Low-grade glioneuronal tumour with novel molecular features associated with unusual partial epilepsy in a child

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DESCRIPTION

A 10-year previously healthy boy presented with unusual episodes of recurrent frontal headaches lasting 30 s associated with the abnormal smell that would occur several times per week. He had no focal weakness, sensory changes or loss of consciousness during the episodes and had a non-focal neurological examination. He was seen in the emergency room for intractable headache where MRI for brain was performed that revealed a T2-hyperintense left mesial temporal lobe mass without enhancement (figure 1). He was subsequently admitted and underwent a robotic-guided stereotactic biopsy that demonstrated a moderately cellular proliferation of round cells with round nuclei, perinuclear halos and a myxoid background, with a small number of scattered admixed mature neurons. Neuronal cells seen appeared irregularly scattered and surrounded by myxoid material, without satellitosis by smaller cells, and were interpreted as a component of the lesion. A small number of scattered mitotic figures were seen without vascular proliferation or necrosis and the Ki-67 labelling index ranged from 1% to 5%. Overall the constellation of histopathological findings was most consistent with a diagnosis of low-grade glioneuronal tumour with features of dysembryoplastic neuroepithelial tumour (figure 2). DNA-based next-generation sequencing panel consisting of 397 cancer-related genes as previously described,1 performed on paraffin-embedded formalin-fixed tumour revealed no reportable mutations and variant of unknown significance of KAT6A. However, chromosomal microarray analysis revealed hyperdiploidy with 77 kb loss at 7q34 encompassing BRAF exons 2–9. In addition there were single copy gains (chromosomes 2,3,10,12,14,16,17,19,20) and high copy gains (chromosomes 6–9, 3q13.2-q13.31).

Following surgery, the patient had continued auras that prompted unsuccessful treatment with two anticonvulsant therapies. A prolonged video electroencephalogram (EEG) captured several olfactory auras associated with headache; however, there was no electrographic seizure correlate seen on surface electrodes. The patient is undergoing workup for intractable epilepsy that includes stereotactic EEG recordings given the deep-seeded tumour location. Follow-up neuroimaging 1 year after diagnosis reveals no evidence of tumour recurrence or progression.

Paediatric low-grade gliomas are the most common brain tumours of childhood and are driven by genetic alterations in the RAS/mitogen-activated protein kinase pathway.2–4 Two-thirds of

Figure 1 Axial fluid-attenuated inversion recovery MRI sequences (A) demonstrated a hyperintense mass involving the left amygdala and hippocampus without enhancement on postgadolinium sequences (B).

Figure 2 (A) H&E staining of the tumour revealed a moderately cellular proliferation of round cells with round nuclei, perinuclear halos and a myxoid background, with a small number of scattered admixed mature neurons. Neuronal cells seen appeared irregularly scattered and surrounded by myxoid material, without satellitosis by smaller cells, and were interpreted as a component of the lesion. A small number of scattered mitotic figures were seen without vascular proliferation or necrosis. (B) The Ki-67 labelling index ranged from 1% to 5%. Overall the constellation of findings is consistent with a diagnosis of low-grade glioneuronal tumour with overlapping features of dysembryoplastic neuroepithelial tumour.

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paediatric low-grade gliomas contain alterations in NF1, BRAF-KIAA1549 fusions and BRAFV600E mutations. However, mutations in FGFR, MYB and other single nucleotide variants and rearrangements have been identified. Paediatric low-grade gliomas with gene rearrangements have improved progression-free survivals than those with single nucleotide variants. The targeted mutations have led changes in management using biologics in the treatment of paediatric low-grade glioma. The deletion involving exons 2–9 of BRAF, which includes the Ras-binding domain, has been described as a possible mechanism of resistance to B-Raf Proto-Oncogene, Serine/Threonine Kinase (BRAF) and Mitogen-activated protein kinase kinase (MEK) inhibition in other non-central nervous system tumours. It is unclear what the clinical ramifications of the BRAF exon 2–9 deletion identified would be in the case of a low-grade glioneuronal tumour in the absence of RNA sequencing data. Our case highlights the limitations of detecting some BRAF alterations by next generation sequencing, especially in cases of large deletions and the potential utility of microarray in the appropriate clinical setting. In summary, the novel histological and molecular features expand the current knowledge and highlight the genetic and clinical diversity of paediatric low-grade glioma.

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