact on development or functional status. This discussion guides the recommendations for prioritization of subsequent diagnostic tests. The choice of tests is based on their potential to further define the ER or CC based on known strengths and limitations and the expected clinical benefit and incremental cost-effectiveness—the point at which convergence of multiple test results is achieved is subjective but is felt to best be accomplished by asking the question “will the additional test change the resection plan”?

1. No additional tests required. Lesions that are known to correlate well with the ER and require no additional testing in the context of convergent clinical and scalp EEG data. With apparent divergence, the possibility of false localization of scalp EEG should be considered and compared to the potential gains of additional testing, especially invasive EEG monitoring, as these do not change the end plan for resection but merely impose unnecessary costs and risk to the evaluation.
2. Ancillary noninvasive tests optional. Discrete substrates such as hippocampal sclerosis, vascular lesions such as Sturge Weber Syndrome and arterio venous malformations can also be taken to surgery without additional testing, although optimally one may choose to obtain additional corroboration and assessment of the lesional penumbra through ancillary noninvasive testing.
3. Ancillary noninvasive tests highly recommended or mandatory: Of the ancillary tests, FDG-PET and SPECT are the most widely used, MEG is strongly advocated by select centers, and 3D EEG source imaging is underutilized. Between the two functional imaging modalities, FDG-PET is easier to perform and proposed, following MRI, as the initial test for FCD, and nonlesional cases. Ictal SPECT is better suited than FDG-PET for the hemispheric cohort with preserved function and tuberous sclerosis or in patients who have had prior resections; but it is technically more challenging and requires seizures to be of sufficient frequency and duration to permit ictal capture. Given the complementary nature of 3D EEG and MEG, use of both tests optimally as simultaneous recordings is encouraged. However, in consideration of the significant cost-differential between the two tests, 3D EEG be used first and MEG used when the former is inconclusive or divergent. MEG may be particularly justified in MRI-negative cases where the source is suspected to be tangential such as rolandic/sylvian, interhemispheric foci, or in postoperative failures where the EEG fields are likely to be distorted.
4. Localization of critical cortex. Either fMRI or MEG may be used when preliminary data reveal ER in proximity to critical regions. Activation seen at expected sites such as the left frontal or temporal language cortex (or their homologs) is generally reliable for lateralization and surgical planning without additional invasive confirmation through Wada test or electrocortical stim-

ulation mapping. Null activation or activation patterns that do not include activation within classical language processing or motor areas should be deemed unreliable and require Wada or electrocortical stimulation mapping confirmation. Wada test is especially used in older cooperative children when memory functions are a concern.

Multidisciplinary review of noninvasive data—next step

A multidisciplinary team (MDT) case conference allows comprehensive analyses of all noninvasive data including amending individual prior test interpretation in light of collective information. For example, identification of subtle FCD lesions on MRI reported normal is often feasible in this setting, as is ascertaining likelihood of false localization of functional tests. Many centers also employ co-registration and 3D reconstruction of multimodality data to assess convergence or plan intracranial electrode placement or surgical navigation. The importance of the case conference cannot be overemphasized, as it defines the surgical candidacy and goals, and has a significant impact on guiding management strategies. Accurate documentation of MDT discussion and database storage is vital for recording of findings, formulations, and plans.

1. Additional noninvasive testing required to further clarify localization of ER or eloquent cortex.
2. No surgery or nonresective surgery. Data conclusively revealing lack of resectable ER either because of generalized or multifocal seizures or definite localization of the ER in eloquent cortex not warranting a postoperative deficit.
3. One-stage resection with or without ECoG. Convergent lesional cases and select nonlesional cases, especially involving the temporal lobe, can be done in one stage. ECoG is optional in most lesional cases, but is highly recommended in FCD and MRI-negative cases. The choice of intraoperative versus extraoperative cortical stimulation is generally guided by the patient's age and the respective center's expertise for either technique. Intraoperative mapping also has the advantage of monitoring during the course of surgery and is desirable for added risk mitigation in some cases. Anesthetic effect may, however, preclude accurate delineation of critical regions.
4. Two-stage surgery with IEM. Extraoperative recordings are generally required when the noninvasive data are inconclusive or significantly divergent, a situation more common in extratemporal MRI-negative cases or multiple lesion cases, and when accurate delineation of critical cortex by cortical stimulation is required. It is worth reiterating that in the context of apparent divergence, due consideration of the limitations of functional noninvasive tests may often help resolve disparity to the satisfaction of the clinical team.

CONCLUSIONS

There has clearly been a need to standardize the presurgical evaluation in children to curtail practices leading to increased costs and risk without documented benefit. A process of standardization, however, faces challenges posed by the lack of class 1 or 2 evidence compounded by cultural biases at each center that dictate utilization. Biases are supported in part by the fact that the definition of the ER is to some extent subjective; each diagnostic test represents a surrogate marker of the epileptogenic substrate. Even when the overall location of the ER is identified with reasonable certainty, determining the minimal/optimal extent of resection carries considerable ambiguity. Some centers adopt a minimalist approach and use ancillary tests very sparingly or not at all, others advocate a number of additional ancillary tests until the data convergence reaches the clinical team's level of confidence: the "comfort" factor.

The consensus-based recommendations presented herein are an important step toward standardization. All participants are skilled medical and surgical pediatric epileptologists with experience in directing pediatric epilepsy programs. As a consequence the report represents an expert opinion; the recommendations aim to optimize the diagnostic evaluation without constraining most standard practices at established epilepsy centers worldwide.

The recommendations strive to achieve an optimal balance between extreme overutilization and underutilization of ancillary tests. Neither the position of doing all diagnostic tests possible nor insisting on one particular ancillary test lends itself to scientific scrutiny or meets to the complex needs of various clinical cohorts. Adoption of clinical care pathways—such as the flow chart of this communication—is an essential step toward addressing the seminal question of how an additional ancillary test changes the planned resection and outcome in any given patient and should help minimize cultural influences across centers.

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DISCLAIMER

This report was written by experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent official policy or position of the ILAE.

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