Optic Pathway Gliomas in Neurofibromatosis-1: Controversies and Recommendations

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Optic pathway glioma (OPG), seen in 15% to 20% of individuals with neurofibromatosis type 1 (NF1), account for significant morbidity in young children with NF1. Overwhelmingly a tumor of children younger than 7 years, OPG may present in individuals with NF1 at any age. Although many OPG may remain indolent and never cause signs or symptoms, others lead to vision loss, proptosis, or precocious puberty. Because the natural history and treatment of NF1-associated OPG is different from that of sporadic OPG in individuals without NF1, a task force composed of basic scientists and clinical researchers was assembled in 1997 to propose a set of guidelines for the diagnosis and management of NF1-associated OPG. This new review highlights advances in our understanding of the pathophysiology and clinical behavior of these tumors made over the last 10 years. Controversies in both the diagnosis and management of these tumors are examined. Finally, specific evidence-based recommendations are proposed for clinicians caring for children with NF1.

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Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder that affects 1 in 3,500 people worldwide.[1] Individuals with NF1 are prone to the development of both benign and malignant nervous system tumors, including Schwann cell tumors (eg, neurofibromas) and glial cell tumors (eg, astrocytomas). The most common tumor in children with NF1 is the optic pathway glioma (OPG), which is seen in 15% to 20% of patients.[2,3] Although the tumors of many patients with NF1-associated OPGs exhibit indolent behavior, approximately one-third to half of these tumors will cause clinical symptoms, including vision loss and precocious puberty.[3–5]

In 1997, based on a task force composed of basic scientists and clinical researchers, guidelines for the management and diagnosis of NF1-associated OPG were proposed.[6] Since that time, there have been significant advances in both basic science and clinical research on these tumors, which has prompted us to reexamine those original recommendations. This new review integrates the progress made over the past decade and extends our initial recommendations for the screening, follow-up, and treatment of optic glioma in children with NF1. Equally important, unanswered questions are raised, which should provide the foundation for future NF1-associated OPG research.

Pathogenesis of NF1 Associated OPG

OPGs arising in children with NF1 are classified by the World Health Organization as grade I astrocytomas (pilocytic astrocytomas [PAs])[7] and are histologically identical to PAs arising elsewhere in the brain in children without NF1. Some NF1-associated OPGs lack classic features of PA and may be classified as World Health Organization grade II fibrillary astrocytoma; however, the clinical significance of this pathological distinction is unknown.[8] The *NF1* protein, neurofibromin, functions as a negative growth regulator for astrocytes by inhibiting RAS activity (Fig 1). In this regard, NF1-associated PAs exhibit loss of neurofibromin expression and increased RAS activation.[9] Studies using genetically engineered mouse astrocytes have confirmed that neurofibromin loss results in increased astrocyte proliferation in vitro and in vivo and high levels of RAS activation,[10] suggesting that RAS blockade by farnesyltransferase inhibitors might be a logical therapeutic strategy for NF1-associated glioma. Unfortunately, mouse *Nf1*-deficient astrocytes exhibit preferential acti-

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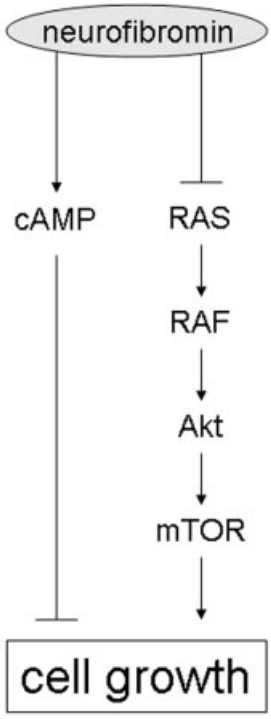

Fig 1. Neurofibromin growth control pathways. The neurofibromatosis type 1 (NF1) *gene product, neurofibromin, has been shown to control cell growth by regulating two major intracellular signaling pathways. First, neurofibromin has been shown to positively regulate intracellular levels of cyclic adenosine monophosphate (cAMP), such that* NF1*-deficient cells have lower baseline levels of cAMP. In some cell types, including astrocytes, cAMP inhibits cell growth. Modulating cAMP levels can be achieved by either increasing cAMP production (adenylyl cyclase activators) or decreasing its degradation (phosphodiesterase inhibitors). Second, neurofibromin also negatively regulates RAS pathway signaling. RAS is an important intracellular protooncoprotein that functions in many cell types to increase cell growth and survival. Loss of neurofibromin leads to increased RAS activity, which, in turns, promotes cell growth. Farnesyltransferase inhibitors block the activation of RAS. In* NF1*-deficient cells, RAS hyperactivation leads to increased activation of downstream signaling intermediates, including RAF, Akt, and the mammalian target of rapamycin (mTOR). Recent studies have suggested that inhibiting mTOR activity with the macrolide rapamycin may have utility in treating tumors in patients with NF1.*

vation of a form of RAS (KRAS) that is relatively insensitive to farnesyltransferase inhibitors.[11] However, further examination of *Nf1*-deficient astrocytes demonstrated hyperactivation of the mammalian target of rapamycin protein (mTOR), such that mTOR inhibition with rapamycin reduced *Nf1*-deficient astrocyte growth in vitro to wild-type levels.[12] Human NF1-associated optic gliomas also have high levels of mammalian target of rapamycin pathway activation, providing the scientific rationale for future clinical studies using rapamycin and rapamycin analogs to treat NF1-associated tumors. Similarly, neurofibromin has also been shown to positively regulate intracellular cyclic adenosine monophosphate levels in mammalian cells,[13,14] such that loss of *Nf1* expression in astrocytes is associated with reduced cyclic adenosine monophosphate generation,[15] suggesting another potential "targeted" therapy for NF1-associated OPG.

In genetically engineered mice, *Nf1* inactivation in astrocytes does not result in glioma formation despite an increase in astrocyte proliferation.[10] However, $Nf1^{+/-}$ mice that lack neurofibromin expression in astrocytes develop low-grade gliomas involving the prechiasmatic optic nerve and optic chiasm.[16,17] These tumors can be monitored in vivo using small-animal magnetic resonance imaging (MRI), forming the foundation for preclinical studies aimed at evaluating potential therapies for NF1-associated OPG and identifying biomarkers of tumor activity.[18,19] Preclinical models of low-grade glioma provide unique opportunities to rapidly screen candidate drugs in an intact animal genetically engineered to resemble the human disease; however, it is important to recognize that drug metabolism and bioavailability may differ between rodents and humans. Lastly, studies are ongoing using these mice and others to define the contribution of specific cell types in the tumor microenvironment to glioma formation, which could represent additional targets for antitumor drug design.[18,20]

Clinical Characteristics

Over the past decade, several salient observations have been made about the clinical characteristics and natural history of NF1-associated OPG, including the recognition that these tumors may arise de novo or progress later in childhood or adulthood,[21] and that visual loss is more likely in children whose tumors involve the posterior optic pathway.[5]

Incidence

Previous studies have shown that if all children with NF1 underwent screening neuroimaging at the time of diagnosis, OPG would be detected in 15% of children.[3,6] Recent studies using international clinical databases similarly have estimated the prevalence rate of OPG at between 5 and 25%.[22–24]

Age at Presentation

Children 6 years and younger with NF1 are at greatest risk for the development of OPG.[2,3,6] However, over the last 10 years, it has become increasingly clear that new symptomatic OPGs may arise in older children and adults with NF1. Eight NF1 patients ranging in age from 8 to 22 years had OPGs that appeared for the first time or progressed after the patient's 7th birthday.[21] Seven had evidence of deteriorating ophthalmological examinations; four of the tumors exhibited ra-

diographic growth, representing much greater rates of progression compared with OPGs presenting in younger children.

Presenting Signs and Symptoms

Children with symptomatic OPG generally have ophthalmological abnormalities at the time of diagnosis, including decreased visual acuity, abnormal pupillary function, decreased color vision, optic nerve atrophy, or proptosis.[3,6] However, young children rarely complain of vision loss, necessitating the use of reliable, reproducible measures to detect visual changes. A recent retrospective analysis of OPG patients in a NF1 referral center demonstrated that 32 of 54 patients (59%) had visual signs at the time of OPG diagnosis.[25] Of the symptomatic patients, 72% presented with decreased visual acuity, 31% had proptosis, and one patient presented with nystagmus. Proptosis was most commonly seen in patients 6 years or younger, whereas precocious puberty was found exclusively in patients older than 6 years. Similar findings were reported in two separate retrospective studies.[26,27]

Symptomatic orbital OPGs represent a unique subset of NF1-associated OPG. One study recently described 12 NF1 patients with orbital OPG, all of whom presented with proptosis at a mean age of 26 months.[28] At the time of tumor diagnosis, 83% of these patients had decreased visual acuity in the affected eye. Although eight of these children received chemotherapy, significant changes in the ophthalmological examination before treatment could be documented in only three patients. Five patients had a decrease in the amount of proptosis or a decrease in the tumor size by MRI, but none had a significant improvement in vision. Notably, there were no documented cases of tumor "spread" from an isolated optic nerve glioma into the optic chiasm. These data confirm previous recommendations that NF1-associated OPG should be treated only if there is clear evidence of radiographic or ophthalmological progression.

Between 12 and 40% of children with chiasmal OPG develop precocious puberty either as a presenting manifestation of the OPG or after diagnosis.[29,30] Because the first sign is generally accelerated linear growth, it is essential that accurate growth charts be kept on all young children with NF1.

Natural History and Prognostic Factors

In recent studies, progressive disease after OPG diagnosis that led to treatment occurred in 35[26] to 52%[25] of cases. However, predicting the natural history of an individual NF1-associated OPG is impossible. Asymptomatic tumors found on "screening neuroimaging" may never grow or cause symptoms. Rapidly progressive intraorbital tumors may cause proptosis and significant unilateral vision loss, yet never grow after initial presentation. Multiple well-documented instances of spontaneous regression of OPG without treatment have been reported.[31,32] In one of the largest studies to date, no single specific epidemiological factor was associated with symptomatic OPG, which could serve as a predictor of the need for future treatment.[26] Despite this, certain generalities can be gleaned from existing data.

The anatomic location of the tumor has clear prognostic significance. One study reported that 62% of NF1-associated OPG patients with postchiasmal involvement, including the hypothalamus and optic tracts, had visual loss compared with 32% of patients whose tumors were limited to the optic nerves and chiasm.[5] In a separate report, seven patients with unusual optic radiation involvement were described, all of whom had visual loss, whereas three had 20/200 vision or worse.[33] Patients who present at 10 years of age or older may be more likely to have progressive disease requiring treatment.[21]

NF1–Associated OPG versus Sporadic OPG

Patients with sporadic OPG are much more likely to present with signs and symptoms of increased intracranial pressure and hydrocephalus, whereas precocious puberty is more commonly seen as a presenting manifestation of NF1-associated OPG.[4] In one study, sporadic cases were twice as likely to have associated vision loss, whereas increased intracranial pressure occurred equally in the two groups.[22] Although progressive disease was more common in the sporadic group, second CNS tumors were more common in the NF1 group, perhaps, in part, because of the use of radiotherapy.

Optic nerve involvement is more common in NF1-associated OPG, whereas chiasmal and postchiasmal tumors are more frequently seen in sporadic OPG.[34,35] Moreover, bilateral optic nerve involvement is seen almost exclusively in NF1 patients. There has been at least one report of a sporadic OPG that exhibited the clinical and radiographic appearance of NF1-associated OPG, suggesting the presence of segmental or mosaic NF1 involving the brain.[36]

Controversies in the Diagnosis and Management of NF1–Associated OPG

Although considerable progress has been made, a number of unresolved clinical issues remain regarding the optimal screening and clinical care of children with NF1-associated OPG that warrant further discussion.

Is Routine "Screening" Neuroimaging Appropriate for All Asymptomatic Children with NF1?

The 1997 OPG Task Force determined that there was no conclusive evidence that early detection of tumors

would reduce the rate of vision loss.[6] Asymptomatic OPG would be identified that would never progress, escalating costs and parental anxiety, and exposing the young child to the risks of repeated sedation. Moreover, studies have found that NF1-associated OPG may emerge after normal neuroimaging despite a rigorous screening program.[37,38]

Subsequently, one institution described their experience using a systematic neuroimaging screening protocol for young children with NF1.[24] Their screening protocol mandated MRI scans and complete ophthalmological examinations yearly between 1 and 3 years of age, and at the time of diagnosis for children first seen between 3 and 6 years of age. OPGs were found in 11 of 54 children with NF1 who had baseline neuroimaging studies; 9 were found in asymptomatic children with normal eye examinations, whereas 2 tumors were discovered in children with abnormal eye examinations at initial presentation. Of the eight asymptomatic, incidentally identified OPGs followed by serial MRI and ophthalmological examinations, only one child experienced visual deterioration requiring chemotherapy. Two other children received chemotherapy for radiographic tumor growth despite a stable ophthalmological examination. Thus, no compelling evidence advocating the efficacy of routine screening neuroimaging remains. However, in the uncommon situation where reliable eye examinations cannot be obtained, there may be a role for neuroimaging.

What Is the Appropriate Ophthalmological Assessment of Asymptomatic Children with NF1?

Visual symptoms are unreliable indicators of the presence of OPG in young children who do not complain of vision loss. Various methods for assessing visual function have been used as primary outcome measures in published studies of children with OPGs, and they include visual acuity,[5] visual fields,[39] and visual-evoked potentials (VEPs).[40–43]

VISUAL ACUITY. Loss of visual acuity is the most reliable and clinically most important indicator of visually symptomatic OPGs, and serial visual acuity measurements are the best way to follow patients with OPGs. Clinically important visual field loss almost never occurs in NF1-associated OPG without concomitant visual acuity loss.[44] Visual acuities can be readily obtained using preferential looking tests in infants (eg, Teller acuity test), Lea figure or HOTV matching in preliterate children and Snellen charts in literate children (see Table 1 and Fig 2). Each visual acuity test has been shown to exhibit high test-retest reliability in young children.[45,46]

Recognizing that visual acuity improves as young children get older, acceptable normal visual acuities for age are 20/40 or better (age 3 years), 20/30 or better (age 4 years), 20/25 or better (age 5 years), and 20/20 or better (age 6 years and older).[5] Pragmatically, symptomatic children can be defined as those with visual acuity two lines worse than normal in either eye. If a definite reduction in acuity is found and changes in refractive error, ocular causes, or the presence of amblyopia have been excluded, MRI is recommended.

VISUAL FIELDS. Some studies have suggested that computerized visual field testing, usually requiring approximately 6.5 minutes per eye, can be performed reliably in young children.[47] However, most children have difficulty with the monotony and length of formal visual field testing, leading to high numbers of fixation errors, false-positives, and false-negatives.[47] Kinetic (Goldmann) visual field testing is easier for young, less cooperative children, but there is still great test-retest variability in this age group, and the results are hard to quantify. Therefore, clinical decision-making based on unreliable visual fields and small changes during serial visual field testing is problematic. Nevertheless, basic bedside confrontation visual field testing with finger counting or toys should be performed during each eye examination.

COLOR VISION AND OTHER NEURO-OPHTHALMOLOGICAL FINDINGS. In children with NF1-associated OPG, color vision loss usually accompanies visual acuity deficits. In this setting, visual acuity loss without color vision loss would suggest refractive error, amblyopia, a functional disorder, or lack of cooperation. Strabismus and nystagmus, when due to an OPG, are also usually

Table 1. Recommended Testing Modality for Visual Acuity Based on Age

Age (yr)	Recommended Testing Modality	Acceptable Normal Visual Acuity
0.5-2	Preferential looking test (eg, Teller acuity test)	Age-based norms
3	Figure matching (eg, Lea figure)	20/40
4	HOTV matching	20/30
5	Snellen	20/25
≥6	Snellen	20/20

The actual testing modality used for any given child depends on that child's level of cooperation and literacy. Normal visual acuities improve with age in young children, thereby necessitating different age-based norms.[62]

associated with visual acuity loss. In contrast, optic disc swelling or atrophy may be associated with, but does not predict, visual acuity loss.

What Is the Role of Visual-Evoked Potentials in the Detection of Optic Pathway Glioma in Asymptomatic NF1 Children?

VEPs have been suggested as a sensitive method of detecting OPGs, but many studies are retrospective or have been performed on patients with known tumors.[40,43] Many asymptomatic patients were identified unnecessarily by VEP screening.[40] Furthermore, VEP is an electrophysiological measure of the integrity of the visual pathway, whereas psychophysical measures such as visual acuity, visual field, and color vision are more representative of true visual function. Serial VEPs would be hard to interpret because small changes in amplitude and delay without changes in vision are of uncertain clinical significance.[48] On the other hand, abnormalities in visual acuity are critical for screening symptomatic patients and for serial follow-up to monitor for clinical progression. Thus, at this juncture, there is no evidence to warrant the use of VEPs as a screening tool.

Until What Age Should Routine Ophthalmological Evaluations Be Performed and at What Intervals?

No consensus has been reached on the appropriate duration of ophthalmological screening in asymptomatic children. Although rare, OPGs may develop in older children and adults.[21] The current UK clinical guidelines suggest that screening should continue until 7 years of age in asymptomatic children with NF1, because the first 6 years of life constitute the time of maximal risk for OPG development.[49] However, other centers have advocated for continued surveillance for 10 to 25 years after initial diagnosis.[6,25,26] Moreover, minor variation exists in the recommendations for intervals between screening tests. Most ophthalmologists perform yearly assessments, whereas others have proposed a gradual increase in the intervals between examinations from the age of 8 to 25 years.[6,50]

If the Clinician Suspects the Presence of an OPG, What Is the Appropriate Imaging Procedure?

MRI of the brain and orbits should be used to confirm the diagnosis of OPG once an abnormal eye examination has been documented. Magnetic imaging spectroscopy, diffusion tensor imaging, and positron emission tomography have not been studied for their utility in guiding the management of NF1 patients with OPG.

How Should Children Younger Than 1 Year Be Evaluated Once the Diagnosis of NF1 Has Been Established?

Visual examinations in children younger than 1 year may not yield reliable, reproducible results. Illustrating the diversity of opinions, at least one NF1 center recommends neuroimaging in children with NF1 younger than 1 year once the diagnosis has been confirmed, particularly if the patient is uncooperative for measurement of visual function (G. Liu, personal communication). Examining all the studies cited in this report in which the age range at presentation of NF1-associated OPG was reported, we found that only two children under the age 1 were identified, at least one of whom was asymptomatic at the time of diagnosis. Thus, it is difficult to make a recommendation for universal screening neuroimaging in this age group.

Once NF1–Associated Optic Pathway Gliomas Have Been Identified, at What Intervals Should They Be Followed and with What Modalities?

Little consensus exists on the frequency of visual examinations and neuroimaging, and proposed intervals between examinations vary between 3 and 24 months, partly depending on the site of the tumor, the degree of visual impairment, and the evidence of progression.[5,6,25,50] VEP is a poor modality for following children with OPG and is not recommended.

What Constitutes Radiographic and Clinical Progression Significant Enough to Warrant Treatment?

There is scant information in the literature as to what constitutes radiological and clinical progression. Some experts advocate treatment when there is radiological progression, whereas others rely on clinical deterioration or a combination of clinical and radiological progression.[6,25,50,51] Radiological progression has been variably defined in the literature as an increase in tumor size, optic pathway extension or hypothalamic involvement, or a change in the pattern of enhancement. Similarly, clinical progression has been defined as the onset of new neurological symptoms or endocrinological abnormality,[25,26,50] a change in visual acuity alone,[5,50] or visual field loss combined with impaired visual acuity.[25] A simple working definition of ophthalmological progression would be either a (1) two-line change in Snellen, HOTV, or Lea visual acuity compared with the previous examination; or (2) two-octave decline in Teller visual acuity. Because optic disc swelling or atrophy may be associated with, but does not predict, visual acuity loss, the de novo appearance of either finding without acuity loss should not constitute evidence of clinical progression.

What Are the Treatment Options for Symptomatic NF1–Associated OPG?

Treatment protocols vary in different centers, and debate exists as to what constitutes optimal therapy.

Table 2. Infectious Disease Society of America – US Public Health Service Grading System for Rating Recommendations in Clinical Guidelines[61]

Category, Grade	**Definition**
Strength of Recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of Evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

SURGERY. Surgical decompression limited to partial removal of the intraorbital optic nerve should be performed on NF1-associated optic nerve gliomas only for cosmetic purposes or to treat corneal exposure. In those cases, there should be a large degree of proptosis and a blind or near-blind eye.[50] Because optic nerve gliomas without chiasmal involvement at initial presentation do not "grow backward" and extend into the chiasm, surgical removal of an optic nerve glioma, particularly the intracranial portion, to prevent "spread" to the chiasm is unnecessary. Hypothalamic or chiasmal gliomas occasionally may require surgical decompression, especially when hydrocephalus occurs due to third ventricular compression. Although surgical biopsy is not generally useful for typical OPG in children with NF1, it may have some utility for NF1-associated OPGs with an unusual location or presentation.[8]

RADIOTHERAPY. Recent studies have advocated radiotherapy for children older than 5 years and for progressive chiasmatic tumors.[25,51,52] However, current data suggest that radiotherapy causes unacceptable neurovascular, endocrinological, and neuropsychological sequelae and poses a risk for second tumors. In a multicenter study, 9 of 18 NF1 patients treated with radiotherapy for progressive OPG were diagnosed sub-

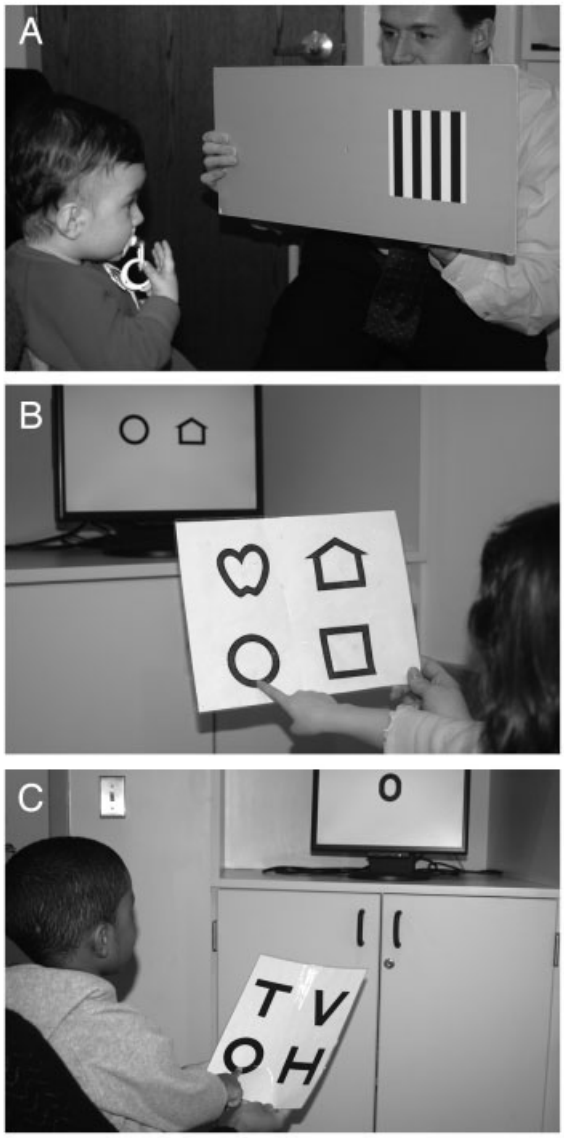

Fig 2. Visual acuity testing in preliterate children. (A) Teller acuity testing. In very young children, preferential looking tests may be used. These tests are based on the principle that a child would rather look at objects with a pattern stimulus (alternating black and white lines of specific widths) than at a homogeneous field. The smallest pattern that the child appears to prefer is an indicator of best visual acuity ("grating acuity"). The stimuli are presented on one side of a series of rectangular handheld cards with gray backgrounds. The frequency difference between the stimuli on each card is approximately 0.5 octave. Visual acuity is determined by decreasing the thicknesses of the black and white stripes and presenting them to the left or right until the child no longer preferentially looks at them against the gray background on the rectangular card. Results are compared with age-based normal control subjects. The grating acuity can be converted to Snellen equivalents. In (B) Lea figure testing and (C) HOTV acuity testing, the child points to one of four choices to match the figure or letter he sees on the computer monitor or chart in the distance. The figure and letter sizes on the computer monitor are varied until the best visual acuity is determined.

Table 3. Evidence-Based Recommendations for the Diagnosis and Management of Children with NF1 and OPG

Screening of asymptomatic children with NF1 for OPG

1. Baseline "screening" neuroimaging or visual-evoked potentials of asymptomatic children with normal visual examinations is not warranted. (A-III)
2. All children with NF1 younger than 8 years should undergo an annual ophthalmological examination that should include measurement of visual acuity, confrontation visual field evaluation, color vision testing, and assessment of pupils, eyelids, ocular motility, irises, and fundi. Formal computerized or kinetic testing of visual fields may be adjunctive if the patient is reliable, but is not necessary. It is recommended that these evaluations be performed by an ophthalmologist or neuro–ophthalmologist skilled in testing young children with NF1 whenever possible. (A-II)
3. Children ≥8 years of age are at a significantly lower risk for the development of OPG. The interval at which ophthalmological examinations should be performed and at what age they may be discontinued is unknown. Until new evidence is presented, it is recommended that children in this age group should receive complete eye examinations every 2 years until 18 years of age. (B-III)
4. No specialized ophthalmological follow-up is necessary for adults with NF1 except for routine eye care. (A-III)
5. All children with NF1 should undergo yearly measurements of weight and height plotted on standard growth charts, looking for the first sign of precocious puberty. (A-III)
6. There is insufficient information available to make an evidenced-based recommendation on the evaluation of children younger than 1 year.
7. In those uncommon situations where reliable eye examinations cannot be obtained, there may be a role for neuroimaging. Further study of neuroimaging in this context is warranted. (B-III)

Evaluation of children with suspected OPG

8. Once an ophthalmological abnormality is detected and confirmed, MRI of the brain with dedicated views of the orbits is the appropriate imaging modality. There is no role for the use of VEP in the diagnosis or follow-up of children with OPG. (A-II)

Longitudinal follow-up of children with known NF1-associated OPG

9. Because the follow-up and management of children with NF1-asociated OPG is complex, they all should be cared for in centers that have significant experience in the treatment of NF1 and childhood cancer, as well as by pediatric ophthalmologists or neuro–ophthalmologists who have significant experience with children who have NF1. (A-III)
10. The previously recommended intervals between MRI and ophthalmological examinations have varied. Typically, once the diagnosis has been established, children should have eye examinations every 3 months for the first year after diagnosis and at increasing intervals thereafter. MRI examinations may be performed at similar or less frequent intervals depending on institutional preference. (A-III)

Treatment of children with NF1-associated OPG

11. No universal agreement has been reached as to what constitutes "progressive disease" (eg, radiographic evidence of tumor growth, decreasing visual acuity, or a combination of the two). Except in those rare cases in which the reliability of serial ophthalmological examinations is limited (eg, children <1 year of age), treatment of symptomatic NF1-associated OPG should be instituted only when there is clear evidence of progressive disease. A change in the pattern of contrast enhancement on MRI is not an indication for treatment. (A-II)
12. Chemotherapy should be the first-line therapy for children with progressive NF1-associated OPG. Currently, the recommended initial therapy includes a combination of carboplatin and vincristine. (A-II)
13. Radiation therapy is not recommended for NF1-associated OPG, because of the risk for secondary malignancies and radiation-induced vasculopathy, unless all chemotherapeutic treatment options have been exhausted. (A-II)
14. Surgical removal of part of the intraorbital optic nerve can be performed in NF1-associated optic nerve glioma for cosmetic purposes or to treat corneal exposure. In those cases, indications include a large degree of proptosis and a blind or near-blind eye. (B-III)

Ratings are in parentheses following recommendations.

NF1 = neurofibromatosis type 1; OPG = optic pathway glioma; MRI = magnetic resonance imaging; VEP = visual-evoked potential.

sequently with 12 secondary brain tumors for a relative risk of 3.04; the greatest risk was in patients treated in childhood.[53] Moreover, the presence of NF1 appears to convey a significant risk for development of cerebral occlusive vasculopathy in children previously treated with radiotherapy.[54]

Fractionated stereotactic radiotherapy has been used in an attempt to combat the side effects of conventional radiotherapy.[55] Fifteen patients were treated with a median target dose of 52.2Gy with a median follow-up period of 97 months. There was a 90% five-year survival rate after fractionated stereotactic radiotherapy, and no endocrine abnormalities or second tumors were observed. However, additional studies will be necessary to evaluate this form of treatment because only 3 of the 15 patients had NF1.

CHEMOTHERAPY. Chemotherapy has been shown to delay the need for radiotherapy in young children and is emerging as the treatment of choice for OPG.[56] Combined chemotherapy with carboplatin and vincristine has been shown to be effective in controlling progressive low-grade gliomas in children younger than 5 years.[57] This chemotherapy was well tolerated with

minimal toxicity. In a retrospective study, 9 children with NF1 received 560mg/mm^2 carboplatin at 4-week intervals for 15 cycles.[58] Improved vision was detected in four children, and radiological regression occurred in four patients. Because a small but significant percentage of children will develop allergic reactions to carboplatin, alternate regimens have been advocated. Although the use of temozolomide alone[59] or the combination of procarbazine, vincristine, 6-thioguanine, and chloroethylcyclohexylnitrosourea (CCNU; lomustine) has been shown to have activity against these tumors,[60] the use of alkylating agents and multidrug regimens in children with NF1 runs the theoretical risk for the development of secondary malignancies. Currently, the first-line therapy for children with symptomatic NF1-associated OPG is the combination of carboplatin and vincristine. No consistent second-line therapy is used routinely. Finally, therapies that target the biochemical or cellular abnormalities in NF1-associated OPG are currently being evaluated in early clinical trials. Drugs that inhibit the RAS pathway, as well as antiangiogenic therapies (vascular endothelial growth factor inhibitors or vinblastine), may find their way into clinical practice alone or in combination with conventional therapies.

Recommendations

Although much work needs to be performed to address the many unanswered questions, clear recommendations can be made based on the above information. Each recommendation has been graded using the US Public Health Service criteria, which assess both the quality of the evidence in the literature and the strength of the recommendation (Table 2).[61] These recommendations are presented in Table 3, with the rating for each recommendation presented in parentheses.

Future Directions

Over the past decade, there has been rapid progress in the development of small-animal models of NF1-associated optic glioma and the identification of new candidate drugs for OPG treatment. Based on these advances, we are uniquely positioned as a community to translate fundamental basic science discoveries to the clinical workplace. Unfortunately, a number of critical clinical issues exist that preclude our ability to make similar advances in the treatment of children with NF1. There is a pressing need to evaluate the available ophthalmological screening tools for NF1-associated OPG in an effort to define clinical progression and decide which children require treatment. Moreover, we require similar outcome measures to determine whether our therapies are effective. In addition, we will need to carefully consider the use of targeted therapies in the pediatric population, where these drugs may have undesirable effects on the developing brain. Future multicenter cooperative studies addressing these issues, especially in very young children, represent the next logical step in our march toward improved care of children with NF1-associated OPG.

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