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REVIEW

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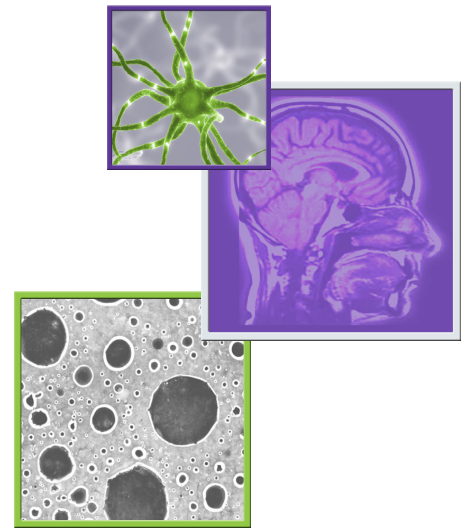

Optic pathway gliomas: a review

Iris Fried[1], Uri Tabori[1], Tarik Tihan[2], Arun Reginald[3] & Eric Bouffet*[1]

Practice Points

- Optic pathway glioma (OPG) is a condition primarily diagnosed during the first decade of life.
- OPGs represent 3–5% of all pediatric brain tumors and affect 6.6–20% of patients with neurofibromatosis type I. Most OPGs are histologically grade I astrocytomas.
- Presenting symptoms are essentially visual.
- Diagnosis is suspected on MRI scan. Pathologic confirmation is recommended in most cases. However, there is currently a consensus that radiological diagnosis is sufficient in infants with hypothalamic/chiasmatic lesions and in children with neurofibromatosis type 1.
- The current consensus is to treat children when the tumor represents a threat to vision.
- Since OPGs are generally not amenable to complete resection, the role of surgery remains limited.
- Treatment is essentially based on chemotherapy. In most series, the 5-year event-free survival is in the range of 30–40%. As a consequence many children require more than one line of chemotherapy.
- The role of radiotherapy has decreased overtime. This treatment is essentially considered as a salvage option, although some physicians still use this modality early in the management of older patients (>10 years old).

SUMMARY Optic pathway gliomas account for 3–5% of all pediatric CNS tumors and represent the most common intrinsic optic nerve tumors. These tumors occur preferentially during the first decade of life and are particularly frequent in children with neurofibromatosis type 1. Although optic pathway gliomas are low-grade tumors, their behavior can be aggressive, and their management is often challenging. Their management includes observation, surgery, chemotherapy and radiation. The role of each modality is discussed as well as current and future developments in treatment, in particular targeted therapies that are currently being investigated.

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The optic pathway includes the retina, the optic nerve, the optic chiasm, the optic radiations and the occipital cortex. The role of this pathway is to conduct visual information from the photoreceptors in the retina to the visual cortex of the brain. Several tumors can arise in the optic pathway, the most common being optic pathway gliomas (OPGs) that represent 66% of all primary optic nerve and pathway tumors [1]. The first reports of tumors involving the optic nerve were published nearly 200 years ago by Panizza [2] who described a large chiasmatic glioma extending anteriorly along both optic nerves and Wishart [3] who described a 13-year-old female patient with proptosis due to abnormal tissue along the optic nerve [4], whereas the occurrence of optic glioma in a patient with neurofibromatosis was first mentioned by Michel in 1873 [5]. Over the last century, numerous reports have improved our understanding of the pathology of optic nerve tumors, their clinical course, their association with neurofibromatosis and their treatment modalities. However, far from leading to a consensus, these reports have raised more questions regarding the behavior of these tumors and the complexity of their management. The objective of this review is to focus on OPG, the most common group of tumors of the optic tract, and to highlight the most recent advances in the diagnosis, the biology and management of these tumors.

Epidemiology

OPGs comprise 3–5% of brain tumors in childhood [4]. One of the most comprehensive reviews regarding the epidemiology of visual pathway gliomas in childhood was written by Dutton in 1994, based on 2297 cases of OPG collected in the literature until 1992 [1]. The median age at diagnosis was 7.0 years and 90% of the patients were diagnosed before the age of 19 years. Males and females were equally affected. A total of 29% of the cases were associated with neurofibromatosis. As far as tumor location is concerned, 25% of the tumors were confined to the optic nerves whereas the majority involved the chiasm. However, the authors acknowledge that this study summarized data published over a long period of time, during which modern imaging techniques were introduced. As a consequence, it may not fully reflect OPG epidemiology in the general population. Younger median and mean ages at diagnosis were reported both in neurofibromatosis type 1 (NF1) and non-NF1 populations in other studies [6–8].

The high incidence of OPG in patients with NF1 has long been known. This autosomal genetic disease is caused by inactivating mutations in a tumor suppressor gene on chromosome 17q that encodes neurofibromin, resulting in stimulation of RAS signaling and subsequent risk of developing RAS-induced tumors [9]. Large variations in incidence and prevalence of OPG in the NF1 population have been reported. Screening studies have shown that if all NF1 patients underwent serial neuroimaging studies, OPGs would be detected in 6.6–20% of children [10–13]. Conversely, the prevalence of neurofibromatosis among patients with OPG ranges between 20 and 40% in most reports [1,7,14,15], but prevalence as high as 58% has been reported [16]. These variations might be related to different factors, such as referral biases (association with a NF1 referral center or an oncology center) or institutional guidelines to acquire baseline MRI in NF1 patients. Although most OPGs diagnosed in the first year of life are not associated with NF1, the median age of diagnosis in NF1 patients is generally lower. In the NF1 population, most symptomatic OPGs are diagnosed before the age of 6 years old [10] but symptomatic OPGs have also been reported in older NF1 patients [17].

Clinical symptoms

A number of patients with OPG are asymptomatic, particularly among patients with NF1. When clinical symptoms are present, they vary depending on the location of the lesion. However, regardless of the location, visual loss is by far the most common symptom observed in patients with OPG [18]. There is no clear correlation between visual loss and tumor size. Other visual abnormalities are common. A relative afferent pupillary defect may be seen in up to 75% of symptomatic patients. Regardless of the location, various field defects can be observed, such as central scotoma, peripheral contraction and bitemporal hemianopia. On fundoscopy, the most common finding is optic atrophy. Disk swelling is unusual, and most commonly observed among patients with intraorbital optic nerve lesions [18].

Tumors located in the anterior optic pathway present with unilateral vision loss, strabismus and/or proptosis. Proptosis is often discrete, but may be severe and associated

with incomplete occlusion of the eyelid, and complications such as corneal ulceration. Proptosis is more common in NF1 patients than in those without NF1 [19]. Patients with chiasmatic tumors present with vision field loss, nystagmus and eventually loss of visual acuity. Patients with lesions extending to the hypothalamic region may present with hydrocephalus, diencephalic syndrome, precocious puberty or endocrinological deficits. The diencephalic syndrome, initially described by Russell in infants and young children, typically associates profound emaciation, growth acceleration, hyperkinesis and euphoria. It has been suggested that this syndrome is more likely to be associated with leptomeningeal dissemination [20]. Large lesions can cause motor deficits and, rarely, cerebrovascular events due to entrapment of major intracranial blood vessels. Data regarding frequency of clinical symptoms are presented in Table 1 [4,15,21].

Visual assessment

Since preservation of vision is the most critical aspect of the management of patients with OPG, ophthalmologic assessment is crucial. This usually includes assessment of different visual parameters, such as visual acuity, visual fields and fundoscopy, to detect visual dysfunction. The Snellen test is the standard test for visual acuity [22]. In children, visual fields are assessed using the Goldmann field exam or increasingly with automated perimetry. Color vision assessment may differentiate between vision loss and other reasons for vision acuity deficit [22,23]. However, for young children and uncooperative patients, these tests can represent a significant challenge. For preverbal toddlers or infants, the preferential looking test allows visual acuity to be measured by tracking eye movements and recording children's response on a television screen. This test does not require any contention and the child can sit in a family member's lap while being tested. The figure matching test is also used in young children. Recent studies have suggested that retinal nerve fiber layer thickness, as measured by optical coherence tomography under sedation, could be used as a biomarker of vision in children who cannot cooperate for visual acuity or visual field testing [24].

Visual screening in NF1 patients

Owing to the high incidence of OPG in the NF1 population, serial visual assessment is considered a screening tool. Yearly visual assessment up to the age of 8 years and assessment every other year until the age of 18 years are recommended by the NF1 Task Force as the best method of early diagnosis of OPG in the NF1 population [22].

However, in the context of a tumor that involves the optic pathway, loss of visual acuity may be a late occurrence and efforts to detect a threat to vision should ideally be identified earlier. The use of visual evoked potential has been suggested as a screening test in this population, but its long duration in young children (up to 30 min) and inconsistencies in reported results do not support its use in standard practice [22,25–27]. Some authors have suggested the sweep visual evoked potential as an alternative to conventional visual evoked potentials for presymptomatic OPGs in patients with NF1 and for the assessment of OPG patients over time, particularly in young children [28]. The use of optical coherence tomography is currently under investigation in the NF1 population [29].

Table 1. Symptoms of optic pathway gliomas in neurofibromatosis type 1 and non-neurofibromatosis type 1 patients.

Symptom	NF1 patients (%)	Non-NF1 patients (%)
Vision deficit	72	90
Proptosis	20–30 (found more in those aged <6 years)	5–12 (found more in those aged <6 years)
Hormonal deficit	30–40	34
Hydrocephalus	24	24
Nystagmus	18	18
Precocious puberty	4–10 (found only in those aged >6 years)	4–10 (found only in those >6 years)

NF1: Neurofibromatosis type 1.

Methods of diagnosis

Along with visual assessment, imaging is critical in the diagnosis and management of OPG. Although biopsy of suspected lesions has been traditionally offered to confirm the diagnosis, this approach is no longer warranted for lesions with characteristic imaging features and a diagnostic biopsy is currently limited to cases with unusual clinical or imaging findings. CT scans are still widely used, but MRI is by far the preferred technique of imaging. On CT scans, OPGs are iso- or hyper-intense lesions that usually enhance after contrast injection. Calcifications are unusual. When they are observed in an optic nerve lesion they favor the diagnosis of meningioma rather than glioma, whereas calcifications of a suprasellar lesion are more suggestive of craniopharyngioma or teratoma. On MRI, OPGs are usually hypo- to iso-intense on T1, and hyperintense on T2 images [30,31]. Bright enhancement of the lesion is seen in more than 50% of tumors after gadolinium injection. OPG can be confined to specific areas of the optic pathway, such as the optic nerve or the chiasm, or show more diffuse development along the optic tracts. When a tumor is confined to the optic nerves, imaging demonstrates well-circumscribed enlargement, often with a tortuous or kinked appearance, of the nerves. Tumors developed from the chiasm show various features on imaging, from a nonenhancing enlargement of the chiasm to bulky suprasellar enhancing lesions with or without an exophytic component. Patients with sporadic OPG predominantly have chiasmatic lesions with optic nerve involvement in a third of cases, while NF1 patients have lesions most commonly located at the optic nerve, which may or may not extend to the chiasm [32,33]. An anatomical classification was proposed in the late 1950s by Dodge *et al.*, defining tumors according to their location, as involving either the optic nerves alone (stage 1) (Figure 1), the chiasm with or without nerve involvement (stage 2), and the hypothalamus or other adjacent structures (stage 3) [34]. With the development of computerized imaging techniques, the accuracy and relevance of this anatomical classification has been questioned and new classifications have been suggested [35].

The size of OPGs is variable. Infants and young children tend to have larger tumors, sometimes associated with evidence of leptomeningeal dissemination [36]. Hydrocephalus may be associated with large lesions that obstruct the cerebrospinal fluid flow [15].

Despite the high incidence of OPG in the NF1 population, brain MRI is not recommended as a screening tool, as treatment is not indicated in the absence of visual symptoms or proptosis. Optic nerve tumors in NF1 patients exhibit specific MRI characteristics: they are often bilateral (Figure 2), and they typically show a double-intensity tubular thickening (also reported as 'pseudo cerebrospinal fluid' intensity signal) and downward kinking of the nerves in the mid-orbit, whereas non-NF1 patients tend to have more fusiform lesions [32,37]. Outside the optic nerve, MRI characteristics of OPG in patients with NF1 do not differ from non-NF1 patients. However, NF1 patients are also known to exhibit hyperintense lesions on T2-weighted brain MRI (formerly called unidentified bright objects) that are probably caused by aberrant myelination or gliosis. These lesions are predominantly located in the cerebral hemispheres, the basal ganglia, the brainstem or the cerebellum [38]. These findings are pathognomonic of NF1 and are so common that they have been proposed as an additional criterion for NF1 diagnosis in children [39]. NF1 children under the age of 4 years have few bright lesions, their number and volume increase between the age of 4 and 10 years, and then decrease progressively until they tend to disappear in adulthood [38].

MRI is also the modality of choice for monitoring progression or treatment response. However, criteria for defining either progression or response to treatment in OPG are still basic; they are generally based on 2D measurements of the lesion on T1-enhanced MRI scans [40]. These tumors are often complex in their shape and heterogeneous, with cystic, solid, enhancing and nonenhancing components and so volumetric assessment appears to be the technique of choice to detect variation in tumor size [41].

Other imaging techniques have been suggested in the management and follow-up of OPG. The reliability of PET in predicting tumor progression was assessed in several studies. Kruer *et al.* reported the results of a study that included 46 patients with low-grade glioma (LGG) who were evaluated by fluorodeoxyglucose-PET. Tumors with fluorodeoxyglucose hypermetabolism were significantly more likely to progress [42]. However, more data are needed to confirm the

potential role of PET in the management of OPG patients.

Magnetic resonance diffusion tensor imaging analyzes the diffusion of water molecules in the body. In the brain, diffusion occurs preferentially in the direction of the axons and so the optic tract represents an ideal model for magnetic resonance diffusion tensor imaging, as it is essentially a pure white-matter tract, anatomically distinct from the brain, which can be imaged using conventional MRI. This technique may be of use with respect to surgical planning in the context of lesions extrinsic to the visual pathway [43]. Given the risk of morbidity associated with surgery in these young patients, any noninvasive imaging tool that may prevent such complications warrants further investigation.

Tumor pathology

OPG are low-grade tumors in most cases. Several studies report OPG pathology to be almost exclusively comprised of LGG [14,44,45] but tumors with higher WHO grades have been reported [7,46,47]. One of the fundamental concepts in the pathological evaluation of OPG is the distinction of tumors that are infiltrative (i.e., diffuse astrocytoma) and circumscribed (e.g., pilocytic astrocytoma [PA]). The histopathological characteristics of these two groups are quite different from one another and these groups of neoplasms may need to be considered separately in terms of behavior and response to treatment. Unfortunately, many studies in the literature fail to make this distinction, leaving PA and diffuse astrocytoma combined under the ill-defined category of 'LGG' or 'LGG not otherwise specified'. Although OPG histology represents an important area of interest, the pathology result has no or little influence in the management of this tumor, and a significant number of patients with LGG are treated without histologic diagnosis, accounting for up to 47% of all patients in published series [48].

We will consider the unique entities defined by the current WHO classification system in separate sections [49].

■ PA, WHO grade I

The concept of PA has matured in the last decade and the neoplasm is now firmly established as a specific entity distinct from other forms of 'low-grade' astrocytomas, especially from the

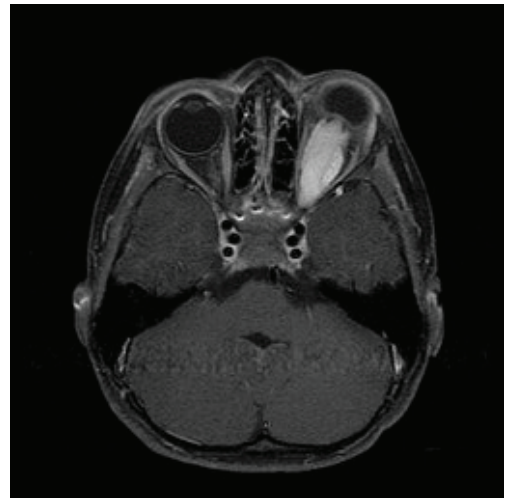

Figure 1. Unilateral optic nerve glioma in a 2-year-old child without neurofibromatosis type 1.

'diffuse' type [49]. PAs are known for their solid (enhancing) and cystic components. Macroscopic features also suggest that PAs of the anterior visual pathways are different from those occurring caudal to the optic chiasm [50]. PA of the optic nerve typically grows within the cylindrical confines of the optic nerve sheath [51]. The cross-sectional anatomy of these anterior visual pathway tumors are distinctive as to be almost pathognomonic – a neoplasm greatly expanding the optic nerve while transgressing the pia and proliferating beneath the optic nerve sheath [52]. The result is an enlarged optic nerve surrounded by neoplastic astrocytes and reactive elements enclosed within dura mater.

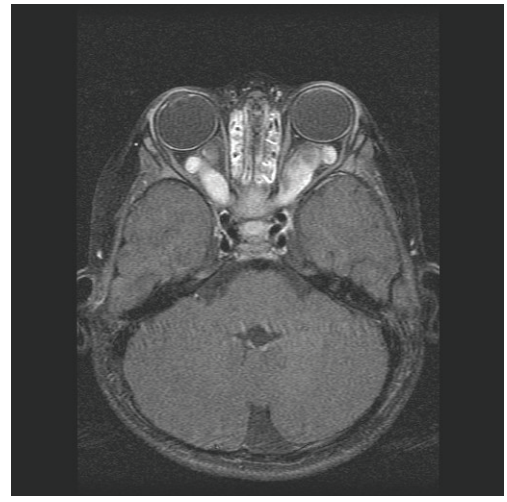

Figure 2. Bilateral optic nerve glioma in a 2-year-old child with neurofibromatosis type 1.

The degree of circumscription is less well defined in the suprasellar/hypothalamic tumors since the tumors can extend into neighboring structures, but this does not seem to influence biological behavior [50]. Hypothalamic and chiasmal tumors are often larger, more cystic and softer, with a texture somewhat resembling altered gray matter [53].

Microscopically, PA is well known for its biphasic architecture with loose and compact areas, although the microscopic variation is impressive and few tumors fit this classic description. Tumors are composed of bipolar spindle cells and often contain Rosenthal fibers. The origin of these Rosenthal fibers is still debated. However, they probably represent degenerated glial fibers [54]. Some tumors also show the so-called 'eosinophilic granular bodies', the microscopic hallmark of an indolent tumor. PAs often harbor calcifications, hyalinized vessels and rare mitotic figures. Vascular proliferation along the cystic component is typically arranged in a linear fashion and has been misrecognized as a sign of aggressive behavior in the past. Two important morphological patterns, the oligodendroglioma-like pattern and the so-called polar spongioblastoma pattern, have also caused PAs to be misclassified under different entities [55]. The histological diagnosis can be difficult in small specimens where it is not always easy to distinguish a PA from a diffuse astrocytoma. Once a tumor is recognized as a PA, specific histological patterns do not seem to be of any prognostic significance. Mitoses, vascular proliferation and even necrosis do not have the same connotations of aggressive behavior as they do in diffuse astrocytomas. However, an extremely rare example of malignant glioma arising in the setting of typical PA has been reported [56].

Immunohistochemical findings are also helpful in differentiation of typical PA from diffuse astrocytomas. Typically PA is a diffusely and strongly positive for GFAP and transcription factor Olig-2. Neuron-specific enolase, which is quite nonspecific, can be positive. It is also critically important to remember that some PAs can be strongly positive for synaptophysin, a neuronal marker, but this has not been construed as evidence of neuronal differentiation in these tumors. As a rule, PA do not harbor significant amounts of neurofilament positive elements and a complete absence of neurofilament protein staining can be used as evidence of a noninfiltrating tumor, such as PA. A critical caveat is the presence of marked neurofilament protein staining in the periphery of PA that can be considered as a sign of infiltration. A more recent discovery is the expression of IDH-1 in diffuse astrocytomas and its absence in PA [57]. This feature has been a very useful adjunct in diagnostic surgical pathology to differentiate diffuse astrocytoma from PA in small biopsy samples. Other immunohistochemical markers that are of less practical utility are positive staining with antibodies against vimentin and S-100 protein. Negative stains include epithelial membrane antigen, cyokeratins, p53 protein and EGF receptor. Immunohistochemical stains for proliferation markers such as Ki-67 (MIB-1) are typically low and under 5% [58]. Recent studies have revealed that the majority of non-NF1-related pediatric PA harbor the *BRAF–KIAA1549* (*B–K*) fusion gene resulting in constitutive activation of the RAS/MAPK pathway [59]. Retrospective analyses have suggested that the presence of the *B–K* fusion is associated with less aggressive behavior in OPG tumors [60].

■ Pilomyxoid astrocytoma, WHO grade II

The pilomyxoid astrocytoma (PMA) is a tumor of early childhood or adolescence that was initially described as a distinct entity in 1999 [61]. This neoplasm is considered as a variant of PA with characteristic clinicopathologic features and a slightly more aggressive behavior [49]. PMA most often arises in the hypothalamic/chiasmatic region, with symptoms referable to that site, including diencephalic syndrome. In older children, headaches, nausea and visual symptoms are more common. On MRI, PMA is a well-circumscribed solid mass along the midline in the hypothalamic/chiasmatic region [62]. Histologic appearance of PMA is that of a strikingly myxoid background and a monomorphous population of highly piloid astrocytic cells with a predominantly angiocentric arrangement. PMA is often a solid and noninfiltrative mass with only a tendency for peripheral infiltration of adjacent brain akin to typical PAs. The tumor cells have hyperchromatic and only minimally pleomorphic nuclei with rare mitotic figures. In contrast to typical PA, PMAs do not harbor Rosenthal fibers and only exceptional examples have eosinophilic granular bodies. PMAs typically lack a biphasic pattern [61].

A word of caution is critical in the diagnosis of PMA in that the typical features described above can be observed as a minor component of otherwise typical PA. More importantly, some high-grade infiltrating astrocytomas can have a significant myxoid background and focal angiocentric pattern that are somewhat hybrid between the typical pilocytic and the PMA [63]. Like most other entities or variants, it is critical to consider all the features of the tumor to avoid misdiagnosis.

Immunohistochemically, PMAs label strongly and diffusely for GFAP and vimentin but are negative for the neuronal markers synaptophysin, neurofilament, chromogranin and epithelial membrane antigen. The MIB-1 labeling index is low but some examples may have indices as high as 8%. The relation of PMA to PA is still debated, but the tumors that began as one and differentiate to the other, as well as hybrid tumors that contain components of both conventional PA and PMA, suggest that the two tumors belong in the same category [64]. These findings have been the main argument in favor of categorizing PMA as a variant of PA. Compared to age- and location-matched PAs, PMAs demonstrate a higher rate of local recurrence and more frequent cerebrospinal dissemination [65]. This relatively more aggressive clinical course resulted in a WHO grade II designation.

■ Diffuse astrocytomas

The term 'fibrillary astrocytoma' is often used synonymously with diffuse astrocytoma. Diffuse astrocytomas account for a minority of pediatric OPGs, although their exact frequency is unclear. In the St Jude and Toronto series, only one patient in each series (out of 42 and 73 biopsy-proven OPGs, respectively) had fibrillary astrocytoma [7,16], whereas 11 out of 26 tumors were described as fibrillary in the series from Philadelphia [66]. In contrast to the pilocytic lesion, diffuse astrocytoma is known for its remarkable infiltration of neuropils.

Histologically, diffuse astrocytomas are well-differentiated (astrocytoma grade II) and present as highly infiltrating lesions. Immunohistochemical stains for glial markers are only occasionally helpful, since many diffuse astrocytomas are variably positive for these markers. One helpful stain is the neurofilament protein that demonstrates the remarkable infiltrative pattern of the tumor. While the majority of diffuse astrocytomas in the adult population are positive for the IDH-1 antibody, this proportion is very low in the pediatric age group, suggesting that pediatric and adult diffuse astrocytoma are associated with distinct genetic signatures [67]. Staining for proliferative markers such as MIB-1 often reflects the grade of these neoplasms but MIB-1 is ususally low in the range of 2% for low-grade diffuse astrocytomas [68].

■ Other gliomas

In addition to the more common astrocytic neoplasms mentioned above, other less common tumors involving the optic tract include occasional gangliogliomas [69] or chordoid gliomas [70].

■ Prognostic markers

Pathological markers predicting clinical course in OPG are not widely used. MIB-1 in LGG varies between studies but it may be used clinically, with levels <1% associated with better outcome [71]. Bartels *et al.* evaluated the predictive value of microvessel density of OPG measured by immunostaining for factor 8 [72]. Elevated microvessel density was associated with significantly higher progression rate in 41 OPG patients [72]. Recent evidence from retrospective studies – that the presence of *B–K* fusion in non-NF1 patients may predict less aggressive behavior – suggests that we may witness a change in the current paradigm in the near future. Upfront biopsies of OPG that have been progressively abandoned in the presence of typical radiological features may be soon encouraged to determine treatment options.

Management options

The management of OPG includes observation, surgery, chemotherapy and radiotherapy. The decision to treat a patient with OPG, and the choice of the type of treatment is one of the most challenging and controversial aspects of the disease. Some authors consider that evidence is lacking to support active treatment of these tumors and have even suggested to change the term glioma to hamartoma [73]. However, the natural history of these tumors is highly variable and there is currently a consensus that, although observation is an important option, in a significant number of patients, OPG will cause a threat to vision, and sometimes a threat to life [74]. Careful assessment of possible gains – prevention of tumor growth and loss

of vital functions, such as vision – should be balanced against treatment side effects. OPG may severely affect a child but long-term survival is the rule, thus long-term side effects of treatment should be part of the decision-making process. Spontaneous regression of OPG, particularly in NF1 patients, is a known phenomenon that may also complicate analysis of treatment outcome [75].

Observation

Some retrospective reviews of OPG patients have shown that a subset of children do not require active intervention [16,76]. Spontaneous regression of these LGGs has been reported anecdotally [75,77]. Based on these observations, the rationale for active management of OPG with surgery, chemotherapy and/or radiotherapy has been challenged by some authors [73]. However, no prospective study has compared observation with active management, and this issue will likely remain unanswered. The current consensus is to treat patients with evidence of visual or neurological deterioration. More careful consideration is requested for children with NF1, as NF1-associated OPG is known to be more indolent [22]. Conversely, many authors agree that there is little role for observation in non-NF1 infants and young children, particularly when there is evidence of dissemination or association with diencephalic syndrome [66,78]. Comparison with historical series of patients with diencephalic syndrome suggests that intervention, particularly with chemotherapy, has changed the natural history of this condition. In a review of the literature, Addy and Hudson collected outcome data on 25 patients who received no intervention, and only three were alive at the time of publication [79]. The median time from onset to death was short, less than 12 months in most cases. Although this condition is still associated with a poor outcome, a recent report from Gnekow *et al.* reports a 10-year survival rate of 47% [78].

Surgery

There is no consensus on the role of surgery in the management of OPG. Complete resection is only feasible when the tumor is confined to the optic nerve and associated with complete blindness. For other tumors, particularly chiasmatic gliomas, the role of surgery was in the past limited to biopsy, with irradiation considered to be the definitive mode of treatment [80]. Over the last 20 years, and particularly with the contribution of modern imaging, the awareness that many patients with these gliomas present with exophytic extension has prompted some neurosurgical teams to revisit the surgical approach of these tumors. However, the benefit of aggressive surgery in these large chiasmatic gliomas has been difficult to demonstrate and radical surgery carries the risk of damage to the visual apparatus, hypothalamus and vascular structures. In a retrospective review, Gillett and Symon reported excellent outcomes and no significant complications in seven hypothalamic glioma patients (age range 9–40 years old) treated by subtotal removal plus radiation therapy, and concluded that "on general grounds, generous subtotal removal is preferable to limited biopsy, where the former can be performed without significant morbidity or mortality [81]." Wisoff *et al.* reported on a series of 16 patients who underwent surgical exploration with the intent to perform a radical resection [82]. A total of 11 children had a radical resection defined as 60–95% debulking. Patients who had limited resection were infants and children with NF1 who had infiltrative tumors. Although the morbidity of surgery is not extensively reported, the authors stated that no child had deterioration of vision as a result of surgery. Six patients who underwent radical resection remained progression free with a median follow-up of 29 months. However, aggressive surgery did not prevent further tumor progression in the four infants of this series. The authors concluded that surgical intervention appeared useful in selected exophytic tumors. Valdueza *et al.* reported their surgical experience in 20 patients with large hypothalamic/chiasmatic OPG (including six NF1 patients; median age of the population: 9 years) [83]. Ten patients underwent a >50% resection, whereas six had a partial resection and four had a limited biopsy. Five patients demonstrated visual improvement following surgery, whereas four had worsening of their vision. One patient developed a large cerebral infarction post-operatively and four patients had endocrine complications, including two with panhypopituitarism. Four patients received elective radiotherapy following surgery. At the time of the publication, all patients were alive [83]. However, seven patients experienced tumor progression during the follow-up

period. Sawamura *et al*. reported their surgical experience in a series of 25 children with optic pathway/hypothalamic gliomas [45]. Twelve patients underwent a biopsy of their tumor and seven patients underwent tumor resection. Five of these seven patients experienced significant complications (panhypopituitarism, hypothalamic dysfunction, cerebral salt wasting, hemiparesis, visual loss and epilepsy) and the authors concluded that the benefit of initial resection surgery in their experience was obscure. Steinbok *et al.* reported the surgical outcome of 18 pediatric patients with chiasmatic/hypothalamic astrocytomas [84]. Eight patients had subtotal resections, six had partial resections, three had limited resections, and one had no surgery. Patients who underwent limited resections had fewer complications, especially with respect to hypothalamic dysfunction. There was no correlation between the extent of resection and the time to tumor progression. The authors concluded that there was no benefit in attempting a radical resection of these tumors. In their opinion, the main role of surgery is to provide tissue diagnosis and to decompress the optic apparatus and/or the ventricular system if needed. In 1995, Sutton *et al.* described the outcome of 33 children (mean age 4.3 years) who, based on imaging findings, would have been candidates for radical surgery and were instead treated conservatively [85]. A total of 32 children underwent surgery: 27 patients had a limited biopsy and five a resection of 20–50% of their tumor. Most children underwent treatment with chemotherapy and/or radiation. At the time of the publication, 28 patients were alive and the authors concluded that their conservative approach did not appear to have compromised the outcome. Their recommendation was to avoid surgical morbidity and to consider adjuvant chemotherapy, particularly in young children. More recently Ahn *et al.* reviewed their surgical experience in 33 patients seen in their institution between 1982 and 1999 [44]. A total of 27 patients underwent radical removal (defined as the resection of more than 90% of the tumor) while six patients had a partial tumor debulking. Perioperative morbidity was significant, with two patients who died of post-operative pulmonary embolism and diffuse cerebral infarction. Five patients experienced transient hemiparesis and seven patients had worsening of their vision on post-operative assessment. Although the authors reported a trend toward better progression-free survival for patients who had radical resection followed by radiation, this difference was not significant.

Nicolin *et al.* pointed out the impact of aggressive debulking surgery in the neurocognitive outcomes of children with optic pathway tumors. In a retrospective series of patients with optic pathway tumors, patients treated with upfront debulking and chemotherapy displayed lower full and verbal scale IQ than those treated with chemotherapy only [16]. Overall, the role of surgery in the management of these tumors is still controversial. There is a consensus regarding surgery as the mainstay of treatment for unilateral optic nerve lesions associated with severe proptosis and/or complete unilateral blindness [21,86].

For other tumors, it is unlikely that a randomized trial will ever address the respective role of debulking surgery versus limited biopsy and the pros and cons of an aggressive surgical approach should be discussed on an individual basis in multidisciplinary meetings. Some specific aspects should be taken into account, such as the presence of a mass lesion obstructing the foramen of Monro causing hydrocephalus. In this context, surgical debulking may avoid the need for cerebrospinal fluid diversion. As OPGs tend to recur, surgery may be considered as part of management at a later stage during the course of the disease. However, most reports on the surgical management of OPGs have combined upfront debulking and salvage procedures, and the risk and the impact of salvage surgery has never been clearly evaluated [45].

Radiotherapy

For decades, radiation therapy has been the most important component of the treatment of OPGs [80]. The aim of radiation is to prevent tumor progression or tumor regrowth, which is associated with a risk of visual loss and neurological deficits. Retrospective and prospective studies have reported 5-year overall survival rates of 79–96% and a 5-year progression-free survival of 48–100% [87–91]. These results usually compare favorably with the event-free survival rates reported in chemotherapy series, which are more generally in the range of 35–50% at 5 years. However, comparisons between radiation therapy and chemotherapy series are flawed, due to the fact that the population groups differ significantly.

The median age of the patients in radiation series usually ranges from 8 to 10 years, whereas the median age of patients in most chemotherapy series is in the range of 3–5 years. It is now recognized that young age and neurofibromatosis are the most important determinants of the behavior of OPG, and OPGs are more aggressive in younger children [7,66,92]. Therefore, the relevance of such comparisons is limited, due to these major differences between chemotherapy and radiation therapy groups.

Traditionally, radiation was delivered through parallel opposed fields and the radiation volumes were usually generous in size for these deeply located lesions, leading to significant late effects, such as endocrinopathies, vasculopathies including strokes, and neurocognitive dysfunction, particularly in younger children. The advent of 3D radiation treatment planning and delivery has dramatically decreased the volume of radiation, minimizing the amount of normal brain tissue irradiated without compromising tumor control [88,93]. For OPG, the agreed clinical target volume (CTV) generally extends 1.0 cm beyond the gross tumor volume and the planned tumor volume extends 0.5 cm beyond the CTV. Recent studies have attempted to further reduce radiation fields. In particular, the study from the Children's Oncology Group ACNS0221 used a CTV defined as the gross tumor volume plus a 5 mm anatomically limited margin and the planning target volume extended 3–5 mm beyond the CTV [201]. The results of this recently closed study are pending. It is clear that modern techniques of radiation (i.e., 3D-conformal radiation therapy, intensity-modulated radiation therapy, stereotactic radiation, tomotherapy and proton therapy) are the techniques of choice for these deeply located tumors. However, taking into account the close proximity of the circle of Willis, it is unlikely that these modern radiation techniques, even proton therapy, will eliminate the risk of vasculopathies. Vasculopathy, also referred to as moyamoya disease, appears to be the major complication of radiation treatment in patients with OPG [94,95]. In 2007 Ullrich *et al.* analyzed the prevalence of moyamoya in 345 children irradiated for brain tumors [96]. A total of 12 patients developed moyamoya disease, including 11 with significant neurological symptoms. Ten out of 12 of these patients had OPG while the total number of OPG patients within the 345 patients was 31. Other risk factors for the development of moyamoya were young age, a dose of more than 50 Gy to the circle of Willis, NF1 and prior surgery. Similar results were demonstrated in a literature review evaluating all cases of moyamoya reported between 1967 and 2002. Among the 54 published cases, 29 had OPG and 56% were irradiated prior to the age of 5 years [97]. In a prospective Phase II trial of conformal radiation therapy, Merchant *et al.* treated 78 pediatric patients with LGG (median age of 8.9 years), including 58 with diencephalic tumors [87]. The CTV margin in this trial was 10 mm and planning target volume margin was 3–5 mm. Four patients had evidence of vasculopathy prior to radiation (two patients had NF1). The vasculopathy of the two NF1 patients worsened after treatment and they both required revascularization surgery. Following radiation, five additional patients, including one with NF1 developed radiographic evidence of vasculopathy 12–99 months post-radiation and three patients required revascularization surgery. In a series of pediatric LGG patients treated with proton therapy, which included seven patients with OPGs (five with neurofibromatosis), Hug *et al.* reported one case of moyamoya disease that required revascularization surgery [98].

Other late effects of radiation include neurocognitive deficits, second tumors and endocrinopathies. The risk of a second tumor after CNS radiation is well documented [99]. Dosimetric comparison and biological modeling of potential radiation-induced toxicities have suggested a decreased risk of secondary tumor with protons compared with intensity-modulated radiation therapy. However, constant improvements in radiation techniques limit the value of such predictions. Endocrinopathies, including growth hormone deficiency, diabetes insipidus, precocious puberty and testosterone deficiency, may also be the effect of the tumor or its surgical management and cannot be attributed solely to the effects of radiation in OPG patients.

Evaluation of radiation-associated neurocognitive deficits in patients with OPG are also challenging, as a number of confounding factors can interfere with interpretation, such as underlying neurofibromatosis, young age at diagnosis, large tumor, hormone deficits or pre-existing hypothalamic damage. Very few

Table 2. Radiologic response and event-free survival in clinical studies using chemotherapy for children with chemotherapy-naive and recurrent low-grade glioma.

Chemotherapy	Total ND/R	Total OPG	Median age; years (range in years)	NF1	CR + PR + MR	SD	PD	PFS; % (years)	OS; % (years)	Ref.
Vincristine–actinomycin	24 ND	24	1.6 (0.2–5.5)	3	9	15	0	NA	NA	[104]
Vincristine–carboplatin (weekly)	78 ND	58	3.08 (0.2–16)	15	33	22	3	68 ± 7 (3)	97 (3)	[106]
Vincristine–carboplatin (weekly)	137 ND	71	NA (all <10)	0	47†	16†	30†	39 ± 4 (5)	86 ± 3 (5)	[111]
SFOP (6 drugs)	84 ND	84	2.7 (0.3–13.6)	23	51	23	11	34 (5)	89 (5)	[110]
Temozolomide	11 ND, 19 R	14	10 (4–18)	4	4	12	14	17 (4)	71 (4)	[48]
Etoposide–cisplatin	31 ND, 3 R	29	3.7 (0.3–16.5)	8	24	10	0	78 (3)	100 (3)	[115]
Etoposide–cisplatin	37 ND	23	6 (0.5–16.5)	7	24	NA	NA	60 ± 9.6 (5)	86.4 ± 8 (5)	[121]
TDPCV	33 ND	33	3 (0.3–16.2)	6	NA	NA	NA	30.3 ± 8 (5)	90.9 ± 5 (5)	[122]
TPCV	137 ND	67	NA (all <10)	0	54‡	16‡	33‡	52 ± 5 (5)	87 ± 7 (5)	[111]
Vinblastine	51 R	34	7.2 (1.4–18.2)	9	18	19	13	42.3 ± 7.2 (5)	93.2 ± 3.8 (5)	[118]
Carboplatin	60 ND, 21 R	51	6.6 (0.5–17)	22	23	46	11	64 (3)	84 (3)	[123]

†Out of 93 patients centrally reviewed.
‡Out of 103 patients centrally reviewed.
CR: Complete response; MR: Minor response; NA: Not available; ND: Newly diagnosed; NF1: Neurofibromatosis type 1; OPG: Optic pathway glioma; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; R: Recurrent; SD: Stable disease; SFOP: Alternating courses of carboplatin–procarbazine, etoposide–cisplatin and vincristine–cyclophosphamide; TDPCV: Thioguanine, dibromodulcitol, procarbazine, lomustine and vincristine; TPCV: Thioguanine, procarbazine, lomustine and vincristine.

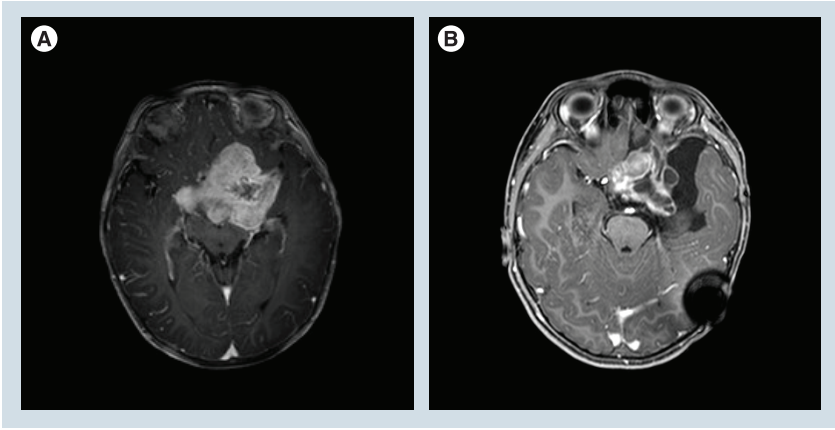

Figure 3. Response to single-agent vinblastine in a child with pilomyxoid astrocytoma. (A) At the time of diagnosis, aged 12 months and **(B)** at end of chemotherapy, 18 months later.

studies have systematically assessed cognitive deficits with baseline evaluation and serial post-radiation cognitive assessments. A recent study from Merchant *et al.* showed that cognitive deficits are limited and predictable in most patients, and that young age is associated with a risk of increased deficits [93]. As far as the choice between photons and protons is concerned, differences in radiation dose distributions, as indicated by modeling changes in cognitive function, suggest that protons would have long-term clinical benefits for children with OPGs [100].

■ Chemotherapy

As experience regarding the long-term complications associated with the use of radiation for treatment of OPG patients gradually accumulated, the search for other active treatment modalities grew in the pediatric oncology community. Early experiences of chemotherapy involved patients who had failed radiation. In the pre-CT scan era, Rosenstock *et al.* reported the successful use of single-agent vincristine in a child with recurrent OPG after radiotherapy [101]. Several limited-size institutional studies in the 1980s confirmed the potential of chemotherapy to control progression and even induce shrinkage of LGGs [102–104]. Larger collaborative studies were conducted in the last two decades and have since confirmed the activity of several agents and combinations [105–109]. However, because of the specific design of chemotherapy studies, the long-term benefit of chemotherapy in patients with OPG is still unclear. In particular, the capacity of chemotherapy to prevent visual impairment has never been formally established. Retrospective studies have suggested that systemic chemotherapy may arrest the decline in visual acuity and stabilize vision. In a recent report on a population of patients with neurofibromatosis treated with chemotherapy, approximately a third of children regained some vision with treatment [109]. However, pre-existing visual damage is the main limiting factor of the ultimate visual outcome [110].

Among the most largely used protocols are the combination of carboplatin and vincristine, and the thioguanine, procarbazine, lomustine and vincristine (TPCV) regimen [106,111]. Other combinations are detailed in Table 2. Comparisons between these regimens are limited due to differences in patient age or tumor status (newly diagnosed or recurrent), inclusion or exclusion of neurofibromatosis patients, tumor location, definition of response and definition of progression. Studies of chemotherapy in LGG have included a majority of OPG patients, but specific analyses of this subgroup are generally lacking. Overall, OPGs respond to chemotherapy, and chemotherapy is able to stabilize disease progression and visual impairment (Figure 3). In a significant number of patients, chemotherapy provides sustained or even permanent tumor control. However, complete response to chemotherapy is exceptional and most patients will show evidence of significant residual MRI abnormalities years after the completion of therapy, even in the absence of further progression.

The activity of chemotherapy on OPG symptoms is variable. The efficacy of chemotherapy in treating the diencephalic syndrome associated with hypothalamic/chiasmatic gliomas has been reported with most regimens Box 1 [112]. Although it should, in theory, represent a major outcome measure, visual response has been reported in a limited number of studies. From the data available, most patients show stable vision, visual improvement is only seen in a minority of patients and visual response does not appear to correlate with radiological response [113]. As previously stated, a number of technical issues are limiting reliable evaluation of visual parameters (visual acuity and visual fields), particularly in young children.

The choice of a chemotherapy regimen should take into account a number of factors. As far

as efficacy is concerned, the lack of consistency in response criteria precludes meaningful comparisons between regimens. Only one randomized study has been conducted and has compared vincristine–carboplatin and the TPCV regimen [111]. Both combinations showed a similar response rate. However, patients treated with TPCV had a higher (although not significant) progression-free survival at 5 years (52 ± 5% for the TPCV regimen vs 39 ± 4% for the carboplatin–vincristine regimen; p = 0.1). Most other studies have reported similar progression-free survival rates, of approximately 40% at 5 years (Table 2). Other criteria may influence treatment choices, in particular short- and long-term toxicity of these regimens. The incidence of carboplatin hypersensitivity reactions reaches 40% in some series and this is limiting the use of this regimen [111,114]. Hearing loss has been reported in 28% of the patients treated with cisplatin-containing regimens, and this represents a questionable toxicity in visually impaired patients [115]. Prolonged exposure to alkylating agents, such as procarbazine, temozolomide, cyclophosphamide and platinum compounds, is questionable in the context of a benign tumor with excellent survival rates. Finally, repeated administration of etoposide is associated with a significant risk of leukemia [116]. Studies are ongoing to confirm the promising results observed with single-agent vinblastine, vinorelbine or the combination of bevacizumab and irinotecan [117–119].

Most patients with OPG will require more than one treatment. Traditionally, radiation was the standard salvage treatment at the time of progression after a first line of chemotherapy. Increasingly, chemotherapy is used as a second or subsequent treatment option, particularly in young children. Recent reports have suggested that repeated chemotherapy administration is feasible and this approach does not compromise the visual outcome of OPG patients [120].

Prognostic factors

The main objective of management in patients with OPG is to prevent visual compromise and neurological damage associated with tumor progression. However, the behavior of these tumors is erratic and the decision to treat is mostly based on subjective criteria, such as the risk of neurological or visual impairment associated with tumor progression. Several factors, such as age at diagnosis (or at start of treatment), tumor location along the optic pathway and NF1 status, have been suggested as potential predictors of OPG behavior. In a systematic review of the literature, Opocher *et al.* identified age <1 year as the most relevant and scientifically documented prognostic factor for progression Box 1 [74]. Absence of NF1 status, posterior tumor extension along the optic pathway (Dodge 3) and pilomyxoid histology also showed some prognostic relevance, but the scientific evidence to support their prognostic value was lacking.

Box 1. Recommended treatment algorithms.

Children under the age of 1 year

- Surgery to be discussed case-by-case depending on clinical presentation (in particular presence/absence of hydrocephalus). Immediate chemotherapy should be considered in most cases (no observation period)

Children 1–5 years old

- Observation in the case of a small tumor without visual impairment. In the context of a bulky tumor, biopsy is recommended, debulking to be discussed case-by-case. Whether surgery/biopsy is performed or not, chemotherapy to be considered if evidence of radiological progression or visual deterioration

Children 6–10 years old

- Observation in the case of a small tumor without visual impairment. In the context of a bulky tumor, biopsy is recommended, debulking to be discussed case-by-case. Chemotherapy to be considered after a period of observation, if evidence of radiological progression or visual deterioration. Conformal radiation treatment is an alternative to chemotherapy in non-NF1 patients

Children >10 years old

- Observation in the case of a small tumor without visual impairment. In the context of a bulky tumor, biopsy is recommended, debulking to be discussed case-by-case. Chemotherapy or conformal radiation treatment to be considered after a period of observation, if evidence of radiological progression or visual deterioration

Conclusion & future perspective

Failure of most chemotherapeutic regimens to achieve long-term disease control and failure to improve vision in a significant number of patients underline the need to search for other treatment options. Evidence of overexpression of VEGF in LGG has triggered an interest in antiangiogenic therapies and in particular for bevacizumab in the management of OPG patients [119]. Other targets involved in the RAS MAPK pathway, including MEK inhibitors or AKT inhibitors, are being currently evaluated.

OPG is a tumor associated with significant potential morbidity. Current treatment options achieve good overall survival but a significant number of patients will require treatment, and some may need more than one line of therapy. Further research is needed to improve visual outcome and better understand the main determinants of OPG behavior.

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