What is the Consequence of Children with Medically Intractable Epilepsy? What are the Treatment Options?

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Introduction
Seizure occurs in as many as 5% of children and epilepsy (recurrent, unprovoked seizures) occurs in 0.5 - 1% of children. More than three-quarters of individuals with epilepsy have their onset in childhood or adolescence. Seizure disorders are one of the most common groups of paediatric neurological condition. The majority of epilepsies in childhood are benign syndromes in which children experience infrequent seizures over a short period, usually with the need for no or little antiepileptic medication. A prospective long term (average follow up period of 37 years) population based study in 144 patients (first seizure < 16 year) with epilepsy showed 67% of them have gone into terminal remission with seizure-free period of > 5 years. However, in the remaining 33% of them, their epilepsy did not remit. 14% of them have on and off remissions and relapses; 19% of them have no remission at all. From a local cross-sectional epidemiological study in NTW cluster in 1997, 14% of paediatric patients with active epilepsy were found to be medically intractable. The definition of intractable epilepsy is uncontrolled seizures that occur with the average frequency of at least one seizure per month over a period of 2 years or more, despite treatment with at least 2-3 different anti-epileptic drugs administered on its own or in combination. Drugs have to be pushed to the maximum tolerated doses and non-compliance has to be ruled out. In our daily clinical practice, medically intractable epilepsy is not uncommon and it is a very challenging problem that we are faced with. Does the discovery of new anticonvulsant drugs help children with intractable epilepsy? There is lack of large scale drug trials in children. The result of more large scale adult drug trials in comparing the new and old anti-epileptic drugs showing both new and old drugs have similar efficacy in controlling seizure, but new anti-epileptic drugs appear to have advantages related to safety, long term side effects. According to the NICE guideline, the newer Anti-epileptic drugs which include Gabapentin, Lamotrigine, Oxcarbazepine, Topiramate, Levetiracetam and Vigabatrin (as an adjunctive therapy for partial seizures), within their licensed indications, are recommended for the management of epilepsy in children who have not benefited from treatment with the older antiepileptic drugs such as Carbamazepine or Sodium Valproate, or for whom the older antiepileptic drugs are unsuitable because of various reasons including possible drug-to-drug interaction and childbearing potential. Although in refractory patients, newer anti-epileptic drugs can reduce seizure frequency when added to pre-existing anti-epileptic drugs, it is still rare for previously refractory patients to become seizure-free.7

The Possible Consequences of Uncontrolled Epilepsy
Apart from causing seizure, uncontrolled epilepsy could affect normal brain development and cause long-term cognitive impairment. One study showed that intellectual dysfunction (defined as IQ <79) was present in 57% of children with temporal lobe epilepsy.3 Age at onset of epilepsy is the best predictor of intellectual dysfunction.3 Another study showed that children with epileptic did show a significantly less gain in Full Scale IQ over 1’s year follow up when compared with normal children and suggested that there is a process of mental deterioration shortly after the onset of epilepsy.15 Another study showed that there is long-term reduction in the white matter of the brain in those children who have chronic temporal lobe epilepsy. The reduction of white matter in the brain is associated with long-term neuropsychological impairment.9

The Current Evidence of Epilepsy Surgery
Epilepsy surgery, including cortical resection, single or multi-lobectomy, and/or disconnection procedures, is an important alternative to drug therapy in selected patients. The goal of epilepsy surgery by resecting or disconnecting the epileptogenic focus is to make the patient seizure-free with no requirement for anti-epileptic medication. However in some patients this goal may not be fully achieved and the aim is to decrease the frequency and severity of the most disabling seizures. Apart from resective surgery which could be curative, there are palliative surgeries for those patients who are not candidate for resective surgery because of absence of an identifiable focus. The palliative surgeries include corpus callosotomy and vagal nerve stimulation.
According to a first randomised trial of surgical versus medical treatment in temporal lobe epilepsy, surgery was successful in 58% of operated versus 8% of medically treated adult patients.21 How about the seizure outcome in paediatric patients after epilepsy surgery? The frequency of seizure-free outcome after epilepsy surgery was similar for infants, children, and adolescents, and is comparable with results from the adult series.22 Are the results different in different types of surgery? For patients with intractable temporal lobe epilepsy who undergo temporal lobectomy, seizure freedom or marked improvement in seizure control is expected in 50-70% of the patients.14,21 Lower seizure-free rates of 50-65% are reported for epilepsy surgery in extratemporal epilepsy, "non-lesional" epilepsy and childhood partial epilepsies.22 The efficacy and safety of epilepsy surgery has been assessed by recent studies and clinical trials14,20,22,23 and it has become an internationally accepted treatment for selected patients with intractable epilepsy.4

Apart from seizure outcome, more and more studies show that earlier surgical intervention can result in better developmental outcome (DQ/IQ) especially in those who became seizure-free after surgery.8 For example, a study shows that there is a catch up in development in catastrophic epilepsy in infancy and young children after surgery23; there is an improvement in verbal and perceptual intelligence quotients for children who underwent early temporal lobectomy.20 More studies illustrated children have better brain plasticity than adults, children with epilepsy have greater functional recovery after temporal lobe surgery when compared with adult patients. When compared to adult TLE patients, TLE children below the age of 16 show a lower risk of postsurgical memory deterioration12 and within a 3-12 months follow-up, the postoperative memory decline appears to be more reversible in children than in adults.20 For children to benefit most from epilepsy surgery, in terms of maximising neurological development in the absence of seizures and adaptation to any neurological deficits, surgery should be performed as early as possible.8,10,13,20

Apart from the developmental and cognitive outcome, talking about the long term psycho-social outcome, significantly higher levels of education, employment status and independence were found in children and adolescent patients who became seizure-free after surgery.5

The Indication of Referral for Pre-surgical Evaluation

Generally speaking, the indication for referral for presurgical evaluation of paediatric epilepsy patients is similar to those for adult patients. This includes patients fulfil the criteria for medically intractable epilepsy with a potentially identifiable epileptic focus for example a focal lesion on MRI with concordant scalp EEG and congruent results of functional evaluation.

But in children, not only medically intractability of seizure is considered, but also the disability caused by seizure (including medication side effects) is considered when choosing possible surgical candidates.4 Compared with adults, the presentation of intractable localisation-related epilepsy is often heterogeneous in childhood. Paediatric patients with hemispheric or unilateral focal aetiologies can have generalised seizures and EEG patterns, progressive neurological disorders and bilateral congenital brain syndromes.4 Childhood epilepsy that cannot be classified as a clearly defined electro-clinical epilepsy syndrome (ILAE classification)4 should be referred for pre-surgical evaluation. This includes patients with stereotyped or lateralised seizures or other evidence of focality (that cannot be definitely attributed to idiopathic partial epilepsies) or in whom MRI reveals a lesion amenable to surgical removal. Developmental delay or very young age should not be a contraindication for paediatric epilepsy surgery.4

According to the NICE guideline, the diagnosis and management of epilepsy in children within the first few years of life may be extremely challenging. For this reason, children with suspected epilepsy should be referred to tertiary services early, because of the profound developmental, behavioural and psychological effects that may be associated with continuing seizures. Behavioural or developmental regression or inability to identify the epilepsy syndrome in an individual should result in immediate referral to tertiary services.

The surgical remedial epilepsy syndromes are specific aetiologies of epilepsy which are medically unresponsive and could be benefited from epilepsy surgery. They include: Malformation of Cortical Development; Mesial Temporal Sclerosis; Developmental benign brain tumour (DNET, ganglioglioma); Unilateral cerebral vascular injury with or without infarction /proencephalic cyst; Vascular malformation e.g. Cavernous Haemangioma; Tuberous Sclerosis; Sturge-Weber Syndrome; Rasmussen’s Encephalitis; Hemi-megalencephaly; Hypothalamic Hamartoma etc.4

Tertiary Level Inter-disciplinary Pre-surgical Assessment in NTWC

Because of the complexity in paediatric medically intractable epilepsy which may be associated with profound developmental, behavioural and psychological effects, a tertiary level inter-disciplinary assessment is mandatory. A comprehensive paediatric pre-surgical evaluation team has been set up in Tuen Mun Hospital since 2006 which entails a multidisciplinary team of experts (paediatricians specialising in epilepsy, neurosurgeons, neuro-radiologists, nuclear medicine physicians, child psychiatrists and neuro-psychologists, occupational therapists). Each patient with intractable epilepsy has undergone detailed pre-surgical evaluation including video EEG, high resolution MRI and neuropsychological assessment. In selected case, PET and ictal SPECT were also performed to identify the epileptogenic focus. Epilepsy surgery was performed when the above investigation results were concordant.

The cornerstone of modern management of epilepsy is video-EEG monitoring with scalp electrodes. It has the following clinical purposes: firstly, to clarify the nature of
clinical event (epileptic or non-epileptic) or classify the nature of seizure in order to guide the management; secondly, to localise seizure focus in pre-surgical evaluation for feasibility of epilepsy surgery, whereby seizure characteristics and ictal EEG recordings provide crucial information about the likely site of seizure onset. In Tuen Mun Hospital, regular inter-disciplinary case conference is held to evaluate each case, each discipline will offer their professional advice and decide whether the patient could be benefited from surgery or not. Overseas expert advice will be sought in any difficult and challenging case to make sure the standard of care is up to international standard. If the patient is not a candidate for surgery, we will try to optimise their medical treatment or try other treatment modalities including ketogenic diet etc. Each epilepsy patient will be followed up post-operatively to monitor the progress, this not only includes the seizure outcome, but more importantly the cognitive, psychological, psychiatric and quality of life outcome.

From 1998 - 2008, 23 children underwent epilepsy surgery in Tuen Mun Hospital. Their age at operation was ranged from 2 - 19 years. 48% of them became seizure-free; 26% of them had seizure reduction; 26% had no change to their seizures. For lesionectomy, 65% of the patients became seizure-free and 18% had seizure frequency reduction after surgery.24

**Conclusion**

For children with epilepsy not adequately controlled by medication, it is believed that early assessment and changing to a more appropriate treatment offers the best prognosis for seizure control, educational achievement and personal development. Epilepsy surgery is shown to be safe and an effective way of treatment in selected groups of children and adolescents with intractable epilepsy and they should be considered for surgical evaluation at whatever age or IQ level they manifest with severe, intractable, disabling localisation-related epilepsy.19,22

In the old days, people view epilepsy surgery as the last treatment option and delay to have surgery until in adult age. Now evidence shows that in order to achieve the best developmental and cognitive outcome, early referral of suitable patients to have pre-surgical evaluation is mandatory.

There is a qualitative change in the treatment of epilepsy, which not only aims at seizure control, but also at preservation or even improvement of the patient’s cognitive performance, his or her psychological situation, and his or her subjectively experienced quality of life. In order to solve this multi-dimensional problem, a close collaboration between different professional experts is essential. I would like to quote what the previous Vice-president of US, Mr Al Gore said to emphasise the importance of interdisciplinary care of medically intractable epilepsy. He said "If you want to walk faster, you walk by yourself. But if you want to walk further away, you have to walk together".

**References**