AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Orbital/Periorbital Plexiform Neurofibromas in Children with Neurofibromatosis Type 1

Multidisciplinary Recommendations for Care

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Topic: Children and adults with neurofibromatosis type 1 (NF1), a common autosomal dominant condition, manifest a variety of ophthalmologic conditions. Plexiform neurofibromas (PNs) involving the eyelid, orbit, periorbital, and facial structures (orbital-periorbital plexiform neurofibroma [OPPN]) can result in significant visual loss in children. Equally important, OPPNs can cause significant alteration in physical appearance secondary to proptosis, ptosis, and facial disfigurement, leading to social embarrassment and decreased self-esteem.

Clinical Relevance: Although NF1 is a relatively common disease in which routine ophthalmologic examinations are required, no formal recommendations for clinical care of children with OPPNs exist. Although medical and surgical interventions have been reported, there are no agreed-on criteria for when OPPNs require therapy and which treatment produces the best outcome.

Methods: Because a multidisciplinary team of specialists (oculofacial plastics, pediatric ophthalmology, neuro-ophthalmology, medical genetics, and neuro-oncology) direct management decisions, the absence of a uniform outcome measure that represents visual or aesthetic sequelae complicates the design of evidence-based studies and feasible clinical trials.

Results: In September 2013, a multidisciplinary task force, composed of pediatric practitioners from tertiary care centers experienced in caring for children with OPPN, was convened to address the lack of clinical care guidelines for children with OPPN.

Conclusions: This consensus statement provides recommendations for ophthalmologic monitoring, outlines treatment indications and forthcoming biologic therapy, and discusses challenges to performing clinical trials in this complicated condition. *Ophthalmology 2017;124:123-132 © 2016 by the American Academy of Ophthalmology*

Neurofibromatosis type 1 (NF1) is a relatively common oncogenic condition that occurs in approximately 1:3500 births.[1,2] Neurofibromatosis type 1 has an autosomal dominant inheritance pattern with approximately 50% of all new cases due to sporadic mutations. Children with NF1 manifest a variety of ophthalmologic conditions, including low-grade gliomas of the afferent visual pathway (termed "optic pathway gliomas"), glaucoma, choroidal nodules, Lisch nodules, and plexiform neurofibromas (PNs) involving the eyelid, orbit, periorbital, and facial structures.[1,3,4] All of these manifestations, except for Lisch nodules and choroidal nodules, can result in visual loss in children, frequently during the age of visual maturation.[2] Ectropion uveae alone should not cause vision loss, although it has been associated with glaucoma.[4] Although most cases of NF1-related vision loss are secondary to optic pathway gliomas, PNs of the orbit and face frequently cause vision loss secondary to deprivational or anisometropic amblyopia, as well as glaucoma.[5–8] Equally important is the alteration in physical appearance secondary to proptosis, ptosis, and facial disfigurement, leading to social embarrassment and decreased self-esteem.

Terminology that describes neurofibromas in NF-1 can be confusing. Discrete neurofibromas arise from small nerves or nerve endings, and include dermal neurofibromas that protrude from the surface of the skin or subcutaneous neurofibromas that present as firm nodules just below the surface of the skin; these tumors tend to be small and generally appear in the second decade of life, becoming more frequent as the patient ages. They have no risk of malignant transformation and rarely cause neurologic deficits. In contrast, PNs are complex nerve sheath tumors that follow multiple nerve branches. Most PNs are diagnosed in early childhood and may demonstrate rapid growth during this period. Plexiform neurofibromas can result in substantial morbidity because of their appearance and proclivity to cause functional and neurologic deficits, and are at risk for malignant transformation.[2] Plexiform neurofibromas

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involving the eyelid, orbit, periorbital, and facial structures (orbital-periorbital plexiform neurofibroma [OPPN]) have been described using a variety of names, including orbitotemporal PNs,[7,9] orbitopalpebral neurofibromatosis,[10,11] orbitotemporal neurofibromatosis,[5,12–14] orbital neurofibromas,[15] and orbitofacial neurofibromatosis.[8,16] Plexiform neurofibromas in these areas are most appropriately labeled as OPPN to encompass all locations where they occur. To provide clarity and consistency within the medical literature, we propose that the medical and research community adopt the abbreviation OPPN.

Ophthalmic and clinical characteristics of OPPNs have not been routinely described in the relatively small number of case reports or case series. In clinical trials assessing the treatment of all PN locations, OPPN comprise a small portion of those subjects and ophthalmologic outcome measures are typically not reported. Surgical case series, primarily in adults, also have not focused on ophthalmic characteristics or outcomes.[12,14,17–20] Although the surgical techniques described in these case series are important, without a well-defined indication for treatment or a formal definition of "therapeutic success," it is difficult to determine if and when intervention is indicated, and whether an intervention is actually beneficial. Improvement in physical appearance and visual outcomes (i.e., avoiding or decreasing amblyopia) are the most common indications for medical and or surgical treatment, yet neither has been well studied nor has been included in clinical trials.

In this review, we will describe the biologic mechanism, provide a formal definition of OPPN, describe the natural history of PN growth, and discuss treatment options and conclude with consensus recommendations for OPPN management.

Biology of Plexiform Neurofibromas

Neurofibromatosis type 1 is caused by a mutation in the *NF1* tumor-suppressor gene on chromosome 17q11.2-350 kb, 60 exons.[2,21] The gene product neurofibromin (2818 amino acids) contains a domain with significant homology to Ras GTPase-activating proteins and thus regulates Ras activity. Lack of functional neurofibromin leads to dysregulated Ras signaling and tumorigenesis.[22] Plexiform neurofibromas are composed of neoplastic Schwann cells, fibroblasts, perineural cells, and mast cells.[23] Neoplastic Schwann cells lack *NF1* gene expression, and loss of neurofibromin is associated with elevated levels of activated Ras.[24,25] Activated Ras results in the initiation of a cascade of signaling events, such as activation of Raf and mitogen-activated protein kinase, that lead to increased cell proliferation.[26,27] In addition, activation of the mammalian target of rapamycin pathway has been identified in benign and malignant NF1 tumors,[28–30] and the tumor microenvironment contributes to the pathogenesis of PN. Schwann cells have been shown to secrete kit ligand, which recruits mast cells and results in abnormal growth.[31–33] Additional cooperating events, such as increased expression of growth factors and growth factor receptors, including endothelial growth factor receptor, platelet-derived growth factor receptor, and vascular endothelial growth factor, may contribute to PN development and progression.[34–37] Many of the potential treatment targets for PNs are shared with cancers, such as Ras, cKIT, angiogenesis, and mammalian target of rapamycin.

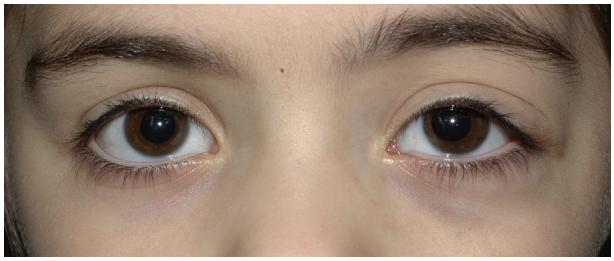

Figure 1. Small plexiform neurofibroma (PN) restricted to the left upper eyelid causing a mild degree of ptosis.

Definition

Most OPPNs track along the distribution of the trigeminal nerve. Plexiform neurofibromas occasionally will involve other facial and head structures. Orbital-periorbital PNs can be categorized by their current anatomic location: Those in the *isolated upper eyelid* frequently assume an "S" shape (Fig 1) and can result in mild ptosis without obscuration of the visual axis. Future progression into the periorbit/orbit is highly unlikely. Those in the *eyelid and periorbital region* extend across the V1 and V2 distribution of the trigeminal nerve. On occasion, the ptosis can be profound, causing deprivational or refractive amblyopia (Fig 2). Future progression into the orbit is possible. Those in the *orbit with/without eyelid involvement* invade the lateral orbit and can invade toward the cavernous sinus, deemed infiltrative (Fig 3A and B). The frequency of OPPN, as categorized, is approximately equal across anatomic locations (i.e., one third per location).[7]

Associated Structural Findings

Absence or marked reduction of the sphenoid bone that comprises the posterolateral wall of the orbit, termed "sphenoid wing dysplasia," is a congenital abnormality that commonly occurs on the same side as the OPPN (Fig 3B). Sphenoid wing dysplasia can permit protrusion of the

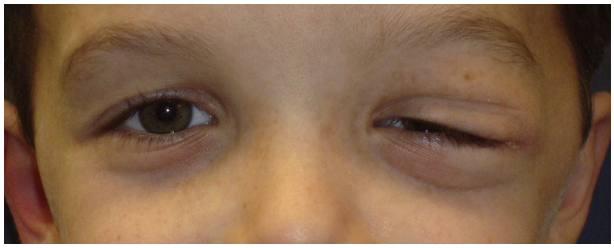

Figure 2. Left upper and lower eyelid plexiform neurofibroma (PN) causing ptosis and subsequent deprivational amblyopia.

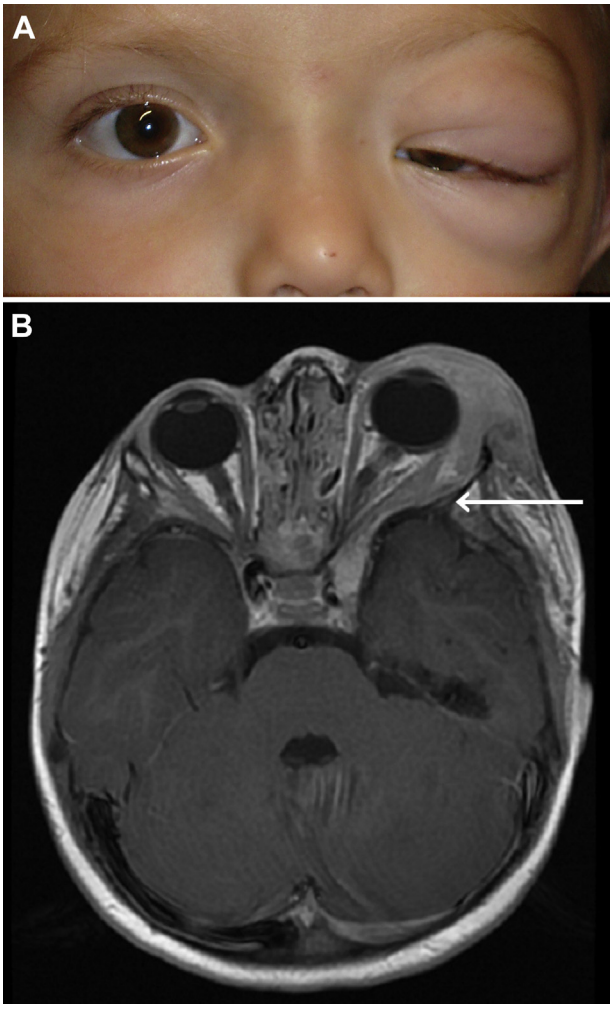

Figure 3. A, Infiltrative orbital-periorbital plexiform neurofibroma (OPPN) resulting in anisometropic and deprivational amblyopia. **B**, Magnetic resonance imaging (MRI) of infiltrative OPPN and sphenoid wing dysplasia. *Arrow* indicates the forward protrusion of the anterior temporal lobe and displacement of the orbital contents.

anterior temporal lobe into the orbit causing compression of the extraocular muscle and the optic nerve. This also likely contributes to proptosis, pulsatile exophthalmos, and strabismus that can be associated with the OPPN.

Diagnosis

An infant or young child presenting with periorbital asymmetry or unilateral proptosis, with or without elevated intraocular pressure, should be evaluated for an OPPN. Although most OPPNs are congenital, they may not be obvious immediately after birth. Although not formally studied, the initial identification of OPPN typically occurs before 5 years of age.[7] The palpable mass of OPPN can be firm or soft; sometimes the cluster of nodules resembles what is described as a "bag of worms." Concurrent eyelid edema can be present. In children diagnosed with NF1, the suspected OPPN should not be biopsied. If the diagnosis of NF1 has not been established, a formal consultation with a physician expert in the care of children with NF1 is recommended before biopsy is considered.

All children with a newly identified OPPN, regardless of whether a diagnosis of NF1 has been confirmed or excluded, should undergo magnetic resonance imaging (MRI) of the brain and orbits to confirm the diagnosis of PN and to better define its extent. Even when the OPPN is suspected to be isolated to eyelid, MRI should still be performed because the entire portion of the OPPN may not be completely visualized on external examination.

Clinical Characteristics

Incidence

The incidence of OPPN in children with NF1 is likely less than 10%. Oystreck and colleagues[8] described 55 patients examined over a 28-year period. Avery et al[7] reported 21 children from 2 institutions over a 10-year period, although they excluded children with concurrent glaucoma or optic pathway gliomas. Of children with PNs enrolled in clinical treatment trials, 9% were classified as having head PN.[38] Approximately 43% of cases in the surgical series by Needle et al[39] included the head, neck, or face. On the basis of our combined clinical experience from multiple large NF1 clinics, OPPN likely occur in less than 10% of children with NF1.

Age at Presentation

Most OPPNs are identified within the first few years of life. Small OPPNs restricted to the eyelid may go unnoticed until later in childhood, especially if the ptosis is mild or unrecognized.

Signs and Symptoms

Blepharoptosis is the most common and notable sign of an OPPN, with an incidence of approximately 100%, followed by proptosis, eyelid edema, and strabismus.[16] Although not reported in an all studies, the report by Chaudhry et al[16] documented proptosis in more than 50% of patients with OPPN.

An OPPN should be considered in infants and young children who present with buphthalmos and/or glaucoma. The exact frequency of glaucoma discovered during the initial diagnosis of an OPPN has not been adequately studied. A cross-sectional study that included both children and adults with OPPN secondary to NF1 reported that approximately 25% of them had glaucoma.[8] It is uncommon that a child's symptom will lead to the initial discovery of an OPPN, because most are visible. Symptoms such as eye pain from exposure keratopathy and diplopia from strabismus do occur in OPPNs that demonstrate significant growth.

Natural History

The introduction of volumetric MRI analysis of PNs has allowed investigators to closely monitor small changes

in PN volume over time and has provided a better understanding of their natural history.[40] This method, which requires imaging of the entire PN with axial and coronal short tau inversion recovery sequences without a gap between slices, has been used in several natural history trials and in multiple treatment trials directed at PN.[41–47] Guidelines for the measurement of response and the imaging of PNs in clinical trials were recently issued by the Response Evaluation in Neurofibromatosis and Schwannomatosis, Tumor Measurement Working Group.[48]

Young children (aged ≤8 years) seem to have the fastest PN growth rates,[49,50] and there does not appear to be acceleration in the PN growth rate during puberty.[51] In adults, PNs typically grow minimally. Although PN growth rates vary between patients, PN growth was relatively constant over prolonged time periods within patients.[49] Spontaneous slow decrease in PN volumes (median 3.4% decrease in tumor volume per year) has been described in one study[52] and was in large part due to measurement error. These studies support the need for treatment intervention directed at PNs in early childhood. Surgery is one option for the treatment of PN, but complete OPPN removal is feasible in only a small subset of patients. Continued PN growth after surgery has been described, particularly in patients with head and neck tumors[39] and in younger patients.[39,53]

Management of Orbital-Periorbital Plexiform Neurofibroma

What Is the Appropriate Ophthalmologic Assessment in Children with Orbital-Periorbital Plexiform Neurofibroma?

A comprehensive ophthalmologic examination should be performed at a minimum of every 6 months throughout the period of visual development (i.e., before the age of 8 years) during which time amblyopia may develop. The mechanisms by which children with an OPPN are susceptible to vision loss are complex. Refractive amblyopia from anisometropia induced by ptosis or increased axial length occurs in up to 43% of children with OPPN.[7,8] Deprivation amblyopia from significant ptosis occurs in approximately one third to one half of patients.[7,8] Amblyopia due purely to strabismus occurs in only 10% to 20%.[7,8] Approximately one quarter of patients may demonstrate elevated intraocular pressure; however, a rigorous longitudinal analysis comparing the incidence among children and adults has not been completed.[8] Proptosis has been reported to occur in approximately 50%,[16] yet surgical treatment for exposure keratopathy is reported to occur less frequently (i.e., 5%).[7] Although the frequency of compressive optic neuropathy is unknown, it has been considered as another mechanism of visual compromise in the setting of an OPPN. The frequency of examinations in children with a rapidly growing OPPN should be increased at the discretion of the provider to monitor for amblyopia, glaucoma, strabismus, or optic nerve disease. Although it is still important to provide ophthalmologic monitoring after the age of 8 years, the frequency of examinations should be based on the patient's clinical course.

Approach to Strabismus

There is a high prevalence of OPPN-associated eye misalignment or strabismus with reported rates ranging from 26% to 75% in several large case series of children and adults with OPPN compared with a rate of approximately 3% to 5% for the more common forms of strabismus in school-aged children.[5,8,54–56] Strabismus may develop from mechanical restriction of the globe by tumor infiltration or compression of orbital tissues and extraocular muscles, by globe displacement from increased axial length, and by globe displacement secondary to orbital and sphenoid wing dysplasia.[10,55] Furthermore, in the setting of severe vision loss, a sensory strabismus also may develop. In their detailed examination of ocular motility in 49 patients with OPPNs, Oystreck et al[55] found that the mechanisms for eye misalignment were multifold and that no specific factor was highly predictive. As expected, more severe ocular misalignment was associated with poorer visual acuity; 37% of patients with strabismus had vision less than 20/200 in the affected eye compared with 0% of patients without strabismus.[55]

The onset of strabismus during the period of visual development in a child has the potential to compromise binocular vision and places a child at risk for strabismic amblyopia. Although the data are limited, strabismic amblyopia occurs less frequently than refractive amblyopia; vision loss from strabismus has been documented to account for 10% to 22% of vision loss associated with OPPNs.[5,7,8] The management of strabismus in these children is complex, and no studies exist to support early versus late surgical treatment of strabismus. Rather, the provider should focus on nonsurgical treatment for strabismic amblyopia, including correcting any induced refractive error, conventional occlusion therapy with patching or atropine penalization, and consideration of prisms for smaller angle eye misalignment. If the severity of strabismus precludes the effectiveness of amblyopia treatment, then surgical correction may be considered at an earlier stage in the disease process. A conservative approach to management would advocate later surgery once the growth phase of the OPPN has attenuated and the overall disease process is more stable.[18,57]

Imaging Evaluation

An MRI scan of the brain and orbits should be performed in all children with a suspected OPPN. High-resolution MRI sequences with and without contrast should be acquired through the orbit, face, and cavernous sinus. The radiation exposure from CT scans should be avoided whenever possible in all children with NF1.

No studies have been informative about the frequency of follow-up MRIs; therefore, clinical progression should be the primary indication. Orbital-periorbital PN involving the orbit or moving toward infiltrating the cavernous sinus should be imaged frequently (i.e., at least every 3–6 months) until clinical stability and lack of further growth

can be confirmed. If the child experiences progressive OPPN growth or demonstrates continued vision loss not related to amblyopia, repeat imaging at higher frequency may be warranted.

Treatment Indications for Orbital-Periorbital Plexiform Neurofibroma

Newly diagnosed OPPNs are best managed by close observation with serial ophthalmological and MRI evaluations because many OPPNs will not progress or cause significant symptoms. Identifying which OPPN to treat and identifying the optimal time to initiate therapy are challenging. Considerations before initiating treatment include the age of the patient and extent of visual maturation, growth rate of the tumor, presence of a concurrent optic pathway glioma, presence of symptoms or a functional deficit (i.e., vision loss, strabismus, proptosis, ptosis, amblyopia, or glaucoma), and extent of OPPN infiltration into other structures (i.e., cavernous sinus).

In the absence of significant tumor growth, initial intervention should be directed toward management of specific symptoms. For growing tumors, indications for debulking surgery or consideration for enrolling in a clinical trial include visual decline, progressive tumor that may soon invade a critical structure (e.g., cavernous sinus) or is likely to cause a new or worsening functional deficit, and potentially progressive disfigurement. Malignant transformation should be considered if the increase in OPPN exceeds the rate of increase typically seen in patients of similar age,[49] along with referral to an oncologist experienced in caring for patients with PN secondary to NF1. Most malignant transformation of PN secondary to NF1 occurs in adults[58] and is infrequently located in the head and neck region.[59,60] Radiation therapy to the orbital region is a known risk factor for malignant transformation.[59]

For adults, an aggressive and more definitive surgical approach might be considered before medical therapy, because OPPN at this age is less likely to have continued growth. It is always crucial to balance present function with the risk to future function imposed by surgical intervention.

Although improvement in visual outcomes and physical appearance is the most common indication to initiate treatment, neither has been well studied or included in clinical trials, making evidence-based recommendations for treatment impossible. In all cases, management decisions should include the input from a multidisciplinary team, including neuro-oncology, ophthalmology/neuro-ophthalmology, oculofacial plastics, craniofacial surgery, and genetics.

Surgical Treatment of Orbital-Periorbital Plexiform Neurofibroma

"All results (of surgery in neurofibromatosis) are compromised by the very nature of the tumor, its diffuse position, its widespread involvement of all the constituents of the region or organ, and its tendency to recur." — Dr. J. Conley[61]

Timing of Surgical Intervention

Optimal timing of surgical intervention is uncertain because the rate and extent of growth of tumors are unpredictable. Adnexal and orbital deformities often continue developing after initial excision and repair. These are not really recurrences but rather a progression of remaining periorbital and orbital tumors. Progression is more rapid in childhood and puberty but can still occur later in life. Rapidly growing OPPN can indicate the possibility of a malignant peripheral nerve sheath tumor, in which surgical and medical therapy may be indicated. Families are extremely motivated for surgery but must be cautioned regarding the likelihood of multiple procedures required for long-term tumor management.

Surgical Management Concerns: Are Multiple Procedures Really Worth the Effort?

In a 20-year study performed at the NF1 Clinic at The Children's Hospital of Philadelphia, 131 patients had 302 procedures for head and neck tumors. The overall freedom from progression was 56%, but head, neck, and facial tumors had double the probability of recurrence compared with tumors excised from the extremities.[39] The conclusion drawn from this study was that patients aged less than 10 years with lesions of the head, neck, and face were unlikely to have long-term benefits from surgery because OPPN recurrence was so common. Development of an effective medical therapy was the recommended goal.

There are a number of concerns with these recommendations. Although medical therapy is a major goal and ideally would be the preferred treatment, 20 years later, we are still searching for an effective medical treatment for OPPN. Furthermore, avoiding surgery does not take into account the functional or psychosocial appearance concerns of these younger patients. Nevertheless, the absence of data supporting a functional or psychosocial benefit from surgical repair, especially in cases of OPPN recurrence, obviates it from being universally recommended.

Functional Concerns

Protecting against amblyopia is the most common functional concern. This problem can be due to occlusion by a ptotic lid (age <8 years) or anisometropia from pressure of orbital or lid tumors on the eye or from strabismus. Corneal exposure problems from proptosis and epiphora from lid malposition are other common functional problems.

Appearance Concerns

Periorbital soft tissue complications include ptosis, lid contour and asymmetry of the eyelids, canthal abnormalities, and skin changes. Facial descent from the weight of OPPNs also can produce cheek and oral commissure deformities. Orbital PNs can produce proptosis, leading to significant alterations in appearance.

Indications and Timing of Surgical Intervention

Both the timing and degree of surgical intervention are controversial subjects. Early surgery before age 10 years may be necessary because of functional concerns regarding amblyopia and the effects of expansion on both the periorbital soft tissues and the bony orbit. Early surgery also is important in attempting to maximize the child's cosmetic outcome and minimize psychosocial concerns from the deformities of OPPN growth because these affect not only the child but also the entire family constellation.

Current Recommendations: Soft Tissues

Management of any associated congenital nasolacrimal problems can be instituted early. Intubation of the nasolacrimal system may offer protection from inadvertent damage during more extensive orbital surgery. Debulking OPPN invading the cheek early is somewhat controversial because of concerns for possible facial nerve damage. Balloon expansion can provide tissue replacement for large areas with skin deformities. Exenteration for use of a facial prosthesis is an option but should be avoided because it has other limitations affecting quality of daily life in hot weather or for other functions (e.g., swimming).[62]

Current Recommendations: Bone

Sphenoid bone defect repair may be needed for progressive proptosis with pulsating exophthalmos. Calvarial bone grafts with titanium mesh are useful to cover the sphenoid defect and minimize bone resorption. This should be considered on a case-by-case basis and is a more critical issue when associated with a seeing eye.[63]

Measuring Surgical Outcomes

At present, surgical management is still largely dependent on clinical judgment. Unfortunately, there are no data-driven recommendations that can be made with confidence. Most studies have a relatively limited follow-up. In addition, limited progression after the second decade may be a myth because there are patients with continued progression into late adulthood. The problems to address in measuring surgical outcomes relate to the diversity of facial abnormalities, a limited sample size for randomization, and the further difficulty of studying changes in appearance over time after multiple interventions.

Despite these limitations, we offer 4 categories that may prove of use in assessing surgical outcomes (Table 1). Although appearance considerations overlap between these categories, they can at least provide specific diagnostic groups for use in measuring surgical outcomes within the limitations and problems related to timing, randomization, multiple interventions, and diversity of procedures.

Table 1. Categories to Assess Surgical Outcomes in Orbital/Periorbital Plexiform Neurofibromas

	Estimated Incidence
Vision Problems	
Occlusive amblyopia	32%–43%
Anisometropia amblyopia	38%–43%
Strabismic amblyopia	10%–20%
Motility disorders	50%
Corneal abnormalities	n/a
Optic nerve compression	n/a
Papilledema	n/a
Optic nerve atrophy	n/a
Appearance and Psychosocial	n/a
Ptosis, lid contour, and symmetry	94%
Motility disorders	55%
Corneal scarring	n/a
Proptosis	57%
Canthal abnormalities	n/a
Skin changes	n/a
Facial descent	n/a
Cheek deformities	n/a
Oral commissure deformities	n/a
Structural Problems	
Bony orbital expansion	n/a
Soft tissue expansion of eyelids	n/a
Laxity of eyelids/canthi	n/a
Facial descent from the weight of tumor	n/a
Soft tissue expansion of cheek	n/a
Other Concerns	n/a
Pain or discomfort	n/a
Suspicion of malignancy	n/a
Overall quality of life	n/a

n/a = not available.

Medical Treatment of Orbital-Periorbital Plexiform Neurofibroma

The medical treatment of PNs has been frustrating with little evidence of efficacy. Standard chemotherapy has not been shown to be of benefit and is associated with the risk of treatment-induced secondary malignant neoplasms. Because of the mutagenic nature of most chemotherapeutic agents, especially alkylator and topoisomerase inhibitors, chemotherapy is not used. Thalidomide demonstrated some activity in one small clinical trial.[64]

In efforts to reduce PN growth or shrink existing PNs, several clinical trials have used targeted agents, including tipifarnib,[45] pirfenidone,[41,44,65] sirolimus,[43,47] and peginterferon alfa-2b.[42,46,66] The tipifarnib trial was double-blinded and included a placebo control group (29 patients), and the median time to progression (TTP) of progressive PNs treated with placebo was 10.6 months. Tipifarnib did not result in a doubling of the TTP compared with the placebo arm.[45] Three subsequent open-label phase II trials used the tipifarnib trial placebo group as comparison; peginterferon alfa-2b was the only agent that resulted in more than a doubling of the median TTP.[46] In these trials, PN volume decrease $\geq$20% was observed only with peginterferon alfa-2b in 4 of 83 patients.

In a phase II trial of the c-kit and platelet-derived growth factor receptor inhibitor imatinib, PN volume decrease ranging from 20% to 40% was observed in 6 of 23 response evaluable patients; however, the tumors that responded were all small (i.e., <20 ml).[67] Most recently, preliminary results of a phase I trial with the mitogen-activated protein kinase

Table 2. Summary Table of OPPN Working Group Consensus Statement for Ophthalmic Monitoring and Management

1. The Task Force recommends the adoption of the uniform terminology orbital-periorbital plexiform neurofibroma (OPPN) for plexiform neurofibromas (PNs) involving the eyelid, orbit, periorbital, and facial structures.
2. Children with OPPN are at highest risk for rapid growth of OPPN before the age of 8 years. Comprehensive ophthalmic evaluation is recommended every 6 months until visual maturity. After that, frequency of examination should be guided by the clinical course.
3. Patients with OPPN confined to the upper eyelid may not need to undergo neuroimaging. For patients with orbital, periorbital, or facial involvement, high-resolution magnetic resonance imaging (MRI) with and without contrast of the orbit, face, and cavernous sinus should be performed.
4. Treatment for related ophthalmic issues, such as ptosis, lacrimal involvement, or amblyopia, is supportive. Early intervention is recommended with the exception of strabismus surgery. Strabismus caused by orbital or periorbital tumor involvement while the tumor is in its rapid growth phase carries a high risk for recurrence after strabismus surgery. Associated problems such as amblyopia and refractive error should be managed aggressively and surgery deferred until the tumor growth has stabilized, if clinically appropriate to do so.
5. Debulking surgery may be indicated for the following:
   - Visual decline
   - Progressive tumor growth involving a vital structure
   - Progressive disfigurement or functional decline

   Debulking is more successful in older patients and adults. Younger patients have a high risk of recurrent progression and need for more surgery.
6. Clinical trials using biologic agents (i.e., mitogen-activated protein kinase kinase [MEK] inhibitors) are under way, but no definitive recommendations can be made at this time.

kinase (MEK) inhibitor selumetinib (AZD6244 hydrogen sulfate) in children with inoperable substantial PNs reported partial responses (tumor volume decreases $\geq$20%) in 6 of 11 patients.[68] Additional phase II trials with the receptor tyrosine kinase inhibitor cabozantinib (XL184) and the MEK inhibitor PD-0325901 are ongoing.

The completed and ongoing phase I/II studies demonstrate that PN-specific clinical trials using biologic agents can be conducted safely in children and young adults. In addition, prolongations in the TTP of progressive PNs and PN shrinkage have been observed in several trials. Thus, there is reason to hope that early intervention with targeted agents in children with established but small, and minimally disfiguring, OPPN may prevent progression and the resultant facial disfigurement.

Current and Future Challenges of Orbital-Periorbital Plexiform Neurofibroma Clinical Trials

Challenges in the design of OPPN therapeutic trials for children include defining when to initiate medical treatments for OPPN, discerning the availability of adequate pediatric drug formulations, and establishing the safety of the prolonged administration of targeted agents in young children. Standardized clinical trial design and selection of trial end points that represent clinical benefit and quality of life assessments will be required to meaningfully assess the efficacy of novel agents on OPPNs. The Response Evaluation in Neurofibromatosis and Schwannomatosis collaboration, an international initiative composed of clinical (i.e., oncology, genetics, pediatrics, ophthalmology, neurology, neurosurgery, radiology, psychology) and laboratory-based scientist with expertise in NF1, was established with the goal of achieving consensus within the NF1 community about the design and end points of future clinical trials for manifestations of neurofibromatosis.[48,69–73]

Although recent molecular-targeted trials have overcome some of the limitations that have slowed the development of more effective medical therapies for OPPNs, significant challenges still remain. The wider availability of MRI volumetric analysis has made interpretation of clinical trials more reproducible and objective. However, because OPPNs reside in a critical anatomic location, functional deficits or therapeutic improvements can develop even in the absence of measurable size changes. Objective functional and patient-reported outcome measures will be essential to meaningfully assess the benefit of novel therapeutics for OPPNs.

Another major issue in proving efficacy is that OPPNs have an unpredictable natural history. Plexiform neurofibromas, including OPPNs, tend to maintain a relatively stable trajectory of growth in young children, but PN growth slows down at some point before reaching adulthood, and PN growth rates vary greatly between individuals.[45] Whether single-arm studies are adequate to determine the efficacy of treatment for OPPNs is unclear, because factors such as age and when in the course of clinical growth patients are treated likely confound results.[49] Slowing of

growth trajectory (increasing TTP) as the primary end point thus may require a randomized trial for meaningful evaluation.

In clinical trials for children with cancer, substantial and sustained tumor shrinkage has been at times accepted by the Food and Drug Administration (FDA) as a surrogate measure for disease control and treatment efficacy. The definitions of response for children with cancer can be difficult to apply to OPPNs, especially for symptomatic tumors with minimal to no objective growth before initiation of therapy. The experience with most molecular-targeted agents used to date for patients with PNs is that they infrequently result in a large amount of tumor shrinkage; they are more likely to result in disease stabilization. This may not be the case with some of the new agents, such as MEK inhibitors. Thus, imaging response will likely only be part of a constellation of outcome measures that could be used for FDA approval for the use of molecularly targeted agents in children with symptomatic or progressive OPPNs.

Approval by the FDA, which is needed to get these novel agents to more patients and not only those entered in a clinical trial, will be dependent on demonstrating improvement in functional measures. What constitutes a validated functional outcome measure in children with OPPNs remains unclear.[72] Measures of vision, cosmesis, and overall quality of life will need to be looked at extremely carefully in these trials.[70,72,73]

Still another issue that must be considered is the relatively young age of patients who develop symptomatic OPPNs and the need to have these agents approved in the age range that would most benefit these patients. Because of the unknown long-term effects of almost all molecularly targeted agents, including the MEK inhibitors, on normal body function and development (including brain development), it is critical to incorporate long-term measures of toxicity into ongoing studies. This will likely include sequential neurocognitive function and developmental assessments, especially in the very young child.[73] To perform these trials adequately and efficiently, studies most likely will need to be multicentered and performed by experienced working groups or by already formed neurofibromatosis translational consortia, such as the Department of Defense Neurofibromatosis Clinical Trials Consortium.

Conclusions

The proposed nomenclature, clinical examination frequency, and indications for medical and surgical treatment of OPPN in children are small, but necessary, first steps (Table 2). The next step of defining therapeutic "efficacy" will be more challenging because this will have to satisfy both industry and regulatory criteria needed for FDA approval, all the while considering what is most beneficial to the patient. Furthermore, multicenter clinical trials will need to include not only young patients who are at the greatest risk for irreversible vision loss but also those vulnerable to lifelong reduced quality of life and self-esteem from their physical appearance.

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Abbreviations and Acronyms:
FDA = Food and Drug Administration; **MEK** = mitogen-activated protein kinase kinase; **MRI** = magnetic resonance imaging; **NF1** = neurofibromatosis type 1; **OPPN** = orbital-periorbital plexiform neurofibroma; **PN** = plexiform neurofibroma; **TTP** = time to progression.

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