Optical Coherence Tomography in the Diagnosis of Optic Pathway Gliomas

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Purpose. To compare visual function assessment, optic disc evaluation by indirect ophthalmoscopy, and retinal nerve fiber layer analysis by optical coherence tomography (OCT) for the screening of optic pathway gliomas in pediatric patients (2–15 years old) affected by neurofibromatosis type 1.

Methods. Fifty-seven consecutive patients with neurofibromatosis type 1 with recent (<6 months) orbital/brain magnetic resonance images (MRI) were included. Patients underwent visual function assessment (Hyvarinen symbols chart and/or Snellen charts) and optic disc evaluation by indirect ophthalmoscopy performed by experienced, masked pediatric ophthalmologists. Spectral domain OCT was performed to assess retinal nerve fiber layer.

Results. Fifteen of 57 enrolled patients (26%) were affected by MRI-proven optic pathway gliomas. Visual function assessment, optic disc evaluation, and retinal nerve fiber layer analysis by OCT were feasible in 84%, 95%, and 88% of patients, respectively. Visual function assessment, retinal nerve fiber layer analysis, and optic disc evaluation results correlated with the presence of optic pathway gliomas ($P = 0.007$, $P < 0.0001$, and $P = 0.03$, respectively). Specificity and negative predictive value of each test were statistically significant in detecting optic pathway glioma ($P < 0.0001$), whereas only retinal nerve fiber layers analysis reached statistically significant sensitivity and positive predictive value ($P = 0.0386$).

Conclusions. Retinal nerve fiber layer analysis assessment using spectral domain OCT is superior to visual function assessment and optic disc evaluation as a clinical screening tool for optic pathway gliomas.

Keywords: glioma, neurofibromatosis, OCT

Neurofibromatosis type one (NF-1) is one of the most frequent human genetic diseases, with a worldwide birth incidence of 1 in 4000 births and a prevalence of at least 1 in 4 to 5000 births.[1–3] NF-1 is a multisystem autosomal dominant disorder with complete penetrance by the age of 8 years old and is characterized by highly variable expression and marked inter- and intrafamilial variation.[2] NF1 is caused by dominant loss-of-function mutations of the tumor-suppressor gene NF-1, encoding neurofibromin (Online Mendelian Inheritance in Man [OMIM] database no. 613113, available in the public domain at http://www.ncbi.nlm.nih.gov/omim), a negative regulator of RAS proteins.[2] Thus, NF-1 patients are at increased risk for developing both benign and malignant tumors, and NF-1 is classified as a tumor predisposition syndrome.[1,2]

Optic pathway glioma (OPG), histologically defined as grade I (low-grade) pilocytic astrocytoma, is the most common tumor in NF-1 children, affecting 15% to 20% of all NF-1 patients.[1] Approximately 65% of these cases are detected in young children (less than 5 years of age), and one-third to one-half of these patients develop progressive disease.[4,5] OPGs show a highly variable and unpredictable growth pattern, ranging from indolent to rapidly progressive tumors, and may lead to visual loss, neurologic sequelae (hemiparesis, ataxia), hydrocephalus, macrocephaly, systemic signs (developmental delay, failure to thrive, diencephalic syndrome), and death.[1,4]

Children with symptomatic OPG may have relevant ophthalmological abnormalities at the time of diagnosis (including marked visual impairment, abnormal pupillary function, optic nerve atrophy, and/or proptosis) due to early onset of the disease and related diagnostic difficulties.[1,4] Decreased visual acuity is considered the most clinically relevant indicator of OPGs, whereas serial visual acuity measurement is the best method of follow-up of affected patients.[1] Unfortunately, a large proportion of NF-1 children have moderate to severe impairment in one or more areas of cognitive function, mainly sustained attention difficulties, reducing the positive predictive value of a visual function examination (as well as any other functional test needing patients' collaboration).[4,6] Moreover, tests that do not require patients' collaboration (e.g., pupillary reflex or optic disc evaluation [ODE]) allow only advanced cases to be theoretically detected because of the low sensitivity of the tests themselves.[1,4–6] This study compared visual function assessment (VFA), ODE by indirect ophthalmoscopy, and retinal nerve fiber layer (RNFL) analysis by optical coherence tomography (OCT) as the diagnostic tools for OPG in pediatric patients (2–15 years of age) affected by NF-1.

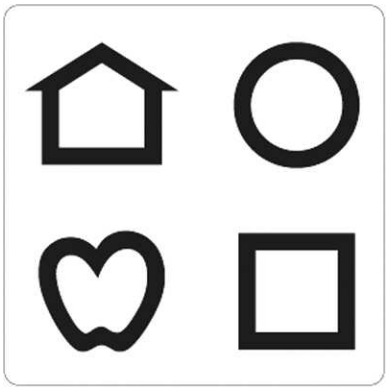

FIGURE 1. The four Lea symbols (apple, house, circle, and square) in Lea symbols charts are shown, used for VFA in patients younger than 6 years old.

METHODS

Patients, Setting, and Design

This was an institutional, observational, masked, case-controlled study with prospective enrolment, compliant with the tenets of the Declaration of Helsinki. Patients were consecutively recruited from those referred between December 2010 and December 2012 to our departments. Informed consent was obtained from each pediatric subject's legal guardian. Subjects older than 6 years of age provided assent additionally. Inclusion criteria were patients affected by NF-1, following National Institutes of Health criteria, aged 2 to 15 years, and having recently (less than 6 months) undergone orbital/brain magnetic resonance imaging (MRI). Exclusion criteria were history of any other ophthalmologic or neurologic disease that could affect visual function or optic nerve function or aspect (e.g., amblyopia, cataracts, retinopathy of prematurity, glaucoma) and lack of scans with standard imaging parameters on MRI (including the administration of gadolinium).

MRI

In each case, a recent (less than 6-month) head and orbital MRI scan obtained with standard imaging parameters and administration of gadolinium was retrieved. MRI diagnosis of OPG was based on the findings of mono- or bilateral optic nerve enlargement with a hypointense to isointense signal on T1-weighted images and mildly to strongly hyperintense signals on T2-weighted images.[7–10] Tumors of the chiasm, tumor extensions along the optic tracts into the lateral geniculate ganglia, and temporal lobes may exhibit a variety of appearances.[7–10] MRI findings were masked to operators, abstracted from the formal reading prepared by a masked (and NF-1 expert) neuroradiologist and classified as showing no evidence of OPG or evidence of OPG (in any location). The tumor was also classified as prechiasmal (OPG involving only the optic nerve without chiasm involvement) or posterior (OPG involving the optic chiasm and/or the posterior structures including the hypothalamus).

Visual Function Assessment

VFA was performed in each case by an experienced, masked pediatric ophthalmologist, who tested the patient first for binocular visual function and then for monocular visual function starting with the right eye. VFA was performed as the first clinical test in each case, before RNFL assessment and ODE. Lea symbols (LEA; Fig. 1) and Snellen charts were used in patients aged 2 to 6 years old and 4 to 15 years old, respectively.[11–14] Patients aged 4 to 6 years old underwent both tests, starting with LEA, and were classified following the better-obtained result. LEA test was performed according to previously published protocols.[13,14] If the patient was uncooperative during the visit, breaks were permitted and testing was reattempted. The examiner was allowed to stop testing in subjects who, despite multiple testing attempts and breaks, would not cooperate. LEA results were then reported in logarithmic values of the minimum angles of resolution (logMAR). Snellen testing was performed using standard procedures.[11,12] Visual acuity measurements were then converted from Snellen to logMAR by using published conversion charts.[11] Because obtaining VFA is an essential component of clinical care, every effort was made to complete VFA. A VFA result in subjects unable to reliably complete testing or those who remained uncooperative was considered "uninformative" (according to the operator's personal judgment based on patient collaboration and acquired data). Each case of monocular failure of VFA after binocular compliance was considered an "informative" result and suspected of OPG. Failure of both binocular and monocular VFA was considered an "uninformative" result. Each informative result was subsequently subclassified as normal or suspected of OPG, using normal visual acuity age-based norms data.[15]

RNFL Assessment by OCT

Spectral domain OCT (SD-OCT; Spectralis, Heidelberg, Germany) to assess RNFL thickness was performed by a single masked operator. The automatic real-time eye tracker was used to eliminate motion artifacts (16–100 averaged images). Each child underwent RNFL assessment after pupil dilation, before ODE, and after VFA, often starting with the right eye. During the measurement, a quality bar visualizes the signal-to-noise ratio. Score quality ranges from 0 (poor) to 40 (excellent). Scans with a quality score < 25 were excluded. Centering of the optic disc was performed manually. At least two high-speed peripapillary RNFL circle scans (circle scan size, 3.5 mm) were obtained.[4] Depending on the quality of the scan and correct scan position around the optic nerve, a single RNFL image was chosen for analysis. Peripapillary RNFL thickness (μm) measurements were automatically calculated by SD-OCT software, providing a global average (G) and average thickness for each of six sectors: temporal (T), temporal-superior (TS), temporal-inferior (TI), nasal (N), nasal-superior (NS), and nasal-inferior (NI) (Figs. 2, 3). RNFL results were classified as "informative" or not by the physician (according to personal operator judgment based on patient collaboration, scan positioning on optic nerve, and acquired data). The RNFL analysis results in subjects unable to complete testing or in those who remained uncooperative were considered uninformative results. Monocular failure of RNFL assessment (lack of fixation) in a single eye, with correct patient compliance in the fellow eye, was considered an informative result and suspected of OPG. Failure of RNFL assessment in both eyes was considered an uninformative result. Each RNFL assessment classified as informative was subsequently subclassified as normal or suspected of OPG by using normative reference ranges for RNFL thickness in children.[16] Values ranging from the fifth to 95th percentiles were considered normal. Patients with one or both eyes showing RNFL values below the fifth or above the 95th percentile at least in a single area (G, T, TS, TI, N, NS, or NI), as well as patients with monocular failure of RNFL assessment with correct patient compliance in the fellow eye were included in the OPG-suspected group.

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Table 1. Clinical and Demographic Characteristics of Included Subjects

Clinical and Demographic Characteristics*	No. of Study Subjects, %†
Age distribution	
<3	7, 12
<4	13, 23
<5	19, 33
<6	24, 42
<7	29, 51
<8	33, 58
<9	36, 63
<10	38, 67
<11	43, 75
<12	47, 82
<13	51, 89
<14	55, 96
<15	57, 100
Male	34, 60
Race	
White/Caucasian	49, 86
Black/African	3, 5
Asian	2, 4
Multiple races	3, 5
Diagnoses	
NF1 without optic pathway glioma	42, 74
NF1 with optic pathway glioma	15, 26
Glioma location	
Prechiasmal	3, 20
Posterior	12, 80

* Mean age (range) 7.2 (2–15 y).
† Total number of subjects, 57.

Optic Disc Evaluation

ODE was performed using indirect ophthalmoscopy by an experienced, masked pediatric ophthalmologist after the patient's pupils were dilated. ODE was performed after VFA and RNFL assessment. Each ODE result was classified as informative or not by the physician (according to the operator's personal judgment based on patient collaboration). ODE in completely uncooperative subjects was considered an uninformative result. Each ODE result classified as informative was subsequently subclassified as normal or suspected of OPG based on the presence of optic disc swelling, pallor, atrophy, asymmetry, or excavation (operator's personal judgment). Patients who had one or both eyes suspected of OPG were included in the OPG-suspected group.

Data Analysis

Statistical analyses were performed using the SAS version 8.2 software (SAS Institute, Cary, NC). A P value < 0.05 was considered statistically significant. Yates' correction was used for χ^2 test. A binomial test was used to analyze the performance indicators of each test (sensibility, specificity, and negative and positive predictive values).

Results

Fifty-seven (114 study eyes) consecutive pediatric patients affected by NF-1 with recent orbital/brain MRI were included. Thirty-four were male (60%) and 23 (40%) were female. Fifteen patients (26%) were affected with MRI-proven OPG, whereas 42 patients (74%) had no evidence of OPG. OPG was classified as prechiasmal in 4 cases (27%) and posterior in 11 cases (73%). Clinical and demographic characteristics are reported in Table 1.

Visual Function Assessment

VFA results were judged informative in 12 (80%) of 15 OPG patients (60%, 80%, and 100% of patients aged <5, 5–10, and 10–15 years old, respectively) versus 36 (86%) of 42 patients who were judged to be OPG-free (64%, 93%, and 100%, respectively; $P > 0.05$; χ^2 with Yates' correction). Considering the twelve OPG patients included in the informative subgroup, 2 patients (17%) were included because of monocular test failure in a single eye, with correct patient compliance in the fellow eye/binocular vision. Success of LEA chart and/or Snellen chart testing by age group is reported in Table 2. VFA was clinically suspected of OPG (at least in one eye) in 7 (58%) of 12 OPG patients (the 2 patients with monocular test failure in a single eye with correct patient compliance in the fellow eye/binocular vision and 5 patients based on acceptable normal visual acuity age-based norms[15]) (Table 3) versus 5 (14%) of 36 OPG-free patients. A VFA result classified as suspected OPG was statistically related to the presence of the OPG ($P = 0.007$; χ^2 with Yates' correction). VFA test sensitivity, specificity, and positive and negative predictive values in detecting OPG are reported in Table 4.

RNFL Assessment by OCT

SD-OCT analysis was judged informative in 12 (80%) of 15 OPG patients (60%, 80%, and 100% of patients aged <5, 5–10, and 10–15 years old, respectively) versus 38 (90%) of 42 patients who were OPG-free (79%, 93%, and 100%, respectively; $P > 0.05$; χ^2 with Yates' correction). Considering the 12 OPG patients included in the informative subgroup, a single patient (9%) was included because of monocular test failure in a single eye (lack of fixation), with correct patient compliance in the fellow eye. Success of SD-OCT analysis by age group is reported in Table 2. RNFL examination results were clinically suspected of OPG (at least in one eye) in 10 (83%) of 12 OPG patients (the single case of monocular lack of fixation and 9 cases of documented RNFL loss based on normative reference ranges for retinal nerve fiber layer thickness in children[16] [Figs. 2, 3])

Table 2. Tests That Could Be Reliable Performed by Age Group

	No. of Subjects/Total no., %		
Age Group, y	VFA	RNFL Analysis	ODE
2–3	4/7, 57	5/7, 71	6/7, 86
3–4	3+1*/6, 67	4/6, 83	6/6, 100
4–5	3+1*/6, 67	4+1*/6, 100	6/6, 100
5–6	4/5, 80	4/5, 80	4/5, 80
6–7	5/5, 100	5/5, 100	5/5, 100
7–8	3/4, 75	3/4, 75	3/4, 75
8–9	3/3, 100	3/3, 100	3/3, 100
9–10	2/2, 100	2/2, 100	2/2, 100
10–11	5/5, 100	5/5, 100	5/5, 100
11–12	4/4, 100	4/4, 100	4/4, 100
12–13	4/4, 100	4/4, 100	4/4, 100
13–14	4/4, 100	4/4, 100	4/4, 100
14–15	2/2, 100	2/2, 100	2/2, 100

* These data were included in the "informative" subgroup because of monocular test failure in a single eye, with correct patient compliance in the fellow eye and/or binocular vision.

Table 3. VFA Results in Patients Affected by OPG

Patient	Age	VFA Threshold: Lowest Fifth Percentile by Age, logMAR	VFA Result in the Worst Eye	Classification by VFA
3	4	0.26	Uninformative	Uninformative
6	7	0.17	0.1	Normal
11	4	0.26	Uninformative	Uninformative
12	3	0.46	Lack of fixation in RE	Suspected of OPG
14	7	0.17	Uninformative	Uninformative
19	4	0.26	Lack of fixation in LE	Suspected of OPG
26	13	0.17	Hand motion	Suspected of OPG
30	3	0.46	0.2	Normal
31	15	0.17	0.1	Normal
32	10	0.17	0.4	Suspected of OPG
36	10	0.17	Light perception	Suspected of OPG
40	5	0.17	0.1	Normal
46	6	0.17	Hand motion	Suspected of OPG
51	11	0.17	0.1	Normal
56	14	0.17	0.8	Suspected of OPG

LE, left eye; RE, right eye.

versus 2 cases (borderline value in a single RNFL analysis area) of the 38 OPG-free patients (6%). Two of the 9 cases with documented RNFL loss (22%) showed the concomitant presence of one or more sectors of thickened RNFL, probably due to optic disc edema. No case showed increases in RNFL thickness without the concomitant presence of the loss of thickness in one or more RNFL sectors. RNFL assessment classified as suspected of OPG was statistically related to the presence of the disease ($P < 0.0001$; χ^2 with Yates' correction). Sensitivity, specificity, and positive and negative predictive values in detecting OPG by OCT are reported in Table 4.

Optic Disc Evaluation

The ODE result was judged clinically informative in 14 (93%) of 15 OPG patients (100%, 80%, and 100% of patients aged <5, 5–10, and 10–15 years old, respectively) versus 40 (95%) of 42 OPG-free patients (93%, 93%, and 100%, respectively; $P > 0.05$; χ^2 with Yates' correction). The optic disc aspect result was clinically suspected of OPGs (at least in one eye) in 5 (35%) of 14 OPG patients versus 3 (7%) of 40 OPG-free patients. ODE classified as suspected of OPG was statistically related to the presence of the disease ($P = 0.03$; χ^2 Yates' correction). Sensitivity, specificity, and positive and negative predictive values of ODE in detecting OPG are reported in Table 4.

Performance Test Indicators

Binomial test results on performance test indicators (sensibility, specificity, and positive and negative predictive values) are reported in Table 5. Specificity and negative predictive values were statistically significant ($P > 0.0001$) for each test (VFA, RNFL analysis, and ODE), whereas only RNFL analysis showed statistically significant sensitivity and positive predictive values ($P = 0.0386$).

Discussion

The use of VFA as a primary outcome in pediatric ophthalmology studies is often problematic, due mainly to the fact that subjects of the same age may not be able to complete the same test.[17] The ability of young children (mainly younger than 6 years old) to cooperate and to provide a reliable visual function result is significantly associated with their comorbid medical condition and intellectual disability.[17] Children with OPG are a clear example of a heterogeneous group of patients requiring frequent and long-term VFA monitoring. Unfortunately, many relevant confounding factors are present in these patients, including NF-1-associated developmental delay and/or attention deficit hyperactivity disorder.[6] The cognitive dysfunction associated with NF-1 is an intriguing aspect of this phenotypically heterogeneous disease. A broad range of both nonverbal and verbal learning disabilities are evident in approximately 50% to 70% of children affected by NF-1.[18] Furthermore, an attention deficit hyperactivity disorder has an estimated prevalence of 30% to 50% in NF-1 patients.[6] These numbers clearly explain the undeniable difficulties of obtaining clinically useful results when performing VFA tests in children with NF-1.

In 2007, Listernick et al.[1] published evidence-based recommendations for the diagnosis and management of children with NF-1 and OPG, suggesting that all children with NF-1 younger than 8 years old should undergo an annual ophthalmologic examination, including measurement of visual acuity, confrontation visual field evaluation, color vision tests, and assessment of pupils, eyelids, ocular motility, iris, and fundus. Those authors also stated that the loss of visual acuity

Table 4. Test Sensitivity, Specificity, and Positive and Negative Predictive Values for Detecting Optic Pathway Gliomas

Test	Sensitivity	95% CI		Specificity	95% CI		PPV	NPV
		Lower Limit	Upper Limit		Lower Limit	Upper Limit		
VFA	0.58	0.28	0.83	0.86	0.69	0.94	0.58	0.86
RNFL analysis	0.83	0.52	0.97	0.95	0.82	0.99	0.83	0.95
ODE	0.35	0.13	0.64	0.92	0.68	0.98	0.62	0.80

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

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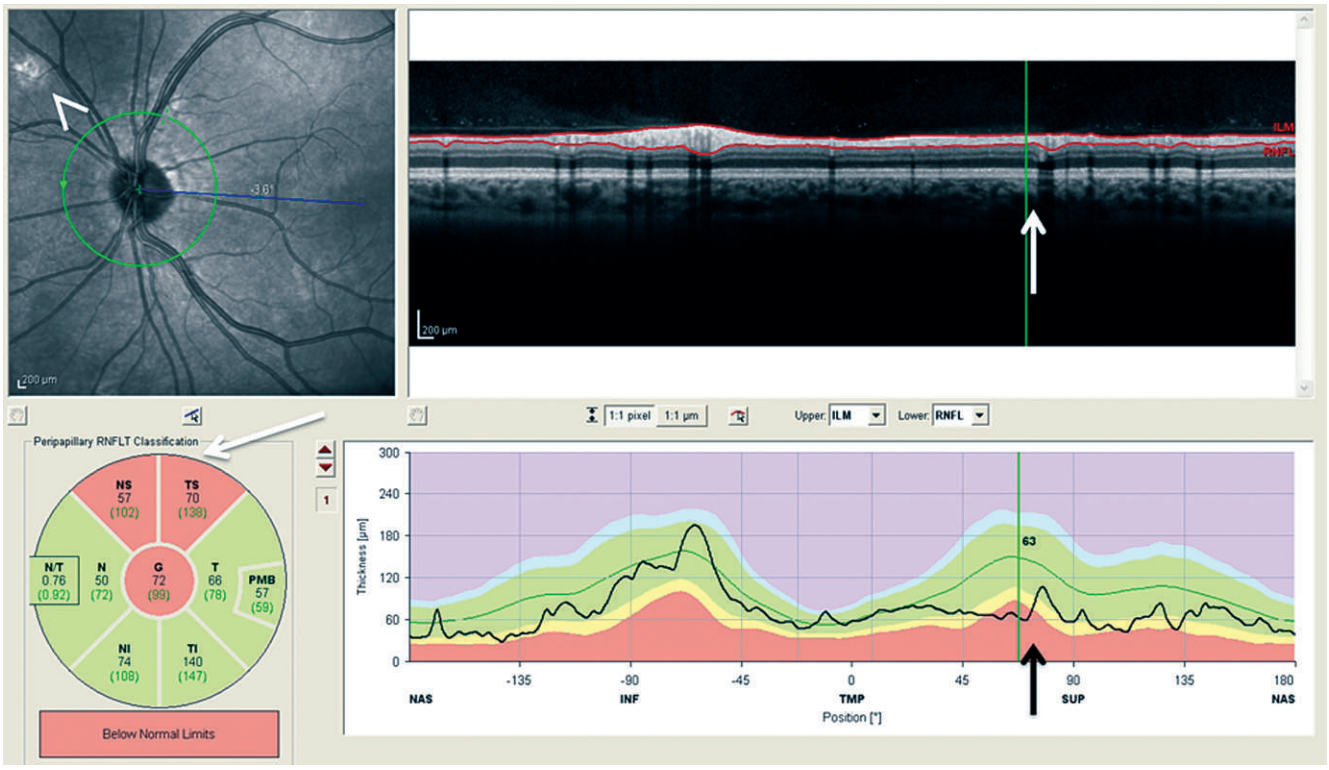

Figure 2. A 4-year-old child with NF-1-related OPG. OCT analysis documented RNFL loss in the superior quadrant (*arrows*) of his left eye. The infrared image (*upper left*) also documented the normal clinical aspects of the optic nerve head and the presence of a single NF-1-related choroidal abnormality in the nasal superior area (*arrowhead*).

should be considered the most reliable indicator of OPG, whereas serial visual acuity measurement was the best way to follow-up with patients with OPG.[1]

However, Avery et al.[17] recently reported that nearly one-third of NF-1 subjects, most of whom were younger than 5 years of age, could not complete visual acuity testing, concluding that young children with NF-1 were frequently unable to complete recognition acuity testing and recommending Teller acuity cards (including HOTV acuity charts only when the subject was developmentally able) be used to test all pediatric OPG patients. In our cohort of patients, a success rate by age group similar to that reported by Avery et al.[17] was obtained using LEA charts in children younger than 6 and Snellen testing in patients older than 4. Unfortunately, our data show that the positive predictive value of VFA test in detecting OPG in NF-1 patients is low (0.58). This result may be explained by the inability of these patients to complete age-appropriate visual function tests, causing a large amount of false-positive results.[6,17]

Many others functional tests are recommended in examining children with NF-1, mainly color vision tests and visual fields.[1] Color vision loss in NF-1 children with OPG often accompanies or follows visual acuity deficits. In this setting, visual acuity loss without color vision loss could suggest a refractive error, amblyopia, a functional disorder, or a lack of cooperation.[1] Thus, this test should often be accompanied by standard VFA test.[1] Moreover, VFA and color vision tests have the same age-related and NF-1-related limits.

Many studies have suggested that computerized visual field testing can be performed reliably in young children.[1,19] However, most children have difficulty with the monotony and length of formal visual field testing, leading to high numbers of fixation errors, and false-positive and false-negative results. Kinetic 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.[1,19] Moreover, visual field testing requires cooperation, making this test impractical for most NF-1 children.[6,17]

Chang et al.[4] recently investigated the role of OCT as a potential tool to assess RNFL abnormalities secondary to optic atrophy due to OPG in a cohort of pediatric patients with NF-1. These authors reported that subjects with OPG had thinner RNFLs than those of control subjects, whereas NF-1 subjects without known OPGs had RNFL thickness equivalent to those of healthy control subjects. The authors also reported a single NF-1 subject with OPG and normal visual function who had abnormal RNFL thickness, raising questions about sensitivity and specificity of VFA versus RNFL assessment by OCT in the diagnosis of NF-1-related OPG.[4] Our data first showed that RNFL analysis by OCT has a higher sensitivity, specificity, and positive and negative predictive values than both VFA assay and ODE. Moreover, binomial test results of performance test indicators revealed that the specificity and negative predictive values of each test were statistically significant in detecting OPG ($P < 0.0001$), whereas only RNFL analysis reached statistically significant sensitivity and positive predictive value ($P = 0.0386$). Our findings also suggest that OPG may cause RNFL loss (likely permanent) before becoming clinically manifest, which may motivate future research of the optimal timing of assessment in NF-1 children and help inform the complex decision-making process that underlies the decision to treat OPG.

Although the use of OCT may be limited by subject cooperation, it is less limited than VFA or visual field testing, requiring only seconds of cooperation.[4,20] Moreover, OCT is readily available in most secondary and tertiary referral centers. OCT is also relatively easily performed in children, and OCT poses minimal risks compared with tests associated with

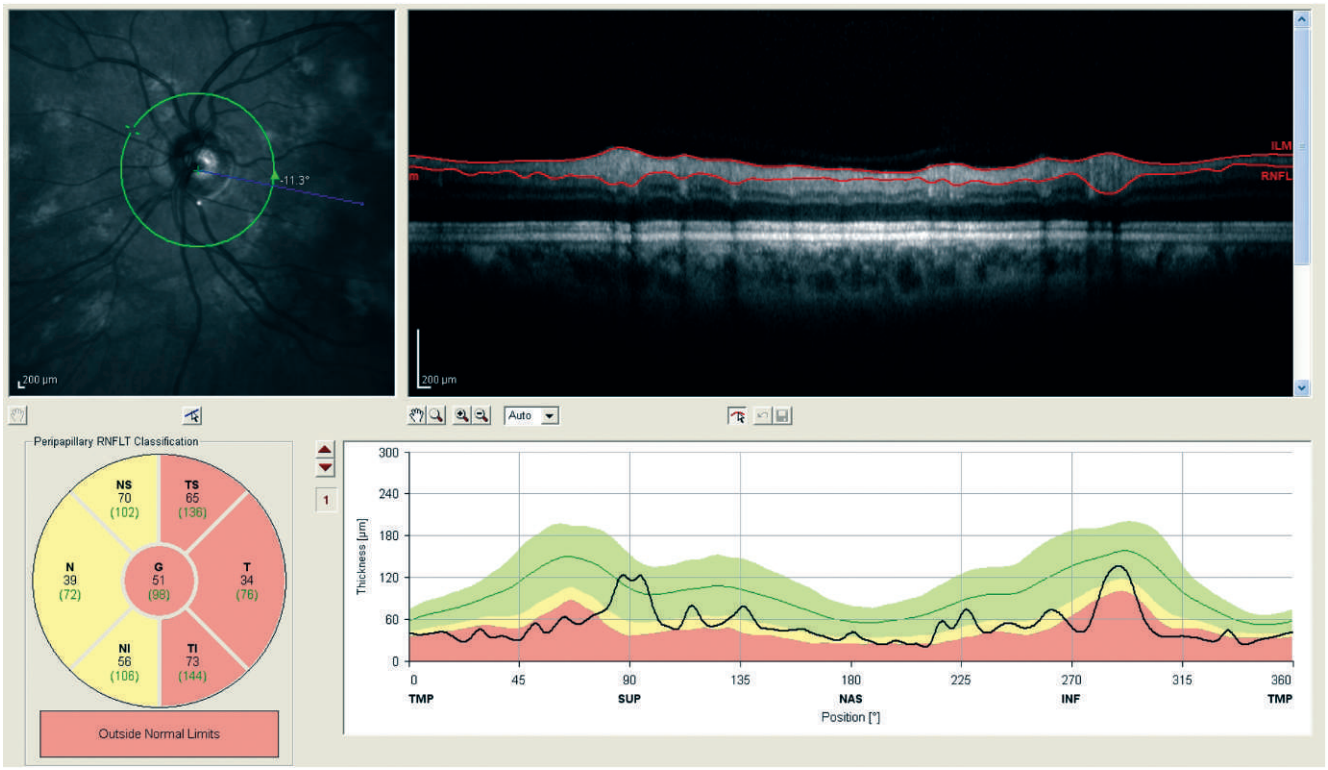

Figure 3. A 5-year-old child with NF-1-related OPG. OCT analysis documented a diffuse RNFL loss in his left eye. The infrared image (*upper left*) also documents the presence of faint optic nerve excavation and the presence of multiple NF-1-related choroidal abnormalities.

neuroimaging and visual evoked potential (VEP) testing.[17,19] We have also observed that the feasibility of OCT is superior to that of VFA in NF-1 patients, and OCT is also superior in predicting the presence of OPG (positive predictive value of 0.83 vs. 0.58 and 0.62 for VFA and ODE, respectively). Although there is variability in cooperation among children younger than 6, reliable OCT results have been obtained in children as young as 3, both in our study and in normative studies.[1,4,20]

We have not found any case showing RNFL increases (secondary to optic disc edema) without areas of RNFL loss associated. This could be partially explained by the presence of a higher proportion of posterior glioma versus prechiasmal tumors (12 vs. 3, respectively). Nevertheless, both RNFL increase and decrease may be used as an indirect indicator of OPG. Further studies are required to better address the clinical and prognostic values of these two different presentations.

Several groups have evaluated VEP in the detection of OPGs, with sensitivity between 67% and 93% and specificity between 60% and 87%.[21–23] Unfortunately, VEP testing relies on experienced electrophysiologists, who are scarcely available.[21,22] Another limitation of serial VEPs in the screening and surveillance for OPGs is the difficulty in interpreting small changes in amplitude during follow-up.[21–23] In our study, RNFL assessment by OCT reached sensitivity and specificity values similar to those reported for VEP, without any problem of interpretation and allowing automatic follow-up quantification of RNFL changes.[4,24]

Table 5. Performance Indicators of VFA, RNFL Analysis, and ODE: Binomial Test Results

Test	Sensitivity	Specificity	PPV	NPV
VFA	NS	<0.0001	NS	<0.0001
RNFL	0.0386	<0.0001	0.0386	<0.0001
ODE	NS	<0.0001	NS	<0.0001

NPV, negative predictive value; NS, nonsignificant.

Although MRI scanning of the brain remains the gold standard diagnostic test for OPGs, its use remains controversial in the absence of clinical signs such as decreased vision.[1,4] Moreover, the evidence-based recommendations for the diagnosis and management of children with NF-1 and OPG reported that baseline "screening" by neuroimaging or VEPs of asymptomatic children with normal visual examinations is not warranted.[1]

A limit of this study is that indirect ophthalmoscopy is not the most accurate method to observe the optic disc for abnormalities in any age group. Nevertheless, biomicroscopy examination is not useful in young children or in uncooperative children with NF-1. A specific study of RNFL analysis versus biomicroscopy in the diagnosis of OPG in children aged 6 and older is ongoing.

In conclusion, RNFL analysis by OCT should be considered superior to VFA examination and ODE in the clinical diagnosis of OPG in NF-1 children. OCT testing also can be used as a sensitive and repeatable outcome measure for future clinical trials.[4] In addition, the examination of RNFL using OCT also can be used theoretically in non-NF-1 patients and adults with brain tumors involving the optic pathway, allowing an objective anatomic assessment of visual pathway involvement.[4]

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References

1. Listernick R, Ferner R, Liu G, Gutmann D. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Ann Neurol*. 2007;61:189–198.
2. Pasmant E, Vidaud M, Vidaud D, Wolkenstein P. Neurofibromatosis type 1: from genotype to phenotype. *J Med Genet*. 2012;49:483–489.
3. Evans D, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. *Am J Med Genet A*. 2010;152:327–332.
4. Chang L, El-Dairi M, Frempong T, et al. Optical coherence tomography in the evaluation of neurofibromatosis type-1 subjects with optic pathway gliomas. *J AAPOS*. 2010;14:511–517.
5. Segal L, Darvish-Zargar M, Dilenge M, et al. Optic pathway gliomas in patients with neurofibromatosis type 1: follow-up of 44 patients. *J AAPOS*. 2010;14:155–8.
6. Pride N, Payne J, North K. The impact of ADHD on the cognitive and academic functioning of children with NF1. *Dev Neuropsychol*. 2012;37:590–600.
7. Miller NR. Primary tumors of the optic nerve and its sheath. *Eye*. 2004;18:1026–1037.
8. Kornreich L, Blaser S, Schwarz M, et al. Optic pathway glioma: correlation of imaging findings with the presence of neurofibromatosis. *AJNR Am J Neuroradiol*. 2001;22:1963–1969.
9. Mentzel H, Seidel J, Fitzek C, et al. Pediatric brain MRI in neurofibromatosis type I. *Eur Radiol*. 2005;15:814–1822.
10. Ferner R, Huson S, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J Med Genet*. 2007;44:81–88.
11. Chou R, Dana T, Bougatsos C. Screening for visual impairment in children ages 1–5 years: systematic review to update the 2004 U.S. Preventive Services Task Force recommendation. Available at: http://www.ncbi.nlm.nih.gov/books/NBK52708/. Accessed May 5, 2013.
12. American Academy of Pediatrics Committee on Practice and Ambulatory Medicine, Section on Ophthalmology. Eye examination and vision screening in infants, children, and young adults. *Pediatrics*. 1996;98:153–157.
13. Cyert L, Schmidt P, Maguire M, et al. Threshold visual acuity testing of preschool children using the crowded HOTV and Lea symbols acuity tests. *J AAPOS*. 2003;7:396–399.
14. Vision in Preschoolers Study Group. Preschool visual acuity screening with HOTV and Lea symbols: testability and between-test agreement. *Optom Vis Sci*. 2004;81:678–683.
15. Pan Y, Tarczy-Hornoch K, Cotter S, et al. Visual acuity norms in pre-school children: the Multi-Ethnic Pediatric Eye Disease Study. *Optom Vis Sci*. 2009;86:607–612.
16. Yanni S, Wang J, Cheng C, et al. Normative reference ranges for the retinal nerve fiber layer, macula, and retinal layer thicknesses in children. *Am J Ophthalmol*. 2013;155:354–360.
17. Avery R, Bouffet E, Packer R, Reginald A. Feasibility and comparison of visual acuity testing methods in children with neurofibromatosis type 1 and/or optic pathway gliomas. *Invest Ophthalmol Vis Sci*. 2013;54:1034–1038.
18. Diggs-Andrews K, Gutmann D. Modeling cognitive dysfunction in neurofibromatosis-1. *Trends Neurosci*. 2013;36:237–247.
19. Stiebel-Kalish H, Lusky M, Yassur Y, et al. Swedish interactive thresholding algorithm fast for following visual fields in prepubertal idiopathic intracranial hypertension. *Ophthalmology*. 2004;111:1673–1675.
20. Avery R, Liu G, Fisher M, et al. Retinal nerve fiber layer thickness in children with optic pathway gliomas. *Am J Ophthalmol*. 2011;151:542–549.
21. North K, Cochineas C, Tang E, Fagan E. Optic gliomas in neurofibromatosis type 1: role of visual evoked potentials. *Pediatr Neurol*. 1994;10:117–123.
22. Wolsey D, Larson S, Creel D, Hoffman R. Can screening for optic nerve gliomas in patients with neurofibromatosis type I be performed with visual-evoked potential testing? *J AAPOS*. 2006;10:307–311.
23. Chang B, Mirabella G, Yagev R, et al. Screening and diagnosis of optic pathway gliomas in children with neurofibromatosis type 1 by using sweep visual evoked potentials. *Invest Ophthalmol Vis Sci*. 2007;48:2895–2902.
24. Liu G, Malloy P, Needle M, Phillips P. Optic gliomas in neurofibromatosis type 1: role of visual evoked potentials. *Pediatr Neurol*. 1995;12:89–90.

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