Pediatric epilepsy surgery: the earlier the better.

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1. The benefits of surgery

Epilepsy surgery is the only curative treatment currently available for focal lesional pharmacoresistant epilepsy. New antiepileptic drugs (AEDs), the ketogenic diet, or vagal nerve stimulation each lead to a worthwhile reduction of seizures in only 40-50% of patients and rarely achieve complete seizure freedom. In sharp contrast, long-term – five or more years - complete seizure freedom rates of around 60% are reached following epilepsy surgery [1]. Although clinicians who take care of children with refractory epilepsy have been convinced of the beneficial effects of surgery for at least two decades [2], it was recently that a randomized controlled trial unequivocally proved the superiority of epilepsy surgery over continued medical treatment in pediatric surgical candidates [3]. Not only is surgery more effective, it is also less costly in the long term than medical treatment in children who are suitable for epilepsy surgery [4]. Surgical outcome depends on several factors, which include age, duration of epilepsy, results and concordance of presurgical investigations, type and lobe of surgery, completeness of resection, and type of pathology [2,5].

In children who undergo surgery, the most frequent causes of epilepsy are malformations of cortical development (MCD, 39.3%), tumors (27.2%) and hippocampal sclerosis (15%) [5]. Over time those undergoing surgery for malformations of cortical development are less likely to be seizure free than tumors or acquired pathologies, but seizure freedom still remains more likely than with medical treatment [6]. Unfortunately however, the average duration of epilepsy before surgery in a total cohort of operated patients continues to be long, recently found to be 16 years, with three quarters of patients having their onset of epilepsy during childhood [5]. The interval from onset to surgery was naturally shorter in children – 5.3 years [5] – and tended to decrease over the last decades [7]. Increased awareness of the benefits of surgery, growing surgical experience, broadening of indications and improved imaging and source localization techniques have all led to an earlier referral pattern of children for surgical evaluation [2], and to a significantly increased number of pediatric surgeries [7,8]. Nevertheless, epilepsy surgery remains an underutilized treatment for children with epilepsy [8].

2. The risks of surgery

Epilepsy surgery has a very low mortality rate, far under 1% [2,9]. Serious complications, defined as requiring invasive treatment or leading to permanent unforeseen neurological deficits, were reported in 3.9% of children who received epilepsy surgery in the Netherlands between 1990 and 2011 [7], which was comparable to the proportion of children who had a serious medical or neurological complication (4.5% and 5.1% respectively) determined in a recent systematic review [9]. The rate of complications increases when invasive recordings are required prior to resective surgery [2,9]. When focal or lobar resections are performed in clearly non-eloquent brain areas, by experienced hands, and in well-selected candidates, pediatric epilepsy surgery can be considered a safe treatment option.

3. The prospects without surgery

In some pediatric epilepsy syndromes, such as childhood absence epilepsy and benign epilepsy with centrotemporal spikes, spontaneous "cure" may come with time; after a certain age seizures do not recur and AEDs can be safely and permanently discontinued. Children who are considered surgical candidates, however, by definition suffer from a – presumed – lesional form of focal epilepsy. When the MRI of a child with non-syndromic epilepsy is abnormal, the chance of reaching spontaneous complete remission, defined as being at least five years seizure-free and medication-free, is only 32.7% [10]. The long-term seizure outcome of children with a single seizure and a brain lesion – who, according to previous definitions would in the past not necessarily have been classified as having epilepsy – is less known. Even when children reach early seizure control after start of AEDs, there is no guarantee for permanent success of drug treatment. Over 40% of children with intractable focal epilepsy met the criteria for intractability only three or more years after diagnosis, and 76% of them had shown a prior remission of at least one year [11]. The only independent factor predicting enduring intractability in newly diagnosed childhood epilepsy was a neuroimaging abnormality [12]. The chance of reaching seizure freedom without surgery in children with early intractability and abnormal neuroimaging was only 8.6% [12]. In other words; a child with focal epilepsy and a documented lesional cause – by definition a likely surgical candidate – has a low chance of spontaneous and permanent cure, particularly if the epilepsy proves resistant to medication from the outset.

4. The timing of surgery

The "time is brain" axiom, often used in the stroke community, also holds true for children with epilepsy. Continuing seizures in focal epilepsy have been associated with changes in global white matter integrity, functional and structural brain network topology, and with hippocampal volume and structure, each of which potentially affect cognitive outcome in children, as reviewed by [13]. In addition, the chronic use of AEDs – particularly in the developing child – may lead to cumulative and potentially irreversible cognitive adverse effects [13,14]. Therefore, shortening the duration of active epilepsy and the exposure to AEDs, by offering epilepsy surgery in a timely manner, will optimize the child's neurodevelopmental potential. Indeed, earlier surgery was significantly associated with a postoperative increase of developmental quotient in a series of 50 preschool children [15]. A shorter duration of epilepsy prior to surgery was recently shown to correlate with higher presurgical IQ – which is an important determinant of postoperative IQ [16] – in 150 children with glioneuronal tumors who underwent epilepsy surgery [17]. Furthermore, early withdrawal of AEDs – i.e. after several months – can safely be considered after epilepsy surgery in well-selected children [18], and drug discontinuation is associated with improved postoperative intelligence [19]. Not only cognitive development benefits from early epilepsy surgery; seizure outcome is also better when the duration of epilepsy is shorter prior to surgery. Of children who received epilepsy surgery for intractable frontal lobe epilepsy, 66% were seizure-free five years after operation if operated on within five years of epilepsy onset, compared to 31% of children who received surgery after an interval of over five years [20]. Chances of seizure freedom have been shown to be significantly lower with longer duration of epilepsy in patients with glioneuronal tumors [21] and cavernomas [22]. In a nationwide cohort of 234 children who underwent epilepsy surgery in the Netherlands, longer duration of epilepsy was an independent predictor of unfavorable seizure outcome [7].

5. Looking ahead

For all of the above reasons, early referral for surgical evaluation is currently advised for all children with lesional focal epilepsy, once criteria of pharmacoresistance [23] are met. Postponing epilepsy surgery decreases their chance of achieving postoperative seizure freedom and diminishes their eventual cognitive abilities.

We expect in the near future a gradual shift of surgical indications towards children with focal epilepsy whose seizures are **well-controlled** using one or more AEDs, provided that the MRI reveals a **distinct brain lesion** that is **surgically amenable** and located **outside eloquent areas**. First, their risk of severe surgical complications and unexpected permanent neurological deficits is acceptably low [6,8]. Second, postoperative seizure outcomes of particular etiologies in children are excellent, with seizure freedom rates of 80% in glioneuronal tumors [5,17,21], 75% in cavernomas [22], and overall 60% in malformations of cortical development [5,7], probably higher in type II focal cortical dysplasia. Third, in the children with MRI lesional focal epilepsy, spontaneous (i.e. non-surgical) permanent and complete remission is rare. A fourth argument in favor of early surgery – even before refractoriness of epilepsy is established – comes from an oncological perspective in children with a suspected low-grade glioneuronal epileptogenic tumor in whom uncertainty remains about future risks of growth or malignant transformation. Early surgery allows for accurate histopathological and molecular tissue characterization. Lastly, early surgery reduces the burden of drugs since early AED withdrawal is safe after anticipated curative resective surgery and has cognitive benefits [18,19].

We therefore advocate that in each child with an MRI-visible lesional focal epilepsy – caused by a vascular lesion, tumor, hippocampal sclerosis, or suspected type II focal cortical dysplasia – localized outside eloquent brain areas, epilepsy surgery should at least be considered early after the diagnosis. This includes children with a single seizure in whom the decision to start AEDs was made. Children should be referred for careful evaluation in an experienced epilepsy surgery unit. Even when seizures are well-controlled with AEDs, benefits of surgery may outweigh its risks and parents should be carefully counseled as such. Epilepsy surgery is an early treatment option, rather than a last-resort.

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