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Review Article

Surgery for drug refractory pediatric epilepsy: Saving and nurturing the developing brain

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ABSTRACT

The drug refractory epilepsy in the pediatric age group can wreak havoc on the developing brain affecting all the important developmental milestones. This not only affects the child but also creates a socioeconomic burden to the family. Pediatric epilepsy poses a special challenge in not only the diagnosis of focal drug refractory epilepsy but also in the selection of surgical candidate. Awareness about the myriad numbers of focal epilepsies, current standard in pre-surgical evaluation, and the available minimally invasive surgical options are important in raising the standard of both the primary epilepsy care and a timely referral to a specialized center. Authors have made an attempt to emphasize the importance of early recognition and intervention along with the reviewing of the current evidences on the surgical management so that any treating pediatrician are informed well enough for a better clinical judgment.

Keywords: Pediatric epilepsy surgery, Drug refractory, Pre-surgical evaluation

INTRODUCTION

Case capsule: A mother noticed frequent smiling and laughing episodes in her male child, at the age of 3 months. This made her happy too and was thought to be a normal milestone and was ignored. One-year later, child started having generalized tonic-clonic seizures for which the medical attention was sought. Magnetic resonance imaging (MRI) was done, which was reported as normal and medication was started with a single drug. However, the seizures progressed in duration, severity, and frequency and the number of drugs was increased to four eventually over a period of next 1 year. Mother also noticed aggressive behavior and appearance of secondary sexual features in a child who is now 4 years. This child was then referred to a specialized center for further evaluation. The initial evaluation with VEEG demonstrated the classical semiology of gelastic seizures with interictal and ictal discharges from frontotemporal region. However, the MRI done in an epilepsy protocol picked up a small DeLalande type I hypothalamic hamartoma measuring 1.5 cm in size. Neuropsychological evaluation showed severe mental retardation with maximal dependency. As there was a good anatomoclinical correlation, child underwent minimally invasive MRI-guided stereotactic radiofrequency ablation of this lesion under general anesthesia. At 1 year follow-up, the child became seizure free and the quality of life score improved. Child was continued on hormonal therapy under endocrinological care. This is a case scenario of one child and a mother among many others who go through this rather heart-wrenching experience of moving from one hospital to another until a final answer was found in a specialized center. Had this been diagnosed early at the age of 3 months or even at

the age of 1 year, the burden on the family could have been prevented. The learning points to be noticed in this case were that: (1) An early semiological features was missed, (2) the MRI done in a non-epilepsy protocol can easily miss a small epileptogenic lesion such as hamartoma or cortical dysplasia, (3) even a VEEG can give an ambiguous picture in a child with an immature brain and a complex epileptogenic lesion, and (4) above all a minimally invasive surgical option rendered the child seizure free. Epilepsy is largely treated with medicines successfully; however, there are subsets of patients who are drug refractory like an above-mentioned case. An estimated 10.5 million children worldwide have epilepsy. The annual incidence is reported to be 61–124/100,000 children in developing countries.[1] Any child affected with seizures is not only an awful experience to the family but also it is equally prone to an unexpected sudden death. Hence, raising the index of suspicion by creating awareness among all the pediatricians who can come across such a child in day-to-day practice is the sole purpose of this review article that follows.

Definitions

As per the ILAE guidelines, the drug refractory epilepsy is defined as a failure to achieve seizure freedom after an adequate trials of two drugs with an optimal dosage for 2 years and with good compliance.[2] This definition can be easily followed in adults, however, for pediatric age, this period of 2 years is not practical as lot more damages can happen in a developing brain as explained earlier. Hence, the subcommission of ILAE was formed to address this and they defined the condition as a failure of either 2 or 3 appropriate AEDs or causing disabling seizure side effects and/or disabling AED side effects.[3] The incidence of drug refractory epilepsy in a child depends on the pathological substrate for the same. However, in general, the incidence is 20–30%,[4] which can be higher in patients with hypothalamic hamartoma for which the mainstay of treatment is surgical and lower in cases like absence seizures, which are treated by drugs.

PRE-SURGICAL EVALUATION

The MR imaging of brain of infants is complex in terms of interpretation due to immature myelination. A "normal" study does not rule out subtle cortical abnormalities, and as per the guidelines, the imaging has to be repeated at an interval of 6 months or after 2 years of age if there is a strong index of suspicion for focal onset seizures.[5] Similarly, electrophysiological evaluation of cortical activity in infants and young children is extremely difficult because of poorly defined "normal" and "abnormal" electroencephalography (EEG) patterns of the immature brain, the absence of well-defined epileptiform discharges, rapidly spreading ictal activity, and the great variability of electrophysiological seizure patterns. These characteristics make the localizing value of EEG findings for children very controversial as opposed to those for adults. As a result, defining the epileptogenic zone in the immature brain is a Herculean task in many cases, one needs to be handled with a great deal of expertise. This in most pediatric cases would require phase wise evaluation with Phase-I involving non-invasive imaging investigations and Phase-II involving invasive depth electrode evaluation. Phase-I investigations consist of nuclear medicine with positron emission tomography and single-photon emission computed tomography used to detect the cellular metabolic changes during the interictal and ictal periods. Magnetoencephalography uses magnetic field to detect the neuronal field changes, which are depicted then on an anatomical head model. If the Phase-I evaluation reveals a focal potential epileptogenic zone with good concordance among different investigations, then one can proceed with surgery. If any of these investigations are discordant, then the pre-surgical evaluation is complemented with invasive depth electrode insertion after which, extraoperative electrophysiological recordings are done to detect and confirm the origin of seizures.

INDICATIONS FOR SURGICAL MANAGEMENT

Some of the potential epileptogenic lesions, which commonly present with drug refractory epilepsies, are as follows: (1) Developmental lesions such as cortical dysplasia, hamartoma, and heterotopia; (2) tumors such as low-grade gliomas, ganglioglioma, and dysembryogenic neuroepithelial tumor; (3) vascular lesions such as AVM and cavernous malformations; (4) injury-related lesions like gliosis (from CVA or trauma); and (5) infectious lesions such as granuloma or parasitic cyst.

Other pediatric epilepsy syndromes, which are drug refractory and are amenable to surgery, are Rasmussen encephalitis, tuberous sclerosis, Sturge-Weber syndrome, hemiconvulsion-hemiplegia-epilepsy syndrome, and hemimegalencephaly. With recent advances in imaging, electrophysiology, and surgical techniques, the infantile spasms, which were largely considered as medical condition hitherto, are now recognized as a surgical condition as well.

TIMING OF A SURGICAL MANAGEMENT AND ITS ADVANTAGES

Surgery is often the treatment option for some of these children with drug refractory epilepsy not only to control seizures but also to prevent and improve the comorbid conditions mentioned previously. Young children have a much greater potential for recovery after a surgery and a significant capacity for reorganization of neurological function.[6] It is of utmost importance that the pediatric

epilepsy surgery team members fully appreciate the functional plasticity and potential of the young brain and take these characteristics into consideration when making pre-surgical assessments and surgical decisions. Because many types of pediatric epilepsy syndromes are inherently medically refractory, there is no need to "prove" medical intractability before embarking on a surgical course of action. The harmful effects of prolonged seizures and the toxic effects of AEDs on synaptogenesis, brain development, and cognitive and psychosocial development bolster the argument for early surgery in pediatric epilepsy patients. All India Institute of Medical Sciences, New Delhi, became the first center to conduct a randomized controlled trial (RCT) trial in pediatric age group to look at the benefits of early surgery which confirmed that children and adolescents with drug-resistant epilepsy who had undergone epilepsy surgery had a significantly higher rate of freedom from seizures and better scores with respect to behavior and quality of life than did those who continued medical therapy alone at 12 months.[7] The potential for significant recovery is highest during the period of high synaptic and dendritic density (ages 3–7 years), when the plasticity of the brain peaks.[8] Surgery performed within this time frame may help hasten recovery, and anticipated post-operative impairments may be milder.[9] In well-selected patients, early surgical intervention may prevent the negative cognitive, psychosocial, and developmental effects of seizures. Hence, the goals of surgery in these patients should be to prevent the possible harmful consequences of uncontrolled seizures; to prevent continued interictal activity resulting in permanent cognitive, behavioral, and psychosocial problems; to prevent secondary epileptogenesis; and to avoid the adverse effects of AEDs.

SURGICAL OPTIONS

Surgery is a well-established modality of treatment in these conditions and the various surgical options can be grouped into those that can render seizure freedom and those, which are palliative. Curative options are hemispherotomy, electrocorticography-guided lobar resections, or disconnective procedures, minimally invasive radiofrequency ablations. The palliative options for generalized seizures are corpus callosotomy for drop attacks and neuromodulative options of deep brain stimulation (open loop – DBS) of anterior thalamic nucleus and other targets, responsive neuro stimulation (closed loop – RNS) and vagal nerve stimulation (VNS). However, timely recognition of these conditions and referral to specialized center is an important predictor of the final outcome. Most important concern w.r.t surgery is safety or the risks involved. The advances in the field of neurosurgery from the introduction of operative microscope onward the results have been tremendous to an extent that now in India we have robotic assisted minimally invasive surgeries as well using which the depth electrodes can be inserted and even the hemispherotomies are performed through tiny twist drill openings. These advances have brought down both the morbidity and mortality. By definition, serious adverse events included, hospital admission or prolongation of an existing hospital stay, and events that resulted in persistent or substantial disability or incapacity or that were considered to be life threatening.[10] The AIIMS group reported 33% of serious adverse events in the randomised controlled trial, which looked at the benefits of early surgical intervention in children. Partly, this is due to the hemiparesis following the large numbers of hemispherotomy, which needs to be considered as an expected consequence of the surgery itself. However, the mortality in this study was zero highlighting the safety.[7]

DISCUSSION

Epilepsy in a child is different from adults in numerous ways. Most importantly, it is the developing brain, which faces the arrest in the growth and development due to on-going seizures. The brain, which is normally bustling with activity in a child, comes to a standstill whenever the seizure spreads. This affects the dendritic formation and the neuronal processing in a significant manner. All the important milestones are achieved and new skills are acquired in the first decade of life. This is lost due to the engagement of brain in seizure activity. The continuous postictal state and frequent interictal epileptiform discharges may cause an irritable, dysfunctional cortex, and, possibly, secondary epileptogenesis. In childhood, intractable seizures can be quite atypical and poorly defined compared with the relatively well-defined clinical and electro-physiological characteristics of epilepsy syndromes in adults.[3] Unilateral localized or hemispheric etiologies in children may present with generalized seizures and EEG patterns, progressive neurological disorders, and bilateral congenital brain syndromes. The seizures in these patients are also frequently extratemporal and cover large cortical areas, including the eloquent cortex. Invasive monitoring, cortical mapping, and stimulation studies may be needed more frequently in these children than in adults. Rapid brain maturation during early infancy and childhood is responsible for a complex evolution of clinical seizure semiology and EEG and neuroimaging findings. This complexity makes the assessment of the clinical, electrophysiological, and imaging findings very challenging.

Although spontaneous remission of the seizure is possible, the risk of permanent neurologic, psychosocial, and cognitive impairment from their recurrence and from the adverse effects of AEDs is significant during this crucial period of brain development. In addition, sudden unexpected death

due to epilepsy (SUDEP) is a definite possibility if the seizures are drug refractory. The incidence of SUDEP goes up from 0.9 to 2.3/1000 person-years in general epilepsy populations to 6.3 to 9.3 per 1000 person-years in epilepsy surgery candidates. One of the major risk factor is the age <16 years and the incidence is known to decrease after the successful surgery.

It is a well-known fact that the comprehensive care of children with epilepsy is challenging. Specialized knowledge of and expertise in the medical and surgical management of such patients are required. Thus, a well-coordinated, collaborative relationship between medical and surgical teams in a multidisciplinary environment is critical for successfully managing pediatric epilepsy patients.

CONCLUSION

To summarise, it is necessary to strike a balance between the two groups of patients.The one who is drug refractory and faces the adverse effects of AEDs because of unrealistic expectations of a spontaneous remission and the other, who undergoes unnecessary surgery and inadvertently causing a patient to experience psychosocial deterioration. This is the unique challenge that the paediatric epilepsy surgery team now faces and are attempting to overcome with a good clinical judgement, pre-surgical evaluation and a timely management.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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