Pediatric Epilepsy Surgery

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EUROTEXT

ISBN : 978-2-7420-1424-8

Published by
Éditions John Libbey Eurotext
127, avenue de la République,
92120 Montrouge, France.
Tél. : 00 33 (1) 46 73 06 60
Fax : 00 33 (1) 40 84 09 99
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CHAPTER 26. Mesial temporal lobe epilepsy in children

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Keypoints

- Mesial temporal surgery is rarer in children than in adults.
- The semiology related to MTLE might be different in young children when compared to adults.
- More extensive temporal lobe resections are performed as compared to adults.
- Surgical outcome after temporal lobe resection is as good in children as in adults.

Pathological substrates of pediatric temporal lobe epilepsy

Temporal lobe epilepsy (TLE) and especially the syndrome of mesial temporal lobe epilepsy (MTLE) in adults represent a well-defined and homogeneous entity with hippocampal sclerosis (HS) as the commonest neuropathological substrate (Mathern *et al.*, 1995). The relationship between the initial precipitating injury (IPI), most frequently a past history of febrile seizures (mainly complex febrile seizures or febrile status epilepticus) in early childhood and subsequent development of HS can be identified in a significant proportion of adult MTLE patients (Cendes *et al.*, 1993).

The neuropathological features of this entity are well-recognized including neuronal loss in most hippocampal regions (the CA1 region being usually the most profoundly affected, with relative sparing of the CA2 region). Different patterns of hippocampal cell loss have been identified and were recently classified by the International League against Epilepsy (ILAE) into four distinct subtypes (Blümcke *et al.*, 2013). Different neuropathological HS subtypes are associated with distinct clinical and electrophysiological syndromes and post-surgical seizure control.

Compared to adults, childhood-onset TLE probably represents a distinct nosological but less homogeneous syndrome. Most importantly, HS is significantly less common in this age group. Maton *et al.* (2008) studied 20 children who underwent temporal resection for intractable epilepsy under the age of 5 years. Cortical dysplasia was identified in 8 children, tumors in 8 including 2 DNETs, 2 gangliogliomas, and 4 malignant tumors. HS was present only in 4 cases, always as dual pathology. Several other series of patients with TLE presenting in early life (Duchowny *et al.*, 1992; Wyllie, 1996) as well as an international survey of pediatric epilepsy surgery programs (Harvey *et al.*, 2008) reported a higher incidence of developmental pathologies and benign tumors, whereas HS rarely occurs in isolation in early life.

Risk factors for pediatric temporal lobe epilepsy

As mentioned above, prolonged seizures in early childhood have long been linked with the occurrence of HS (*Figure 1*) and the subsequent development of (mesial) temporal lobe epilepsy. Approximately 30-50% of patients with intractable TLE associated with HS have had an episode of convulsive status epilepticus or complex febrile seizures (defined as seizure duration longer than 10 minutes, with focal semiology and/or recurrence within 24 hours) in childhood (Mathern *et al.*, 1995, Cross, 2012, Yoong *et al.*, 2013). However, the risk for developing epilepsy after early febrile seizures is low, reported to be 2.4% in children with no additional risk factors (compared to 1.4% in the general population). However, the risk of developing afebrile seizures

Figure 1

Mesial temporal sclerosis in children has the same imaging characteristics of that seen in adults: decreased hippocampal volume seen on T1 and increased signal on T2 images.
A: right MTS seen on T1 image.
B: right MTS seen on T2 image.
C: left MTS seen on T2 image.

increases to 21% in children with prolonged febrile seizures and to 49% in children with all three features of a complex febrile seizure (Annegers *et al.*, 1987, Cross, 2012).

Undoubtedly, the relationship between febrile seizures and the later development of epilepsy is complex. There are well-defined epilepsy syndromes associated with the occurrence of febrile seizures and evolution to other seizure types. Typical examples include Dravet syndrome, frequently caused by *SCN1A* gene mutations, and epilepsies associated with protocadherin 19 (*PCDH19*) mutations (Scheffer *et al.*, 2009, Cross, 2012). Affected children typically present with prolonged, usually lateralized seizures during the first year of life and later develop other (focal and generalized) seizure types together with features of progressive epileptic encephalopathy. Although neuro-imaging findings typical of HS are identified in a minority of this cohort, none of the reported cases clinically presented with typical TLE or MTLE syndrome (Guerrini *et al.*, 2011).

A new clinical febrile seizure presentation called "febrile infection related epilepsy syndrome" (FIRES) has recently been described (Kramer *et al.*, 2011). Previous descriptions of the same condition include "idiopathic catastrophic epileptic encephalopathy" (Baxter *et al.*, 2003), "devastating encephalopathy in school age children" (DESC, Mikaeloff *et al.*, 2006), "new-onset refractory status epilepticus" (NORSE, Wilder-Smith *et al.*, 2005), "fever-induced refractory epileptic encephalopathy syndrome" (FIRES, Van Baalen *et al.*, 2010) and "fever-induced refractory epileptic encephalopathy in school aged children" (FIRES, Nabbout *et al.*, 2011). In this disorder, previously normal children present with status epilepticus, preceded by a febrile illness in 96% of patients. Seizures often prove refractory to treatment and last for several days or weeks. The prognosis of affected children is generally poor, with a mortality of up to 30%; most children develop refractory epilepsy and profound neurocognitive deficits (Kramer *et al.*, 2011). MR imaging of surviving patients may later show bilateral mesial temporal atrophy and high T2 signal, but approximately half remain normal (Howell *et al.*, 2012).

The underlying cause of FIRES is unknown. A relation to a febrile illness suggests an underlying immune process, although antibody testing is negative in most patients, and the response to immunotherapy is disappointing (Cross, 2012). A genetic susceptibility has been suggested; one patient with a similar clinical course had a missense mutation of the *PCDH19* gene (Specchio *et al.*, 2011); however, there were no *SCN1A* mutations or copy number variants among 10 patients with FIRES (Carranza Rojo *et al.*, 2012). Seizures in FIRES are resistant to standard AEDs, and immunosuppressive treatment is of no benefit. Thiopentone coma may abolish seizures in the acute phase, but seizures often return upon reduction of anesthesia (Cross, 2012).

Whether prolonged seizure activity directly causes brain injury, including progressive hippocampal damage, and ultimately leads to TLE in later life remains a matter of broad debate. MR imaging of children in the first few days following prolonged febrile seizures consistently reveals acute increases in hippocampal volume and hyperintensities on T2-weighted sequences suggesting acute hippocampal edema (Scott *et al.*, 2006, Shinnar *et al.*, 2012). However, progressive hippocampal damage may occur after convulsive status epilepticus of any etiology and is not limited to prolonged febrile seizures (Yoong *et al.*, 2013).

The hypothesis that prolonged seizures might damage the vulnerable immature brain and produce HS and epileptogenesis is supported by numerous experimental studies (Haut *et al.*, 2004, Auvin *et al.*, 2007). However, it is unknown whether hippocampal neuronal loss precedes seizure onset or results from ongoing seizures. It remains possible that a genetic predisposition or structural change (see dual pathology section) may cause a heightened hippocampal

susceptibility, and that a "second hit" such as prolonged febrile seizure may promote the development of HS and later development of temporal lobe epilepsy (Cross, 2012).

A history of encephalitis or meningitis is another important risk factor for developing TLE and HS. Epidemiologic studies reveal a 2.7 to 6.7% frequency of epilepsy after CNS infection; this risk is higher for encephalitis than for meningitis (Marks *et al.*, 1992, Davies *et al.*, 1996). However, whereas meningitis is commonly associated with HS, most encephalitis patients have neocortical foci. Marks *et al.* (1992) demonstrated that age at CNS infection is important in predicting mesial temporal or neocortical localization of epileptic foci. In their experience, encephalitis before, but not after age 4 years, was associated with HS. As most patients who developed HS in their study experienced meningitis before age 4 years, the data provide support for an age-dependent susceptibility of medial temporal lobe structures to early insults. Later-onset encephalitis produced extra-hippocampal neocortical seizure foci.

Patients with TLE after CNS infections have less favorable outcomes following temporal resection than patients with a history of complex febrile seizures (Davies *et al.*, 1996). Meningitis and encephalitis are more frequently associated with bilateral hippocampal volume loss compared to patients with complex febrile seizures (Free *et al.*, 1996). The timing of CNS infection could also play a prognostic role: a history of meningitis or encephalitis below age 4 years predicted better outcomes after temporal lobectomy regardless the type of infection (O'Brien *et al.*, 2002).

Role of dual pathology in pediatric temporal lobe epilepsy

The co-occurrence of distinctly unrelated pathology, often focal cortical dysplasia with HS in patients with temporal lobe epilepsy has been recognized for over two decades (Cendes *et al.*, 1993). This association, loosely termed "dual pathology", is now known to refer to possible associations of multiple clinico-anatomic entities including cortical malformations, porencephaly, remote trauma, vascular lesions and tumors, and can involve extratemporal sites (*Figures 2-4*). Most associated lesions are detectable on routine MR imaging protocols but cortical malformations, and focal cortical dysplasia (FCD) in particular, may be less evident. Higher field strength MR imaging has further broadened the spectrum of malformation-related dual pathology through its ability to detect more subtle grades of neocortical FCD which is now regarded as being particularly prevalent, especially in the pediatric population. Growing recognition that dual pathology is not rare and that subtle FCD may go undetected has important implications for the management of patients with HS who become surgical candidates.

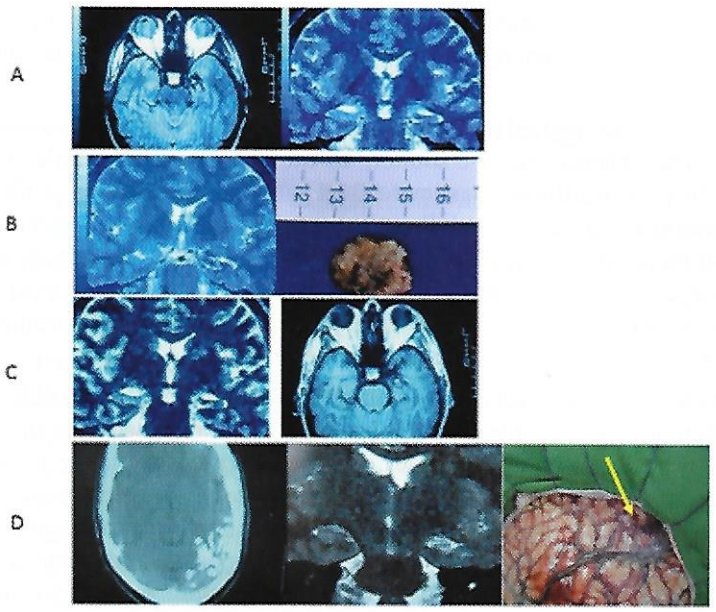

Figure 2

Dual pathology-MTS associated to vascular lesions.
A: Uncal cavernoma (left) and MTS (right).
B: hippocampal cavernoma (left) and surgical specimen (right).
C: MTS (left) and uncal cavernoma (right).
D: Sturge-Weber (left), left MTS (center) and intra-operative view showing the vascular malformation over the anterior temporal lobe (arrow).

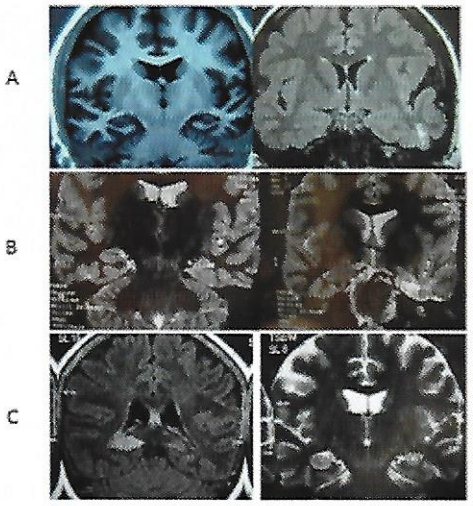

Figure 3

Dual pathology: MTS and tumour.
A: left MTS (left) and fusiform gyrus DNET (right).
B: left MTS (left) and mesial ganglioglioma (right).
C: right astrocytoma (left) and left MTS (right).

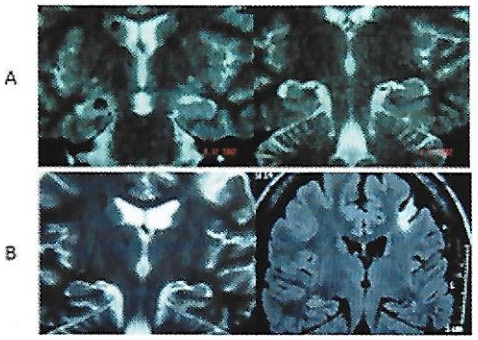

Figure 4

Dual pathology – misceleanous etiology.
A: hippocampal calcification (left) and MTS (right).
B: left MTS (left) and parietal gliosis (right).

A more formal neuropathology-based classification of dysplastic cortical changes in association with HS was recently adopted by the International League Against Epilepsy (Blümcke *et al.*, 2011). Designated focal cortical dysplasia Type IIIa, this category is defined by the occurrence of cortical lamination abnormalities that are either adjacent to the HS or located within temporal neocortex. The involved neocortical architecture typically evidences cortical dyslamination or hypertrophic neurons outside layer 5. Other pathological findings include granular neurons in the outer part of layer 2 (temporal lobe sclerosis), subtle "lentiform" nodular heterotopias, and hypertrophic neurons in layers 2-4. Many of these neocortical changes are subtle, remain undetected on routine MR imaging and are only recognized in surgical specimens.

Data from surgical series suggests that the association of FCD and HS is common in patients with temporal lobe epilepsy, but the subtlety of the neocortical dysplastic cellular changes render its true frequency difficult to estimate. Dual pathology (association of HS with different lesions) was observed in 56% of 55 adult patients undergoing temporal resection and 68% of these cases had HS (Bautista *et al.*, 2003). FCD had been suspected pre-operatively in less than 10% of cases. In a retrospective review of a large cohort of 200 children undergoing surgery for FCD, hippocampal MRI abnormalities were common and included atrophy in 26% and signal intensity change in 19% of patients (Krsek *et al.*, 2008).

No single unified theory can explain the common association of HS and FCD. Whereas prolonged and often unilateral febrile convulsions are a known risk factor for the later development of HS, it is unclear whether the prior existence of dysplastic tissue predisposes to the severe febrile convulsions ("dual hit hypothesis"). This susceptibility hypothesis is supported by experimental evidence that immature rats with cortical malformations subjected to hyperthermia-induced seizures have a lower threshold for hippocampal damage (Germano *et al.*, 1996). Compared to controls, rats with cortical malformation experience more prolonged hyperthermia that results in hippocampal pyramidal cell loss which is independent of seizure

activity; the extent of neuronal damage correlated positively with the duration of hyperthermia.

Other important considerations favor a common etiology for HS and FCD type IIIa ("single hit hypothesis") (Blümcke *et al.*, 2013). Both the HS and FCD sub-populations experience a similar age of seizure onset and a similar incidence of prior febrile seizures as a precipitating factor. Furthermore, there are no significant clinical differences in clinical presentations of either group. These similarities point to a pathogenesis whereby both pathologies could result from a pre-existing genetic or early environmental insult that simultaneously compromises cellular migration and hippocampal development (Bocti *et al.*, 2003).

A comparison of the clinical features of children with isolated HS and FCD IIIA (Johnson *et al.*, 2014) reveal little difference in the frequency of initial precipitating events, age at precipitating event, frequency of febrile seizures, age at seizure onset, or the presence of aura. Precipitating events include febrile seizures or febrile status epilepticus, central nervous system infection and head trauma. Focal EEG ictal and interictal discharges occurred in similar proportions in isolated HS and FCD IIIA.

In contrast, MRI differences between HS and FCD IIIA were significant in a retrospective study of 73 children and adults (Johnson *et al.*, 2014). Compared to isolated HS, patients with FCD and HS evidenced higher rates of hippocampal atrophy (76%), hippocampal T2 signal change (69%), temporal grey-white matter blurring (38.5%), temporal white matter volume loss (39%) and extra-hippocampal atrophy (48.8%). There were no differences in grey-white matter blurring, white matter volume loss or atrophy.

PET scanning may also offer important clues about the existence of occult FCD in HS patients. In a study of 23 patients undergoing temporal resection for focal epilepsy, isolated HS correlated with mesial temporal hypometabolism whereas combined HS and FCD correlated with lateral temporal hypometabolism (Diehl *et al.*, 2003). Reduced temporal lobe volume on anatomic MRI correlated significantly with the metabolic change in the lateral temporal lobe in the dual pathology group but not in patients with isolated HS.

The co-occurrence of FCD in patients with HS is also associated with greater intellectual deficiency. In a study measuring intelligence, language, memory, and executive function in 61 children with isolated HS, temporal lobe tumor, cortical dysplasia (CD) or dual pathology, children with single pathologies performed significantly better than children with HS and FCD on all standardized measures (Bigel & Smith, 2001). Children with tumors performed significantly better than children with dual pathology on receptive vocabulary. These findings suggest that children with dual pathologies are more likely to have adversely affected cognitive networks.

Clinical manifestations of temporal lobe epilepsy in children

While the clinical manifestations of TLE and especially MLTE syndrome have thoroughly been studied in adults, relatively few studies have examined TLE in infants and children in detail. It has repeatedly been reported that clinical features of focal seizures in infants and young children differ from adult patients. Seizures in early life are more frequent, have a more limited repertoire of ictal manifestations, and features indicating localized onset (such as auras) may be absent or unidentifiable.

Acharya *et al.* (1997) analyzed 125 seizures in 23 children with localization-related epilepsy younger than 2 years, with seizure-free outcome after subsequent resective surgery. Whereas seizures characterized by a decrease in behavioral motor activity, indeterminate level of consciousness and minimal or no automatisms ("hypomotor" seizures) arose from temporal, temporo-parietal, or parieto-occipital regions, seizures with localized or bilateral clonic, tonic, or atonic motor phenomena originated predominantly from frontal, fronto-central, central, or fronto-parietal areas. Infantile spasms occurred from all locations. Other studies reporting seizure semiology in infants and toddlers (0-3 years) with TLE (Jayakar & Duchowny, 1990;

Brockhaus & Elger, 1995; Hammer *et al.*, 1999; Fogarasi *et al.*, 2002; Ray & Kotagal, 2005) agree that auras are rare or difficult to recognize, while motor phenomena are more prominent compared to older children/adults including tonic, clonic and myoclonic convulsions which may be bilateral and symmetric. Automatisms are common and are usually simple in character and frequently oro-alimentary. In pre-school and early school children (3-6 years) with TLE, auras become more common, motor manifestations are less pronounced (may show dystonic posturing or version) and automatisms become more complex with increasing age (*e.g.*, hand automatisms appear in addition to oro-alimentary ones). Clinical manifestations in older children and adolescents (> 6 years) are similar to adults.

EEG features of pediatric temporal lobe epilepsy

Similar to seizure semiology, more studies reveal that scalp EEG patterns in children with TLE differ from adults. In general, epileptiform EEG abnormalities in infants and younger children with focal epilepsy may have limited localizing value due to their widespread distribution (Duchowny, 1987). Extratemporal and generalized interictal sharp waves, commonly seen in addition to temporal spikes, have been described in children with TLE under 3 years of age, especially patients with tumors (Wyllie *et al.* 1993; Wyllie, 1995; Brockhaus & Elger, 1995; Ray & Kotagal, 2005). The same studies reported poorly localized, falsely lateralized and occasionally generalized ictal EEG seizure patterns.

Focal lesions may even present with generalized scalp EEG patterns (such as hypsarrythmia and burst-suppression) within the first years of life. It has been suggested that the diffuse EEG expression may be due to an interaction between the early lesion and the developing brain (Gupta *et al.*, 2007, Wyllie *et al.*, 2007). Generalized and multiregional EEG abnormalities in the absence of a dominant seizure focus may not preclude successful epilepsy surgery in children with congenital or acquired lesions on MRI. EEG findings which help to identify a region of cortical abnormality in children with poorly localized or generalized epileptiform EEG patterns include (1) predominance of spikes over one region; (2) localized slowing, decreased background activity or absent sleep spindles over one region; (3) unilateral electrodecremental events; and (4) asymmetric EEG seizures (Gupta *et al.*, 2007, Wyllie *et al.*, 2007).

On the other hand, Maton *et al.* (2008) in their surgical series of children with TLE younger than 5 years reported that interictal EEG successfully provided concordant localizing information in 75% of patients and ictal EEG successfully localized epileptogenic zone in 90%.

Surgical outcome in children with hipocampal sclerosis and dual pathology

• Timing of surgeries in relation to neuropsychological outcome

There is an expert consensus that early operations might have a positive impact on cognitive development and quality of life, but high-level of evidence data is lacking. Although short-term results are available (Williams *et al.*, 1998; Westerveld *et al.*, 2000), the long-term neuropsychological impact of surgery in children with HS are only beginning to be understood and the available data do not allow for adequate comparison between adult and pediatric populations. The relevance of surgery is easy to demonstrate in children with catastrophic epileptic syndromes clearly associated with an epileptic encephalopathy, but difficult to establish in children with more focal epileptic syndromes.

There is emerging evidence (Skirrow *et al.* 2015; York *et al.*, , 2003) that children with HS show cognitive improvement after temporal lobe resection in the long-term and that early referral and surgery might be beneficial for their ultimate prognosis. These studies clearly revealed that the long-term cognitive outcome of children undergoing surgery was better compared to that of matched non-operated children. As in adults, children with higher preoperative memory scores and normal MRI are at higher risk for postoperative memory loss (Meekes *et al.*,

2013). Additionally, contralateral task specific memory improvement has been noted after HS surgery in children that is similar to adults (Vadera *et al.*, 2012; Gonzalez *et al.*, 2012). It is unclear, however, if there is a unique window for plasticity and recovery of memory, as occurs in motor and speech functions, and resecting smaller tissue volumes could yield better cognitive outcomes. These studies also suggest that cognitive and quality of life improvement occur only after prolonged follow-up (more than 6 years), an observation that might explain why shorter follow-ups are unable to document improvement.

Surgical technique

Numerous surgical techniques have been used for performing temporal lobe resection in patients with refractory epilepsy. These include "standard" procedures consisting in varying degrees of cortical resection (cortico-amygdalo-hippocampectomy) or "selective" procedures with no cortical resection (amygdalo-hippocampectomy). In children, tailored resections must be tailored based on variable seizure types, locations and pathologies. Both the standard and selective procedures appear to yield similar outcomes compared to adults and cognitive outcomes also appear similar. There is no high-level evidence in the pediatric population assessing the comparative outcome from these procedures. On the other hand, large uncontrolled individual series suggested that cortico-amygdalo-hippocampectomy is more effective in the pediatric population then selective procedures (Maehara *et al.*, 1996; Lee *et al.*, , 2010); possibly in relation to higher incidence of dual pathology cases among children. The need for larger resections in children might also be related to age-specific characteristics of epileptogenesis; most of the pediatric epilepsy surgery centers employ "standard" resection for pediatric patients.

Outcome regarding seizures

There is Class A evidence that temporal lobe resection is effective in adults with HS (Wiebe *et al.*), but there is no pure pediatric study available. It is likely safe, borrowing the results from adult series, to conclude that temporal lobe resection is effective in children older than 6 years with mesial temporal sclerosis and a 60-90% postoperative seizure-free rate should be expected (Englot *et al.*, , 2013); there is 1% morbidity associated to the procedure and mortality is very rarely reported (Mittal *et al.*, 2005; Terra-Bustamante *et al.*, 2005; Sinclair *et al.*, 2003; Visudhiphan *et al.*, 1999; Bourgeois, 1995; Duchowny *et al.*, 1992; Hopkins & Klug, 1991; Davidson & Falconer, 1975). Outcome in children under age six years might be heterogeneous and related to the distinct features of epilepsy syndrome in this age category. The presence of HS is the only well-defined positive outcome predictor (Smyth *et al.*, 2007; Benifla *et al.*, 2006; Kasasbeh *et al.*, 2012). Postoperative follow-up includes outcome regarding seizure frequency, sequential neuropsychological evaluations and interictal EEG.

Fortunately for pediatric surgical epileptologists, the outcome of focal resection for children with isolated HS and dual pathology is similarly favorable as long as the excision completely eliminates both pathologies. More often, these pathologies are contiguous and can be resected in a single procedure, but these lesions may be distant from each other; two craniotomies might be needed in this situation. Completeness of resection is highly correlated with seizure-freedom for both pathological subtypes irrespective of the intrinsic epileptogenicity of the hippocampus (Li *et al.*, 1999; Fauser *et al.*, 2004; Kim *et al.*, 2010). Rates of seizure-freedom are in the 60-70% range after complete resection, and the likelihood of relapse is acceptably low at long-term follow-up (Fauser *et al.*, 2004).

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