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Chorioretinal Changes in a Genetically Confirmed Case of Boucher-Neuhäuser Syndrome

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Abstract

Purpose—To describe the retinal findings in a 25-year-old white female in whom a diagnosis of Boucher-Neuhäuser Syndrome (BNS) was supported by genetic testing, which identified a missense and novel nonsense mutation in the PNPLA6 gene.

Methods—Observational case report of a 25-year-old female who presented with primary amenorrhea, cerebellar ataxia and mild retinal pigmentary abnormalities. Neurologic, endocrine and genetic evaluations established a diagnosis of BNS.

Results—Clinical examination and multimodal imaging documented focal outer retinal and retinal pigment epithelium (RPE) changes including bilateral foveal stippling and a circular area of hypopigmentation in the superior macula of the left eye. Optical coherence tomography showed a linear area of outer retinal attenuation superonasal to the fovea and multiple foci of pinpoint outer retinal defects in the temporal macula of the left eye. Humphrey visual field (HVF) 24-2 testing showed non-specific defects in both eyes. Full-field electroretinography showed no evidence of a generalized retinal dysfunction.

Discussion and conclusion—Recognition that the chorioretinal abnormalities occurring in BNS can be rather subtle is essential, as the diagnosis of BNS may depend on their detection. To the best of our knowledge, this is the first report in the ophthalmic literature of mild chorioretinal changes in a BNS patient testing positive for a mutation in the PNPLA6 gene.

Keywords

Boucher-Neuhäuser Syndrome; chorioretinal dystrophy; hypogonadotropic hypogonadism; PNPLA6 genetic mutation; spinocerebellar ataxia

Introduction

Boucher-Neuhäuser Syndrome (BNS) is one of the many autosomal recessive hereditary ataxias described to date. There is much controversy surrounding the classification and distinguishing clinical features of these hereditary ataxias, but in the case of BNS, the ophthalmic findings are essential in establishing the diagnosis.⁵

BNS was first defined as a triad by Limber et al., after he combined the research performed by Boucher (1960) and Neuhäuser (1975).¹ Today, the autosomal recessive syndrome, which consists of spinocerebellar ataxia, chorioretinal dystrophy, and hypogonadotropic hypogonadism, is no longer just a clinical diagnosis. In 2014, Deik et al. confirmed that patatin-like phospholipase domain containing 6 (PNPLA6) mutations are the leading cause of BNS.⁸ However, the full phenotypic spectrum of PNPLA6 related disorders and the predictive value of the clinical features for identifying an underlying PNPLA6 related disorder remain to be confirmed.¹⁰ Hence, the ophthalmic findings are key to distinguishing BNS from other hereditary ataxias. To our knowledge, this is the first report of BNS with positive testing for a PNPLA6 gene mutation to appear in the ophthalmic literature.

Case Report

A 25-year-old Caucasian female presented with a history of hypogonadotropic hypogonadism, balance instability and intellectual disability. A genetic workup, which involved the PCR amplification of all 33 exons in PNPLA6, uncovered a missense variant, c.2890G>A (p.G964S) predicted, in *silico*, to be disease causing, FATHMM score = 0.98, Align GVGD = GV: 41.63 - GD: 46.81, SIFT = 0.05, MutationTaster (p-value) = 1. A novel stop-gain variant, c.1287T>A (p.C429*) was also identified, which terminates translation at exon 15 (33 exons in total) resulting in a severely truncated protein [Table 1]. As it was relatively unclear whether this variant negatively affected PNPLA6 gene function, a definitive diagnosis of BNS versus other hereditary ataxias could not be established. The patient was thus referred for an ophthalmic examination, to determine if there were any associated ocular findings consistent with BNS.

At the initial exam, the patient was asymptomatic and best corrected visual acuity was 20/30 in her right eye and 20/50 in her left eye. Intraocular pressure and color perception by Ishihara plates were normal in both eyes. The patient had full extraocular movements bilaterally, with horizontal gaze-invoked nystagmus. Anterior segment examination was normal. Dilated funduscopy showed stippling in the fovea of the right eye, as well as circular hypopigmentation superonasal to the fovea and focal changes in the temporal macula of the left eye [Figure 1].

Fluorescein angiography (FA) showed normal findings in the right eye and a hyperfluorescent window defect in the left eye with no leakage. Fundus autofluorescence (AF) showed subtle focal areas of hypoautofluorescence in the temporal macula of the right eye and a granular appearance of the RPE changes superonasal to the fovea in the left eye [Figure 2].

Optical coherence tomography (OCT) had normal findings in the right eye. In the left eye, OCT showed a linear area of outer retinal attenuation superonasal to the fovea and multiple focal disruptions of the ellipsoid and interdigitation zones in the temporal macula [Figure 2]. Humphrey visual field (HVF) 24-2 testing showed non-specific defects in both eyes.

There was no generalized retinal dysfunction noted on electroretinographic examination (ERG). Pupils were maximally dilated and ERG recordings were acquired with silver impregnated fiber electrodes (DTL) in accordance with extended testing protocols outlined by the International Society for Clinical Electrophysiology of Vision standards.¹¹ Transient photopic ERG b-wave amplitudes were 160 and 192 microvolts respectively in the right and left eye. Photopic 30-Hz flicker ERG had implicit times and amplitudes of 25 milliseconds; 90 microvolts, and 26 milliseconds; 140 microvolts respectively in the right and left eye. Maximal ERG a-wave and b-wave amplitudes were 275 and 325 microvolt, and 425 and 530 microvolts in the right and left eye respectively. Scotopic rod-specific ERG b-wave amplitudes were 209 microvolts in the right eye and 217 microvolts in the left eye [Figure 3].

On general exam, the patient was 68 inches tall and weighed 165 pounds. She was diagnosed with spinocerebellar ataxia, primary amenorrhea secondary to hypogonadotropic hypogonadism and impaired cognitive functioning. The patient was born to non-consanguineous parents from Denmark and Poland and there was no confirmed family history of BNS. However, she reported two unaffected siblings and one older sister with similar systemic symptoms, who was not available for examination.

Discussion

Boucher-Neuhäuser Syndrome is a rare disease that was first recognized as a triad of symptoms in 1989 by Limber et al., after he recognized the similarities between the findings noted by Boucher in 1960 and Neuhäuser in 1975. Limber confirmed that ophthalmic manifestations were present and named the triad of cerebellar ataxia, hypogonadotropic hypogonadism and chorioretinal dystrophy, Boucher Neuhäuser Syndrome (BNS).¹

The neurological symptoms of BNS have a varied age of onset between 4 and 40 years.⁹ Ataxia usually develops during adolescence or young adulthood. However, in some patients an earlier onset has been observed, and is generally slowly progressive or non-progressive.⁶ According to Baroncini et al, hypogonadism is always clinically obvious. Its hypogonadotropic evidence has been obtained in all patients whose endocrinological studies were carried out.⁶ The clinical findings in our patient are consistent with the diagnosis of BNS. In addition, she likely has an affected sibling with similar systemic symptoms and two unaffected siblings, consistent with Limber et al.'s conclusion that BNS

likely has an autosomal recessive mode of inheritance.⁷ Our patient exhibited the main ocular manifestations seen in previously reported cases, including atrophic changes of the outer retina, nystagmus and lack of optic atrophy. However, independent of the severity of the observed chorioretinal degeneration, the visual outcome may vary, ranging from almost intact vision to blindness.¹ This variability may be attributed to the fact that PNPLA6 encodes for neuropathy target esterase (NTE), which serves a dual function in the pathogenesis of organophosphorous compound-induced delayed neuropathy and in intracellular membrane trafficking.⁸ Diek et al. concluded that the diverse functionality of NTE may lead to variable phenotypic expressions associated with mutations in PNPLA6.⁸ Synofzik et al. found that to date, no obvious correlation has been established between genotype and phenotypic expression.¹⁰ Interestingly, it has been established that PNPLA6 pathogenic variants may yield a wide spectrum of phenotypic presentations and rates of disease progression.¹⁰ Our patient was found to be compound heterozygous for two novel variants: a nonsense variant, p.C429*, that truncates the PNPLA6 protein at exon 15, omitting the second and third cNMP, as well as patatins and phospholipase domains necessary for phosphatidylcholine deacetylation, and a missense variant, p.G964S, predicted as deleterious and observed within patatin catalytic region in which mutations attributed to BNS, spastic paraplegia, spastic ataxia and Gordon-Holmes syndrome occur.^{12,13} The phenotypes are independent of the mutation location or pathogenic variant (i.e., missense versus frameshift) but, complete penetrance is present in patients with biallelic pathogenic variants of PNPLA6 mutations.¹⁰ The variability of presentation underlies the vast range of ocular complaints among BNS patients. The onset of their visual disturbances varies from 4 to 46 years of age.¹ Ocular motor abnormalities are found in the majority of patients and may include horizontal gaze-evoked nystagmus, saccadic smooth pursuit eye movements and spontaneous vertical nystagmus.⁹ In addition, one study found that only 59% of patients had visual field defects and 55% had impairment of color vision. The inconsistency and variability in ophthalmological findings illustrates the diversity of ocular manifestations of BNS.

No ocular histopathological studies of the disorder have been reported.² By using clinical and electrophysiological data, it has been suggested that the degeneration involves primarily the outer retinal layers, retinal pigment epithelium and choriocapillaries combined with disruption of the vascular supply to the retina.² Macular outer retinal and RPE disturbances were detected in our patient by OCT, FA, and FAF, which support that BNS affected her outer retina. Full-field ERG showed no generalized retinal dysfunction in the context of mottling of the retina and RPE hypopigmentation a little over one disc diameter in size. This contrasts Tarnutzer et al. who found that 15 of 16 cases showed abnormalities on ERG.⁹ This could be due to the various expressions and progression of the disease and confirms the importance of a careful ophthalmological exam with multimodal imaging.

PNPLA6-related disorders span a wide spectrum with diverse phenotypic expression.¹⁰ This can be attributed to the PNPLA6's domain and its complex role in multisystem effects as illustrated by involvement in brain lipid metabolism, neuronal development, intercellular membrane trafficking and axon maintenance.⁸ PNPLA6-related disorders include BNS, PNPLA6-related Gordon Holmes syndrome, Oliver-McFarlane syndrome, PNPLA6-related Laurence-Moon syndrome and Spastic paraplegia type 39 (SPG39).¹⁰ Identifying the genetic

mutation(s) in combination with clinical exam findings is necessary in diagnosing and assessing the severity of a specific disorder caused by the mutation(s). Hence, ophthalmologic evaluation remains key in diagnosing and improving our understanding of BNS as well as distinguishing it from other similar hereditary disorders.⁷

In conclusion, BNS was first reported in the ophthalmic literature in 1995 and at that time, only five families were reported and diagnosis was based on clinical presentation only.³ In 2014, Deik et al. established that PNPLA6 mutations were identified in families with BNS and that this mutation is the leading cause of the disease.⁸ However, a PNPLA6 gene mutation does not confirm the diagnosis of BNS, thus making the ophthalmic exam the most important element in differentiating it from other similarly presenting movement disorders. Our report serves as the first genetically and clinically confirmed case of BNS in the ophthalmic literature. Further investigation is needed to better understand PNPLA-6 mutations, how they affect the gene's function and translate to clinical manifestations in the retina.

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Summary Statement

Boucher- Neuhäuser Syndrome (BNS) is a clinical entity characterized by the triad of spinocerebellar ataxia, chorioretinal dystrophy, and hypogonadotropic hypogonadism. To the best of our knowledge, this is the first genetically confirmed case of BNS with the PNPLA6 mutation and chorioretinal changes presented in the ophthalmic literature.

Figure 1.

A. Color photographs: Right eye shows mild retinal pigment epithelium (RPE) stippling (white arrowheads in the right inset). Left eye shows RPE changes including foveal stippling, circular hypopigmentation superonasal to the fovea (blue arrowhead), and focal hypopigmented changes in the temporal macula (yellow arrowheads in the left inset). B. Color montage photographs show no evidence of peripheral RPE abnormalities.

Figure 2.

A. Fundus autofluorescence (AF): Right eye shows subtle focal areas of hypo-AF in the temporal macula. Left eye shows a granular, hypo-AF appearance of the RPE changes superonasal to the fovea (blue arrowhead) and hypo-AF foci in temporal macula (yellow arrowhead). B. Optical coherence tomography (OCT) of the right eye appears normal. The left eye's OCT shows a linear area of outer retinal attenuation (blue arrowhead in Upper inset) and a focal disruption temporal to the fovea involving the ellipsoid and interdigitation zones (yellow arrowhead in Lower inset). C. Mid-phase fluorescein angiogram of right eye

appears normal. Mid-phase angiogram of the left eye shows a hyperfluorescent circular window defect superonasal to the fovea without leakage.

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Full-Field Electroretinogram

Figure 3.

Full field electroretinography (ERG) showed no generalized retinal dysfunction. Transient photopic ERG b-wave amplitudes were 160 microvolts in the right eye and 192 microvolts in the left eye. Photopic 30-Hz flicker ERG of the right eye had implicit times and amplitudes of 25 milliseconds and 90 microvolt and, in the left eye, 26 milliseconds and 140 microvolts. Maximal ERG a-wave and b-wave amplitudes were 275 microvolts and 325 microvolts in the right eye and 25 and 530 microvolts in the left eye.

Table 1

Presentation of *in silico* analysis of patatin-like phospholipase containing 6 mutations gene (*PNPLA6*) variants in a patient with Boucher-Neuhäuser syndrome (OMIM# 215470) by predictive programs

In silico analysis of *PNPLA6* variants in a patient with Boucher-Neuhäuser syndrome (OMIM# 215470) by predictive programs.

Exon	Nucleotide Change	Protein Variant	Coding Effect	FATHMM	AGVGD	Sift	MutTaster	RefSeq
27	c.2890G>A	p.Gly964Ser	Missense	Pathogenic (score 0.98)	Class C0(GV: 41.63 – GD: 46.81)	Deleterious (score: 0.05)	Disease causing (p-value: 1)	NM_006702.4
15	c.1287T>A	p.Cys429*	Nonsense	-	-	-	-	NM_001166112.1

Abbreviations: FATHMM, Functional Analysis through Hidden Markov Models; AGVGD, Align-Grantham Variation and Grantham Deviation; SIFT, Sorting Intolerant From Tolerant; MutTaster, MutationTaster; RefSeq, Reference Sequence