CASE REPORTS

Paraneoplastic Ophthalmoplegia as the Presenting Sign of Paediatric Glioblastoma Multiforme: A Case Report

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ABSTRACT

Glioblastoma multiforme (GBM) is an aggressive glioma that is infrequently diagnosed in the paediatric population. GBM and other primary brain tumours have rarely been associated with paraneoplastic syndromes. We report an unusual case of an 8-year-old boy presenting with an inability to abduct his left eye and almost complete ophthalmoplegia of his right eye, prior to any radiological evidence of GBM. This is the first documented case of paediatric GBM presenting with bilateral asymmetric ophthalmoplegia.

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Introduction

Glioblastoma multiforme (GBM) is an aggressive glioma and is the most lethal primary central nervous system malignancy found in adults.¹ GBM is relatively rare in paediatric populations,^{2–5} resulting in a paucity of literature describing the clinical course of paediatric GBM. There are documented cases of paediatric GBM presenting with altered sensorium, hemiparesis, aphasia, vomiting, headache, diplopia, vertigo, and seizures.^{6,7}

Paraneoplastic syndromes are a set of signs and symptoms resulting from organ and tissue damage distinct from the site of a primary tumour or its metastases.⁸ Most cases of paraneoplastic syndrome affecting the nervous system are autoimmune-mediated processes, leading to damage of non-cancerous tissues expressing an antigen that the immune system recognises as ‘foreign’.⁸ Paraneoplastic syndromes have rarely been found to be associated with primary brain malignancies, including GBM.^{9–11}

We report the first documented case of GBM presenting with bilateral asymmetric ophthalmoplegia in a paediatric patient. The tumour was supratentorial with no brainstem involvement, suggesting a paraneoplastic cause for the ophthalmoplegia.

Case description

An 8-year-old boy with a history of attention deficit hyperactivity disorder was noticed by his mother to have increased prominence of both eyes. Over the next few weeks, he developed an upper respiratory tract infection, followed by double vision, and began dragging his left foot. Initially, he could not abduct the left eye, but the right eye moved normally. A week later, he developed almost complete ophthalmoplegia of the right eye. He also had frequent headaches, loss of appetite, but no nausea or vomiting. On initial examination, his visual acuity was 20/25 in both eyes with no relative pupillary afferent defect (RAPD). He had a normal slit lamp exam and normal optic discs. In the right eye, there was almost complete ophthalmoplegia, with a small amount of preserved vertical movement. In the left eye, there was lid retraction and loss of abduction, with relative preservation of adduction, supraduction and infraduction (Figure 1a). No further eye movements were elicited by Doll’s head manoeuvre. Neurologic exam revealed mild facial diplegia, palatal weakness, left upper and lower limb weakness, left arm ataxia and bilateral hyperreflexia.

Initial magnetic resonance imaging (MRI) showed two small poorly defined non-enhancing areas of T2 and fluid-attenuated inversion recovery (FLAIR)

Figure 1. Eye movements (a) at presentation and (b) 7 months later. At presentation, there was questionable ptosis and almost complete loss of horizontal and vertical movements in the right eye. In the left eye, there was lid retraction and loss of abduction, with relative preservation of adduction, supraduction and infraduction. At 7 months after presentation, there was bilateral ophthalmoplegia with minimal vertical and horizontal movement of either eye. Lid retraction was more prominent.

hyperintensity and possible increased bulk in the posterior right medial frontal lobe (Figure 2), consistent with infection, inflammation, or a low-grade neoplasm. It was felt that these changes were not related to his ophthalmoplegia and thus no biopsy was pursued. Lumbar puncture and full body computed tomography were unremarkable. Negative laboratory investigations included thyroid peroxidase antibodies, thyroid stimulating hormone, free-T3, free-T4, neuromyelitis optica antibodies, anti-neutrophilic cytoplasmic autoantibodies, acetylcholine receptor antibodies (ARAB), muscle-specific kinase (MuSK) antibodies, cryoglobulins, anti-GQ1b, C-reactive protein, anti-phospholipid antibodies, Borrelia serology, anti-glutamic acid decarboxylase (GAD) antibodies, anti-N-methyl D-aspartate receptor (NMDA-R) antibodies, and a paraneoplastic panel (including anti-Hu, anti-Yo, anti-Ri, anti-amphiphysin, and anti-MA). Anti-GAD, anti-NMDA-R, and the paraneoplastic

panel were also tested in the cerebrospinal fluid and were negative. Electromyography and nerve conduction studies were performed, including repetitive nerve stimulation, and showed no decrement or increment and normal velocities and amplitudes. Abnormal bloodwork included a mildly elevated erythrocyte sedimentation rate of 18 mm/hr, respiratory syncytial virus, and anti-RO autoantibodies.

The patient was treated with three courses of intravenous immunoglobulin, seven courses of plasmapheresis and 5 days of intravenous methylprednisolone followed by oral prednisone with mild improvement in his left-sided weakness and headaches, but no change in the ophthalmoplegia. A repeat MRI of the brain and spine remained unchanged.

He was readmitted 3 months after his initial presentation with progression of his symptoms and found to have new T2 and FLAIR hyperintensity

Figure 2. FLAIR MRI (a) axial section and (b) coronal section at presentation. An ill-defined hyperintensity at the right cingulate gyrus was present. No enhancement was seen with gadolinium (not shown).

around the occipital horns on MRI. Despite the change in imaging, a brain biopsy was not performed due to the presumed benign nature of the lesion and the procedural risk involved.

Repeated admissions, investigations, and imaging were performed with no new abnormalities found until 7 months after his initial presentation, when he had significant worsening of his left leg weakness resulting in frequent falls, word-finding difficulties, disinhibited behaviour, and urinary incontinence. His visual acuity remained 20/20 bilaterally, but there was now bilateral impairment of vertical and horizontal movements of both eyes (Figure 1b). He had a right exotropia of 10–18 prism dioptres depending on his head position, and the left lid retraction was slightly more prominent. Both optic discs were moderately swollen, left more than right, with a mild left RAPD. MRI showed an ill-defined area of T2 hyperintensity involving the right cingulate gyrus.

Over the course of the next month, his neurological status continued to decline with worsening left-sided weakness, increased reflexes, left facial droop, dysphagia, and urinary incontinence. Further, MRI (Figure 3a,b) revealed the presence of a new heterogeneous, ring-enhancing cystic lesion prompting a brain biopsy which revealed GBM, which was isocitrate dehydrogenase one (IDH1) negative and p53 mutated (Figure 4). Due

to increasing intracranial pressure, a decompressive right craniectomy was performed with further debulking of the tumour mass. He was treated with temozolomide, lomustine, and whole brain radiation, but passed away 18 months after presentation. An autopsy was not performed.

Discussion

GBM is a lethal glioma that is rare in the paediatric population.^{2–5} To the best of our knowledge, this is the first reported case of a paediatric GBM presenting with bilateral asymmetric ophthalmoplegia. As no tumour location could explain the eye movement abnormality, we propose that the ophthalmoplegia was a paraneoplastic phenomenon. This conclusion was reached after careful expert neuroradiological review of thin brainstem slices including pre- and post-contrast T1, T2, and FLAIR (Figure 3c,d).

Malignant gliomas are known to invade diffusely throughout the entire brain, and so direct tumour infiltration could not be excluded despite lack of visible abnormalities on multiple MRIs.¹² We systematically considered anatomic locations which would cause our patients findings, even in the absence of visible tumour on imaging. A possible mechanism in this case was direct infiltration of tumour cells into cranial nerves. At initial presentation, the eye movement abnormalities could be described as a left 6th

Figure 3. FLAIR MRI (a) axial section and (b) coronal section 9 months after presentation. A heterogeneous, ring-enhancing (not shown) cystic lesion with surrounding oedema was seen, consistent with GBM. The brainstem was completely normal, as shown in representative images (c) coronal T1 post-contrast and (d) axial fast spoiled gradient echo sequence.

nerve palsy, followed by a right 3rd, 4th and 6th nerve palsy, sparing the lid and pupil. A total of 19 patients with glioma and direct infiltration of cranial nerves have been reported, with two cases involving the 3rd cranial nerve, and none involving the 4th or 6th nerves.¹³ Unlike in our case, there was radiological confirmation of infiltration in all but three patients, who were reported prior to widespread use of modern imaging. The disproportionate impairment of the extraocular muscles compared to the levator palpebrae muscle also argues against a fascicular 3rd nerve palsy.

Involvement of the cranial nerve fascicles also does not explain the contralateral lid retraction, and so we considered the possibility of a nuclear lesion, sparing the levator subnucleus. A phenomenon termed the plus-minus lid syndrome describes contralateral lid retraction in a nuclear third nerve palsy due to a lesion of the nucleus of the posterior commissure (NPC).^{14,15} Lid retraction is thought to occur as a result of failure of inhibitory signals normally sent

to the levator palpebrae superioris nucleus by the NPC. In these cases, complete ipsilateral ptosis was reported, suggesting that the lid retraction would not overcome the ptosis from a complete 3rd nerve palsy.

Another possible mechanism of action could involve the neuromuscular junction, as seen in myasthenia gravis (MG) or Lambert-Eaton myasthenic syndrome (LEMS). LEMS is an autoimmune disorder, most often occurring as a paraneoplastic phenomenon in small cell lung cancer, whereby patients develop autoantibodies against the voltage-gated calcium channels (VGCC) of the neuromuscular junction.¹⁶ Symptoms of fatiguable weakness can mimic MG, however, ocular and bulbar weakness is not consistent with LEMS,¹⁷ which usually presents with leg weakness, areflexia, and autonomic dysfunction.¹⁶ Our patient was hyperreflexic, had normal nerve conduction studies, including repetitive nerve stimulation, negative ARAB and MuSK antibodies, and was unresponsive to corticosteroid and IVIG therapy, which will often provide at least

Figure 4. Histopathology from a brain biopsy 9 months after presentation: haematoxylin and eosin stain (a) demonstrating microvascular proliferation (arrow) and palisading necrosis (arrowhead) consistent with GBM. Numerous tumour cells expressed cytoplasmic and fibrillary GFAP (glial fibrillary acidic protein) (b), but were negative for IDH1-R132H (isocitrate dehydrogenase) (c). The majority of nuclei were positive for ATRX (alpha-thalassemia/mental retardation, X-linked) (d) and tumour protein p53 (e). NFP (neurofilament protein) can highlight the infiltrative nature, but was negative among neoplastic cells (f). The Ki-67 index was greater than 50% (g).

temporary improvement in MG.¹⁸ The pattern of presentation, the normal repetitive nerve stimulation, the lack of clinical fatiguability of weakness, and the negative myasthenia antibodies make a neuro muscular junction disorder highly unlikely.

Our patient presented with lid retraction and bilateral ophthalmoplegia without significant ptosis that could not be localised. Only 7 months later was the diagnosis of GBM discovered. We propose that

the aetiology for the abnormal eye movements was a paraneoplastic phenomenon, despite the absence of known paraneoplastic antibodies. Paraneoplastic syndromes have rarely been described in primary brain tumours,^{1,9} including a case report of Guillain-Barré syndrome (GBS) in a patient undergoing chemotherapy for GBM.¹¹ As well, in a study of 33 patients with primary brain tumours, including 15 with GBM, abnormalities were detected in

both sensory and motor peripheral nerves compared with controls, but no antineuronal antibodies were found.⁹ Our patient's extra-ocular movement abnormalities were consistent with patchy involvement of his cranial nerves, suggestive of an inflammatory aetiology rather than neoplastic invasion. Furthermore, he presented with signs and symptoms consistent with lower motor neuron lesions, including facial weakness, limb weakness, and sensory ataxia. This diffuse and patchy constellation of findings is reminiscent of a GBS-type syndrome,¹⁹ which has previously been reported to occur in the context of GBM. We therefore propose that our patient developed ophthalmoplegia as the result of a yet uncharacterised antibody against peripheral motor nerves. This case illustrates that ophthalmoplegia, as a paraneoplastic phenomenon, may present prior to radiological evidence of GBM and this presentation should prompt a clinician to consider GBM in their differential diagnosis.

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Declaration of interest statement

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