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Phenotypic variant of CLN3 mutation

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ABSTRACT

Purpose: To report a case of bilateral chorioretinal scarring due to CLN3 heterozygous deletion in an asymptomatic patient.

Observations: A 63 year-old patient with a history of well-controlled diabetes presented as a referral for diabetic retinopathy. He was asymptomatic with 20/20 visual acuity in both eyes. Exam revealed bilateral multifocal chorioretinal scarring left worse than right, sparing the fovea. He was unable to provide a family history due to adoption, and his remaining medical history and review of systems were noncontributory. Inflammatory and infectious workup was negative; however, genetic testing revealed heterozygous deletion of CLN3 exons 8 and 9. His disease has been nonprogressive at all follow-up appointments.

Conclusions and importance: Mutations of CLN3 can present with retina-specific findings including bull's-eye maculopathy and electroretinogram (ERG) deficits; to our knowledge this patient's presentation is unique among those with CLN3 mutations.

1. Introduction

Inherited retinal diseases (IRDs) are a group of disorders with considerable variability of both genotype and phenotype. Widespread availability of genetic testing in patients suspected of IRDs has allowed for an increasing library of genotype-phenotype connections. Here, we present a case of a patient with a heterozygous CLN3 deletion mutation with a phenotype hitherto undescribed in the literature. While patients with CLN3 mutations can present with various ocular-specific abnormalities, including bull's-eye maculopathy, rod-cone degeneration, and optic disc pallor, to our knowledge no patient has presented asymptomatically with the posterior pole changes seen here.

2. Case report

A 63 year-old white man presented to our clinic as a referral for possible diabetic retinopathy. He had no vision complaints; additionally, he denied any past ocular history, including history of laser treatments, eye surgeries, or intravitreal injections. He was adopted at birth and did not have contact with his eight siblings that lived in Canada. His past medical history was notable for diabetes with a hemoglobin A1C of 6.5 (insulin-dependent), and a distant history of stroke and quintuple bypass surgery. His medications included Lantus insulin, empagliflozin, metoprolol, losartan, low-dose 81 mg aspirin, allopurinol, sertraline, and rosuvastatin. He denied any neurological issues.

His visual acuity was $20/20^{-1}$ without correction in both eyes, with normal intraocular pressures and pupil exam. He had mild nuclear sclerosis in both eyes. His funduscopic exam revealed numerous pigmented chorioretinal scars in the posterior pole of both eyes, left greater than right (Fig. 1a). These tracked into the macula in the left eye but spared the fovea (Fig. 2). Fundus autofluorescence highlighted the chorioretinal scarring as discrete patches of hypofluorescence, some with hyperfluorescent edges (Fig. 1b). Fluorescein angiography showed bilateral coalescent patches of hypofluorescence surrounded by early staining followed by late leakage in the posterior pole, sparing the fovea, along with rare peripheral punctate hyperfluorescence (Fig. 3). Full-

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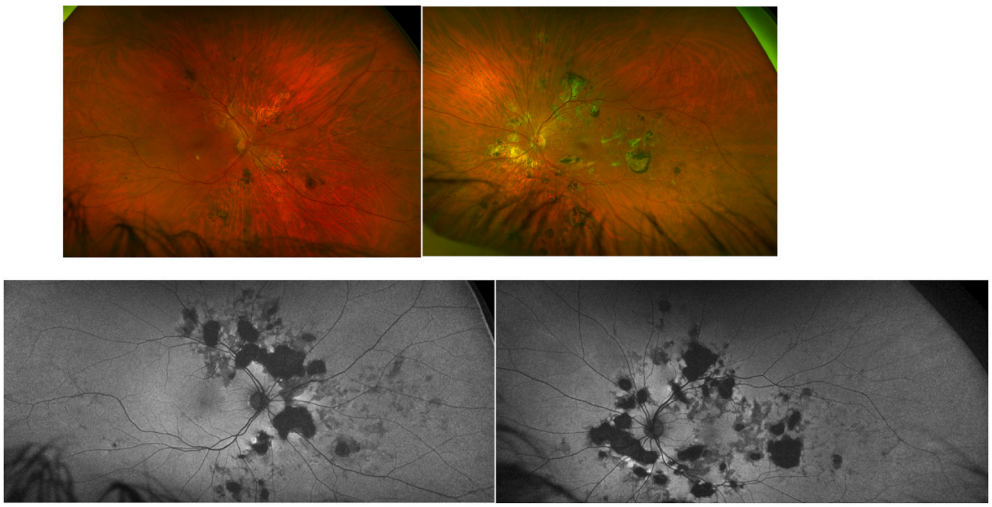

Fig. 1. Widefield fundus photography (a) and autofluorescence (b) of both eyes.

field electroretinography (ffERG) was normal without evidence of rod or cone dysfunction in either eye. After discussion with the patient, we obtained further bloodwork. Treponemal IgG and IgM, rapid plasma reagin (RPR), and quantiferon gold tuberculosis testing were negative. Finally, genetic testing revealed a heterozygous CLN3 deletion of exons 8 and 9. The patient has since remained stable and asymptomatic on all follow-up appointments.

3. Discussion

CLN3 belongs to a family of transmembrane proteins involved in lysosomal function. A recent study demonstrated that in the eye, CLN3 localizes to the junction of the retinal pigment epithelium (RPE) microvilli and is involved in photoreceptor outer segment phagocytosis.[1] Homozygous mutations in the gene can produce juvenile neuronal ceroid lipofuscinosis (JNCL; Batten Disease), characterized by early-onset vision loss and behavioral and cognitive dysfunction (between four and ten years old), eventually leading to motor decline and seizures in early adolescence and death in the patients' twenties or thirties.[2] Ninety-six percent of patients with JNCL possess a founder mutation of 1.02 kb deleting exons 7 and 8 (74% homozygous and 22% heterozygous), though it is unclear whether this mutated protein is expressed or degraded.[3,4] These exons map within the second of four luminal loops of the protein. Interestingly, many compound heterozygous mutations of this disease map within the same loop, suggesting criticality of this domain to the structure and function of the protein.[5] Our patient's deletion was found within exons 8 and 9, which maps to the fourth of six transmembrane domains of CLN3. Eye findings in patients with homozygous CLN3 mutations include bull's-eye maculopathy, widespread RPE dysfunction, optic nerve pallor, and ERG abnormalities.[6] There is a distinct population of mutations of CLN3 that cause retina-specific, nonsyndromic abnormalities with varied penetrance.[7] Notably, patients with isolated retinal degeneration from CLN3 mutations appear to fall into two phenotypic groups – a mild rod-cone dysfunction with preserved visual acuity, and a more severe category with widespread macular atrophy and rapid visual acuity loss.[8] In direct contrast to our patient (with normal ffERG), even those in the milder phenotypic category possessed significant ffERG changes, ranging from severely diminished dark-adapted responses to undetectable waveforms. While we also considered the possibility that this patient has an underlying inflammatory condition such as multifocal choroiditis and panuveitis (MCP), acute posterior multifocal placoid pigment epitheliopathy (APMPPE), or serpiginous choroidopathy, his stability over several months, lack of leakage on fluorescein angiography, and asymptomatic presentation suggested otherwise. This patient's presentation is unique among CLN3 literature and may perhaps expand the library of phenotypes of this disease.

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Consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors have no potential conflicts of interest associated with this manuscript.

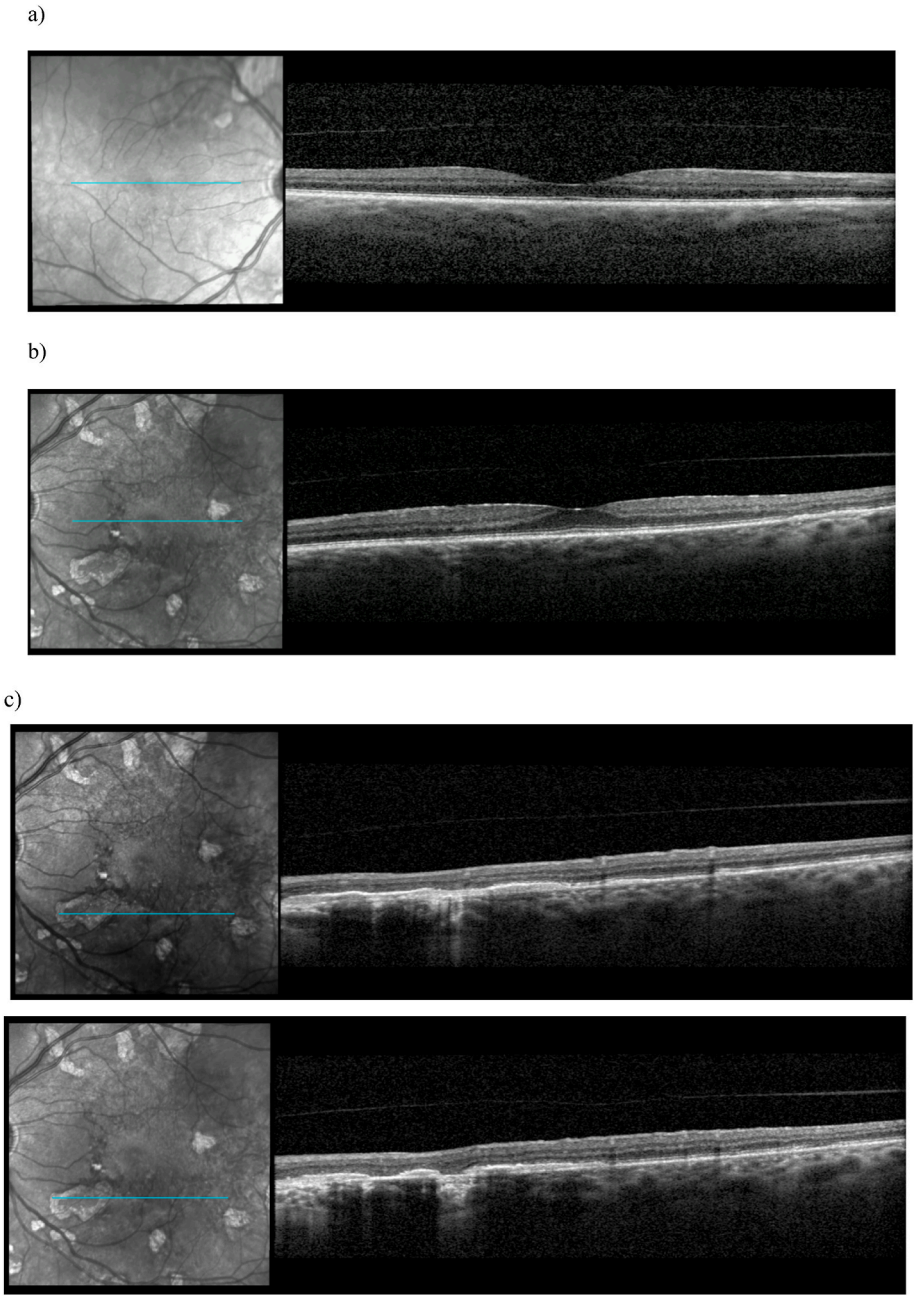

Fig. 2. Optical coherence tomography (OCT) of the right (a) and left (b) eyes. OCT through a macular lesion in the left eye (c) demonstrates a broad, low-lying pigment epithelial detachment, retinal pigment epithelium atrophy, and disruption of outer retinal architecture.

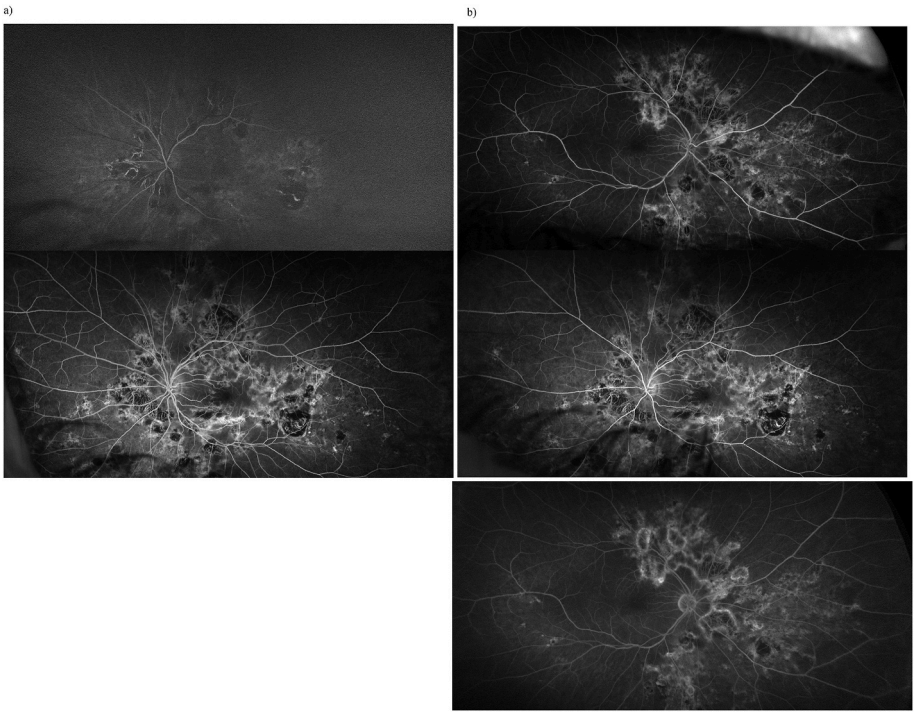

Fig. 3. Fluorescein angiography of right (a) and left (b) eyes.

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None.

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