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Epilepsy Surgery for Pediatric Epilepsy: Optimal Timing of Surgical Intervention

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Abstract

Pediatric epilepsy has a wide variety of etiology and severity. A recent epidemiological study suggested that surgery might be indicated in as many as 5% of the pediatric epilepsy population. Now, we know that effective epilepsy surgery can result in seizure freedom and improvement of psychomotor development. Seizure control is the most effective way to improve patients neurologically and psychologically. In this review, we look over the recent evidence related to pediatric epilepsy surgery, and try to establish the optimal surgical timing for patients with intractable epilepsy. Appropriate surgical timing depends on the etiology and natural history of the epilepsy to be treated. The most common etiology of pediatric intractable epilepsy patients is malformation of cortical development (MCD) and early surgery is recommended for them. Patients operated on earlier than 12 months of age tended to improve their psychomotor development compared to those operated on later. Recent progress in neuroimaging and electrophysiological studies provide the possibility of very early diagnosis and comprehensive surgical management even at an age before 12 months. Epilepsy surgery is the only solution for patients with MCD or other congenital diseases associated with intractable epilepsy, therefore physicians should aim at an early and precise diagnosis and predicting the future damage, consider a surgical solution within an optimal timing.

Key words: pediatric epilepsy, epilepsy surgery, surgical indication, seizure outcome, psychomotor development

Introduction

Poorly controlled seizures in childhood have a detrimental impact on the developmental brain, especially when the seizures are frequent, prolonged, and are associated with status epilepticus. The goals of epilepsy therapy in children are complete control of their seizures, improve or maintain their psychomotor development, and enhance the quality of life for them and their family. Epilepsy surgery is the method of choice to achieve those purposes, especially in patients with intractable epilepsy. Hence, epilepsy surgery for a child is decisive and requires appropriate timing.

When considering surgical therapy for childhood epilepsy, we should clearly differentiate therapeutic surgeries from the palliative ones. Neurosurgeons should aim for complete resection of epileptic focus and achieve seizure-free result. Because pediatric brain possesses extensive neural plasticity, surgical indications can be, to some extent, towards an aggressive surgical procedure, as functional recovery takes place even after resection of eloquent areas in some situations. Early surgery has an advantage to recover function and improve psychomotor development. For cases with bilateral multiple epileptic foci, negative magnetic resonance imaging (MRI), and poor general condition, the surgeon can select palliative surgery. The purposes of palliative surgery are to reduce the epileptic injury and prevent further damage of the epileptic child's development. This is an alternative for patients without indications for definitive curative epilepsy surgery.

Understanding the natural history of each etiology is important for deciding optimal surgical timing in both curative and palliative surgeries. The optimal surgical timing should allow the patients to catch up their corresponding psychomotor development. In this review, we will summarize recent advances in basic and clinical research related to pediatric epilepsy surgery, and consider its ideal timing.

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Characteristics of Child's Brain and Epilepsy

Child's brain, especially in the first few years of life, has bipolar characteristics such as neural plasticity and vulnerability.

Neural plasticity is a well-known characteristic of the developing brain. The risk for postoperative deficits can be modified if surgery is performed during stages of active brain maturation due to re-arrangement of functional localization. Areas that can compensate for motor function were reported in the premotor cortex, supplementary motor area, and parietal lobe of the affected and the contra-lateral hemisphere.[1–4] In order to allow compensation for the motor function, only removal of cortex without the descending cortico-spinal tract is essential.[5,6] From those basic evidences, resection of only the primary motor cortex with preserving underlining corticospinal tract in a young child allows compensation of motor weakness. Therefore, motor weakness after hemispherectomy cannot be compensated completely. Projection fibers for motor function to the lower extremity, contra-lateral to the disconnected hemisphere, come partially from the ipsilateral motor cortex (non-decussating fibers). Consequently, patients can partially recover the lower extremity, but compensation for the upper extremity is less after hemispherectomy. Speech function should be under concern especially in dominant hemisphere surgery. Since we do not know any factors influencing the remodeling of brain function, we have to rely on the clinical experience accumulated in relation to patient's age. From the available literature on speech plasticity, age under 5 at the time of surgery was favorable for speech recovery.[7,8] For children with progressively deteriorating cognitive function due to intractable seizures, surgery aiming at psychomotor recovery has to be considered even in those above 5 years.[9,10] Recovery or improvement of cognitive function can be expected even in older children. Memory function does not rely only on hippocampal network integrity, but also on systematic neural networks. If a region associated with cognition is damaged, neural networks may re-organize to compensate for the affected higher cerebral function.

Child's brain is also vulnerable against insults such as fever, electrolyte abnormalities, ischemia, and intracranial hypertension.[11] Neurosurgeons should take cerebral vulnerability into account and prepare for peri-operative management together with experts in pediatric anesthesiology and clinical general pediatrics. The comprehensive management of effective and safe epileptic surgery for children is conducted in specialized facilities with the necessary level of expertise. The risk-benefit ratio influences the surgical timing. In principle, patients with complex localization of the epileptic foci and high-risk factors should be referred to the specialized epilepsy surgical unit without delay.

Surgical Candidates

As a general rule, epilepsy surgery is indicated for patients with drug resistant epilepsy. The International League Against Epilepsy (ILAE) published a consensus definition of "drug-resistant epilepsy" as a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom.[12] The definition of seizure freedom which is the achievement of a seizure-free duration that is at least three times the longest inter-seizure interval prior to starting the new intervention, or at least 12 months.[12] These definitions can be adapted for deciding surgical indications in pediatric epilepsy. Children with intractable epilepsy can be considered for surgical indications within 12 months from starting adequate AEDs. Because the most important goal for pediatric epilepsy surgery is improvement of psychomotor development, a catch-up of an acceptable degree can be achieved even after the evaluation of AEDs according to these definitions.

Candidates of curative epilepsy surgery are those with intractable focal epilepsy. They have seizure onset before the age of 2 and have frequent seizures and mental retardation. Indeed, seizure onset of intractable epilepsy in children was 1 year or less in 46%, and less than 2 years in 60% of the patients from data of the United States, European, and Australian epilepsy centers.[13] Physicians should actively evaluate to confirm or exclude focal epilepsy even in very young infants. Guidelines for imaging studies in infants and children with recent-onset epilepsy from ILAE recommend performing imaging studies when the patient shows any findings suspected as focal in seizure semiology or electroencephalogram (EEG) or focal neurological deficit.[14] The Commission on Neurosurgery of the ILAE also published recommendations on proper referral and pre- and postoperative assessments.[11] In this publication, they list up the candidates for epilepsy surgery in pediatric age as follows: cortical dysplasia, tuberous sclerosis complex, polymicrogyria, hypothalamic hamartoma, hemispheric syndromes, Sturge–Weber syndrome, Rasmussen syndrome, Landau–Kleffner syndrome, tumors, and vascular diseases (Table 1). The majority of these diseases can be diagnosed using the current advanced imaging studies. Nearly 50% of imaging studies in children with new focal onset epilepsy would be abnormal, and 15–20% would provide useful information on etiology and focus localization.[15–17] The majority of pediatric epilepsy surgeries are for malformations of cortical development (MCD) and glioneuronal tumors, not

Table 1 Candidates for epilepsy surgery in children

Etiology	Remarks
Cortical dysplasia	Most common. The lesion is not always apparent on magnetic resonance imaging. Complete resection is associated with the best seizure control.
Tuberous sclerosis complex	May have a single epileptogenic region despite having multiple tubers. A role may exit for multistaged resective procedures. α-methyl tryptophan positron emission tomography (PET) is better to detect an epileptic tuber.
Polymicrogyria	Milder seizures may spontaneously remit. Perirolandic and perisylvian regions are common. Abnormal tissue may retain critical function.
Hypothalamic hamartoma	Gelastic seizure is common. Several different surgical approaches, including stereotactic, endoscopic, and radiosurgical procedures have been used successfully.
Hemispheric syndromes	Including hemimegalencephaly, hemispheric dysplasia. Hemispherectomy is frequently used to treat epilepsy. Patients are usually evaluated and treated at pediatric centers with specialized expertise.
Sturge–Weber syndrome	Potential candidates for hemispheric and focal resection. May require urgent evaluation at a specialized surgical center when seizure first occurs in infancy or when epilepsy is associated with developmental delay.
Rasmussen syndrome	Hemispherectomy is the only cure for progressive epilepsy and should be considered early in the course to prevent comorbidity.
Landau–Kleffner syndrome	Few children are considered suitable for multiple subpial transection, but pediatric specialist review remains a requirement.
Other situations	Certain epilepsies from lesions (e.g., dysembryoplastic neuroepithelial tumor, cerebrovascular insults) are common, and require evaluation at a pediatric center because of the higher risk of behavior and cognitive morbidity associated with seizure presentation in childhood.

The Commission on Neurosurgery of the International League Against Epilepsy list up the etiology for evaluating the surgical indications.

hippocampal sclerosis as in adults.[13] If MRI before 2 years of age is normal and seizures persist, repeated studies with 6-month intervals are recommended, after the age of 24–30 months, when more mature myelination has already taken place, they can reveal unsuspected cortical dysplasia.[14]

Some focal in origin epilepsy might sometimes clinically mimic generalized seizure semiology.[18] It is well known that focal cortical dysplasia (FCD) presents with infantile spasms or non-lateralized tonic seizures, especially in early infant age. EEG is also sometimes non-indicative of localization in patients with lesional epilepsy, just showing bilateral or generalized interictal or ictal epileptic discharges. Epileptic discharges in child's brain have a tendency to spread rapidly through the commissural fibers. Therefore EEG, especially in congenital or early-acquired focal epilepsy, shows generalized or multi-focal epileptic discharges. Non-lateralized seizure semiology and non-localized epileptic discharges on EEG are not a contraindication for future epilepsy surgery in children. Additionally, degenerative lesions such as ischemic etiology reduce the amplitude of epileptic discharges and the EEG record cannot depict the focal abnormality.[19] Occasionally, Sturge–Weber syndrome and others with degenerative changes do not present clear EEG abnormality although they have progressive developmental delay.[20] In such situations, subclinical seizures might continue, hence we have to take care of their clinical course and evaluate their epileptic activity.

Surgical Timing

The critical age of irreversible brain dysfunction is a fundamental limitation for surgical treatment of children with intractable epilepsy. That depends on etiology. Therefore, for deciding the optimal timing of surgery, we must first take into account the natural history of their specific type of epilepsy. For example, the natural history of hemimegalencephaly results in uncontrolled seizures and severe developmental deterioration.[21] In such cases, early surgery is the sole resort to overcome their fate, although there may be a burden in the peri-surgical management. Expert evaluation with a specialized surgical team

is needed for such patients. Very young age is not a contraindication to surgery in children with refractory epilepsy.[22] When neural plasticity is expected to compensate the impaired functions, early surgery can be advantageous.

According to a UK survey of pediatric neurologists' views regarding resective surgery, 86% of clinicians working at epilepsy surgery centers completed the pre-surgical work-up of their patients within 1 year, others who referred them to external epilepsy surgery centers decided on surgical eligibility within 1 year in 59% and 2 years in 97%.[23] Their decision for referral to surgery was based on two AED trial failures and positive findings in neuroimaging.[24] Expert pediatric neurologists seldom use AED combinations for lesional cases such as glioneuronal tumors, MCD, and vascular diseases. To decide on surgical indications for patients with intractable generalized epilepsy and MRI negative focal epilepsy, the neurologist should use two single AEDs and polytherapy. These patients may also be indicated for invasive monitoring or palliative surgery. AED efficacy should not be evaluated for a very long time, as it may result in missing the optimal timing of surgery.

Surgical Procedure

A major proportion of epileptic areas in children with epilepsy can be categorized as extratemporal, multilobar, and hemispheric.[11] Because large resections are indicated in many cases, surgery is planed considering compensation due to neural plasticity for patients less than 4 years. Patients who are older than 5 years should be evaluated to confirm functional localization using cortical mapping before the resection. When discordant data from non-invasive studies are obtained, the surgeon should consider implantation of intracranial electrodes even in infants.[25] Invasive video-EEG monitoring can lead to successful surgical treatment.[19] Very young age is not a contraindication for implantation of intracranial electrodes. Young children less than 4 years of age often have inadequate cortical functional arrangement, and do not respond to standard cortical stimulation.[25] Definite language mapping by cortical stimulation is also less likely with children younger than 10.2 years.[26] In this process, we should always consider the difficulty to identify functional localization in children and the accuracy of the result.

Hemispherectomy and mulilobar disconnection techniques have been under development until recently.[27–31] These disconnection approaches can reduce surgical invasiveness and consequently surgical indications can be adopted at an earlier than before for children with large epileptic foci. These multilobar surgeries should be planed expecting neural plasticity. In many instances, surgical candidates already have neurological deficit, such as hemiparesis before surgery. Therefore, the risk of further neurological deterioration after surgery is small, and we can expect them to benefit from an additional neurological improvement. The disconnection method can also be indicated in single lobe surgery, for example frontal or temporal lobe disconnection (Fig. 1). Incomplete disconnections seldom improve seizure severity or occasionally change seizure semiology. Epileptic discharges can propagate to adjacent areas through an incompletely disconnected white matter pathway.

Higher mortality and severe morbidity related to epilepsy surgery occurs in children younger than 3 years of age.[32] Carson et al. reported three deaths in a series of 52 hemispherectomies in patients younger than 21 years of age, and all deaths occurred in patients aged 3 years or younger. There is a significant incidence of coagulopathies in younger children as a result of the large percentage of blood volume loss during these procedures.[32,33] In order to reduce the risk of mortality and morbidity, strict control of blood loss and management of coagulation are mandatory. The surgeon should resort to small craniotomies and shorter surgical time.[27,31]

Surgical and Cognitive Outcome

Acceptable surgical seizure outcomes were obtained in the reported pediatric epilepsy surgical series. Almost 50–60% of the patients resulted in being seizure free, and 20–30% of them had rare seizures after surgery.[34,35] The etiology of childhood epilepsy was predominantly MCD, therefore complete resections lead to seizure-free outcomes. Seizure-free outcome rate of extra-temporal surgeries was relatively lower than that of temporal surgery. Even multilobar and hemispheric surgeries resulted in a better outcome than those of extratemporal single lobe, consequently achieving seizure-free outcome in 70–80% of the patients.[27–31,36] The reasons for better outcome in multilobar surgeries is the complete deafferentation carried out in younger infants, without preservation of eloquent cortex and relying on neural plasticity.

Favorable variables with seizure freedom after epilepsy surgery are reported in relation to unifocal lesion on MRI, older age at seizure onset, temporal lobe resection, complete lesionectomy, and the presence of glioneuronal tumors.[34] Zentner et al. reported seizure-free rates on the basis of underlying pathology in 80% of neoplastic lesions, 52% of

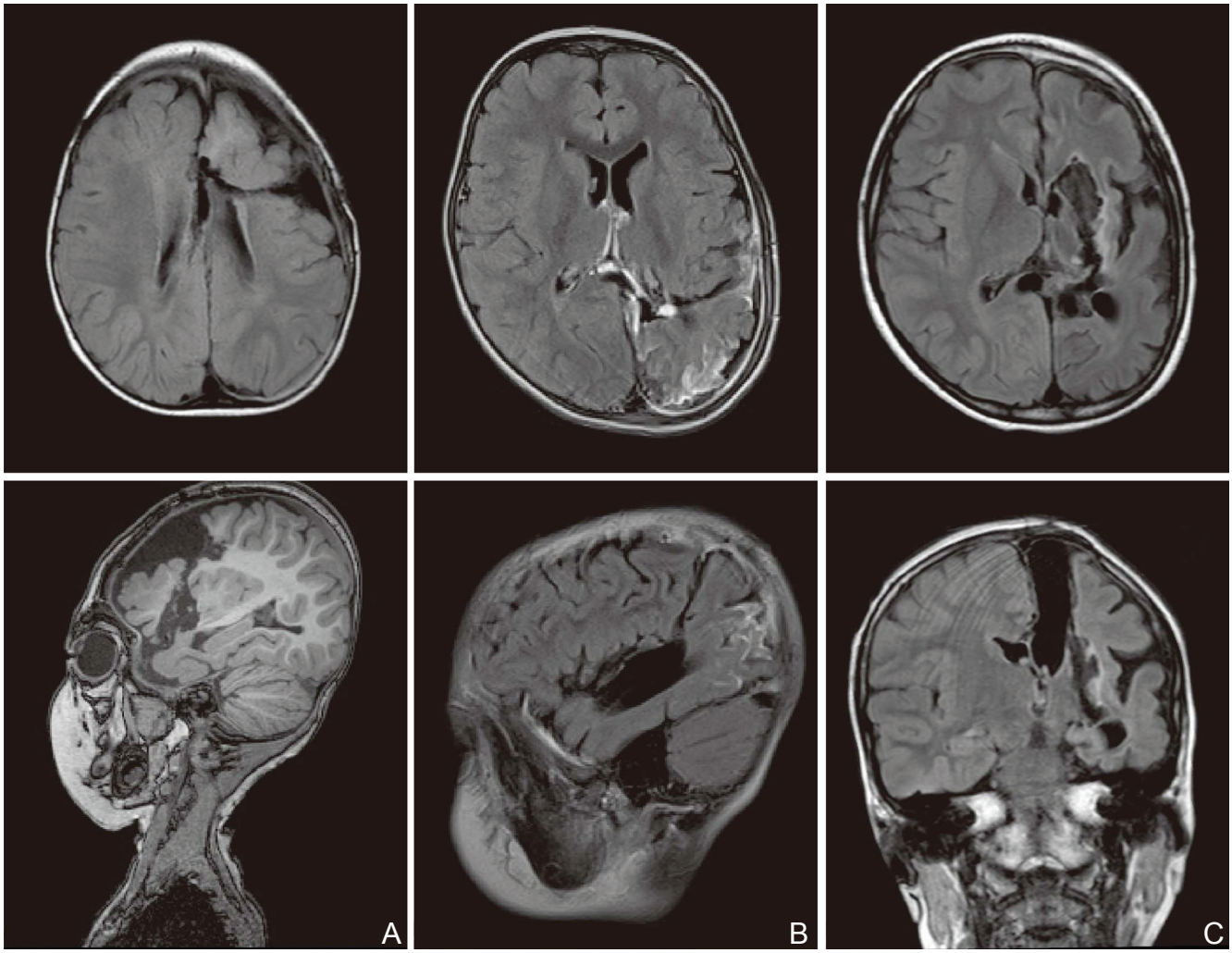

Fig. 1 Disconnection surgeries. A: frontal lobe disconnection, B: posterior quadrantectomy, C: hemispherotomy.

non-neoplastic lesions, and 20% of cases without histopathological abnormalities.[37] FCD has been associated with worse surgical outcomes.[38] The reasons for this might be multiplicity of lesions, poor detection on neuroimaging of structural abnormalities especially in type 1 of FCD, and poor correspondence of EEG and imaging findings. Epileptogenic zones in FCD are usually more extensive than the visible lesion and are multilobar in more than 70% of the patients.[39,40]

Children with early onset epilepsy are more likely to have a poor neurodevelopmental outcome, because they have a tendency of having large areas of morphological and electrophysiological abnormalities. Therefore, if early surgery has a possibility to cease seizures, this successful seizure control will facilitate cognitive development and help reduce the behavioral and/or psychological burden of epilepsy on the child and the family. Many studies to date have shown that a shorter duration of epilepsy is more likely to be associated with neurodevelopmental improvement.[22,27,34,35,41] Patients operated on at less than 12 months of age tended to improve more often than those operated on later.[22,27,42] Recent advancement of neuroimaging and electrophysiological studies facilitate early prompt diagnosis and comprehensive modern surgical management can provide the performance of surgery even before 12 months of age.

Palliative Surgery

Corpus callosotomy (CCS) has shown beneficial effect in 70–80% of children with drop attacks and 30% in those with tonic-clonic seizures.[43,44] Current recommendations are that the procedure should be directed to the seizure type rather than the epileptic syndrome. Total CCS resulted in a better

outcome on drop attacks than the partial one.[43,44] Total CCS is essentially indicated in children. For older children and adults, the extent of callosal section is determined according to the extent of EEG abnormality.[43,44] Bilateral synchronous interictal epileptic discharges (IEDs) and frequent seizures are detrimental for child's cognitive development, therefore desynchronization of the IEDs using CCS as soon as possible after appearance of drop attacks with bilateral synchronized IEDs is practical to prevent their psychomotor deterioration.[43,44] After CCS, interictal and ictal epileptic discharges in EEG can change into focal, as well as seizure semiology can also become focal. Staged surgeries to control residual seizures after CCS can be planned and performed.

Vagus nerve stimulation (VNS) is also a palliative type of epilepsy surgery to ameliorate seizure severity and improve quality of life even in children with intractable epilepsy.[45–47] VNS is applied in principle when a curative epileptic focus resection is not indicated or has failed at a previous surgery, and the majority of these patients do not have EEG defined epileptogenic areas. An additional diagnostic difficulty is the presence of the implanted device, incompatible with proper MRI evaluation. CCS, however, as a procedure interrupting synchronization, may reveal existing focal EEG phenomena afterwards, and that can be indicated for additional curative resective surgery.

Palliative surgeries are an important alternative to improve seizure severity and development of cognition in childhood. Physicians can apply several therapeutic strategies to combine with palliative epilepsy surgeries to attain the fundamental goal of therapy.

Conclusion

Recent progress in neuroimaging and electrophysiology for pre-surgical evaluation to identify the etiology and epileptic foci location has provided significant improvement in pediatric epilepsy surgery.[18] Improvement of peri-surgical management in pediatric epilepsy also gave the possibility of earlier surgery than before. The effectiveness and safety of epilepsy surgery for children have been established, and it is no longer a last resort of management.[48]

Conflicts of Interest Disclosure

None of the authors have any conflicts of interest to disclose. The authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1) Alkadhi H, Kollias SS, Crelier GR, Golay X, Hepp-Reymond MC, Valavanis A: Plasticity of the human motor cortex in patients with arteriovenous malformations: a functional MR imaging study. *AJNR Am J Neuroradiol* 21: 1423–1433, 2000
2) Calautti C, Leroy F, Guincestre JY, Baron JC: Dynamics of motor network overactivation after striatocapsular stroke: a longitudinal PET study using a fixed-performance paradigm. *Stroke* 32: 2534–2542, 2001
3) Chollet F, DiPiero V, Wise RJ, Brooks DJ, Dolan RJ, Frackowiak RS: The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. *Ann Neurol* 29: 63–71, 1991
4) Yoshiura T, Hasuo K, Mihara F, Masuda K, Morioka T, Fukui M: Increased activity of the ipsilateral motor cortex during a hand motor task in patients with brain tumor and paresis. *AJNR Am J Neuroradiol* 18: 865–869, 1997
5) Barba C, Montanaro D, Frijia F, Giordano F, Blümcke I, Genitori L, De Masi F, Guerrini R: Focal cortical dysplasia type IIb in the rolandic cortex: functional reorganization after early surgery documented by passive task functional MRI. *Epilepsia* 53: e141–e145, 2012
6) Chamoun RB, Mikati MA, Comair YG: Functional recovery following resection of an epileptogenic focus in the motor hand area. *Epilepsy Behav* 11: 384–388, 2007
7) Devlin AM, Cross JH, Harkness W, Chong WK, Harding B, Vargha-Khadem F, Neville BG: Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. *Brain* 126: 556–566, 2003
8) Müller RA, Chugani HT, Muzik O, Rothermel RD, Chakraborty PK: Language and motor functions activate calcified hemisphere in patients with Sturge-Weber syndrome: a positron emission tomography study. *J Child Neurol* 12: 431–437, 1997
9) Pataraia E, Billingsley-Marshall RL, Castillo EM, Breier JI, Simos PG, Sarkari S, Fitzgerald M, Clear T, Papanicolaou AC: Organization of receptive language-specific cortex before and after left temporal lobectomy. *Neurology* 64: 481–487, 2005
10) Vargha-Khadem F, Carr LJ, Isaacs E, Brett E, Adams C, Mishkin M: Onset of speech after left hemispherectomy in a nine-year-old boy. *Brain* 120(Pt 1): 159–182, 1997
11) Cross JH, Jayakar P, Nordli D, Delalande O, Duchowny M, Wieser HG, Guerrini R, Mathern GW; International League against Epilepsy, Subcommission for Paediatric Epilepsy Surgery; Commissions of Neurosurgery and Paediatrics: Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for

Pediatric Epilepsy Surgery. *Epilepsia* 47: 952–959, 2006
12) Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J: Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 51: 1069–1077, 2010
13) Harvey AS, Cross JH, Shinnar S, Mathern GW, Mathern BW; ILAE Pediatric Epilepsy Surgery Survey Taskforce: Defining the spectrum of international practice in pediatric epilepsy surgery patients. *Epilepsia* 49: 146–155, 2008
14) Gaillard WD, Chiron C, Cross JH, Harvey AS, Kuzniecky R, Hertz-Pannier L, Vezina LG; ILAE, Committee for Neuroimaging, Subcommittee for Pediatric: Guidelines for imaging infants and children with recent-onset epilepsy. *Epilepsia* 50: 2147–2153, 2009
15) King MA, Newton MR, Jackson GD, Fitt GJ, Mitchell LA, Silvapulle MJ, Berkovic SF: Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. *Lancet* 352: 1007–1011, 1998
16) Berg AT, Testa FM, Levy SR, Shinnar S: Neuroimaging in children with newly diagnosed epilepsy: A community-based study. *Pediatrics* 106: 527–532, 2000
17) Shinnar S, O'Dell C, Mitnick R, Berg AT, Moshe SL: Neuroimaging abnormalities in children with an apparent first unprovoked seizure. *Epilepsy Res* 43: 261–269, 2001
18) Depositario-Cabacar DT, Riviello JJ, Takeoka M: Present status of surgical intervention for children with intractable seizures. *Curr Neurol Neurosci Rep* 8: 123–129, 2008
19) Wyllie E, Lachhwani DK, Gupta A, Chirla A, Cosmo G, Worley S, Kotagal P, Ruggieri P, Bingaman WE: Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. *Neurology* 69: 389–397, 2007
20) Sugano H, Nakanishi H, Nakajima M, Tanaka K, Shimoji K, Karagiozov K, Arai H: Seizures continue even after prompt anti-epileptic drug medication in Sturge-Weber syndrome—study from prolonged video electrocoticography, a case report. *Childs Nerv Syst* 25: 143–146, 2009
21) Guerrini R, Dobyns WB: Malformations of cortical development: clinical features and genetic causes. *Lancet Neurol* 13: 710–726, 2014
22) Steinbok P, Gan PY, Connolly MB, Carmant L, Barry Sinclair D, Rutka J, Griebel R, Aronyk K, Hader W, Ventureyra E, Atkinson J: Epilepsy surgery in the first 3 years of life: a Canadian survey. *Epilepsia* 50: 1442–1449, 2009
23) Hall-Patch L, Gayatri N, Ferrie C, Morrall MC: Clinical reasoning and investigations for resective surgery for medically refractory epilepsies in children. *Epilepsy Behav* 23: 442–446, 2012
24) Hakimi AS, Spanaki MV, Schuh LA, Smith BJ, Schultz L: A survey of neurologists' views on epilepsy surgery and medically refractory epilepsy. *Epilepsy Behav* 13: 96–101, 2008
25) Centeno RS, Yacubian EM, Sakamoto AC, Ferraz AF, Junior HC, Cavalheiro S: Pre-surgical evaluation and surgical treatment in children with extratemporal epilepsy. *Childs Nerv Syst* 22: 945–959, 2006
26) Schevon CA, Carlson C, Zaroff CM, Weiner HJ, Doyle WK, Miles D, Lajoie J, Kuzniecky R, Pacia S, Vazquez B, Luciano D, Najjar S, Devinsky O: Pediatric language mapping: sensitivity of neurostimulation and Wada testing in epilepsy surgery. *Epilepsia* 48: 539–545, 2007
27) Delalande O, Bulteau C, Dellatolas G, Fohlen M, Jalin C, Buret V, Viguier D, Dorfmüller G, Jambaqué I: Vertical parasagittal hemispherotomy: surgical procedures and clinical long-term outcomes in a population of 83 children. *Neurosurgery* 60(2 Suppl 1): ONS19–ONS32; discussion ONS32, 2007
28) Schramm J, Kral T, Clusmann H: Transsylvian keyhole functional hemispherectomy. *Neurosurgery* 49: 891–900; discussion 900–901, 2001
29) Shimizu H, Maehara T: Modification of peri-insular hemispherotomy and surgical results. *Neurosurgery* 47: 367–372; discussion 372–373, 2000
30) Daniel RT, Meagher-Villemure K, Farmer JP, Andermann F, Villemure JG: Posterior quadrantic epilepsy surgery: technical variants, surgical anatomy, and case series. *Epilepsia* 48: 1429–1437, 2007
31) Sugano H, Nakanishi H, Nakajima M, Higo T, Iimura Y, Tanaka K, Hosozawa M, Niijima S, Arai H: Posterior quadrant disconnection surgery for Sturge-Weber syndrome. *Epilepsia* 55: 683–689, 2014
32) Carson BS, Javedan SP, Freeman JM, Vining EP, Zuckerberg AL, Lauer JA, Guarnieri M: Hemispherectomy: a hemidecortication approach and review of 52 cases. *J Neurosurg* 84: 903–911, 1996
33) Piastra M, Pietrini D, Caresta E, Chiaretti A, Viola L, Cota F, Pusateri A, Polidori G, Di Rocco C: Hemispherectomy procedures in children: haematological issues. *Childs Nerv Syst* 20: 453–458, 2004
34) Cossu M, Lo Russo G, Francione S, Mai R, Nobili L, Sartori I, Tassi L, Citterio A, Colombo N, Bramerio M, Galli C, Castana L, Cardinale F: Epilepsy surgery in children: results and predictors of outcome on seizures. *Epilepsia* 49: 65–72, 2008
35) Duchowny M, Jayakar P, Resnick T, Harvey AS, Alvarez L, Dean P, Gilman J, Yaylali I, Morrison G, Prats A, Altman N, Birchansky S, Bruce J: Epilepsy surgery in the first three years of life. *Epilepsia* 39: 737–743, 1998
36) Basheer SN, Connolly MB, Lautzenhiser A, Sherman EM, Hendson G, Steinbok P: Hemispheric surgery in children with refractory epilepsy: seizure outcome, complications, and adaptive function. *Epilepsia* 48: 133–140, 2007
37) Zentner J, Hufnagel A, Ostertun B, Wolf HK, Behrens E, Campos MG, Solymosi L, Elger CE, Wiestler OD, Schramm J: Surgical treatment of extratemporal

epilepsy: clinical, radiologic, and histopathologic findings in 60 patients. *Epilepsia* 37: 1072–1080, 1996
38) Hirabayashi S, Binnie CD, Janota I, Polkey CE: Surgical treatment of epilepsy due to cortical dysplasia: clinical and EEG findings. *J Neurol Neurosurg Psychiatr* 56: 765–770, 1993
39) Palmini A, Andermann F, Olivier A, Tampieri D, Robitaille Y: Focal neuronal migration disorders and intractable partial epilepsy: results of surgical treatment. *Ann Neurol* 30: 750–757, 1991
40) Palmini A, Andermann F, Olivier A, Tampieri D, Robitaille Y, Andermann E, Wright G: Focal neuronal migration disorders and intractable partial epilepsy: a study of 30 patients. *Ann Neurol* 30: 741–749, 1991
41) Wyllie E, Comair YG, Kotagal P, Bulacio J, Bingaman W, Ruggieri P: Seizure outcome after epilepsy surgery in children and adolescents. *Ann Neurol* 44: 740–748, 1998
42) Loddenkemper T, Holland KD, Stanford LD, Kotagal P, Bingaman W, Wyllie E: Developmental outcome after epilepsy surgery in infancy. *Pediatrics* 119: 930–935, 2007
43) Maehara T, Shimizu H: Surgical outcome of corpus callosotomy in patients with drop attacks. *Epilepsia* 42: 67–71, 2001
44) Sunaga S, Shimizu H, Sugano H: Long-term follow-up of seizure outcomes after corpus callosotomy. *Seizure* 18: 124–128, 2009
45) Elliott RE, Rodgers SD, Bassani L, Morsi A, Geller EB, Carlson C, Devinsky O, Doyle WK: Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. *J Neurosurg Pediatr* 7: 491–500, 2011
46) Levy ML, Levy KM, Hoff D, Amar AP, Park MS, Conklin JM, Baird L, Apuzzo ML: Vagus nerve stimulation therapy in patients with autism spectrum disorder and intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. *J Neurosurg Pediatr* 5: 595–602, 2010
47) Morris GL, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C: Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the guideline development subcommittee of the American academy of neurology. *Epilepsy Curr* 13: 297–303, 2013
48) Cross JH: Epilepsy surgery in children—no longer a last resort. *Dev Med Child Neurol* 52: 111–112, 2010

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