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

Jason W Adams,1 Denise Malicki,2 Michael Levy,3 John Ross Crawford4

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 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).

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 pilocytic acidic protein (not shown). 400× magnification; scale bar=50 µm.

Figure 2 Neuropathological features of the ganglioglioma. (A) H&E staining showing moderately cellular mixed proliferation of glial and neuronal cells with extensive 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 fibrillary acidic protein (not shown). 400× magnification; scale bar=50 µm.

The patient remains stable under neuroimaging...
Observation more than 2 years postdiagnosis and seizure-free on antiseizure therapy.

AHDS is caused by loss-of-function mutations in X-linked SLC16A2, which encodes a transporter specific for thyroid hormone delivery to the developing brain. Cerebral hypo-thyroidism is severely detrimental to neurodevelopment, and clinical supplementation with thyroid hormone or its derivative has produced mixed results. AHDS consequently exhibits a profound, heterogeneous clinical presentation featuring craniofacial deformity, intellectual disability and neurological abnormalities including seizures, developmental delay and impaired mobility. 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, that activate MAP kinase pathways, these were not observed in our patient’s ganglioglioma, which presented a novel mutation profile. Gangliogliomas are proposed to arise from dysplastic clonal precursors, and thyroid hormone preeminently influences neural stem cells and progenitors. 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.

Contributors JWA was responsible for the design and drafting of the case report. DM was responsible for the design and drafting of the case report. ML was responsible for the design and drafting of the case report. IRC was responsible for the design and drafting of the case report. Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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.

REFERENCES
