Neurochirurgie 63 (2017) 197–203

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Article original

Prevention and management of postoperative seizures in neuro-oncology

Prévention et traitement des crises postopératoires en neuro-oncologie

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ARTICLE INFO

Article history:
Received 25 May 2016
Received in revised form 2 October 2016
Accepted 14 October 2016

Keywords:
Brain tumor
Glioma
Epilepsy
Neurosurgery
Anti-epileptic drugs
Anticonvulsant prophylaxis

ABSTRACT

Introduction. – Epilepsy related to brain tumors is often difficult to treat and may impact the quality of life. We performed a review of current recommendations for the prevention of postoperative seizures and optimizing the anti-epileptic treatment.
Material and methods. – Based on studies performed since 2000 we conducted the review by (1) analyzing the incidence of tumoral epilepsy and mechanisms of epileptogenicity; (2) describing the current medical and surgical strategy according to oncologic treatments; (3) discussing the management of postoperative seizures; (4) considering the drug withdrawal after oncologic therapy.
Results. – Epilepsy related to supra-tentorial brain tumors is frequent (40–60%) especially in low-grade gliomas, glioneuronal tumors, fronto-temporal and eloquent cortex locations. Seizures can occur as a presenting symptom or during the course of the tumor, including after surgery and oncological treatments. Maximal safe surgical resection is the more effective therapy, alone or combined with adjuvant therapy (chemotherapy, radiotherapy). Anti-epileptic drugs are not indicated for epilepsy prophylaxis in patients without seizures but only after the first seizure due to high risk of recurrence. As they may generate adverse effects and interfere with oncological treatments, the choice is based on efficacy, tolerability and potential interactions. New anti-epileptic non-enzyme-inducing drugs are recommended in first-line monotherapy in association with adjuvant oncological therapies. Enzyme-inhibiting drugs could have a favorable effect on survival. Late seizures are often related to tumor progression or recurrence. Discontinuation of anti-epileptic drugs could be considered after successful oncological treatment and a stable medical condition.
Conclusion. – These guidelines are helpful for a rational therapy in tumoral epilepsy.

Mots clés :
Tumeur cérébrale primitive
Gliome
Épilepsie
Neurochirurgie
Médicament antiépileptique
Prophylaxie anticonvulsivante

RÉSUMÉ

Introduction. – L'épilepsie symptomatique des tumeurs cérébrales est souvent difficile à traiter. Nous avons réalisé une revue des recommandations actuelles pour prévenir les crises postopératoires et optimiser le traitement antiépileptique.
Matériel et méthodes. – À partir d'études réalisées depuis 2000, nous avons analysé (1) l'incidence et les mécanismes des épilepsies tumorales; (2) les stratégies médico-chirurgicales liées aux traitements oncologiques ; (3) la prise en charge des crises post-opératoires ; (4) le sevrage des médicaments antiépileptiques après traitement oncologique.

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http://dx.doi.org/10.1016/j.neuchi.2016.10.013
0028-3770/

Résultats. – L'épilepsie tumorale est fréquente (40–60 %), en particulier dans les gliomes infiltrants de bas-grade, les tumeurs glioneuronales, les régions fronto-temporales et fonctionnelles. Les crises peuvent révéler la tumeur ou survenir en cours d'évolution, y compris après traitement oncologique. L'exérèse chirurgicale maximale avec préservation fonctionnelle est la plus efficace pour traiter l'épilepsie, seule ou associée à un traitement adjuvant (chimiothérapie, radiothérapie). Les médicaments anti-épileptiques ne sont pas indiqués en prophylaxie primaire mais sont justifiés dès la première crise en raison du risque élevé de récidive. Ils peuvent générer des effets indésirables et interférer avec les traitements oncologiques. Les nouveaux antiépileptiques non-inducteurs enzymatiques ont une efficacité similaire et une meilleure tolérance que les anciens et sont recommandés en monothérapie de première intention. Ceux ayant des propriétés d'inhibition enzymatique auraient un effet favorable sur la survie. Les crises tardives sont souvent liées à la progression ou à la récidive tumorale. L'arrêt des médicaments antiépileptiques est discuté après le traitement oncologique si l'état médical est stable.
Conclusion. – Ces recommandations sont utiles pour un traitement rationnel des épilepsies tumorales.

1. Introduction

Epilepsy associated with primary brain tumors is a frequent condition requiring both oncological and Anti-Epileptic Drug (AED) therapies. Consequences of epilepsy imply cognitive impairment, worsening of neurological deficits, restrictions in social and professional activities, including driving, and increased risk of mortality. However, AED may generate serious adverse effects and interfere with oncological treatment. All of these factors may negatively impact on the Quality Of Life (QOL). Thus, prevention of postoperative seizures is a major issue when considering the global care of patients with brain tumors. Furthermore, AED use may have an influence on survival. The choice of an AED therefore implies to consider the specificity of tumoral epilepsy.

Based on our experience in epilepsy surgery and neurological management of patients with brain tumors operated on in our center, we performed a review of current recommendations for the prevention of postoperative seizures and optimizing the treatment of brain tumor-related epilepsy. We will focus on the prevention of postoperative seizures in neuro-oncology, taking into account that the patients may have had no seizures before surgery. We will also describe, for neurosurgical daily practice, the management of patients who had epilepsy prior to surgery, either responding or resistant to AED.

2. Material and methods

2.1. Search strategy and selection criteria

We identified references for this review through searches of PubMed with the search terms "brain tumor", "glioma", "glioblastoma multiforme", "meningioma", "metastasis", "gangli-oglioma", "dysembryoplastic neuroepithelial tumors", "epilepsy", "anti-epileptic drugs", "drug-resistance", "neurosurgery", "oncol-ogy", in various combinations, from January, 2000, to March, 2016 (Table 1). We also identified articles through searches of our own files. Only papers in English were reviewed. Data available as an abstract and case reports were not included. Retrospective single-center studies based on a population less of 50 patients, specific children population studies, preliminary data and redundant publications were excluded. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

2.2. Conduct of the Review

We organized the review by first analyzing the incidence of epilepsy related to brain tumors, and the known mechanisms of epileptogenicity in this etiology. We described the current medical and surgical strategy for epilepsy according to the histological types of tumors and the oncologic treatment, with special attention given to the adverse effects of AED in this patient population. We considered retrospective studies, meta-analyses and therapeutic trials. Comparative studies using new AED and prospective controlled studies were privileged for AED recommendations. Later, we will discuss the specific problems related to early and late postoperative seizures. Finally, we will examine the conditions for considering the withdrawal of AED after surgery and oncologic therapy and compared them to those proposed in epilepsy surgery.

3. Results

3.1. Epilepsy associated with tumors (EAT): characteristics and therapeutic principles

Epileptic seizures are common symptoms for brain tumors, either as initial features or occurring during the course of the disease. Considering all types of tumors together, the incidence of EAT is 40–60% [1–3]. It may be a single isolated seizure revealing the tumor without recurrence after surgery. In contrast, long lasting drug-resistant epilepsy with early onset may also be due to a brain tumor and time for considering surgery may take years. The clinical features consist in partial seizures with or without secondary tonic-clonic generalization. EAT is considered difficult to treat medically and can be a severe and disabling condition with major consequences on QOL. In tumors located in eloquent areas, seizures may induce postictal or interictal deficits (motor or cognitive) worsening the clinical status of the patients. Status epilepticus related to brain tumors (7% of status epilepticus etiology) would have a worse prognosis and higher mortality rate than those of other causes [4]. Notably, the response to AED is opposite to the tumor grade, the lower the histological grade, the higher is the AED resistance. Moreover, epilepsy as a presenting symptom is a positive prognostic factor associated with longer survival duration in patients harboring a glioma [5].

Based on these data, the most refractory epilepsy tumors are found in epilepsy surgery series and are mainly represented by low-grade gangliogliomas and dysembryoplastic neuroepithelial tumors. [6–8] These glioneuronal tumors share the characteristics of early epilepsy onset, high epileptogenicity and benign course without evidence of tumor progression. Epilepsy is also very common in diffuse Low-Grade Gliomas (LGG). It has been reported in 60–90% of the cases while the incidence of epilepsy varies between 25 and 60% in higher-grade gliomas [1,2]. Tumors with high epileptogenicity are mainly located in supra-tentorial cortical areas, especially in fronto-temporal regions, including the