
Epilepsy Surgery in Childhood

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ABSTRACT: Historically, epilepsy surgery has been considered a treatment of last resort. Advances in neuroimaging, particularly high resolution magnetic resonance imaging (MRI) techniques and functional neuroimaging, advances in neuroanesthesia and neurosurgery have all contributed to the development of safe and effective epilepsy surgery in infants and children. Furthermore, epilepsy surgery may prevent the chronic deleterious effects that uncontrolled epileptic seizures have on brain development. The main challenges that clinicians face are early identification of infants and children who have epilepsy which is amenable to epilepsy surgery, the timing of epilepsy surgery and the investigation of patients where no lesion is demonstrable on MRI. It is imperative that children be followed after epilepsy surgery to assess the long-term outcomes not only in relation to seizure control, but also to assess quality of life, psychoeducational achievement, and psychiatric co-morbidity.

RÉSUMÉ: Chirurgie de l'épilepsie dans l'enfance. Historiquement, la chirurgie de l'épilepsie était considérée comme un traitement de dernier recours. Les progrès en neuroimagerie, particulièrement les techniques d'imagerie par résonance magnétique de haute résolution (IRM) et la neuroimagerie fonctionnelle, les progrès en neuroanesthésie et en neurochirurgie ont contribué au développement de la chirurgie de l'épilepsie qui est maintenant sûre et efficace chez les nourrissons et les enfants. De plus, la chirurgie de l'épilepsie peut prévenir les effets chroniques délétères que certaines crises épileptiques non contrôlées ont sur le développement du cerveau. Le principal défi que les cliniciens rencontrent sont l'identification précoce des nourrissons et des enfants qui ont une épilepsie traitable chirurgicalement, le moment d'effectuer cette chirurgie et l'évaluation des patients chez qui l'IRM ne détecte pas de lésion. Il est essentiel que les enfants soient suivis après la chirurgie de l'épilepsie afin d'évaluer les résultats à long terme, non seulement quant au contrôle des crises, mais aussi pour évaluer la qualité de vie, le niveau psychoéducatif atteint et les comorbidités psychiatriques.

Epilepsy is the most common neurological disorder in childhood affecting 0.6% of Canadians and in 75-85% of individuals the onset is before the age of 18 years¹. In 30% or more of individuals with epilepsy, seizures do not respond to medical therapy^{2,3}. Treatment resistant epilepsy is currently defined as failure to respond to two or more appropriate anti-seizure medications⁴. Uncontrolled seizures in the developing brain may be associated with life long effects on intellectual function, attention and behavior^{5,6}. Furthermore, uncontrolled epilepsy is associated with a two to four fold greater mortality rate compared to age matched individuals.

The early identification of children with treatment resistant epilepsy who might benefit from epilepsy surgery is extremely important⁷. The timing of epilepsy surgery to optimize intellectual function in light of brain plasticity is also critical. There is often reluctance among neurologists and pediatricians to consider referral for epilepsy surgery evaluation at an early stage due to the possibility of long-term remission in children treated medically^{8,9}. The alternative therapeutic options of dietary therapy using the ketogenic diet, modified Atkin's diet or low glycemic index diet and vagus nerve stimulation are often more appealing to neurologists in light of their less invasive nature in comparison with epilepsy surgery.

However, epilepsy associated with malformations of brain development, hippocampal sclerosis, diffuse hemispheric disorders (Sturge-Weber syndrome, hemimegalencephaly, hemispheric cortical dysplasia, Rasmussen syndrome), tuberous sclerosis complex, hypothalamic hamartomas, brain tumors, and stroke are commonly associated with treatment resistant epilepsy

and furthermore are often amenable to successful epilepsy surgery^{9,10}.

Types of Epilepsy Surgery

Surgical procedures performed in children are very similar to those performed in adults with the exception of surgery for diffuse hemispheric disease. However, epilepsy surgery involves extra-temporal lobe structures more commonly in children than adults.

Hemispheric surgery was first reported as a treatment for epilepsy by Krynauw in 1950¹¹ and since then there have been modifications in the surgical techniques. Anatomic hemispherectomy and hemidecortication are performed infrequently nowadays. There are several functional hemispherectomy procedures but in Canada, the most frequent functional hemispheric surgery performed is that proposed by Dr. Villemure called "peri-insular hemispherotomy"¹². This procedure involves creating a window in the insula allowing

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RECEIVED JANUARY 26, 2012. FINAL REVISIONS SUBMITTED AUGUST 7, 2012.
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access to the lateral ventricle. From within the lateral ventricle, the cortex is disconnected from deeper structures. Medial temporal lobe structures are resected and the corpus callosum is divided in its entirety. Hemispheric surgery is performed for diffuse hemispheric disorders such as Sturge-Weber syndrome, large strokes, with or without a porencephalic cyst, malformations of brain development, hemimegalencephaly, Rasmussen's syndrome and rarely for diffuse brain tumors. Hemispheric surgery is very successful when seizures are lateralized to the affected hemisphere and there is complete disconnection of the hemisphere¹³. In various series, up to 70-80% of patients of patients are seizure free following hemispheric surgery^{14,15}.

Lesionectomy and focal cortical resections involve resections of the lesion with or without surrounding epileptogenic cortex. These resections can be confined to one lobe of the brain or multi-lobar. Very large multi-lobar resections are usually performed for malformations which do not involve the entire hemisphere or destructive processes involving several lobes¹⁶. Surgery for mesial temporal lobe sclerosis, most commonly involves en-bloc resection that includes the mesial temporal lobe structures, parahippocampalgyrus, and often the inferior temporal gyrus^{17,18}.

Selective amygdalohippocampectomy is performed in children infrequently, due to the fact that isolated mesial temporal lobe sclerosis is often associated with other pathologies such as focal cortical dysplasia or tumors. Tuberectomy or resection of multiple cortical tubers in children with tuberous sclerosis complex and treatment resistant epilepsy is increasingly performed^{19,20}.

Corpus callosotomy which involves division of the corpus callosum, either in its anterior two thirds or in its entirety, is primarily performed in children with disabling seizures which cause them to fall abruptly to the ground, with tonic or atonic seizures. This results in improvement in tonic or atonic seizures in up to 80% of patients. Other seizure types may also be helped by corpus callosotomy. When it is not possible to adequately lateralize or localize epileptic seizures, corpus callosotomy may assist in lateralization following the procedure. However, with advances in functional neuroimaging techniques (PET) and magnetoencephalography (MEG), it is usually not necessary to form a corpus callosotomy for this reason²¹.

Multiple subpial transections was proposed by Morrell in 1989²² as an epilepsy surgery procedure in order to preserve function in eloquent cortex such as in the language area and the motor area for the hand. This procedure involves division of the horizontal fibers at 5 mm intervals in the cortex and this is thought to disrupt the epileptic discharges but preserve function. It may be performed with or without cortical resection. A multicentre analysis of multiple subpial transection in 211 patients demonstrated efficacy for both focal and generalized seizures²³. It has also been used in refractory Rolandic and Sylvian epilepsy and Landau-Kleffner syndrome²⁴.

Surgery for hypothalamic hamartomas has gained popularity following successful surgery in the last decade. This procedure can be performed transcallosally, endoscopically or via skull base approach depending on the size of the lesion and the surgeon's experience. Complete resection of the hamartoma and resolution of gelastic seizures is associated with markedly

improved neurodevelopmental outcome. Alternatives to resective surgery to the hypothalamus include gamma knife radio surgery. The choice of surgical approach for hypothalamic hamartomas is influenced by the type of epilepsy, the location and size of the lesion and available resources^{25,26}.

Selection of Surgical Candidates

Phase I of the pre-surgical evaluation begins with a careful review of the clinical history. Details of the pregnancy, perinatal history, presence of febrile seizures, status epilepticus, central nervous system infection and brain trauma are associated with certain types of brain pathology. Review of neurodevelopment milestones, handedness and intellectual function are very important in children. Details of the family history, in light of the advances in our understanding of the genetics of epilepsy may allow us to identify genetic epilepsies where surgery would not be recommended such as autosomal dominant frontal lobe epilepsy and autosomal dominant temporal lobe epilepsy.

The neurological examination is often of limited contribution other than in patients with diffuse hemispheric disorders or large structural lesions. Assessment for neurocutaneous abnormalities and visual field examination with formal perimetry are recommended.

Neuropsychological testing and review of prior psycho-educational assessments allows one to determine whether there has been any regression or plateau in cognitive function. Dichotic listening test may be useful to lateralized language but is not specific. In children under the age of three years, who often have continuous or extremely frequent epileptic seizures and epileptiform discharges, formal assessment of their neuropsychological function is often not possible or may have limited value.

Due to the high prevalence of psychiatric co-morbidity in children with epilepsy, it is important to screen children as part of the pre-surgical work up for anxiety, mood, attention and other behavioral disorders. Attention to family history of psychiatric disorders is also important. Screening can be performed by the neurologist, neuropsychologist, or depending on resources, a psychiatrist. A systematic approach to screening for psychiatric co-morbidity pre and post surgery is recommended and there are many excellent resources available²⁷.

Review of interictal EEGs and in most cases ictal video-EEG monitoring to document habitual seizures are important. However, if there is a clear structural lesion such as a tumor in the temporal lobe and seizure semiology typical of temporal lobe involvement, it may not always be necessary to perform intensive video-EEG monitoring. High resolution MRI, reconstruction and 1 mm thick T1, T2 and FLAIR imaging is necessary²⁸.

If there is congruence between the clinical, structural neuroimaging, EEG and neuropsychological data, more extensive investigations may not be required.

However, in cases where there is a lack of congruence or the area of epileptogenesis has not been adequately identified, further investigations using more detailed analysis of MRI data, looking at cortical thickness and functional are warranted²⁹.

Neuroimaging studies using positron emission tomography PET or ictal and interictal single-photon emission computed

tomography (SPECT) and MEG may provide further data regarding the localization of the ictal onset zone. Functional MRI is a non-invasive tool for assessment of language, motor function and the visual pathway and memory^{30,31}. Children as young as six to seven years of age are usually able to co-operate for these studies. Due to the fact that up to 30% of children with epilepsy may have language in the non-dominant or both hemispheres, knowledge of language lateralization is critical in the decision making for epilepsy surgery^{32,33}. Functional MRI studies have replaced sodium amytal testing for language lateralization in children in many centres.

Resources vary from centre to centre and country to country and any surgical candidates can be identified with good quality EEG, high resolution MRI studies.

Phase II

The decision to proceed to phase II evaluation using subdural grid and/or depth electrodes should be based on a well thought out hypothesis as to a region of epileptogenesis and eloquent brain functions. Subdural and depth electrodes have benefits and limitations. Depth electrodes permit access to deep structures which are difficult to access with subdural grid and strip electrodes, such as mesial frontal lobe, cingulate gyrus and hippocampus. However, with these latter techniques, the risk of bleeding and infection is increased and blood transfusion with its attendant risks may be needed. High frequency oscillations (HFOs) appear excellent markers for the epileptogenic zone and it has been related to better postsurgical outcome than removing the seizure onset zone, Their potential needs to be assessed by future research³⁴.

Complications of Surgery

Complications of epilepsy surgery are summarized in Table 1. They may be classified as general or non-specific risks applicable to any surgery. Infection risk in epilepsy surgery includes meningitis; however aseptic meningitis due to irritation of the meninges by blood is more common finding and can

mimic bacterial meningitis. Symptoms include headache, vomiting, fever, lethargy. This complication should be treated with steroids and typically resolves within several days.

Complications may also be classified as transient or permanent. Transient mutism or dyspraxia has been described after callosotomy and supplementary sensory motor or mesial frontal lobe resections and usually resolve within days to weeks. Permanent complications are related to the lobe of the brain which has been operated on. In temporal and occipital resections visual field defects may be present prior to surgery and thus need to be assessed formally pre and post-operatively. Post-operative deficits include partial quadrantanopsia, quadrantanopsia or hemianopsia. Surgery in the parietal lobe, may occasionally be associated with visuospatial defects, alien hand, or reading deficits. Stroke may complicate surgery in any part of the brain but vulnerable areas include surgery in the insula where the branches of the middle cerebral artery are vulnerable to damage. During corpus callosotomy, the anterior communicating artery is also vulnerable as it is located just above the corpus callosum and damage to this vessel may result in weakness of the contralateral leg. Large hemispheric surgeries are associated with hemiparesis and hemianopia but these deficits are commonly present in patients with diffuse hemispheric disorders prior to surgery. Damage to the dominant hemisphere, if speech is located in the dominant hemisphere, will result in a deterioration in speech but if the surgery is performed in young children, language will transfer to the contralateral hemisphere.

Surgery in infants and children under the age of three years is particularly challenging³⁵. In infancy, the blood volume is very low and the risk/benefit ratio of major surgery in this age group needs to be very carefully considered. It is critically important to have anesthesia and intensive care expertise in the management of infants and very young children. Brain swelling may occur particularly with hemimegalencephaly and surgeons may choose to resect a larger area than they would typically do a peri-insular hemispherotomy. This is to facilitate any swelling that may occur in the post-operative period. Blood transfusion may be

Table: Complications of Epilepsy Surgery

General Complications	Specific Complications
Infection	Visual field defects
Bleeding	Stroke due to damage of arterial or venous system
Anesthetic complications	Early post-operative seizures
Aseptic meningitis	Memory deterioration
	Mutism
	Dyspraxia
	Depression
	Psychosis
	Mortality

required in infants and young children undergoing diffuse hemispheric disorders. Despite the risks of surgery in children under the age of three years, our own experience and that of colleagues suggest that surgery is safe and effective in this age group^{35,36}. Hypothalamic hamartomas pose special surgical challenges and surgery in this location requires special surgical expertise. Early control of seizures is associated with an improved neuropsychological outcome²⁵. Following hypothalamic surgery, diabetes insipidus may occur and may be difficult to manage.

CONCLUSIONS

Epilepsy surgery is effective and safe in the pediatric population when carried out in experienced centers by a pediatric multidisciplinary team. Phase I evaluation involves high resolution MRI studies, video-EEG monitoring, and neuropsychological assessment. Functional MRI and/or MEG may be useful in indentifying eloquent brain functions and areas of epileptogenesis. Functional imaging studies using PET and SPECT are useful if MRI does not demonstrate a clear lesion. Phase II evaluation with invasive EEG electrodes should only be embarked when one has a clear hypothesis to test.

Assessment of psychiatric comorbidity and pre and post surgery is important.

The goals of epilepsy surgery need to be established clearly between the family and the epilepsy surgery team. Long-term follow-up after epilepsy surgery should comprise assessment of seizure outcome, quality of life, and neuropsychologic and psychiatric co-morbidity.

The Future

Advancement in technology is helping our understanding of epilepsy and it is progressing at a dizzying pace. There has been an explosion of knowledge in the field of genetics translated in a better genotype of some epileptic syndromes and exploring the genetic basis of malformations of brain development at the gene and cellular level including cellular signaling pathways. The most exciting example is the role of the mTOR pathway in tuberous sclerosis complex³⁷. The promising development of inhibitors of signal transduction pathways are currently being investigated and nanotechnology has emerged as an exciting multidisciplinary field promising to provide breakthrough solutions. The mTOR pathway may be central to the pathophysiology of epilepsy in a spectrum of cortical malformations and may serve as a common target for novel therapeutic approaches for epilepsy, including potential anti-epileptogenic and disease-modifying therapies³⁸.

The advances in MRI techniques, the availability of 7T MRI, advances in EEG with high frequency oscillations will allow a more non-invasive approach to the evaluation for epilepsy surgery. It is important in the area of epilepsy surgery in childhood that we abide by the Hippocratic Oath and first do no harm (*primum non nocere*).

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