Fundus Albipunctatus: A Novel Mutation

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Abstract

Background: The aim of this paper is to describe a patient with fundus albipunctatus from Africa who is developing a cone dystrophy with a new mutation in RDH5.

Methods: A 24-year-old female from Burundi presented with difficulty to adapt to darkness after being in the light since the age of 9 years old. The clinical history, visual field, electroretinogram (ERG), dark adaptation test, spectral-domain optical coherence tomography (SD-OCT); fundus autofluorescence (FAF) and polymerase chain reaction (PCR) plus DNA analysis (by Sanger sequencing) were performed.

Results: Fundus examination revealed scattered, homogenous, yellow-white dots throughout both fundi. OCT showed extrafoveal numerous well-demarcated homogenous dome-shaped lesions originating in the RPE. FAF showed a lack of autofluorescence (AF). Electoretinogram of the cone and the mixed rod-cone system had a normal morphology but with a significant decrease in the a and b wave amplitudes and a delayed peak time. The rod-mediated ERG was non-detectable. However, after a prolonged (3-hour) period of dark adaptation, the rod-mediated ERG was detectable and the b-wave reached 48% of normal value. The DNA analysis and sequencing of RDH5 revealed a homozygous c. 524-526delACT mutation, leading to a protein change of p.Tyr175del, which has not been reported before. The cone ERG results, strongly suggest that she is developing a cone dystrophy, despite the fact that she is asymptomatic and still maintains 20/20 vision and normal color discrimination.

Conclusion: We identified a new deletion in RDH5 responsible for fundus albipunctatus with a progressive cone dystrophy; c. 524-526delACT in a patient from Burundi.

Keywords: Fundus albipunctatus; RDH5; Cone dystrophy; 11-cis retinol dehydrogenase; Dark adaptation; Spectral-domain optical coherence tomography (SD-OCT); Fundus autofluorescence

Introduction

Fundus albipunctatus (FA) is an autosomal recessive congenital nightblindness disorder characterized by the presence of retinal white dots caused by mutations in the RDH5 gene [1,2], encoding for the retinol dehydrogenase (RDH). RDH acts in the retinoid cycle to replenish 11 cis retinal and is responsible for the oxidation of 11-cis-retinol to 11-cis-retinal [3,4], the last step of the vitamin A cycle.

In the RPE cell somata, 11-cis retinol dehydrogenase (11-cis RDH) is an abundantly expressed transmembrane protein [1,5]. The enzyme catalyzes the final step in the visual cycle, the biosynthesis of 11-cis retinal before it binds to opsin in rods and to the cone opsin in cones, to form rhodopsin and the cone opsins [6].

A clinically distinct disorder, retinitis punctata albescens (RPA) is also characterized by nyctalopia, reduced visual acuity, multiple round white deposits in the retina, but has progressive attenuation of retinal arterioles, and non-detectable or severely reduced ERG recordings [7]. The first distinction between FA and RPA was made by Lauber (1910) [8]. RPA is associated mostly with mutations in the RLBP1 gene and occasionally in RHO, RDS, and RDH5 [9].

Fundus albipunctatus has a variable regeneration of dark adaptation and full-field
Electroretinography (ERG) responses after prolonged dark adaptation, which helps in differentiating it from other disorders of the visual cycle.

Currently 22 RDH5 mutations are known [10]. In this article, we present clinical and molecular genetic data in a 24-year-old African woman with fundus albipunctatus, with a new deletion in RDH5, the c. 524-526delACT mutation.

Materials and Methods

The patient provided written informed consent on behalf of herself in accordance with the Declaration of Helsinki. Ethical and scientific approvals for our studies have been approved by McGill University Health Centre.

Clinical exam included visual acuity assessment with Snellen chart, color vision with Ishihara plates, dilated fundus exam, color photography, SD-OCT, FAF were obtained with a confocal scanning laser ophthalmoscope, Goldmann visual field, ERG, dark adaptation test, blood extraction for genetic analysis.

ERGs were done in accordance with International Society for Clinical Electrophysiology of Vision (ISCEV). Short flash (20 µs; white xenon light) cone- (background: 30 cd.m⁻²; flash intensity: 0.69 log cd.sec.m⁻²; ISI: 1.5 sec), rod- (dark adaptation: 15 minutes and 3 hours; flash intensity: -2.3 log cd.sec.m⁻²; ISI: 10 sec) and rod/cone- (dark adaptation: 15 minutes and 3 hours; flash intensity: 0.69 log cd.sec.m⁻²; ISI: 10 sec) mediated electroretinograms (ERGs) were recorded using the Espion E² system (Espion E² system stimulator, Diagnosis LLC, Lowell, MA, USA). The recording bandwidths were set from 1.25 to 300 hertz.

The a-wave amplitude was measured from the pre-stimulus baseline to the first negative trough of the ERG, whereas the b-wave amplitude was measured form the trough of the a-wave to the most positive peak of the ERG. For rod-mediated ERGs, where there is no a-wave, the b-wave amplitude was measured from the pre-stimulus baseline to the most positive peak of the ERG. Peak times of both the a- and b-waves were calculated from the flash onset to the respective wave peak.

DNA was extracted from whole blood by using FlexiGene kit according to the manufacturer’s protocol. NanoDrop was used to check DNA’s quantity and quality. Primer3 software was used to design the RDH5 primers (http://frodo.wi.mit.edu/primer3/). The HotStarTag Master Mix kit from QIAGEN was used to perform the PCRs following the manufacturer’s protocol. The purity and specificity of the fragment was verified by agarose gel electrophoresis. Then the fragment was sent for sequencing by Sanger sequencing using Applied Biosystems 3730xl DNA Analyzer technology. The DNA Sequencing Software Sequencher from Gene Codes was used to analyze the results.

Results

This 24 year old black female from Burundi, presented to the hereditary retinal degeneration clinic, McGill Ocular Genetics Laboratory (MOGL) at the Montreal Children’s Hospital, with a complaint of difficulty adapting to the dark after being in the light, since she was 9 years old. She was also complaining of nyctalopia which was improving with her age. Her past medical history was insignificant and she was not on any medications. She came from a non-consanguineous family, and had a sister who was living in Burundi with the similar complaint.

The patient underwent a complete ocular exam. Her visual acuity was 20/20 in both eyes. Her color vision was normal in both eyes. There was no afferent pupillary defect. The intraocular pressure and the anterior segments were normal for both eyes. Fundus examination revealed scattered, homogenous, yellow-white dots throughout both fundi, relatively sparing the macula (Figure 1).

The optic nerve had a normal color with a normal cup-to-disc ratio. The retinal vessels were of normal caliber size.

A Spectral-Domain Optical Coherence Tomography (SD-OCT) exam was performed, and showed the presence of extramacular numerous well-demarcated homogenous dome-shaped lesions, extending from the retinal pigment epithelium (RPE) level into the inner/outer segment junction of the photoreceptors (Figure 2).

Images for fundus autofluorescence (FAF), showed some increased autofluorescence corresponding to the white dot lesions (Figure 3).

The patient underwent a Goldmann manual perimetry, which was normal in both eyes.

The cone-mediated electroretinograms recorded from the patient revealed significantly decreased a- and b-wave amplitudes. More specifically, the a- and b-waves were decreased by 60% and 65% respectively compared to normal values. Their peak times were also delayed by approximately 3-4 ms. While the rod-mediated ERG response did not demonstrate a-b wave after 15 minutes of dark adaptation, a small b-wave could be recorded after a 3-hour period of dark adaptation. The amplitude of the rod-mediated b-wave...
after prolonged dark adaptation was 48% of normal values with delayed peak times (approximately 10 ms). Finally, the rod/cone-mediated ERG recorded after 15 minutes of dark adaptation showed significantly decreased a- and b-wave amplitudes, 28% and 15% of normal values respectively, with abnormal peak times. However, after a 3-hour period of dark adaptation the amplitude of the a- and b-waves increased to reach values that were 85% (a-wave) and 69% (b-wave) of normal values. Peak times remained abnormal even with prolonged dark adaptation (Figure 4).

PCR, DNA analysis and sequencing of the RDH5 gene revealed a new deletion mutation in the RDH5, c. 524-526delACT mutation, which has not been previously reported (Figure 5).

Discussion

The SD-OCT exam in our FA patient showed numerous outer retinal lesions at the level of the retinal pigment epithelium, which extended into the overlying inner segment/outer segment (IS/OS) junction of the photoreceptors as well as the outer nuclear layer. This finding is similar to a recent finding reported by Genead [11].

The cone-mediated electroretinograms from our patient was significantly reduced in both a- and b-wave amplitudes which indicates a cone dystrophy, and implies that patient will get worse and that the disease is not a stationary disease. To prove this hypothesis, it is necessary to observe patients with FA for a long period.

To complicate the differential diagnostic process in the clinical setting, improvement of the dark-adapted ERG responses following prolonged dark adaptation has been reported also in patients with RPA [12]. However, in RPA patients with RLBP1 mutations, recovery of ERG responses to the normal range has been observed only after 20 or more hours of dark adaptation [12] and apparently not after a shorter (10 h) adaptation time [13]. No recovery after 2 h and only a modest recovery after 17 h has also been recently reported in a RLBP1 -negative RPA patient [7]. Our patient had an increase in the amplitude of the rod/cone-mediated ERG by 85% (a-wave) and 69% (b-wave) of normal values after a 3-hour period of dark adaptation. The cone ERG results, strongly suggest that she is developing a cone dystrophy, despite the fact that she is asymptomatic and still maintains 20/20 vision and normal color discrimination.

Our molecular genetic analysis demonstrates a new deletion mutation in RDH5, a homozygous 3bp deletion c. 524-526delACT.

Some patients with FA and RDH5 mutations are stable, while others develop cone dystrophy. The genetic changes found in RDH5 do not appear to predict which will progress and which will be stable.

Conclusion

In conclusion, we present a case of a young patient from Burundi from a non-consanguineous family with fundus albipunctatus who is developing a progressive cone dystrophy with a new deletion mutation in the RDH5 gene. We discovered that despite her 20/20 vision, she has developed a subclinical cone dystrophy that will progress over time.

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References


