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CASE REPORT

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Ophthalmic Presentation of Diffuse Intrinsic Pontine Glioma in Children (Case Series and Literature Review)

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ABSTRACT

Diffuse intrinsic pontine glioma (DIPG) is a rare aggressive brainstem lesion, affecting mainly young children. This report describes sixth cranial nerve palsy as the initial ophthalmic presentation in children with this pathology. Case series and literature review. All children presented with sixth nerve palsy were consecutively recruited from the pediatric clinic at the East Sussex NHS Healthcare Trust within the last 10 years. Full ophthalmic examination, orthoptic assessment, and refraction check were done in three patients. Magnetic Resonance Imaging was carried out using 1.5 Tesla (Siemens Symphony, Erlangen, Germany) to establish the diagnosis.The patients' age ranged from 5 to 14 years at the time of presentation. All presented with sudden onset esotropia and limited abduction, suggestive of presence of sixth nerve palsy, requiring urgent medical attention. On detailed questioning and assessment, all children showed various neurological symptoms including nystagmus, liquid dysphagia, balance problems, and nocturnal enuresis. Two out of three patients died within 7 months following diagnosis. Sudden onset esotropia, especially due to sixth nerve palsy in children, should be considered a red flag symptom, prompting proper urgent specialist assessment. Sixth nerve palsy in patients with DIPG was associated with severely reduced life expectancy in this case series of three patients, shorter than in reported non-ophthalmic presentations.

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Introduction

Diffuse intrinsic pontine glioma (DIPG) is a rare aggressive brainstem lesion, affecting mainly young children, with a median survival of 11–13 months, and 5-year survival rate of 2.2–3.3%.[1,2] Some studies report longer survival rate in older children[3]; others suggest that prognosis is more dependent on tumor histology and presence of particular genetic mutations, such as *H3.3 K27M*, which is associated with poorer prognosis.[2] In spite of recent advances in treatment modalities, including chemotherapy and targeted agents, palliative radiotherapy remains the mainstay of treatment.[4]

The diagnosis of DIPG is mainly based on clinical and radiological findings, and rarely requires histological confirmation in cases of diagnostic uncertainty. A recent multicenter study by Erker et al.[1] showed that children with DIPG most often present with cranial nerve (CN) involvement, and pyramidal and cerebellar signs or symptoms are less frequent. Being the most common presentation (over 70–82% of cases), CN palsies are associated with the higher mortality rate in univariable analysis.[2] Several case presentations of ophthalmic manifestation of DIPC by Osborne et al.[5] Schreuders et al.[6] and Gilbert et al.[7] described acute concomitant esotropia without limitation of ocular motility. Information about incomitant strabismus as a presentation of DIPG is limited. Das[8] described a single case of child with sixth nerve palsy in DIPG. In this case series, we present the clinical and radiological findings in three patients with sixth nerve palsy as ophthalmic manifestation of DIPG, and provide a literature review, aiming to increase awareness of the condition, and help with timely diagnosis.

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Materials and methods

All children presented with sixth nerve palsy were consecutively recruited from the pediatric clinic at the East Sussex NHS Healthcare Trust within the last 10 years. All patients (one male (6 years-old at the time of DIPG diagnosis) and two females (5 and 14 years-old)) had a standard ophthalmology examination including best-corrected visual acuity (BCVA, measured with a logMAR test, Vision Visual Acuity Testing (Precision Vision, La Salle, IL, USA), orthoptic examination, refraction, slit-lamp examination, intraocular pressure measurements, and dilated fundoscopy. After neuroimaging, all children had a neurological assessment in the pediatric unit and were referred to the regional oncology center for treatment.

Magnetic Resonance Imaging (MRI) was done using 1.5 Tesla (Siemens Symphony, Erlangen, Germany) including sagittal MPRAGE (TR/TE/TI 1850/3.9/1100, flip angle = 15°, base resolution = 256, FOV = 300, voxel size 1.2 mm × 1.2 mm × 1.2 mm) and axial CISS (TR/TE 11.4/5.7, flip angle 70°, base resolution = 256, FOV = 200, voxel size 0.8 × 0.8 × 1 mm). Patients 2 and 3 had MRI done under general anaesthetic.

The study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the parents/carers.

Results

The current study reports three pediatric patients who presented with sudden eye misalignment and were later diagnosed with DOPG.

Patient 1

A 14-year-old Caucasian girl was referred to the eye clinic urgently with sudden onset esotropia and binocular horizontal diplopia. On clinical assessment, she adopted an anomalous head posture with a head turn to the right. Visual acuity was 0.1 logMAR in both eyes. Orthoptic assessment showed a clinical picture of right sixth nerve palsy with right esotropia, measuring equally for near and distance (20^ base out (BO), Figure 1a), limitation of right eye abduction (−1.0, Figure 1b) with persistent limitation on doll's head maneuver, and conjugate gaze evoked nystagmus. Anterior and fundus examinations were normal. Generally, she felt well in herself; however, a review of systems showed difficulties with swallowing liquids. The MRI scan of the brain (Figure 1b,c) showed a solitary pontine lesion, extending into the inferior medulla with compression of the fourth ventricle. Tumour biopsy showed *H3K27* mutation. After a course of radiotherapy, the patient was reviewed. Bilateral limitation of abduction with increased amplitude of the gaze-evoked nystagmus were the only notable changes from the initial eye examination (Supplementary video) on the last assessment 6 months after initial presentation.

Patient 2

Six-year-old Caucasian boy was under the care of orthoptic clinic with partially-accommodative right esotropia for almost 3 years. Initial orthoptic assessment showed visual acuity of 0.825 logMar

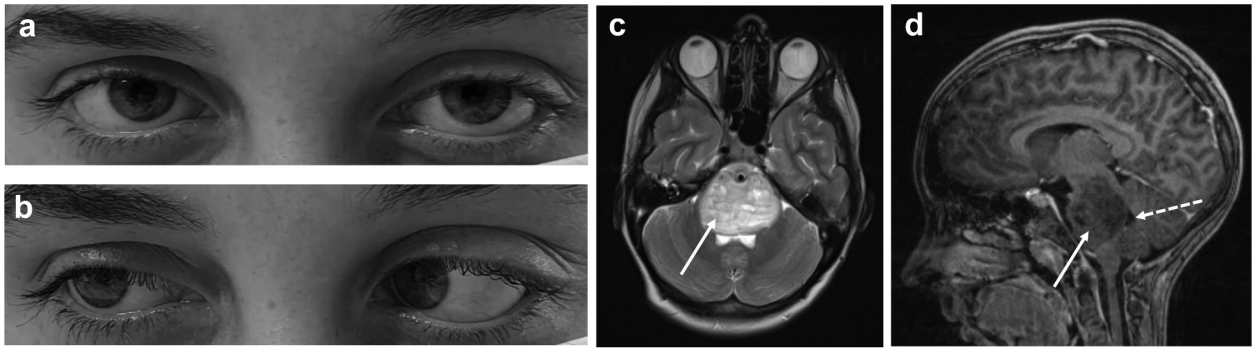

Figure 1. Eye photography (a, b) and magnetic resonance imaging (MRI, c and d) of patient (a) Photography of the eyes in primary position, showing right esotropia. (b) – photograph, showing limited abduction in the right eye. (c) – Axial T2WI of the brain showing hyperintense pontine lesion (solid arrow). (d) – Sagittal post-contrast T1WI of the brain showing the lesion extending into the inferior medulla (solid arrow), and compression of the fourth ventricle (dotted arrow).

with both eyes open; it was not possible to assess single-eye vision, as the child did not like either eye being covered. Motility assessment showed full eye movements, with equal, partially accommodative esotropia at near and distance (20^ BO without glasses and 10^ with glasses). Cycloplegic refraction assessment showed severe hypermetropia (+6.0 DS). After adaptation period, and occlusion treatment for 2.5 years, vision improved to 0.250 LE 0.100 logMar (for the right and left eye, respectively), with full motility and residual microtropia. The patient was planned to be discharged from orthoptic clinic; however, on the pre-discharge assessment, examination showed dramatic increase in esotropia (30^ BO without and 25^ with glasses); motility assessment indicated limitation of abduction in the right eye up to −1.5, suggestive of the presence of sixth nerve palsy. On neurological assessment, mild ataxia with walking difficulties, and nocturnal enuresis were found. By the time of the brain scan, performed several days later, the child adopted an anomalous head posture, with right face-turn and severe limitation of right abduction up to −4.0. The MRI showed a diffuse pontine lesion with mild hydrocephalus (Figure 2a,b). A course of radiotherapy was provided in the regional oncology referral center. The child died 7 months after the initial diagnosis.

Patient 3

Five-year-old Asian girl was seen by a general practitioner after presenting with a raised temperature. Parents also noted sudden onset of esotropia. After

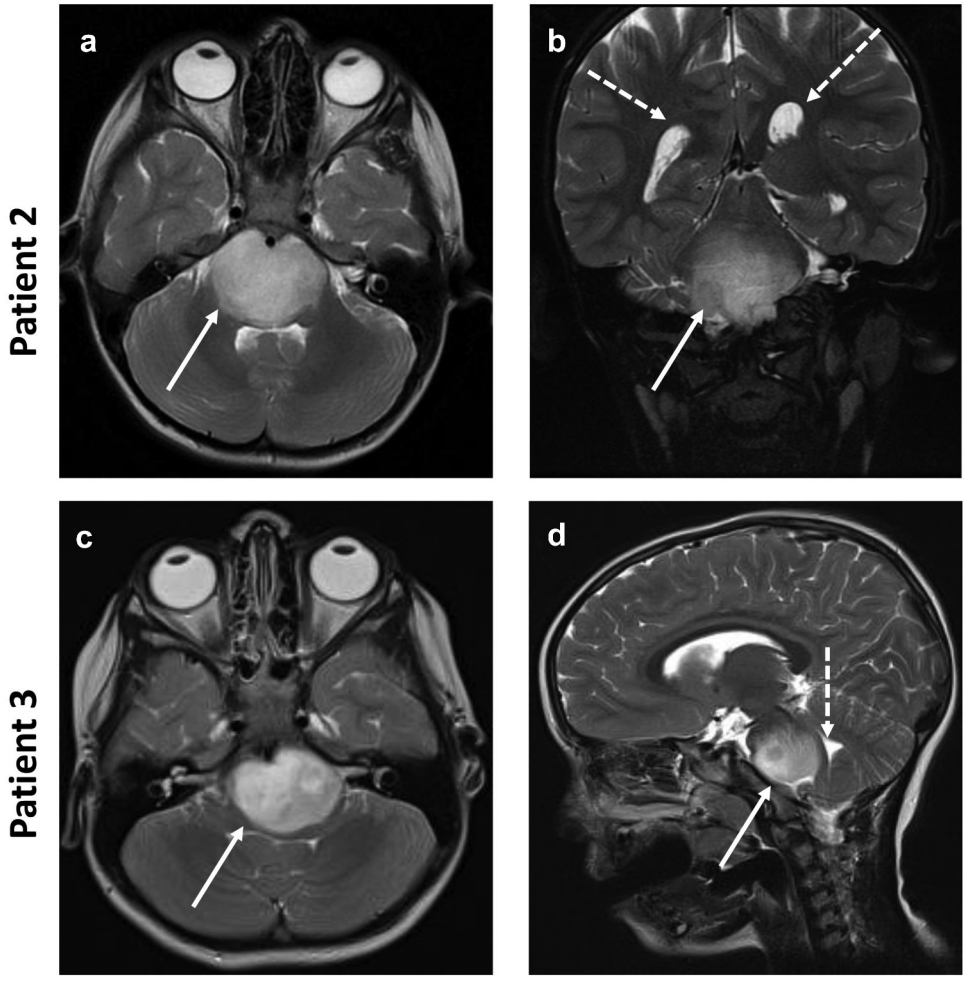

Figure 2. MRI scan of the brain showing a diffuse pontine lesion. (a) – Axial T2WI, (b) – Coronal scan of the brain showing a hyperintense, solitary diffuse lesion of the pons of patient 2 (solid arrow). Dotted arrows indicate mild dilatation of the lateral ventricles. (c) – Axial (d) – Sagittal T2WI scan of the brain showing a pontine glioma infiltrating the pons (solid arrow) and compressing the fourth ventricle (dotted arrow).

a course of oral antibiotics, the child was referred to the eye clinic. Visual acuity was 0.1 LogMAR in either eye, anomalous head posture with left turn was noted. Orthoptic assessment showed an incomitant strabismus with left esotropia, measuring more at distance and severe limitation of abduction in the left eye (up to −4.0), establishing a diagnosis of left sixth nerve palsy. Urgent MRI scan of the brain showed presence of DIPG (Figure 2c,d). Despite management using radiotherapy, the child died 6 months after diagnosis.

Discussion

To our knowledge, this is the only case series of patients with CN VI palsy as the initial ophthalmic presentation of DIPG.

Two out of three patients presented in this case series were initially referred with sudden onset of esotropia. Patient 2 was monitored with partially accommodative esotropia and was investigated further when the esotropia has suddenly increased in angle and became incomitant.

Acute onset of esotropia (AOE) is one of the most common ocular motility disorders in children. Being reasonably harmless in some patients, it could be a sign of serious underlying pathology in others. The incidence of acute onset strabismus associated with intracranial pathology varies from 3.6% to 8% of patients.[9,10] In a study by Chong et al.[11] the proportion of the patients with abnormal neuroimaging in the cohort with sudden-onset strabismus was much higher when children also had other neurological symptoms at the time of presentation (70.6% vs 7.5% in isolated strabismus group).

A case series by Kemmanu et al.[12] showed three out of five patients with acute comitant esotropia had intracranial pathology, two of whom were subsequently diagnosed with DIPG. Several publications describe different ophthalmic presentations of DIPG (Supplementary table 1). In all these studies, children presented with acute esotropia without limitation of motility.[5,6,8]

Interestingly, only in one patient esotropia was more noticeable at distance,[6] which could suggest possible subclinical abduction deficit. At the moment, the mechanism of AOE in the presence of a neurological condition is still unclear.[9,13]

It is possible that AOE in DIPG could be the short-term predecessor of the sixth nerve palsy, as it was seen in one of the patients from Osborn et al.[5] series.

Lee et al.[14] investigating the etiology of sixth nerve palsy in children found that the most common causes were space occupying lesions or their removal, responsible for 45% of cases. Other pathological causes included raised intracranial pressure (non-localizing sign, 15%), trauma (12%), congenital (11%), inflammation (7%), miscellaneous (5%), and idiopathic (5%). A recent, much smaller study by Hanna et al.[15] showed intracranial hypertension and anti-GQ1B syndrome among the most common causes for sixth nerve palsy in children.

Literature data on CN involvement in DIPG is slightly controversial. Mabray et al.[16] report incidental cases with direct involvement of the CN III–XII, whereas a multicenter study of children >10 years found that CN involvement was the most common presentation (70%), followed by pyramidal and cerebellar signs or symptoms.[1] In another multicenter study, Hoffman et al.[2] also documented more frequent CN involvement in short-time survivors (83% vs 73% in long-time survival group). Interestingly, the median overall survival rate in the latter study was 11 months. DIPG patients with shorter duration of symptoms also had a shorter survival rate. In our cohort, the duration of sixth nerve palsy before radiological diagnosis was less than 2 weeks. Patient 1 is alive at the time of report preparation (6 months after diagnosis). Two patients died within 6.5 months after diagnosis. This life expectancy was much shorter than reported among the patients with non-specified CN involvement.[1,2,4] This could be explained by the anatomical position of the sixth nerve nuclei in the pons at the floor of the fourth ventricle. Space occupying lesions in this location are known to affect basic vital functions such as breathing, heart rate and blood pressure control, as well as consciousness and sleep.[17]

All patients showed diffuse invasion of the brainstem at the level of pons on the MRI scan.

In addition to sudden-onset esotropia secondary to sixth nerve palsy, all patients had other neurological signs.

Patient 1 had gaze evoked nystagmus, which in isolated presentation could be a sign of medication side effects (sedatives, anticonvulsants, not used by patient 1), or can be associated with lesions in the brainstem or cerebellum.[13] Two out of three patients had other symptoms including dysphagia (patient 1), nocturnal diuresis (patient 2), which, in the context of co-existing sixth nerve palsy, suggested a neurological origin due to possible brainstem pathology.[3,18] Presence of these additional signs and symptoms, developing over a short time frame, further substantiates the need for emergency MRI in this subset of patients (children), due to high index of suspicion for DPIG.

This case series shows the largest cohort of children with sixth nerve palsy and DIPG. However, the data may not be adequately represented due to the limited number of the patients. Therefore, further multicenter studies could give more information on the clinical presentation and provide strategies to improve timely diagnosis of DIPG.

In summary, sudden onset esotropia in children requires urgent specialist assessment to provide timely diagnosis. Acute sixth nerve palsy in pediatric patients should carry a high index of suspicion for DIPG. Sixth nerve palsy in DIPG could indicate more aggressive disease, potentially leading to shorter life expectancy, as shown in this case series.

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Author contribution statement

All authors were involved in the conception or design of the work; data collection/analysis and interpretation; drafting/critical revision of the article and final approval.

Data availability statement

Data is available on request.

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