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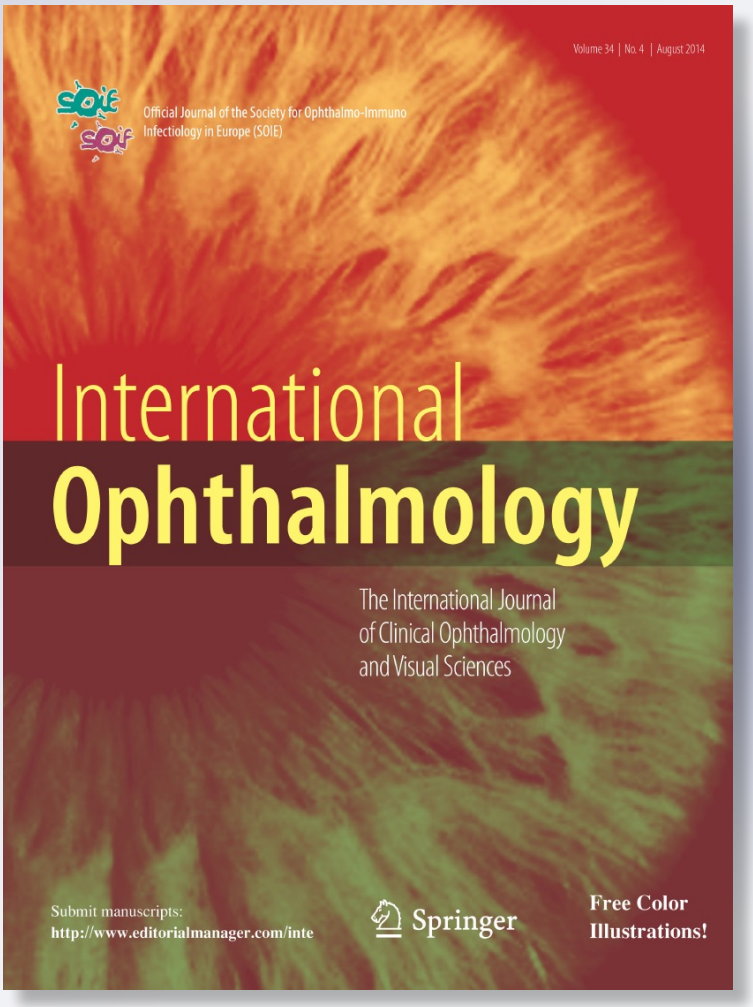

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REVIEW PAPER

Optic nerve glioma: an update

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Abstract Optic nerve glioma is the most common optic nerve tumour. However, it has an unpredictable natural history. The treatment of optic nerve gliomas has changed considerably over the past few years. Chemotherapy and radiation therapy can now stabilize and in some cases improve the vision of patients with optic nerve gliomas. The treatment of optic nerve glioma requires a multidisciplinary approach where all treatment options may have to be implemented in a highly individualized manner. The aim of this review article is to present current diagnostic and treatment protocols for optic nerve glioma.

Keywords Optic nerve glioma · Proptosis · Neurofibromatosis · Tumour

Introduction

Optic nerve gliomas are the most common tumours of the optic nerve. Optic nerve tumours are classified as either those arising from the optic nerve matter or those arising from the surrounding sheath. These tumours are difficult to treat and manage owing to the high risk of damage to the optic nerve itself. More than 90 % of primary optic nerve tumours are either benign gliomas of childhood or optic nerve sheath meningiomas [1]. Optic nerve gliomas comprise about 1 % of all intracranial tumours [2].

Optic nerve gliomas are of two different types—one being the juvenile benign pilocytic astrocytoma and the other being the malignant glioblastoma of adulthood.

Benign optic nerve glioma

These benign tumours usually present in the first decade of life. They are almost always unilateral and occur more frequently in females. While the incidence may be sporadic or sometimes familial, most of the patients presenting with optic nerve gliomas have neurofibromatosis type 1 (NF-1). Reports have shown varying levels of incidence of NF-1 among patients of optic nerve glioma: 10−70 %, whereas the incidence of optic nerve glioma in patients with NF-1 varies from 8 to 31 % [3, 4].

Clinical features

Proptosis is usually gradual, painless and often associated with infradisplacement of the globe.

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However, on rare occasions, a patient may present with acute loss of vision. This is associated with development or worsening of proptosis, which results from haemorrhage into the tumour [5]. Optic disc swelling or pallor, visual acuity loss, visual field loss and relative afferent pupillary defect are seen due to compressive effects of the tumour. The tumour eventually causes optic nerve atrophy because of pressure effects on the nerve fibres as well as the nutrient arteries. Primary and secondary strabismus is seen, along with restriction of extra ocular muscle motility. Also, dissociated vertical nystagmus may be seen in suprasellar extending lesions [1]. Chronic compression of the central retinal vein can cause central retinal vein occlusion (CRVO). As a result, venous stasis retinopathy, optociliary shunt vessels are seen. Furthermore this may lead to rubeosis irides and even neovascular glaucoma [3]. Chiasmal gliomas may present with slow bilateral visual loss associated with bitemporal field defects, optic disc changes and strabismus [6]. Endocrinal disturbances may also be seen in patients with chiasmatic gliomas. Sporadic optic nerve glioma more often present with symptoms of raised intracranial pressure owing to their spread beyond the chiasm; in contrast to the tumours associated with NF-1 in whom precocious puberty is more commonly seen [7–9].

Diagnosis

Gliomas that are limited to only one optic nerve do not cause bilateral blindness and are not life threatening. The prognosis for life and vision worsens once the optic chiasm is involved [10]. Optic nerve gliomas can involve both, the chiasm and one or both optic nerves, and half of those extending to the chiasm also involve the hypothalamus [11]. Therefore, early diagnosis and management are of importance in these cases. Given the association of NF-1 with optic nerve gliomas, there are well-defined recommended guidelines for the management and diagnosis of NF-1 associated gliomas [7]. They state that all children with NF-1 younger than 8 years of age should undergo a thorough annual ophthalmological examination but baseline 'screening' neuroimaging or visual evoked potentials of asymptomatic children with normal visual examinations is not warranted. The optimal frequency of ophthalmological assessment for children older than 8 years is not known. The current recommendation is that eye examinations be performed every 2 years until 18 years of age. No particular screening for optic nerve gliomas in adults with NF-1 is recommended [6, 7].

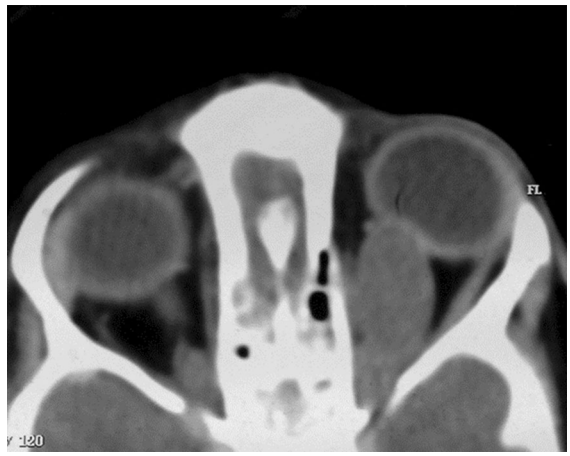

Fig. 1 Optic nerve glioma in a 3-year-old girl with left proptosis. Axial noncontrast CT image shows an isodense lobulated intraconal mass along the left optic nerve that causes left proptosis

Radiological findings

On CT, the tumour appears as an iso- to hypoattenuating fusiform enlargement of the optic nerve, sometimes with kinking or tortuosity of its course (Fig. 1). Less commonly, it is an eccentric or discrete mass arising from the nerve [12]. CT can also reveal subtle erosions and enlargement of the optic canal and the rare fine calcifications [13]. Although intrinsic contrast with intraconal fat on CT allows for evaluation of the optic nerve, MR imaging is the modality of choice to evaluate intracranial extent, including extension to the optic chiasm, hypothalamus and beyond.

MR imaging protocols using coronal and axial thin-section T1-weighted and fat-saturated T2-weighted images are useful [14], as is additional evaluation with paramagnetic contrast agents. The size and course of the nerve are best evaluated on T1-weighted images without fat saturation [12] (Fig. 2a). The tumour is iso- to hypointense to the optic pathway on T1-weighted images and slightly hyperintense on T2-weighted images, with rare areas of haemorrhage and calcification. Variable patterns of enhancement are seen with intravenous gadolinium. Two architectural

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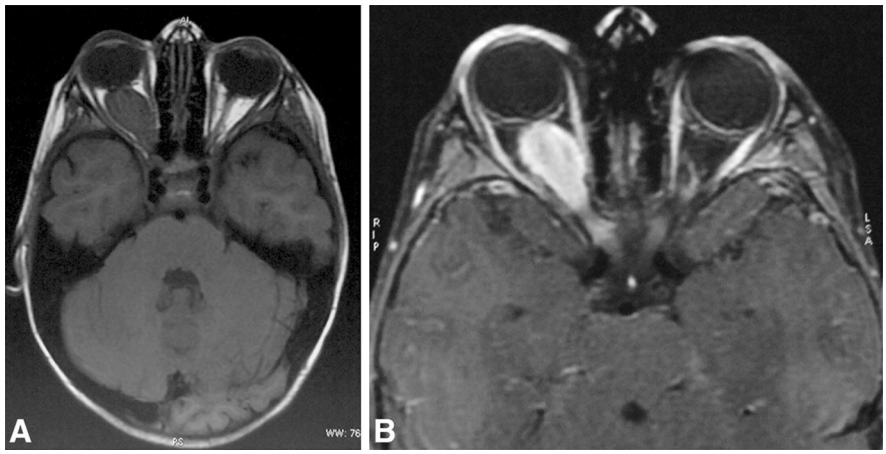

Fig. 2 Optic nerve glioma in a 4-year-old boy with right proptosis and headache. **a** Axial unenhanced T1-weighted image shows a fusiform, isointense mass along the right optic nerve. The normal hyperintense intraconal fat provides intrinsic contrast to delineate the mass. **b** Postcontrast fat-suppressed T1-weighted axial image at the same level shows intense enhancement in the mass

patterns are evident with contrast. In the diffuse type, which grows predominantly within the optic nerve parenchyma, the nerve is enlarged and the surrounding subarachnoid space is effaced (Fig. 2b). In the other form, enhancing tumour in the subarachnoid space compresses the normal-sized minimally enhancing nerve [12]. Cystic tumours show enhancement of the wall of the cyst. Enhancement in optic nerve gliomas is associated with a more aggressive behaviour [13]. Extension of the tumour into the intracanalicular and retrocanalicular portions of the optic nerve seen only with postcontrast imaging has important management implications. Extension to the chiasm through the optic canal produces a characteristic dumbbell-shaped configuration. Large tumours in the suprasellar area may simulate other suprasellar tumours, but involvement of intraorbital optic nerves helps differentiate from other suprasellar masses [15]. Rarely, the tumour may extend into the lateral geniculate bodies and optic radiations [12].

Some imaging findings of optic pathway tumours differ between children with and without neurofibromatosis. Bilateral optic nerve tumours are pathognomonic for NF-1. Tumours isolated to the optic nerve are more commonly seen in patients with NF-1, while intracranial extension is more common without NF-1 [12]. The tumour causes nerve enlargement without altering its configuration in most patients with NF-1 but in only a small minority without NF-1. Tumour diameter and volumes tend to be greater in non-NF-1 cases. Cytic components are rare in NF-1. Hydrocephalus is almost exclusively seen in non-NF-1 cases [12]. Dural ectasia seen in NF-1 should not be confused with involvement of the subarachnoid space by tumour. In dural ectasia, the enlarged subarachnoid space follows the signal intensity of CSF and does not enhance [14] (Fig. 3).

Treatment

As discussed earlier, optic nerve gliomas may sometime involve the chiasm and cause visual symptoms in the contralateral eye as well. This occurence, however, is rare [3]. The treatment of optic nerve gliomas, consisting of a multi-disciplinary approach with fractionated stereotactic radiotherapy (FSRT), is now emerging as one of the preferred treatment modalities.

1. *Observation* The natural history of childhood optic nerve gliomas is almost always benign and most tumours grow slowly in a self-limited manner and some even spontaneously regress. Some long-term studies indicate that patients who are not treated may retain stable visual function [3]. It has been recommended that most patients with unilateral optic nerve gliomas, particularly those with NF-1, be followed at regular intervals both clinically and with neuroimaging without intervention unless there is documented visual deterioration. Once visual deterioration occurs, treatment may be considered.
2. *Chemotherapy* The optimal role of chemotherapy in paediatric optic nerve glioma has not been determined. Chemotherapy holds the possibility of delaying or entirely avoiding the implementation of therapies that have potentially greater

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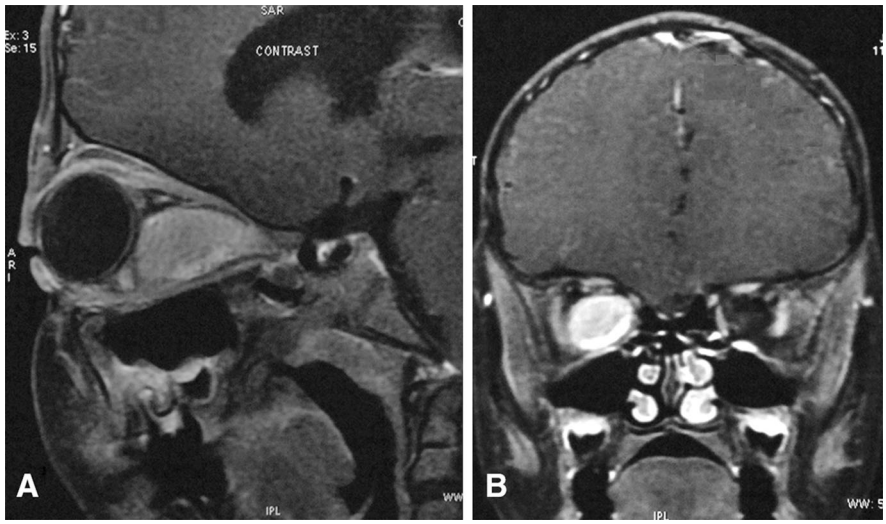

Fig. 3 **a** Postcontrast fat-suppressed T1-weighted sagittal image shows that the mass is confined to the orbit, without extension into the chiasm. **b** Postcontrast fat-suppressed T1-weighted coronal image again shows the enhancing right optic glioma and the normal nonenhancing left optic nerve

long-term toxicities (i.e. radiotherapy and surgery) [16]. This is particularly important for the youngest patients, and reports have suggested that chemotherapy should be the primary treatment modality for ONG in children under age 3 years [17]. Chemotherapy was first studied in 1977 (Vincristine with Actinomycin D) and was found to be effective. Numerous studies have been published since then addressing the chemotherapeutic management of low-grade gliomas as a whole. Packer and colleagues [18, 19] were one of the first to evaluate concurrent carboplatin and vincristine chemotherapy in patients with newly diagnosed progressive disease and patients with recurrent disease. A 10-week induction phase, followed by 48 weeks of maintenance carboplatin/vincristine was used resulting in a progression-free survival (PFS) of 75 % at 2 years and 68 % at 3 years. Children aged 5 years or younger had a notably more favourable overall rate of response. This is presently the most commonly used regimen for low-grade gliomas. On comparing toxicity of TPCV (6-thioguanine, procarbazine, CCNU and vincristine) with the Packer regimen (carboplatin/vincristine), another study concluded that TPCV had bone marrow toxicity comparable to that of carboplatin/vincristine, and found it suitable for second-line therapy [20]. A vast majority of children experience disease progression and require salvage therapy, most commonly including radiation therapy. Risks associated with chemotherapy are also substantial like renal toxicity, myelosuppression, peripheral neuropathy, ototoxicity, etc. These toxicities are difficult to recognize in very young patients, and hence strict monitoring with thorough evaluation at regular interval during and after treatment is prudent. Newer targeted therapies are being studied for their use in young children with optic pathway gliomas including bevacizumab and temozolomide but none have shown dramatically better results compared to the standard chemotherapy regimen even in phase II studies.

3. *Radiotherapy* Radiotherapy has been used for a long time for treatment of optic pathway gliomas [21–23]. There are many single institution studies reported in literature that indicate that patients with optic nerve glioma treated with radiotherapy have 10-year PFS of approximately 80 %. About a third of patients experience objective improvement in vision, and approximately half of them show some sign of tumour regression on imaging. [24–27].

Treating young patients with ionizing radiation poses a challenge. If patients are treated with conventional portals, then a large part of developing brain, contralateral orbit, pituitary, internal ear and other vital structures receive high doses of radiation which increases morbidity and hampers the quality of life. Also since these patients have a long-term survival, there is a higher probability of developing a second malignancy. Various

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investigators have used a wide variety of doses but majority of them range from 45 to 58 Gy. As a standard, most institutes now use 3D conformal radiotherapy to a dose of 45−50.4 Gy in conventional fractionation. Radiotherapy can also be delivered in daily fractions to treat larger tumours—this ensures that the surrounding tissues benefit from normal tissue sparing properties of fractionated radiotherapy. FSRT combines the target and dose localization characteristics of stereotactic radiosurgery with the obvious advantages of fractionation [18]. It has been seen that radiotherapy is effective in achieving functional improvement and stabilizing disease even with conventional techniques [22]. In a retrospective analysis, Dororetz et al. [23] reported that early radiotherapy had a positive influence on PFS. Combs et al. [30], while evaluating the tolerance and long-term outcome of FSRT of optic pathway gliomas, have reported that FSRT was safe and well tolerated in all patients. FSRT was delivered to a total dose of 52.2 Gy in 29 fractions at 1.8 Gy/fraction. In their study of 15 patients with optic gliomas, the PFS rate at 3 and 5 years was 92 and 72 %, respectively. The 5-year survival rate after FSRT was 90 %. Also, they did not observe secondary malignancies. Furthermore, compared to conventional techniques, FSRT has the potential of sparing the pituitary gland in chiasmatic lesions. However, radiotherapy must be employed with caution as it increases the risk of having neurocognitive sequelae [31, 32], endocrine impairment [33], late vascular effects like Moya Moya syndrome (especially in NF-1) [34] and second malignancies (reported relative risk of 3.04 for NF-1 patients) [10]. Hence, a longer follow-up is required. In summary, radiotherapy is indicated in children >5 years of age who have significant visual or neurological impairment at presentation, who have clinical or radiological progression while on close observation or <5 years of age who progress on chemotherapy.

4. *Surgical excision* Only if there is cosmetically unacceptable proptosis, definite radiologically documented tumour enlargement or extension (not involving the optic chiasm), or a combination of these, should surgical excision of the lesion be considered [3]. In the presence of good vision, surgery carries the risk of vision loss. Either an orbital approach or a craniotomy may be performed to excise the tumour. However, with the advent of advanced radiotherapy delivery techniques, which are safer and efficient, surgical intervention is not the treatment of choice.

Malignant optic nerve glioma

Optic nerve gliomas are usually histologically benign and have a fairly predictable course as discussed above. However, rarely malignant astrocytomas that involve the anterior visual system are known to occur. These malignant tumours are known to have a rapid clinical course, characterized by progressive visual loss, neurologic deficits and, eventually, death. The age of presentation varies from the second to the eighth decade, and there is no specific sex predilection.

Clinical features and diagnosis

The clinical features depend on the site of the tumour. Patients with tumours in the proximal part of the optic nerve present with unilateral blurring of vision. Posterior pole haemorrhages—resembling an ischaemic CRVO—and neovascular glaucoma may develop. This does not remain, however, a monocular disease. Within 5−6 weeks, both eyes are affected, leading to completely blindness. Hypothalamic dysfunction, hemiparesis, and other neurologic deficits develop in the latter stages of the disease, and death usually occurs in less than 1 year [3, 37]. Because of the acute visual loss, it may be confused with optic neuritis or anterior ischaemic optic neuropathy [38]. In contrast to ischaemic disease, marked enhancement of the optic nerve is seen on MRI. In the early stages of the disease, MR imaging with gadolinium demonstrates slight enlargement of the anterior optic pathway on postcontrast imaging, simulating optic neuritis and sarcoid. In contrast, nonarteritic ischaemic disease does not enhance. With tumour growth, features are similar to other aggressive malignant gliomas [15].

Patients with tumours in the distal portion of the optic nerve present with progressive unilateral visual loss, neurologic symptoms and death; however, the visual loss in these patients is associated with a normal-appearing optic disc that eventually becomes pale [39].

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The histopathology of this tumour is completely different from that of the typical optic nerve glioma, being characterized by extreme cellular pleomorphism, nuclear hyperchromaticity and scattered mitoses.

Treatment

No therapy seems to be able to stop the tumour; radiation is only palliative. Short-term successes have been seen with a combination of chemotherapy and radiation.

Conclusion

Diagnosis of optic nerve gliomas is based on clinical presentation and imaging. The ability to recognize systemic features of NF-1 is important in early diagnosis of optic nerve gliomas. Most tumours present with progressive visual loss and variable proptosis. Neuroimaging helps in diagnostic dilemmas such as differentiation between meningiomas and gliomas, and diagnosing infiltrative optic neuropathies such as leukaemia or lymphoma [40]. The visual outcome and management differ depending upon on the nature of the tumour. The treatment of optic nerve glioma has undergone a paradigm shift, and ophthalmologists must be aware of the signs and symptoms and the management options available. Management of a case of optic nerve glioma requires a team effort among the ophthalmologist, radiologist and oncologist as not only diagnosis but also subsequent treatment and follow-up involves all the three clinicians.

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Conflict of interest None.

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