Int Ophthalmol (2019) 39:2545–2552
https://doi.org/10.1007/s10792-019-01102-y

ORIGINAL PAPER

Multimodal imaging including optical coherence tomography angiography in patients with type B Niemann–Pick disease

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Received: 27 November 2018 / Accepted: 1 April 2019 / Published online: 11 April 2019

Abstract

Purpose To evaluate accumulation patterns of deposits in retinal layers of type B Niemann–Pick patients by multimodal imaging.

Methods Seven patients with type B Niemann–Pick disease were included in this study. All participants underwent a complete ophthalmologic evaluation, high-resolution digital colour imaging, spectral-domain optical coherence tomography, blue light fundus autofluorescence and optical coherence tomography angiography (OCTA).

Results We demonstrated different accumulation patterns in the retinal ganglion cell layer, the retinal nerve fibre layer and the subfoveolar region by multimodal imaging. Local retinal capillary nonflow areas in the superficial plexus, increased vascular tortuosity and deformed foveal avascular areas were shown in OCTA scans.

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Conclusion Multimodal imaging including OCTA is a useful technique for the identification of different types of accumulation patterns, diagnosis and follow-up of type B Niemann–Pick patients.

Keywords Niemann–Pick · Multimodal imaging · Optical coherence tomography · Optical coherence tomography angiography

Introduction

Niemann–Pick disease (NPD) is a rare, autosomal recessive, lysosomal storage disease associated with intracellular deposition of sphingomyelin in different tissues [1]. NPD types A and B are a result of a deficiency of the lysosomal enzyme acid sphingomyelinase (ASM) activity [2]. Type A is the most common form, appearing in early childhood with central nervous system (CNS) involvement, and patients rarely survive beyond two years of age. Type B, without CNS involvement, is a milder form with hepatosplenomegaly, hyperlipidaemia, thrombocytopenia and diffuse pulmonary infiltrates that is generally diagnosed in adulthood and has a better prognosis [3]. Type C is a subacute form that causes lysosomal accumulation of cholesterol in spleen, liver, lung and CNS and has a highly variable age of onset [1].

The traditional retinal finding in NPD of a cherry-red spot was first described by Cogan in 1982 [4]. There are limited reports including optical coherence tomography (OCT) findings in patients with NPD. In this report, we describe multimodal imaging using OCT angiography (OCTA; AngioVue OCT angiography system, Optovue, Inc.), spectral-domain OCT (SD-OCT) and blue light fundus autofluorescence (B-FAF) in seven patients with type B NPD.

OCTA is a non-invasive technique that provides high-resolution capillary details including superficial, intermediate and deep capillary plexuses separately [5]. It is a practical technique which does not require the injection of exogenous dyes and provides detailed data.

Materials and methods

This retrospective case series study was carried out between December 2017 and May 2018 at the Okmeydani Training and Research Hospital in Istanbul, Turkey. Informed consent was obtained from all participants and the study was carried out in agreement with the Declaration of Helsinki for research involving human subjects. Patients with type B NPD who were being followed at the University of Cerrahpasa Medical School Paediatric clinic were referred to the Okmeydani Training and Research Hospital Retina Department.

Diagnosis was confirmed in all cases by deficient ASM enzyme activity, and all participants underwent a complete ophthalmic evaluation including slit-lamp biomicroscopy, dilated fundus examination, Goldmann applanation tonometry and Snellen decimal visual acuity testing. High-resolution digital colour imaging (VISUCAM 524, Carl Zeiss Meditec), SD-OCT (Spectralis HRA + OCT, Heidelberg Engineering Inc, Heidelberg, Germany), B-FAF and OCTA were performed for all patients. Forty-nine sections composed of 40 averaged SD-OCT scans were obtained within a $30° \times 20°$ rectangle centred on the fovea. The macular vascular density (VD) with OCTA was measured at two different levels of segmentation, the superficial and the deep retinal vascular plexus, with a 6×6 mm macula scan. The superficial capillary plexus slab was taken from the internal limiting membrane to the inner plexiform layer, and the deep capillary plexus slab was taken from the inner plexiform layer to the outer plexiform layer.

Results

Seven patients (four males and three female) diagnosed with type B NPD were enrolled in this study. Table 1 shows the demographic, ocular and clinical characteristics of the subjects. Patient ages ranged from 10 to 22 years (mean 13.7 years, median 13 years). Intraocular pressures of all the patients were between 14 and 19 mm Hg. Both eyes were affected in all the patients.

While patients 1 and 6 had only retinal pigment alterations, others had increased tortuosity of retinal vessels, circular granular deposits in the parafoveal region and cherry-red spot appearance on dilated

Table 1 Demographic, ocular and clinical characteristics in patients presenting with type B Niemann–Pick disease

Patient	Sex	Age	BCVA (Snellen)	Systemic involvement	Consanguineous marriage	Retinal findings
1	Male	12	1.0/1.0	Hepatosplenomegaly	+	Retina pigment alterations
2	Female	15	1.0/1.0	Hepatosplenomegaly	+	Cherry-red spot, increased tortuosity of retinal vessels
3	Male	13	1.0/1.0	Hepatosplenomegaly	−	Cherry-red spot, increased tortuosity of retinal vessels
4	Male	13	0.8/0.7	Hepatosplenomegaly Thrombocytopenia	+	Cherry-red spot, increased tortuosity of retinal vessels
5	Male	10	1.0/1.0	Hepatosplenomegaly	+	Cherry-red spot, increased tortuosity of retinal vessels
6	Female	11	1.0/1.0	Hepatosplenomegaly	+	Retina pigment alterations
7	Female	22	1.0/1.0	Hepatosplenomegaly	+	Cherry-red spot, increased tortuosity of retinal vessels

BCVA best-corrected visual acuity

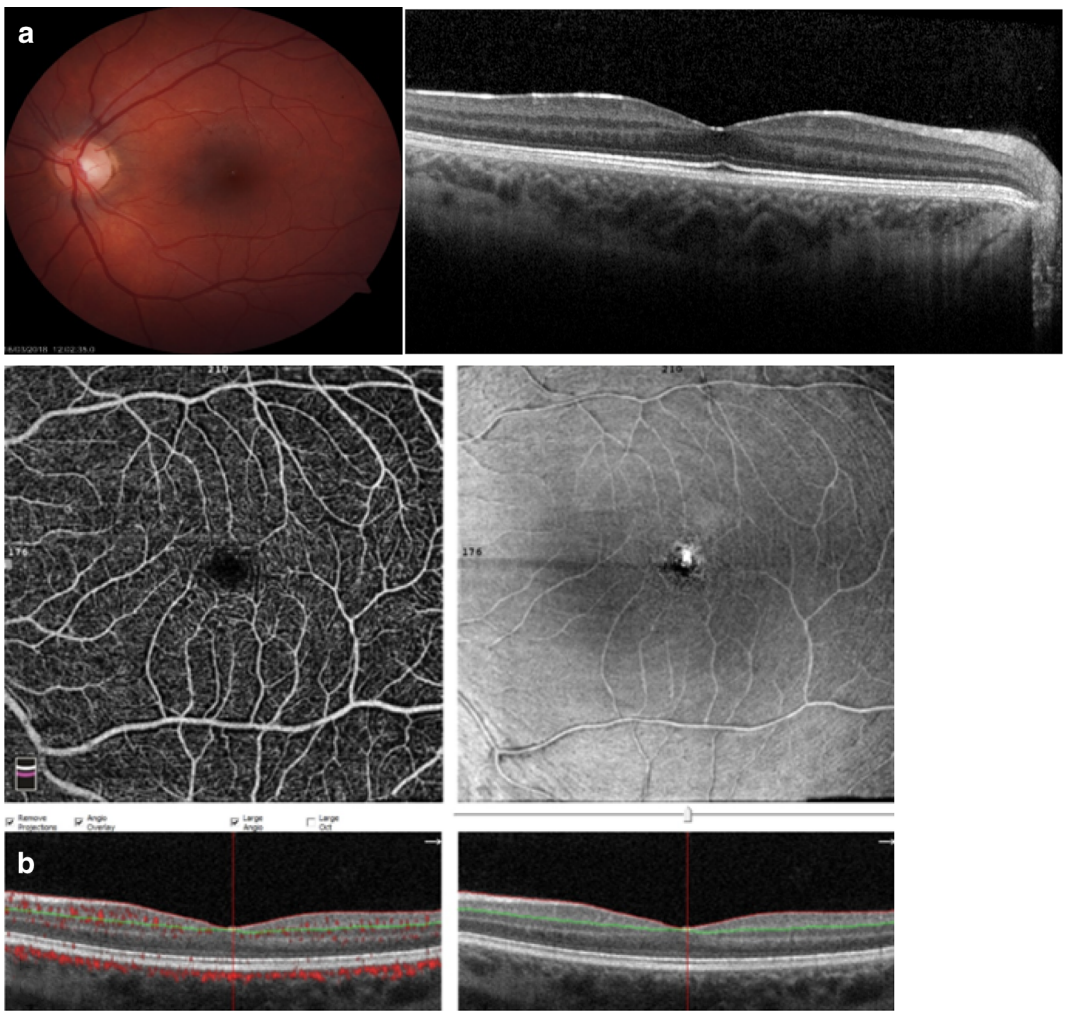


Fig. 1 Fundus photograph showing retinal pigmentary changes in a patient, 12 years of age (patient 1), with type B Niemann–Pick disease. While SD-OCT (**a**) is completely normal, en-face OCTA (**b**) scan shows hyper-reflective tissue in the foveal region

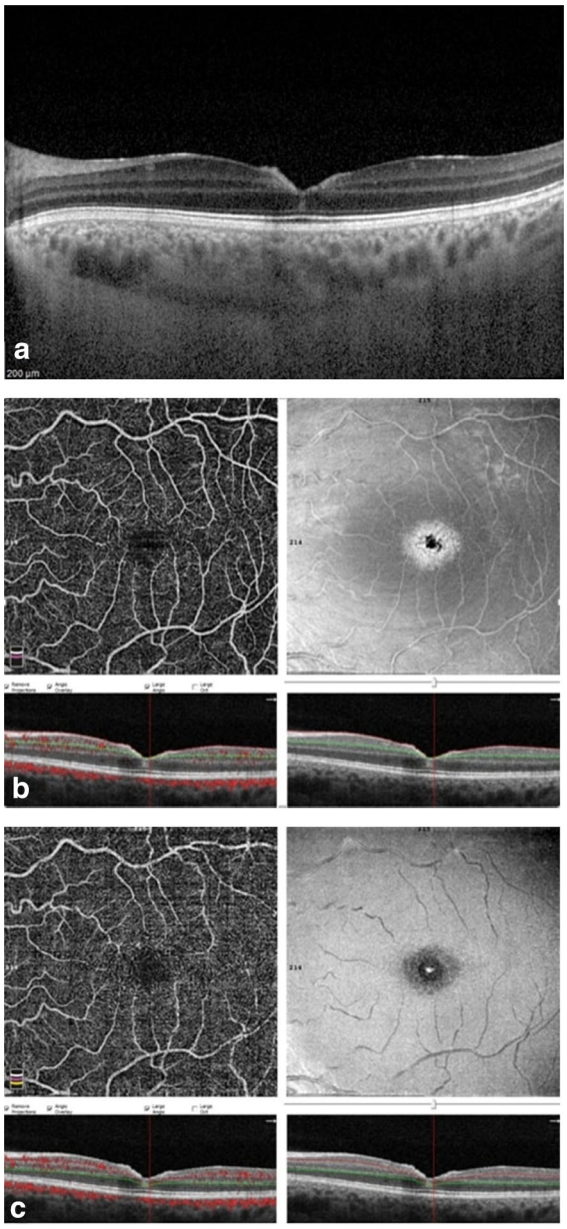


Fig. 2 SD-OCT (**a**) and OCTA en-face (**b**, **c**) images of patient 4, 13 years of age, with type B Niemann–Pick disease. SD-OCT image shows hyper-reflective band in the retinal ganglion cell layer at the shoulders of the foveal depression extending to external limiting membrane vertically at the foveal centre. Deposits with irregular surface are seen protruding from the retinal surface to the vitreous. OCTA demonstrates increased perimacular vascular tortuosity. En-face OCTA scans show ring-shaped hyper-reflectivity (b) at the shoulders of the foveal depression due to accumulation of materials in the retinal ganglion cell layer and dot-shaped hyper-reflectivity (c) due to possible accumulation of material in Müller cells

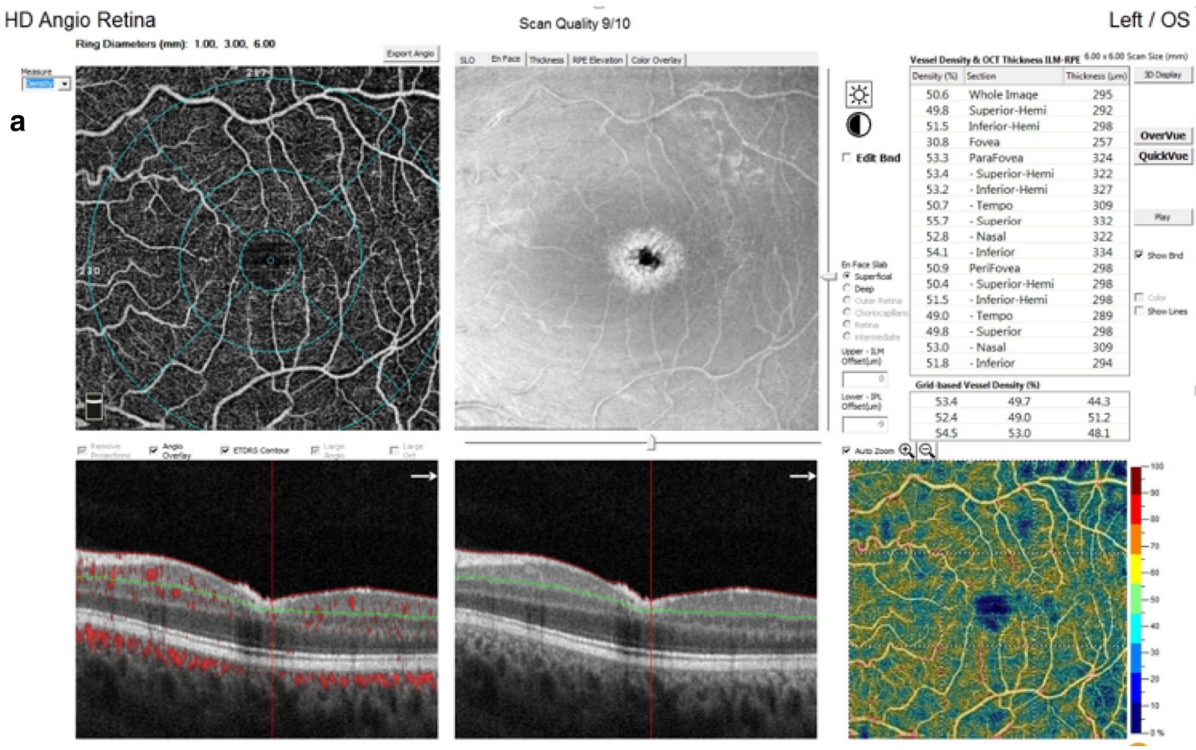
Fig. 3 Maps of the vessel density and retinal thickness in type B Niemann–Pick disease. Optovue software calculates vessel density in whole macular area, fovea and perifovea. Local retinal capillary nonflow areas (blue areas) in superficial plexus, increased perimacular vascular tortuosity and deformed foveal avascular areas were demonstrated in OCTA scans of patient 4 (**a**) and patient 5 (**b**) ▶

fundus examination and high-resolution digital colour images. Except for patients 1 and 6, all other patients had hypoautofluorescence at the foveal accumulation region.

When we considered both the SD-OCT and OCTA scans together, we identified three different patterns. In patients 1 and 6, while the SD-OCT was completely normal, there was hyper-reflectivity with irregular margins in the foveal region in the en-face OCTA scans (Fig. 1). In patients 2, 3, 4 and 5, SD-OCT images showed hyper-reflective band in the retinal ganglion cell layer at the shoulders of the foveal depression, extending to the external limiting membrane (ELM) vertically at the foveal centre (Fig. 2a). En-face OCTA scans revealed ring-shaped hyper-reflectivity (the appearance of accumulation surrounding foveal avascular zone) (Fig. 2b) at the shoulders of the foveal depression due to accumulation of materials in the retinal ganglion cell layer and dot-shaped hyper-reflectivity (Fig. 2c) due to possible accumulation of materials in Müller cells. Local retinal capillary nonflow areas in the superficial plexus, increased vascular tortuosity and deformed foveal avascular areas were demonstrated in OCTA scans of patients 4 and 5 (Fig. 3). In patient 7, SD-OCT revealed three different accumulation patterns. The first was a hyper-reflective band in the retinal nerve fibre layer at the outside of the fovea (parafoveal region), the second was a hyper-reflective band in the ganglion cell layer at the shoulder of the foveal depression and the third was hyper-reflective dots under the foveal centre (Fig. 4c).

Discussion

There are histopathological and microscopic studies showing that lipid accumulation occurs in the ganglion cell layer in type A and type B NPD [6, 7]. In a study of patients with type A NPD, light and electron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Density (%) Section Thickness (µm)
50.6 Whole Image 295
49.8 Superior-Hemi 292
51.5 Inferior-Hemi 298
30.8 Fovea 257
53.3 ParaFovea 324
53.4 - Superior-Hemi 322
53.2 - Inferior-Hemi 327
50.7 - Tempo 309
55.7 - Superior 332
52.8 - Nasal 322
54.1 - Inferior 334
50.9 PeriFovea 298
50.4 - Superior-Hemi 298
51.5 - Inferior-Hemi 298
49.0 - Tempo 289
49.8 - Superior 298
53.0 - Nasal 309
51.8 - Inferior 294
Grid-based Vessel Density (%)
53.4 49.7 44.3
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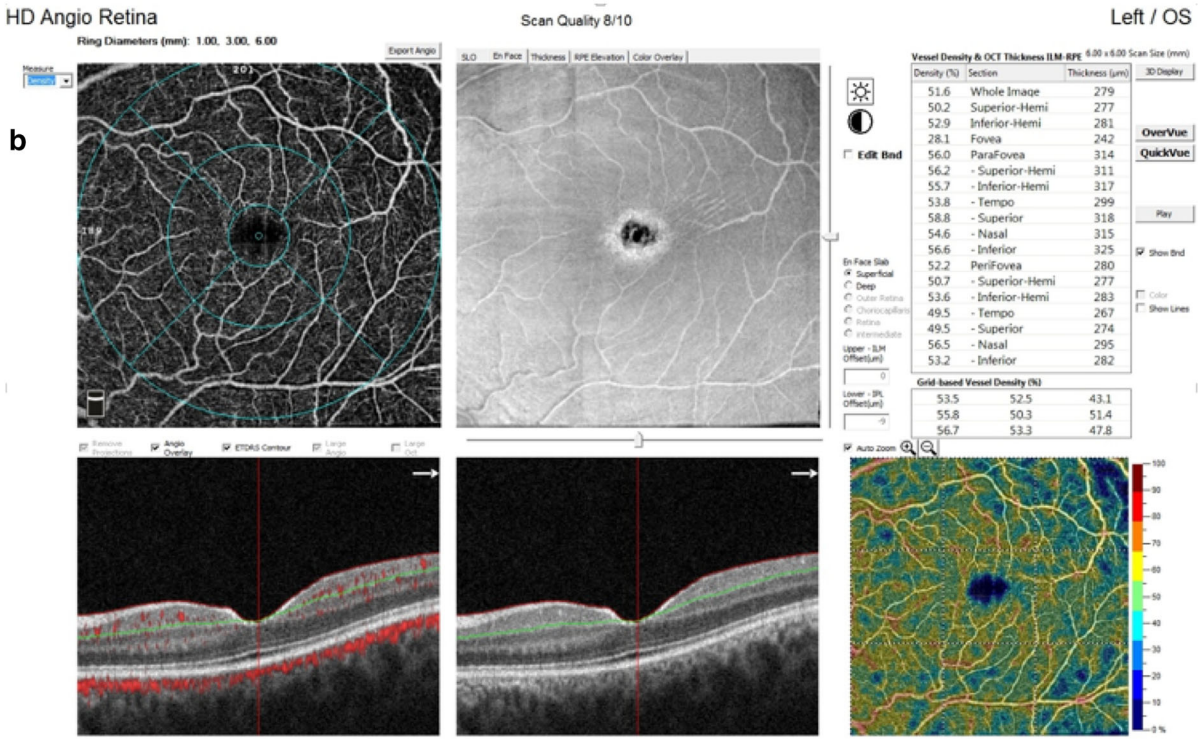
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51.6 Whole Image 279
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52.9 Inferior-Hemi 281
28.1 Fovea 242
56.0 ParaFovea 314
56.2 - Superior-Hemi 311
55.7 - Inferior-Hemi 317
53.8 - Tempo 299
58.8 - Superior 318
54.6 - Nasal 315
56.6 - Inferior 325
52.2 PeriFovea 280
50.7 - Superior-Hemi 277
53.6 - Inferior-Hemi 283
49.5 - Tempo 267
49.5 - Superior 274
56.5 - Nasal 295
53.2 - Inferior 282
Grid-based Vessel Density (%)
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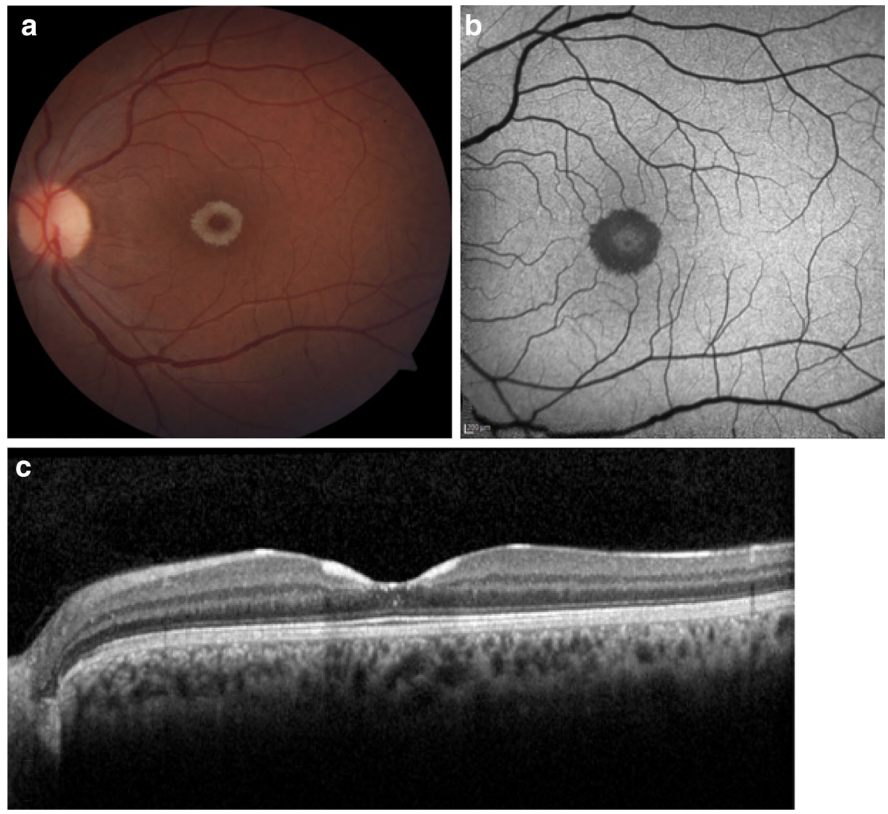

Fig. 4 Fundus photograph (**a**), B-FAF (**b**) and SD-OCT (**c**) images of patient 7, 22 years of age, with type B Niemann–Pick disease. Fundus photography shows macular halo with red centre (cherry-red spot), and B-FAF demonstrates hypoautofluorescence at the foveal region. SD-OCT shows three different accumulation patterns. The first is visible in the retinal nerve fibre layer outside the fovea (parafoveal region), the second in the ganglion cell layer at the shoulder of the foveal depression and the third in granular deposits under the fovea

microscopy of the autopsy material showed accumulation in the retinal ganglion and pigment epithelial cells [7].

In the literature, there are a few studies of NPD using SD-OCT. Rudich et al. [8] detected hyper-reflectivity in the retinal ganglion cell layer corresponding to depositions located in the parafoveal inner retina. Our study is the first report showing that deposits can accumulate vertically between the internal limiting membrane and the ELM under the foveal centre. We think this vertical hyper-reflective band may be related to accumulation of the deposits in Müller cells. Under the fovea centralis are Müller cells and cone photoreceptors packed at their highest density, an area known as the central bouquet of cones [9]. In a three-dimensional microscopic study, Alexander et al. [10] showed the presence of extremely large Müller cells in the central foveola of monkeys and humans. In an animal study with Niemann–Pick type C mutant mice, Yan et al. [11] indicated that electron-dense inclusions accumulated in ganglion cells, bipolar cells, Müller cells and in the optic nerve. This particular configuration under the fovea centralis and the high metabolic activity in this area may explain the accumulation of sphingomyelin in Müller cells. These findings suggest that subfoveolar sphingomyelin deposits may accumulate in Müller cells.

Fundus fluorescein angiography may not always be performed in children due to the difficulty of the study technique. OCTA is a novel technique which does not require dye injection, and it enables advanced retinal capillary imaging, measurement of capillary tortuosity and vasodilation and quantification of retinal microvascular attributes such as vessel density and foveolar avascular zone area. High-quality images make it easy to detect early signs of diseases [12, 13].

Our report is the first study to evaluate the OCTA findings of type B NPD. We demonstrate local retinal capillary nonflow areas in the superficial plexus, increased vascular tortuosity and deformed foveal avascular areas in OCTA scans (patients 4 and 5). With the increasing clinical use of OCTA, new approaches are being reported in the literature in order to make an early diagnosis and study the pathophysiology and progression of various retinal

diseases. In a study on patients with Best vitelliform dystrophy, Wang et al. [14] showed a significant decrease in superficial flow density. Carlo et al. [15] indicated vascular density loss and foveolar avascular zone enlargement with OCTA in patients with no clinically diabetic retinopathy. Similar to these reports, type B NPD patients with more severe findings may have a higher risk of capillary nonflow areas and deformed foveolar avascular areas, which is consistent with the possible presence of vasculopathy in the pathogenesis of the disease. In a histopathological study of patients with type B NPD, it was shown that sphingomyelin may accumulate in vascular endothelial cells [16].

In patients 1 and 6, no accumulation was observed in SD-OCT scans, fundus examination or B-FAF, but there was hyper-reflectivity in en-face OCTA scans. This finding suggests that a lack of evidence of deposits in SD-OCT scans does not mean that there is no accumulation between the retinal layers. We propose that en-face OCTA images are needed to confirm whether there is accumulation or not.

When we examined all the images, we realized that there are different accumulation patterns and reflectivities. In patient 7, granular subfoveal deposits were observed in SD-OCT scans. More hyper-reflective material was detected in this case than in the others. In patients 4 and 5, deposits with irregular surfaces were seen protruding from the retinal surface to the vitreous. Apart from patient 4, all the patients' best-corrected visual acuity was 10/10. In patient 4, accumulation material was thicker in the foveal region and it can be associated with the decrease in visual acuity. There are few studies in the literature about NPD eye findings, and sufficient data are not available. Fabry disease is another inherited lysosomal storage disorder involving glycolipid metabolism. In a study regarding the relationship between Fabry disease and retinal vessel tortuosity, Roman et al. [17] found a correlation between retinal vessel tortuosity and systemic severity. In patients 4 and 5, more prominent retinal vessel tortuosity and local retinal capillary nonflow areas may be associated with a more severe course of the disease.

The limitations of this study are the small number of patients and the lack of age-matched control groups. To understand which factors affect different accumulation patterns, we need more histological and microscopic studies. Although we consider that deposits may accumulate in Müller cells under the fovea centralis, animal experiments are needed to accurately show in which cells they accumulate. The relationship between enzyme levels and disease severity was also not assessed due to the low number of cases. Nevertheless, our study shows that multimodal imaging techniques, especially en-face OCTA, may play an important role in diagnosis and follow-up.

Compliance with ethical standards

Conflict of interest None of the authors has any financial or conflicting interests to disclose.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

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