CASE REPORT

Glioblastoma in a boy with fragile X: an unusual case of neuroprotection

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Glioblastomas in children usually occur in the brainstem and are often untreatable and associated with an extremely poor prognosis. Such tumours may however occur in supratentorial locations more typically associated with adult gliomas, where the outcome is more variable, but still poor. We report the case of a boy with fragile X who also developed an inoperable midbrain glioblastoma, but who has survived 8 years after diagnosis.

The boy had severe learning difficulties and large stature due to fragile X, as shown by DNA analysis at the age of 2 years 8 months with the karyotype being 46 XY Fra [X] [q27]. At time of diagnosis he weighed 21 kg (99th centile), with height 101 cm (99th centile) and head circumference 51 cm (80th centile). He was an adopted child and his birth mother had moderate learning difficulties. At 10 years of age he started to have periods of headaches, vomiting and drowsiness, culminating in an episode lasting 24 h in association with a mild left hemiparesis. MRI demonstrated significant dilatation of the supratentorial ventricles with a poorly defined mass in the region of the third ventricle.

A right ventriculoperitoneal shunt was inserted to relieve the hydrocephalus together with neuroendoscopic biopsy of the third ventricular mass, which proved non-diagnostic. CSF cytology was negative as were the germ cell tumour makers. A presumptive diagnosis of low-grade astrocytoma was made. The tumour was not amenable to excision in view of the site and involvement of critical structures and an expectant course of management was followed. Yearly repeat scans showed the tumour size remained static. The patient stayed healthy, apart from one episode of isolated left ventricle hydrocephalus due to

obstruction by the tumour, which was relieved by endoscopic pellucidotomy.

Four years later, at the age of 14, the patient developed a gradual reduction of consciousness and became bed bound. A repeat scan demonstrated an increase in tumour size (from 32×32×45 mm to 45×55×53 mm) (figs 1 and 2). The tumour was still considered inoperable, but a stereotactic biopsy was performed to help determine future management. Histology surprisingly revealed the tumour to be a highly malignant glioblastoma (grade 4) (fig 3), which was pleomorphic with necrosis, vascular proliferation and significant numbers of mitoses. In view of the extremely poor prognosis, and the fact that the patient was comfortable without any distressing symptoms, palliative care was arranged with 24 h nursing at home. To the surprise of all, 6 weeks later the patient slowly began to recover and returned to his normal state.

Two years later at age 16 he remained well apart from an occasional headache and repeat MRI showed that the tumour had regressed slightly in size (to 4×5×5 cm). At age 17 his shunt became blocked, requiring revision. Aged 18, he remains well with no specific neurological abnormality 8 years after the initial diagnosis; repeat CT scan shows considerable calcification of the tumour, which has stayed the same size.

DISCUSSION

Malignant astrocytoma, or glioblastoma, is often locally invasive and extensively infiltrative. Complete surgical resection is not usually a realistic goal and adjuvant therapy with radiotherapy and chemotherapy is typically considered in an attempt to restrict the growth of the tumour whilst recognising that none of these of treatment can offer a long-term cure.^{1 2} These tumours occur most commonly in adults, who generally have a life expectancy of less than 2 years after diagnosis. Prognosis is thought to be better in children and young adults

Figure 1 MRI coronal view of the brain showing the tumour in the midline at 14 years of age.

Figure 2 MRI sagittal view of the brain at 14 years of age.

Figure 3 Histopathology slide: cellular astroglial tumour showing microvascular proliferation and thrombosis.

with glioblastoma. Sneed *et al*³ reported a number of patients aged 18–30 surviving to 3 years and beyond, but this was following surgical resections and radiotherapy. Potential reasons for these results may include genuinely different biological behaviour of the tumour in younger populations and also inaccuracies in the original diagnosis. Indeed, subsequent re-examination of histological specimens from patients surviving an unexpectedly long time with tumours previously diagnosed as high grade gliomas has occasionally led to rediagnosis of the tumour as a pleomorphic xanthoastrocytoma (Dr K Robson, Consultant Neuropathologist, Nottingham, personal communication). Notably in this case, the biopsy specimens have been independently reviewed 2 years after the original biopsy and are still felt to be entirely consistent with high-grade glioma.

In our patient, the reduction in size and increasingly multicystic nature of the tumour with calcification implies a degree of autoinfarction, perhaps due to torsion on a vascular pedicle or growth outstripping its blood supply. The absence of FMRP (fragile X mental retardation protein) might have played a role in the growth of the tumour. Our patient was most unfortunate in having fragile X and then developing a

glioblastoma, two completely unrelated conditions. However with genetic abnormality affecting intercellular communication, fragile X does involve a mild connective tissue disorder with hyper-elasticity. It is possible that this may have led to either a cytogenetically or a physically unusual tumour in our patient, which has protected him from its full impact. A most fortunate form of neuroprotection; two wrongs can sometimes make a right.

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