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Major review

Ophthalmic manifestations in neurofibromatosis type 1

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ABSTRACT

Neurofibromatosis type 1 (NF1) is a relatively common multisystemic inherited disease and has been extensively studied by multiple disciplines. Although genetic testing and confirmation are available, NF1 remains a clinical diagnosis. Many manifestations of NF1 involve the eye and orbit, and the ophthalmologist, therefore, plays a significant role in the diagnosis and treatment of NF1 patients. Improvements in diagnostic and imaging instruments have provided new insight to study the ophthalmic manifestations of the disease. We provide a comprehensive and up-to-date overview of the ocular and orbital manifestations of NF1.

1. Overview

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, was classically described by the pathologist Friedrich Daniel Von Recklinghausen in 1882.[215] In 1849, however, 33 years earlier, Robert William Smith described 2 cases of neurofibromatosis in his monograph *Treatise on the Pathology, Diagnosis, and Treatment of Neuroma,*[199] but his work received little attention.

The clinical diagnostic criteria for NF1 were defined in 1988 by the National Institutes of Health.[1] NF1 diagnosis is based on having 2 or more of the criteria listed in Table 1. In children with NF1, the 3 most common clinical manifestations are café-au-lait macules, intertriginous freckling, and Lisch nodules, which are found in 95%–100%,[35,41] 81%,[34,35] and 50%–90% of the patients,[20] respectively. Neurofibromas (15%[158]), osseous lesions (up to 60%[20]), and optic pathway gliomas (OPGs, 15%)[121] together with an affected first-degree family member complete the criteria. Approximately 95% of NF1 patients meet the diagnostic criteria by age 8 years, and all do so by age 20 years.[4] Individuals with NF1, however, are also prone to develop other neurologic, ophthalmic, dermatologic, cardiovascular, gastrointestinal, and endocrine manifestations not included in diagnostic criteria.[20,77,184,220]

The eye and the ocular adnexa are frequently involved in patients with NF1. Some of these manifestations, such as Lisch nodules, OPGs, and plexiform neurofibromas, are hallmarks of NF1 and serve as diagnostic criteria. Although Lisch

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Table 1 – Diagnostic criteria for neurofibromatosis type I[149,*]

1. Six or more cafe-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
2. Two or more neurofibromas or 1 plexiform neurofibroma
3. Axillary or inguinal freckling
4. Optic pathway glioma
5. Two or more Lisch nodules
6. Characteristic skeletal dysplasia (sphenoid wing dysplasia, long-bone dysplasia)
7. An affected first-degree relative diagnosed by the above criteria

* At least 2 must be present.

nodules likely play only a diagnostic role, OPGs and plexiform neurofibromas may be physically disfiguring and vision threatening.[11,14,55,163,230] Other ocular features of NF1 are not considered diagnostic for NF1, but most of them are well documented in the literature. Here, we review the ocular and orbital manifestations of NF1.

2. Epidemiology, etiology, and pathogenesis

NF1 is one of the most common genetic diseases, affecting 1 in 2,500 to 3,500 people worldwide, irrespective of sex or ethnic origin.[53,83,108,126,163,184,185] NF1 is an autosomal dominant disorder caused by a defect in a single gene.[128,184] The inheritance of NF1 follows a classic Mendelian pattern of autosomal dominant disease with complete penetrance and variable expression affecting 50% of the offspring of an affected individual.[184] Virtually, every person who inherits the gene displays signs or symptoms by 5 years of age.[184] The new mutation rate of the NF1 gene (*NF1*), 1:10,000,[99,184] is one the highest of any gene[110]; therefore, approximately half of NF1 cases are sporadic mutations.[110]

The *NF1* gene, localized to chromosome 17q11.2 in the late 1980s[18,111] and cloned in the early 1990s,[227] is one of the largest genes in which mutations lead to diseases in humans.[210] Several features of the *NF1* gene, such as its large size, the existence of pseudogenes, the lack of clustering of the mutations in a particular region of the gene, and the great variety of possible lesions, make mutation detection laborious and complex; however, direct genetic testing now exists and allows a high mutation detection rate (more than 95%) in typical NF1 patients.[144] At present, the diagnosis of NF1 is still a clinical one, and genetic testing is usually reserved for reproductive decision-making or in unusual presentations when the diagnosis is suspected, but not clinically confirmed.[4,77]

The *NF1* gene encodes for neurofibromin, a cytoplasmic protein that functions as a negative regulator of the *Ras* proto-oncogene, a key signaling molecule in the control of cell growth.[42,71,73] Most mutations of the *NF1* gene produce a truncated form of neurofibromin and disrupt the normal cell cycle regulation. This may explain why patients with NF1 have a higher risk of benign and malignant tumors.[77,129]

An individual cell can function with only 1 normal copy of the gene, but when the second somatic mutation occurs in selected cells, a complete loss of gene function ("loss of heterozygosity") results in the clinical features of NF1 from loss of the normal regulation of the cell cycle.[32,72,75,182,184] Mutations in *NF1* can also occur during development, which can lead to somatic mosaicism. This results in a segmental NF1 phenotype in which the characteristic findings are limited to 1 portion of the body.[183,207] Segmental NF1 is less common than NF1, affecting 1 in 36,000–40,000 individuals.[183] Patients with segmental NF1 do not typically pass the disease on to their offspring unless the germ line is affected as well.

3. Eye and ocular adnexal involvement

3.1. *Anterior segment*

The best known and commonest feature of NF1 in the anterior segment is Lisch nodules, one of the hallmark manifestations of NF1. First described by Lisch in 1937,[119] these are melanocytic hamartomas of the iris.[184] Histologically, they contain irregular collections of spindle-shaped cells.[221] They are more common in familial cases (93%), compared to sporadic cases (54%),[161] and are more frequently observed on the inferior half of the iris.[20] The presence of Lisch nodules is correlated with age and not to the severity of the disease, number of neurofibromas, or café-au-lait macules.[118] Lubs and colleagues reported a prevalence of Lisch nodules in only 5% of children with NF1 under the age of 3 years, 42% at the age of 3–4 years, 55% at the age of 5–6 years, and 100% of all adults over 21 years.[135] Beauchamp reported a prevalence of 53% in patients under the age of 10 years and 100% over the age of 29 years.[20] Therefore, the absence of Lisch nodules in a child does not rule out NF1.

Lisch nodules do not impair vision or cause any medical problems, but are of great diagnostic value as they are specific to NF1, as opposed to café-au-lait macules.[214] Moreover, they occur earlier than neurofibromas in affected children and are therefore useful in making the diagnosis.[135,214] Lisch nodules have been categorized into several variants based on their clinical appearance,[20] but these remain merely descriptive terms with no clinical or prognostic significance.[184]

An important differential diagnosis of Lisch nodules are iris mammillations. These nipple-like protuberances on the anterior part of the iris are most commonly found in association with melanosis oculi but also with other conditions, even NF1.[57,176] In contrast to Lisch nodules, iris mammillations uniformly overlie areas of hyperpigmented iris and do not differ significantly in pigmentation from the underlying tissue. Lisch nodules are "fluffier," irregularly placed on the iris, and tend to have a different color than the underlying tissue[176] (Fig. 1).

Other rare manifestations of the anterior segment include neurofibromas of the conjunctiva, found in approximately 2% of the patients with NF1. These are pink growths that tend to affect the limbal conjunctiva.[85] Malignant melanoma of the conjunctiva has also been described in a patient with NF1.[208] Diffuse thickening of corneal nerves is also associated with NF1, although seen more commonly in multiple endocrine neoplasia syndromes.[214]