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Use of antiepileptic drugs in children with brain tumors: A review for acute management

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ABSTRACT

Patients with primary or secondary tumors in the central nervous system may have seizures resulting from direct tissue damage, metabolic abnormalities, infection, or toxic side effects of medications. In pediatric patients, it is more frequent to use drugs to control secondary epilepsy. In this article, we discuss the main nuances of antiepileptic drugs for the proper management of children with central nervous system tumors.

1. Introduction

Patients with primary or secondary tumors in the central nervous system (CNS) may have seizures resulting from direct tissue damage, metabolic abnormalities, infection or toxic side effects of medications. The frequency of epilepsy in patients with brain tumors is estimated at 30% of the cases or even more and is influenced by the histological types of tumor and the location in the CNS[1]. A higher incidence of seizures occurs in patients with low-grade tumors like oligodendroglioma, low-grade astrocytomas and neuroepithelial tumors, manifesting itself in childhood or adolescence. Those tumors located in the frontal, temporal or parietal lobe are most commonly associated with crisis and they can become refractory to medical treatment[1]. It is attributed to the cortex adjacent to the peritumoral area as the epileptogenic focus in

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CNS tumors, but the precise mechanisms are poorly understood[2].

2. Nomenclature from International League Against Epilepsy

Nomenclature from International League Against Epilepsy-2016 is simple and straightforward: 1. Primary generalized can only be name given a clinical presentation, but on electroencephalo-graph (EEG), there will at least be a few nanosecond gap between the focal site of origin to global spread choice; 2. Complex partial when dissected gets a new name: focal onset with impaired awareness choice; 3. Focal with retained awareness is simple partial choice; 4. Complex partial with secondary generalization dissected to be named: focal to bilateral tonic clonic. Also, the presentation has a component fitting with the name 'autonomic seizure' in the form of epigastric raising. To sum up, it could be focal seizure with retained awareness with an autonomic component.

3. Epileptogenesis and brain tumors

The attribution of the epileptogenic focus as the peritumoral area of brain tumors has support from functional studies[3,4]. Aronica *et al*.[5] suggested that altered the GABAergic system may contribute to the complexity of abnormal function in perilesional regions especially in tumors as gangliogliomas. There are two interesting hypothesis for epileptogenesis in brain tumors: the first hypothesis refers to the invasion of brain gliomas-glioma cells in experimental models release glutamate in excitotoxic concentrations providing a mechanism for both tumor growth and for tissue invasion (killing neighboring cells) and possibly generating a seizure[6]; the second hypothesis has been tested in both animal models and in human tissues, where it was evidenced that while invasion gliomatosas cells occur, changes occur in the properties discharge neighboring neurons, turning to "pacemaker" cells that provide and lead neural networks surrounding the tumor[6].

An intriguing hypothesis based on such changes in excitability, although not directly tested in the context of epileptogenesis tumor, explains that when it generates at least a temporary loss of integrity of the Barrière Hémato-Encéphalique, there are changes in the function of glial protection with neuronal hyper excitability and this condition can occur in different circumstances, including trauma, stroke, infection, tumor and seizures themselves[7]. Generalized seizures are not prevalent in brain tumors. Focal seizures are more frequent and depend on the site location for its manifestation[8].

4. Epilepsy secondary to brain tumors in children

Epileptic seizures occur in 78% of the patients with oligodendroglial tumors, 92%-100% in neuroepithelial tumors, 20%-35% in metastatic tumors and 10% in primary CNS lymphoma[1].

Neuroepithelial tumors: commonly present in childhood with a peak in the second decade[9] and before age 20[10]. It frequently appears in the temporal lobe, with presentation of calcifications but no areas of necrosis and rarely malignancy transformation occurs. Epileptogenesis in these tumors has shown high levels of inotropic receptors and metabotropic glutamate[11,12]. The perilesional cortex plays a role in the onset of the seizures and this area may be considered to be surgically ressected if possible[13].

5. Ganglioglioma

This tumor represents 4.01% of all CNS tumors in the pediatric population, but it is one of the most frequently associated with epilepsy. They may cause focal epilepsy and is responsible for about 40% of the epileptogenic tumors in children[14-16]. It often occurs in infancy at an average of 8.5 years, and can also occur at any age. It appears anywhere in the CNS, including the spinal cord and cerebellum (Lhermitte-Duclos syndrome), but the most frequent site is the temporal lobe[14,15,17]. Lesions may present microcysts and calcifications. Ogiwara *et al*.[18] found in a retrospective study of 51 patients who had gangliogliomas that 58.8% had seizures and, in 83.3% of cases, they were complex partial seizures. They used the surgery as definitive treatment for epilepsy and EEG was also used intraoperatively. Twenty one cases were located in the temporal lobe. They reported that, if patients had active spikes or sharp attenuation on EEG, resection of adjacent tissues additionally to lesionectomy was performed. After 3.4 years of follow-up, seizure free was reported in 90% of cases, most of which were without antiepileptic drugs. Giulioni *et al*.[19] reported that the outcome after isolated lesionectomy to gangliogliomas in the temporal lobe were relatively worse than gangliogliomas outside the temporal lobe. Although it is still controversial, resection of the adjacent tissues may improve seizure control of these tumors[20].

6. Angiocentric glioma

This is a rare subtype of glioneuronal tumors[17] generally associated with refractory epilepsy[21]. It is typically located in the fronto-parietal cortex, having a slow growth rate[22]. In some cases it may spread to the ventricular wall.

7. Antiepileptic drugs for children with brain tumors

Treatment of the tumor correlates with the occurrence of seizures and the antiepileptic drug used may also have association with tumor control[23]. It is of paramount importance to understand many factors such as the pharmacology of the drug, tumor growth, tumor hyperactivity or resistance and their relationship with the medication

used to seizure control[23].

We reported a brief review of the main antiepileptic drugs used in CNS tumors and their mechanism of action.

7.1. Tricyclic derivatives

7.1.1. Carbamazepine

It stabilizes the presynaptic and post synaptic neuronal membrane acting on Na^+ channels causes a voltage-dependent hyperpolarization, longer reducing the possibility of emergence of new action potentials. It inhibits hydrogen ions Na^+, Ca^{++} to the cell through the N-methyl-D-aspartate receptor. Its absorption takes place in the digestive tract; it is metabolized in the liver and excreted in the urine without any change. Valproate, erythromycin and inhibit propoxyphene epoxide hydroxylase, thus increasing the levels of the active metabolite of carbamazepine. This drug is indicated in simple, complex partial seizures and generalized to a lesser extent[24] crisis.

7.1.2. Oxcarbazepine

Lock channels voltage dependent Na^+ increases the permeability modulates K^+ and Ca^{++} entry into the cell. Its absorption is complete and is not affected by the intake. The active metabolite is the 10-monohydroxy, responsible for the action of oxcarbazepine. Hepatic metabolism that has oxcarbazepine is indicated in partial epilepsies monotherapy and adjunctive therapy[24] or refractory to Carbamazepine epilepsies.

7.1.3. Hydantoins

Phenytoin blocks Na^+ channels voltage dependent, stimulates the activity of ATP in the Na^+/K^+ ATPase pump, decreases Ca^{++} entry into the cell and increases the action of GABA[24]. Its metabolism is strictly liver. It can present pharmacological interaction with antacids, calcium and enteral nutrition causing a reduction in the absorption of phenytoin. Increase in bioavailability of the drug when administered with carbamazepine or phenobarbital positions that these drugs compete for liver enzymes[24]. Valproate, isonacida and fluconazole decrease the concentration of oral anticoagulants, ACO, antiretrovirals and cyclosporine. This drug is used in simple, complex partial seizures and the generalized[24].

7.2. Barbiturates

Phenobarbital: agonist GABAA receptor, prolongs opening Cl^- channels causing hyperpolarization of the neuronal membrane. Blocks the entry of Ca^{++}, inhibits the release of excitatory neurotransmitters by reducing[24] such transmission. Intestinal absorption reaches a plasma concentration over a period of time of 1-3 h; a total of 25% of the drug is eliminated by the kidneys and the remaining 75% by liver enzymes, CYP-450. It is indicated in crisis in newborns, second line for generalized seizures except absence and used in partial seizures[24].

7.3. Others

1. Valproate: it increases the concentration of GABA, blocks Na^+ channels and inhibits neurotransmitters excitatory[24]. It presents a rapid and complete absorption VO, has active metabolites such as 3-glucuronide oxovalproato[24]. It is suitable for idiopathic generalized epilepsies, partial and generalized epilepsy, myoclonic and absence seizures[24].

2. Lamotrigine: lock channels Na^+-dependent voltage channels also blocks voltage-dependent Ca^{++}. It presents a complete oral absorption, which reaches maximum concentration in a time span of 1-3 h, hepatic metabolism and renal excretion. Enzyme inducers such as phenobarbital, phenytoin, carbamezepine reduce drug half-life and enzyme inhibitors such as valproate increases the half-life of the drug over 60 h[24]. It is indicated in the treatment of partial epilepsies photosensitive, primary generalized, cryptogenic and symptomatic[24].

3. Levetiracetam: GABAA receptor agonist and Cl^- current. It inhibits Ca^{++} channels and K^+[24]. It has an intestinal absorption, is hydrolyzed in the liver, plasma and other tissues; it is not related with the enzyme system cytochrome P450[24]. It is indicated as a treatment for partial epilepsies, possibly effective primary generalized seizures in photosensitive epilepsy[24].

4. Tiagabine: it increases the concentration of GABA in the synaptic space reversibly inhibiting the GABA transporter (GAT-1)[24]. VO complete absorption with a bioavailability of 96%, intake can slow its absorption but decrease the bioavailability of the drug, hepatic metabolism by CYP3A and renal elimination. It can be displaced by other drugs having high binding proteins such as albumin[24]. It is indicated for the treatment of partial epilepsies[24].

5. Topiramate: it blocks Na^+ channels thus achieving a decrease in repetitive neuronal firing, modulates the action of GABAA receptor, increases the flow of Cl^- into the cell, blocks glutamate receptor-amino-3-hydroxy-5 methyl-4-isoxazolepropionic[24]. It hyperpolarizes the membrane acting on K^+ channels, Ca^{++} channels blocks and inhibits carbonic anhydrase[24]. It has a 100% bioavailability, intake may delay its absorption, metabolized in the liver and eliminated by the kidneys. It is indicated as monotherapy or adjunctive therapy in partial epilepsy, idiopathic generalized epilepsies.

Young *et al*.[25] discusses several studies in which the focus was to test the effectiveness of anticonvulsant drugs in patients with brain tumors[25-28]. Anticonvulsant prophylaxis has demonstrated efficacy by 25%-50% in patients who have already undergone a craniotomy[25].

The effectiveness of prophylactic anticonvulsants in patients with brain tumors has been studied in many ways, prospective, double-blind[26]; in which the use of anticonvulsants according to the meta-analysis of Glantz *et al*. is not recommended[23, 26].

Another controversial point is the use of anticonvulsants in the peri operative period: the evidences are not clear and the guidelines of the American Academy of Neurology allow to use antiepileptic until

a week after craniotomy for tumor resection[26]. However, these recommendations were not primarily for pediatric patients.

Douglas *et al*.[29] conducted a study in 223 pediatric patients with brain tumors without previous crises, showed that at least 7.4% of patients had crisis in the perioperative period, of which 51% were supratentorial tumors, being the gliomas about 50% of the cases and the others were mainly composed by primitive neuroectodermal tumors. A total of 59% of patients were younger than 2 years and only 4.4% of patients received anticonvulsant prophylaxis; they consider not routinely prescribe anticonvulsant therapy in pediatric patients under 2 years, either in recently diagnosed with brain tumors or in the perioperative period.

In contrast, Sogawa *et al*.[30] conducted a retrospective study of 32 children with brain tumors, of which 21 patients received anticonvulsants, reported that 94% had temporary location supratentorial tumors in 70% of cases; in this study, levetiracetam was the drug most often used by the safety profile compared with phenytoin and oxcarbazepine, which suggested that antiepileptic drugs of the new generation should be considered as first-line prophylaxis in children with brain tumors.

Drug interactions of these medications should be considered: it has been well demonstrated that anticonvulsants can accelerate the clearance of antitumor agents[25] reducing its bioavailability[31]; *e.g.* valproate decreases the antitumor effects[31] through inhibition of histone deacetylase[25,32,33]. Patients receiving valproate had better benefits together with its antitumor therapy than patients receiving enzyme-inducing anticonvulsants[25,34]; moreover, the use of levetiracetam has increased dramatically and is not currently approved by the Food and Drug Administration as monotherapy in treatment of epilepsy in children but is an attractive drug for its low impact on the appearance of serious side effects and drug interactions especially with chemotherapeutic[25,35]. Additionally, phenytoin has been associated with Stevens-Johnson syndrome, severe erythema multiforme and toxic epidermal necrolysis[31] and also features interaction with some chemotherapy agents[36].

Another important aspect for which this therapy with antiepileptics in patients with brain tumors is not recommended that is class I evidence[26,34], is the low levels of anticonvulsant that have been reported in 60%-70% of patients[23,26,34]. Schaller *et al*.[23] pose a possible genetic explanation of anticonvulsant drugs, brain tumors and *MDR* gene. Specifically we are speaking of P-glycoprotein (P-gp) which carries lipophilic substances such as anticonvulsants through the hemotencefálica barrier[23]. The coding of the *MDR–1* gene is also associated with the P-gp rises in brain tissue thus demonstrating the drug resistance of patients' anticonvulsants[23]; another example to support this idea is the CC polymorphism C3435T genotype, which also showed resistance relation anticonvulsants[23].

The effectiveness of new anticonvulsants such as lamotrigine, oxcarbazepine, topiramate and levetiracetam in managing seizures has not been thoroughly investigated[34]. In patients who have seizures and concomitantly treatment with chemotherapeutic agents, anticonvulsants enzyme inducers should be avoided (level B evidence)[34].

8. Role of neuroimaging

Nuclear image such as positron emission tomography and single photon emission computed tomography (SPECT) are potentially useful for temporal lobe epilepsy secondary to tumors. Pre-ictal SPECT is more useful as hypoperfusion is better picked up with this scan. SPECT is repeated up to 4 h after seizuring.

9. Conclusions

Although there are many controversial issues involved anticonvulsants in children with brain tumors, prophylactic antiepileptic drugs are not recommended by the majority of the literature-even using new generations drugs.

There are scarce literature involving CNS tumors and epileptogenesis in children. Some studies suggested that those younger than 2 years were more likely to develop seizures, especially in the perioperative period.

It is essential that this group of patients should be handled by a multidisciplinary teams to make the best decision regarding the medical and surgical management of each specific case.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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