Original Article

Multimodal Imaging Characteristics and Diagnostic Value of Choroidal Nodules in Patients with Neurofibromatosis Type 1

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Abstract

Objectives: Yasunari nodules are choroidal lesions observed in patients diagnosed with neurofibromatosis type 1 (NF-1) and characterized by relatively irregular dome-shaped, plaque-like, or patchy boundaries. The present study examines the multimodal imaging characteristics of Yasunari nodules and their value in the diagnosis of NF-1.

Materials and Methods: Medical records including optical coherence tomography (OCT), enhanced depth imaging OCT, infrared reflectance (IR) imaging, OCT angiography, and color fundus images of NF-1 patients who were examined at the Department of Ophthalmology in Dokuz Eylül University Faculty of Medicine between January 2022 and December 2023 were retrospectively reviewed for the presence of Yasunari nodules.

Results: A total of 54 eyes of 27 patients were included in the study. At least one choroidal nodule was detected on IR imaging in 52 eyes (96.3%). In 31 (72.1%) of the 43 eyes (79.6%) with available high-quality OCT angiography images, choroidal nodules were observed as areas showing a flow deficit in the choriocapillaris layer. Of the total 54 eyes included, Lisch nodules without choroidal nodules were observed in 2 eyes (3.7%). In 16 eyes (29.6%), Lisch nodules were not detected despite the presence of choroidal nodules. Both Lisch nodules and choroidal nodules were detected in the other 36 eyes (66.7%).

Conclusion: Yasunari nodules are frequently observed in NF-1 cases and can be easily detected with multimodal imaging techniques, especially IR imaging. The ability to visualize choroidal nodules before the appearance of Lisch nodules demonstrates the importance of Yasunari nodules in the diagnosis of NF-1.

Keywords: Choroidal nodules, infrared imaging, multimodal imaging, neurofibromatosis type 1, Yasunari nodules

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Introduction

Neurofibromatosis type 1 (NF-1) is an autosomal dominant disease caused by deletions or mutations in the neurofibromin gene located on chromosome 17p11.2.[1] It has a reported incidence of approximately 1/3000 and a prevalence between 1/4000 and 1/5000.[2] NF-1 is characterized by a range of findings, including nerve tumors that can develop in various parts of the body, cutaneous pigmentation changes (cafe au lait spots, axillary and inguinal freckling), vascular abnormalities, and bone lesions (pseudoarthrosis, sphenoidal wing hypoplasia), and is also commonly associated with ocular involvement.[3,4,5]

The NF-1 diagnostic criteria determined by the National Institutes of Health include the presence of two or more Lisch nodules on the iris and optic nerve glioma as ophthalmological findings.[6] In 2021, Legius et al.[7] suggested that the presence of at least two choroidal abnormalities described as "bright, patchy nodules" on optical coherence tomography (OCT) or infrared reflectance (IR) imaging should also be used as a diagnostic criterion for NF-1. These lesions, which occur at the level of the choroid, are hamartomatous nodules also referred to as "Yasunari nodules".[8] Their reported prevalence in NF-1 cases ranges from 28% to 100%.[8,9,10,11]

The aim of this study was to evaluate the incidence of choroidal nodules in patients with NF-1, their multimodal imaging characteristics, and their place in the diagnosis of NF-1.

Materials and Methods

This retrospective study was conducted within the framework of the principles of the Declaration of Helsinki and approved by the Dokuz Eylül University Local Ethics Committee (approval number: 2023/10-01, date: 29.03.2023). We retrospectively

analyzed the medical records and recorded OCT, enhanced depth imaging OCT (EDI-OCT), IR, OCT angiography (OCTA), and color fundus images of patients who were examined in the Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology between January 2022 and December 2023 and had at least two of the National Institutes of Health diagnostic criteria for NF-1.[6] Exclusion criteria were optic media opacity that could interfere with posterior segment imaging, comorbid systemic or ocular disease other than NF-1, and a history of systemic drug use.

All patients included in the study underwent a comprehensive ophthalmological assessment including anterior and posterior segment examination. Spectral-domain OCT images (7-mm fovea-centered radial B-scan sections with a 30-degree lens, ART: 9), EDI-OCT images (9-mm horizontal sections passing through the fovea) and IR images (fovea-centered 55-degree area) were obtained with a standard protocol using the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) device. OCTA images covering a 12x12-mm area centered on the fovea and/or optic disc were obtained using the DRI OCT Triton (TOPCON, Tokyo, Japan) device, and central 45-degree color fundus images including the optic disc and macula were obtained using the VISUCAM 500 (Carl Zeiss Meditec, Jena, Germany) or DRI OCT Triton device. We recorded the patients' age, gender, presence of cafe au lait spots, and cranial magnetic resonance imaging (MRI) findings for each patient; central macular thickness (CMT) and presence of Lisch nodules, eyelid plexiform neurofibroma, optic glioma, and Yasunari nodules in each eye; and subfoveal choroidal thickness (SFCT) for eyes with EDI-OCT images passing through the fovea.

Using the device software, CMT was determined by manually measuring the shortest vertical distance between the internal limiting membrane and Bruch's membrane in OCT images passing through the fovea, and SFCT was determined by manually measuring the shortest vertical distance between the hyperreflective outer border of the retinal pigment epithelium (RPE) and the choroid-sclera junction in EDI-OCT images passing through the fovea.

The presence of optic glioma was evaluated by examining contrast-enhanced orbital MRI.

Lisch nodules were defined as yellowish brown dome-shaped solid hamartomatous lesions 1-2 mm in diameter on the iris surface on slit-lamp examination.[10]

Choroidal nodules were identified on IR images as domed, placoid, or patchy choroidal lesions with relatively irregular borders and high reflectivity.[8] The presence of these nodules was also evaluated on OCT images with image quality ≥18 and OCTA images with image quality ≥40 for patients with recorded images.

Informed consent was not obtained because the study was retrospective and used no identifying data or images.

Statistical Analysis

Statistical analyses were performed using the SPSS statistical program (IBM Corp, Armonk, NY, USA). Descriptive statistics were used to summarize the data. Categorical variables are presented as numbers and percentages, and quantitative variables are presented as mean ± standard deviation.

Results

The study included a total of 54 eyes of 27 patients. Descriptive statistics of the study group are given in Table 1; detailed demographic and clinical characteristics are shown in Table 2.

Fourteen (51.9%) of the patients were male and 13 (48.1%) were female. The mean age of the patients was 22.33±14.62 years (range, 8-57 years). All patients (100%) had at least 6 cafe au lait spots.

Table 1. Descriptive statistics of the patients and eyes included in the study

Number of patients/eyes, n	27/54
Age, years	22.33±14.62[a]
Gender, M/F	14/13[a]
Cafe au lait spots, n (%)	27 (100)[a]
Lisch nodule, n (%)	40 (74.1)[b]
Eyelid neurofibroma, n (%)	1 (1.9)[b]
Optic glioma, n (%)	9 (64.3)[c]
Central macular thickness, µm	244.31±25.17[b]
Subfoveal choroidal thickness, µm	320.49±63.63[b]
Choroidal nodule on IR imaging, n (%)	52 (96.3)[b]
Choroidal nodule on OCTA, n (%)	31 (72.1)[d]

[a]: According to number of patients, [b]: According to number of eyes, [c]: According to number of patients with contrast-enhanced orbital magnetic resonance imaging, [d]: According to number of eyes with adequate quality OCTA images, M: Male, F: Female, IR: Infrared reflectance, OCTA: Optical coherence tomography angiography

Table 2. Demographic and clinical characteristics of the patients

Patient	Sex	Age (years)	Cranial MRI findings	Eye	Lisch nodule	Eyelid neurofibroma	Optic glioma	CMT (µm)	SFCT (µm)	Choroidal nodule on IR	Choroidal nodule on OCTA
1	M	52	No cranial MRI	Right Left	+ +	- -	- -	220 380	351 354	+ +	+ No OCTA
2	F	41	No pathology	Right Left	+ -	- -	- +	214 209	307 299	+ +	+ +
3	F	12	Hamartoma	Right Left	+ +	- -	+ -	268 243	347 337	+ +	- -
4	F	16	Hamartoma	Right Left	+ +	- -	- -	242 236	387 362	+ +	+ +
5	F	16	Hamartoma	Right Left	+ +	- -	+ -	237 228	373 408	+ +	+ +
6	F	13	Non-specific hyperintense foci	Right Left	+ -	- -	No orbital MRI No orbital MRI	227 228	349 363	+ +	No OCTA No OCTA
7	F	14	No cranial MRI	Right Left	+ +	- -	- -	232 262	345 346	+ +	+ +
8	M	10	Hamartoma	Right Left	- -	- -	No orbital MRI No orbital MRI	240 237	389 384	+ +	+ +
9	M	13	Hamartoma ICA thinning	Right Left	- -	- -	+ -	232 232	359 305	+ +	+ +
10	M	57	Encephalomalacia	Right Left	+ +	- -	No orbital MRI No orbital MRI	228 221	177 139	+ +	+ +
11	M	15	Venous anomaly	Right Left	+ +	- -	No orbital MRI No orbital MRI	244 250	277 356	+ +	+ +
12	M	24	Bone dysplasia Plexiform neurofibroma	Right Left	+ +	- +	No orbital MRI No orbital MRI	249 181	352 No EDI-OCT	+ +	+ No OCTA
13	F	25	No pathology	Right Left	+ +	- -	- -	237 236	No EDI-OCT No EDI-OCT	+ +	- -
14	F	23	Hamartoma	Right Left	+ +	- -	- -	282 263	323 316	+ +	+ +
15	M	48	Ventricular dilatation	Right Left	+ +	- -	No orbital MRI No orbital MRI	237 238	254 224	+ +	+ +
16	M	19	Hamartoma Glial tumor	Right Left	- +	- -	+ -	235 244	302 300	+ +	+ +
17	F	18	Hamartoma Chiari type I anomaly	Right Left	+ +	- -	No orbital MRI No orbital MRI	262 255	No EDI-OCT No EDI-OCT	+ +	- -
18	F	11	Hamartoma Ventricular dilatation	Right Left	+ +	- -	+ -	249 256	337 313	+ +	+ +
19	M	17	Venous anomaly	Right Left	+ +	- -	+ -	248 249	330 316	+ +	No OCTA No OCTA
20	F	47	No cranial MRI	Right Left	- +	- -	No orbital MRI No orbital MRI	240 250	206 167	+ +	No OCTA No OCTA
21	M	19	Hamartoma	Right Left	- -	- -	No orbital MRI No orbital MRI	253 268	307 271	+ +	+ +
22	F	40	No cranial MRI	Right Left	- -	- -	No orbital MRI No orbital MRI	251 258	284 275	+ +	+ +
23	F	12	Expansile lesion in pons	Right Left	- +	- -	- +	223 223	324 317	+ +	- -
24	M	11	Non-specific hyperintense foci	Right Left	+ +	- -	No orbital MRI No orbital MRI	244 254	359 360	- -	- -

Table 2. continued

Patient	Sex	Age (years)	Cranial MRI findings	Eye	Lisch nodule	Eyelid neurofibroma	Optic glioma	CMT (µm)	SFCT (µm)	Choroidal nodule on IR	Choroidal nodule on OCTA
25	M	10	No pathology	Right Left	+ +	- -	No orbital MRI No orbital MRI	245 264	No EDI-OCT No EDI-OCT	+ +	No OCTA No OCTA
26	M	12	Hamartoma Arachnoid cyst	Right Left	+ +	- -	+ +	253 248	426 469	+ +	- +
27	M	8	Hamartoma	Right Left	- +	- -	No orbital MRI No orbital MRI	238 250	302 313	+ +	No OCTA No OCTA

MRI: Magnetic resonance imaging, CMT: Central macular thickness, SFCT: Subfoveal choroidal thickness, IR: Infrared reflectance, OCTA: Optical coherence tomography angiography, ICA: Internal carotid artery, EDI-OCT: Enhanced depth imaging optical coherence tomography

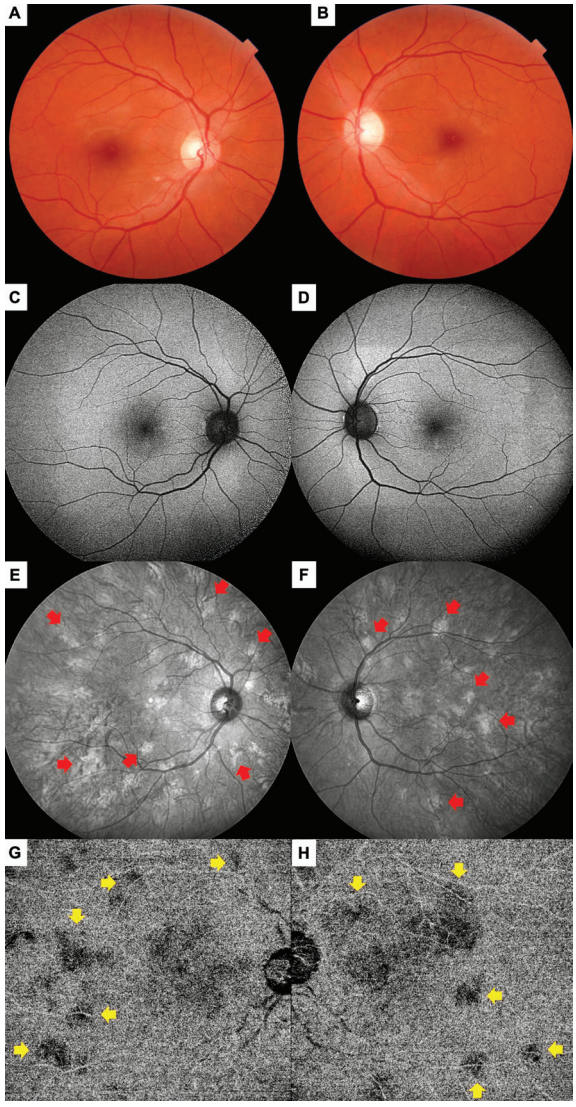

Figure 1. Patient 2 (female, 41 years old) exhibited no pathological findings in either eye on color fundus images (A and B) or fundus autofluorescence images (C and D). However, infrared reflectance imaging revealed patchy, highly reflective choroidal nodules (red arrows) widespread across the posterior pole (E and F), and corresponding areas of flow deficit (yellow arrows) in the choriocapillaris layer were observed on optical coherence tomography angiography (G and H)

Lisch nodules were observed on slit-lamp examination in 40 (74.1%) of the 54 eyes. Neurofibroma on the upper eyelid was noted in 1 eye (1.9%) (patient 12, left eye).

Contrast-enhanced cranial MRI was performed in 23 patients (85.2%). Hamartoma was detected in 12 patients (52.2%); non-specific hyperintense foci, venous anomaly, and ventricular dilatation were each detected in 2 patients (8.7%); and thinning of the internal carotid artery, encephalomalacia, sphenoid bone dysplasia, plexiform neurofibroma, glial tumor, Chiari malformation type I, expansile lesion in the pons, and arachnoid cyst were each detected in 1 patient (4.3%). Three patients (12.9%) had no pathological findings.

Of 14 patients (51.8%) who underwent contrast-enhanced orbital MRI, 9 (33.3%) had optic glioma (unilateral in 8 patients [57.1%] and bilateral in 1 patient [7.1%]).

The mean CMT for all eyes was 244.31±25.17 µm (range, 181-380 µm), while the mean SFCT for 47 eyes with EDI-OCT images passing through the fovea was 320.49±63.63 µm (range, 139-469 µm).

IR imaging revealed at least one choroidal nodule in 52 eyes (96.3%). One pediatric patient (3.7%) had bilateral Lisch nodules but no detectable choroidal nodule in either eye (patient 11, 11 years old). Adequate quality OCTA images were available for 43 eyes (79.6%). In 31 (72.1%) of these eyes, choroidal nodules were observed as areas of low reflectivity in the choriocapillaris layer.

Two (3.7%) of the 54 eyes included in the study had no choroidal nodules despite the presence of Lisch nodules. In contrast, 16 eyes (29.6%) had no Lisch nodules despite the presence of choroidal nodules. In the remaining 36 eyes (66.7%), both Lisch nodules and choroidal nodules were detected.

The multimodal imaging characteristics of patient 2 are shown in Figures 1 and 2, and those of patient 18 are presented in Figures 3 and 4 as examples.

Discussion

Histopathological studies have revealed that the choroidal nodules observed in NF-1 are hamartomatous in character, consisting of ovoid bodies that contain Schwann cells which proliferate in an annular structure around axons, and may also include neural crest-derived melanocytes and ganglion cells.[1,12,13]

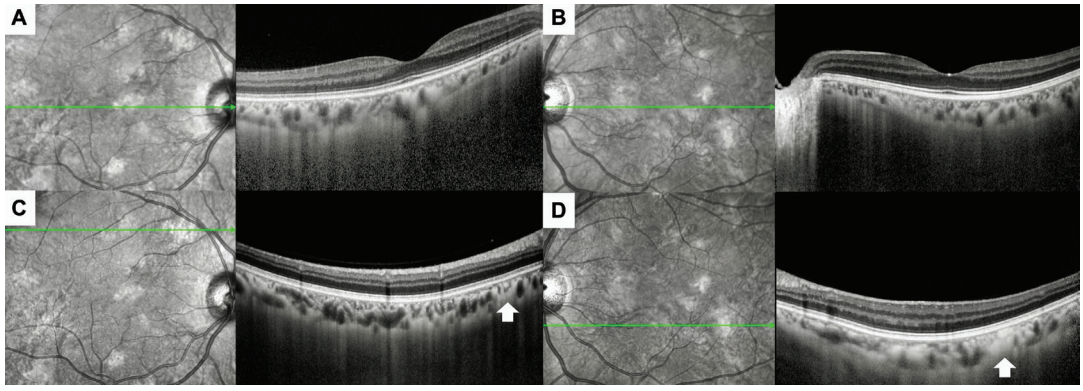

Figure 2. On enhanced depth imaging optical coherence tomography in patient 2, no pathology was detected in sections passing through the fovea (A and B), whereas sections passing through areas of high reflectivity on infrared reflectance imaging showed the surrounding large-caliber choroidal vessels with highly reflective choroidal nodules (white arrows) causing relative compression of the adjacent choroidal vascular structures (C and D)

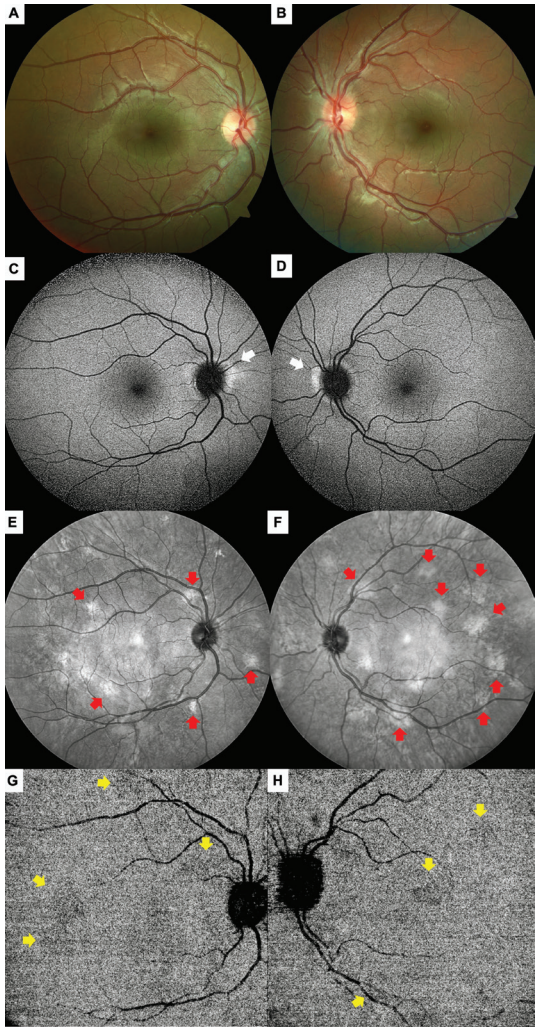

Figure 3. Patient 18 (female, 11 years old) exhibited no pathological findings in colored fundus images (A and B), while fundus autofluorescence imaging showed areas of hyperautofluorescence (white arrows) nasal to the optic disc in both eyes (C and D). Patchy, highly reflective choroidal nodules (red arrows) widespread across the posterior pole were observed on infrared reflectance imaging (E and F), and areas of flow deficit (yellow arrows) in the choriocapillaris layer were seen on optical coherence tomography angiography (G and H)

These nodules are reported to impact choroidal blood flow, causing compression and thinning of the choriocapillaris and subsequently leading to choroidal and retinal thinning.[14,15] These lesions also show structural similarities to the cutaneous neurofibromas and Lisch nodules observed in the iris.[16]

Due to the high wavelength light used, IR imaging is a suitable modality for evaluating the ocular structures that lie beyond the RPE and is useful in detecting changes at the choroidal level.[15] Although the choroidal nodules of NF-1 patients are not visible on fundoscopic examination, fundus autofluorescence imaging, or fluorescein angiography, they appear as bright, patchy areas in IR imaging and as hypocyanescent, patchy areas in the early phases of indocyanine green angiography.[8,13] In addition, the bright, patchy areas observed on IR imaging were found to be areas of high flow in the deep choroidal segment of OCTA.[17] In our study, choroidal nodules were observed in 31 (72.1%) of 43 eyes with adequate quality OCTA images, appearing as areas of flow deficit in the choriocapillaris layer. Although it is generally accepted that these nodules cannot be observed on fundoscopic examination, some authors have stated that the degree of pigmentation may vary and as a result, areas of hyperpigmentation in the fundus might be detectable in some cases.[11,13]

Studies in the literature that used IR imaging to examine choroidal nodules in NF-1 are summarized in Table 3.[8,11,13,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32]

There are publications reporting that choroidal abnormalities, which can be detected up to 100% of NF-1 patients, are much more common than cafe au lait spots (98%) and Lisch nodules (41-68%) (classically considered the most common findings of the disease) and may actually be the most common sign of NF-1.[13,33] Similar to cutaneous findings and Lisch nodules, choroidal findings are observed more frequently with older age, but they occur earlier than Lisch nodules. The prevalence of choroidal findings and Lisch nodules in pediatric cases has been reported to be 64-95% and 41-52%, respectively.[19,28]

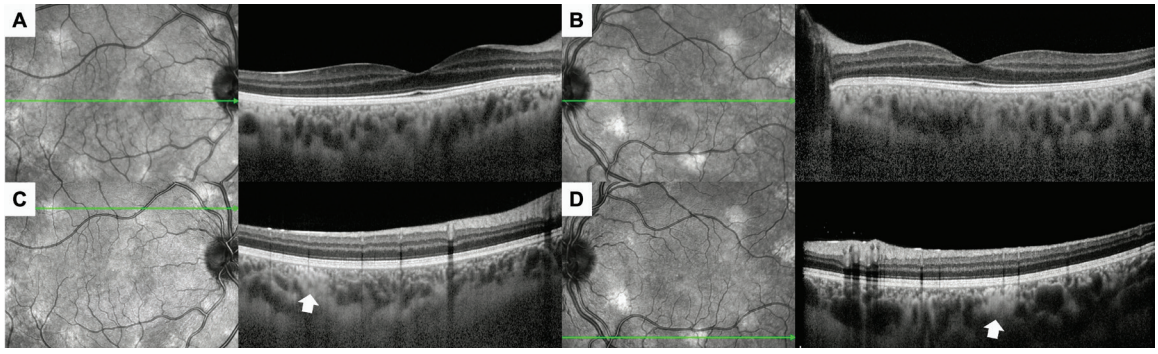

Figure 4. Enhanced depth imaging optical coherence tomography images of patient 18 showed no pathology in sections passing through the fovea (A and B), whereas in sections passing through the areas of high reflectivity on infrared reflectance imaging, choroidal nodules (white arrows) were observed as highly reflective lesions causing relative compression of the adjacent choroidal vasculature, along with the surrounding large-caliber choroidal vessels (C and D)

Table 3. Studies evaluating the presence of choroidal nodules with infrared reflectance imaging in neurofibromatosis type 1

Authors (reference)	Number of patients/eyes, n	Age (years) mean ± SD	CN presence, n (%)	Remarks
Yasunari et al.[8]	17 patients	29.2±18.0	17 (100%)	- The bright patchy areas seen on infrared fundus examination and the hypofluorescent areas corresponding to these areas on indocyanine green angiography are likely of choroidal origin. - The high frequency of these abnormalities suggests that choroidal tissue is one of the most commonly affected structures in NF-1.
Arigon et al.[11]	211 patients	32.0±14.0	61 (28.9%)	- CN have a hamartomatous character and increase in incidence with age, similar to Lisch nodules. - CN are the most common ophthalmologic finding in NF-1 patients after Lisch nodules. - Red-free imaging is the most effective method for detecting CN. - CN may appear hypopigmented or hyperpigmented on ophthalmoscopic examination and hypofluorescent or hyperfluorescent on fluorescein angiography.
Moramarco et al.[13]	249 patients	33.0±17.1	238 (95.6%)	- Hyperpigmentation can be observed on fundoscopic examination in areas corresponding to the location of CN. - These areas tend to be located at the posterior pole because the area between the vascular arcades has thick choroidal tissue and is rich in melanocytes and neural cells.
Abdolrahimzadeh et al.[18]	19 patients	42.8±14.3	17 (89.4%)	- In NF-1 patients, CN may appear as a dome or placoid shape. - These lesions lead to changes in choroidal thickness and morphology.
Vagge et al.[19]	78 patients	8.1±3.5	54 (69.2%)	- CN are very common in children with NF-1. - CN can be visualized on IR imaging as bright patchy areas and are diagnostic.
Cassiman et al.[20]	34 patients	22.0	23 (68%)	- CN are easily detected with a confocal laser scanning ophthalmoscope. - CN may vary in prevalence and number according to different genotypic subtypes of NF-1 and aid in the differential diagnosis from Legius syndrome. - Detecting CN facilitates the diagnosis, especially in young patients without the fully developed clinical picture.
Chilibeck et al.[21]	74 patients	Unspecified	56 (75.7%)*	- CN detected by IR imaging are common in NF-1 and appear at an early age. - IR imaging can aid in the diagnosis of NF-1 in young children.
Godinho et al.[22]	44 eyes	16.4±7.3	28 (63.4%)	- The presence of CN correlates with the presence of central nervous system findings in NF-1 patients.
de Rivas et al.[23]	30 patients	57.0	25 (83.3%)	- CN, which can be detected on IR imaging, are common in NF-1 patients, similar to Lisch nodules, and are even more common than Lisch nodules when high myopic eyes are excluded.
Goktas et al.[24]	19 patients	8.6±3.2	15 (78.9)	- Choroidal abnormalities are common in NF-1 patients. - Choroidal abnormalities detectable by OCT and IR imaging can be used to diagnose NF-1.

Table 3. continued

Authors (reference)	Number of patients/eyes, n	Age (years) mean ± SD	CN presence, n (%)	Remarks
Viola et al.[25]	95 patients	28.0±16.0	79 (82%)	- CN appear as bright, patchy areas on IR imaging and are common in NF-1. - IR imaging should be considered as a new diagnostic criterion in order to detect CN in NF-1 patients.
Makino et al.[26]	10 patients	20.6±13.2	9 (90%)	- Choroidal abnormalities in NF-1 patients increase with age and are correlated with the number of Lisch nodules.
Vagge et al.[27]	31 patients	22.7±13.7	24 (77.4%)	- Retinal thickness changes and CN are among the ocular symptoms described in NF-1 cases. - OCTA is an important technique in detecting the retinal and choroidal vascular flow changes that may occur early in NF-1.
Moramarco et al.[28]	160 patients	32.0±17.0	156 (97%)	- IR imaging is a non-invasive, sensitive, and reproducible in vivo imaging method that can be used to detect CN in NF-1 patients. - Choroidal changes are a diagnostic feature of NF-1.
Estrela et al.[29]	41 patients	11.8±3.3	39 (47.6%)	- Choroidal abnormalities are common in children with NF-1 and optic glioma but may not be detected in all cases. - Although choroidal abnormalities are a diagnostic criterion for NF-1, their presence and size have no impact on visual function.
Touzé et al.[30]	141 patients	8.6	97 (68.8%)	- With age, NF-1 patients show an increase in CN number and area on IR imaging.
Flores Pimentel et al.[31]	94 patients	10.3±4.2	60 (64%)	- In pediatric NF-1 patients, CN are more common than Lisch nodules, regardless of age and genetic confirmation. - Combining ophthalmological examination with IR imaging will be beneficial for early diagnosis in children.
Parrozzani et al.[32]	119 patients	8.3±4.5	72 (60.5%)	- Choroidal abnormalities can be regarded as a diagnostic criterion for the diagnosis of NF-1 in children. - The main advantage of this finding is that it aids early diagnosis, while the main drawback is that patient cooperation is required for its detection.
Ahmadova et al.	54 eyes	22.3±14.6	52 (96.3%)	- CN are more common than Lisch nodules in NF-1 patients. - The earlier appearance of CN compared to Lisch nodules may facilitate early diagnosis in these patients.

SD: Standard deviation, NF-1: Neurofibromatosis type 1, CN: Choroidal nodules, IR: Infrared reflectance

Moreover, choroidal findings without Lisch nodules have been observed in 14-37% of NF-1 cases, while Lisch nodules without choroidal findings were observed in 2.5-16%.[28,31,33] In our series, choroidal nodules were observed in 29.6% of eyes without Lisch nodules, whereas 3.7% of the eyes had only Lisch nodules.

Study Limitations

The main limitations of this study are that it was retrospective and single-centered with a relatively small number of patients. In addition, assessments that can indicate functional status, such as visual acuity and visual field, were not included in our study. However, the reason for this is that most previous publications examining choroidal nodules in NF cases have stated that these findings are asymptomatic and do not cause functional problems. Furthermore, as the OCTA images in our study were recorded for the purpose of evaluating for choroidal nodules, 12x12-mm images were obtained in order to evaluate the largest possible area. However, due to the features of the OCTA device we used, we could not obtain data on quantitative parameters such as vascular density and the foveal avascular zone with 12x12-mm images. Considering that choroidal nodules can lead to vascular alterations, especially at the choriocapillaris level, this can also be considered a limitation.

Conclusion

As NF-1 can cause ophthalmological findings, patients often present or are referred to ophthalmology clinics, both through outpatient clinic admissions and consultations by other medical disciplines. Therefore, it is important for ophthalmologists to recognize the ocular findings of NF-1. Although the presence of Lisch nodules can be evaluated by biomicroscopic examination, choroidal nodules can be observed much more frequently in these patients, as in our series, and can be easily detected using IR imaging, which is a rapid and non-invasive method. The presence of choroidal nodules before the appearance of Lisch nodules may facilitate early diagnosis in these patients.

Ethics

Ethics Committee Approval: Dokuz Eylül University Local Ethics Committee (approval number: 2023/10-01, date: 29.03.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: M.K., S.K., A.O.S., Design: M.K., E.H., Data Collection or Processing: N.A., M.K., E.H., Analysis or Interpretation: M.K., S.K., A.O.S., Literature Search: N.A., M.K., S.K., Writing: N.A., M.K., A.O.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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