Epilepsy surgery in children: Time is critical

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Surgery is now long established as standard management of carefully selected children with focal epilepsy. It is seen to be effective over a wide age range, and over a spectrum of clinical presentations and pathologies. There are many aspects to children, however, that can be particularly challenging and deserve special consideration in the evaluation for surgery and planning of surgical strategy. Further, the likely impact that can result from early evaluation and surgery with resulting seizure control means that children and especially infants should be referred and assessed early in their clinical course. A high index of suspicion is consequently required on the part of the caring physician as to when a child may be a candidate for resective surgery or at least for presurgical evaluation.

Epilepsy surgery in children is not new. The first hemidisconnection reported was in 1928 by Dandy for malignant glioma (Dandy, 1928), with McKenzie performing the procedure first for seizures later in 1938 (McKenzie, 1938). Later, however, it became evident that although hemispherectomy might be a very specific consideration for surgery in children, adults coming to surgery for temporal lobe resection often had onset of epilepsy in childhood. With the high rate of psychosocial morbidity also reported in the adults coming to surgery, the premise arose that surely this could be avoided if surgery were performed earlier in the clinical course of the epilepsy (Falconer, 1972). Further, with advances in structural and functional neuroimaging, focal or hemispheric abnormalities were detected in life thus identifying possible surgery candidates earlier (Cross *et al.*, 1993). These issues were discussed in depth during the 6th International Bethel-Cleveland Clinic Epilepsy Symposium specifically dedicated to Epilepsy Surgery in Children (Bielefeld, Germany, March 23-26, 1995), and in the subsequent book published in 1997 (Tuxhorn *et al.*, 1997). Over time, there has been an increasing body of experience with regard to epilepsy surgery in children, with growing recognition of the differences seen in children compared to adults and the need for specialized assessment and centres. The International League Against Epilepsy Subcommission and later Task Force for Epilepsy Surgery in Children has worked over some time to determine standards for referral and evaluation. A workshop in 2003 resulted in the publication in 2006 of an initial consensus statement on the criteria for referral and evaluation of children for epilepsy surgery (Cross *et al.*, 2006). This product not only outlined consensus at the time but also outlined the work that needed to be done to achieve the evidence base for further consensus. Subsequently the group has continued to work toward this end, with subsequent publication of epidemiological data (Harvey *et al.*, 2008) and evaluation of advanced diagnostic techniques in presurgical evaluation (Jayakar *et al.*, 2014). This book is the result of continued collaborative working between epilepsy surgery centres over the years. Within the book we aim to set out the key elements of presurgical evaluation, the specific electroclinical presentations, comorbidities and pathologies encountered in childhood, and the range of outcomes to be monitored. The key to optimized outcome in children is early appropriate recognition of possible surgical candidates and timely referral.

Why are children different?

The primary aim of epilepsy surgery is cure of seizures, or at the very least reduction of seizures provided that it will bring substantial improvement in quality of life. The aim of evaluation is therefore to determine the area of brain required to be removed to maximize the chance of seizure freedom, and also to determine the risk to function should this area be removed. In other words to evaluate the benefit/risk ratio whilst taking into account the plasticity of the child's brain. Whereas semiology may be highly suggestive of focus and risks in older children, in young children immaturity of brain development means that semiology may not be so reliable. For example infants may express apparent generalized manifestations despite definitive focal pathology. The question of when a child should be referred and evaluated for surgery then arises. For many reasons the answer is as soon as possible (Cross *et al.*, 2006). Certainly any child with ongoing seizures of any age, with lateralized or localized brain abnormality evident on MRI should be referred as a priory for evaluation and further any child with evidence of clinical or EEG lateralization. Epileptic encephalopathies identified via stagnant developmental profiles, altered behavioural states, or near-continuous EEG abnormalities are not uncommon and should be considered reasons for prompt referral. The discussion often arises as to whether failure of drugs should be demonstrated. One could argue as to the extent that drug resistance needs to be demonstrated with a readily apparent resectable lesion visible in early childhood. The ILAE recently proposed a definition for drug resistance which can be utilized in this circumstance, defined as a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules, whether as monotherapies or in combination, to achieve sustained seizure freedom (Kwan *et al.*, 2010). No time course is specified so this is relevant to even the infant who is treated with multiple drugs over a very limited period of time.

Range of syndromes and aetiologies

Many of the electroclinical syndromes within the classification of the epilepsies are age related with a multitude of aetiologies recognized as the cause (Berg *et al.*, 2010). Some appear definitively age dependent, and can arise as the result of focal pathology. The classic example are infantile spasms, with or without the full triad of clinical presentation (with neurodevelopmental plateau and hypsarhythmia on EEG) fulfilling West syndrome. Ohtahara recognized at an early stage there appeared to be an age dependency to expression of an electroclinical syndrome, with some children evolving from one syndrome to another – early infantile epileptic encephalopathy to West syndrome and ultimately to Lennox Gastaut syndrome (Ohtahara & Yamatogi, 2003). With the advent of newer imaging techniques, initially FDG positron emission computed tomography and later magnetic resonance imaging, some children presenting with West syndrome appeared to have lateralized pathology. UCLA reported their initial series of children undergoing multilobar resections for treatment of spasms in the early 1990s, with apparent improvement in both seizure control and long term neurodevelopment (Chugani *et al.*, 1993). What has become clear over time and with growing experience is that lateralization may be apparent on clinical semiology and or EEG, and a high index of suspicion required to evaluate further with structural and functional imaging.

There are additional specific pathologies that may require early consideration, manifestations either limited to childhood or an associated neurobehavioural profile that requires specific consideration. Rasmussens encephalitis primarily presents in childhood; it is an acquired, presumed auto-immune disorder of one hemisphere. Although medical treatments may alleviate seizures in the short term, ultimately surgery is likely to be required and careful assessment required as to the optimal timing of such (Varadkar *et al.*, 2014). Gelastic seizures associated with an underlying hypothalamic hamartoma can be difficult to recognize, but again early assessment and review is required to determine optimal ablative, disconnective, or resective management of the hamartoma to prevent longer term untoward consequences from the development of multiple seizure types to the characteristic adverse neurobehavioural profile

(Berkovic *et al.*, 1988). Developmental brain tumours may have a range of presentation, including a high rate of behaviour and cognitive abnormality warranting early evaluation and intervention in the absence of frequent seizures.

The effect of epilepsy on early brain development

The consequence of long term recurrent seizures on the developing brain would appear to be apparent. Many early onset epilepsies have an extremely poor prognosis for neurodevelopmental outcome, and although the debate continues on the relative contribution of the underlying pathologies, there is also the consideration of the additional impact of ongoing epileptic activity and seizures – so called epileptic encephalopathy, where the ongoing epileptic activity has an impact on cognition and behaviour over and above that would be seen from the underlying pathology alone (Berg *et al.*, 2010). A study of children with static pathology suggests an additional impact in the longer term from early onset of epilepsy (Muter *et al.*, 1997). Further, ongoing seizures in children with earlier onset epilepsy are associated with poorer long term neurodevelopmental outcome (Berg *et al.*, 2004). Acknowledging the possibility of a degree of epileptic encephalopathy, one could presume that such neurodevelopment could be at the very least improved with early cessation of seizures. Increasing numbers of studies suggest this can be seen in both the short (Loddenkemper *et al.*, 2007; Freitag *et al.*, 2005) and longer term (Freitag *et al.*, 2005; Skirrow *et al.*, 2011), although comparative studies are not available of children with and without surgery.

Heterogeneous presentation of focal epilepsy in childhood

As outlined above focal brain pathology in infants and young children may not lead to the recognizable classic features of focal seizures. Assumed to be the result of immaturity of key pathways, this may be seen as spasms, atonic drops, apparent absence with 3 Hz spike and wave or generalized tonic clonic seizures all without focal features, with a generalized EEG. To complicate the issue, magnetic resonance imaging may be misleading with incomplete myelination in the very young. Malformations of cortical development remain the most common cause of epilepsy coming to surgery in childhood (Cross *et al.*, 2006), and require specific parameters/protocols to visualize with MRI. Lesions have been seen to both apparently appear and disappear with completion of myelination (Gaillard *et al.*, 2009), and therefore repeat imaging as well as evaluation of earlier imaging maybe required to definitively exclude visible focal pathology (Eltze *et al.*, 2005). Such evaluation requires specific paediatric neuroradiology expertise. With increasingly sophisticated techniques available for the localization of tissue responsible for seizure onset, it is apparent that certain techniques have individual roles in assessment according to underlying cause within a centre with expertise in the assessment of children (Jayakar *et al.*, 2014).

The potential for functional plasticity

Similar to the premise that early seizures may impact longer term neurocognition, there remains the discussion about the possibility of relocalization of function should there be early injury, namely earlier surgery. Children with large lesions and early onset epilepsy appear to relocalize at an early stage – hemispheric language dominance may be guided by the size of the lesion and age of onset of epilepsy. In older children, the situation may be a little less straight forward. Studies in Rasmussens encephalitis of the dominant language hemisphere have shown that relocalization of language is very likely with onset under the age of five years, but the later the presentation the less plasticity can be demonstrated (Hertz-Pannier *et al.*, 2002; Boatman *et al.*, 1999).

Motor relocalization is less predictable, and even if seen is unlikely to be complete. However, owing to later development of somato-sensory projections, thalamo-cortical projections can still react to injury postnatally, and consequently somato-sensory functions can be relatively well preserved despite large lesions (Staudt, 2010).

Potential to improve long term psychosocial outcome

The adverse long term psychosocial outcome from ongoing seizures through childhood is apparent (Sillanpaa, 1990; 1993; Ounsted *et al.*, 1995; Camfield & Camfield, 2013; Geerts *et al.*, 2011). The question therefore remains whether social, behavioural and cognitive outcomes can be improved in the long term with early cessation of seizures through surgery. Quality of life (QOL) has also been demonstrated to be most related to seizure control (Jacoby & Baker, 2008). Despite the diversity of children coming to surgery, better long-term outcomes are seen in qualifications attained, employment gained, and financial independence achieved are seen for patients who are seizure free post-surgically; better outcome is associated with shorter lifetime duration of epilepsy (skirrow & Baldeweg, 2015). Further, improvements in QOL and psychosocial functioning, when evident, are consistently associated with seizure freedom (Smith & Puka, 2015). Increasing evidence suggests earlier surgery where appropriate will optimize psychosocial outcome in the long term. Improved cognitive outcomes may be particularly related to withdrawal of medication, seen specifically in the longer term (Skirrow *et al.*, 2011). There is evidence that relapse of seizures postoperatively following withdrawal of medication is likely to be inevitable rather than related to timing of withdrawal and therefore consideration should be given to withdrawal as soon as possible if there is a good prognosis for seizure control (Boshuisen *et al.*, 2012).

The aims of this book

This book sets out to outline the key aspects with regard to evaluation of children with epilepsy for surgery. The first section looks at the key components of the presurgical evaluation. The subsequent section then reviews in detail the role of clinical semiology, and how this may direct the clinician to the area of the brain from where seizures arise, with specific aspects for consideration in children. The relevant pathologies commonly encountered in paediatric epilepsy surgery then receive detailed emphasis, specifically with regard to the investigative evaluation required. A short section follows on palliative rather than resective procedures. Unique to this book, however, is the later perspective on the various aspects to be considered when reviewing outcome, as well as an overview of procedures from a surgical perspective, targeted at the neurologist. We conclude by reviewing what the future may hold, setting precedent for questions to be addressed in the future. Children warrant early referral and evaluation – it is our duty to ensure this occurs and consequently optimize their outcomes.

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