In Vivo Detection of Choroidal Abnormalities Related to NF1: Feasibility and Comparison With Standard NIH Diagnostic Criteria in Pediatric Patients

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PURPOSE. To evaluate the feasibility of near-infrared (NIR) imaging acquisition in a large sample of consecutive pediatric patients with neurofibromatosis type 1 (NF1), to evaluate the diagnostic performance of NF1-related choroidal abnormalities as a diagnostic criterion of the disease, and to compare this criterion with other standard National Institutes of Health (NIH) diagnostic criteria.

METHODS. A total of 140 consecutive pediatric patients (0–16 years old) affected by NF1 (at least two diagnostic criteria), 59 suspected (a single diagnostic criterion), and 42 healthy subjects (no diagnostic criterion) were consecutively included. Each patient underwent genetic, dermatologic, and ophthalmologic examination to evaluate the presence/absence of each NIH diagnostic criterion. The presence of NF1-related choroidal abnormalities was investigated using NIR confocal ophthalmoscopy. Two masked operators assessed Lisch nodules and NF1-related choroidal abnormalities.

RESULTS. Neurofibromatosis type 1–related choroidal abnormalities were detected in 72 affected (60.5%) and 1 suspected (2.4%) child. No healthy subject had choroidal abnormalities. Feasibility rate of this sign was 82%. Sensitivity, specificity, and positive and negative predictive values of NF1-related choroidal abnormalities were 0.60, 0.97, 0.98, and 0.46, respectively. Compared with standard NIH criteria, the presence of NF1-related choroidal abnormalities was the third parameter for positive predictive value and the fourth for sensitivity, specificity, and negative predictive value. Compared with Lisch nodules, NF1-related choroidal abnormalities were characterized by higher specificity and positive predictive value. The interoperator agreement for Lisch nodules and NF1-related choroidal abnormalities was 0.67 (substantial) and 0.97 (almost perfect), respectively. The use of this sign moved one patient from the suspected to the affected group (0.5%).

CONCLUSIONS. Neurofibromatosis type 1–related choroidal abnormalities represent a new diagnostic sign in NF1 children. The main advantage of this sign seems the theoretical possibility to anticipate NF1 diagnosis, whereas the main obstacle is the cooperation required by very young patients.

Keywords: neurofibromatosis, NF1, choroidal abnormalities

Neurofibromatosis type 1 (NF1) is one of the most common inherited disorders, occurring in approximately 1 in 3000 individuals.1,2 Since the original National Institutes of Health (NIH) Consensus Development Conference in 1987, a minimum of two diagnostic criteria are required for NF1 diagnosis, including six or more café-au-lait spots, axillary or inguinal freckling, two or more cutaneous neurofibromas, a single plexiform neurofibroma, distinctive osseous lesions, optic glioma, two or more Lisch nodules, and a first-degree relative with NF1.3 New data about NF1 have been found during the past 27 years: in addition to the availability of increasingly precise molecular analyses, some new clinical signs, such as NF1-related choroidal abnormalities or the brain “unidentified bright objects” have been reported.4

Choroidal involvement was considered to be a rare finding in NF1, most often described in postmortem examinations.5 The delay in the in vivo detection of NF1-related choroidal abnormalities was mainly related to the clinical characteristics of these lesions, which are fully asymptomatic and undetectable using conventional ophthalmoscopy or fluorescein angiography.6 Neurofibromatosis type 1–related choroidal abnormalities were originally described as hypofluorescent patches in the early choroidal angiographic phases when performing indocyanine-green angiography.7,8 More recently, confocal near-infrared (NIR) reflectance imaging, a fully
noninvasive tool, was claimed to provide superior visibility of these features. Following this evidence, Viola et al. analyzed 95 consecutive patients (mostly adults) affected by NF1, concluding that choroidal abnormalities frequently occurred in NF1 patients, and suggesting that these findings should be investigated as a new diagnostic criterion of NF1, also in pediatric populations.

The aims of this study were to evaluate the feasibility of NIR choroidal imaging acquisition in a large sample of consecutive pediatric patients with NF1; to evaluate sensitivity, specificity, and positive and negative predictive value of NF1-related choroidal abnormalities as a diagnostic criterion of the disease; and to compare this criterion with those established by the original NIH Consensus Development Conference.

METHODS

Patients, Setting, and Design

This was an institutional, observational, masked, cross-sectional study with prospective enrollment, compliant with the tenets of the Declaration of Helsinki. Patients were consecutively recruited from those referred between July 2013 and January 2014 to the Clinical Genetics Unit of the University of Padova. Informed consent was obtained from each pediatric subject’s legal guardian. Subjects older than 6 years of age provided consent additionally. Institutional review boards of our institutions approved the study protocol. Inclusion criteria were as follows: patients aged 0 to 16 years, having at least one NIH criterion for the diagnosis of NF1. Exclusion criteria were as follows: history of any ophthalmologic disease that could affect choroidal or retinal aspect (e.g., uveitis, retinopathy of prematurity, maculopathy, congenital ocular malformations) or that could impair adequate fundus visualization (e.g., congenital cataract or other media opacities).

Each patient underwent a detailed genetic, dermatologic, and ophthalmologic assessment aimed to detect and confirm the presence or absence of each NIH diagnostic criterion. After these assessments, enrolled patients were divided into two groups: NF1 affected (affected) and NF1 suspected (suspected). The affected group was composed of patients with two or more proven NIH diagnostic criteria, whereas the suspected group was composed of patients fulfilling a single diagnostic criterion. Forty-two sex- and race-matched healthy subjects were also enrolled as a healthy control group.

Genetic and Dermatological Assessment

Café-au-lait spots, axillary or inguinal freckling, and cutaneous neurofibromas were assessed on whole skin. To evaluate the presence of familiarity for NF1, both parents of the pediatric subjects were clinically examined. The presence of distinctive osseous lesions was also clinically examined in each patient. Ophthalmologic findings were masked to the pediatric geneticist and dermatologist performing patient evaluation.

Ophthalmologic Assessment

The presence or absence of each NIH diagnostic criterion, as well as final patient classification (healthy, suspect, and affected), was masked to ophthalmologists performing patient examination. Briefly, ophthalmologic evaluation included visual acuity assessment using age-appropriate visual function tests, cycloplegic refraction, stereopsis assessment, pupillary reflex evaluation, biomicroscopy evaluation of anterior segment, air-puff tonometry in children older than 6 years, fundus examination using indirect ophthalmoscopy, and, when allowed by patient cooperation, biomicroscopic evaluation of optic nerve head.

Lisch Nodules. The presence of Lisch nodules as a diagnostic criterion was defined as the presence of at least two Lisch nodules (NIH criteria) and was assessed by using slit lamp biomicroscopy. Anterior segment photos also were taken depending on patient fixation stability and cooperation. To obtain the feasibility rate of Lisch nodules detection, each test was classified as informative or not according to personal operator judgment based on patient cooperation (i.e., the physician marked with yes or no the following question: “Was the cooperation of the patient sufficient to evaluate the presence versus absence of this criterion?”). If the patient was uncooperative at the beginning of eye examination, slit lamp examination was later reattempted. The examiner was allowed to stop testing in subjects who, despite multiple testing attempts, were uncooperative. Two masked ophthalmologists evaluated each patient. In case of disagreement, adjudication was given by a third party. In case of lack of cooperation with the second operator, anterior segment photos were used to carry out the interoperator agreement analysis. Each examiner also was masked for the presence/absence of NF1-related choroidal abnormalities.

Neurofibromatosis Type 1–Related Choroidal Abnormalities.

The evaluation of the presence/absence of NF1-related choroidal abnormalities was obtained using Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) in NIR reflectance modality, after pupil dilatation. Images of the posterior pole and the midperiphery of the retina were obtained using a 50° lens centered onto the posterior pole. An internal or external fixation target was used depending on age and patient cooperation. For younger children, a second operator handled a smartphone playing a cartoon movie as external fixation target to obtain patient cooperation. If the patient was uncooperative during image acquisition, examination was later reattempted. The examiner was allowed to stop the test in subjects who, despite multiple testing attempts, were uncooperative. The Spectralis automatic real time (ART) modality (16–100 averaged images) was used to avoid motion artifacts. Based on the quality and correctness of the position of the scan to the fundus oculi, a single image was chosen for analysis. The presence of NF1-related choroidal abnormalities was defined as the presence of at least two hyperreflective choroidal spots, as suggested by Viola et al. (cutoff value: 1.5). Two masked ophthalmologists evaluated each image. To obtain the feasibility rate of NF1-related choroidal abnormalities, each test was classified as informative or not by each physician evaluating acquired images, according to personal operator judgment based on quality of acquired images (i.e., the physician marked with yes or no the following question: “Was the quality of the images sufficient to evaluate the presence versus absence of this criterion?”). In case of disagreement, adjudication was given by a third party. Each examiner was also masked for the presence or absence of Lisch nodules.

Optic Pathway Glioma. Evidence-based recommendations for NF1 children (strength of recommendation A; quality of evidence III) suggest to reserve magnetic resonance imaging (MRI) of the brain for those patients clinically classified as suspected of optic pathway glioma (OPG), according to data obtained from clinical ophthalmic examination or in the presence of other clinical indications. Patients with visual acuity inferior to age-based normative data; strabismus without refractive errors; absence of stereopsis, proptosis, and pathological pupillary reflex; and those with reduced retinal nerve fiber layer thickness, obtained by optical coherence tomography (OCT) analysis of optic nerve head, were clinically classified as OPG suspected. These patients underwent brain
A total of 199 patients were consecutively included in this study. Among these, 140 (70.3%) patients were classified as affected by NF1 (at least two diagnostic criteria) and 59 (29.7%) as suspected (presence of a single diagnostic criterion). The demographic and clinical characteristics of the studied population, including race, iris color, and refractive errors are reported in Table 1.

The presence of NIH diagnostic criteria for NF1 was analyzed for each group. Each diagnostic criterion was classified as present, absent, or uninformative. None of the diagnostic criteria for NF1 was found in patients enrolled in the “healthy (control) group” (including the presence of NF1-related choroidal abnormalities). Among 140 affected patients, diagnostic criteria were distributed as follows: 36 (18.2%) had two diagnostic criteria, 49 (24.7%) had three criteria, 37 (18.7%) had four criteria, 17 (8.6%) had five criteria, and 1 (0.5%) had six criteria. The distribution of each nonophthalmologic criterion among the groups is reported in Table 2.

**Lisch Nodules.** Among 199 patients, 174 (87.4%) were classified as informative, whereas 25 (12.6%) patients were classified as uninformative (the cooperation of each patient was judged insufficient to evaluate the presence versus absence of the criterion). No statistical differences were found between patients classified as informative versus uninformative in terms of their baseline characteristics, except for age, which was lower for the uninformative group (P < 0.0001). Among these 174 cases, 83 (47.7%) patients were classified as positive for this sign. Among patients with Lisch nodules, 80 (96.3%) were affected by NF1, whereas 3 (3.7%) were suspected. Therefore, among 140 patients affected by NF1, 80 (57.1%) were positive for the presence of this sign, whereas 3 (5.3%) of 56 suspected patients were positive. The sensitivity, specificity, and positive and negative predictive value of the sign “Lisch nodules” were 57.1%, 94.6%, 96.3%, and 94.6%, respectively.

**Optic Pathway Glioma.** Among 199 subjects, 34 (17%) were clinically classified as suspected for the presence of OPG and underwent brain MRI. Of these, 29 (85.2%) were confirmed to be affected by OPG, whereas 5 (4.8%) were considered false positive. Considering children positive for OPG, 28 (96.5%) were affected by NF1 and 1 (3.5%) was in the suspected group. Therefore, among 140 patients affected by NF1, 28 (20.0%) were positive for the presence of this sign, whereas a single patient among 59 suspected patients was positive (1.7%). The sensitivity, specificity, and positive and negative predictive values of the sign “OPG” were 20.0%, 98.5%, 96.5%, and 34.1%, respectively.
Neurofibromatosis Type 1–Related Choroidal Abnormalities. Among 199 patients, 3 (1.5%) patients were excluded because of missing data. Among 196 patients, 160 (81.6%) were classified as informative, whereas 36 (18.4%) patients were classified as uninformative (the quality of the acquired images was judged insufficient to evaluate the presence versus absence of this criterion). No statistical differences were found between patients classified as informative versus uninformative in terms of their baseline characteristics, except for age, which was lower for the uninformative group ($P < 0.0001$).

Among 160 patients classified as informative, 73 (45.6%) showed the presence of this sign (Fig.). Considering the patients having NF1-related choroidal abnormalities, 72 (98.6%) patients were affected, whereas a single case was suspected (1.4%). Therefore, among 119 patients affected by NF1, 72 (60.5%) were positive for the presence of this sign, whereas a single case on 41 suspected was positive (2.4%). The sensitivity, specificity, and positive and negative predictive values of the sign “NF1-related choroidal abnormalities” were 60.5%, 97.6%, 98.6%, and 46.0%, respectively.

Comparison of Diagnostic Performance and Intergrader Agreement of Analyzed Criteria

The comparison of sensitivity, specificity, and positive and negative predictive values of each criterion is reported in Table 3. The new sign “NF1-related choroidal abnormalities” was the third parameter for positive predictive value and the fourth for sensitivity, specificity, and negative predictive value.

The interoperator agreement obtained in the evaluation of Lisch nodules and NF1-related choroidal abnormalities was 0.67 (95% confidence interval [CI] 0.56–0.77) and 0.97 (95% CI 0.94–1.00), respectively. Therefore, according to the interpretation of the Gwet parameters, correlation was “substantial” (0.60–0.80) for Lisch nodules and “almost perfect” (>0.80) for the NF1-related choroidal abnormalities.

![Near-infrared imaging of a 4-year-old boy with NF1 showing no NF1-related choroidal abnormalities in his right eye (left). Near-infrared imaging of a 5-year-old boy with NF1 showing several bright NF1-related choroidal abnormalities (right).](image-url)
TABLE 3. Comparison Among Diagnostic Indicators, Rate (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PLR</th>
<th>NLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Café-au-lait spots</td>
<td>98.6</td>
<td>32.2</td>
<td>77.5</td>
<td>90.5</td>
<td>1.45</td>
<td>0.04</td>
</tr>
<tr>
<td>(94.9–99.8)</td>
<td>(20.6–45.6)</td>
<td>(70.7–85.4)</td>
<td>(69.6–98.5)</td>
<td>(1.22–1.74)</td>
<td>(0.01–0.18)</td>
<td></td>
</tr>
<tr>
<td>Axillary or inguinal freckling</td>
<td>92.9</td>
<td>100</td>
<td>100</td>
<td>85.5</td>
<td>n.a.</td>
<td>0.07</td>
</tr>
<tr>
<td>(87.2–96.5)</td>
<td>(93.9–100.0)</td>
<td>(97.2–100.0)</td>
<td>(74.9–92.8)</td>
<td>(0.04–0.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisch nodules</td>
<td>32.9</td>
<td>98.3</td>
<td>97.9</td>
<td>38.2</td>
<td>n.a.</td>
<td>0.68</td>
</tr>
<tr>
<td>(53.0–70.4)</td>
<td>(81.7–98.5)</td>
<td>(89.8–99.2)</td>
<td>(35.6–56.9)</td>
<td>(3.1–28.0)</td>
<td>(0.32–0.50)</td>
<td></td>
</tr>
<tr>
<td>Neurofibromas</td>
<td>20</td>
<td>35</td>
<td>55.0</td>
<td>23.4</td>
<td>(24.4–39.9)</td>
<td>(0.76–2.53)</td>
</tr>
<tr>
<td>(40–17)</td>
<td>(40–7)</td>
<td>(82.2–99.4)</td>
<td>(27.0–41.8)</td>
<td>(1.6–84.7)</td>
<td>(0.74–0.89)</td>
<td></td>
</tr>
<tr>
<td>Familiarity§</td>
<td>60.5</td>
<td>97.6</td>
<td>98.6</td>
<td>46</td>
<td>24.8</td>
<td>0.4</td>
</tr>
<tr>
<td>(51.1–69.3)</td>
<td>(87.1–99.6)</td>
<td>(92.6–99.8)</td>
<td>(35.2–57.0)</td>
<td>(3.6–172.9)</td>
<td>(0.32–0.51)</td>
<td></td>
</tr>
<tr>
<td>NF1-related choroidal abnormalities</td>
<td>98.6</td>
<td>32.2</td>
<td>77.5</td>
<td>90.5</td>
<td>1.45</td>
<td>0.04</td>
</tr>
<tr>
<td>(94.9–99.8)</td>
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<td>(69.6–98.5)</td>
<td>(1.22–1.74)</td>
<td>(0.01–0.18)</td>
<td></td>
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</table>

n.a., not applicable; NLR, negative likelihood ratio, (1 – sensitivity)/specificity; NPV, negative predictive value; PLR, positive likelihood ratio, sensitivity/(1 – specificity); PPV, positive predictive value.

Relationship Between Classical NIH Diagnostic Criteria and NF1-Related Choroidal Abnormalities in Affected Patients

A statistically significant correlation was found between NF1-related choroidal abnormalities and café-au-lait spots (<0.001), freckles (<0.001), Lisch nodules (0.0002) and neurofibromas (0.0013). However, whereas for the first two signs the correlation was moderate (0.40–0.60), for the last two it was fair (0.20 to 0.40) (Table 4).

Contribution of the New Sign “NF1-Related Choroidal Abnormalities” in the Diagnosis of NF1

To evaluate the contribution of the new sign in the diagnosis of NF1, we made a simulation adding this sign to the standard NIH criteria, maintaining a minimum of two diagnostic criteria required for the diagnosis. The introduction of this sign changed the diagnosis in a single case (0.5%), moving a patient from the suspected to the affected group (Supplementary Table S1). In other 72 affected patients (51.4%), this new sign confirmed and strengthened the diagnosis of NF1. A second simulation replacing the standard NIH criterion “presence of distinctive osseous lesions” (the less frequent and determinant sign in our cohort of patients) with this new sign was conducted, obtaining similar results (Supplementary Table S2).

Correlation of the Diagnostic Signs With Age

Considering suspected and affected children, freckles, Lisch nodules, neurofibromas and gliomas, and NF1-related choroidal abnormalities showed statistical correlation with age (Supplementary Table S3).

DISCUSSION

Our study was designed to compare the diagnostic performance of a new clinical sign detected by NIR imaging, namely NF1-related choroidal abnormalities, versus classic NIH diagnostic criteria for NF1, to determine its role in the diagnosis of this disease.

The main technical issue in the detection of NF1-related choroidal abnormalities in a pediatric clinical setting is the amount of cooperation required to obtain adequate choroidal images. Recently, Viola et al. reported 95 cases of NF1 patients analyzed by confocal scanning laser ophthalmoscopy...

TABLE 4. Relationship Between Classic NIH Diagnostic Criteria and NF1-Related Choroidal Abnormalities in the Affected Group, n = 119

<table>
<thead>
<tr>
<th></th>
<th>Concordant Pairs</th>
<th>Discordant Pairs</th>
<th>n/Total</th>
<th>%</th>
<th>AC1*</th>
<th>SE</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Café-au-lait spots</td>
<td>++</td>
<td>- -</td>
<td>71/119</td>
<td>59.7</td>
<td>0.405</td>
<td>SE</td>
<td>0.027–0.583</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Axillary or inguinal freckling</td>
<td></td>
<td></td>
<td>75/119</td>
<td>63.1</td>
<td>0.405</td>
<td>SE</td>
<td>0.022–0.583</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lisch nodules</td>
<td></td>
<td>++</td>
<td>76/119</td>
<td>63.0</td>
<td>0.297</td>
<td>SE</td>
<td>0.116–0.478</td>
<td>0.0015</td>
</tr>
<tr>
<td>Neurofibromas</td>
<td></td>
<td></td>
<td>75/119</td>
<td>63.0</td>
<td>0.262</td>
<td>SE</td>
<td>0.086–0.437</td>
<td>0.0038</td>
</tr>
<tr>
<td>Familiality§</td>
<td></td>
<td></td>
<td>51/117</td>
<td>43.6</td>
<td>–0.099</td>
<td>SE</td>
<td>0.097–0.291–0.093</td>
<td>0.3099</td>
</tr>
<tr>
<td>OPG</td>
<td></td>
<td></td>
<td>57/119</td>
<td>47.9</td>
<td>–0.004</td>
<td>SE</td>
<td>0.098–0.197–0.189</td>
<td>0.9634</td>
</tr>
<tr>
<td>Distinctive osseous lesions</td>
<td></td>
<td></td>
<td>46/119</td>
<td>38.7</td>
<td>–0.079</td>
<td>SE</td>
<td>0.109–0.295–0.137</td>
<td>0.4688</td>
</tr>
</tbody>
</table>

* Statistically significant coefficients are reported in bold character.
† According to interpretation of the Gwet parameters, agreement is moderate (0.40–0.60).
‡ According to interpretation of the Gwet parameters, agreement is fair (0.20–0.40).
§ Total = 117 because of two missing data for familiarity.
to detect the presence of NF1-related choroidal abnormalities. These authors did not report the feasibility rate of the NIR image acquisition. Moreover, most included children were older than 12 years, whereas the clinical diagnosis of NF-1 is most commonly made in early pediatric age (<10 years old). Goktas et al.12 recently analyzed 19 pediatric patients with NF1, concluding that infrared reflectance imaging can be used as an aid in the diagnosis of NF-1. Unfortunately, the feasibility of the procedure was not specified.

The use of any ophthalmological imaging tool in pediatric patients with NF1 is complicated by the frequent cognitive dysfunctions associated with this disease (mainly NF1-associated learning disabilities and attention deficit hyperactivity disorder).10,11 In our pediatric population, a feasibility rate of 82% was achieved. This rate is obviously inferior compared with that of detecting most of the standard nonophthalmologic criteria, and is also slightly inferior to that achieved for Lisch nodules (87%). A technical difference between NIR image acquisition and slit lamp biomicroscopy is the light used in these tests. Theoretically, NIR imaging should be better tolerated because an invisible NIR light is used, whereas slit lamp examination uses a bright light. Nevertheless, in our experience, younger patients are more comfortable with slit lamp examination and a low light intensity can be used, avoiding direct pupil illumination. Conversely, for NIR image acquisition, the patient is asked to look into a black hole with a small blue light, a challenging task for a child. The child’s approach to the instrument is also complicated by the background noise, which can be worrying for a child. Nevertheless, the key factors to explain the feasibility rate difference between the two tests are the stability of fixation and the time of examination. Fixation stability is not mandatory for slit lamp examination, and frequent and multiple testing reattempts allow visualization of the entire iris. Conversely, imaging of the fundus needs to obtain (and maintain) a perfect focalization of the retina with a stable fixation for the automatic start of the ART image-capturing system during all time.

Another reason that may partly explain the reported difference in feasibility is that NIR imaging acquisition was performed at the end of the ophthalmological examination. NIR image acquisition needs pupil dilatation (in our experience, nonmydriatic image acquisition of the fundus is almost impossible in a child), and therefore it is performed after eye drops instillation, modifying the patient cooperation with the ophthalmologist environment.

We have obtained the reported feasibility rate using skills acquired using the same device in the detection of OPG in NF1 pediatric patients in a routine clinical setting, as well as handling electronic devices playing cartoon movies as external fixation target.10 Therefore, a lower feasibility rate may be expected in less experienced centers.

Another key factor in the feasibility of NIR image acquisition is the patient’s age.14 The influence of age is clearly evident analyzing the feasibility rate of the two groups of enrolled patients (71% for the suspected group versus 85% of the affected group) that is directly correlated with the mean age of these groups (mean age: affected group 8.3 years; suspected group 6.4 years; \( P = 0.009 \)). We cannot exclude that the difference in cooperation between the two groups (affected and suspected) may have partly biased our study because the examined proportion of each group may be not fully representative of the entire population. Nevertheless, this uninformative portion of the population is the clinical measure of test applicability, and the only statistical difference between informative and uninformative patients in terms of their baseline characteristics is age. Therefore, a longitudinal study will better address the role of this sign in anticipating the diagnosis of NF1 in a pediatric population.

Despite the challenging technical feasibility in young patients, the interpretation of acquired images is simple and unambiguous. The standard ophthalmologic evaluation of patients with NF1 is historically flawed by clinical methods that provide sometimes uncertain or ambiguous clinical data.10,15 The ophthalmoscopic assessment of fine optic disc alterations (or the challenging evaluation of fluctuating visual acuities) in small children to detect OPG, as well as the quantification of Lisch nodules, which commonly are visualized (or “become visible”) only after the diagnosis of NF1, are clear examples of this problem.10,15 In 1995, Beauchamp15 analyzed 151 NF1 patients to characterize the incidence of iris changes consistent with NF1, including their variability and reliability.10 The masked evaluation yielded fair to poor correlation, raising the question of their clinical reliability and validity. Conversely, NF1-related choroidal abnormalities are easy to be assessed in NIR images. Therefore, in our experience, the detection of this sign is almost unequivocal (Fig.), reaching an interobserver agreement considerably higher than those obtained with Lisch nodules in the same cohort of patients. Additionally, the absence of this sign in healthy subjects included in the control group reinforces its diagnostic performance.

In our simulation, adding choroidal abnormalities as an additional diagnostic criterion, just a single case moved from the suspected to the affected group. Nevertheless, calculating that a single patient on 59 suspected cases moved to the affected group based on the new criterion, approximately 2% of the suspected patients may be reclassified as affected. This result may be probably considered clinically irrelevant, but it may be epidemiologically relevant, mainly considering NF1 prevalence as well as the prevalence of each NF1 diagnostic criterion in the pediatric population. Moreover, this sign has strengthened the diagnosis of NF1 in more than 50% of patients who have been already diagnosed as NF1 affected. Furthermore, there is the theoretical possibility to anticipate NF1 diagnosis in some cases by adding this new diagnostic sign. In fact, the subject who moved from the suspected to the affected group by using this sign was a 2-year-old boy.

In conclusion, choroidal abnormalities, identified by NIR confocal imaging, represent a new diagnostic sign in NF1 children. The main advantage of this sign seems to be the theoretical possibility to anticipate NF1 diagnosis, whereas the main obstacle is the cooperation required by very young patients. Nevertheless, the diagnostic performance of this new sign, paired to the higher interobserver agreement compared with those of Lisch nodules, is absolutely promising in a scenario characterized by fast improvement of eye-imaging technology.

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