Low-grade glioma with novel mutations in *KRAS* and *PMS2* in an adolescent with Down syndrome

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DESCRIPTION

A 12-year-old boy with Down syndrome (DS), myeloproliferative disorder and autism spectrum disorder presented for new-onset seizures. The patient did not report any headaches, weakness, nausea or vomiting, and neurological examination was non-focal. MRI revealed a mixed solid and cystic 13 mm mass with surrounding vasogenic oedema immediately lateral to the posterior horn of the left lateral ventricle in the periatrial white matter (figure 1). The mass lesion was similar in appearance to the adjacent choroid plexus cyst and demonstrated contrast enhancement without reduced diffusivity. Neuroradiographic differential diagnosis included low-grade astrocytoma, gangliocytoma or ganglioglioma. The patient underwent robotic-guided biopsy and laser ablation. Neuropathology revealed a hypercellular tumour with angiocentric proliferation consisting of spindle-shaped to ovoid-shaped cells with pale cytoplasmic nuclei and scattered inclusions. Denser areas of the neoplasm, comprising astrocytes with a dense fibrillar matrix, contrasted with looser areas consisting of more widely spaced cells separated by an oedematous to myxoid stroma (figure 2). Scattered Rosenthal fibres and eosinophilic granular bodies were observed, as well as rare mitotic figures. No significant necrosis was appreciated. Immunohistochemistry showed diffuse positivity for glial fibrillar acidic protein and weak positivity for synaptophysin. Sparse (1%–2%) tumour nuclei stained Ki67+. Immunostaining for epithelial membrane antigen was negative. Next-generation sequencing (NGS) revealed three novel clinically significant variants, two in *KRAS* (c.64C>A and c.35G>C) and one in *PMS2* (c.538-2A>G). NGS likewise detected multiple variants of unknown clinical significance, within genes including *TAF1, RARA, DNMT3A, ITK, KIF5B, CHD4, AKT1* and *GRIN2A*; no *BRAF* mutation or fusion was detected. Microarray analysis was consistent with constituent trisomy 21 but otherwise detected no clinically significant abnormalities. The complete neuropathological profile was most consistent with a diagnosis of low-grade glioma (WHO grade I), histologically favouring pilocytic astrocytoma. Follow-up imaging has shown no evidence of residual or recurrent tumour within 18 months after laser ablation, and the patient remains seizure-free on anticonvulsant medication.

DS is associated with an altered neoplastic risk profile and may influence the frequency of particular types of brain tumours.[1–6] Cases of glioma in DS occur rarely,[2 3 7–11] and whether DS affects glioma behaviour is unclear. We present a rare case of low-grade glioma with novel *KRAS* and *PMS2* mutations in an adolescent with DS. Low-grade gliomas nearly exclusively harbour mutations that upregulate the Ras/MAPK pathway.[12–15] Of these, only a slight proportion (<1%) involves the pathway effector *KRAS*,[16] heightening surprise at the dual novel *KRAS* mutations observed in the present case. Mutation of the DNA mismatch repair gene *PMS2* has previously been documented in hypermutated paediatric high-grade glioma,[17] suggesting that its

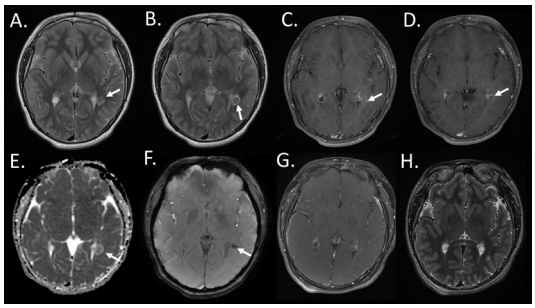

Figure 1 Neuroimaging features of a low-grade glioma in a patient with Down syndrome. T2-weighted MRI (A, B) reveals a left-sided periventricular hypointense mass (arrows) adjacent to a choroid plexus cyst with rim-like enhancement (C, D) on postgadolinium sequences, no evidence of reduced diffusivity on apparent diffusion coefficient sequences (E) and susceptibility weighted artefact (F). The tumour had similar appearance as the normal adjacent choroid plexus cysts (G,H).

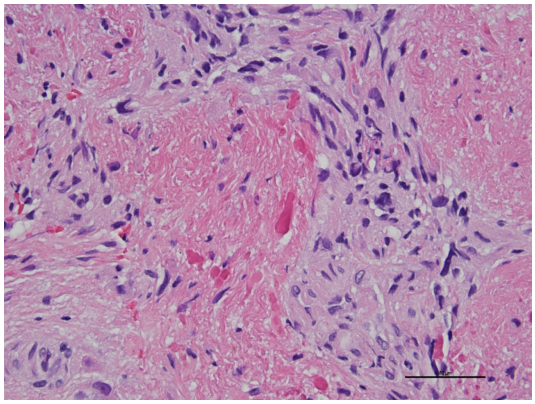

Figure 2 Neuropathology of a low-grade glioma in a patient with Down syndrome. H&E-stained section showing a low-grade glial neoplasm characterised by a proliferation of elongate cells with mildly pleomorphic and variably hyperchromatic nuclei growing predominantly in perivascular spaces, accompanied by Rosenthal fibre formation. A rare mitotic figure was seen. 400× magnification.

mutation in the low-grade neoplasm here may be permissive of mutational burden. Future investigation should further explore the mutational landscape of glioma in DS.

Learning points

- Low-grade gliomas are nearly universally associated with mutations in the Ras/MAPK pathway, but mutations in *KRAS* comprise a very small proportion (<1%)
- The occurrence of central nervous system tumours in association with Down syndrome is rare, and the mechanism of the role, if any, for trisomy 21 is unclear.
- We report the case of low-grade glioma with a unique molecular profile in association with Down syndrome, expanding the genetic complexity of low-grade glioma.

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