Summary

Epilepsy surgery is a particularly effective management option for children and adolescents with drug-resistant focal epilepsy. Recent advances in diagnostic modalities and surgical techniques have widened the spectrum of epilepsies amenable to surgery, whereas progress in neuroanesthesia and critical care has rendered this treatment increasingly safe and viable, even in the first years of life. Focal cortical dysplasia, glioneuronal tumors, and porencephaly due to perinatal stroke are the most frequent etiologies in this age group. In contrast to adult cohorts, temporal and frontal corticectomies are performed at similar rates, whereas one-third of children and adolescents undergo multilobar or hemispheric procedures. The younger the patient, the larger the resection or disconnection: infants often require more extensive procedures than older children and adolescents. The poor specificity of electroclinical correlations and the challenging MRI interpretation due to the ongoing myelination still pose considerable obstacles to candidate selection in very young children that, however, benefit the most from the opportunity to compensate functional deficits due to pronounced brain plasticity. Overall, seizure freedom is achieved in two-thirds of cases, with surgical success rates varying according to the underlying etiology and duration of follow-up. Global cognitive development remains stable after surgery; individual developmental trajectories are determined by presurgical cognitive development, age at surgery, seizure freedom, and antiepileptic drug tapering. Epilepsy surgery in children and adolescents is no longer a treatment of last resort but may be considered “disease-modifying”, particularly in the first years of life, considering the vulnerability of the immature brain to the ongoing processes of epileptogenesis.

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Key words: Pediatric epilepsy surgery, focal cortical dysplasia, glioneuronal tumors, hemispherotomy, cognitive development

Strategien und Ergebnisse der Epilepsiechirurgie vom Säuglingsalter bis in die Adoleszenz

Stratégies et résultats de la chirurgie épileptique pratiquée de la naissance à l'adolescence

La chirurgie épileptique est une option thérapeutique particulièrement efficace chez les enfants et les adolescents souffrant d'épilœpsie focale pharmaco-résistante. Les avancées de ces dernières années en matière de modalités diagnostiques et de techniques neuro-chirurgicales ont élargi le spectre des formes d'épilepsie pouvant être traitées par chirurgie épileptique. De plus, les progrès réalisés en anesthésie et en soins intensifs ont contribué à permettre l'utilisation de cette option thérapeutique également dans les premières années de vie. Les dysplasies corticales focales, les tumeurs cérébrales glioneuronales et la porencéphalie due à des accidents hémorragiques ou ischémiques périnataux constituent les étiologies les plus fréquentes dans cette tranche d'âge. Contrairement à ce que l'on observe dans les cohortes d'adultes, les résections frontales et temporales sont réalisées à une fréquence presque identique. Un tiers des enfants et des adolescents subissent des hémisphérotoomies ou des multi-lobec- tomies. Les patients sont jeunes, plus la résection ou déconnexion est grande : les jeunes enfants ont souvent besoin d'interventions plus importantes que les enfants plus âgés et les adolescents. Les résultats de l'EEG et la sémiologie des crises dans cette tranche d'âge offrent rarement des indices permettant d'orienter le diagnostic et la myélinisation progressive complique fréquemment les résultats de l'IRM. Ces particularités représentent souvent des obstacles considérables pour la sélection des candidats durant les premières années de vie, les nourrissons et les jeunes enfants pouvant généralement bien compenser les déficits neurologiques potentiels en raison de leur plasticité fonctionnelle. Deux tiers des enfants ne présentent plus de crises à long terme après une intervention de chirurgie épileptique, le taux de réussite pouvant varier selon l'étiole sous-jacente et la durée du suivi postopéra- toire. Le développement cognitif postopératoire reste stable dans l'ensemble. Les trajectoires individuelles d'évolution sont déterminées par le développement cognitif préopératoire, l'âge au moment de l'opération, l'absence de crises après l'opération et l'arrêt des anti- convulsifs. La chirurgie épileptique chez les enfants et les adolescents n'est plus perçue comme la dernière option, mais doit au contraire, en particulier dans les premières années de vie, être considérée comme un « modificateur de la maladie » étant donné la sensibilité du cerveau immature aux effets de l'épileptogénèse.

Mots-clés : Chirurgie épileptique pédiatrique, dysplasies corticales focales, tumeurs cérébrales glioneuronales, hémisphérotoomie, développement cognitif

Introduction

Epilepsy is one of the most frequently encountered neurologic disorders in childhood: the incidence of epilepsy is particularly high in the first years of life and remains high in childhood to decrease significantly after the age of ten years [1, 2]. One of three children diagnosed with epilepsy before the age of three [3] develops pharmacoresistance, defined as the failure of two appropriate treatment trials with well-tolerated and suitably selected antiepileptic drugs (AED) used alone or in combination [4]. One-third of children with early pharmacoresistance may reach permanent remission without surgery at long-term follow-up. However, the presence of a structural brain lesion precludes such a favorable outcome, strongly correlating with seizure recurrence [5]. Failure to respond to AED may lead to significant comorbidities, including impaired cognitive development, physical injury, sudden unexpected death in epilepsy (SUDEP), depression and anxiety disorders, and poor quality of life. On the other hand, beyond seizure control, cognitive development, behavior, and quality of life can improve considerably after epilepsy surgery in selected candidates. Despite recent advances, epilepsy surgery is not without risks. However, careful surgical planning, utilizing modern tools, has drastically decreased morbidity, offering an acceptable risk-benefit ratio. Pharmacoresistance is usually established early in the course of epilepsy and children with structural brain lesions, or other clinical features that point to a focal seizure onset, should be urgently considered for presurgical evaluation [6].

Presurgical evaluation aims 1) to define the epileptogenic zone, i.e. the cortical region that needs to be removed surgically for seizures to cease, and 2) to differentiate the epileptogenic zone from eloquent cortical areas. The extent of the epileptogenic zone can vary widely from a focal area to a whole hemisphere. Although focal pediatric refractory epilepsy is commonly associated with a MRI-visible structural lesion, the epileptogenic zone may match the extent of the lesion, extend beyond the lesion [7, 8] or even appear...
Indications and referral for epilepsy surgery

The seminal paper by the ILAE Subcommission for Pediatric Epilepsy Surgery [6] underlined that, in line with recommendations for adult populations, presurgical evaluation in an epilepsy center with pediatric expertise is warranted for 1) children with persisting or disabling seizures despite two or more AED trials as well as for 2) children with an unclassifiable epilepsy, particularly when seizures are stereotyped or lateralizing or when MRI reveals a structural lesion. However, two significant disparities are encountered when comparing children and adults referred for presurgical evaluation: 1) focal epilepsy in children may be linked to age-specific etiologies, and 2) persisting seizures may lead to developmental arrest or regression, particularly in early catastrophic epilepsies. It should be noted that impairment in cognitive development, psychiatric disease, or very young age constitute no contraindications to presurgical evaluation and, eventually, to surgical treatment.

The incidence of childhood-onset drug-resistant focal epilepsy provided by a community-based US American cohort study was 11.3 per 100'000 per year, whereas that of resective epilepsy surgery in the same population was 1.3 per 100’000 per year [23]. The vast disparity between the number of children and adolescents with focal refractory epilepsy and the annual number of surgeries for epilepsy may at least partly be attributed to the limited access to comprehensive presurgical evaluation for a subset of these patients. However, this disparity may also reflect the still restrained attitude of some pediatricians and child neurologists to epilepsy surgery, despite its increasing acceptance nowadays.

Presurgical investigations

Epilepsy surgery in childhood and adolescence calls for specific pediatric epilepsy expertise [6], considering that particular neurobiological aspects of epilepsy are unique in pediatric cohorts, particularly in the first years of life. The 2006 recommendations by the ILAE Subcommission for Pediatric Epilepsy Surgery proposed the following investigations as overall mandatory for the presurgical evaluation of pediatric cohorts: interictal scalp EEG (including natural sleep recordings), a dedicated MRI epilepsy protocol, and age-appropriate neuropsychological assessment. Additional recommended components were ictal scalp EEG and access to functional imaging when required.

The role of further investigations for specific pediatric disorders has been the subject of a more recent paper on the utility of diagnostic tests [24]. The authors concluded that no additional tests are required in lesions with concordant seizure semiology and scalp EEG findings that are known to correlate well with the epileptogenic zone, such as hypothalamic hamartoma, Rasmussen encephalitis, and hemispheric lesions without residual function in the affected hemisphere. Further non-invasive diagnostic tests may or may not be performed in the case of more discrete substrates including hippocampal sclerosis, distinct tumors, FCD type II, and vascular lesions such as Sturge Weber Syndrome, arteriovenous malformations, and stroke. Finally, additional investigations are highly recommended in FCD type I, in tuberous sclerosis, or hemispheric le-
Epilepsy surgery outcomes

Seizure freedom

The most robust predictor of favorable postsurgical seizure outcomes is the completeness of resection [8, 17, 18, 37], invariably defined as the surgical removal of the MRI-visible structural lesion and the adjoining area of ictal onset. Especially in the context of FCD, the prevalent etiology in pediatric epilepsy surgery cohorts, incomplete lesion resection has been identified as the strongest predictor of seizure recurrence [38]. It should be noted that FCD type II, typically better discernible in MRI, is associated with superior rates of seizure freedom. This observation holds true for further etiologic substrates, such as glioneuronal tumors [8], but not for polymicrogyria that presents with more complex interrelations of the MRI-visible lesion with the epileptogenic zone [9]. Further predictors of postsurgical seizure freedom include EEG and MRI concordance as well as lesions located distant from eloquent cortex [17, 18]. The use of chronic invasive EEG and intraoperative ECoG has not been predictive of postsurgical outcome [39, 40].

Temporal resections account for 25% of pediatric epilepsy surgery procedures [14]. Similar to adult cohorts, results for temporal lobe surgery remain superior to those of extratemporal epilepsy surgery in children and adolescents, reaching 70 - 90% [41]. This observation underlines the treatment gap, considering that temporal lobe epilepsy is a pediatric onset disorder in many adults referred for presurgical evaluation. Furthermore, a recent study of temporal lobe epilepsy surgery in children with a follow-up to adult life [42] points to a unique opportunity regarding cognitive development, additional to long-term seizure control: 85% patients achieved seizure freedom, with a subset presenting a significant increase in IQ. In stark contrast to adult cohorts, hippocampal sclerosis as the only epilepsy substrate presents in only 7% of children undergoing surgical resection, with dual pathology (e.g. co-existence of FCD) presenting more frequently [14].

Extratemporal resections correspond to 20% of pediatric epilepsy surgery: most resections concern the frontal lobe [14]. Two recent studies have underlined the significance of early surgical intervention for superior seizure outcomes in frontal lobe surgery. In a study including 158 children and adults [43], both younger age at surgery (< 18 years) and shorter epilepsy duration (< 5 years) predicted seizure freedom. In a more recent study including 75 children and adolescents [18], shorter epilepsy duration, along with strictly regional epileptic discharges in EEG and an epileptogenic zone and/or lesion distant from eloquent cortex correlated with seizure freedom. In this study, seizure cessation was reached in 63% of patients, half of them off AED in the long-term follow-up. Resections in the parietal

sions with residual function, and are mandatory in MRI-negative cases, multiple MRI-visible lesions and cortical malformations adjacent to eloquent cortical areas.

Among additional diagnostic modalities, fluorodeoxyglucose positron emission tomography (FDG-PET) is easier to perform and thus often constitutes the first step in FCD or in MRI-negative cases, whereas SPECT, often utilized in tuberous sclerosis, is technically more challenging and requires seizures of sufficient frequency and duration. Source localization deriving from EEG or magnetoencephalography (MEG) is rapidly gaining ground in the last decades [25 - 29] and may provide further information for availing or planning invasive EEG explorations [30]. Beyond the precise delineation of the epileptogenic zone, additional investigations may be necessary in cases of proximity to eloquent cortex [24]. Functional (f-)MRI or MEG may be used to estimate the localization of motor or language cortex in frontal or temporal regions. Activation at expected cortical sites is considered reliable for lateralization and surgical planning without invasive tests, such as the Wada test or the electrocortical stimulation, whereas lack of activation or activation at atypical sites calls for further (invasive) confirmation.

Despite the turn towards a less generous utilization of invasive investigations in the last decade, driven by recent advances in numerous non-invasive diagnostic techniques [31 - 33], invasive EEG recordings are still required, as increasingly complex cases are considered for epilepsy surgery [34]. The cornerstone of rational invasive investigations is a reasonable hypothesis regarding the underlying etiology, the epileptogenic zone, and its relation to eloquent cortex that may lead to surgical resection. No invasive EEG should be carried out merely as a “fishing expedition”, involving extensive bilateral electrode implantations without a clear objective. Invasive EEG is not warranted when further non-invasive investigations can provide the data necessary to proceed to resective surgery and should not be performed when cognitive, behavioral, or other comorbidities render invasive recordings particularly risky. Another key question to be answered is if an invasive EEG in the intraoperative setting (electrocorticography: ECoG) would suffice or if extraoperative chronic recordings, carrying higher morbidity risks, are indeed required. Overall, invasive EEG is indicated to precisely delineate the epileptogenic zone at the presence of inconclusive non-invasive data, to resolve the discrepancy of non-invasive data pointing to more than one brain regions, and to map eloquent cortical areas that overlap with the presumed epileptogenic zone [34]. The choice of the invasive EEG modality between subdural grids and strips [28, 29] and stereotactically implanted depth electrodes (stereo-electro-encephalography: SEEG) [9, 35, 36] or a combination of both depends on the primary hypothesis as well as on the experience of the epilepsy center [30].
and/or occipital lobe, sometimes including the posterior part of the temporal lobe, are comparably effective, leading to seizure freedom in 60 - 86% of patients in recent studies [17, 44], half of them off AED. In a recent study including 50 children and adolescents [17], seizure recurrence correlated with left-sided as well as parietal epileptogenic zones and resections, with longer epilepsy duration to surgery identified as the only modifiable independent predictor.

Hemispherotomy currently accounts for 20 - 40% of resections in pediatric epilepsy surgery [14]. The vast majority of children and adolescents undergoing hemispherotomy remain seizure free after surgery [11], with etiology identified as the main predictor of surgical success: dysplastic lesions, particularly hemimegalencephaly, have less favorable long-term outcomes compared with acquired brain lesions, such as those occurring due to perinatal stroke [45]. Additional predictors of seizure recurrence, as identified in a recent meta-analysis [45], include lack of lateralizing seizure semiology or EEG pathology and contralateral MRI abnormalities.

Cognitive development

Beyond seizure freedom, the stabilization or even improvement of cognitive development constitutes a major goal of epilepsy surgery. The majority of surgical candidates presents with severe developmental delay and cognitive deficits before surgery, with cognitive development remaining stable after surgery in most cases [8, 10, 11, 18]. Individual developmental trajectories are determined by the degree of presurgical developmental impairment, age at surgery, seizure freedom, antiepileptic drug tapering, and other case-specific factors [8, 10, 11, 18, 22, 46, 47]. Compared to adults, children may better compensate for a functional deficit, due to the pronounced plasticity of the young brain. This superior capacity for compensation has been previously demonstrated in a seminal study of temporal lobe epilepsy surgery [20]. In children with severe developmental impairment, postsurgical improvements may escape detection in the formal neuropsychological evaluation, despite their significance for families regarding the quality of life [10, 11].

Postsurgical AED withdrawal

Pediatric epilepsy surgery aims at seizure freedom and AED withdrawal, with the condition of “no seizures, no drugs” corresponding to a true “healing” of epilepsy. Another motivation to taper AED after surgery lies in the hope for developmental improvement in seizure-free patients. AED in the first years of life may negatively impact cognitive development by triggering neuronal apoptosis and by impeding neurogenesis, synaptic plasticity, cell proliferation and migration and synaptic plasticity [48 - 50]. Moreover, many AED are known to have cognitive side effects in all age groups, particularly regarding attention, processing speed and global executive functions [51 - 53]. Drug load, i.e. treatment with more than one AED, is considered as one of the most relevant factors that affect cognitive performance [54]. The TimeToStop study, a recently published large multicentric retrospective study [55], has provided evidence that the timing of AED withdrawal does not significantly impact long-term seizure outcomes, but facilitates the timely identification of children and adolescents requiring long-term AED treatment, whereas others may be spared the unnecessary continuation of AED treatment. In a follow-up study focusing on pre- and postsurgical cognitive development in pediatric epilepsy surgery [46], AED withdrawal independently correlated with postoperative IQ and change in IQ scores. The more AEDs were reduced, the higher the postoperative IQ and IQ change. These observations are particularly significant for medication policies following epilepsy surgery, but are yet to be verified in a prospective randomized clinical trial.

Functional plasticity and the timing of intervention

Pronounced brain plasticity in childhood, especially in the first years of life, presents a particular advantage of pediatric epilepsy surgery, facilitating a significant reorganization of neurologic function after an insult. The differences between pediatric and adult patients regarding postsurgical cognitive functioning [56] are attributed to the higher degree of plasticity that accounts for the superior reorganization and compensatory capacities of the developing brain. Functional plasticity is the key to the recovery of linguistic competence in very young children. On the other hand, the same beneficial forces of plasticity may harm by triggering abnormal or delayed cognitive development [6].

The choice of the optimal timing for intervention is crucial since it constitutes a potentially modifiable factor. Two-thirds of children undergoing epilepsy surgery in the 2004 ILAE survey [14] were younger than three years at epilepsy manifestation, but only a minority of these children received surgery within two years following seizure onset. Early epilepsy onset in the first years of life with frequent epileptic seizures will eventually lead to a developmental arrest, or even to a loss of already acquired functions [57]. These severe courses are presumably caused by the epileptic seizures per se as well as by the underlying etiology [58]. When considered for epilepsy surgery, these children are often candidates for extensive multilobar or hemispheric resections and disconnections [10, 11, 16]. In addition, longer epilepsy duration hinders cognitive development in affected children [8, 22]. In recent years, numerous
studies have emphasized the need for early intervention, particularly in very young children with early-onset catastrophic epilepsy, to prevent permanent cognitive deficit [59].

Conclusion

Epilepsy surgery in children and adolescents is no longer a treatment of last resort but may be considered “disease-modifying,” particularly in the first years of life, considering the vulnerability of the immature brain to the ongoing processes of epileptogenesis. Overall, two-thirds of children undergoing epilepsy surgery remain seizure-free at long-term follow-up, one-third off AED. Besides seizure freedom, the improvement of cognitive development is an essential goal of epilepsy surgery in children and adolescents, with overall cognitive development remaining stable in the majority of patients. Multicenter studies with standardized evaluation protocols and longer follow-up intervals, extending beyond childhood and adolescence, are urgently needed. These studies are expected to provide deeper insights into seizure control as well as cognitive development after epilepsy surgery, to shed some light on the interaction between different predictors, and to facilitate the selection of appropriate candidates and the counseling of patients and their families.

References

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