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Brain tumors constitute the most frequent solid tumors in childhood. The presentation depends on age, developmental stage and tumor location. The aim of this study is to present the ophthalmic manifestation of pediatric neuro-oncology disease and to discuss their screening and management based on methods of practice developed at Leeds Teaching Hospitals National Health Service (NHS) Trust using internationally developed standardized protocols. Children with brain malignancies may present to ophthalmologists with a variety of reasons including visual signs and symptoms, radiation and chemotherapy induced ocular complications and screening for oncogenic syndromes. Magnetic resonance imaging is the preferred method of imaging. However, quantitative monocular vision testing is found to be the most useful screening tool for optic pathway gliomas. Surgery, irradiation and chemotherapy may be used in the management of brain tumors. New treatment modalities including anti-VEGF therapy and molecular targeted therapy are promising therapies for the treatment of optic pathway gliomas.

Brain tumors constitute the most frequent solid tumors in childhood, accounting for 15–20% of pediatric malignant disease [1]. They are the second most common pediatric tumors with an incidence of 2.8/100000/year slightly lower compared to 3.1/100000/year documented in leukemia.

Glial tumors represent over half of brain tumors in children mainly involving the optic nerve and chiasm but also showing a predilection for the posterior fossa and brain stem. Embryonal tumors of the CNS represent about a quarter of pediatric brain malignancies. Other childhood CNS tumors that present to ophthalmologists include craniopharyngiomas, germ cell tumors arising in the suprasellar or pineal region and parameningeal rhabdomyosarcomas (RMS). A number of tumors can arise in association with inherited syndromes such as neurofibromatosis (NF) type 1 and 2, tuberous sclerosis and Li–Fraumeni syndrome. A classification of pediatric brain tumors is presented in Table 1.

The presentation depends on age, developmental stage and tumor location, and symptoms are usually nonspecific. Infants present with increasing head circumference, lethargy, nausea, vomiting and loss of developmental skills while older children tend to present more frequently with headache, behavioral changes, loss of cognitive skills, seizures and endocrine dysfunction. In addition, brain tumors frequently present with a constellation of typical symptoms and signs involving the visual system. Lag times are longer than for any other pediatric cancer, and delay in diagnosis may result in increased long-term disability.

The aim of this study is to present the ophthalmic manifestation of pediatric neuro-oncology diseases which are known to have various ophthalmic presentations including reduced vision, proptosis, nystagmus or new onset of squint (Table 2). Children may present via the optometrist or the primary care physician with swollen optic discs found on routine examination as well as due to screening for oncogenic syndromes. The screening and management of these patients will be discussed based on the methods of practice developed at Leeds...
Teaching Hospitals National Health Service (NHS) Trust using internationally developed standardized protocols.

**Ocular manifestation of pediatric CNS tumors**

**Vision loss**

Brain tumors can affect vision in three different ways. Vision loss can occur either by intrinsic optic pathway tumors or by extrinsic direct compression of the visual pathway as well as due to papilledema and optic disc atrophy secondary to raised intracranial pressure (RICP).

Visual loss is a commonly presenting sign in children with intrinsic optic pathway tumors. Optic pathway gliomas (OPGs) are the most common intracranial optic pathway tumors presenting with decreased visual acuity (VA). Although the mechanism is not entirely clear, vision loss from OPGs is typically caused by damage to the axons of the visual pathway, direct nerve fiber compression and demyelination [2]. Overall 25% of OPGs are confined to the optic nerve, while 40–75% involve the chiasm [3].

OPGs show a highly variable growth pattern ranging from indolent to rapidly progressive causing severe visual loss. Most children with NF 1-OPG have an indolent or even asymptomatic course and therefore benefit from screening and early detection. 50–75% of patients are asymptomatic at the time of diagnosis. In contrast, sporadic OPGs nearly always present with diminished vision ranging from mild visual loss to complete blindness.

The natural history of vision loss in children with OPG is dynamic and can occur at any age and can be separated by many months or years and can vary in severity. This unpredictability of the disease course reflects the poor understanding of OPG clinical behavior. However, some authors advocate that diagnosis of late-onset OPGs may be previously undiagnosed tumors and the late onset of symptoms may be indicative of further disease progression [4].

Balcer et al. suggested that VA loss might be dependent on the tumor extent and location by MRI at the time of diagnosis [5]. In their study, a significantly higher proportion of children with involvement of the postchiasmal visual pathway developed visual loss (62%) compared with those with chiasmal and optic nerve involvement alone (32%). Similarly, previous studies demonstrated worse prognosis for binocular acuity in tumors with chiasmal involvement, indicating that isolated optic nerve gliomas have a better clinical course [6].

Craniopharyngiomas may present with visual failure as a result of compression of the visual pathway, particularly the chiasm. However, the extent of visual loss is often not appreciated until other abnormalities become apparent. This tumor’s close relationship to the anterior visual pathway gives rise to a dynamic and complex visual picture.

### Table 1. Anatomical classification of pediatric brain tumors.

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<thead>
<tr>
<th>Posterior fossa</th>
<th>Supratentorial</th>
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<tr>
<td>Intraparenchymal</td>
<td>Extra-axial</td>
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<tr>
<td>Astrocytoma</td>
<td>Choroid plexus papilloma/carcinoma</td>
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<tr>
<td>Medulloblastoma</td>
<td>Langerhans cell histiocytosis</td>
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<tr>
<td>Ependymoma</td>
<td>Desmoplastic neuroepithelial tumor</td>
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<tr>
<td>Brainstem glioma</td>
<td>Metastasis</td>
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<tr>
<td>Periventricular glioma</td>
<td>Germ cell tumors</td>
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<tr>
<td>Desmoplastic neuroepithelial tumor</td>
<td>Pituitary adenoma</td>
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<tr>
<td>Embryonal tumors</td>
<td>Langerhans cell histiocytosis</td>
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<td>Atypical teratoid/rhabdoid tumors</td>
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<th>Table 2. List of reasons that children with brain malignancies present to ophthalmologist.</th>
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<td>Ocular symptoms</td>
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<tr>
<td>Vision loss</td>
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<td>Visual field impairment</td>
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<td>Ocular motility disorders</td>
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<td>Proptosis</td>
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NF: Neurofibromatosis.
variety of visual signs. Patients generally present late, and the visual symptoms are often preceded by a long history of systemic symptoms.

According to previous reports, VA loss is the most common ocular complaint and constitutes the circumstance of diagnosis in 30–50% of patients with craniopharyngiomas [7]. In children, ophthalmological signs are not the main circumstances of diagnosis because young patients do not complain of a mild or unilateral reduction in VA or visual field (VF) loss.

Age less than 6 years is an unfavorable predictor of the visual outcome as many of children of this age group have poor vision at the time of diagnosis [8]. This may be attributed to late diagnosis diminishing the chance of visual recovery. In addition, visual symptoms, optic disc atrophy and calcification at presentation of craniopharyngioma were associated with a significant poorer visual outcome [9].

VF impairment
Craniopharyngiomas and pituitary tumors tend to compress the chiasm from behind and above as they grow on the infundibulum between the brain and the pituitary gland. This posterosuperior compression of the chiasm produces variable bitemporal hemianopia. Several authors have documented bitemporal hemianopia as the most common initial VF defect in children with craniopharyngioma [10].

In these cases, the extensive loss of the temporal VF disrupts fusion, and children can then suffer VF-related diplopia. These patients can also describe a hemiretinal slide because the VF of both eyes are segregated from one another and cannot be synchronized by the normal fusion. This creates significant reading problems with either deletion or duplication of portion of the target in children with convergent and divergent squint, respectively.

In addition, patients with bitemporal hemianopia may present with post-fixational blindness defined by a blind area distal to the fixation point. These patients while fixing bifoveally cannot respond to targets beyond the fixation target which causes lack of perception of the object.

VF in children with craniopharyngiomas is sometimes atypical due to the infiltrating nature of the tumor. Variable temporal changes in VF defects have been reported as a characteristic feature of the tumor resulting from intermittent emptying of cyst fluid into the ventricular system [7].

Germ cell tumors arising in the suprasellar region often present with VF defects. Bitemporal hemianopia is a sequel to these tumors as they expand dorsally and compress or invade the optic chiasm.

Progressive VF loss, including central depression and bitemporal hemianopia, is reported in 70% of patients with OPGs [11]. With extrinsic compression of the optic nerve, the VF typically shows a central scotoma with ‘breaking through’ as the defect increases. This leaves a peripheral crescent of preserved vision. However, in young children, VF defects may not be readily apparent and are only infrequently a presenting symptom without associated VA loss.

Screening of children with NF 1
Children might present to ophthalmologists to have visual screening and surveillance of NF 1. Approximately 15% of patients with NF 1 have low-grade pilocytic astrocytomas of the optic pathway [5,6,12]. In NF 1 children, the most common presenting signs are proptosis and VA loss (Figure 1) [6].

One-third to one-half of children with NF 1-OPG may experience vision loss, and in those cases in which tumor is confined to the optic nerve, proptosis is a frequent clinical presentation [13]. Interestingly, absence of the greater wing of the sphenoid bone in NF 1 may lead to pulsatile proptosis. Greater than one-third of NF 1 subjects may also develop optic disc atrophy.

The likelihood of vision loss in children with NF 1-associated OPGs is dependent on the tumor extent and location [5]. Although NF 1-OPGs typically involve the anterior visual pathway (optic nerves, chiasm and tracts), significant optic radiation involvement posterior to the lateral geniculate ganglion has also been reported [14]. Bilateral optic nerve gliomas without chiasmal involvement are virtually diagnostic of NF 1.

The natural history of NF 1-associated OPGs is unpredictable. Most OPGs in children with NF 1 are diagnosed before age 6 years after which the appearance of symptomatic OPGs and progression of known OPGs requiring therapy is uncommon [12,15]. However, a number of reports have demonstrated newly symptomatic NF 1-OPGs even after previously normal neuroimaging in children older than 8 years [12].

Compared with sporadic OPGs, NF 1-related gliomas are less likely to have visual impairment at diagnosis and are more likely to remain stable over time [16]. Most patients with NF 1 had stable or even normal VA, but some experienced slow progressive visual loss and a few developed sudden and profound vision loss according to previous study [17]. A high proportion of NF 1 patients (28%) in Balcer et al. series developed visual loss between 1 and 6 years after the diagnosis of OPG [5].

While most NF 1-OPGs are diagnosed before 6 years of age, the typical age of presentation for sporadic OPGs is less than 8 years [18]. However, onset can occur in the second decade. Nearly 90% of children with sporadic OPGs present with neurologic or ophthalmic pathology requiring neuroimaging. In addition, diagnosis may be assisted by accompanying endocrinopathy or short stature.

Impaired VA is more common at presentation in sporadic OPGs. Children without NF 1 are more likely to present with nystagmus and hydrocephalus. Sporadic OPGs are frequently associated with RICP and neurological findings as they mainly affect the posterior optic pathway including the chiasm and hypothalamus. In cases of chiasmal or hypothalamic invasion, precocious puberty is the presenting manifestation found in 40% of children [19].

Papilledema/optic disc atrophy
Papilledema is the crucial clinical sign of RICP resulting from axoplasmic flow stasis with intra-axonal edema in the area of
the optic disc. Most symptoms are secondary to the underlying elevation in intracranial pressure including headaches, nausea and vomiting, whereas, occasionally, cases can be found on routine examinations in asymptomatic individuals.

Vision is usually well preserved with acute papilledema. With prolonged RICP, the disc becomes paler secondary to a decrease in number of physiologically active nerve fibers. This eventually leads to consecutive optic disc atrophy which is often associated with VA or VF loss, although this might be mild.

Children with intracranial OPGs can present with obstructive hydrocephalus with subsequent obstruction of the ventricular system and RICP [13,20]. Signs and symptoms of RICP, including headache and papilledema, are more often noted in larger chiasmal-hypothalamic sporadic OPGs [18].

Optic atrophy occurs in up to 60% of children with cranio-pharyngioma and is commoner than disc swelling [21]. However, papilledema is more common in children compared to adults [21]. Longstanding chiasmal compression produces bitemporal hemianopia with loss of half of the maculopapillary bundle on the temporal side and the hemiretinal fibers into the nasal side of the optic disc taking the form of ‘bow-tie’ atrophy. With RICP, papilledema occurs only in the remaining temporal retinal nerve fibers streaming into the top and bottom of the disc. This type of swelling was named ‘twin-peaks’ papilledema.

Over 80% of children with pineal and brain stem tumors have, at presentation, features of RICP and subsequent papilledema due to blockage of the Sylvian aqueduct. Similar presentation can be found in tumors of the cerebellopontine angle and midline malignancies including medulloblastomas, as well as in tumors arising in the lateral, third and fourth ventricles, with ependymomas being the most frequently involved neoplasm (Figure 2).

**Nystagmus**

Nystagmus from an OPG can be horizontal, rotary, asymmetric or monocular. Gliomas affecting the chiasm and the nerves asymmetrically may cause a dissociated, high-frequency, low-amplitude, horizontal, asymmetric and pendular nystagmus mimicking spasmus nutans. Other features of spasmus nutans, including head nodding and torticollis, may or may not be present.

In young subjects, asymmetric nystagmus particularly in the presence of optic atrophy or hydrocephalus is suggestive of chiasmal glioma with or without posterior extension into the optic tracts. In infancy, a common presentation of OPGs is often with vertical or asymmetric rotary nystagmus, an association known as Russel diencephalic syndrome frequently associated with increased lesions confined to the rostral mesencephalon.

Convergence-retraction nystagmus is a disorder in which attempted elevation produces a series of rapid jerky convergent movements with associated retraction of the globe. This synchronous retraction and convergence of the eyes is seen almost exclusively in the setting of dorsal midbrain syndrome.

Dorsal midbrain syndrome in infancy suggests the diagnosis of congenital hydrocephalus producing the characteristic ‘setting sun’ sign characterized by upgaze paresis and downward drifting of the eyes. Its recurrence in children who have had a ventriculoperitoneal (VP) shunt placed for hydrocephalus usually signifies shunt failure. In contrast, the onset of dorsal midbrain syndrome in an older child usually indicates the presence of pineal tumor.

Upbeating nystagmus, in which the fast phase is in the upward direction, is a common sign seen with pontine syndromes. It is usually mild in the primary position and increases in the upgaze. Upbeating nystagmus in infancy is frequently associated with congenital abnormalities of the afferent visual system, while in older children it is caused by structural lesions involving the brainstem or cerebellum.

In contrast, downbeating nystagmus, in which the fast phase is downward, is a characteristic feature of medullary disease and lesions of the craniocervical junction, with medulloblastomas being the most commonly involved neoplasms. Downbeating nystagmus is diagnostic and helps to localize the site of pathology to the area of craniocervical junction and is a common finding in children with Chiari Type 1 malformation.

The presence of opsoclonus characterized by involuntary, chaotic, multidirectional saccades, also known as ‘dancing eyes syndrome’, usually suggests occult localized neuroblastoma. These movements can persist during sleep. An autoimmune mechanism has been proposed in the pathogenesis of opsoclonus. Autoantibodies directed against neurofilaments, surface and intracellular antigens of neuroblastoma cell lines as well as
secondary lymphoid follicles observed in neuroblastomas have supported its autoimmune origin [22]. Neuroblastoma constitutes the major diagnostic consideration for opsoclonus in the first several years of life and is found in approximately half of cases with opsoclonus in this age range [23]. However, the primary tumor in these cases is in the chest or abdomen and not in the brain.

Posterior fossa malformations can give rise to periodic alternating nystagmus (PAN) characterized by periodic changes in nystagmus direction and in head posture. This occurs because of an actively shifting null zone always seen in PAN, which is defined as the position of gaze where the nystagmus is less and therefore vision is better. Although in childhood PAN is frequently associated with albinism, a high incidence was found with structural lesions involving the cerebellum as well as with Arnold–Chiari malformation.

Cerebellar and brain stem disease almost always present with nystagmus. The commonest presentation is with horizontal jerk nystagmus arising from lesions of the vestibulocerebellar pathways or vestibular nuclei. The nystagmus may be spontaneous in the primary position but is more often seen with greater amplitude on gaze to the side of lesion.

Nystagmus is present in over 60–90% of cerebellopontine angle tumors, with acoustic schwannomas and pontine gliomas being the most common types presenting in this area. The gaze-evoked nystagmus to the side opposite to the lesion is fine and rapid, whereas to the side of the lesion the nystagmus is of low frequency and large amplitude.

**Ocular motility disorders**

Brain tumors can present with a variety of ocular motility deficits as a result of involvement of the cranial nerves. Single infranuclear cranial nerve palsies, especially sixth or fourth nerve palsy, may be a false localizing sign of RICP.

The acute-onset incomitant esotropia is often the initial and only sign of intracranial pathology in the young population. It occurs in the context of RICP caused by stretching of the nerve in its long intracranial course, or compression against the petrous ligament or the ridge of the petrous temporal bone.

The abducens nerve leaves the brain stem at the pontomedullary junction and may therefore be damaged by tumors of the pons and medulla. Thus, the acute-onset esotropia in an older child needs to be investigated. Similarly, such tumors can cause horizontal gaze palsies, while skew deviation is well recorded, with both pontine and medullary malignancies invading the median longitudinal fasciculus (Figure 3).

Upgaze palsy is a common feature of early dorsal midbrain syndrome, while a similar presentation can be found in tumors of the third ventricle with ependymomas being the most common type and in germ cell tumors arising in the pineal region. In addition, dorsal midbrain syndrome is frequently associated with bilateral fourth nerve palsies.

Cranial nerve palsies are less common presenting signs in OPGs. However, fascicular lesions of the oculomotor nerve are frequently diagnosed in children with mesencephalic gliomas [24].
Complications of radiotherapy

Delayed radiation-induced damage to components of the visual system results in morbidities varying in severity and latency. Anterior segment involvement is more frequently observed with external beam radiotherapy, while plaque-brachytherapy mainly affects the posterior segment.

Opacities. The severity of cataract formation is related to total dose and fractionation, and the onset is usually within 2 to 3 years [31]. A threshold for detectable opacity has been suggested to be 2 Gy on a single exposure, although other studies have demonstrated the cataract formation to occur at doses 8–10 Gy [32].

Dry eye is commonly reported as a frequent radiation-induced complication resulting from the effects of radiation to the conjunctival epithelium, goblet cells, cornea and lacrimal glands. For doses over 45 Gy, symptoms developed within 1 month after radiation, whereas the mean time to manifestation of corneal damage was reported to be 9 months [33]. Dry eye is a common complication following radiation therapy for RMS. Children often need long-term conservative treatment with ocular lubrication, whereas resistant cases may be managed by punctal occlusion.

Radiation-induced retinopathy usually presents with the non-proliferative form at an early stage, progressing rapidly to the proliferative type due to capillary closure, retinal ischemia and neovascularization. The upper limit of a safe dose was suggested to be 35 Gy in one early study, but cases of retinopathy have been reported with doses as low as 20 Gy [34].

The incidence of radiation-induced optic neuropathy increases with an increase in the total dose to the optic nerve over 55 Gy, although optic chiasmal damage at 50 Gy has been observed [35]. However, the effect of radiation on the optic nerve is not yet fully understood.

Complications of chemotherapy

Systemic drug-induced ocular side effects are increasing because of the number of new chemotherapeutic agents being introduced. Although the eye is usually considered a protected site, the visual system has a potentially high degree of sensitivity to toxic substances. The increased use of new drugs has resulted in longer patient survival. Consequently, the ophthalmologist is seeing more patients with adverse ocular side effects secondary to these antineoplastic agents.

Ocular toxicity includes a broad spectrum of disorders which can be grouped into adnexal, anterior/posterior segment and neuro-ophtalmic [27]. Dose reduction or discontinuation of incriminated drugs may help in reducing severity and duration of side effects.

Posterior segment involvement including optic neuropathy, retinopathy and maculopathy is commonly seen with administration of chemotherapeutic agents used for the treatment of CNS tumors such as cisplatin, vincristine, etoposide and carboplatine. Visual loss has been reported with the use of cisplatin and may be bilateral and irreversible [28]. In addition, cortical blindness in association with cisplatin may occur.

Anterior segment side effects have been reported less frequently, with corneal toxicity being the most common adverse event. Cranial nerve palsies can occur occasionally with the use of vinblastine and vincristine. In addition, children receiving vinca alkaloids commonly present with neurotoxicities, including encephalopathies and eyelid ptosis. Interestingly, fibrosis and thickening of the extraocular muscles has been recorded with local injection of carboplatin and cisplatin [29].

Reversible accommodation palsy is common in children with stage 4 advanced neuroblastoma following intravenous infusion with anti-disialoganglioside antibodies [30]. Short-term optical treatment with +3.0 dioptries sphere convex lenses can be used concurrently during the course of immunotherapy providing symptomatic relief.

Monitoring of pediatric CNS tumors

MRI scanning

MRI is the preferred method of imaging for CNS tumors. However, in OPGs, although standard MRI assessment can identify and delineate the extent of the tumor, it cannot be used to predict the likelihood of tumor progression or change in visual function [15,36].

Historically, in OPGs, the decision to initiate treatment is based on the clinical or radiographic progression of the tumor [37]. However, there continues to be little agreement about the indication for initiating treatment of an OPG beyond decline in VA. Although neuroimaging progression is cited frequently, there still are many who believe that this should not drive treatment in the absence of changes in vision [38].

Neuroimaging in OPGs is usually reserved for those with symptoms or abnormal findings on examination and should be considered in cases when accurate and reliable VA testing is not possible. In addition, symptomatic OPGs can develop in a nerve that appears normal in the first year of life; thus, normal neuroimaging findings in an infant or young child would not provide assurance that the optic nerve will remain tumor free [39].

VA testing

Due to the poor correlation between VA and radiographic outcomes found in previous studies, routine radiographic imaging of asymptomatic NF 1 patients should not be used as a screening tool for the disease [40–42]. Visual deterioration can precede the appearance of OPG on imaging studies, and OPGs can manifest radiologic progression without visual symptoms or
tude of VA changes, standardized methods are being used to account for differences in scoring and quantifying the magnitude of deficits can compromise accurate and reliable testing of VA. To further assess cooperation and attention. This is especially true for children younger children, scoring one line better or worse on repeat examination in children as young as the age of 4, whereas previous reports have documented the reliability of VF testing methods are considered recognition acuity testing methods are used depending on the child's age. For infants and very young preverbal children, Teller acuity cards (TAC) are used for providing reliable measurements. VA is assessed by the preferential looking test which is considered a grating acuity testing method. In older children who have learned all of the letters of the alphabet, VA can be measured by having the child verbalize or point to the matching HOTV letter or Lea symbol. These computer-based HOTV testing methods are considered recognition acuity tests. Both grating and recognition acuity values can be converted into Snellen equivalents providing reproducible VA values. In younger children, scoring one line better or worse on repeat testing is not uncommon since testing methods require cooperation and attention.

In an effort to standardize VA results, the logarithm of minimal angle of resolution (logMAR) can be used where acuity charts have each line separated by 0.1 logMAR units. This method facilitates better description of VA changes and produces continued VA values providing an international unit ideal for data analysis in longitudinal clinical trials. Since several factors can influence VA results, a ‘two line’ decline in VA is recommended as progression sufficient to initiate treatment.

**VF testing**

VF testing in very young children can be difficult, and the clinical significance of small field changes is often unclear. However, previous reports have documented the reliability of VF examination in children as young as the age of 4, whereas Safran et al. showed that automated VF examination is feasible in children between 5 and 8 years of age.

Nevertheless, testing by confrontation should be attempted at all visits when more objective testing is not possible due to patient’s age. In older children, better VF assessment is provided by Goldmann perimeter assessing the extent of vision along both horizontal and vertical axes measured in degrees.

**Color vision & contrast sensitivity testing**

There is no evidence in literature that color vision and contrast sensitivity testing add value to screening for pediatric CNS tumors.

**Relative afferent papillary defect**

An afferent papillary defect always accompanies optic nerve changes. Relative afferent papillary defect (RAPD) represents significant optic nerve damage and is therefore vital for the clinician to look for papillary reactivity if the diagnosis of optic nerve compression is to be made.

**Visual evoked potentials**

Attempts have been made to detect vision loss or correlate VA with visual evoked potentials (VEP) in children with OPGs. VA represents the central 2° of the VF, while the VEP is generated by cortical neurons representing the macula and the surrounding central 20° of the VF.

Several groups have evaluated VEP in the detection of OPGs and showed a sensitivity between 67 and 93% and specificity between 60 and 87% for VEP compared with VA for detection or radiological tumor progression. In their study, sensitivity and specificity of between-visit variations in VA and VEP were evaluated and correlated with changes in tumor volume and VEPs found to show a higher correspondence with MRI findings (68–86%) than VA similar to previous report. However, in previous study conducted by the same authors, VEP was found to be superior to VA only at presentation and detection of early optic nerve damage.

Previous studies advocated that severe pre-existing damage in the visual system limits detection of OPG progression using VEP testing and thus do not support its use as a screening tool. It is not certain how much of a change of VEP defines worsening when patients are followed longitudinally and the ability to detect progressive visual loss in a child with severely reduced VEP is limited.

Additional limitation in the use of VEPs for screening and surveillance of OPGs is the difficulty in interpreting small changes in amplitude without changes in VA while it is known that the accuracy of VEP testing and interpretation relies on experienced electrophysiologists who are not widely available. Therefore, a number of experts recommend against the use of VEPs for monitoring of OPGs in the long term.

In addition, no role of VEPs for screening of craniopharyngiomas has been demonstrated in literature.

**Optical coherence tomography**

Many young children with OPGs have difficulties completing quantitative VA and VF testing, whereas others may not complain of vision loss. To better guide therapy, a reliable
quantitative biomarker of vision that does not rely on patient’s cooperation is needed in young children with OPGs [38].

A recent study demonstrated a strong relationship between visual function and retinal nerve fiber thickness (RNFL) measured by optical coherence tomography (OCT) in children of 6 years or older with sporadic or NF 1-associated OPG [53]. RNFL was found to be decreased in the majority of children. Similarly, Chang et al. found that older subjects with OPG had a thinner RNFL compared with control individuals using the Stratus time-domain OCT [54].

Although the use of Stratus OCT is also limited by subject’s cooperation, it is to a lesser extent than VF testing requiring only seconds of cooperation. Despite variability in cooperation among children younger than 6, reliable OCT imaging has been obtained in children as young as 3 years of age [55]. However, it is likely that very young patients who cannot cooperate with VA testing are unable to cooperate with conventional OCT devices.

Recently, a number of investigators have used a spectral-domain handheld (HH) OCT device to image the optic nerve of infants and young children with a variety of conditions [56]. Avery et al. used the spectral-domain HH-OCT during sedation in young subjects with OPG and extended the findings of previous studies where testing was performed with the time-domain OCT [57]. The authors demonstrated that the spectral-domain is a much higher resolution device compared with the time-domain OCT.

OCT may aid in early detection of OPGs, thus allowing for timely initiation of chemotherapy and arrest of visual deterioration. This is critical because lost vision has not widely been documented to recover with current treatment. OCT could be used as a noninvasive and inexpensive screening tool for OPGs reducing the need and frequency of MRIs, visit duration and total cost. In addition, repeated HH-OCT imaging sessions are safe and fall well within standard recommendations.

Management of pediatric CNS tumors

Surgery
The role of surgery in the treatment of OPGs is controversial because of the risk of further visual compromise due to the intrinsic to the optic pathway nature of the tumor. However, surgery is the primary therapy for pediatric low-grade astrocytomas in other brain locations [58].

Ahn et al. found that radical removal of OPGs was of no survival benefit, although a benefit was documented in controlling hydrocephalus and postponing radiation therapy in younger children [59]. Surgery is typically not warranted in NF 1 subjects as they tend to have more diffuse disease and surgical intervention tends to fail at a rate almost twice than of their counterparts without NF 1 [13].

The optimal therapeutic approach of craniopharyngiomas continues to polarize options. Given the increased morbidity and inability to depend on radiotherapy in the very young population, several authors agree with radical resection of tumor by an experienced surgeon as the optimal management of this age group [60].

Previous reports demonstrated less postoperative VA deficits following transcranial surgery compared to the transsphenoidal group, whereas others advocated better visual outcomes with the endoscopic endonasal approach [61,62]. Radical resection of craniopharyngiomas was associated with decreased recurrence rate in children aged less than 6 [60]. However, surgery for craniopharyngioma is related with hypothalamic obesity with increased risk of weight gain and polyphagia.

Radiation therapy
Despite documented tumor stability and prevention of recurrence following irradiation, this treatment can yield a myriad of adverse side effects [63]. Radiation detrimental effects were found to be more pronounced in children younger than 5 and include further visual decline, hormone deficits, cerebrovascular disease, neurocognitive deficits, progressive decline of IQ and secondary malignant neoplasms [64]. The latter is especially true for NF 1 subjects. In contrast, sporadic OPGs have a second tumor occurrence rate of zero after radiation [4].

Radiotherapy is therefore reserved for children older than 5 to 7 years of age or even for younger individuals who have exhausted chemotherapy options, while it should be avoided in the treatment of oncogenic conditions [15].

Chemotherapy
Given the risks of surgery and radiotherapy, chemotherapy is the initial treatment for most OPGs (Figure 4). The combination of carboplatin and vincristine is the most common regime with a 3-year progression-free survival of 77% and a 5-year progression-free survival of 69% in NF 1 children [65]. Temozolomide and vinblastine are both effective as single agents for recurrent or refractory low-grade OPGs [66].

Although several studies suggested that vision loss prior to OPG treatment is irreversible, Fisher et al. reported VA improvement or stabilization in most subjects of their study following chemotherapy [67]. Moreno et al. reported that 50% of children had stable VA and 14% showed improvement after chemotherapy [68]. Overall, it has been shown that some visual improvement may occur only when treatment starts relatively early during the natural course of OPGs. Unfortunately, if VA is not regained after treatment, the VA loss is permanent.

However, it has been reported in the literature that some patients with NF 1-OPG and VA loss improve spontaneously, and this has been suggested as a reason to hesitate initiating chemotherapy in patients with vision loss. Despite several demonstrated poor prognostic factors including age less than 2 or more than 5 years and optic disc pallor at the time of treatment, there were children who regained vision with chemotherapy [67]. However, although chemotherapy is found to stabilize or reduce tumor, up to 60% of children demonstrate tumor progression after 5 years [69].

Anti-VEGF
Previous findings indicate that continuous glioma growth depends mostly on its angiogenic potency [70]. Bartels et al.
investigated the prognostic significance of angiogenic features in OPGs and found that angiogenesis and microvessel density was a predictor of tumor progression [71].

It has been demonstrated that tumor cells recognize oxygen deficits via receptors and respond with a release of VEGF that induces neovascularization to allow further tumor growth [72]. Thus, drugs targeting tumor angiogenesis have been introduced and are being evaluated for the treatment of recurrent and refractory OPGs. Treatment was thought to be reasonable as VEGF receptor is found to be overexpressed in pediatric OPGs [71]. Vinblastine as an anti-angiogenic agent has been widely used in children with OPGs [66]. In addition, several studies have demonstrated objective response and long-term efficacy of bevacizumab-based therapy in children with recurrent low-grade gliomas [73,74]. Objective response rates were observed to be as high as 86% [73].

Combination therapy with irinotecan was found to be more effective than the drugs utilized individually [75]. This apparent synergy was attributed to the assumption that bevacizumab suppresses the pro-angiogenic effect of glioma stem cells allowing for irinotecan to target the more differentiated tumor cells.

In pediatrics, there is limited experience with bevacizumab as a single agent. The issues of potential thromboembolic disease, impaired renal failure, intracranial hemorrhages or hypertensive crisis are problematic. However, in previous studies, toxicity was not significant and in most cases was irreversible [73]. Overall, bevacizumab-based therapy in OPGs may greatly improve visual outcomes and should be considered in appropriate clinical situations. However, further study regarding optimal dosing and long-term toxicity is warranted.

**Cyclic AMP targeted therapy**

In addition to anti-angiogenic therapy, further investigation of the biological mechanisms involved in the pathogenesis of OPGs is ongoing. Warrington et al. found that cyclic AMP suppression via expression of phosphodiesterase 4A1 (PDE4A1) is sufficient to induce gliomagenesis in a mouse model of NF 1 [76].

Since OPGs seem to grow where there are low levels of cyclic AMP, the authors hypothesized that pharmacologic elevation of cyclic AMP and targeted inhibition of PDE4A1 may dramatically inhibit optic glioma growth and attenuate tumor size, thus justifying the implementation of cyclic AMP-targeted therapies for OPG.

Interestingly, cyclic AMP levels were found to rise with age, and this may be likely responsible for the decreased incidence of OPG in the older population.

**New molecular targeted therapy**

The outstanding progress in advanced molecular technologies has allowed a better understanding of the molecular pathogenesis of pediatric brain tumors. This knowledge has altered the way that pediatric CNS tumors are being categorized, allowing stratification of patients into appropriate risk groups by identifying prognostic markers. In addition, further insights into tumorigenesis have opened new avenues for targeted therapies.

Pfister et al. uncovered mechanisms of mitogen-activated protein kinase activation in pilocytic astrocytomas. In addition, they identified a tandem duplication of the BRAF gene locus (7q34) in more than 50% of these tumors [77]. Thus, a number of Phase I and Phase II clinical trials are ongoing using these targets for novel therapeutic approaches. Targeted therapies testing small-molecule inhibitors of mitogen-activated protein kinase are currently being used for the treatment of OPGs [78].

Recent studies have provided further insights into the dysregulated signaling pathways in diffuse intrinsic pontine glioma [79]. Overexpression of EGFR and platelet-derived growth factor receptor α (PDGFRα) have been reported, and clinical trials with the respective inhibitors are in progress.

When compared to standard chemotherapy and radiation, the use of biological agents has several advantages. They can target cancer cells and spare normal cells in the developing CNS of children and can be used to delay irradiation avoiding its detrimental effects. In addition, their low molecular weights allow for better blood–brain barrier penetration. However, their efficacy has not yet been proven.

**Surveillance of pediatric CNS tumors**

MRI scanning remains the gold-standard diagnostic test and recommended means of follow-up in children with brain tumors. However, due to the poor correlation between VA and
MRI findings, radiographic imaging should not be used as a screening tool for OPGs.

Given the variable natural history of OPG, initial management in most case is close observation with serial neuro-ophthalmic evaluations. Quantitative monocular VA testing is the most useful test in detecting OPGs requiring treatment [37]. All children must have TAC testing and HOTV-computer-based assessment when old enough.

A clinically significant change in VA of more than two lines is most important and should drive the decision to treat [38]. No other visual or investigative test is mandatory. Among other tools that have been used, OCT may provide a reliable and quantitative structural marker of visual pathway integrity that can be followed over time and should be welcome [57].

As OPG progression mainly occurs in the first 2 years after diagnosis, frequent follow-up examinations are indicated during this critical period [33]. In addition, due to the potential for late diagnosis of OPGs, vigilant observation of patients until age 12 is currently recommended [26].

In Leeds, the current practice for the follow-up of children with NF 1 and not identified OPG include neuro-ophthalmologic examinations at 3-month intervals during the first 2 years of life. Children are then followed at 6-month intervals until the age of 4 and thereafter annually until age 8. Beyond this age, patients are being discharged to the community optometrist.

Children with NF 1 and known OPGs are followed at 3-month intervals for the first 12 months following diagnosis. Thereafter, neuro-ophthalmic assessment is performed at 6-month intervals for 2 years, then annually through adolescence.

VA is a useful tool in monitoring for recurrence in children with craniopharyngioma. However, its role in diagnosis should not be overestimated and cannot replace radiographic imaging since by the time that causes new visual deterioration, tumor is sizable and the likelihood of retrieval therapy is diminished. Thus, MRI remains the recommended means of follow-up in a child with craniopharyngioma. The UK consensus guidelines recommend MRI surveillance at 6-month intervals [80]. In contrast, most centers in North America suggest neuroimaging within 2 years after definitive treatment as most tumors tend to recur beyond this period.

Conclusion
To provide optimal care for children with OPGs and brain tumors affecting the optic pathway one must provide a multidisciplinary approach including neurosurgery, pediatrics, neuro-oncology and ophthalmology. Oncologists and neuro-ophthalmologists should work more closely so that patients with OPG can benefit from the combined expertise of physicians in both disciplines.

Given the clinical and molecular heterogeneity of OPGs, more studies are still needed to establish evidence-based guidelines for the management of children with these lesions. Oncologists have to make the tough ‘red button’ decisions, but ophthalmologists can help. VA testing is mandatory, and a low threshold for suspicion regarding amblyopia, headaches and acquired strabismus with diplopia is needed.

Although surgery, radiation therapy and chemotherapy are currently involved in the management of CNS tumors, there are new treatments and more on the near horizon targeting cellular microenvironment which make it worth screening for tumors affecting the optic pathway. Children with brain tumors are best managed in a tertiary center, but there are often cases that present more locally.

Expert commentary
Brain tumors may cause a variety of ocular symptoms and signs. MRI scanning remains the gold-standard diagnostic test and recommended means of follow-up in children with brain tumors. However, quantitative monocular VA testing is the most useful test in detecting OPGs requiring treatment. The current practice for the follow-up of children with NF 1 with/without OPGs developed in Leeds is presented using internationally developed standardized protocols. The neuro-ophthalmic examination is a key component in the diagnosis and management of OPGs. RAPD always signifies significant optic nerve damage and is therefore vital for the clinician to look for it. Gross total resection of tumor is related with longer recurrence-free intervals. However, when tumor total removal is not possible, irradiation may prevent recurrence, although it is not recommended in young children and in NF 1 patients due to increased risk of radiation detrimental effects. Combination chemotherapy regimens are being used with variable success in the treatment of pediatric brain tumors. Bevacizumab-based therapy in OPGs may greatly improve visual outcomes and should be considered in appropriate clinical situations, while the implementation of molecular targeted therapies for OPG is promising. A multidisciplinary approach including neurosurgery, pediatrics, neuro-oncology and ophthalmology is essential in order to provide optimal care in children with brain tumors.

Five-year view
Hand-held OCT may provide a reliable and quantitative structural marker of visual pathway integrity that can be followed over time and is welcome. It could be used as a noninvasive and inexpensive screening tool for OPGs reducing visit duration and total cost. New techniques of delivering radiation including fractionated stereotactic and proton beam radiotherapy are being pursued. Drugs targeting tumor angiogenesis such as bevacizumab may be widely used for the treatment of recurrent and refractory OPGs as long as issues regarding optimal dosing and long-term toxicity are solved. In addition, there are new treatments and more on the near horizon targeting cellular microenvironment which make it worth screening for tumors affecting the optic pathway.

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Key issues

- Children with brain tumors can present to ophthalmologist with a variety of ocular symptoms and signs.
- MRI is the preferred method of imaging for CNS tumors. However, due to the poor correlation between visual acuity and MRI findings, radiographic imaging should not be used as a screening tool for optic pathway gliomas (OPGs).
- Quantitative monocular visual acuity testing is the most useful test in detecting OPGs requiring treatment. All children must have teller acuity card testing and HOTV-computer based assessment when old enough. No other visual or investigative test is mandatory.
- OCT may aid in early detection of OPGs, thus allowing for timely initiation of chemotherapy and arrest of visual deterioration.
- The fundamental goal of surgery in patients with brain tumors is removal as much of the tumor as possible in order to improve long-term survival and decrease recurrence rate. However, surgery is not warranted in NF 1 subjects as they tend to have more diffuse disease.
- Radiotherapy is efficacious for the management of pediatric brain malignancies, although it should be avoided in children younger than 5 years of age and in subjects with oncogenic conditions.
- Combination chemotherapy regimens are being used with variable success in the treatment of pediatric brain tumors. The combination of carboplatin and vincristine is the most common regime in NF 1-related OPGs.
- Bevacizumab-based therapy in OPGs may greatly improve visual outcomes and should be considered in appropriate clinical situations, while the implementation of molecular targeted therapies is promising.
- Oncologists and neuro-ophthalmologists should work more closely so that patients with OPG can benefit from the combined expertise of physicians in both disciplines.
- Leeds Teaching Hospitals NHS Trust has developed methods of practice for the screening of NF 1 patients with/without OPGs using internationally developed standardized protocols.

References

Papers of special note have been highlighted as:

• of interest
•• of considerable interest


**Authors highlight the importance of quantitative visual acuity testing as a useful tool in detecting optic pathway gliomas (OPGs) requiring treatment.**


**Authors advocate that hand-held optical coherence tomography may be a reliable, noninvasive and inexpensive screening tool.**
tool for OPGs reducing visit duration and cost.


• Authors highlight the role of anti-VEGF agents for the treatment of recurrent or refractory OPGs.


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