Ganglioglioma with novel molecular features presenting in a child with Allan-Herndon-Dudley syndrome

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DESCRIPTION

A boy with hemizygous *SLC16A2* variant (Xq13.2; p.R371C) Allan-Herndon-Dudley syndrome (AHDs) presented with new-onset seizures. Physical examination revealed normal contour of the cranium and a normal hairline. The face exhibited a long and narrow profile, but individual features were unremarkable in size, shape or position. Neurological examination was notable for central hypotonia and developmental delay. MRI demonstrated a T2-hyperintense, T1-isointense cortical lesion along the left inferior mesial temporal lobe consisting of cystic and solid components, without reduced diffusivity, and multiple solid enhancing nodules on postgadolinium sequences (figure 1). The neuroradiographic differential diagnosis included ganglioglioma, dysembryoplastic neuroepithelial tumour and pleomorphic xanthoastrocytoma, with lesser consideration for pilocytic astrocytoma. A stereotactic biopsy of the lesion was performed, and neuropathological evaluation revealed biphasic neoplastic architecture comprising regions of densely compact eosinophilia and other, more microcystic, areas (figure 2A).

Figure 2 Neuropathological features of the ganglioglioma. (A) H&E staining showing moderately cellular mixed proliferation of glial and neuronal cells with extensive mixed calcification. A rare mitotic figure (<1/10 per high-power field; Ki-67 ~2% of tumour cells) and perivascular lymphocytic cuffing were identified. (B) NeuN immunohistochemistry showing atypical neuronal cells highlighted with clustering and binucleation; background cells were positive for glial fibrillar acidic protein (not shown). 400x magnification; scale bar=50 µm.

Piloid cells and a fibrillar background with focal Rosenthal fibres were visible within the compact eosinophilic areas. Large dysmorphic ganglion cells with vesicular chromatin were interspersed throughout the tumour, in addition to intermixed lymphocytic infiltrates. No significant mitotic activity, necrosis or microvascular proliferation were observed. Immunostaining revealed a mixed population of neoplastic cells, with some neoplastic cells and the fibrillar background immunopositive for glial fibrillar acidic protein and other neoplastic cells immunopositive for synaptophysin and NeuN (figure 2B). Sparse (2%) Ki-67 immunopositivity and numerous leucocytes positive for leucocyte common antigen were detected; BRAF p.V600E was not observed (not shown). Microarray analysis and next-generation sequencing (NGS) of tumour tissue detected no clinically significant abnormalities. However, NGS revealed six variants of uncertain significance in *PBRM1* (c.3505C>G), *FAT1* (c.4434C>G), *TRRAP* (c.3636G>C), *TSC1* (c.3008C>T), *DDIT3* (c.466C>T) and *SOX9* (c.769C>T). The functional pathogenic likelihood of each variant, according to the American College of Medical Genetics and Genomics guidelines,¹ was predicted using the InterVar tool based on human reference genome hg38.^{2,3} The mutations in *PBRM1*, *FAT1*, *TSC1* and *DDIT3* were classified as 'pathogenic', while those in *TRRAP* and *SOX9* were predicted to be 'benign'. Overall, the neuropathological findings were considered most consistent with a diagnosis of ganglioglioma (WHO Grade 1), a rare central nervous system (CNS) tumour.⁴ The patient remains stable under neuroimaging

Figure 1 Neuroimaging features of a ganglioglioma in a child with Allan-Herndon-Dudley syndrome. Fluid-attenuated inversion recovery MRI sequence reveals a diffuse infiltrative left temporal lobe tumour (A), without reduced diffusivity (B), and multiple areas of punctate enhancement on postgadolinium sequences (C, D).

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observation more than 2 years postdiagnosis and seizure-free on antiseizure therapy.

AHDS is caused by loss-of-function mutations in X-linked *SLC16A2*,⁵⁻⁹ which encodes a transporter specific for thyroid hormone delivery to the developing brain.^{10 11} Cerebral hypothyroidism is severely detrimental to neurodevelopment,^{12 13} and clinical supplementation with thyroid hormone or its derivative has produced mixed results.¹⁴⁻¹⁷ AHDS consequently exhibits a profound, heterogeneous clinical presentation featuring craniofacial deformity, intellectual disability and neurological abnormalities including seizures, developmental delay and impaired mobility.^{18 19} We report the first case of a ganglioglioma—and perhaps the first CNS tumour overall—in a paediatric patient with AHDS. Although gangliogliomas preponderantly exhibit *BRAF* mutations, particularly p.V600E,²⁰⁻²⁴ that activate MAP kinase pathways,^{21 25} these were not observed in our patient's ganglioglioma, which presented a novel mutation profile. Gangliogliomas are proposed to arise from dysplastic clonal precursors,^{26 27} and thyroid hormone preeminently influences neural stem cells and progenitors.²⁸⁻³⁰ However, whether AHDS pathophysiology influenced emergence of the ganglioglioma in this patient or it arose stochastically is indeterminate and may be worthy of future investigation.

Learning points

- ▶ Allan-Herndon-Dudley syndrome (AHDS) is a multisystemic developmental disorder characterised by a heterogeneous clinical presentation that can include craniofacial deformity, severe intellectual disability and neurological abnormalities.
- ▶ AHDS results from loss-of-function mutations of *SLC16A2*, an X-linked gene that encodes a transporter to deliver thyroid hormone to the brain during development.
- ▶ We present the first case of a ganglioglioma with novel molecular features in a patient with AHDS that may be worthy of future investigation.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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