

# Focus



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## Optic pathway Gliomas in childhood

### DEFINITION

Low grade gliomas (LGGs) are the most common primary CNS tumour in childhood. Optic pathway gliomas (OPGs) are intrinsic to the optic nerve, chiasm, tracts, radiations, and hypothalamus. They typically develop during early childhood, with the greatest tendency for growth in the first 3-5 years of life.<sup>1,2</sup>

### EPIDEMIOLOGY

OPGs constitute 5% of all childhood intracranial tumours with an estimated population incidence of 0.3 per million annually.<sup>3</sup> Most children diagnosed with OPGs have neurofibromatosis type 1 (NF1), the remainder being sporadic. The median age at presentation in childhood is 5 years. There is a female predominance in patients with NF1, suggesting a possible hormonal influence. 20-30% of patients with NF1 will have OPGs, 50% of which will be symptomatic, and 100% of which are present by 7 years of age.

### CLINICAL PRESENTATION

OPGs cause painless vision loss (affecting acuity, fields, contrast sensitivity and colour vision). Asymmetric disease can cause a relative afferent papillary defect and sensory strabismus. Orbital optic nerve gliomas can cause proptosis. A quantitative acuity (Teller, HOTV or Snellen) is the most important measurement. There is a limited role for colour, contrast sensitivity, and VF testing. Optic atrophy is a post-change finding of little prognostic value. Intracranial extension may result in hypothalamic and endocrine disturbances. Precocious puberty, especially in a child with NF1, should raise the suspicion of an OPG.

### NATURAL HISTORY

Tumour stabilisation, progression and spontaneous regression can sometimes occur. The rate of progression declines with age at presentation. Hypothalamic/chiasmatic tumours demonstrate the most sustained tendency to progress. Progression after the age of 12 years is uncommon, but some patients may still lose their vision in adolescence.

### PATHOLOGY

LGGs are heterogeneous, well-differentiated tumours originating from glial cells. Histologically, most OPGs

are juvenile pilocytic astrocytomas (WHO Grade I tumours) characterised by the presence of Rosenthal fibres. Lack of the NF1 gene product, functional neurofibromin (a tumour suppressor gene) results in dysregulated RAS signalling, resulting in increased cell proliferation and tumour formation. A small nonrandom duplication in the 7q34 region has also been identified in the majority of sporadic pilocytic astrocytomas. This duplication involves BRAF, a known oncogene implicated in numerous cancers.<sup>1</sup>

Biological mechanisms under investigation include angiogenesis and the tumour microenvironment, telomere maintenance, and glioma-associated antigens. Low cAMP levels in susceptible NF1 mice are sufficient to promote glioma formation. Pharmacologic cAMP elevation with phosphodiesterase inhibitors (e.g. rolipram) dramatically inhibits OPG growth in vivo suggesting a potential role for cAMP-targeted therapy.

### INVESTIGATIONS

MRI is the preferred technique for identifying and delineating the extent of OPGs, as well as monitoring for progression. Sporadic tumours typically arise within the chiasmatic-hypothalamic region (70-90%) affecting optic nerves alone less frequently than in NF1. Typical MRI characteristics include a fusiform appearance, diffuse enlargement of the nerve and/or chiasm, a downward kink in mid-orbit and enlarged optic canal. The original Dodge classification referred to tumours involving the optic nerves alone (Dodge I), the chiasm with or without nerve involvement (Dodge II), and the hypothalamus or other adjacent structures (Dodge III). The PLAN classification (modified Dodge) provides a more detailed description of tumour number, location and size required for the prediction of visual outcome and surgical access whilst taking into account the interaction with NF1 status.<sup>4</sup>

Current imaging is virtually always diagnostic, so biopsy of suspected tumours is no longer warranted. VEP and OCT have experimental roles at present. VEPs are neither sensitive nor specific to warrant their use as a screening test. The strong relationship between visual function and peripapillary RNFL thickness may predict visual deterioration.

## SCREENING IN CHILDREN WITH NF1

Screening of children with NF1 remains controversial. Children 6 years old and younger are at the greatest risk of developing OPGs. However, OPGs can present and progress beyond the preschool years. Published guidelines recommend annual ophthalmological examinations in all children with NF1 up to the age of eight years and reduced to every two years until 18 years of age<sup>5</sup>. However, there is no agreed UK approach. Baseline "screening" neuroimaging or VEP of asymptomatic children with normal visual examinations is not warranted.

## MANAGEMENT

The clinical course of OPGs may be unpredictable and highly variable, making diagnosis and management complex and controversial. Furthermore, the methods available for treatment have advanced considerably in the last 10 years. The management of OPGs is highly individualised and ophthalmologists should be aware of the benefits and disadvantages of the various treatment options.

The LGG trials are two large multi-centre, international clinical studies which have been conducted involving the UK childhood population. The trial summaries and plans for LGG3 are presented in table 1.

Close observation with serial MRI is the initial management in most cases. Initiating treatment at presentation is rarely necessary, but may be considered if there is severe visual impairment along with poor prognostic factors (e.g., sporadic OPG, optic tracts/radiation involvement). Loss of VA (e.g. 2-line decrease in Snellen) compared with previous examination, and tumour progression on MRI are the most common and accepted indications for treatment. It is likely that future studies will limit indications for treatment to functional visual problems.

Surgery is rarely appropriate for OPGs because of almost inevitable visual loss, endocrine deficits and cerebrovascular events. Indications for surgery include resection of large intra-orbital OPGs for painful or disfiguring proptosis, or corneal exposure in patients whose eye has severe visual impairment.

Radiotherapy (RT) is associated with visual, endocrinological, cerebrovascular, and neurocognitive sequelae, especially following its use in childhood. Moreover, RT significantly increases the risk of secondary malignant neoplasm development and vascular complications in patients with NF1. RT is therefore reserved for children who are older

(teenagers) or for younger children with progression or recurrence following exhaustion of chemotherapy options.

Chemotherapy (CT) is the first-line treatment of choice for most OPGs at all ages. The carboplatin and vincristine ("Packer") regimen is the most common with a 5-year progression-free survival (PFS) of 69% in NF1 patients.<sup>6</sup> Preliminary results from the LGG2-2004 study showed that VA was compromised in 43% before treatment. CT resulted in stable visual function in more than 2/3 of children but only improved VA in 11%. Although the carboplatin regimen appears relatively well-tolerated, neutropaenia, thrombocytopenia and allergic reactions may occur.

Another alternative regime, TPCV (thioguanine, procarbazine, lomustine and vincristine) was found to have a non-significant trend for improved event-free survival when compared to carboplatin/vincristine. TPCV is avoided in NF1 patients because of the risk of secondary leukemia associated with lomustine and procarbazine. Cisplatin plus etoposide has a reported 3-year PFS of 73%. Temozolomide and weekly vinblastine are both promising as single agents for recurrent/refractory OPGs with initial studies indicating stable disease in the majority of children.

A multi-disciplinary approach is imperative to address and support the complex changing care needs of patients (including access to special support services for visual impairment and educational support), their relatives and carers.

## FUTURE DIRECTIONS

The 5-year overall survival for OPGs is above 90%. Visual outcomes have only been evaluated as a trial end-point in recent years. Whilst reliable testing of VA is possible in very young children, compliance was poor in the LGG2-2004 study. Future studies of NF1-associated OPG will set VA as a primary outcome measure to ensure compliance with visual testing.

Our developing understanding of the signal transduction pathways that lead to LGGs carries the promise of improved outcomes for this tumour as newer molecularly targeted drugs may also be developed as therapeutic options. There are now research based animal models of NF1-associated OPG, whilst inhibitors of BRAF (e.g. vemurafenib), MEK, and mTOR are already in clinical trials. Drugs targeting tumour angiogenesis (e.g. bevacizumab) have recently been shown to result in objective functional and radiological improvements in recurrent/refractory OPG and are being evaluated in larger studies.

TABLE 1

TRIAL	INTERVENTION	OUTCOME
LGG1 (1997-2004)	• Observation vs CT (carboplatin and vincristine) for up to 12 months to delay RT	• Radiotherapy used in minority • 80% 5-year OS • 48% PFS
LGG2 (2004-2012)	• ≥ 8 years: RT. If NF1 also receive standard induction (vincristine + carboplatin) • < 8 years old with NF1: standard induction • < 8 years old without NF1: standard induction vs. intensified induction (vincristine + carboplatin + etoposide)	<b>NF1 only</b> • 98% OS • 75% PFS
LGG3	• Low-risk progression: PDE4 or dual biologic vs placebo • High-risk progression: vinblastine alone vs. vinblastine + bevacizumab	

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