Children with Tumor-Related Epilepsy: A Surgical Dilemma

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Summary

Children with drug resistant focal epilepsy due to both low grade as well as high grade neuronal and glioneuronal tumors can be treated surgically. However the neurosurgical approach is challenging, especially the decision on extent of resection. The latter should be tailored to the individual patient based on the clinical presentation, the appearance and location of the lesion, the results of phase I and II epilepsy investigation and epidemiological data.

Familiarity with the clinical presentation and seizure semiology as well as the epidemiology of brain tumors in children, including age, localization and neuroimaging features, is pivotal for deciding on the appropriate surgical approach.

In this communication we aim to give an overview on the epidemiology of pediatric brain tumors associated with epilepsy and their clinical features. We discuss the surgical dilemma on the extent of resection in order to achieve favorable seizure control and oncological outcome, while minimizing morbidity and optimizing cognitive development.

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Key words: Pediatric epilepsy surgery, temporal lobe tumors, lesionectomy, pediatric tumors of the central nervous system, focal symptomatic epilepsy

Kinder mit tumorbedingter Epilepsie: ein chirurgisches Dilemma

Kinder mit arzneimittelrefraktärer fokaler Epilepsie aufgrund von niedriggradigen oder auch hochgradigen neuronalen und glioneuronalen Tumoren können chirurgisch behandelt werden. Allerdings stellt der chirurgische Ansatz eine Herausforderung dar, insbesondere hinsichtlich der Entscheidung über den Resektionsumfang. Dieser sollte sich im Einzelfall nach dem klinischen Bild, dem Erscheinungsbild und der Lokalisation der Läsion, den Ergebnissen der Phase-I- und Phase-II-Diagnostik sowie nach epidemiologischen Kriterien richten.

Die Entscheidung über den angemessenen chirurgischen Ansatz setzt eine genaue Kenntnis der klinischen Merkmale und der Anfallssymptomatik sowie der Epidemiologie von Hirntumoren bei Kindern – unter anderem in Bezug auf Alter, Lokalisation und Charakterisierung in neurobildgebenden Studien – voraus.

Im Rahmen dieser Mitteilung wollen wir einen Überblick über die Epidemiologie und die klinischen Merkmale der mit Epilepsie assoziierten pädiatrischen Hirntumoren geben. Wir erörtern das chirurgische Dilemma des Resektionsumfangs, das darin besteht, einerseits eine gute Anfallskontrolle und ein günstiges onkologisches Resultat zu erzielen, gleichzeitig aber die Morbidität zu minimieren und die bestmögliche kognitive Entwicklung zu ermöglichen.

Schlüsselwörter: Pädiatrische Epilepsiechirurgie, Temporallappentumore, Läsionektomie, pädiatrische Tumore des Zentralennervensystems, fokale symptomatische Epilepsie

Enfants souffrants d'épilepsie liée à une tumeur : un dilemme chirurgical

Les enfants atteints d'épilepsie focale pharmacorésistante liée à des tumeurs neuronales et glioneuronales de faible grade comme de grade élevé peuvent être traités par chirurgie. L'approche neurochirurgicale est cependant délicate, notamment quant au choix de l'étendue de la résection. Cette dernière doit être adaptée à chaque patient en fonction de la présentation clinique, de l'apparence et de la localisation de la lésion, des résultats obtenus aux examens pratiqués en phase I et II sur l'épilepsie, et des données épidémiologiques.

La bonne connaissance de la présentation clinique et de la sémiologie des crises ainsi que de l'épidémiologie des tumeurs cérébrales chez l'enfant, y compris l'âge, la localisation et les caractéristiques de neuroimagerie, est cruciale pour décider de l'approche chirurgicale appropriée.

Cette communication vise à donner un aperçu de l'épidémiologie des tumeurs cérébrales pédiatriques associées à l'épilepsie et de leurs caractéristiques cliniques. Nous abordons ce dilemme que constitue en chirurgie le choix de l'étendue de la résection pour obtenir un contrôle favorable des crises et de bons résultats oncologiques, tout en réduisant le plus possible la morbidité et en optimisant le développement cognitif.

Mots clés : Chirurgie de l'épilepsie chez l'enfant, tumeurs du lobe temporal, lésionnectomie, tumeurs pédiatriques du système nerveux, épilepsie symptomatique focale

Introduction

The aim of this communication is to highlight the surgical dilemma in the management of pediatric patients presenting with a seizure and a space occupying lesion in the neuroimaging evaluation.

Children with drug resistant focal epilepsy due to structural anomaly can be treated surgically. Possible structural etiologies for focal epilepsy include focal cortical dysplasia, mesial sclerosis and both low grade as well as high grade neuronal and glioneuronal tumors. Criteria for consideration of surgical management include: Preoperative identification of the epileptogenic zone, the lack of involvement of eloquent cortical areas and the natural history of the underlying disease [1]. The latter is especially critical in cases of higher grade tumors, which demand a different, more radical surgical resection. Thus in these cases the surgical goal is primarily "tumor-surgery" with extensive resection for optimization of tumor outcome rather than the less aggressive "epilepsy-surgery" for seizure control only. Familiarity with the clinical presentation and seizure semiology as well as the epidemiology of brain tumors in children, including age, localization and neuroimaging features, is pivotal for deciding on the appropriate surgical approach. The following case demonstrates this challenge of decision making concerning the surgical strategy.

Illustrative case

A five-year-old boy presented with a one-day history of vomiting and headache followed by a generalized seizure. The cranial magnetic resonance imaging (cMRI) (**Figure**) showed a space occupying lesion in the right mesial temporal lobe. It had an inhomogeneous appearance with two small cystic changes and with spotted contrast enhancement, no perifocal edema or midline shift were seen. The findings were consistent with glioma. Electroencephalogram (EEG) showed temporal slow activities corresponding to the location of the lesion, thus confirming the seizure semiology. The patient underwent temporal craniotomy and stereotactic total tumor resection under neuro-monitoring. The total resection was confirmed in the postoperative MRI. Unexpectedly, the histopathological diagnosis was an anaplastic astrocytoma IDH-wild type World Health Organization (WHO) Grade III, and one month later an MRI showed a new cystic lesion with perifocal edema. Therefore, the patient underwent a second operation, this time with fronto-temporal craniotomy, and extended resection followed by radiotherapy and chemotherapy.

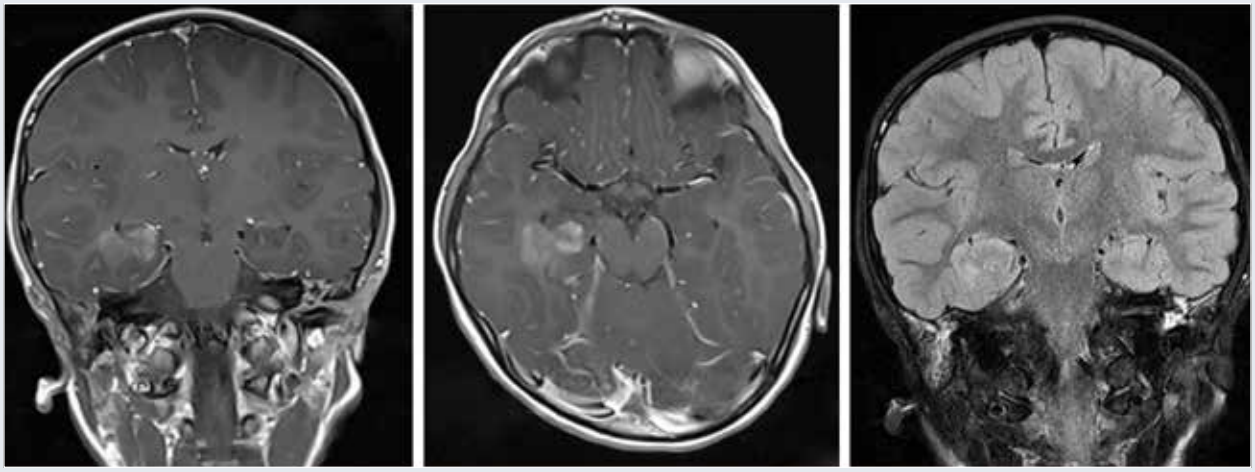

Figure: MRI images of a 5-year-old boy presenting with headache, vomiting, reduced level of conscience and generalized seizure. From left to right: T1-MRI with contrast as well T2-FLAIR-MRI showing an inhomogeneous space occupying lesion in the right mesial temporal lobe with two cystic components without perifocal edema.

Clinical features

Pediatric brain tumors are often associated with seizures, sometimes as the initial and only presentation. Epilepsy is a comorbidity in more than half of the children with supratentorial tumors [2, 3]. Supratentorial location, which in children is less common than infratentorial location, is considered a risk factor for seizures, especially when the neoplasm is in the temporal lobe [2, 4, 5]. Children with temporal lobe tumors and epilepsy tend to be of young age, to have a well differentiated histology, to lack additional neurological symptoms or signs and to have a long history of seizure disorder [5]. It is estimated that 80% of children with a temporal lobe neoplasm have epilepsy, probably because of its low threshold for convulsions. Epilepsy is usually the onset symptom, and often remains the only clinical manifestation in approximately 60% of the cases [2, 6, 7]. In a series of 37 pediatric patients with temporal lobe epileptogenic tumors Iannelli et al. found 14% to have simple focal seizures, 56% focal dyscognitive seizures and 16% secondarily generalized seizures and, another 14% had more than one seizure type. The range of age was between three months and 15 years and most subjects (73%) were male. Low grade neoplasms are the most common mass lesions in children with temporal tumor-related epilepsy [5]. Low-grade tumors tend to be more epileptogenic and are usually associated with chronic development of epilepsy as opposed to high-grade neoplasms, which are less epileptogenic and typically present with acute seizures and are often associated with other neurological signs such as increased intracranial pressure or focal neurological deficits caused by acute tissue damage [3]. Extratemporal epilepsy is less common and occurs predominantly in the perirolandic area, it presents with various clinical manifestations and origins [1, 8].

Epidemiology

Brain tumors are the second most common tumors in pediatrics after leukemia, and the most common solid tumors, with a yearly incidence of approximately 5/100'000. They are the leading cause of pediatric cancer-related mortality [9]. The 2016 WHO classification of tumors of the central nervous system incorporates new molecular and genetic features to the older classifications which were based mostly on histology and tissue origin [9, 10]. The classification grades tumors according to increasing level of malignancy (I, II, III, IV).

Gliomas, which are tumors of neuroepithelial tissue derived from glial cells, namely, astrocytes, oligodendrocytes and ependymal cells, account for approximately half of brain tumors and are mostly of low grade [9, 11]. Glioneuronal tumors, mainly gangliogliomas (GGs) and dysembrioplastic neuro-epithelial tumors (DNETs) consist of a mixture of glial and neuronal elements [12]. Medulloblastoma is the main tumor of embryonal origin [9].

In children approximately 60% of brain tumors are localised infratentorially and 40% supratentorially [13], the latter are more often associated with seizures. The most common infratentorial tumors are astrocytomas, especially pilocytic astrocytoma, followed by medulloblastomas and ependymomas. Supratentorially, astrocytomas are the most common type followed by GGs and DNETs, oligodendrogliomas and supratentorial primitive neuroectodermal tumors. Fortunately, low grade tumors are much more frequent than higher grade tumors.

Long term epilepsy associated tumors (LEATs), the benign and epilepsy associated neuro-epithelial brain tumors, constitute only 2 - 5% of the tumors of the central nervous system [14]. This term has been coined by the Epilepsy Group of Bonn in order to distinguish this entity from other brain tumors in which epilepsy is considered an epiphenomenon. LEAT's have an onset at young age, are characterized by a slow or no growth and are cortical and mostly located in the temporal lobe. Nevertheless they are the second most frequent focal pathology in epilepsy surgery, following hippocampal sclerosis in adults and focal cortical dysplasia in children [15]. These patients show a successful surgical outcome with a seizure free rate of 60 to 100% [16]. In contrast to pathologies such as focal cortical dysplasia the oncological outcome is of utmost importance in the management of LEAT's. The histological classification remains difficult and is subject to diverse interpretations, therefore special expertise is crucial [17, 18]. Immuno-histochemical, molecular genetic testing and novel biomarkers are of increasing importance in the classification of LEAT's and these new techniques will hopefully improve prognostic prediction and treatment of these tumors [10, 18, 19].

In a series of 129 pediatric patients, less than 19 years old, with intractable seizures associated with tumors, 60% of the tumors were located in the temporal lobe [7] and the following tumor types were found: GGs (WHO grade I) 48 (37%), low grade glial/glioneuronal tumor (WHO grade I/II) 18 (14%), DNETs (WHO grade I) 17 (13%), low grade astrocytoma (WHO grade II) 15 (12%), low grade mixed glioma (WHO grade II) 8 (6%), and other various tumors in smaller numbers of patients (1 - 4%).

GGs and DNETs most commonly arise in the temporal lobe and are an important cause of focal epilepsy in children [12], they are also the most common type of tumors causing long standing medically intractable epilepsies [20]. In a series 21 children (< 18 years) who underwent epilepsy surgery, 9 had DNET, 10 had GG and 2 had gangliocytomas (GC) [20]. In a study of mesial temporal lobe epilepsy, the histopathological distribution in a group of 30 patients (age of onset 7 - 51 years) with epilepsy-associated low-grade tumors included: 13 GG, 3 GC, 5 pleomorphic xanthoastrocytoma, 3 DNET, 2 an-

giocentric glioma, and 1 each: fibrillary astrocytoma, melanocytoma, neurocytoma, and papillary glioneuronal tumor [21]. GG is considered the most common neoplasm causing focal epilepsy, accounting for approximately 40% of all epileptogenic tumors [22].

Looking specifically at epileptic temporal lobe tumors, in a series of 37 patients Ianneli et al. found that 84% were benign: Oligodendroglioma, astrocytoma WHO Grade I or II, GG, cavernoma; and 16% malignant: Glioblastoma, ependymoma and astrocytoma WHO Grade III. A group of 30 children aged 3 - 18 years with focal epilepsy associated with low grade tumors were included in the study of Babini et al. [6]. In 83% of the patients the tumor was located in the temporal lobe. 67% had GG, 13% DNET and 5 patients had various other types. A study on supratentorial tumors in children younger than 3 years of age [23] showed the following histopathological findings in the group of patients with epilepsy: 5 cases with WHO Grade I tumors (3 pilocytic astrocytoma, 2 GG), 4 cases with WHO grade II (3 astrocytoma, 1 oligodendroglioma), 7 cases of WHO grade III (4 choroid plexus carcinoma, 1 anaplastic oligodendroglioma, 1 anaplastic ependymoma, 1 immature teratoma) and 4 cases with WHO grade IV tumors (2 glioblastoma multiforme, 1 primitive neuroectodermal tumor, 1 neuroblastoma).

Surgical considerations

Tumor related epilepsy poses a challenge to the pediatric neurosurgeon because the pathological diagnosis is usually unknown when decisions regarding the extent of resection are made [3].

The preoperative likelihood that a lesion is benign is based on the clinical presentation, EEG and neuroimaging findings while bearing in mind epidemiological data. In these cases, the primary goal of surgery is to eliminate the epileptogenic focus without causing functional deficits [8, 24] in order to improve the patient's quality of life and psychosocial integration [8]. Some authors advocate early intervention [4, 8, 25] in order to prevent further brain injury from the underlying lesion, the seizures themselves or the antiepileptic medications and because of the beneficial effect on cognitive development [4]. Simple resection of the tumor alone, lesionectomy, is advocated by some investigators, while others recommend resection of the epileptogenic zones in addition [4]. In contrast when a high grade tumor is suspected radical resection is the main goal as this is the main prognostic factor for a good outcome while the ablation of the epileptogenic tissue is of a minor importance [2].

Despite the increasing reports and experience with surgery for tumor-related epilepsy in children, it is unfortunately inevitable that in exceptional cases second operations will be needed due to unexpected high grade histopathological findings. The importance of serial post-surgical clinical and MRI follow ups cannot be overemphasized, especially in view of the fact that also low grade tumors, including GG's and DNET's, can recur [26, 27] or rarely undergo malignant transformation [28 - 30].

Conclusion

The neurosurgical approach to children presenting with tumor-related epilepsy is challenging. The extent of resection should be tailored to the individual patient [27] based on the clinical presentation, the appearance and location of the lesion, the results of pre-epilepsy surgery evaluations and epidemiological data. The goal is to achieve favorable seizure control, excellent oncological outcome, while minimizing morbidity and optimizing cognitive development. Regardless of the surgical approach chosen, be it lesionectomy with or without epileptogenic zone resection or extensive tumor resection, serial post-surgical MRI follow up is invaluable, especially in patients with evidence of residual tumor [9, 26].

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