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ORIGINAL ARTICLE

Ophthalmological assessment of children with neurofibromatosis type 1

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Abstract Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder, caused by mutations in the NF1 gene, located on chromosome band 17q11.2. In 1988, the National Institutes of Health created specific criteria for the diagnosis of NF1. Four cardinal criteria are assessed through ophthalmological screening: Lisch nodules, optic pathway glioma, a distinctive osseous lesion (sphenoid dysplasia), and the (orbital) plexiform neurofibroma. NF1 patients are prone to the development of central and peripheral nervous system tumors. Especially young children are at risk for growing optic pathway gliomas that can threaten their sight. From an early age, children with NF1 undergo regular ophthalmological examinations. Little is known about the natural progress of these clinical features and the guidelines for screening and follow-up are controversial. Several questions remain unanswered. *Conclusion:* Most of these questions could be solved by better understanding of the natural history of optic pathway gliomas. There is a tendency towards using vision as a primary objective in clinical treatment trials; this way we can evaluate new treatment strategies and focus specifically on visual evolution so we will be able to select even more carefully which patient would benefit treatment. For future clinical trials, a standardized visual acuity assessment protocol is therefore mandatory.

Keywords Neurofibromatosis type 1 · Optic pathway glioma · Ophthalmological screening · Lisch nodules

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Introduction

Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder, affecting 1 in 3,500 to 4,000 people worldwide [42, 43]. The disease is also known as "von Recklinghausen disease."

NF1 is caused by mutations in the *NF1* gene, located on chromosome band 17q11.2. This gene encodes the tumor suppressor protein neurofibromin, which downregulates the RAS proteins [6]. In about 50 % of individuals, the disease is caused by a spontaneous mutation, and in the other 50 %, the disease is inherited from one of the parents. Penetrance is virtually 100 %, but the expression is highly variable; almost every organ can be affected [19].

Many features of NF1 can be explained by abnormalities of cells derived from the neural crest. The hallmarks of NF1 are the café-au-lait macules, freckles, and neurofibromas [19]. In 1988, the National Institutes of Health (NIH) created specific criteria for the diagnosis of NF1 [45]. At least two of these seven criteria are required for a clinical diagnosis. Diagnosis can be made sometimes at an early age; exceptionally in newborns. Children without a family history of NF1 frequently do not fulfill the NIH diagnostic criteria under the age of 6 years. The clinical picture of NF1 becomes more evident with age [45] (Table 1).

Four cardinal criteria are assessed through ophthalmological screening: Lisch nodules, optic pathway glioma, a distinctive osseous lesion (sphenoid dysplasia), and the (orbital) plexiform neurofibroma. From an early age, it is recommended that children with NF1 undergo regular ophthalmological examinations. The natural progress of these clinical features is not sufficiently documented and understood, and the guidelines for screening and follow-up are controversial [5, 23, 43].

In this article, an overview is given on the ophthalmological characteristics and screening strategies of patients with NF1.

Table 1 The diagnostic criteria for neurofibromatosis 1 developed by the National Institutes of Health in 1988 [45]

The NIH diagnostic criteria are met in an individual with ≥2 of following features:
1. Six or more café 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 of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal regions
4. Optic glioma
5. Two or more Lisch nodules
6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
7. A first-degree relative (parent, sibling, or offspring) with NF1 as defined by the above criteria

Ophthalmological characteristics in NF1

Four ocular features are included in the NIH diagnostic criteria of NF1: Lisch nodules, optic pathway glioma, sphenoid wing dysplasia, and orbital plexiform neurofibroma.

Lisch nodules are melanocytic hamartomas (Fig. 1). They can easily be detected through slit-lamp magnification as well-defined, gelatinous, dome-shaped masses on the iris surface [33].

Lisch nodules are often pigmented. Color may vary from creamy white in dark irides to brown in blue and green irides [36]. They have a tendency to cluster in the inferior hemifield, most likely due to the sunlight-shielding effects of the upper eyelid. Light irides show significant more nodules than dark irides. This could be explained by the photo-protective effects of pigmentation [5].

From the age of 2.5 years, Lisch nodules develop on the surface of the iris. They are generally asymptomatic. Lisch nodules are rarely seen in patients without NF1. Fifty percent of NF1 toddlers harbor nodules, and by adulthood, this number increases to over 90 % [36, 44] (Fig. 2). The presence of Lisch nodules in combination with café-au-lait spots is diagnostic for NF1 and rules out other possible syndromes associated with multiple café-au-lait spots (with or without freckling) such as Legius syndrome, McCune–Albright syndrome, Noonan syndrome, ring chromosomes, and constitutional mismatch repair deficiency syndromes [7, 38].

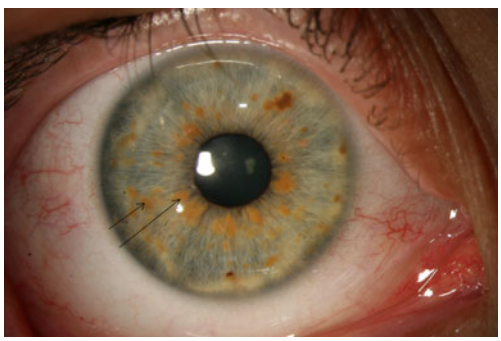

Fig. 1 Lisch nodules

Optic pathway gliomas (OPGs) are benign low-grade pilocytic astrocytomas. Of all children with an OPG, one third has NF1, with a reported prevalence of OPG between 5 and 25 % in this group [2, 4, 26, 28, 43]. But, these tumors behave differently in NF1 patients compared to the sporadic cases. They tend to be less aggressive and respond different to (radio)therapy. NF1-associated OPGs are usually located on the optic nerve with or without chiasmic involvement and rarely invade the optic radiations, whereas sporadic OPGs are found predominantly on the chiasm and extend more frequently beyond the optic pathway. Bilateral optic nerve gliomas are seen more frequently associated with NF1 [4, 26, 29, 39].

OPGs usually involve the optic nerve but can arise anywhere along the optic pathway or hypothalamus [2, 42]. Diagnosis is confirmed by magnetic resonance imaging (MRI) of the brain. Most OPGs are diagnosed under the age of 6 years [2, 42, 43]. Although benign, they can cause significant morbidity by their mass effect. Tumor location dictates the presenting symptoms. Optic nerve gliomas may result in unilateral proptosis, visual loss, visual field defect, strabismus, relative afferent pupillary defect, and optic disc edema or atrophy. In chiasmal tumors, precocious puberty can be the main presenting manifestation [2, 28]. Nevertheless, less than half of OPGs in NF1 actually become symptomatic; up to 40 % may require treatment depending on the criteria used to start therapy [16, 42].

Since NF1-associated OPGs are characterized by a more indolent course and are less likely to experience neurological progression, close observation is the primary approach for nonprogressive lesions.

When treatment is mandated, the therapeutic options are chemotherapy and/or surgery. The most commonly used chemotherapy regimen is vincristine combined with carboplatin. This therapy has become the treatment of choice especially in young children because it is well tolerated with limited toxicity [26]. Surgery is preserved for safely accessible lesions causing symptoms by their mass

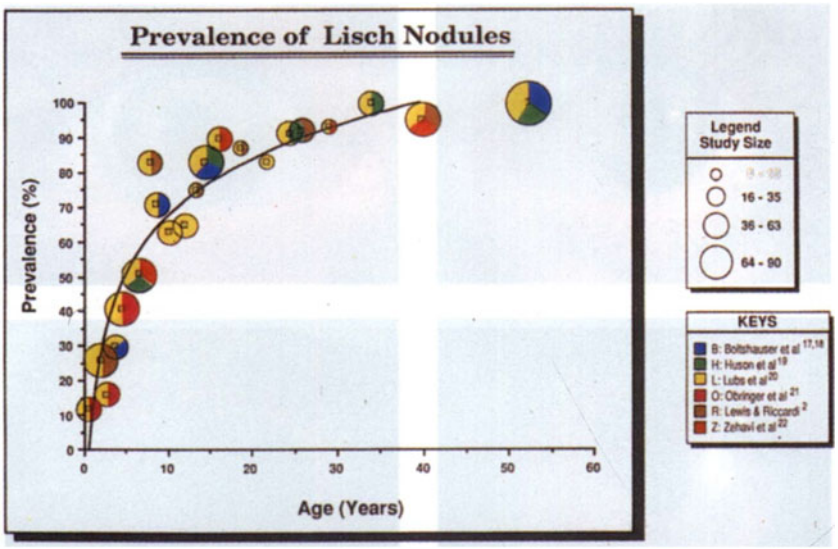

Fig. 2 Prevalence of Lisch nodules. Graph showing the prevalence of Lisch nodules with age. The diameter of the circles represents size of pooled data; colour coding represents studies used to construct that data point [36]

effect in near-blind eyes. Possible indications are intraorbital OPGs causing disfiguring proptosis with corneal exposure or diencephalic OPGs that comprise the third ventricle thereby causing obstructive hydrocephaly [39]. An optic nerve glioma without chiasmal involvement will never grow backwards to invade the chiasm when progressive [26]. Radiotherapy is virtually abandoned in NF1 patients because of known late-onset cerebrovascular complications such as vascular occlusions and significant decline in intellectual function and also because of a much higher risk of developing malignant secondary tumors in the radiation field [26, 39, 42].

Plexiform neurofibromas develop in NF1 patients from childhood and it is believed that they are congenital in origin; the incidence published in literature varies from 20 to >50 % [31, 32]. Orbital plexiform neurofibromas present with eyelid swelling and mechanical ptosis. Despite their benign character histologically, these hamartomas can cause serious visual and ocular motility problems by their expansive growth. Furthermore, they can be very mutilating for the patient. For a yet unknown reason, congenital glaucoma is frequently diagnosed in the eye at the affected side [13, 23].

Orbital neurofibromas are frequently accompanied by skull deformities, in particular dysplasia to complete absence of the greater wing of the sphenoid, allowing direct communication between the orbit and the middle cranial fossa (Fig. 3). The temporal lobe can herniate into the middle cranial fossa causing pulsating exophthalmos. Less frequently, the orbital content moves intracranially, resulting in enophthalmos. Knowledge about the natural history of these lesions is limited; they tend to grow especially in childhood. Surgical treatment is tailored, depending on the residual visual function and the degree of bony and soft tissue involvement. Treatment guidelines are based on rather small case studies [13, 23].

Case reports of other ophthalmological manifestations in NF1 are found in literature: juvenile xanthogranuloma of the corneoscleral limbus, encephalocraniocutaneous lipomatosis with lipodermoids of the sclera or cloudy cornea, abnormal patterning of facial hair growth, and eyebrows or both and underdeveloped eyeglobes combined with large facial plexiform neurofibromas [9, 20, 24].

Ophthalmological screening of NF1 patients

Rationale for screening for OPG

The actual need for screening for OPG is questioned in itself. As mentioned earlier, little is known about the natural behavior of OPGs and their response to therapy. Some progress rapidly, some stabilize, and a few even shrink spontaneously [28]. To date, treatment for OPG is solely initiated when symptomatic and/or when progression is confirmed on MRI [16, 39]. Unfortunately, few data exist about the visual outcome after treatment [16, 21]. Fisher et

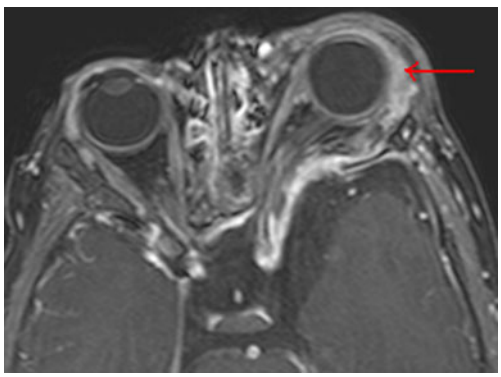

Fig. 3 Orbital MRI T1-weighted image with gadolinium showing contrast enhancement around eye and lateral orbital wall: a plexiform neurofibroma

al. published retrospectively the clinical data of 115 subjects and found poor correlation between radiographic and visual acuity (VA) outcomes; furthermore, only one third of patients regained some vision after treatment [16].

Institutes from Europe and the USA are collaborating to conduct large clinical trials to evaluate the efficacy of treatment for OPGs. In Europe, the Society of Pediatric Oncology, SIOP-LGG trial, studies the effects of radiation therapy or combination chemotherapy on clinically or radiologically progressive low-grade gliomas such as OPGs in both non-NF1 and NF1 children (http://clinicaltrials.gov/ct2/show/NCT00276640). In the USA, a cooperative group, the Department of Defense Neurofibromatosis Clinical Trials Consortium, was formed, leading several trials for LGG. Newer treatment modalities are being evaluated; for example, RAD001 (Everolimus) is being tested for children with NF1 and chemotherapy-refractory progressive LGGs. (http://clinicaltrials.gov/show/NCT01158651).

Since OPGs do not greatly increase mortality rates, preservation of vision has become a primary outcome measure in these trials [1, 21].

Children who acquire poor vision do not always complain of poor vision. Unilateral visual loss, either acute or chronic, is not noticed by a young child unless or until the other eye becomes involved. Screening for visual loss caused by an OPG is therefore mandatory for its diagnosis. The main question is how? Currently, there are three options: the ophthalmological examination, MRI, and visual evoked potentials (VEPs).

Screening guidelines

In 1997, the NIH NF1 Optic Glioma Task Force published guidelines concerning the screening, monitoring, and treatment of OPGs in NF1 patients [27].

They imply an intensive follow-up scheme during the first 6 years of life, continued until the age of 25 years, but with longer time intervals between visits.

A newly diagnosed NF1 patient, without known OPG, should undergo a complete ophthalmological examination at diagnosis, followed by annual examinations until the age of 6 years and longer intervals thereafter (at 8, 10, 13, 16, 20, and 25 years). Ophthalmological assessment includes VA, color vision, visual field, ocular motility, pupillary reflexes, slit-lamp examination, and fundoscopy. The guidelines recommend neuroimaging only when clinically indicated.

When an OPG is diagnosed, regular ophthalmological visits and repeat neuroimaging (at 3, 9, 15, 24, and 36 months) are advised. There is no clear consensus for evaluation after the first 2 years.

Recently, criticism arose against the NIH guidelines. Listernick et al., the founders of these guidelines, suggested extending the annual screening until age 7 years [26]. Symptomatic OPGs are diagnosed mainly before the age of 6 years, but once a patient is older; there is still a substantial risk of developing a symptomatic OPG [4, 42, 43]. Until new evidence is present, they recommend an ophthalmological screening every second year between ages 8 and 18 years [26].

With regard to identify OPGs, several authors state that, though the majority may remain quiescent, clinicians should stay vigilant in observing patients for a longer duration than described by the NIH guidelines. Most of the OPGs indeed have a rapid early growth and stay stationary after; only sporadically, they show a delayed phase of progression. A follow-up with increasing time intervals until the age of 17 years is proposed [16, 26, 37, 42, 43].

Ophthalmological examination

A complete clinical ophthalmological exam should be performed. This includes VA, color vision, visual field, ocular motility, slit-lamp examination, and fundoscopy.

Findings suspicious for an underlying OPG include: decreased VA, disturbed color vision, visual field defect, a pupillary abnormality, strabismus, proptosis, nystagmus, and optic disc pallor or edema.

Of all these tests, a correct measurement of VA seems most useful in detecting OPGs requiring treatment [1, 2, 4, 21, 26]. From the age of 6 months, Teller Acuity Cards can be used to quantify vision (Fig. 4). This test is based on the infant's natural preference to fixate on a striped pattern, rather than a blank homogenous area. The grating acuity that is measured with this test is a measure of "resolution" acuity. This is not equivalent to the acuity for symbols or letters, which is a "recognition" acuity. Grating acuity tends to overestimate the VA, but there is a close relationship between both [11].

Older children can be tested with different optotypes such as Lea figures and H-O-T-V optotypes, according to their age and intellectual capacities [26]. Some of these tests are comparable after correcting for age [10, 12].

Fig. 4 Teller Acuity Cards

Avery et al. published their recommendations for a more uniform visual assessment in all NF1 centers [1]. The authors propose to use the Teller Acuity Cards in all children, since it can be performed at any age. In older children, HOTV testing should be executed additionally. These recommendations could be used as a standard for VA testing in future clinical trials.

To allow data analysis, VA should be quantified in logMAR units, a continuous value. LogMAR stands for logarithm of the minimum angle of resolution. Snellen equivalents can be easily converted into logMAR units. A significant deterioration is considered when VA drops two logMAR lines [1, 16, 26]. All other causes of vision loss, such as refractive error, amblyopia, lack of cooperation, or structural diseases, must be excluded. Color vision and pupillary reflexes can be helpful in differentiating. Testing should be repeated within 1–2 weeks to confirm the results [26].

More than 70 % of patients with OPGs show a scotoma or a depression in the central visual field [22].

Visual field testing in NF1 children by computerized tests, Goldmann, or confrontation tests is difficult and has high test–retest variability [28]. Physical characteristics of OPGs imply that visual field loss is almost always accompanied by visual loss. Nevertheless, it should be a part of the examination if possible [25, 26].

The aspect of the optic nerve can raise suspicion and help in the differential diagnosis when vision loss is noted. But optic atrophy or disc edema can also be found when VA is perfectly normal.

Magnetic resonance imaging

The gold standard for the diagnosis of an OPG is MRI [2, 28]. An MRI can be performed routinely or based on clinical suspicion. Lesions are sometimes enhanced with gadolinium. The images show a fusiform appearance of the optic nerve in an optic nerve glioma. Chiasmal gliomas appear as an enlargement of the chiasm, sometimes with a cystic appearance. Rarely, these lesions affect the optic radiations [28, 29].

MRI is an expensive, time-consuming exam which requires the use of anesthetics in young patients. Little is known about the natural history of OPG [42]. An initially normal imaging does not exclude the possible growth of tumors in the future [42, 43]. Treatment is rarely initiated solely on the basis of abnormal findings on MRI. In most centers, treatment is anticipated when clinical progression is noticed together with changes on MRI. For these reasons, one can argue about the use of routine MRI screening in NF1 patients and is therefore not recommended by the "Optic Glioma Task Force" [35, 41].

New (bio)imaging techniques such as magnetic resonance diffusion tensor imaging (MRDTI) or diffusion tensor tractography (DT) are being evaluated to detect microstructural abnormalities in the optic pathway that can predict growth or link anatomy with visual function [14, 15, 30].

Visual evoked potentials

Visual acuity measurements and visual field exams may fluctuate over time, depending on the attention span of the child when performing the test. Cognitive deficits are frequently encountered in NF1 subjects; other children are simply too young to participate.

Electrophysiological monitoring of patients is a possible alternative to quantify visual function. The child's cooperation is limited; it only has to fixate the stimulus for a short period of time.

The use of VEP in screening for OPG is debated for years. We can summarize that this is a safe and cost-effective tool compared to MRI. Several studies have shown promising results regarding their high sensitivity (67–93 %). Nevertheless, the results in these studies are incomparable and have important limitations including small sample size, retrospective design, and lack of an appropriate control group in some studies. In addition, results show low specificity (6–87 %) and poor test reliability in children younger than 5 years. To assess the real diagnostic value of VEP, it would be necessary to perform a large prospective multicenter study in which children are evaluated with an ophthalmic examination, MRI, and VEP at diagnosis and during follow-up [2, 4, 17, 18, 21, 22, 40, 46, 47].

Optical coherence tomography (OCT)

Hence, ophthalmologists continue their search for a more objective assessment of visual function. The newest proposed screening tool is OCT of the retina. Scans in NF1 patients with OPG showed a thinner retinal nerve fiber layer and macula compared with age-matched controls and NF1 patients without OPG. Main advantage of this technology is the fast and objective acquisition of data, but it is limited by subject cooperation [3, 8].

Conclusion

Neurofibromatosis type 1 is a common genetic disorder with a characteristic phenotype. Patients are prone to the development of central and peripheral nervous system tumors. Especially young children are at risk for progressive OPG that can threaten their sight. Since children do not report vision loss spontaneously, screening is mandatory, preferably in a center experienced in the follow-up of NF1 children.

In 1997, the first screening recommendations were published. Since then, our knowledge about NF1 has largely

expanded. Nevertheless, several questions remain unanswered. Until what age do we need to screen and at what time interval? Which screening strategies can or should be used? How do we screen children under the age of one? What about the longitudinal follow-up of NF1 patients diagnosed with OPG? What constitutes "progressive disease" and when to initiate treatment? Some question treating any OPG since there is no clear correlation between vision and tumor growth or size [34]. Some of these questions may be answered by a better understanding of the natural history of this common tumor in NF1 children.

There is a tendency towards using vision as a primary objective in clinical treatment trials [1, 21]. This could learn us more about the relationship between VA and tumor behavior. For future clinical trials, a standardized VA assessment protocol is therefore mandatory. Avery et al. published their first recommendations in 2012 [1, 16].

By making VA screening tests comparable, we obtain a huge amount of data that can help us in the future to select even more carefully which patient would benefit treatment. This way we are able to evaluate new treatment strategies and focus specifically on visual evolution.

All of this can only be possible, if we establish a uniform protocol and screen all NF1 patients accordingly worldwide.

Conflict of interest None

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