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BRAF inhibition efficacy in drug-refractory epilepsy

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Abstract

Low-grade gliomas (LGG) are the most frequent pediatric tumors associated with epilepsy. Molecular sequencing analyses have defined the genomic landscape of these tumors leading to the use of targeted therapies, which have proven to be efficacious. Ongoing clinical trials are testing the incorporation of these drugs, especially in unresectable LGG that progress after standard treatment. Nevertheless, this strategy is not extended in the field of tumor-induced epilepsy. We present a patient with drug-resistant epilepsy secondary to a BRAF V600E-mutated ganglioglioma treated with dabrafenib who showed a dramatic radiological and clinical response with marked improvement in her quality of life.

Introduction:

Low-grade gliomas can appear in any region of the neuroaxis. When located in particular areas of the brain, seizures can be a common manifestation at diagnosis. Characteristically, temporal-mesial and insular lobe areas tend to harbor such lesions (1). Not infrequently, tumor-associated epilepsy may be hard to control and even refractory to multiple antiepileptic drugs (AED). In the context of long-term epilepsy associated tumors (LEATS), extensive neurosurgical interventions are usually necessary to improve seizures control (2). Quality of life of children and adolescents under multiple AED and/or with post-surgical neurologic sequelae must be taken into consideration when proposing a treatment plan for these challenging patients. Frequently, these tumors tend to present an aberrant activation of MAPK signaling either through a *BRAF* tandem duplication or *V600E* mutation. The development and introduction of oral targeted therapies including*BRAF* inhibitors are changing the treatment paradigm for these patients. However, its clinical efficacy in tumor-associated epilepsy has not been reported.

Case report:

A previously healthy 12-year-old girl presented with a 12-month history of intermittent right facial paresthesias which occasionally extended to the right superior and inferior limbs, associated with variable tonic-clonic movements, headaches, and aphasia. Video-EEG monitoring showed left temporal/parietal ictal activity. A brain and spine magnetic resonance imaging (MRI) identified a lesion involving the left insular cortex and frontal operculum with extension into the deep white matter suspicious of low-grade glioma (Fig1A, 1B). The patient was started on 3 different AED without efficacy in seizures control. Furthermore, and secondary to her poor controlled epilepsy, she developed panic attacks and symptoms of anxiety and depression, isolating herself at home from friends and family. Ten days after the first scan, a functional MRI for language localization with diffuse tensor imaging (DTI) was performed. The lesion had significantly increased in size (Fig1C) and depicted a close relationship with language areas and major white matter tracts (arcuate fasciculus and corticospinal tract, Fig1D). Because of the high risk associated with a radical surgery, a stereotactic biopsy was performed without complications. The pathology review was consistent with a WHO grade 1

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ganglioglioma. The *BRAF p.V600E* mutation, in addition to monoallelic *CDKN2A* deletion was identified by using droplet digital PCR (ddPCR).

Treatment was initiated with dabrafenib at 150 mg BID. A few weeks into therapy, seizures frequency decreased and two months later, they stopped. After 4 months on dabrafenib, a follow-up MRI showed no evidence of disease (Fig2). After 14 months, AED were discontinued with no clinical signs nor epileptic activity in the EEG. Anxiety and depression symptoms decreased, and the patient was able to go back to her normal activities including school and sports. Therapy was overall well tolerated. However, because of fatigue and headaches, the dosage had to be decreased progressively to 75 mg BID with further good tolerance and compliance. She is still in complete remission and seizures free 30 months after diagnosis.

Discussion:

Long-term epilepsy-associated tumor (LEAT) is a challenge for pediatric epilepsy teams. This condition and the co-morbidities secondary to the lesion and associated with its treatment, result in long-term disabilities, psychosocial difficulties, and poor quality of life for these patients (2, 3).

Ganglioglioma and dysembryoplastic neuroepithelial tumor (DNET) are the most common tumors identified in LEAT patients that undergo surgery for seizures control, followed by other low-grade gliomas (1, 2, 4, 5). The co-existence of these LGG with focal cortical dysplasia (FCD) has been commonly described in LEATs. It has been suggested that the coincidence of both entities, in addition to the temporal lobe and neocortical location in younger patients at the onset of symptoms contribute to chronic and intractable epilepsy (3, 6, 7). Tumor directed therapies, such as chemotherapy or irradiation have been reported in a few case series without major impact on this condition (3, 8, 9). Therefore, in order to improve seizures control, complex neurosurgical interventions may be needed.

Dramatic technological advances in recent years have expanded our knowledge of the molecular landscape of pediatric brain tumors, moving the field towards precision diagnostics and targeted therapies.*BRAF V600E* mutation is identified in approximately 40% of LGG (4, 5, 10). Particularly, pleomorphic xanthoastrocytomas followed by gangliogliomas and DNETs harbor this mutation in almost 75%, 50%, and 25% respectively (6, 11-13). Of note, it has been also identified in FCD(14).

Remarkable clinical and radiological responses have been reported using*BRAF* inhibitors in the treatment of unresectable *BRAF V600E* mutated pediatric gliomas. In addition, several phase I and II clinical trials in children have demonstrated its effectiveness and safety with an acceptable toxicity profile. Consequently, its use is increasing with promising results (5, 15). However, the use of*BRAF* inhibitors in the context of intractable epilepsy has been suggested but not previously reported(6). Interestingly, Ko *et al*developed a mouse model demonstrating that the presence of *BRAF V600E* somatic mutation during early brain development contributes intrinsically to epileptogenesis(16). Therein, intraventricular vemurafenib was used, resulting in seizures control. Subsequently, other authors have supported the hypothesis that *BRAF* inhibition may be considered in patients with persistent post-surgical seizures when*BRAF* mutated lesions are identified after surgery (2, 8, 16).

In our patient, and because of the high risk of sequelae secondary to the tumor resection, we opted for starting treatment with dabrafenib. She presented a spectacular radiologic and most importantly clinical response, being able to recover her normal daily activities, without major toxicities. Of note, her seizures vanished, allowing the withdrawal of the AED.

This case is a good proof of principle that *BRAF* inhibition should be taken into consideration in the treatment of refractory epilepsy secondary to an unresectable *BRAF V600E* mutated LGG.

Additionally, because of the accumulated experience in the indication and management of these drugs, we suggest that pediatric oncologists should be involved in epilepsy units when discussing tumor-associated seizures.

Conflict of interest: Authors declare no conflict of interest.

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Figure legends:

Figure 1.

Initial MRI. A: axial 3D T1 with gadolinium, B: coronal FLAIR T2. Tumefactive white matter lesion with gadolinium enhancement (A) and subtle cortical component with

peripheral edema (B). A low-grade glioma was suspected.

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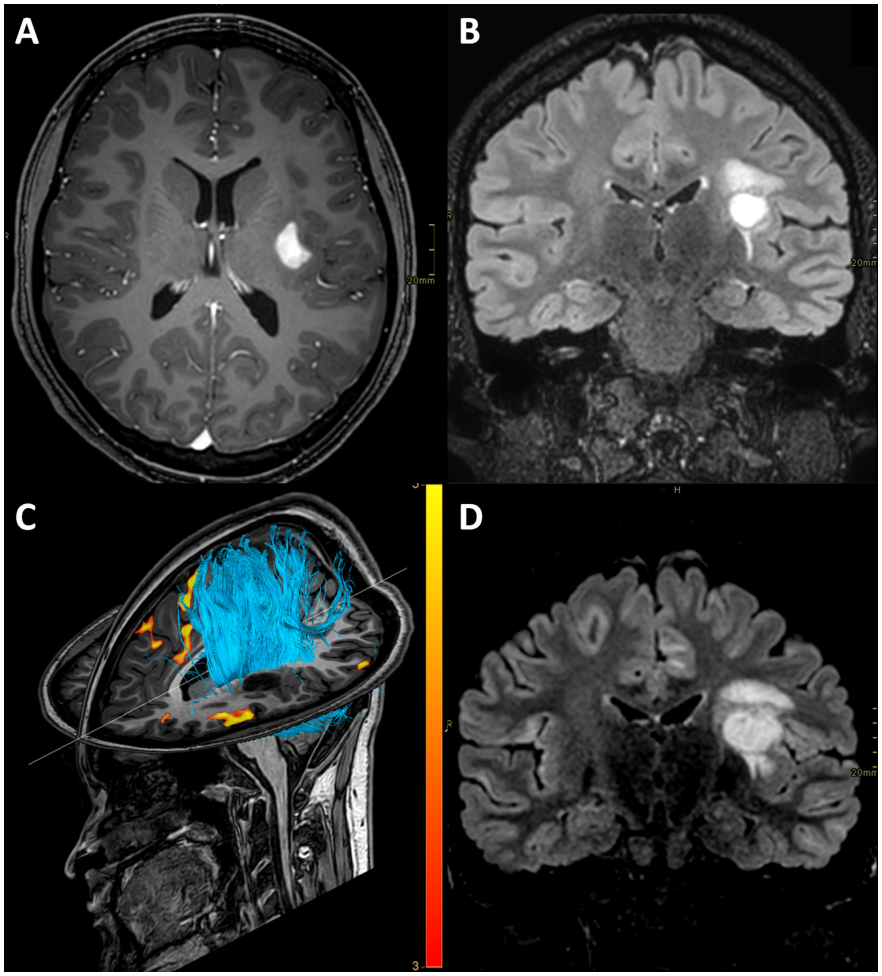
MRI study 10 days later. C: MPR 3D T1 with tractography of the pyramidal tract and language functional MRI (BOLD) study. D: coronal FLAIR T2. This second study was

performed to depict anatomic landmarks of the lesion with the pyramidal tract (blue in C) and language areas (yellow-orange areas in C). More tumefaction and edema

was also found in just 10 days (D).

Figure 2.

1. Axial 3D T1 with gadolinium. MRI before stereotactic biopsy.
2. Axial 3D T1 with gadolinium 4 months after treatment. The lesion has almost disappeared and there isn't any enhancement.
3. Axial 3D T1 with gadolinium 8 months after treatment shows the same findings as in B.



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