

# Recent Aspects of Pediatric Epilepsy Surgery

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## Review

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Surgery has been and is now a well-established treatment indicated for adults and children with drug-resistant epilepsy (DRE). The surgical landscape for children with DRE appears to be expanding, and surgical cases of pediatric epilepsy have increased significantly in the past decade, contrary to adult epilepsy. Several fundamental changes have led to the widespread surgical treatment for DRE in children, based on a risk-benefit analysis of pediatric epilepsy surgery, and a change in our overall approach to evaluation. There are unique and age-related differences associated with pediatric epilepsy surgery, characterized by different types of etiologies, concerns for developmental progress, and safety issues. Indications for "pediatric epilepsy surgery" have been broadened to include a wide spectrum of etiologies without excluding children with "generalized" seizures, "generalized or multifocal electroencephalography", or patients with contra-lateral epileptiform activity or magnetic resonance imaging abnormalities. Furthermore, epilepsy surgery is increasingly considered in infancy and early childhood, which has similar surgical outcomes as the case of late childhood, in an effort to improve the eventual development outcome. Seizure freedom, or at least seizure reduction, is an excellent result with resolution of the associated epileptic encephalopathy, normalization of the EEG, and decrease in the total epileptic burden in the pediatric field. (2019;9:87-92)

**Key words:** Pediatric epilepsy surgery, Drug resistant epilepsy, Epileptic encephalopathy

## Introduction

Surgery has been and is now a well-established treatment indicated for adults and children with drug-resistant epilepsy (DRE). A recent epidemiological study suggested that surgery might be indicated for as many as 5% of the pediatric epilepsy population.<sup>1</sup>

The surgical landscape for children with DRE appears to be expanding, and surgical cases of pediatric epilepsy have increased significantly in the past decade, contrary to adult epilepsy. Indications for "pediatric epilepsy surgery" have been broadened to include a wide spectrum of etiologies without excluding children with "generalized" seizures, "generalized or multifocal electroencephalography (EEG)", or patients with contra-lateral epileptiform activity or magnetic resonance imaging (MRI) abnormalities.<sup>2-4</sup> These changes have been already recommended for early determination of surgical eligibility in children and the early referral of such individuals to specialized surgical centers by the Subcommission for Pediatric Epilepsy Surgery of The International League Against Epilepsy.<sup>5</sup>

Several fundamental changes have led to the widespread surgical treatment for DRE in children, based on a risk-benefit analysis of pediatric epilepsy surgery, and a change in our overall approach to evaluation.<sup>6</sup> Recent advances in neuroimaging and electrophysiology have contributed to presurgical evaluation and improvement of peri-surgical management. However, there are still remaining misconceptions regarding surgical options, which may make general neurologist and families reluctant to use the epilepsy surgical treatment, such as the idea that all drugs need to be tried, and bilateral EEG spikes or normal MRI were contraindications to surgery. Focal lesions can be removed without detailed presurgical evaluation.<sup>7</sup>

In this review, we will focus on the unique and age-related differences associated with pediatric epilepsy surgery, based on the following seven issues: the surgery for West syndrome or Lennox-Gastaut syndrome (LGS); the surgery for MRI negative lesion; the etiology of pediatric surgery; the surgery for young age; the corpus callosotomy (CC) for relief of seizure burden; the safety issue; the surgery outcome in recent years.

## Surgery for widespread EEG abnormality with/without age-related phenomena such as development of West syndrome or LGS

West syndrome and LGS are best known age-related epileptic conditions, distinct from adult epilepsy.<sup>8,9</sup> These epileptic conditions are known as epileptic encephalopathy (EE), as the epileptic process pervasively inhibits cognition and cognitive development.<sup>10</sup> The age-dependent expression suggests susceptibility of the immature brain to West syndrome or LGS phenotype. In addition, epileptic discharges in pediatric brain have a tendency to spread rapidly through the commissure fibers.

Wyllie et al.<sup>3</sup> reported that congenital or early-acquired brain lesions, despite abundant generalized or bilateral epileptiform discharges on EEG, were successfully treated with surgery. Since then, many reports related to epilepsy surgeries for these conditions were published.<sup>4,11,12</sup> Furthermore, the findings suggest that the epileptic process is potentially reversible if an underlying lesion can be identified and removed early. Due to their abnormal background EEG, extreme disorganization seen in hypsarrhythmia, infantile epileptic encephalopathies, and seizure semiology may erroneously suggest global or multi-focal epilepsy, potentially hiding an underlying epileptogenic focus. For example, up to 25% of patients with LGS manifest persistent focal abnormalities or asymmetry related to slow spike-wave discharges on EEG.<sup>13</sup>

Some of the children with severe epilepsies characterized by signs of focal abnormality eventually turn out to be candidates for epilepsy surgery, particularly in the very young age group.<sup>14</sup> These children frequently suffer from severe EE, with early onset of epilepsy during the first year of life, daily seizures with a generalized or multifocal interictal EEG and a negative MRI, arrest of mental development, or loss of already acquired skills. Early, focal curative resection of a child with EE and reversal of EE is well established. Indeed, children with EE currently stand a better chance of recovery with successful epilepsy surgery compared with the conditions 20 to 30 years ago when EE was considered a fatal disease.<sup>2</sup>

### Epilepsy surgery for MRI negative lesion

MRI is the most powerful tool for the structural diagnosis of epilepsy, with a negative lesion MRI in presurgical evaluation estimated as high as 30% to 40% in pediatric epilepsy series.<sup>11,15</sup> Focal cortical dysplasia (FCD) is the most possible structural cause of epilepsy in a

young child with negative MRI findings.<sup>14,16</sup>

MRI is often negative at ages younger than 18 months because of lack of contrast due to immature myelination.<sup>17</sup> After the age of 24 to 30 months, following mature myelination, MRI may reveal unsuspected cortical dysplasia.<sup>18</sup> FCD diagnosis is complicated by not only the subtypes such as type I, which is more difficult to find than type IIb, but also by the age of onset because type I usually occurs early.<sup>2</sup> Thus, if children with severe epilepsy presented with hints of focality consistently in presurgical evaluation in the presence of normal MRI, the possibility for surgical intervention cannot be disregarded.

Children with negative MRI may not test negative under optimal conditions. In such cases, additional evaluation with single photon emission computed tomography<sup>19</sup> or FDG-positron emission tomography<sup>20</sup> or both, and long-term video EEG recording are helpful.<sup>21</sup> Specifically, in long-term video EEG, interictal patterns were as important as ictal EEG results: localized epileptiform activity including spikes, paroxysmal fast activity with clinical or subclinical pattern, other focal abnormalities, and asymmetric physiological waveforms.<sup>22</sup>

### Etiology

The most common etiologic categories are focal, multilobar or extensive hemispheric malformations of cortical development (MCD), of which FCDs are the most prevalent, accounting for around 30% to 70% of pediatric surgical series.<sup>23,24</sup> Developmental tumor is the second most common etiology, followed by other less common causes such as hippocampal sclerosis, encephalitis or vascular malformation.<sup>24</sup>

The incidence of FCDs was reported increasingly due to better identification of the lesions through improved MRI resolution and a better understanding of the electro-clinical characteristics of various FCD subtypes, resulting in favorable post-operative seizure outcome.<sup>11,14</sup> After the introduction of the new ILAE classification of three major pathological FCD subtypes in 2011, many studies have reported distinct imaging, clinico-electrophysiological, and outcome characteristics based on pathological subtypes.<sup>11,25,26</sup> The majority of FCDs in pediatric epilepsy surgery was FCD type II, which was mostly visible on MRI compared with other subtypes of FCD.<sup>27</sup> In addition to its two different subtypes including type IIa and IIb, more restricted and localized epileptic processes were observed in type IIb.<sup>11</sup> The clinical expressions of mild pathologies, such as mild MCD and FCD type I, are very different from epilepsies caused by FCD type IIb.<sup>11,27-29</sup> Several series showed that pathologically mild phenotypes cannot be

directly correlated clinically because pathologically mild forms such as FCD type I may frequently manifest negative MRI lesions, early-onset seizures accompanying delayed development, multilobar or hemispheric lesions, and the lower rate of seizure-free outcome, which ultimately result in severe epileptic burden.<sup>2,11,14</sup>

On the other hand, global epilepsies related to underlying genetic syndromes may be difficult to identify given the short period of neurological development at the time of presentation. Clinicians must be cautious against misleading focal abnormalities detected on functional imaging, or subtle changes in MRI, which may be caused by molecular genetic mutations or chromosomal abnormalities. Therefore, accurate investigations are needed, for example, with "Next Generation Sequencing" panels of genes, containing the relevant epilepsy genes, and comparative genomic hybridization arrays, which detect very small chromosomal abnormalities.<sup>30</sup> These genetic technologies are needed when it comes to the decision for epilepsy surgical treatment.

### Epilepsy surgery at a young age

Pediatric epilepsy surgery in the early phase is generally performed for late childhood period. Epilepsy surgery during infancy differs in many ways compared with surgeries in older children and adolescents. Poorly-controlled seizures and the negative impact of the anti-epileptic drugs have a detrimental effect on the developing pediatric brain, particularly in the infant. Hence, epilepsy surgery is considered increasingly in the case of a very young child, in an effort to improve the eventual development outcome. Historically, surgical intervention at a very young age was contraindicated not only due to safety issues associated with complex neurosurgical procedures, anesthesia and intensive care, but also increasingly challenging and complex cases mentioned above.<sup>31</sup>

Early surgical intervention was shown to be effective in ameliorating seizures in 46% to 80% of children operated before the age of three in 1996-2015, with similar outcomes in older children.<sup>32</sup> However, the reported risks of brain surgery were the highest in the younger age group. On the other hand, brain plasticity and potential recovery are significantly higher during early life, especially in the first year of age.<sup>33,34</sup> Improved surgical outcomes are possible in case of reversible dysfunction outside the epileptogenic zone (EZ).<sup>35</sup> A successful case presentation is a child with West syndrome showing major improvement after removal of the EZ leading to resolution of diffuse EE after the surgery.<sup>3,11</sup>

Studies showed improvement in development quotient (DQ) after epilepsy surgery, especially in children operated at a younger age lower than the optimal age for acquisition of specific developmental milestones.<sup>36,37</sup> However, several limitations exist in studying the developmental progress in early age, and other studies related to cognitive outcome showed "no significant change", or a minority of patients presented with a "decline" in epilepsy surgery.

Understanding development outcome after surgery depends on the basic pathophysiology, including balance between the EZ, dysfunctional zone outside EZ, and cognitive role of EZ.<sup>35</sup> Furthermore, the underlying etiology, age at surgery, presurgical DQ or intelligence quotient, postoperative seizure freedom, cessation of antiepileptic medication, and follow-up interval have all been independently correlated with post-operative developmental outcomes.<sup>35</sup> Additional prospective studies using standardized outcome measures of development are needed, especially in the very young age group with the highest potential for improved developmental outcome after control of epilepsy.<sup>37</sup>

### CC for relief of seizure burden

CC partially disconnects the cerebral hemispheres, for prevention of interhemispheric spread of seizure activity. It is a palliative surgical procedure designed to control the most injurious seizures. Callosotomy is considered particularly helpful for atonic, tonic, and tonic-clonic seizures, and typically limited to those with catastrophic DRE and moderate-to-severe intellectual disability.<sup>38</sup> In a minority of patients, CC is planned as a staged procedure, for example, as a first step toward resective surgery.<sup>39</sup> In specific cases, a focal seizure onset might be demonstrated once callosotomy stopped the rapid bilateral synchronization of epileptic discharges.

Overall, seizure outcome is shown to be comparable to earlier series, with up to 20% of patients becoming seizure-free in the short-term follow-up.<sup>40</sup> However, it is limited to evaluation of the outcome of CC within the standard seizure outcome classification since its primary goal is to reduce the number of traumatic drop attacks. Despite the lack of consistent outcome classification, all the studies reported that CC is safe and effective against refractory generalized epilepsy in pediatric patients.<sup>38</sup> Secondary outcome involved reduction of other types of seizure or decreased intake of antiepileptic drugs, resulting in a lower epileptic burden. These primary and secondary goals of callosotomy are hardly achieved by other treatment modalities.

Total callosotomy and anterior or anterior two-thirds section were

the two major subtypes of CC.<sup>40</sup> However, a recent study composing of selective posterior callosotomy showed that 30 out of 36 patients were either free or almost free of drop attacks at the last follow-up.<sup>41</sup> Variable extensions of anterior callosotomy frequently resulted in failure to control drop attacks and prompted the need for total callosotomy, in which the posterior resection was the most crucial segment of the surgical procedure.

## Safety issue

Hemispherectomies and multilobar resections are associated with significant risks in children, due to their small body weights and lower blood volumes. Surgical and anesthetic risks in infants were increased significantly due to their delicate physiology, friable brain parenchyma, and often aberrant brain anatomy. These safety issues represent major reluctant factors in intervening surgical intervention.

Mortality in pediatric epilepsy surgery series ranges between 1% and 2% and should be weighed against risks of sudden unexpected death in epilepsy, with the incidence of sudden death estimated at 1:295 per year.<sup>42</sup> Morbidity ranges approximately 2% to 5%, including hemorrhage, infection, and hydrocephalus as well as neurologic deficits.<sup>42</sup> In other studies, rates increased in surgical series of infancy from zero to 47%.<sup>32,43,44</sup> Neurological complications of epilepsy surgery decreased substantially. However, implantation of intracranial electrodes increased the frequency of adverse events due to increased number of staged operations performed in children. These adverse events required additional surgical procedures.

## Surgery outcome in recent years

Despite increased frequency of surgical interventions against more complicated forms of pediatric epilepsy, it is encouraging that the overall outcomes continue to be highly beneficial, not only with respect to seizure frequency, but also improved quality of life. Almost 50% to 70% of the patients were seizure-free, and 20% to 30% manifested rare seizures after resective surgery.<sup>45</sup>

The seizure outcomes after surgery are not universal and vary critically between different patient populations.<sup>46</sup> First, the seizure outcome based on etiology varied. A recent study showed that developmental tumors showed an 80% seizure-free outcome in children followed by cortical malformation accounting for 60% seizure-free results 1 year after surgery.<sup>24</sup> Longitudinal outcome studies have shown that FCD surgery yields less favorable results compared with

other well-recognized epileptic pathologies, also showed unsustainable seizure outcomes over time. Second, hemispheric surgeries resulted in more favorable outcome than extratemporal single-lobe or multilobar resections, yielding almost 70% to 80% of seizure-free outcome. In 2015, a Cochrane systematic review showed that the absence of MRI evidence of focal abnormalities decreased the relative probability of favorable outcome more than 20%.<sup>47</sup> Compared with adult epilepsy, candidates for pediatric surgery, carrying one or more unfavorable predictors, presented with high incidence of non-lesional epilepsy or cases of FCD warranting relatively complicated surgery, resulting in less favorable outcome.<sup>45</sup>

Seizure freedom or at least seizure reduction is an excellent result with resolution of the associated EE and normalization of the EEG and decrease in the total epileptic burden in the pediatric field. In addition, an increasing number of experts support the notion that surgical intervention converts DRE to a drug-responsive condition.<sup>48</sup>

## Conclusions

In contrast to adult epilepsy surgery, the change in surgical landscape in children does not appear to be epidemiological, but rather probably reflects a change in our understanding of the problem of medically refractory childhood epilepsy. Recent progress in pre-surgical evaluation and peri-surgical management provides significant improvement and the possibility of earlier surgery than before. The effectiveness and safety of epilepsy surgery for carefully and appropriately selected children have been established, but additional prospective studies using standardized outcome measures of development and multi-center studies are needed for determining the individual chance of improvement.

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