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Pediatric Optic Pathway Gliomas: Diagnosis, Management, and Outcomes

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Abstract: Optic pathway gliomas (OPGs) are the most common brain tumor that pediatric ophthalmologists and neuro-ophthalmologists care for. These low-grade gliomas are found along the anterior portion of the visual pathway and demonstrate unique features in their growth, impact on visual function and response to treatment. The standardized approach to the ophthalmologic evaluation and testing positions the ophthalmologist to play a vital role in the care of these unique tumors. This review will cover the epidemiology, clinical evaluation, treatment and outcomes of OPGs.

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INTRODUCTION

Representing ~30% of all childhood brain tumors, pediatric gliomas are a type of neoplasm arising from glial cells.[1] Among these, optic pathway gliomas (OPGs) are a distinct subset of these neoplasms that affect the anterior visual pathway.[2] OPGs occur primarily in the pediatric population, while adult cases are exceedingly rare.[3] Of note, OPGs are frequently associated with neurofibromatosis type 1 (NF1), with around 20% of patients with NF1 developing an OPG.[2] OPGs exhibit highly variable and unpredictable growth patterns, causing the management of OPGs to be a subject of debate among neuro-ophthalmologists and oncologists alike. This chapter explores the latest insights into the pathology of pediatric OPGs, highlighting recent advancements in clinical assessment, imaging techniques, and treatment approaches.

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Definition

OPGs are defined as low-grade gliomas [World Health Organization (WHO) grade I juvenile pilocytic astrocytomas, grade I pilomyxoid astrocytomas, and grade II diffuse fibrillary astrocytomas] that primarily affect the anterior visual pathway (AVP), which includes the optic nerves, optic chiasm, optic tracts, radiations, and the hypothalamus.[2,4] OPGs can occur sporadically or in association with the tumor predisposition syndrome NF1.[2] The diagnosis of OPGs is not defined by distinctive clinical or radiologic criteria and instead is based on a combination of imaging findings, clinical examination, and patient history.[5]

Epidemiology

In most cases, an OPG diagnosis is made without a diagnostic tissue biopsy due to the significant risk of vision loss associated with the procedure itself, so the exact incidence of each tumor type is unknown.[2] That said, OPGs represent roughly 5% of all childhood CNS tumors.[3] In addition, children with NF1—the most common autosomal dominant genetic disorder, affecting ~1 in every 3000—have an increased risk of developing OPGs, with around 1 in 5 individuals with NF1 having an OPG.[2,6]

In patients with NF1-related OPGs, the majority of tumors are found within the optic nerve and chiasm, as compared with the optic tracts and radiations.[3,7] OPGs affect males and females at similar rates.[3,8–11]

CLINICAL PRESENTATION

Age of Presentation

Approximately 83.7% of OPGs occur in the pediatric population, with ~70% of OPGs diagnosed within the first decade of life and 90% diagnosed by the second decade, while adult cases are exceedingly rare.[3,12] The age of onset for NF1-related OPGs can vary significantly depending on the clinician, since neuroimaging for OPGs in asymptomatic NF1 patients remains controversial.[13,14] Some clinicians opt to perform neuroimaging regardless of the ophthalmologic examination results, while others may only do so if there is a specific indication.[13,14] However, most NF1-related OPGs are generally diagnosed before the age of 7, with an average diagnosis age of 4.5 years.[15] While incredibly rare, symptomatic NF1-related OPGs can also be diagnosed after 8 years of age or even into adolescence.[8,16] The typical age of diagnosis of

sporadic OPGs is slightly older, with the majority of sporadic OPGs diagnosed before the age of 8 years. Furthermore, like NF-1-related OPGs, diagnosis can also occur in the second decade of life or even into late adulthood.[13,17,18]

Signs and Symptoms

Symptomatology varies greatly and can be impacted by the location and type of the OPG.[19] Ophthalmologic symptoms and observations identified at the time of OPG diagnosis include: decreased visual acuity (VA), visual field (VF) defects, color vision loss, relative afferent pupillary defect (RAPD), optic disc pallor, and new-onset nystagmus, proptosis, strabismus, optic disc edema or atrophy.[4,5,20] It should be noted that detecting visual deterioration in patients with OPGs by parents and clinicians alike is challenging due to the typically young age at which symptoms develop and the gradual and insidious progression over months to years before becoming noticeable.[13,21] The nystagmus associated with an OPG may present as horizontal or rotary and can be either asymmetric or monocular.[13] A distinctive form of pendular nystagmus characterized by rapid, small-amplitude, horizontal movements—often described as "shimmering"—may also occur and can serve as an early indication of an OPG with optic chiasm involvement.[13] Other neurological findings include: headache, nausea/vomiting, seizures, cranial nerve palsy, and developmental regression.[19] OPG extension into the hypothalamic region can lead to precocious puberty, short stature, diabetes insipidus, hydrocephalus, and diencephalic syndrome.[19,20]

The clinical presentation of NF1-associated and sporadic OPGs varies in symptom onset, progression, and severity, with these differences largely driven by variations in tumor location.[13] NF1-related OPGs tend to show indolent growth and have a lower likelihood of clinical progression.[4] As such, 60% to 76% of NF1-related OPGs are asymptomatic and often discovered incidentally through screening MRI or imaging for unrelated reasons.[13] In contrast, ~90% of sporadic OPGs are diagnosed following the onset of a new neurological or ophthalmological abnormality that prompts neuroimaging.[4,13] NF1-related OPGs are most frequently isolated to the optic nerves—with bilateral optic nerve tumors seen exclusively in NF1—and typically present with mild or no vision loss, infrequent proptosis, and rare endocrinological defects.[4,13,19,22–24] In contrast, sporadic OPGs are more frequently found in the chiasm and posterior optic pathways and present with more aggressive features, including severe, rapidly progressive vision loss, sudden proptosis, and a higher incidence of endocrine dysfunction.[4,13,19,24]

Neuro-ophthalmic Evaluation

Visual Acuity

The most crucial assessment for patients with OPGs is age-appropriate, best-corrected quantitative visual acuity (VA) testing.[4,5,13,25] Qualitative visual acuity assessments, such as fix-and-follow or the constant-steady-maintained method, are commonly used in young children but are inadequate for detecting subtle and/or significant changes in VA with sufficient accuracy.[5] Instead, quantitative measurements are essential for monitoring patient vision during ophthalmologic evaluations for patients six months of age or older.[25] Teller acuity card (TAC) testing, a preferential looking test, can be used in children as young as 6 months and has shown a moderate correlation with Snellen VA testing at later ages.[25–27] For children 3 years and older, VA can be assessed using matching LEA pictures or HOTV optotypes.[4,5,13,25]

Since measuring VA in the pediatric population is inherently challenging due to limited patient cooperation, ensuring accurate and reliable VA results can be difficult. In addition, patients with NF-1 frequently have neurodevelopmental delays and have a higher prevalence of attention deficit hyperactivity disorder, further complicating the accuracy of VA assessments.[5,9] Using skilled examiners for VA testing in this population is imperative to ensuring accurate results. For patients with limited cooperation or testing anxiety during an ocular examination, parents should be advised to practice VA testing at home (eg, matching LEA symbols or HOTV testing) to improve cooperation for the next visit.

Although there is no universally established definition of clinically significant vision loss, experienced clinicians often view a decrease of two Snellen lines from baseline as indicative of disease progression.[13] However, it is important to note that the magnitude of change between lines varies nonlinearly within or across acuity tests. To make comparisons of acuity more reliable across different acuity levels, clinical trials often use the logarithm of the minimal angle of resolution (logMAR) scale, which provides a linear measure of visual acuity changes, meaning the difference between lines is consistent across all values. Usually, a VA loss of 0.2 log MAR is considered a significant VA decline.[28] Furthermore, if a significant difference in VA is identified, factors such as poor patient cooperation, refractive error, amblyopia, and functional visual loss should be considered before attributing the clinical findings to tumor progression. In addition, tumor-related decreases in VA should be confirmed before determining treatment options.

Visual Fields

VF testing in young children may be difficult due to their age and ability to fixate on a central target. However, this is an essential component of the exam and should be attempted when feasible as VF defects can be the predominant symptom in some children. In addition, in NF1-OPGs, Heidary and colleagues found a relatively high percentage (76%) of patients experienced VF loss following chemotherapy treatment, demonstrating the utility of VF testing for monitoring treatment efficacy.[29] Furthermore, of the patients who received VF testing before and after treatment, 38% of patients who underwent chemotherapy treatment experienced VF loss, while 44% experienced VF stability and 19% showed VF improvement.[29] Posterior tumor location with optic tract

and/or optic radiations involvement was the main risk factor for VF loss, and earlier age of chemotherapy treatment was also correlated with poorer VF outcome.[29] It should be noted that changes in VF were not always associated with changes in VA.[29] With this said, VF testing should be introduced when the child is developmentally able to fully understand the extent of visual impairment and guide treatment decisions.

Color Vision

When the child is of sufficient age, color vision testing should be performed at each visit, as it helps differentiate vision loss caused by amblyopia from vision loss caused by optic neuropathy. Color vision loss in conjunction with VA loss is usually an indicator of optic neuropathy due to OPG progression, while VA loss with preservation of color vision could be due to amblyopia, functional disorder, poor cooperation, or refractive error.

Fundus Examination

Fundus visualization should be included during all exams to detect optic nerve pallor or edema. The occurrence of optic nerve swelling varies significantly across studies and is most frequently observed in sporadic OPGs confined to the optic nerve.[8,13,30–32] Optic disc pallor typically indicates chronic damage to the axons of that is often observed in protracted cases of OPGs that have affected the visual pathway proximal to the lateral geniculate nucleus.[13] Previous studies suggest that optic disc pallor is a significant risk factor for poorer visual outcomes and treatment responses in patients with OPG, emphasizing the importance of regular fundus examinations to monitor disease progression and guide management decisions.[31,33–35]

Other Ophthalmic Findings

Pupil reactivity, ocular ductions, and ocular alignment should be evaluated at every visit.[4,13] RAPD occurs in up to 75% of symptomatic OPG patients, typically due to optic neuropathy caused by tumor compression.[8,13] Proptosis is more common in NF1-associated OPGs than sporadic OPGs and is usually nonaxial with temporal or downward displacement of the eye.[8] Nystagmus is present in ~18% to 24% of OPGs.[8,32]

Visual Evoked Potentials

Visual evoked potentials (VEPs) are a noninvasive neurophysiological test that measures the integrity of the visual pathway in response to a visual stimulus. Abnormal VEP findings, such as delayed latency or reduced amplitude, indicate damage to the visual pathway.[4] While VEP has been identified as a tool for detecting OPGs, its effectiveness and practicality remain controversial among clinicians. Although VEP demonstrates high sensitivity (90% to 100%) for OPG detection, its specificity is only moderate (60% to 69%), consequently leading to a high rate of false positives.[36–39] Most notably, VEP has been shown to be ineffective in distinguishing between symptomatic and asymptomatic OPGs, and it cannot reliably predict, detect, or monitor VA loss in patients with OPGs.[5,36,40] In addition, VEP testing is further limited by its lack of universal availability, time-consuming protocol, and difficulty in uncooperative patients.[5,36] Because of these limitations, VEP is not recommended as a standard tool for guiding treatment decisions in patients with OPGs.

Optical Coherence Tomography

Optical coherence tomography (OCT) is a noninvasive imaging technique used to capture detailed, cross-sectional images of the retina and measure the thickness of retinal axons, known as the retinal nerve fiber layer (RNFL), which collectively form the optic nerve and visual pathway.[4,13,41] Recent advancements in OCT, combined with studies exploring its application in monitoring OPGs, have led to significant and promising discoveries.[42]

The introduction of handheld OCT (HH-OCT) devices has revolutionized the assessment of young children, particularly those unable to cooperate with standard VA tests, since HH-OCT can effectively measure RNFL thickness during sedation and differentiate between children with and without vision loss due to OPGs.[43] In addition, Avery et al[44] reported a significant correlation between RNFL thinning and VA and/or VF deficits in children between the ages of 6 and 21 with OPGs. Parrozzani and colleagues confirmed these findings in a study with 57 patients with NF-1-associated OPGs and further concluded that RNFL analysis demonstrates superior reliability as a clinical screening method compared with visual function assessment and/or optic disc evaluation.[44–46] More specifically, Avery et al[28] determined that a greater than 10% RNFL thickness decline in either one or more quadrants or the global average is highly predictive of new vision loss in patients with OPGs, and a lack of progressive RNFL thinning on follow-up exams is a strong predictor of stable vision in patients with OPGs. Furthermore, OCT analysis of the macular ganglion cell–inner plexiform layer (GCL-IPL) showed excellent diagnostic performance, with an area under the curve (AUC) >0.90 for distinguishing children with OPGs who had vision loss from those who did not; nevertheless, its effectiveness for monitoring new-onset vision loss has not been demonstrated in longitudinal studies.[47] Collectively, these studies indicate that decreased RNFL thickness is a key indicator of anterior visual pathway (AVP) damage and now serves as a biomarker and visual outcome measure for children with NF1-OPGs, particularly those unable to undergo VA testing.[4,13,41,48] However, beyond confirming the presence/absence of RNFL thinning during the baseline assessment of OPGs, it remains unclear how longitudinal OCT measures can be utilized for clinical decision making. For example, the timing between tumor insult to the visual pathway axons and when atrophy is visualized using OCT has not been firmly established. The magnitude and duration of the insult, as well as the distance from the optic nerve head, are factors that likely contribute to when optic atrophy

can reliably be measured. Multiple longitudinal OCT studies are ongoing that will hopefully clarify its utility in caring for children with OPGs.

Neuroimaging

MRI of the brain and orbits using thin slices through the optic nerves and chiasm is the preferred imaging method to evaluate the extent of an OPG and to monitor for any changes over time.[4,13] OPGs typically cause diffuse enlargement of the optic nerves and/or the optic chiasm, and, in some cases, the OPG also has optic tracts or optic radiation involvement (see Fig. 1 for an example of an OPG with bilateral optic nerve and chiasm involvement).[4,13] Optic nerve gliomas often appear spindle-shaped (fusiform) and may have a characteristic downward bend in the middle part of the orbit.[4,13] Occasionally, not only is the optic nerve itself enlarged, but there may be abnormal tissue surrounding the nerve while still enclosed within the nerve sheath.[4,13] This can occur either because the tumor has extended through the pia-arachnoid membranes or due to underdevelopment (hypoplasia) of the arachnoid layer.[4,13] When the tumor extends through the pia-arachnoid, the extra-axial intradural tissue may resemble cerebrospinal (CSF) fluid on MRI, a finding known as the "pseudo-CSF" sign.[4,13] Chiasmal gliomas, best seen on coronal MRI slices, appear as an enlargement of the chiasm or as a suprasellar mass, and may sometimes contain cystic components.[4,13] These tumors are usually isointense on T1-weighted MRI images and are either isointense or hyperintense on T2-weighted images.[8] Tumors that have cystic parts are more commonly seen in sporadic cases than in NF1-associated OPGs.[49] Of note, increases in gadolinium enhancement were not associated with VA decline nor the initiation of tumor-directed therapy in both longitudinal and newly diagnosed patients with NF1-associated OPGs.[50]

Recent studies have identified correlations between imaging features and the likelihood of tumor progression. First, children who do not have an OPG detected on brain/orbital screening MRI at age 15 months or later are found to have a very low risk for OPG progression, vision loss, or the need for therapy.[11] Furthermore, this same study found that early identification and treatment of an OPG through MRI led to better visual outcomes overall.[11] Tumor location additionally has been identified as a risk factor for vision loss in patients with OPGs; Fisher and colleagues identified an increased risk of poor visual outcomes in patients with NF1-OPGs involving the optic tracts, while Shofty and colleagues and Azizi and colleagues identified that both optic tract and optic chiasm involvement are associated with worse visual outcomes.[31,51,52] MRI abnormalities such as optic nerve tortuosity and nerve sheath thickening are frequently observed in children with NF1 but are distinct from OPGs.[5] Optic nerve tortuosity may be associated with an increased risk of developing an OPG but has not been found to correlate with a higher likelihood of requiring treatment compared with other NF1-OPG patients without optic nerve tortuosity.[5]

Volumetric MRI analysis methods have provided new insights into the utility of MRI for monitoring OPGs and assessing disease progression. Avery et al[53] were the first to demonstrate that greater OPG volume and the total volume of the anterior visual pathway (AVP), as measured by quantitative MRI segmentation, are significantly associated with vision loss in children with NF1. This relationship was supported by corresponding reductions in RNFL thickness on OCT.[53] Interestingly, they also found that increased total brain volume was independently linked to a higher risk of visual impairment.[53] Avery and colleagues confirmed this result, finding that NF1-OPG size, most notably total AVP volume, is a risk factor for both VA loss and decreased circumpapillary retinal nerve fiber layer (cpRNFL), a comprehensive, objective, and reliable measure of axonal injury to the AVP.[41,53] Specifically, for every 1 mL increase in AVP volume, the cpRNFL thickness decreased by ~5 μm, and all participants with an optic chiasm volume >1.3 mL exhibited axonal damage, indicated by RNFL thickness below 80 μm.[41] Building upon this, Jiang et al[54] developed a fully automated framework (effectively removing interobserver variability) for predicting VA loss by integrating a transformer-based segmentation network of the AVP, radiomic feature analysis, and machine learning techniques. The framework achieved an average accuracy of 0.80, with a sensitivity of 0.69 and specificity of 0.92, potentially using volumetric MRI data to provide objective biomarkers for the early identification of children at risk for vision deterioration and enabling prompt therapeutic intervention.[53]

Diffusion tensor imaging (DTI) is an advanced MRI technique that uses the Brownian movement of water molecules to provide valuable insights into the arrangement of visual pathway fibers and the microstructural integrity of white matter tracts, including the optic radiations.[55] Applying DTI to the optic nerves presents significant technical challenges, as the intricate neuroanatomy neighboring the optic nerve can lead to susceptibility artifacts during image acquisition.[5] Due to these limitations, DTI was typically only used in surgical planning in patients with OPGs; however, recent studies have demonstrated that DTI is a valuable tool for assessing the severity and potentially predicting the progression of OPGs.[13]

Recent studies have found significant DTI abnormalities in the optic radiations of patients with OPGs, suggesting that specific microstructural alterations are linked to the presence of OPGs. A study by Filippi et al used DTI to identify statistically significant decreases in fractional anisotropy (FA) and increases in mean diffusivity (MD) in the optic nerves and radiations of patients with NF1-OPGs compared with age-matched controls.[56] A study by Çeşme[57] found comparable results, demonstrating that patients with NF1—regardless of the presence of OPGs—exhibited microstructural damage in the optic radiations when compared with healthy controls when analyzing DTI. Furthermore, de Blank and colleagues found that decreased FA in the

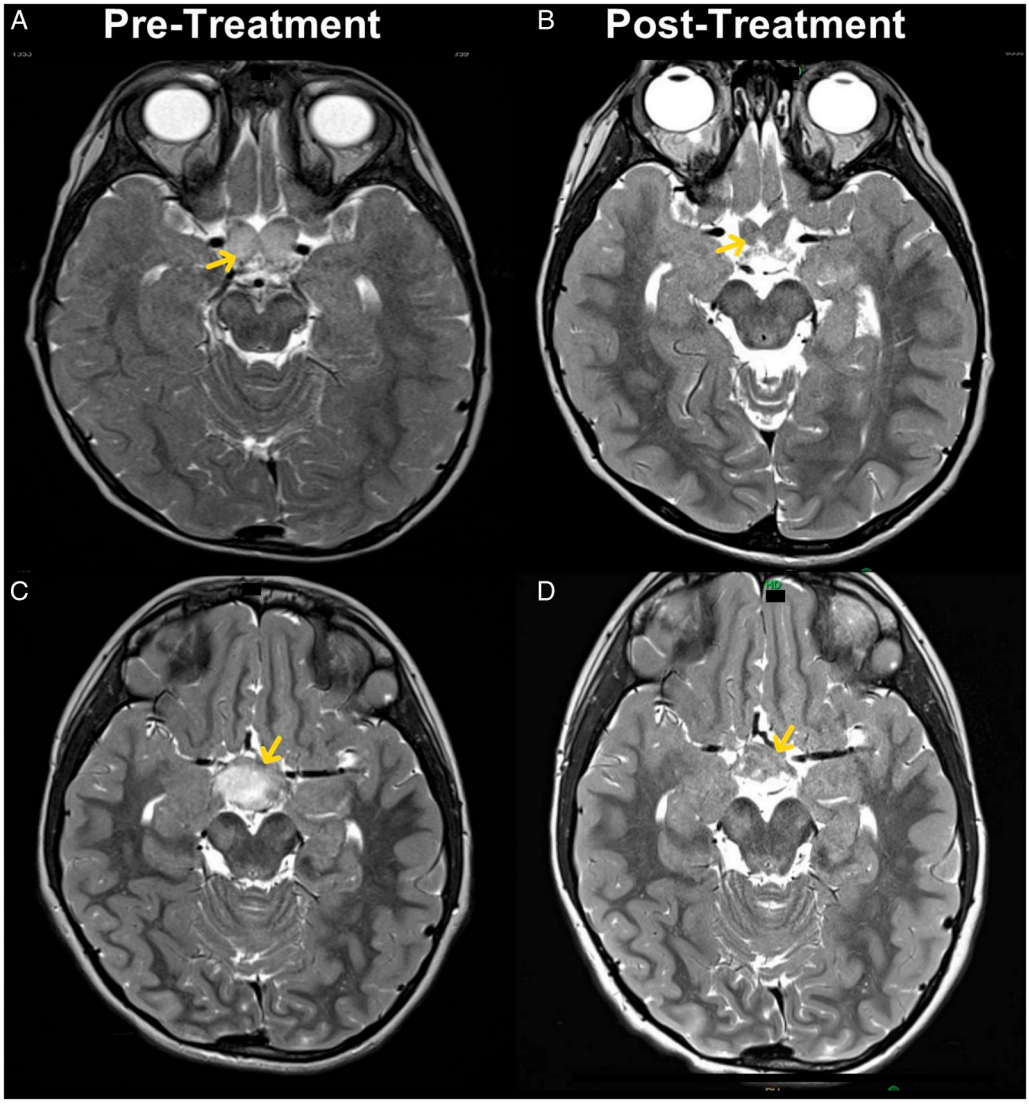

FIGURE 1. A, A 22-month-old child with NF1 presents with progressively increasing size of bilateral gliomas involving the optic nerves and chiasm (arrow, Panel A). B, Attempts to measure quantitative VA were unsuccessful due to poor cooperation. Treatment was initiated using a combination of carboplatin and vincristine, which resulted in a marked improvement in tumor size (arrow, Panel B) following completion of treatment. C, Four years later, the now 7-year-old patient experienced substantial interval growth of his OPG (arrow, Panel C) along with a significant 2-line worsening in VA. Treatment with carboplatin and vincristine was begun, but VA continued to worsen, so bevacizumab was added to the chemotherapy regimen. D, The patient demonstrated a good response upon treatment completion, with stable VA and a marked decrease in NF1-OPG size (arrow, Panel D). full color online

optic radiations of NF1-OPG patients was associated with decreases in VA; similarly, Hales and colleagues identified that decreased FA values in both the optic nerves and optic radiations were strongly associated with poorer vision.[58,59] Finally, by using image analysis and machine learning techniques, Pisapia et al[60] found that changes in white matter tracts along the optic radiations, as detected via decreased FA in DTI, are the most predictive feature of OPG progression and visual decline, with an astonishing accuracy of 86%, sensitivity of 89%, and specificity of 81%. While further investigation into the utility of DTI is essential, these studies cumulatively suggest that DTI metrics could serve as potential biomarkers for visual function and tumor progression in patients with OPGs.

While positron emission tomography (PET) is used extensively in managing adult brain tumors, its utility in the management of OPGs appears to be limited due to expense, radiation exposure and lack of additive information over MRI and clinical assessments.

Growth Patterns and Prognostic Factors

The clinical course of OPGs is highly variable and unpredictable, with cases of tumor stabilization, progression, and even spontaneous regression reported.[4,5,13] There are currently no definitive prognostic features for OPGs, but patient sex, age, tumor location, and NF1 status have been associated with an increased risk of tumor progression.[7,20]

Sex

Females with NF1-associated OPGs have been reported to be more likely to experience clinically significant vision loss and to undergo treatment for vision decline than their male counterparts. However, results from these retrospective reviews should be interpreted cautiously until they have been evaluated in rigorous prospective studies.[20,25,61,62]

Age

Age appears to be a factor in when children are treated for their NF1-associated OPGs. Fisher and colleagues found a peak incidence of treatment at 18 months of age and then another peak around 5 years of age, although children throughout the first and second decades have received treatment. Patients diagnosed before age 2 or after the ages 8 to 10 are found to be more aggressive in nature compared with OPGs diagnosed between the ages of 2 and 8.[16,20,63] Earlier age of OPG diagnosis (the age threshold ranged from 1 to 5 years, depending on the study) was also associated with a poorer visual outcome.[4,64–66]

Optic Disc Pallor

Previous studies have indicated that optic disc pallor upon fundoscopic evaluation is a significant risk factor for poorer visual outcomes and treatment responses in patients with OPG.[31,33–35]

Location

OPGs in the posterior optic pathways typically present with more aggressive clinical features compared with OPGs in the optic nerve and chiasm.[20,25] More specifically, and as aforementioned, OPG involvement in the optic tracts and/or radiations has been identified as a consistent prognostic indicator for poor visual outcome.[25,31,51,52] Furthermore, OPG involvement of the chiasm and/or hypothalamus significantly elevates the risk of bilateral vision loss.[66] It is important to note that sporadic OPGs isolated to the optic nerve will not progress to involve the chiasm over time.[4] Conversely, OPGs anterior to the chiasm are associated with a better prognosis for visual outcome and often affect the vision of only one eye.[66]

NF1 Status

NF1-OPGs are often less aggressive and less likely to have visual impairment compared with sporadic OPGs.[4,25] The majority of NF1-OPGs are isolated to only the optic nerves and chiasm and are less likely to extend posteriorly into the optic tracts or radiations.[4,7] Moreover, bilateral optic nerve gliomas in the absence of chiasmal involvement are considered highly characteristic of NF1-OPGs.[4] Conversely, sporadic OPGs are more likely to experience posterior extension, which, as previously stated, is associated with worse visual and neurological outcomes.[20,25,67]

Tumor Size and Progression

As previously stated, recent studies have identified that larger OPG volume and larger AVP volume correlate with greater axonal injury and vision loss in patients with OPGs.[41,53,54] These studies have also found that tumor size is a greater contributor to vision loss compared with posterior tumor location in children with NF1-OPGs.[41,53,54] However, previous studies have found no significant correlation between the progression or change in sporadic OPG size and visual outcomes.[25,68] Rather, some patients with OPGs may experience visual decline without significant changes in OPG volume, while others may have stable vision despite OPG growth.[13,69–71] In addition, variation in the cystic component of OPGs is characteristic of the natural course of the tumor.[72,73] Shofty and colleagues demonstrated sub-segmentation of the solid and cystic components of OPGs via volumetric MRI analysis may prove beneficial in predicting positive response to chemotherapy.[72] In their cohort, patients whose tumors had a cystic component at presentation were found to be more likely to show a reduction in the solid tumor portion following treatment, even though the cystic component continued to grow.[72] In summation, while studies suggest a link between tumor volume and visual outcomes, this relationship is not universally applicable to all patients with OPGs. Nevertheless, radiographic volumetric analysis may prove useful in informing OPG management and predicting treatment response and visual outcomes.

Genetic and Molecular Insights

The majority of OPG pathology consists of low-grade gliomas (LGG), although tumors with higher WHO grades have also been reported.[8] The most common histologic type of OPGs is pilocytic astrocytoma (PA) (WHO grade I), but other LGG variants like grade 2 pilomyxoid astrocytoma and grade II diffuse fibrillary astrocytomas have also been identified.[8,13] Histologically, the majority of OPGs appear benign, characterized by the absence of mitotic activity, cellular atypia, and necrosis.[13] Although most pediatric OPGs are low-grade and exhibit benign behavior, rare cases have demonstrated histopathologic features of aggressiveness, including elevated proliferative indices.[74]

While several pathologic markers have been identified in predicting OPG progression, they are not widely utilized. For instance, the MIB-1 immunostaining technique (used to detect the Ki-67 antigen, a protein associated with cell proliferation) and the silver nuclear organizing region (AgNOR) (which results in a measure

of mitotic activity) can uncover underlying proliferative activity not visible on routine microscopy.[13,74] Of note, better clinical outcomes are associated with MIB-1 levels < 1% in patients with OPGs.[8]

As previously stated, approximately half (59%) of OPGs are associated with NF1, an autosomal dominant disorder resulting from inactivating mutations in the *NF1* gene, which is located on chromosome 17q11.2.[21] *NF1* encodes neurofibromin, a tumor suppressor protein that negatively regulates the Ras–mitogen-activated protein kinase (MAPK) pathway.[9,21] Loss of functional neurofibromin leads to overactivation of the RAS pathway, promoting unchecked cellular proliferation and glioma formation. It is important to note that possessing a germline NF1 gene deletion does not cause the formation of OPGs.[15] Rather, the somatic deletion of the remaining NF1 gene—whether that be through loss-of-function mutations, loss of heterozygosity, or epigenetic modification—is the critical factor that leads to OPG development, an idea otherwise known as the 2-hit hypothesis.[15] Notably, there are 3 distinct RAS effector pathways, each accompanied by different treatments that will be discussed later in the chapter: the phosphatidylinositol-3 kinase (PI3K)/protein kinase-B (AKT)/mechanistic target of rapamycin (mTOR) pathway, the mitogen activated protein kinase (MEK)/mitogen activated protein kinase (ERK) pathway (usually known as the MAPK pathway), and the cyclic adenosine monophosphate (cAMP) pathway.[21]

In contrast to NF1-associated OPGs, many sporadic cases are a result of alterations in the *BRAF* gene, a gene encoding B-Raf protein, which is a critical component in the MAPK signaling pathway that regulates cell growth and division.[75] The most common somatic genetic alteration in sporadic OPGs (59% of cases) is the KIAA1549–BRAF fusion, in which a tandem duplication at chromosomal region 7q34 results in the kinase domain of the BRAF gene fusing with KIAA1549, a gene of unknown function.[9,76–78] This fusion then leads to constitutive activation of the MAPK/ERK signaling pathway, promoting increased cell proliferation.[9] Other less common alterations in the BRAF gene resulting in the formation of sporadic OPGs include: *BRAF* V600E or, less commonly, *BRAF* V600K point mutations, K-RAS mutations, SRGAP3:RAF1 fusions, and small BRAF insertions, all of which lead to an overactive B-Raf protein and result in a dysregulated MAPK signaling pathway and increased cell proliferation.[79,80] It should be noted that previous studies have identified the genetic alteration *BRAF* V600E to result in more aggressive pediatric LGG (including OPGs) progression and worse outcomes with conventional treatment options.[79,81,82] Notably, recent studies have also identified that some patients with NF1-OPGs additionally have heterozygous duplications of KIAA1549:BRAF in addition to a complete inactivation of the NF1 gene.[21,80,83] The identification of *BRAF* alterations has spurred interest in targeted therapies, including BRAF and MEK inhibitors. Early-phase clinical trials have demonstrated promising responses, particularly in tumors with the *BRAF* V600E mutation, which will be described later in the treatment section of this chapter.

Beyond driver mutations, the tumor microenvironment (TME), specifically the presence of nonneoplastic cells, has emerged as having a crucial role in the pathogenesis of OPGs.[21,84] Studies have shown that non-neoplastic stromal cells, mainly microglia, account for 35-50% of the cellular makeup of NF1-associated gliomas.[84–86] Furthermore, an increase in astrocyte and microglia cell production has been shown to precede the development of OPGs. Microglia additionally incorporate additional molecules, such as stromal cell-derived factor 1 (CXCL12), chemokine ligand 5 (Ccl5), meningioma-expressed antigen-5 (MGEA5), and interleukin-1β (IL-1β), which have been identified to facilitate or even begin tumor growth.[21] Specifically, a study found that the administration of Ccl5-neutralizing antibodies prevented murine OPG formation, suggesting that OPG emergence and proliferation rely on Ccl5, a signaling molecule released by microglia.[21,84,87] Collectively, these studies demonstrate that the TME of OPGs can actively facilitate OPG growth and survival, suggesting that targeting these non-neoplastic cells could be a promising therapeutic strategy.[87]

Management and Treatment

Surveillance

For children with NF1, the recommendations for surveillance typically call for annual, comprehensive ophthalmologic exams beginning at the age of diagnosis until at least age 8.[4] The risk for OPG progression and visual loss is most likely before the age of 6, so surveillance is most critical in this age group.[8] As previously stated, obtaining an age-appropriate, best-corrected quantitative VA assessment should be prioritized, as well as a dilated fundoscopic examination and assessments of visual fields, color vision, pupillary testing, and eye movements.[5] If an accurate ophthalmologic exam cannot be completed due to poor patient cooperation, MRI may be used as an alternative to assess for OPGs in patients with NF1. After age 8, the risk of NF1-OPG progression and vision loss declines, so ophthalmologic exams can be performed every 1 to 2 years until age 18 unless new symptoms of vision loss or clinical concerns arise, in which a prompt, comprehensive ophthalmologic exam should be completed.[13]

Following a new OPG diagnosis, ophthalmologic evaluations and MRI scans are typically recommended every 3 months during the first year.[5] After this first year, and if OPG size and VA are stable, then MRI scans and ophthalmologic evaluations can be adjusted to every 6 months.[5] Studies have shown that OPGs that remain stable for more than 3 years are unlikely to progress; therefore, after 3 years of radiographic OPG stability, the frequency of MRI surveillance may be reduced to annually.[5] However, ophthalmologic examinations should continue every 6 months until age 8, after which they may also be extended to annually.[5,31]

Indications for Treatment

There is currently no one symptom that has been definitively validated as a sole indication for initiating treatment of OPGs. Instead, therapeutic intervention is generally guided by a combination of clinical factors, most commonly a significant decrease in VA and radiographic evidence of tumor progression.[2,5] A VA measurement in one eye that deviates by ≥0.2 logMAR from age-adjusted normative values is considered abnormal, and a change in VA of ≥0.2 logMAR from previous examinations is regarded as clinically significant.[2,5] Furthermore, evidence of new or progressive deficits in VF (assuming proper patient cooperation) would also represent clinically significant visual deterioration and warrant consideration for therapeutic intervention.[5] Additional ophthalmic abnormalities that should raise concern and prompt closer OPG monitoring include: new onset color vision loss, optic nerve swelling, disc pallor, afferent pupillary defect, strabismus, or nystagmus.[5] The aforementioned prognostic factors (such as OPG location, NF1 vs. sporadic OPG status, presence of optic disc pallor, age, sex, and radiographic OPG progression or abnormalities) should also be factored into the decision whether to initiate treatment.

Patients with OPGs who already have significant vision loss monocularly (worse than 1.0 logMAR relative to age-based norms) and demonstrate either new visual decline (worse than 0.2 logMAR) in the better-seeing eye or evidence of tumor progression on MRI may be appropriate candidates for chemotherapy to preserve monocular vision.[5] Similarly, patients who experience VA loss monocularly nearing the functional threshold (0.6 to 1.0 logMAR relative to age-based norms) may be candidates for treatment, given the potential functional impact of even small declines in vision.[5]

The presence of precocious puberty or changes in growth hormone should not be used as indications for OPG treatment.[5] In addition, NF1-related proptosis alone is not considered a sufficient indication for initiating treatment.[5] Intervention is typically reserved for cases where the affected eye has no or limited vision and therapy is needed to address corneal exposure or significant cosmetic concerns.[5]

Treatment

The currently available treatment options for OPGs include the following: observation, chemotherapy, use of anti-VEGF monoclonal antibodies, radiation therapy, and surgery.

Chemotherapy

Chemotherapy is currently considered the standard, first-line treatment for OPGs.[2,84] The combination of vincristine and carboplatin is the preferred combination therapy since its 3- and 5-year progression-free survival (PFS) rates for OPGs are 77% and 69%, respectively (see Fig. 1 for an example of OPG response to chemotherapy).[2,84] While this regimen is generally well-tolerated, up to 40% of patients can experience hypersensitivity reactions to carboplatin.[2] If a hypersensitivity reaction occurs, the tumor progresses during treatment, or there is an early relapse upon completing treatment, alternative drug combinations may be used. A combination of thioguanine, procarbazine, lomustine, and vincristine (TPCV) has shown a nonsignificant trend toward higher rates of 5-year event-free survival when compared with the combination of vincristine and carboplatin in NF1 patients.[2,9,84] However, because lomustine and procarbazine are associated with a heightened risk of secondary leukemia, their use should be avoided in patients with NF1 and reserved exclusively for those with sporadic OPGs.[2,84] Another chemotherapy regimen includes cisplatin and etoposide, which has demonstrated a rather promising 3-year PFS rate of 78%, but this combination should also be used cautiously due to the potential for etoposide-induced secondary leukemia and cisplatin-associated ototoxicity.[9,84,88] Monotherapy with agents such as temozolomide (12-month PFS of 39%), vinblastine (5-year PFS of 53%), or vinorelbine (5-year PFS of 34% to 42%) have recently shown promising results and low toxicity in cases of progressive or refractory disease, but temozolomide should not be used in patients with NF1.[2,9,32,84,89–94]

Unfortunately, VA improvement following chemotherapy is limited at best. A systematic literature review examining the visual outcomes following chemotherapy for OPGs from 1990 to 2009 found that only 14.4% of patients experienced an improvement in vision, while 47.1% had stable vision.[95] A large, multicenter retrospective study found that VA improved in 32%, remained stable in 40%, and declined in 28% in patients with NG1-OPGs following chemotherapy treatment.[31] Another large, prospective, multicenter study found that, after treatment with chemotherapy, there was no significant difference in visual outcomes when comparing NF1-OPGs to sporadic OPGs; VA improved in 24%, remained stable in 35%, and worsened in 41% of children with NF1-OPGs, and VA improved in 18%, remained stable in 43%, and worsened in 39% of children with sporadic OPGs.[96] It should be noted that most studies reporting the effects of chemotherapy on VA outcomes in patients with OPGs reflect treatment with the combination of carboplatin and vincristine.[2] In addition, while radiologic changes in OPGs have been shown to have poor correlation to VA outcomes, a 2022 systematic review and meta-analysis did demonstrate that 72% of patients with OPG who underwent chemotherapy treatment had a favorable radiologic outcome.[2,97]

Radiation Therapy

While ionizing radiation was historically the standard approach to treating OPGs, it is now reserved for those only with sporadic OPGs. While studies show that the 10-year PFR rate is up to 90%, concerns about side effects, long-term toxicity, and its effect on the quality of life of OPG patients have led physicians to prioritize alternative therapy options when treating OPGs.[32,84] More specifically, radiotherapy use in children is associated with mye-

losuppression, worsening vision, neurotoxicity, vasculopathy, endocrine dysfunction, secondary malignancies, and cognitive and developmental impairments.[2,9,97] In addition, 50% of NF1-OPG patients treated with radiotherapy during childhood later developed brain tumors secondary to radiotherapy, often being high-grade gliomas with poor prognoses.[84,98] While there are currently different techniques of radiotherapies under investigation for OPG treatment that minimize radiation exposure to surrounding structures—such as proton beam radiotherapy, conformal treatment, fractionated stereotactic radiation therapy, and stereotactic radiotherapy—the long-term outcomes remain uncertain, limiting their routine usage.[9,84] Consequently, regardless of NF1 status, radiotherapy is now considered a therapy of last resort and is generally reserved for older patients and for those who have exhausted all other chemotherapy options.[2,84]

Surgery

Surgical resection of OPGs is rarely performed due to the high risk of complications associated with the procedure itself, including vision deterioration, multiple endocrine deficiencies, cerebrovascular events, and hypothalamic dysfunction.[32] That said, resection through an orbital approach and/or craniotomy may be indicated in cases or combinations of painful or disfiguring proptosis, exposure keratopathy in a severely visually impaired eye, radiologically documented OPG enlargement, or extension into the hypothalamus that causes endocrine disruption and affects surrounding structures.[2,9,13,79]

Targeted Therapy and Emerging Treatments

MEK/BRAF inhibitors

As previously mentioned, most pediatric LGGs (including OPGs) are the result of an overactivation of the MAPK pathway, most commonly through a KIAA1549–BRAF fusion or, less frequently, a BRAF V600E point mutation.[9,78] In NF1, the biallelic (2-hit) inactivation of the NF1 tumor suppressor gene leads to overactivation of the RAS-MAPK pathway.[9,21] Recently, mitogen-activated protein kinase inhibitors (MEK inhibitors) have been approved for the treatment of LGGs, targeting downstream components of the RAS pathway to prevent MAPK overactivation and subsequent tumorigenesis.[79] These MEK inhibitors, such as selumetinib, refametinib, trametinib, and cobimetinib, have had promising results with a 2-year PFS of up to 69%.[67,99] It should be noted that MEK inhibitors are said to be more productive in treating OPGs in patients with BRAF aberrations.[84]

A phase II trial in patients with recurrent OPGs without NF1 of selumetinib—a potent, selective, orally available, non-ATP-competitive small-molecule inhibitor of MEK—demonstrated a 2-year PFS rate of 78%.[100] Vision was reported to improve in 21% of patients and was stable in 68% of patients.[100] Another phase II trial of selumetinib in patients with common BRAF aberrations and NF1-associated pediatric LGG found a 40% response rate, a 2-year PFS rate of 96%, and no worsening of vision (11.1% of patients had an improved vision while the other 88.9% reported stable vision).[101] The findings from these trials have led to 2 Children's Oncology Group phase III studies in newly diagnosed pLGG patients, both with and without NF1, evaluating the efficacy of standard carboplatin/vincristine-based chemotherapy compared with selumetinib.[84,101] The potential of treating OPGs with selumetinib is quite promising given its significant advantages compared with traditional chemotherapy treatment: oral administration (eliminating the need for central lines), minimal immunosuppression, less severe nausea, reduced risk of hair loss, and a reduced frequency of clinic visits (monthly after initial monitoring rather than weekly or biweekly).[67,84] Nevertheless, selumetinib usage has potential risks, including creatine phosphokinase elevation, anemia, diarrhea, headache, fatigue, and an increased likelihood of ocular toxicities such as optic neuropathy, retinal vein occlusion, uveitis, outer retinal layer separation (Fig. 2), and retinopathy.[67,79,84,102] Fortunately, these ocular side effects are likely reversible in the pediatric population.[79] Still, patients undergoing MEK inhibitor therapy should have ophthalmic examinations to monitor for the development of any of these ocular toxicities.[79]

Although selumetinib is currently the most researched MEK inhibitor for OPGs, other MEK inhibitors and/or BRAF inhibitors have shown promising results for LGG, including OPG, treatment as well. Physiologically, selective type I BRAF inhibitors target the ATP-binding site of BRAFV600E-mutant BRAF proteins.[67] By competitively inhibiting ATP binding, these agents disrupt downstream signaling through the BRAF/MEK/ERK pathway, thereby suppressing tumorigenesis in BRAFV600E-mutant LGGs.[67] It should be noted that OPGs harboring KIAA1549::BRAF fusions should not utilize BRAF inhibitors since there is a risk of paradoxical tumor growth.[103]

An initial review of a phase II trial comparing the efficacy of standard chemotherapy treatment to the combination of MEK inhibitor trametinib and BRAF inhibitor dabrafenib in patients with pediatric LGG has shown promising results. The MEK/BRAF inhibitor combination demonstrated a significantly higher overall response rate (47% vs. 11%), an increased clinical benefit rate (86% vs. 46%), and a prolonged PFS (20.1 mo vs. 7.4 mo) compared with the standard carboplatin/vincristine treatment.[104] Furthermore, a study found that the 5-year PFS for LGGs with BRAFV600 aberrations for radiotherapy and chemotherapy were 50% and 35%, respectively.[79,81] In contrast, that same study demonstrated that LGGs with BRAFV600 mutations treated with the MEK/BRAF inhibitor combination of dabrafenib or vemurafenib had an 80% objective response (OR) rate and 53% of patients experienced a $>50\%$ reduction in tumor size.[79,81] A phase I/II study of trametinib monotherapy treatment in 13 pediatric patients with LGGs demonstrated a 15% OR rate (all partial responses), an additional 46% achieved disease stabilization, and the median PFS was 16.4 months.[105] Vemurafenib has additionally shown promising results in 7 patients with BRAF

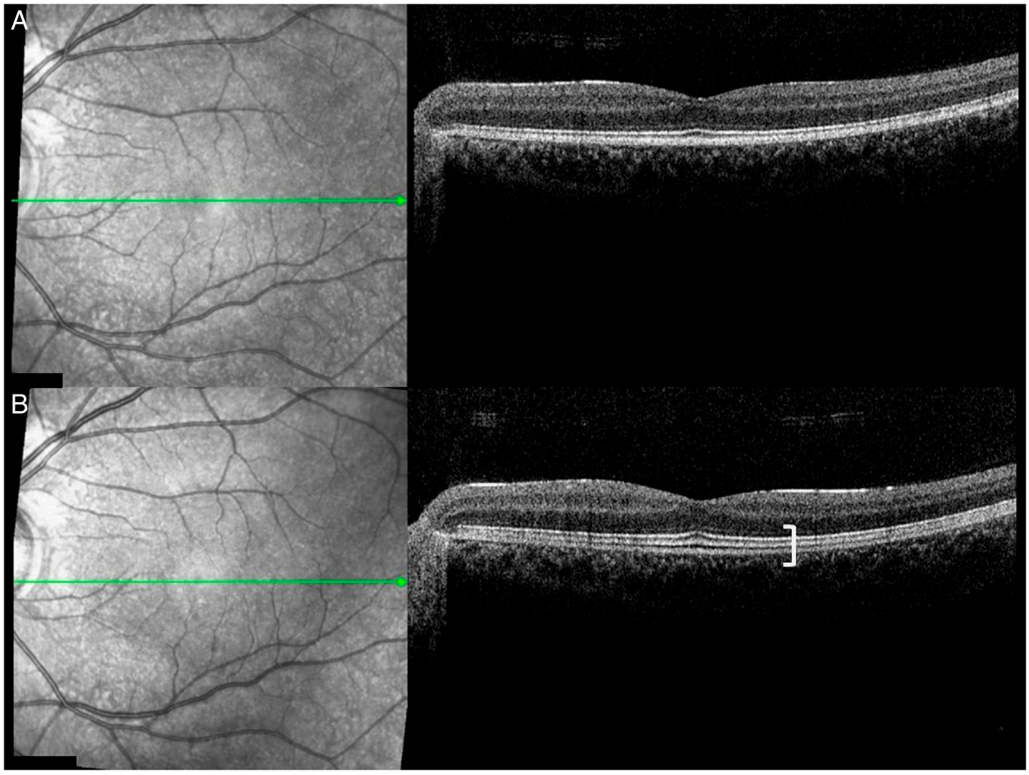

FIGURE 2. OCT imaging of a patient with a sporadic OPG who was initially treated with a combination of carboplatin and vincristine, followed by dabrafenib and trametinib (a MEK inhibitor). A, The patient's normal retinal layer morphology before treatment with dabrafenib and trametinib is represented. B, Outer retinal layer separation (bracket) 6 months after initiating treatment with dabrafenib and trametinib is demonstrated. full color online

V600E-mutated LGGs, with a 60% response rate.[106] Finally, the MEK inhibitor binimetinib demonstrated a 56% radiographic response rate in treating progressive or recurrent pediatric LGGs, including NF1-associated and sporadic cases, irrespective of BRAF fusion status.[107] That said, 22% of patients terminated treatment early due to toxicity, and 49% of patients required dose reductions to manage side effects, suggesting that further research is necessary to determine proper binimetinib dosing strategies.[107] Current phase II trials are underway exploring multiple therapeutic options for LGGs, including the immunomodulatory agents lenalidomide and pegylated interferon alfa-2b, histone deacetylase (HDAC) inhibitor entinostat, topoisomerase inhibitor irinotecan, and proton therapy; however, further investigation is warranted before their efficacy can be determined.[84,108–110]

Bevacizumab

OPGs are highly vascular tumors, with vascular endothelial growth factor (VEGF) playing a key role in promoting blood vessel formation, and this increased microvascular density is associated with poorer PFS in patients with OPGs.[111,112] Bevacizumab, a humanized monoclonal IgG1 antibody, binds to and inhibits VEGF, consequently decreasing tumor growth and vascular permeability.[2,79] Recently, the use of bevacizumab, either as monotherapy or in combination with vinblastine or irinotecan, has shown promising results in the management of OPGs, including those confined to the optic nerve.[2] A phase II study of bevacizumab in combination with the chemotherapy agent irinotecan in children with LGG refractory to traditional chemotherapy/radiotherapy regimens discovered prolonged disease stabilization in 80% of patients and a 2-year PFS of 47.8%.[113] Similarly, in a retrospective review of 14 children with recurrent LGGs who failed at least 2 previous treatment regimens and were then treated with bevacizumab-based therapy, 12 patients had an OR and improved visual and neurological symptoms, while 2 experienced stable disease.[114] That said, upon discontinuation of bevacizumab, the vast majority (13 out of 14) patients experienced LGG progression at a median of 5 months.[114] Finally, in a case report of 4 patients with OPGs (2 NF1-associated and 2 sporadic) who received bevacizumab-based treatment following declines in VA or VF despite previously undergoing traditional OPG treatment regimens, all 4 patients experienced significant improvement in VA and/or VF.[115] Notably, 2 of the 4 patients had already received prior treatment with bevacizumab, sug-

gesting possible benefits to re-treatment.[115] Common side effects of bevacizumab include: hypertension, fatigue, joint pain, bleeding events, and proteinuria, but these effects often resolve upon discontinuation of therapy.[2,79]

Prognosis and Long-Term Outcomes

Children with OPGs generally have excellent long-term survival, with overall survival rates exceeding 90% at 10 years.[3] Notably, one study found that there was a sharp decrease in overall survival rate after 15 years, with overall survival rates of 80.7% at 15 years and 75.5% at 18 years.[116] A 2024 study found similar results, finding a 20-year conditional overall survival rate of 79.9%.[117] Death was primarily due to OPG progression, although secondary malignant neoplasms, cerebrovascular disease, cardiac disease, and chemotherapy toxicity were also reported etiologies.[33,117]

Although mortality rates from OPGs are relatively low, patients with OPGs unfortunately face a high risk of significant long-term morbidities; the same 2024 study demonstrated that 95% of patients surviving at least 5 years after OPG diagnosis suffered from at least one medical condition (with the average number of health conditions being 2.5).[117] More specifically, 79% of OPG patients experienced ophthalmologic sequelae, with a decrease in VA occurring in 57% of patients, altered VF occurring in 11%, or alteration in both VA and VF occurring in 11% of patients.[117] In addition, 21% of OPG patients suffered from binocular blindness, while 33% experienced monocular blindness.[117] Pituitary deficiency and neurocognitive impairments were observed in 58% and 49% of 5-year OPG survivors, respectively.[117]

Vision loss has a substantial impact on quality of life (QOL); a 2013 study found that children with OPGs experiencing significant vision loss report decreased vision-specific QOL compared with those with normal vision.[118] These researchers recommend incorporating vision-specific QOL assessments, like the Children's Visual Function Questionnaire, to obtain a more comprehensive understanding of OPG treatment benefits beyond traditional clinical endpoints.[118]

CONCLUSIONS

OPGs are a subset of LGGs that primarily affect the pediatric population. OPGs can arise sporadically or in association with the tumor predisposition syndrome NF1, in which 1 in 5 NF1 patients develop an OPG. OPGs vary widely in presentation and progression, making the management and treatment highly complex and often a subject of debate among clinicians. Recently, exciting advancements in imaging techniques have led to the development of new biomarkers for vision, such as volumetric MRI, more specifically AVP volume and OPG volume, DTI, cpRNFL measurements via OCT, and radiographic image analysis machine learning models to predict the risk of OPG progression and visual decline. Furthermore, the emergence of new molecularly targeted therapies, like MEK inhibitors, BRAF inhibitors, and anti-VEGF monoclonal antibodies, has introduced new, promising therapeutic options for patients with recurrent OPGs who did not respond well to traditional first-line chemotherapy treatment. While new and exciting insights into the management and progression of OPGs have been uncovered, there is still much that remains unknown. Multicenter prospective studies with standardized ophthalmic and MRI measures are essential to establish evidence-based guidelines for the management of OPGs, and further longitudinal studies of the aforementioned new therapeutic options are necessary to determine their long-term efficacy in treating OPGs.

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