Pediatric Epilepsy Surgery (I): Special Considerations and Presurgical Strategies

Pediatrik Epilepsi Cerrahisi (I): Yaş Grubuna Özel Sorunlar ve Cerrahi Öncesi Yaklaşım Stratejileri

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INTRODUCTION

Although, the application of epilepsy surgery techniques in children have been reported since 1960s, the surgical management of epilepsy only recently became a mainstream management method for children (18,19,21,23,57). In the earlier series, majority of the cases were older children (17,24,38). Gradually, the age of epilepsy surgery cases in childhood decreased and even series about epilepsy surgery in infants started to be seen in journals in 1990s. We also witnessed increased number of new pediatric epilepsy surgery programs in most major children's hospitals during the last decade. This increased interest provided us very valuable clinical and electrophysiological data which helped our understanding of etiopathogenesis of the disease, provided necessary background to define some epileptic syndromes in childhood, to improve our protocols for presurgical patient selection, to develope new surgical techniques and to document surgical outcome. As a result, we reached a remarkable stage in epilepsy surgery in infants and young children. However, there are still significant controversies regarding patient selection criteria, presurgical assessment methods, surgical indications, timing of surgery as well as appropriate surgical techniques (2,18,28,36,38,40,50,51,61).

The infants and young children constitutes a very peculiar group among epilepsy surgery patients because of some inherent characteristics. The children with intractable seizures challenge us with unique problems and require special approaches for presurgical evaluation and surgical strategy. Awareness of age related characteristics, special paradigms and controversies regarding this patient group have utmost importance to provide a good surgical outcome. This review aims to define important characteristics of this patient group and review controversies, present patient selection criteria and presurgical strategies. Surgical techniques and strategy in pediatric epilepsy cases will be the subject of second part of this review.

SPECIAL CHARACTERISTICS AND CONSIDERATIONS

Age: Age related issues and characteristics dominate the discussion about this patient group and needs to be taken into account to create a reliable presurgical evaluation protocol. Level of cognitive maturation and language development may be a significant obstacle for our understanding and assessment of subjective manifestations of seizures during early. Age may also be a limitating factor for some presurgical and surgical tests, such as WADA

test and cortical mapping techniques during surgery under local anesthesia. Young children are developing human beings anatomically, physiologically as well as psychosocially. They are psychosocially more fragile than adults because of more vulnarable self-image, less developed social adjustment ability, and a very significant peer-pressure effect in their daily life. Seizures itself and anti-convulsive medications might easily cause psychosocial developmental problems and significantly distruptive behavioral changes in this age (18,28,30,36,45,50,51).

Harmful Effects on Immature Brain: The effect of seizures may be much more harmful, at times catastrophic, on developing brain. Intractable frequent seizures itself might cause direct adverse effects on neuronal development. In addition, young children may have very frequent even continuous postictal states and frequent interictal epileptiform discharges may cause "nociferous cortex" and possible secondary epileptogenesis. The number of clinical and subclinical seizures may be much more frequent in infants, sometimes up to a hundred in a day. Consequently, intractable seizures may have a deleterious effect on developing brain and may cause mental retardation and debilitating behavioral problems during emotionally formative years of childhood. It is not infrequent to observe a "plateauing" or decline in development of infants with catastrophic seizures. Especially, the patients with infantil spasms without seizure control are almost never developmentally normal (18,28,30,34,50,61,62,63).

Special Epilepsy Syndromes: In childhood, the type of intractable seizures are quite atypical and poorly defined comparing to relatively well defined epileptic syndromes of adults. There are some epileptic syndromes exclusively seen in children and rarely or never occur in adults, such as infantile spasms, Lennox-Gastaut, Rasmussen encephalitis and Sturge-Weber syndrome(18,34,45,50). These epileptic syndromes might be catastrophic because of associated cognitive and developmental delay or regression and constitute a very significant challenge which needs to be handled with a great deal of expertise. The anatomical distribution of seizure focuses in children also present special diagnostic and surgical challenges. Intractable seizures in children more likely arise from extratemporal epileptogenic zones whereas temporal lobe epilepsy is seen more frequently in adults. Because of this characteristic, epileptogenic activity in children may cover relatively larger cortical areas and may include indispensable functional cortical regions. In addition, extratemporal seizures have a tendency of easy and fast propagation to a wider cortical areas. These characteristics make these cases more challenging. Therefore, these patients frequently need invasive EEG monitoring and stimulation studies with subdural electrode arrays to localize seizure onset as well as functionally important areas (1,8,9,16,20,21,32,50,51,61).

Electrophysiological Characteristics: Electrophysiological evaluation of young children's, especially newborn and infants' cortical activity, might be very challenging because of poorly defined normal and abnormal patterns of immature brain and great variability of seizure patterns. Even localizing value of the EEG findings is a controversial issue in this age group. Frequently, no interictal epileptiform discharge is seen in young children and rarely well defined epileptiform discharges are seen on EEG. Ictal discharges spread more rapidly in this age and it causes significant difficulty to define epileptogenic zone. Finally, extratemporal origins of seizures, frequent involvement of eloquent cortex and epileptogenic zones covering relatively larger cortical areas in this age group may increase the difficulty to define the epileptogenic focus. Invasive monitoring and special stimulation paradigms may be frequently needed in these cases. Therefore, a special expertise in pediatric electrophysiology has utmost importance for determination and localization of an epileptogenic area in young children (1,8,32,34,50,51,58,59,63).

Brain Plasticity: Brain plasticity is the ability of the immature brain to recover and to reorganize following a cerebral injury including surgical insults. It is a remarkable asset of early childhood. There are significant implications about plastic capacity of young brain from experimental animal studies and from experiences in humans following surgical resections or cerebral insults. This data shows that eloquent brain areas in developing brain, such as motor and language cortex, can functionally reorganize after cerebral injury (36,47,55). Although there is not enough data for a reliable guideline, critical age for neuronal plasticity has generally been accepted as 6 to 7 years of age. Younger children have a greater potential for functional recovery of neural integrity following resective brain surgery or other insults. Best known example of this potential is shifting language function following cortical resection or hemispheric brain damage in early childhood. Therefore, brain plasticity should be taken

into account as a significant positive factor for deciding surgical intervention at early ages (28,31,45,50-,52).

Medical Intractibility: Another significant issue is medical intractibility criteria in children. In adults, general consensus is to use major antiepileptic drugs (AED) for a certain length of time, which may be a few years, before to decide medical intractibility of seizures. The criteria to define medical intractibility in children is significantly different than adults. First of all there are limited number of AEDs available for young children and long-term application of AEDs may cause significant cognitive and psycosocial effects on children. Developing brain is much more vulnerable to AEDs side effects, therefore risk/ benefit ratio for long-term trials of AEDs is more critical in children. In addition, presence of certain syndromes cause intractable seizures by their very nature and does not need a trail period with all AEDs. On the other hand, there is still not enough data regarding natural history of certain pediatric epilepsy syndromes. Epilepsy in childhood is not a fixed condition but a process. It may evolve toward intractibility fastly or may stop spontaneously incertain types. This characteristics make the issue more complicated (2,16,18,28,29,50,51,59,61,62).

Timing of Surgery: Obviously, timing of surgery is an important decision at this age group. Early surgical intervention is crucial not just because of brain plasticity, but also to eliminate toxic side-effects of anti-epileptic medications and their negative psychosocial effects. Immature brains undergo complex process of maturation and frequent seizures itself, frequent postictal status, interictal epileptiform discharges, effects of antiepileptic drugs as well as underlying lesion itself may cause serious harm on developing brain during waiting period. It has been documented that even if seizures are controlled with anti-epileptic drugs, interictal discharges may effect on synaptogenesis, may cause cytoarchitectural changes and a possible secondary epileptogenic focus in immature brains. This potential constitutes another significant concern in children. It was reported that Sturge-Weber patients with intractable seizures have a better developmental outcome if they are operated before 1 year of age (41). Some authors believe that the earlier the surgical intervention, the less the eventual functional deficit. Therefore, early surgical intervention has been recommended in these cases to permit attainment of the child's full developmental potential without further psychosocial harm and to maximize developmental potential (2,5,18,27,30,38,45,50,59,61).

Goal of Surgery: Surgical management of epilepsy in well selected cases may help children for a normal transition into adulthood by preventing some psychosocial problems including dependency, poor self-esteem, learning disability and by avoiding significant side-effects of long-term exposure to anti-convulsive medications. As a result, the purpose of surgery is also somewhat different in this age group than adults. The goal of the surgery is not only controlling seizures but also preventing the possible harmful consequences of uncontrolled seizures and "nociferous" cortex, secondary epileptogenesis, psychosocial problems secondary to cognitive and behavioral effects of epilepsy, and avoiding side-effects of antiepileptic medications by succeeding discontinuation or significant decrease of medications (2,16,18,20,28,29,30,36,45,50,51,61-63).

SPECIAL EPILEPSY SYNDROMES OF CHILDHOOD

Some epileptic syndromes are exclusively or mostly seen in children and frequently present a diagnostic and surgical challenge. A brief overview of these syndromes will help to define unique characteristics and problems of this patient group.

Sturge-Weber Syndrome: There are a great variability in the severity of epilepsy in patients with Sturge-Weber syndrome (SWS), however seizures usually start within the first year of life. The children with SWS are characterized by facial and ipsilateral cerebral angiomatosis. Some patients have medically intractable epilepsy with very frequent seizures and progressive neurological deficits, whereas some other patient's seizure remit and neurological deficits do not progress. These patients may develop progressive hemiparesis, hemianopsia and become mentally retarded after the onset of uncontrollable seizures. On the other hand, accumulating data shows that early surgery, especially surgery before 1 year of age, leads to the best outcome by ensuring maximal recovery and avoiding further cognitive decline. This unpredictable course of disease and benefit of early surgical intervention makes management plan very challenging and controversial. Therefore, it has been recommended that each case should be assessed individually. Surgery should be considered if the patient had uncontrollable seizures despite of adequate medical management and had progressive cognitive deterioration and progressive hemiparesis. Depending on the size of involved cortical area, a

limited cortical resection or hemispherectomy might be procedure of choice. Diffuse hemispheric involvement accompanied by a progressive deep hemiparesis leads patient to hemispherectomy. The result of surgery is excellent for seizure control (5,22,26,27,28,41,45,51).

Rasmussen's Encephalopathy: Although, it was described as encephalitis initially, the causative factors of Rasmussen's encephalopathy are still unknown. A typical patient presents with infrequent partial seizures between 4 and 9 years of age. The seizure frequency increases along gradually increasing hemispheric involvement and the patient may develop epilepsia partialis continua, progressive hemiplegia and mental retardation. Although cortical biopsy may be obtained to confirm the diagnosis in controversial cases, focal resections neither stop the progression of the disease nor significantly decrease the number of seizures. Eventually, chronic inflammation spreads to the entire ipsilateral hemisphere. Procedure of choice is hemispherectomy when the patient has severe hemiparesis with absent fine finger movements (4,28,45,48,51,62,63).

Infantile Hemiplegic Epilepsy; This is not a well-defined entity. Some authors prefer to use "infantile hemiplegic epilepsy" term for a group of congenital disorders characterized with intractable partial seizures and hemiparesis secondary to hemispheric insults. The underlying lesion in this group of patients might be cortical dysplasia, hemimegalencephaly, congenital porencephaly, or perinatal cerebrovascular events. The patients usually present with severe and intractable seizures within the first few months of life, and hemiparesis becomes prominent between the ages of 3 and 6 months. The procedure of choice is hemispherectomy (45,48,50,51,54,56,57,62,63).

Infantile Spasms: Infantile spasms is a disease of infancy period. A typical patient presents with myoclonic seizures which starts between 4 and 8 months of age and characteristic hypsarrhythmic EEG pattern. The patient frequently proceeds profound mental retardation. Seizures are often resistant to medical management, although ACTH might help in some cases. Underlying focal lesion may be cortical dysplasia, ischemic injury or electrophysiological findings provide very limited help to identify the site of seizure onset at this age. Therefore, functional imaging studies to define structurally abnormal area have utmost importance for surgical planning. These patients are very difficult cases unfortunately. However, resection of structurally abnormal area may provide some benefit in properly selected patients (14,28,34,45,61-63).

Lennox-Gastaux Syndrome: The patients present with frequent, intractable seizures (tonic, atonic, myoclonic), mental retardation and typical slow spike and wave pattern at EEG. It has been generally accepted as generalized seizure disorder and surgical options are limited to corpus callosotomy and vagal nerve stimulation. However, there are some documented cases with focal radiological abnormalities and these cases respond focal resection well (18,45,51,61-63).

Laundau-Kleffner Syndrome: Landau-Kleffner syndrome is characterized with partial and secondarily generalized seizures and language regression. The natural course of the disease is variable. The seizures cease spontaneously in many cases. In case of intractable seizures, the children may benefit from multiple subpial transection technique (39).

Neuronal Migrational Disorders: Although it is not an exclusively childhood syndrome, neuronal migrational disorders constitutes a large group of congenital structural lesions which frequently cause intractable epilepsy. NMDs result from disruption of normal process of neuronal cell migration and characterized by disorganization of cortical architecture and ectopic location of neurons. They represent broad variety developmental abnormalities including agyria/pachygyria (lissencephaly), focal cortical dysplasia, polymicrogyria, schizencephaly, unilateral megalencephaly, gray matter heterotopias and microdysgenesis. Focal resection is the treatment of choice in the management of epilepsy secondary to focal neuronal migrational disorders. Focal NMD are often accompanied by an epileptogenic area which often more widespread than seen in MRI. Therefore, determining the extent of structural lesion and epileptogenic zone involves an enormous challenge during presurgical evaluation. Invasive monitoring with subdural plates and intraoperative ECoG are best tools to determine the extent of epileptogenic areas. Identification and complete resection of lesion and ictal onset zone is an excellent predictor of good outcome along the concordance of structural, functional and electrographical abnormalities. If the resection of the lesion is not possible because of eloquent cortex, multiple subpial transection may be an option (1,3,6,7,10,44,49).

Temporal Lobe Epilepsy in Children: Temporal lobe epilepsy constitutes a smaller percentage of surgical cases in childhood comparing to adult epilepsy patients (46,51). A typical temporal lobe epilepsy patient presents with simple/complex partial seizure with/without secondarily generalized tonic-clonic convulsions. Electrophysiologically, epileptiform discharges are often localized in mesial temporal lobe, although neocortical involvement is not rare. Although children older than 6 or 7 years often have similar clinical features to those seen in adulthood, clinical features of complex partial seizures in infants and young children may be very subtle or atypical. Routine interictal EEG might be normal at this age. EEG-Video monitoring has very critical importance for definitive diagnosis. Underlying lesion is rarely mesial temporal sclerosis in this age contrary to adult patients, but often slow growing tumors, developmental abnormalities such as cortical dysplasia, infarction secondary to perinatal ischemic events and previous infections. Another important difference in children with temporal lobe epilepsy is chance of having spontaneous remission up to 10 to 18%. However, seizures originating from temporal lobe with developmental abnormalities in infants and young children are already intractable by its inherent caharacteristics.

SELECTION OF SURGICAL CANDIDATES

Main principles applied to surgical candidates in adult epilepsy patients are also relevant to children: presence of medically intractable seizures preventing normal daily activity and/or interfering with normal quality of life, preferably localized epileptogenic zone and strongly favorable risk/benefit ratio with low risk of post-operative new neurological deficit. However, children present a number of unique challenges as mentioned above. Many childhood seizure disorders may remit spontaneously. But even if spontaneous remission of seizures occurs, long term effects of seizures, frequent postictal states, frequent interictal discharges and side-effects of anti-epileptic drugs may still cause significant psychosocial and neurological impairment, neuro-developmental problems or arrest of maturation during this period. Brain plasticity and recovery/reorganization potential of the brain is a time-limited major advantage. Under the light of these characteristics, children with intractable epilepsy should be selected carefully for surgical evaluation based on an individualized assessment criteria (18,20,21,28,36,45,50,51,59,61-63).

The primary goal of the presurgical evaluation is determining whether or not there is any focal origin of seizures. If there is a focal epileptogenic area, then the goal is determining whether or not that focus can be removed without causing any unacceptable neurological deficit. If there is no epileptogenic focus or resective surgery would cause serious neurological deficits, then the goal of presurgical evaluation is to determine if there is any other surgical technique which may help the patient such as corpus callosotomy, multiple subpial transection or vagal stimulation. After selecting the patients as a surgical candidate, the presurgical evaluation starts with relatively simple and non-invasive procedures, but may progress to quite complex and invasive procedures. Critical information is obtained primarily by recording habitual seizures during EEG-Video monitoring to characterize their clinical manifestations and to correlate the clinical findings with the electroencephalographic abnormalities. The data provided by history, neurological examination, neuropsychologic evaluation, and both anatomic and functional neuroimaging studies also provide very valuable supporting information. Therefore at this point,, it will be helpful to review briefly major diagnostic tests used for pre-surgical evaluation.

PRESURGICAL EVALUATION

Neuropsychological Tests: Pre-operative neuropsychological tests to assess verbal and non-verbal communication skills and the level of psychosocial adjustment are well-established tools in adults. It may also provide adjunctive information about the localization or at least the lateralization of the epileptogenic region. It is also significant diagnostic test for children. However, neuropsychological assessment of young children is difficult because of limited cognitive skills and cooperation (28,45).

Neuroimaging Studies:

MRI: MRI with special parameters is a very valuable tool for detecting any structural abnormality and for surgical planning in epilepsy patients. The evaluation of MRI in pediatric cases with developmental abnormalities might be difficult because of subtleties in some cases such as dysplastic gyral abnormalities and should be reviewed by a radiologist experienced in epilepsy. MRI volumetric studies and MR spectroscopy are valuable tools in adults but the experience with children is still lacking in these areas and they are not a routine part of

presurgical study at this point. Although, MRI volumetric studies probably have not much critical importance in children, MRS may have a potential of providing some important information in future. On the other hand, functional MRI has already been an imaging study which provides invaluable data in epilepsy patients. Functional MRI maps functional brain activation indirectly by detecting focal changes in cerebral hemodynamics and metabolism secondary to a specific function related neuronal activity. The location of the epileptogenic zone with respect to eloquent cortex, including sensorimotor, language, memory, and visual areas has a critical importance in resective surgery. Several factors such as individual variability, anatomic distortion by cortical lesions, or cortical reorganization can make functional localization based on classical anatomical landmarks imprecise and unreliable during surgery. Therefore, fMRI constitutes a powerful non-invasive method to map functional cortical areas in relation to epileptogenic zone and increases the precision, accuracy, and safety of neurosurgical procedures. However, fMRI has a limited value in young children because it requires a significant amount of cooperation from patients throughout the study (18,28,33,45,51).

SPECT AND PET: Functional neuroimaging techniques have an important place in identification of surgical cases in epilepsy. Cerebral blood flow increase during seizure at epileptogenic focus and this hyperperfused area can be detected by ictal. Single photon emission tomography (SPECT), while hypoperfusion is seen on the interictal SPECT. Ictal SPECT is especially helpful for localizing seizure focus in children given the high proportion of children with extratemporal seizures whom present with normal or nonspecific MRI scans. Like SPECT, positron emission tomography (PET) is another noninvasive, functional imaging study which may provide significant data to localize epileptogenic zone and cortical abnormality. Interictal PET scan reliably demonstrates a region of hypometabolism corresponding with the zone of cortical abnormality and correlates well with electrocorticographical findings. PET scan detects metabolic changes associated with cytoarchitectural disturbances and dysgenesis in children in whom MRI reveals little or no structural lesions. Although data is much less limited for children with epilepsy comparing to adults, PET and SPECT have been shown as very valuable tools in the patient selection process in children (12,13,14,25,28,51).

Electrophysiological Techniques:

Electroencephalography and EEG-Video Telemetry: Electroencephalography is most critical test for localizing epileptogenic focus and planning surgery. Although, routine EEG may document interictal electroencephalographic abnormalities, it is a very limited study to localize epileptogenic focus. Determining the onset of electroencephalographic seizures is considered the most reliable localizing sign and it is almost only possible with long-term continuos EEG monitoring techniques. Therefore, EEG-Video Telemetry is cornerstone of presurgical assessment. EEG-Video monitoring gives us very valuable data during presurgical evaluation including clinical and electroencephalographic characteristics and consistency of seizures, the site of electroencephalographic seizure onset and its clinical correlates (28,46,51,59-61).

Invasive Electrophysiological Monitoring: Not infrequently, the site of seizure onset can not be localized using surface electrodes or clinical semiology, neuroimaging and neuropsychologic data may not concordant with the EEG findings. Invasive electrophysiological monitoring techniques including subdural, epidural or depth electrodes may need to be used in these cases. More specifically; (1) partial seizures in the setting of normal or non-localizing imaging data, (2) epileptogenic zone that are more widespread than the structural lesion, (3) absolute non-congruence data, (4) multiple lesions and/or multifocal interictal epileptiform activities and (5) superimposed epileptogenic areas and eloquent cortex constitute main indications for invasive electrophysiological monitoring. Invasive monitoring techniques have a key importance in children. Depth electrodes are rarely used in children in contrast to subdural electrodes. Subdural electrodes are used frequently because of higher incidence of extratemporal epilepsy in this age group. Although subdural electrodes provide more detailed and precisely localized information, it has a disadvantage of being less helpful in exploring more widespread localization problems over large cortical areas because of limited sampling potential (1,11,15,18,28,32,35,51,59).

Cortical Mapping: Eloquent cortex show significant variability by being in different locations in different patients and by being in considered surgically safe areas based on gross anatomic criteria. In addition, essential language areas can be spread to multiple small areas in some patients and intrinsic

lesions in brain may cause displacement of functionally important areas from their usual anatomic location. This substantial individual variability of functionally critical areas underscores the importance of individualized mapping. However, it should be reminded that whether or not a certain cortical region is critical for a particular task may be difficult to determine and generally depends on the mapping techniques used. All mapping techniques provide approximations, therefore several cortical mapping techniques should be used to improve resolution of map in difficult cases. Cortical EEG and mapping can be performed in the operating room after craniotomy with the patient under local anesthesia or extraoperatively after implantation of subdural grids. Although, children as young as 8 years old may tolerate and cooperate intraoperative cortical stimulation for functional mapping procedures, this may be very difficult with some children, especially very young children. Extraoperative mapping techniques with implanted subdural electrodes should be preferred in these children. Extraoperative electrical cortical stimulation with subdural grids is particularly helpful to map eloquent cortex for planning a safe and effective resection in children with an epileptogenic zone adjacent to functionally critical areas. However, extraoperative cortical stimulation may still be difficult in young children because of limited language abilities, short attention span and cooperation problems. In addition, children under age 2 or 3 years may not show motor responses with cortical stimulation techniques (11,42,43,53).

Intraarterial Amobarbital Test: Amobarbital test (IAT) is used to lateralize dominant side for language and memory function to prevent possible postsurgical language and memory deficits in some cases. Although IAT is reliable to determine language dominance, it is not so reliable in determination of memory dominance in children. Its application in children is limited with more complex situation, such as the identification of the origin of seizure onset in the middle or posterior portion of the temporal lobe in the language-dominant hemisphere. The plasticity of the young brain and its ability to switch language dominance in young children also make this test less pertinent for young children (18,45).

CONCLUSION

Overall, epilepsy surgery in children constitutes a significant advancement in the management of medically intractable epilepsy of a highly vulnerable group of patients. However, available data does not provide well-defined guidelines and parameters for presurgical assessment and decision making process in this patient group. The children are developing human beings and epilepsy in children is not a fix but an evolving and complicated process. Therefore, selecting and referring young patients to surgery is a delicate process which needs to be handled by an experienced team. It is very important to find a delicate balance between avoiding an unnecessary surgery and causing psychosocial deterioration as well as experiencing side effects of antiepileptic medications based on unrealistic expectations of spontaneous remission. Present data shows satisfactory evidence that epilepsy surgery in childhood is a safe and effective therapy with well selected cases and adequate surgical technique. Earlier surgery and earlier seizure control contributes to a greater reduction in overall morbidity and improves quality of life in children. Children with retractable epilepsy should be identified without delay and evaluated.

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