Predictors of IQ after Pediatric Epilepsy Surgery

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Abstract

Pediatric epilepsy surgery can significantly improve seizure control in a carefully selected group of individuals. However, improvements in intellectual functioning are variable and depend on several factors. We reviewed the literature to determine predictors of overall IQ and changes in IQ in patients undergoing epilepsy surgery. In children, epilepsy surgery is more likely to result in neurodevelopmental gains in patients with short duration of epilepsy, younger age of surgery, unilobar pathology, fewer anti-seizure medications, post-operative reduction in seizure frequency and long postoperative follow-up. Patients requiring a hemispherectomy at a very young age or who have infantile spasms usually have a more pronounced intellectual improvement, although eventual outcome is limited. Early age at seizure onset is a predictor of poor overall intellectual outcome. This may be due to the fact that their epilepsy reflects more severe pathology that intrinsically affects cognitive function. Management of anti-seizure medications following epilepsy surgery is also of primary importance regarding cognitive outcomes, as early medication discontinuation is associated with significant neurodevelopmental gains at no cost for seizure outcome.

Introduction

Epilepsy affects between 0.5% and 1% of the population and starts in childhood in two-thirds of patients. Approximately 30% of patients with epilepsy who are less than 18 years of age have medically refractory seizures [1, 2]. Seizures may adversely impact intellectual functioning [3-6] and therefore good seizure control is of critical importance. Compared with the mature brain, the impact of seizures on the developing brain may be more detrimental by slowing or halting development, or leading to derailment from the normal developmental trajectory. Therefore, it has been hypothesized that the reduction or elimination of seizures can lead to cognitive improvements. Seizure freedom may be possible in some with anti-seizure medications alone, but polypharmacy and high doses can lead to additional cognitive complications. In select cases, medically refractory patients may benefit from surgical intervention as treatment of their epilepsy. Epilepsy surgery may result in seizure freedom by anatomically disrupt neural networks necessary for cognitive processing.

Although epilepsy surgery may improve intellectual functioning, improvements are not uniform and some improvements may not be evident for years after surgery. In addition, unsuccessful epilepsy surgery may accelerate existing dysfunction or produce new dysfunction that may not have otherwise occurred. We did a literature review to determine predictors of overall IQ and for changes in IQ from pre-operative to post-operative testing after pediatric epilepsy surgery.

Literature review
A literature search was carried out on PubMed (January 1987–January 2017) to identify publications on intellectual functioning in children who underwent pediatric epilepsy surgery. Combinations of the keywords were used: pediatric epilepsy surgery; childhood epilepsy surgery; intelligence, mental development; cognitive outcome; neuropsychological outcome; cognition. Studies written in English, described IQ of children who underwent epilepsy surgery and which provided pre- and post-operative scores were included in the review. Overviews and review articles were excluded. We reviewed 47 articles that met our criteria.

Possible Predictors of Intellectual Function and Improvement after Epilepsy Surgery (Refer to table 1)

### Age of Onset of Epilepsy and Early Pharmacoresistance

Many infants and children who undergo epilepsy surgery have a neurodevelopmental delay from birth, even prior to the onset of seizures. It is likely their developmental capacities were restricted due to the underlying epileptogenic pathology. Therefore, as expected, numerous studies have found early age of onset of epilepsy to be a predictor for overall lower intellectual functioning after surgery [7-14]. Patients with onset of epilepsy in the first year of life have been found to have an exceptionally high incidence of intellectual impairment (82.4%) [15]. Prevalence

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Post-op IQ</th>
<th>Change in IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Malformation of cortical development – (41)</td>
<td>Cortical dysplasia + (28), mesial temporal sclerosis, Tumor + (12,23), Vascular malformation + (23)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female – (7)</td>
<td>Male + (9)</td>
</tr>
<tr>
<td>Age at onset of seizures</td>
<td>Younger – (7, 8)</td>
<td>Younger – (14, 11, 12)≤10 y – (13)</td>
</tr>
<tr>
<td>Duration of epilepsy</td>
<td>Shorter – (29)</td>
<td>Shorter ++ + (14, 20)</td>
</tr>
<tr>
<td></td>
<td>Shorter + (7, 14, 21-25, 28)</td>
<td></td>
</tr>
<tr>
<td>Age at epilepsy surgery</td>
<td>Younger – (29, 41)</td>
<td>Younger + (23, 26)</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(37)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>Hemispherectomy – (41)</td>
<td></td>
</tr>
<tr>
<td>Extent of pathology</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Unilobar + (12)</td>
<td></td>
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<tr>
<td></td>
<td>Extensive – (25)</td>
<td></td>
</tr>
<tr>
<td>Post-operative seizure freedom</td>
<td>+ (28, 23, 48), +MCD (42)</td>
<td>+VIQ, + (12, 14, 23, 49, 51, 52)</td>
</tr>
<tr>
<td>AED’s post-op</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Fewer drugs + (10, 23, 14, 26)</td>
<td></td>
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<tr>
<td>Follow-up interval</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Longer –VIQ (30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Longer + (49, 10)</td>
<td></td>
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<tr>
<td>Socio-economic status</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>More parental education + (23)</td>
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<tr>
<td>Pre-op seizure frequency</td>
<td>Frequent seizures Sturge Weber Syndrome – (11)</td>
<td>Less than 50% reduction – (Yang)</td>
</tr>
<tr>
<td>Frequent EEG abnormality</td>
<td>Frequent spike wave pre-op – (11)</td>
<td></td>
</tr>
<tr>
<td>Contralateral side</td>
<td>N + hemispherectomy (43, 51)</td>
<td></td>
</tr>
<tr>
<td>Pre-op IQ</td>
<td>Higher + (7, 28, 37)</td>
<td>Higher – (37),VIQ (9, 10) Lower VIQ + (30) Lower + (20, 23, 29, 51, 52)</td>
</tr>
</tbody>
</table>

Table 1: Possible Predictors of Post-Surgical Intellectual Outcome
of autistic spectrum disorder is higher in children with onset of seizures in the first year of life than the general population [16].

Patients with childhood onset temporal lobe epilepsy are noted to have poorer cognitive status than older patients [17] and the prevalence of intellectual disability is significantly higher for patients with seizure onset at ≤ 24 months of age [18]. In a study by Cormack et al., 79 children with unilateral temporal lobe epilepsy underwent preoperative neuropsychological testing and it was found that intellectual dysfunction (defined as IQ<79) was present in 57% of children, and age at onset of epilepsy was the best predictor of intellectual function [15]. Another study showed that younger age of onset led to lower intellectual function after temporal lobe epilepsy surgery for treatment resistant epilepsy in children less than 15 years of age [8]. However, changes in IQ scores after temporal lobectomy were not significantly related to age at onset of epilepsy [9, 10]. With regards to extra-temporal resections, children with younger age at onset of epilepsy were also found to have a statistically significant lower cognitive outcome level [7], likely due to the fact that early onset epilepsy reflects severe epileptogenic pathology that inherently restricts future cognitive abilities.

Early pharmacoresistance is also important in the cognitive trajectory after epilepsy surgery. In a prospective cohort study of children with epilepsy diagnosed before 8 years of age, early age of onset and pharmacoresistance resulted in lower full-scale intelligence quotient (IQ) [19]. The impact of pharmacoresistance was most profound in children less than 3 years of age, although in the absence of pharmacoresistance, age of onset did not affect outcome. These findings are persuasive for early aggressive treatment to achieve seizure control in infants and young children with intractable epilepsy.

### Duration of Epilepsy

A shorter duration of epilepsy was associated with higher postsurgical IQ in many studies examining postoperative IQ, including extra-temporal resections in childhood [7, 14, 20-27] and hemispherectomy [28]. However, one hemispherectomy cohort noted that shorter duration of epilepsy was predictive of poor postoperative cognition [29].

In a study of preschool children treated surgically for severe epilepsy [27] duration of epilepsy was the only significant predictor of long-term cognitive change; children with shorter intervals between onset of epilepsy and surgery had greater gains in developmental quotient (DQ). Conversely, duration of epilepsy was not a significant predictor of IQ change after temporal lobectomy [10, 30], nor after epilepsy surgery in Sturge Weber Syndrome [31].

It is known that cognition in medically intractable temporal lobe epilepsy is especially vulnerable to long duration and recurrent seizures. Anatomic studies in this clinical cohort revealed progressive atrophy of both gray and white matter structures. Atrophy correlates with duration of epilepsy and seizure frequency, particularly seizures of left hemisphere onset [32-34]. Early childhood-onset temporal lobe epilepsy reduces brain volume, particularly white matter tracts, leading to reduced cognitive function [35]. A shorter duration of active epilepsy limits the potentially irreversible effects of ongoing seizures and anti-seizure medications on brain function. This likely is independent of underlying pathology.

### Pre-operative Intellectual Functioning

Although both cognitively impaired and high-functioning children may benefit from seizure reduction after surgery, high-functioning patients are at higher risk for postoperative declines [36]. Even though those with low pre-operative IQ are more impaired after surgery, they tend to show more significant gains [7, 9, 10, 28, 30, 37].

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**Table 1 Legend:**
Post-op IQ refers to the overall post-operative IQ
Change in IQ refers to the change in IQ from pre to post-operative assessment
+ = positive predictor or improvement
- = negative predictor or decline
comparing patients with medical treatment versus temporal lobectomy, seizure control and a higher baseline cognitive status were predictors of more favorable outcome [38]. Skirrow et al compared the cognitive outcome of children with medical management and temporal lobectomy and found that patients with low preoperative IQs demonstrated the most significant postoperative improvements [10].

Patients undergoing hemispherectomy for intractable childhood epilepsies experience improvements in both motor and language development, particularly if seizure freedom is achieved early on [28, 39]. This may be because patients with early hemispherectomy usually have a severe epileptic encephalopathy, with arrested development or regression and surgical treatment can lead to more pronounced cognitive improvement, although eventual cognitive outcome is limited.

**Age of Surgery**

Some studies have statistically tested the influence of age at surgery on intellectual function and found that age was an important determinant of improvement in developmental status [9, 23, 26, 30, 31, 37, 40, 41]. Younger age at surgery was associated with a larger positive change in cognitive scores after epilepsy surgery in infants and young children, especially in those with epileptic encephalopathy or early pharmacoresistance [9, 31, 37]. The relation between age at surgery and eventual cognitive outcome after hemispherectomy is such that younger age was associated with lower postoperative IQ scores [29, 40]. In contrast, a study of temporal lobectomies [30] revealed that older age at surgery was found to be predictive of more improvement in VIQ. This is corroborated by other studies that have also shown that later age of onset leads to more favorable results and change, possibly due the fact that these patients have less severe epilepsy, different etiologies and higher pre-operative intellectual function. [23, 26].

**Etiology and Extent of Lesion**

Some studies tested the influence of etiology on eventual postsurgical cognitive outcome and found no significant correlation [7, 28, 29,37]. Others have found that patients with tumors, mesial temporal sclerosis or vascular malformation did better than other lesions, particularly malformations of cortical development, which may be due to smaller extent of the lesion and also due to the fact that they had higher pre-operative IQ [12,23]. However, in one study on cognitive outcome after hemispherectomy[41], etiology was the most significant predictor of cognitive skills at follow-up, with malformations of cortical development patients scoring lower in intelligence. Children with hemicortical dysplasia showed the most progress in Vineland Adaptive Behavior Scales DQ scores after hemispherectomy, while children with Rasmussen’s encephalitis and vascular causes did not have as good progress [28].

Children with developmental pathology seem to have worse eventual cognitive outcomes but have most to gain from surgery, with relatively high chances of postsurgical cognitive improvement. Hemispherectomy candidates often are associated with early epileptic encephalopathy and developmental arrest. After surgery there is improvement of development, although the end level is limited, possibly related to a more diffuse or bilateral nature of the underlying pathology. Structural integrity of the remaining hemisphere thus influences cognitive functioning after hemispherectomy. Loddenkemper et al found that patients with epileptic spasms were younger and had a lower developmental quotient at presentation, but the increase in developmental quotient was higher in this subgroup [37].

Regarding the extent of lesions, a unilobar epileptogenic focus was a significant independent predictor of higher postsurgical IQ [12, 14, 23, 25, 43]. Multilobar epileptogenic foci (in contrast to unilobar foci) may be a sign for widespread neural abnormalities which have been associated with greater cognitive deficits [35].

**Anti-seizure Medications**

Anti-seizure medications have cognitive side effects which may affect intellectual functioning particularly in children. It is postulated that early exposure to anti-seizure medications can interfere with normal brain development, by inducing
neuronal apoptosis, and impairing neurogenesis, synaptogenesis, cell proliferation and migration, and synaptic plasticity [43, 44]. In addition, many anti-seizure medications have cognitive adverse effects, with attention, vigilance, and psychomotor speed being most affected. In many studies evaluating the long-term intellectual outcome after extra-temporal or temporal lobe resections in childhood [10], cessation of anti-seizure medication was an independent predictor of cognitive improvement after surgery [10, 14, 23, 26]. In one study of patients who underwent hemispherectomy, however, the number of anti-seizure medications used at postoperative neuropsychological evaluation did not differ between the children who had significant improvement in intellectual functioning and those without postoperative improvement after surgery [29]. A change in the number of anti-seizure medications after surgery was not associated with the level of development after epilepsy surgery in infancy [37].

The TimeToStop (TTS), a large European multi-center study, demonstrated that anti-seizure medication withdrawal does not significantly influence long-term seizure outcomes [45]. A subsequent study by the same group evaluated the effect of anti-seizure medication withdrawal on postoperative intelligence. It was demonstrated that anti-seizure medication withdrawal is independently associated with postoperative IQ and change in IQ scores in children who undergo epilepsy surgery. The more anti-seizure medications are reduced, the higher the postoperative IQ and IQ change. This data may lead to altered practices in weaning medication after surgery [26].

Post-operative Seizure Freedom and Frequency

There are variable results with regards to seizure freedom and intellectual functioning after epilepsy surgery. Some have found that good seizure control has an impact on cognitive outcome. Postsurgical seizure control was shown to be correlated with improvement of DQ/IQ and VIQ [30, 31, 46-51]. In other studies however, seizure outcome did not significantly contribute to cognitive changes [9, 10, 27, 29, 40, 41]. These findings may suggest that complete seizure freedom is not a prerequisite for cognitive improvement after epilepsy surgery. A study on corpus callosotomy discovered that improvement in seizure frequency by at least 50% was more predictive of cognitive outcome than seizure freedom [52].

Posturgical seizure control predicted higher DQ scores after hemispherectomy [28]. In another study on cognitive outcome after hemispherectomy in children, persistence and severity of seizures were significantly related to follow-up IQ for the malformation of cortical development group only [41]. Helmstaedter et al. [38] examined memory and non-memory functions in a longitudinal study comparing adult patients with intractable epilepsy who were undergoing temporal lobectomy to patients who were managed medically. Both the medically and surgically treated groups experienced memory decline, whereas non-memory function remained stable. Seizure-free patients, more commonly treated with surgery, were more likely to recover memory and non-memory functions over time.

Duration of Follow up

A longer postoperative period may be needed for identifiable improvements in IQ to be observed [9, 30]. To date, studies of paediatric epilepsy surgery examining short-term outcomes (ranging from 6 months to 2 years) have found little or no change in cognitive functioning [53]. However, due to the time course of neurodevelopment, 1 to 2 years may be too short for considerable change to occur [54]. Puka et al found that four to 11 years after paediatric epilepsy surgery, seizure freedom, whether attained through epilepsy surgery or other means, was found to be associated with intellectual improvements [49]. Skirrow et al. compared the long-term cognitive follow-up of children undergoing temporal lobectomy to patients on medical management. Patients treated surgically experienced improvement in their full-scale IQ, but not until 6 years after therapy [10].

Psychosocial Factors

Psychosocial, family and environmental factors likely have an impact on intellectual functioning.
Meekes et al. found that children whose parents had higher education demonstrate on average a greater increase in IQ after surgery and a higher postsurgical, but not pre-surgical, IQ than children whose parents completed at most lower secondary education [23]. Therefore, parental education and perhaps other environmental variables should be considered in the prognosis of cognitive function after childhood epilepsy surgery. Another group evaluated the association between socioeconomic status and intellectual functioning in children with medically refractory epilepsy, before and after resective epilepsy surgery since family environment is a strong contributor to cognitive development in children. They were unable to identify a significant association between IQ and socioeconomic status [12]. Future research should evaluate the impact of multiple aspects of family environment.

**Conclusion**

The efficacy and safety of surgery have been established in patients. However, the impact of epilepsy surgery on intellectual functioning and overall function is more variable and needs to be determined on a case by case basis. The ultimate goals of epilepsy surgery are to achieve freedom from seizures, enable anti-seizure medication discontinuation, and improve developmental capacities. Some may argue that when counseling patients and families about epilepsy surgery, it is as important to discuss the impact of surgery on cognition, as it is on seizure reduction. We specifically looked at intellectual function, although this has limitations as there are many other aspects of cognition, as well as cognitive outcome measures, such as academic achievement.

When reviewing the studies, significant associations between timing variables and cognitive outcome were revealed. Younger age at onset of epilepsy predicted poor overall outcome. Younger age at surgery predicted poor eventual outcome, especially after hemispherectomy, extra-temporal resections and infantile spasms, but patients still showed postoperative cognitive improvement. Short duration of epilepsy was a positive predictor of improvement and good overall outcome. Longer duration of follow-up and discontinuing anti-seizure medications post-operatively was also a good predictive factor. The studies we reviewed were heterogeneous with variable ages, types of resections and follow-up intervals. In the future, good prospective studies looking at standardized interventions and outcomes are necessary.

**References**


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