Epilepsy surgery for children and adolescents – evidence based but underutilised

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Key Messages

1. Epilepsy surgery is safe effective treatment option to carefully selected children, offering the potential of cure (no seizures with no medication)
2. Epilepsy surgery in children with drug resistant epilepsy leads to optimised outcomes in cognition and health related quality of life
3. Children with epilepsy resistant to two anti-seizure medications should be referred for evaluation at a comprehensive epilepsy centre
4. Evaluation and consequent decisions about the possibility for epilepsy surgery should be made at specialist epilepsy surgery centres; early referral is therefore imperative.

Abstract

Surgical treatment of epilepsy in children is an increasingly used evidence-based management option with low risks for complications. Developments in neuroimaging techniques and other advanced diagnostics have widened the spectrum of children who may benefit from epilepsy surgery, and it is now considered standard management. Available data indicate that early surgery improves outcomes. Despite these considerable advances, epilepsy surgery in children is still underutilised.

In this review we summarise the indications, patient selection, principles of presurgical investigations, optimal timing and types of surgery. Following this we examine comprehensive outcomes including seizure outcome, complications, cognitive, neurodevelopmental and vocational outcomes as well as health related quality of life of children and their parents after epilepsy surgery. Successful epilepsy surgery may lead to improvement in all these areas. Children should therefore be referred early for evaluation in an appropriately competent centre.

Introduction

Epilepsy surgery in children has increased in its availability around the world. Although highlighted initially in the 1960s, with the recognition that many adults coming to surgery had experienced epilepsy since childhood, it is only since the advent of magnetic resonance imaging (MRI) and the subsequent development of other advanced presurgical techniques that epilepsy surgery has been opened up to a wider range of children. The International League Against Epilepsy (ILAE) Paediatric Epilepsy Surgery Task Force highlighted in 2006 that surgery in children with drug resistant epilepsy should be considered early in order to enhance neurodevelopmental outcomes and quality of life[1], but data supporting this premise were relatively limited. Since this time, with an increasing number of centres developing expertise, further data are available on optimal presurgical evaluation, criteria for centres and overall predictors of outcome. Further, the spectrum of children to which this management option is now available has widened, leading to the question as to the timing of when to consider surgery to optimise seizure and neurobehavioural outcomes. Despite this there is still evidence that epilepsy surgery in children is underutilised. This review summarises the evidence base now underpinning case selection and overall decision making.

Indication and patient selection

Traditionally, individuals have been considered epilepsy surgery candidates if they demonstrate focal onset, antiseizure-medication resistant seizures arising from a functionally silent area of the brain. The International League Against Epilepsy (ILAE) has redefined drug resistance as failure of adequate trials of two tolerated, appropriately chosen and used antiseizure drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom[2]. This definition has far greater relevance to the very young who may fail trials of antiseizure medications over a relatively short period of time.

The ILAE Subcommission for Paediatric Epilepsy Surgery consensus in 2006 also recognized that certain pathologies were specifically associated with drug resistant epilepsy in children and consequently should be considered early for preoperative assessment[1]. These included malformations of cortical development (focal cortical dysplasia (FCD), hemispheric syndromes such as hemimegalencephaly or hemispheric dysplasias and polymicrogyria), neurocutaneous syndromes (Tuberous sclerosis complex, Sturge-Weber syndrome), Rasmussen encephalitis and hypothalamic hamartoma. Since this time, further consensus has been brought together to outline the stages of presurgical evaluation dependent on the underlying

cause/pathology/finding on MRI[3] (Figure 1). A global Delphi consensus has also recently been published highlighting requirements for two levels of paediatric epilepsy surgery centre dependent on complexity of the patient and investigations required[4] (Appendix 1).

Indications for surgery have broadened in the last decades including more complex cases, e.g. extratemporal epilepsies (frontal, insular or posterior cortex epilepsies), epilepsies caused by multiple, bilateral and widespread lesions, non lesional or MRI negative epilepsies[5]. The increasing complexity of patients is highlighted by publications showing the increase in paediatric operations[6], and numbers of investigations being performed preoperatively[7,8] as well as younger age at surgery[9]. Discussion has also been provoked about the role of surgery for well circumscribed lesions in non eloquent areas even in drug sensitive patients in view of the potential for cure and weaning from medication, and the likely low morbidity from surgery[10]

Optimal timing

The primary aim of epilepsy surgery in children remains seizure control, or, at the very least, reduction in seizure frequency. Secondary aims include improved neurodevelopmental/cognitive outcome and health related quality of life (HRQoL). However, the aims should be evaluated along with the risks individually in accordance with the age of the patient, type of epilepsy, aetiology and type of surgery required.

In terms of seizure control, early surgery (meaning younger age at surgery and shorter epilepsy duration) has demonstrated more favourable outcome, regardless of pathology[11] (Figure 2) whereas longer duration of epilepsy is associated with a reduced chance of seizure and drug freedom[,11,12]. A longer duration of epilepsy has also been demonstrated to have a negative impact on cognitive development[13] with a wean of medication associated with better IQ postoperatively[14]. In epilepsy the result of a structural lesion, resective surgery offers the only likely chance of a cure; no seizures in the absence of anti-seizure medication. This adds further weight to consideration of surgery for lesions in low risk regions in the absence of drug resistance.

One premise for consideration of early surgery has been the presumption of neural plasticity and the ability of young children to recover impaired functions after surgery. This has most relevance to language function where dominance and location may be determined, particularly in the very young, by the location of the lesion and age of onset of epilepsy. Motor

function when located in the epileptogenic zone does not appear to relocate or recover if removed/disconnected, although sensory release may be seen in hemiparetic children with frequent seizures[15].

Decisions about optimal timing of surgery in certain acquired pathologies such as Rasmussen encephalitis however may be difficult. In this syndrome a rapid clinical course with drug resistant seizures, cognitive regression and motor deficit in a patient with non-dominant disease would be a clear indication to proceed to hemidisconnection. In contrast, patients with a slower course and mild deficit involving the dominant hemisphere could benefit from immunotherapy[16]. There is a longstanding debate as to whether hemidisconnection should be performed early, and thereby force relocalisation of language, or whether a wait is required and hence the role of immunotherapy. Studies are scarce and there are no actual data demonstrating whether disconnection should be performed sooner or later in these patients[17].

Presurgical evaluation

Preoperative investigations in epilepsy surgery have three main goals:

1. Localizing the lesion primarily responsible for seizure onset
2. Defining the epileptogenic zone (EZ)
3. Mapping functional areas to preserve during surgery

The ILAE Paediatric Epilepsy Surgery Task Force reviewed available evidence for presurgical investigations, and proposed an algorithm dependent on the presentation, and underlying responsible pathology[3] (Figure 1). It was recognised that limited evaluation in certain cases would provide enough information to move forward, with a minimal data set including clinical history, 3T MRI, ictal recording, and neurodevelopmental/cognitive assessment. Additional tests are required in approximately 30% of patients. Many of the advanced technologies have proven their value experimentally but their use remains limited in the clinical setting. Second line presurgical evaluation currently depends on the availability and expertise in the different technologies at each epilepsy centre. This is incorporated into the assessment of level 1 and level 2 surgical centres[4]. However, it must be remembered that in early childhood the evaluation may be particularly challenging, with lesions on MRI being unclear or clearer in the unmyelinated brain[18], and EEG demonstrating bilaterality in the presence of a localised/lateralised lesion.

There are no randomised controlled trials comparing the relative merits of different methods of evaluation and no guidelines as to the use of additional required studies when unconclusive or discordant results are obtained from the initial evaluation. New diagnostic technologies and a multimodal approach eg image registration and post processing of MRI, will be increasingly incorporated in the clinical routine which is expected to improve surgical strategy and outcome[19], already demonstrated in some centres[20]. The utilisation of new technologies is particularly important in patients with no lesion on MRI or bilateral, diffuse or multiple lesions where only a restricted area could be epileptogenic and consequently target for surgery.

When data are discordant, the exact limits of the epileptogenic area are unclear, or the area is in close proximity to presumed eloquent cortex, invasive recordings from the surface or within the brain may be required. Originally subdural grids became the primary invasive tool of choice in children in view of the premise that the primary epileptogenic pathological substrate in childhood was neocortical[21]. However, in parallel, stereoEEG was developed in France and Italy, with many centres now increasingly utilising this technique in children in preference to subdural grids even in a younger population[22] with recognition of the wider applicability and lower morbidity[22-24]. The hypothesis by which electrode insertion is defined needs to be clear however. Subdural grids may still hold an advantage in rare circumstances e.g. language mapping and in children under 2 years of age in view of the minimum skull thickness required to secure the electrodes in stereoEEG.

Types of surgery

The spectrum of epilepsy surgery in children is wider and different to that seen in adults. Data collected by the ILAE Paediatric Subcommission for Epilepsy Surgery revealed the majority of procedures to be multilobar and hemidisconnections[25]. Increases in the relative proportion of multilobar and extratemporal procedures have also been noted over time[7] but malformations of cortical development continue to be the major surgical pathology in children[6] . Minimally invasive techniques in specific situations have also been increasingly utilised, e.g. thermocoagulation following stereoEEG[26] and laser ablation for hypothalamic hamartomata and other localised lesions[27].

Seizure outcome after paediatric epilepsy surgery

The primary outcome following epilepsy surgery is seizure control; seizure outcome in children

is often evaluated using the Engel classification[28], originally developed for adults undergoing temporal lobe resection, in which Engel class I denotes freedom from seizures with impairment of consciousness. It is, however, important when assessing the benefits of surgery to distinguish those patients who are completely seizure free since surgery: Engel IA. The concept of worthwhile seizure improvement is subjective in assessment and, although highly relevant in many younger children coming to surgery with frequent seizures, can be problematic when reporting studies of outcome.

There is only one randomized controlled study (RCT) of epilepsy surgery in children, and this clearly shows the benefits in the short term over medical therapy. This single-centre study included 116 patients <18 years on a waiting list for surgery of whom 57 underwent diverse surgical procedures including disconnective procedures[29]. One year after surgery 77% had been seizure free for at least the last six months versus 7% in the medical group; 36.7% had been completely seizure free since surgery (ILAE class 1). With regard to longer term seizure freedom, observational cohort studies have related outcome according to type of procedure, underlying pathology and duration of epilepsy.

Several recent systematic reviews have reported short-term (≥1 year) seizure outcomes in observational studies after paediatric resective epilepsy surgery procedures (Table 2) with the highest proportion seizure free following temporal lobe resection (TLR)[30] followed by hemispherotomy[31] and the lowest after extratemporal resection[32].

Table 1 near here

In a recent systematic review and meta-analysis, 258 studies of both temporal lobe resections, extratemporal resections and hemispherotomies were included. Outcome was seizure freedom (not further specified) at 12 months or longer; there was a decline in the proportion of seizure-free patients over time from 64.8% at one year to 39.7% at 10 years. Seizure freedom was highest for hemispheric surgery followed by TLR and extratemporal surgery [33].

Posterior cortex surgery for selected paediatric candidates with lesions has also been shown to lead to good surgical outcome with 60% seizure free (Engel I) even at long-term follow-up[34]. For suitable candidates, epilepsy surgery in infancy and early childhood is increasingly successful: in four recent studies together including 175 children, 45-68% became seizure free (Engel I) after various procedures[35,36].

A recent large retrospective study of seizure and medication outcomes related to histopathology with more than 9000 adults and children from 37 European countries showed histopathology to be an independent determinant of freedom from disabling seizures (Engel I) 5 years after surgery[11]. Lesions such as low-grade epilepsy associated neuroepithelial tumours and vascular malformations carried a better prognosis than cortical malformations, shorter duration of epilepsy was more favourable, and children were more often seizure-free and drug-free than adults.

More detailed studies of subtypes of focal cortical dysplasias (FCDs) have shown that around 50% of patients become completely seizure free (Engel IA) but with complete resection seizure free rates up to 80% can be achieved[37-40]. Polymicrogyria has long been considered unsuitable for surgical treatment but recently good results have been presented in subsets of patients in several small series[41-43].

As in adults, longitudinal studies disclose recurrences in a certain proportion of children. Recurrences are more common after multilobar resections[44] than after focal resections[45] and least common after hemispherotomies in which bilateral PET abnormalities and acute postoperative seizures have been shown to be independent predictors of seizure recurrence[46].

The first systematic review of seizure outcome following corpus callosotomy, a palliative procedure directed at reducing 'drop' attacks, included 1742 patients from 58 studies, both adults and children[47]. The overall seizure free rate (not further specified) for this palliative procedure was 19% with presence of infantile spasms, normal preoperative MRI, and a shorter epilepsy duration as positive predictors. Freedom from drop attacks, was seen in 55%, with idiopathic epilepsy aetiology and complete callosotomy as positive predictors.

Complications related to paediatric epilepsy surgery

The surgical risks must be considered and weighed against the chances of seizure freedom or substantial improvement when families are counselled about epilepsy surgery.
Epilepsy surgery has risks related to the anesthesia and the operation as is the case for all major surgical procedures. Apart from these surgical complications there is a risk for neurological complications which depend on the location and extent of the surgical resection. In epilepsy surgery it is of special importance to distinguish unexpected complications from

expected adverse events which are not uncommon and need to be discussed preoperatively with the patient/family and accepted as part of the trade-off. Examples of such expected adverse events may be worsening of hand function after hemispherotomy and visual field deficits in the superior quadrant after temporal lobe resections[48].

There is however a lack of a common definition of what constitutes a complication of epilepsy surgery. This is illustrated by the reporting of adverse events in the paediatric RCT by Dwivedi and colleagues in which as many as 33% of the operated patients were reported to have serious adverse events[30]. After a questioning letter to the editor the authors clarified that the majority of these were due to 15 cases of worsened hemiparesis after hemispherotomy, i.e., expected adverse events, and after exclusion of them the rate of complications classified as major was 3.5%[49]. Unexpected neurological complications are often considered minor if temporary and major if they persist beyond 3 months[50]. Major neurological complications occur in around 5% of children according to a systematic review[51] and in 2.4% in a recent large population based prospective study[48].

Cognitive and Behavioural Outcomes

Up to 80% of children with active epilepsy experience cognitive and/or behavioural disorders[52]. These impairments may impact significantly on the child's social and academic achievements, and quality of life, as well as serve as stressors within the family. One of the common hopes among parents of surgical candidates is that these disorders will show improvement in concert with improved seizure control after surgery. Most studies of cognitive and behavioural outcomes have examined relatively short periods of follow-up of six months to two years, have involved heterogeneous surgical samples with respect to site and extent of resection, and many have not included an appropriate comparison group to determine whether changes may be secondary to developmental factors rather than to surgery. Findings are quite variable as to whether or not seizure outcome is related to these outcomes.

Cognition after paediatric epilepsy surgery.

The majority of studies evaluating cognition have examined intelligence (IQ), or, in young children or those with significant developmental delays, the development quotient (DQ). The average change in IQ/DQ is small, and may not represent improved functional capacity. Some studies have applied criteria for clinically meaningful change (although there is no consensus

on what criteria to use), and have found that approximately 70% of children do not experience a meaningful change in IQ/DQ, and improvement or deterioration are experienced relatively equally (10-15%)[13,53,54]. Children with lower IQ/DQ are more likely to show increases after surgery[54-57]. Gray matter volume change in the contralesional dorsolateral frontal cortex has been found to be predictive of IQ improvement[55]. Gains in IQ have been reported after antiepileptic drug withdrawal in post-surgical seizure-free children[14].

A small number of studies have questioned whether potential restitution and plasticity may take a considerable length of time and thus have examined longer-term outcomes. Again, most of this work has not demonstrated an improvement in overall IQ[58]. However, improvements in IQ were demonstrated in children who had undergone temporal lobe surgery, with changes seen only six or more years after surgery; IQ outcomes were not related to seizure outcome but were related to weaning of medicaiton[56]. Modest improvements in IQ were documented on average seven years after surgery in a sample heterogeneous with respect to site of resection; these changes were not related to length of follow-up but were related to seizure freedom[57].

The second most frequently studied cognitive outcome has been memory, primarily investigated in children who have had temporal lobe resection, due to the known importance of temporal lobe structures in memory. The majority of studies have found no change in episodic learning or memory at the group level after either left or right temporal lobectomy[53,58], although a decline in semantic memory (specifically naming) has been reported in children undergoing left temporal lobe surgery[59]. When individual change has been examined, results show that the majority have stable memory (57%), with improvements in 17% and declines in 25%[53]. Children with excisions including left mesial temporal lobe structures, and those with intact performance preoperatively are at greater risk for a decline in verbal memory[60,61]. In long-term follow-up, visual memory improved in those with left temporal excisions, and verbal memory improved after right temporal resections[62,63].

Behavioural function after paediatric epilepsy surgery

A recent systematic review of behavioural outcomes found that in group studies using validated, standardized parent-report measures, the most common finding was of no significant change after surgery[64]. When change was found, it tended to be on a small number of the subscales on questionnaires, and typically indicated modest improvements. In contrast,

studies in which children received formal psychiatric evaluations have reported no significant change in the proportion of children diagnosed with psychiatric disorders after surgery[65-67.] These reports noted changes at the individual level, with 4-16% of children losing a diagnosis at follow-up, and 9-12% being diagnosed after surgery with a new disorder. Studies including a nonsurgical comparison group of children with medical refractory epilepsy have yielded mixed results, with three studies finding an advantage in some aspects of behaviour over time for the surgical group, but two others not finding any differences[30, 68-71]. Little research has examined the role of post-operative seizure outcome on behavioural change, but the existing evidence suggests that seizure freedom is associated with positive changes in some, but not all aspects of the child's behavioural presentation[68-71]. Children's self-report indicated decreases in depression and anxiety symptoms irrespective of seizure control over two years after surgery[72]. There are mixed findings with respect to change in behavioural function after frontal lobe resections which has been reported in some, but not all, investigations[70,73,74]. No other demographic or clinical factors have consistently been found to be predictive of change[64] with little consistency across studies in the aspects of behaviour or emotional function that do change[64.] A study specifically examining attention deficit hyperactivity disorder (ADHD) found surgical candidates to have high rates of symptoms of ADHD, and two years after surgery, the number of children in the at-risk range for ADHD did not change[75]. However, improvements in parent-reported symptoms were found, and were related to higher pre-operative scores, right hemisphere surgery and seizure freedom.

Health Related Quality of Life (HRQoL) in children who have undergone epilepsy surgery

Epilepsy in childhood has a very significant negative long-term effect on HRQoL[76] even compared with other chronic conditions such as diabetes, asthma and cerebral palsy[77]. Thus, assessing HRQoL, in addition to seizure outcome, when evaluating treatments such as epilepsy surgery is important. When considering possible factors associated with detriments in HRQoL in children with epilepsy, behavioural and cognitive difficulties should be an important consideration as they often impact more on HRQoL than seizures[78].

A combined systematic review and meta-analysis showed that HRQoL after paediatric epilepsy surgery typically improves compared with pre-surgical functioning but also compared with controls with drug resistant epilepsy who have not undergone surgery[79]. Improvements in HRQoL have also been found in children with intellectual disability highlighting that low cognitive level should not be a barrier to surgery[80]. Most studies have been of mixed pathology

and surgery types but two studies focusing on children who have undergone hemispherotomy also showed improvement in HRQoL[81,82]. The majority of studies have however, been retrospective, involved parental but not child report of HRQoL and follow-up assessment has been at 1-2 years but not longer.

Regarding contributors to improvements in HRQoL after surgery, the focus has predominantly been on seizure freedom which has consistently been shown to be associated with better HRQoL[79]. Additionally, improvements in HRQoL may be reduced for children who come from families with limited resources[83]. Few studies have considered behavioural-emotional functioning. However, symptoms of anxiety and depression were found to be the major determinant of HRQOL in a study 4–11 years after epilepsy surgery highlighting the need to consider behavioural-emotional functioning in these children[84.]

Parental HRQoL is significantly reduced compared to population norms in children being considered for epilepsy surgery[85]. One study has shown that the impact of surgery on parents' HRQoL and emotional wellbeing is largely positive although scores on some HRQoL domains were still below population norms at follow-up[86].

Vocational outcomes of paediatric epilepsy surgery

Childhood onset epilepsy potentially has very significant implications for the life chances of those affected. Population-based studies of long-term outcome in childhood epilepsy indicate that the condition is associated with significant adverse outcomes in a range of domains including education and employment[87]. The risk for adverse outcomes is particularly high for children with difficult to treat epilepsy but also for those with cognitive and behavioural comorbidities[88,89]. Given that epilepsy surgery can result in a reduction of seizures or seizure freedom, improvements in HRQoL[79] and behavioural-emotional functioning[64] there exists the potential for successful surgery to significantly enhance vocational opportunities. A small number of studies have attempted to address this suggesting that seizure outcome and absence of cognitive impairment are important determinants of vocational outcome.

The largest study of vocational outcomes to date was undertaken in Sweden by Reinholdson et al. 2020[90]. This population-based study of 203 children who had undergone surgery included data on educational and employment outcomes at five, ten, fifteen and twenty years. The study considered those with intellectual disability (ID: preoperative IQ <70) and without ID

(preoperative IQ>69) separately. At the 20-year follow-up, 77% of those without ID were employed compared to only 10% in those with ID. Educational attainment and employment outcomes were similar to the general population for those without ID. Seizure-free patients were significantly more likely to work full-time .

Puka and Smith[91] undertook assessments 4-11 years after epilepsy surgery in 51 individuals with epilepsy who had undergone surgery in childhood and a matched group of 27 individuals who did not undergo surgery but had intractable epilepsy. They found that although educational and vocational outcomes were similar to the general population, fewer patients with epilepsy were in the highest income category. Surgical and nonsurgical patients did not differ on any outcome variable. A higher IQ (i.e. IQ>85) was associated with better outcomes in educational outcomes whilst more seizure-free patients had a driving licence and were living independently.

Keene et al.[92] followed 64 patients who underwent surgery in childhood after a mean of 7.6 years. Patients who had become seizure-free or had had a significant improvement in their seizure frequency were more likely to have completed a higher level of education and be employed than were patients who continued to have frequent seizures after surgery. However, even for those who were seizure free, levels of independent living and employment were lower than the general population. Benifla et al.[93] reported on a group of 42 patients 10-20 years after undergoing temporal lobe surgery and found that more patients who were seizure-free were employed. Similarly, Jarrar et al.[94] followed 37 patients who had undergone temporal lobe surgery and found again that a good seizure outcome was associated with better psychosocial outcome.

Epilepsy surgery in children- is it fully utilised?

Despite the advances made over the last decade in this area, there is still evidence that epilepsy surgery may be underutilised in children. Epidemiological data, calculated from imaging and follow-up data on a newly diagnosed cohort of children suggest 52/1 000 000 childhood-onset epilepsy patients should undergo epilepsy surgery evaluation, with approximately 27/1 000 000 suitable for epilepsy surgery[95]. From this, population estimates can be made of numbers of children likely to be suitable for epilepsy surgery, However studies reporting on utilisation in different countries, generally report figures considerably below those that would be calculated[96,97], and although studies suggest increasing utilisation over time in some areas of the world[98,] , no study to date has demonstrated alignment with these

population estimates with consistent lack of awareness reported amongst referring paediatricians of the full merits of evaluation[99] . Further, despite the possibility of cure in a drug resistant population, resources limit availability of epilepsy surgery in many areas of the world[4].

Discussion

Epilepsy surgery is now considered standard management in children, with no question that improved outcomes are seen in carefully selected individuals. Available data highlight that early surgery, whether younger age or shorter duration of epilepsy, yields greater likelihood of good outcome, primarily seizure outcome. Improved neurodevelopmental and vocational outcomes as well as improved HRQoL have been determined following successful surgery. Investigation and technology now available have expanded the spectrum of candidates but the case complexity has also increased. Children should therefore be referred early for evaluation in an appropriately competent centre.

The overall aim of epilepsy surgery remains seizure freedom, with no adverse effect on neurological or cognitive deficit. Although risks are associated with elective surgery, following appropriate evaluation and surgery in specialist centres the rate of unexpected complications remains low. Traditionally surgery has been considered for individuals who have demonstrated drug resistant epilepsy. A number of factors could argue for considering surgery in the absence of drug resistance in cases with well-defined lesions in non-eloquent low risk areas[10]. These considerations include the low likelihood of long term seizure freedom and/or a wean of medication in the presence of a structural lesion, the safety of weaning medication in children, and the relation of cognition with duration of epilepsy and weaning of medication [100]. Further study may be required to look directly at outcomes from early vs. later surgery for such lesions.

There is little need for further study to prove the effectiveness of epilepsy surgery in carefully selected individuals. However, questions remain, not least why better seizure outcomes cannot be achieved, as well as what factors may indicate surgery is not an option in the management of the epilepsy, so curtailing inappropriate investigation. In the light of advanced genomics, increasingly the question arises as to what role genetic evaluation may have in addressing these questions[101]. Although certain genetic mutations are associated with structural lesions and probable good outcome following surgery e.g. mTOR pathway genes, others may indicate more widespread pathology and less likelihood of seizure freedom[102]. This however requires further study as to the role of genomics in determining surgical candidacy.

The observed improvements in HRQoL in children who have undergone epilepsy surgery emphasises that it can have positive effects beyond seizure freedom or reduction for the majority of children. However, most studies reported have had small sample sizes, involving only parental report and have focused predominantly on seizure freedom in relation to possible contributors to improved HRQoL. Few have considered types of surgery and pathologies separately. Large scale prospective multicenter studies are required with multiple respondents (i.e. both parents and child) and appropriate controls with drug resistant epilepsy. Understanding what other factors including emotions and behaviour, antiseizure medication (ASM) usage and parental HRQoL contribute to better HRQoL is important as it would lead to a better understanding of the broad impact of epilepsy surgery and would aid presurgical counselling.

Vocational outcome appears to be better in the presence of seizure freedom and the absence of cognitive impairment but the role of neuropsychiatric and socioeconomic aspects has not been considered to any great extent. The question therefore remains largely unanswered concerning the relationship between seizure freedom and outcome after accounting for other factors. The need for long term follow-up is important given the time taken to go through the educational system and develop a career; gains in cognitive function have been only been demonstrated after longer duration following surgery that will have an impact on vocational and educational outcomes.

As we move forward, questions also arise as to the role of minimally invasive techniques rather than open resective surgery. Thermocoagulation has been shown to have a role as a safe option and possibly effective option following SEEG[26]. Laser ablation is increasingly used in the management of hypothalamic hamartoma[103] and is being trialled for other lesions. The definitive role with long term outcomes however needs to be evaluated over time. This said, there is continuing evidence of under-referral of possible candidates to specialist centres and we should continue to strive toward education to ensure this is rectified, so offering the potential of cure to the full range of candidates and so optimising long term outcome

Conclusions

Epilepsy surgery in childhood is established as a safe and effective management option in carefully selected individuals. Presurgical evaluation, case selection and surgery should be undertaken in an appropriate level of specialist centre, now defined. The spectrum of possible candidates has widened, and concepts challenged with regard to optimal timing. Children

presenting with persistent focal onset seizures with or without a lesion on MRI should be referred early for assessment; an assessment does not mean surgery will take place, but it does mean optimal decision making will occur and consequently lead to optimised outcomes.

Search strategy

Data were collected from MEDLINE and EMBASE for articles published in the last 10 years, between Jan 2010 and March 2021. The following Medical Subject Headings (MeSH) terms and keywords were used: “Drug resistant epilepsy” , ‘’children’’ and “surgery”. A specific search for each topic was also implemented adding terms such as “epilepsy surgery” and “presurgical investigations”, “advanced neuroimaging”, “functional MRI” “magnetoencephalography” “intracranial EEG”, “resective surgery” “minimal invasive techniques” “radiofrequency thermocoagulation” “laser therapy” “complications” “seizure outcome”, “cognitive outcome” “ behavioural outcome” and “quality of life”. We also reviewed reference lists from all relevant specialty journals. Only articles published or translated into English were considered. We included all types of articles (reviews, meta-analysis, clinical trials and observational studies) for review except case reports. Exceptions to these limits were made when the work was considered relevant.

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Conflict of Interests

JHC has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo, Ovid, Marinius and Stoke Therapeutics. She has been a speaker and on advisory boards for GW Pharma, Biocodex, Zogenix, and Nutricia; all remuneration has been paid to her department. R has been a speaker for GW Pharma

EGD has no conflicts of interest to declare.

MLS has no conflicts of interest to declare.

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Contribution statement

JHC was involved in conception of the article, literature review, initial draft and final editing of the article

CR contributed to the literature search and to writing and reviewing the final manuscript

EGD was involved in the main literature search, writing the manuscript and reviewing the final draft of the article

MLS contributed to the literature search and to writing and reviewing the final manuscript.

KM was involved in conception of the article, literature review, initial draft and final editing of the article

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Figure 1: Presurgical evaluation protocol

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