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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 2016;■:1–10 © 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 involving the eyelid, orbit, periorbital, and facial structures (orbital-periorbital plexiform neurofibroma [OPPN]) have

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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.

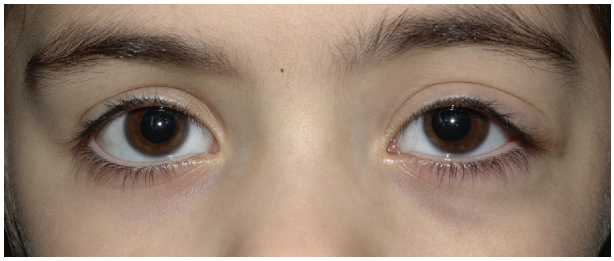

Figure 1. Small plexiform neurofibroma (PN) restricted to the left upper eyelid causing a mild degree of ptosis.

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 anterior temporal lobe into the orbit causing compression of the extraocular muscle and the optic nerve. This also

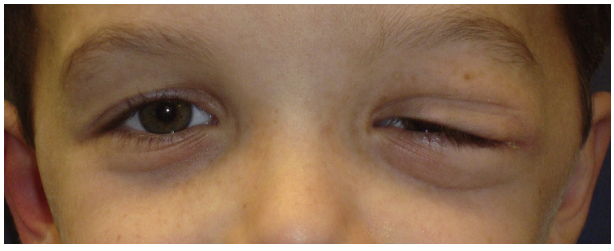

Figure 2. Left upper and lower eyelid plexiform neurofibroma (PN) causing ptosis and subsequent deprivational amblyopia.