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CASE REPORT

Macula halo syndrome

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Abstract
Introduction Niemann–Pick disease (NPD) is a hereditary lysosomal storage disorder in which mutations in the sphingomyelin phosphodiesterase gene leads to partial or complete deficiency of the sphingomyelinase enzyme. Niemann–Pick Type B is the intermediate form associated with hepatosplenomegaly, foam cells in the bone marrow, hyperlipidemia and diffuse pulmonary infiltrates, which is generally diagnosed in late adolescence. Central nervous system is not affected, and some cases may display macular halo.
Case A 45-year-old female seen in ophthalmology clinic for the examination of the eyes. Extraocular motility was normal bilaterally, and the visual acuity was 20/25 for both eyes. Biomicroscopic examination revealed faint corneal haze bilaterally, Circular pale granular depositions were detected in the parafoveal retina on both eyes. Optical coherence tomography (OCT) revealed thin hyperreflective band corresponding to depositions located in the parafoveolar inner retina. Microperimeter showed slight depression in retinal sensitivity, which was more pronounced particularly on perifovea rather than parafovea.
Conclusions Challenge to identify the NPD subtype of this case is associated with phenotypic characteristics on a wider spectrum that overlap the currently described subtypes.

Keywords Macula halo · Niemann–Pick · Microperimeter

Niemann–Pick disease (NPD) is a hereditary lysosomal storage disorder in which mutations in the sphingomyelin phosphodiesterase gene leads to partial or complete deficiency of the sphingomyelinase enzyme, resulting in sphingomyelin accumulation in tissues, leading to cell death and multisystem failure [1]. There are four major types of NPD. The most severe form is type A, characterized by central nervous system involvement and death around 5 years of age. Ophthalmologic hallmark of type A disorder is the cherry-red appearance in the macula. Sphingomyelinase activity is almost undetectable [2] Type B is the intermediate form associated with hepatosplenomegaly, foam cells in the bone marrow,

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hyperlipidemia and diffuse pulmonary infiltrates, which is generally diagnosed in late adolescence. Central nervous system is not affected, and some cases may display macular halo. Sphingomyelinase activity is about 20% lower compared to normal population [2]. Type C is the subacute form in which the subjects show signs of neurodegeneration after 1 year of age and deteriorate rapidly within a few years [2]. NPD type D closely resembles type C disorder clinically; there is sphingomyelin accumulation in the tissues, but the sphingomyelinase activity is normal. Crocker additionally proposed type E and F disorders, but a consensus has not been reached regarding the criteria for these variants [2]. Table 1 summarizes subtypes of Niemann–Pick disease and relevant ocular and general symptoms.

Macula halo syndrome was first proposed by Cogan in 1983 and defined as a finding in the macula characterized by bilateral, symmetric, pallid circular and granular accumulations [3]. Cogan considered the finding to be a possible milder form of cherry-red appearance and a variant of NPD type B [3].

In this report, we present a case with bilateral macula halo with hepatosplenomegaly, pulmonary and bone marrow involvement and sparing of the central nervous system who is considered to be intermediate type (IT) of NPD with microperimetric assessment first time.

Case

A 45-year-old female seen in the internal medicine outpatient clinic for the chief complaints of abdominal distention and fatigue was referred to the

Table 1 Niemann–Pick disease and relevant ocular and general symptoms

Subtypes of Niemann–Pick	Ocular symptoms	General symptoms
Niemann–Pick type A	Corneal opacification	Generalized hypotonia
	Brown discoloration of the anterior lens capsule	Central nervous system involvement hepatosplenomegaly
	Retinal opacification with a macular cherry-red spot	
Niemann–Pick type B	Macular halos and cherry-red maculae	Bone marrow foam cells
		Hyperlipidemia diffuse pulmonary infiltrates thrombocytopenia
Niemann–Pick type C	Optic nerve pallor	Accumulation of glycosphingolipids in the nervous system
	Perimacular gray discoloration	Supranuclear vertical gaze palsy
		Ataxia
		Developmental regression

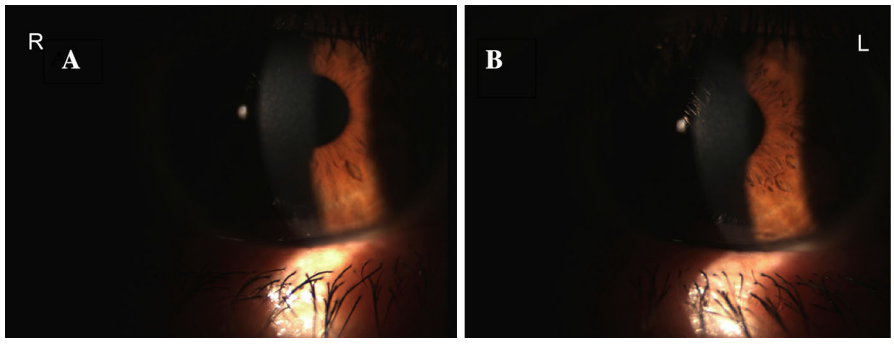
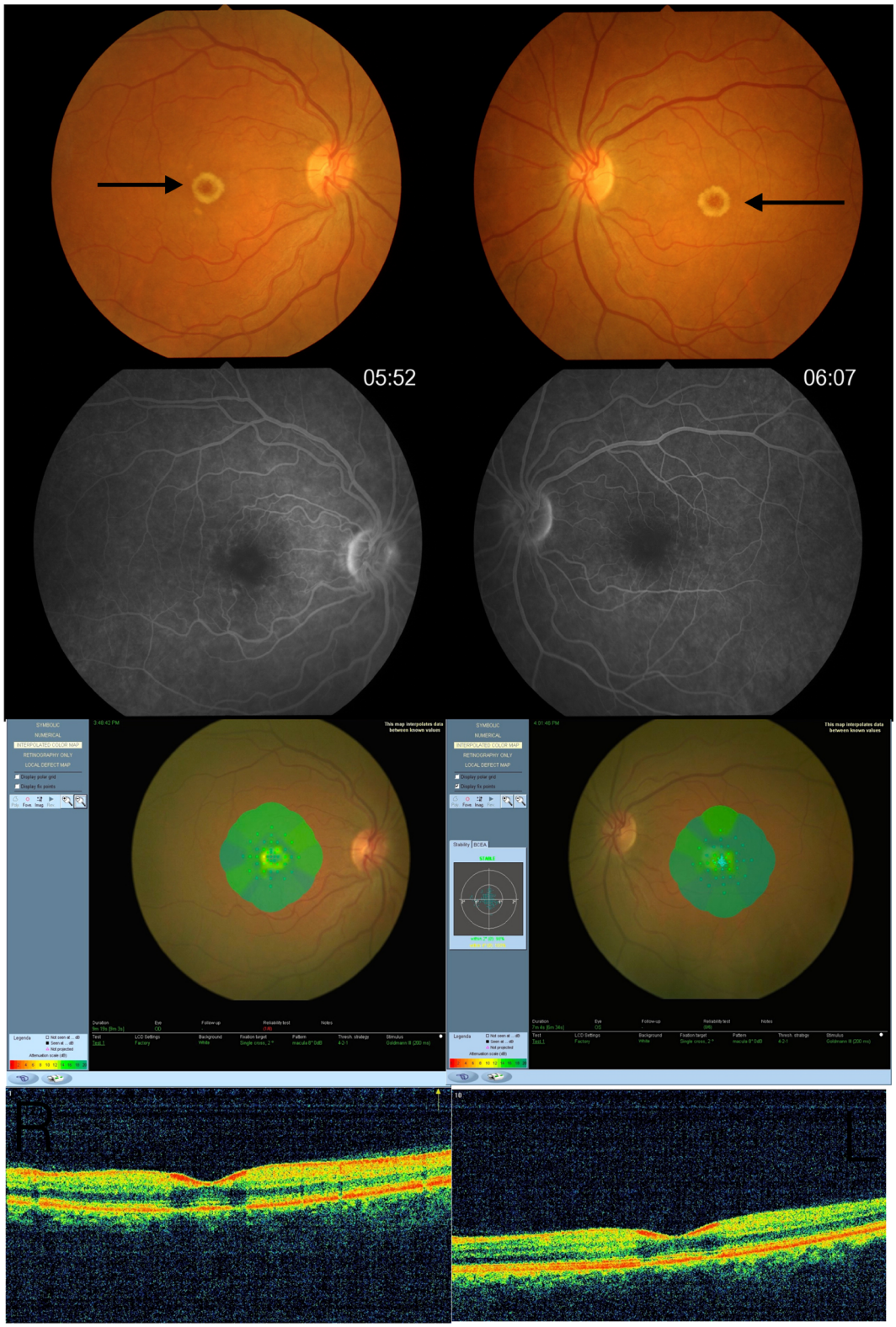


Fig. 1 Bilateral corneal haze, **a** right eye **b** left eye

Fig. 2 Right eye and left eye macula halo (black arrow) and bilateral normal fundus fluorescein angiography. Right eye and left eye microperimeter test showed slight depression in retinal sensitivity. Bilateral optical coherence tomography revealed thin hyperreflective band in the parafoveolar inner retina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endocrinology clinic with suspected storage disorder after the detection of hepatosplenomegaly and anemia. In the physical examination, blood pressure was 110/70 mmHg, heart rate was 76 beats per minute and the respiratory rate was 22 per minute. Liver was palpated 10 cm and the spleen 8 cm below the costal margin. No other pathologic finding was detected in the physical examination including the neurologic assessment. Bilateral reticular interstitial image was observed on the chest X-ray. Complete blood count revealed microcytic hypochromic anemia with hemoglobin at 10.8 g/dL, mean corpuscular volume at 77 fL. Biochemistry panel results were within normal limits. The patient was diagnosed with NPD after typical foamy histiocytes, known as Niemann–Pick cells, were observed in the bone marrow biopsy. The sphingomyelinase enzyme activity, checked after the bone marrow biopsy findings, was within normal limits.

The subject was referred to the ophthalmology clinic for the examination of the eyes. Extraocular motility was normal bilaterally, and the visual acuity was 20/25 for both eyes. Biomicroscopic examination revealed faint corneal haze bilaterally (Fig. 1); lens, vitreous and intraocular pressure were normal on both eyes. Circular pale granular depositions were detected in the parafoveal retina on both eyes. Optical coherence tomography (OCT) revealed thin hyperreflective band corresponding to depositions located in the parafoveolar inner retina (Fig. 2). Retinal and choroidal vascular pattern was normal on fundus fluorescein angiography (FA). However, microperimeter showed slight depression in retinal sensitivity, which was more pronounced particularly on perifovea rather than parafovea (Fig. 2).

Although the enzyme activity was normal, the retinal findings were consistent with the macula halo syndrome defined by Cogan. Change in visual acuity from 20/25 to 20/30 was also detected in the ophthalmologic examination performed 3 years later. In addition, the patient was referred to another tertiary referral hospital for electrophysiological evaluation. Accordingly, full field flash ERGs amplitude was prominently decreased in both eyes apart from normal a, b wave latencies. Flash VEPs, however, revealed both slightly prolonged latencies and decreased amplitude in either eyes in which latencies recovered under bilateral testing. No ophthalmologic pathology was detected in the examination of the 24-year-old daughter of the subject.

Discussion

Ocular findings in NPD type A display a wide spectrum ranging from corneal opacification to brown pigmentation in the anterior lens capsule and cherry-red appearance in the macula [4]. On the other hand, retinal findings including macular halo and cherry-red appearance are more prominent in type B disorder [5–7]. Ocular findings in NPD type C may include supranuclear vertical gaze palsy, optic nerve pallor and perimacular gray discoloration [1].

In NPD, disease activity is related to the rate and amount of sphingomyelin accumulation in the tissue [8]. Bilateral parafoveal circular granular accumulation in the presence of normal retinal function, hepatomegaly and foam cells in the bone marrow is considered to be macula halo syndrome which generally accompanies NPD type B. Moreover, cherry-red appearance in the macula develops due to the intracellular accumulation of undegradable chemicals in various metabolic disorders including Tay–Sachs and NPD type A. Circular accumulation in the macula is considered to be a milder form of cherry-red appearance [2]. Spectral domain optical coherence tomography (SD-OCT) studies detected hyperreflective focal thicknesses in the ganglion cell layer in macula halo syndrome which does not involve the foveola [9].

Histopathologic and microscopic studies have shown the lipid accumulation to occur mainly in the retinal ganglion cells in NPD type B [10]. Robb and Kuwabara [11] detected membranous cytoplasmic bodies in lamellar formation in the retinal ganglion and pigment epithelial cells in the autopsy material of a 2.5-year-old subject with NPD type A.

As in visual field assessments, any opacities through optical media may affect microperimetric scores. Of note, reduction in retinal sensitivity is more pronounced particularly on perifovea rather than parafovea, wherein depositions are located. Case presented in this report has mild-to-moderate decreased visual acuity that we attribute this both to corneal opacity and to retinal involvement along with slight reduction in retinal sensitivity as documented by microperimetry. Sphingomyelinase enzyme activity was found to be normal for this case, consistent with

the description for NPD type B. Other options in the differential diagnosis of corneal haze have been eliminated, and the observed corneal involvement is considered to be reminiscent of the ocular findings in NPD type A, even though cornea is spared as a rule in NPD type B.

Slight deterioration in flash VEPs and prominent decrease in amplitudes in flash ERGs confirm decrease in visual acuity and microperimetric scores, which suggest involvement of retina and possibly optic visual pathway in this case. Reduced ERG responses and abnormal VEPs have been previously reported in NPD type C mice models [12, 13]. Moreover, a recent study executed with acid sphingomyelinase knockout mice as an experimental model for NPD types A and B revealed significant age-dependent reduction in ERG amplitudes, when compared to control animals [14]. Therefore, outcomes of ERG, VEP tests may not be unique for any NPD subtypes.

Challenge to identify the NPD subtype of this case is associated with phenotypic characteristics on a wider spectrum that overlap the currently described subtypes. Pavlu-Pereifnara et al. [15] reported wide phenotypic variations in NPD types A and B in a series of 25 Czech and Slovakian subjects. Only 9 of the 25 subjects, 5 diagnosed as rapidly progressive neurovisceral infantile type A and 4 as slowly progressive visceral type B, could be categorized according to the historical classification system. The remaining 16 NPD subjects (64%) were grouped as the IT variant which represent cases who fail to be classified with the current system. Therefore, it is most likely that the case presented in this report may be an IT variant.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with 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.

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