Case Report

Hypotrichosis with Juvenile Macular Dystrophy in a Patient with Cadherin 3 (CDH3) Mutation

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ABSTRACT

Introduction: Hypotrichosis with juvenile macular dystrophy (HJMD) is an autosomal recessive disease with progressive macular degeneration leading to blindness in the first three decades of life along with hypotrichosis.

Case: We herein report a case of a five year old boy with hypotrichosis with juvenile macular dystrophy diagnosed with multi-modal imaging which was later confirmed by genetic testing by whole genome sequencing.

Observations: Fundus examination of both eyes revealed symmetrical hypopigmentation in peripapillary retinal pigment epithelium (RPE) involving posterior pole and surrounded by a mottled hyperpigmented border. Fundus autofluorescence showed central hypo autofluorescence with surrounding hyper autofluorescence corresponding to RPE atrophy and a faint hypo autofluorescence at the junction of normal retina. SD-OCT showed segmental outer retinal and choriocapillaris atrophy temporal to fovea with interdigitation zone and ellipsoid zone loss and RPE irregularities with hyperreflective subretinal deposits at the fovea. Electroretinogram showed normal waves but a slight reduction of b wave amplitude in both eyes. He had sparse scalp-hair.

Conclusion: Children with reduced vision not falling into a typical macular degeneration should be examined systemically and may just have sparse scalp hair and still have a genetic disease. A regular follow-up should be emphasized in view of progressive nature of the disease.

Key words: Cadherin 3, CDH3 mutation, Hypotrichosis, Juvenile macular dystrophy.

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INTRODUCTION

Hypotrichosis with juvenile macular dystrophy (HJMD) is a rare autosomal recessive disease, with progressive macular degeneration along with scanty scalp hair (hypotrichosis), leading to blindness in the first three decades of life (Sprecher et al, 2001). We herein report a five year old boy with HJMD with multi-modal imaging and genetic testing by whole genome sequencing.

CASE

A five-year-old boy, born out of a consanguineous marriage presented with diminution of vision in both eyes, discovered for two months with best corrected vision of 6/18 in both eyes. Patient was using hypermetropic spectacles for two months. There was no positive family history of similar disease. No diurnal variation in vision was noticed. There was no developmental delay or eventful birth history and there were no systemic complaints other than sparse scalp hair. Anterior segment examination was unremarkable. Color vision was reduced with Ishihara chart and pupillary reaction was brisk. Fundus examination of both eyes (Figures 1a and 1b) revealed symmetrical peripapillary hypopigmented areas of retinal pigment epithelium (RPE) involving posterior pole surrounded by a mottled hyperpigmented border. Fundus autofluorescence (Figures 1c

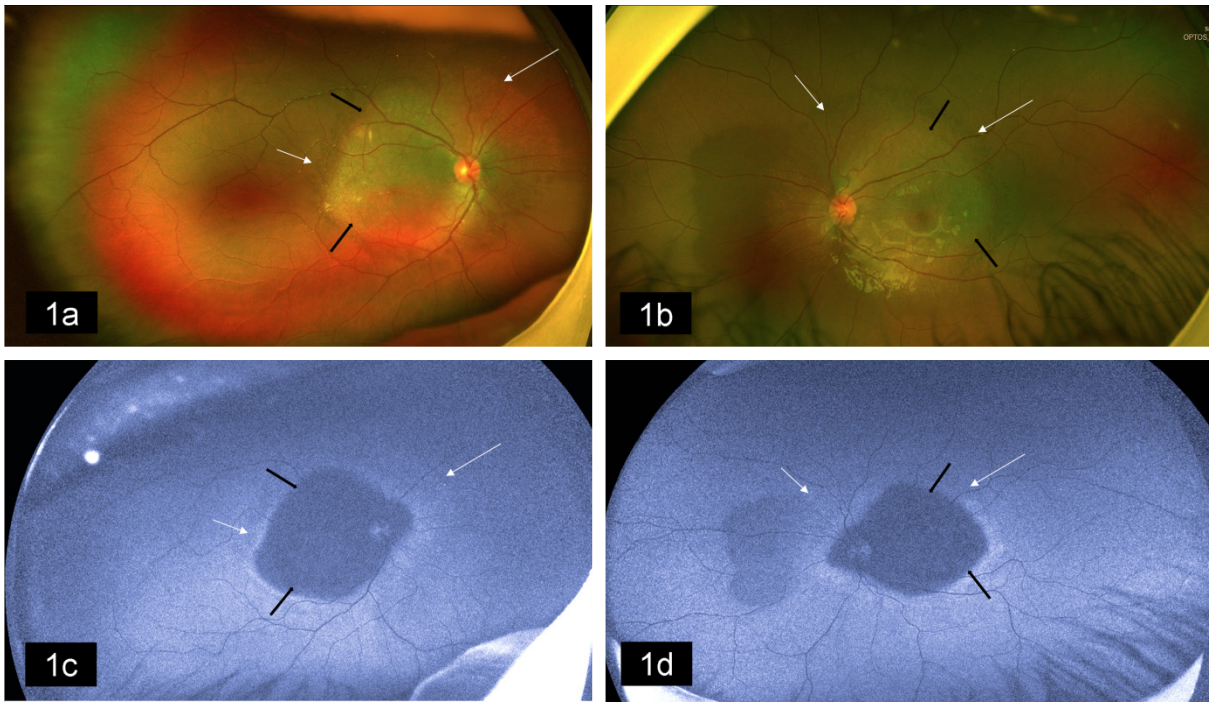

Figure 1: Widefield fundus photograph (OPTOS) of both eyes (1a and 1b) showing symmetrical peripapillary area of RPE hypopigmentation (black arrows) involving posterior pole surrounded by a zone of mottled pigmentation (white arrows). Fundus autofluorescence (OPTOS) (1c and 1d) showing hypo autofluorescence in the center (black arrows) surrounded by a zone of hyperfluorescence and a faint hypofluorescence (white arrows).

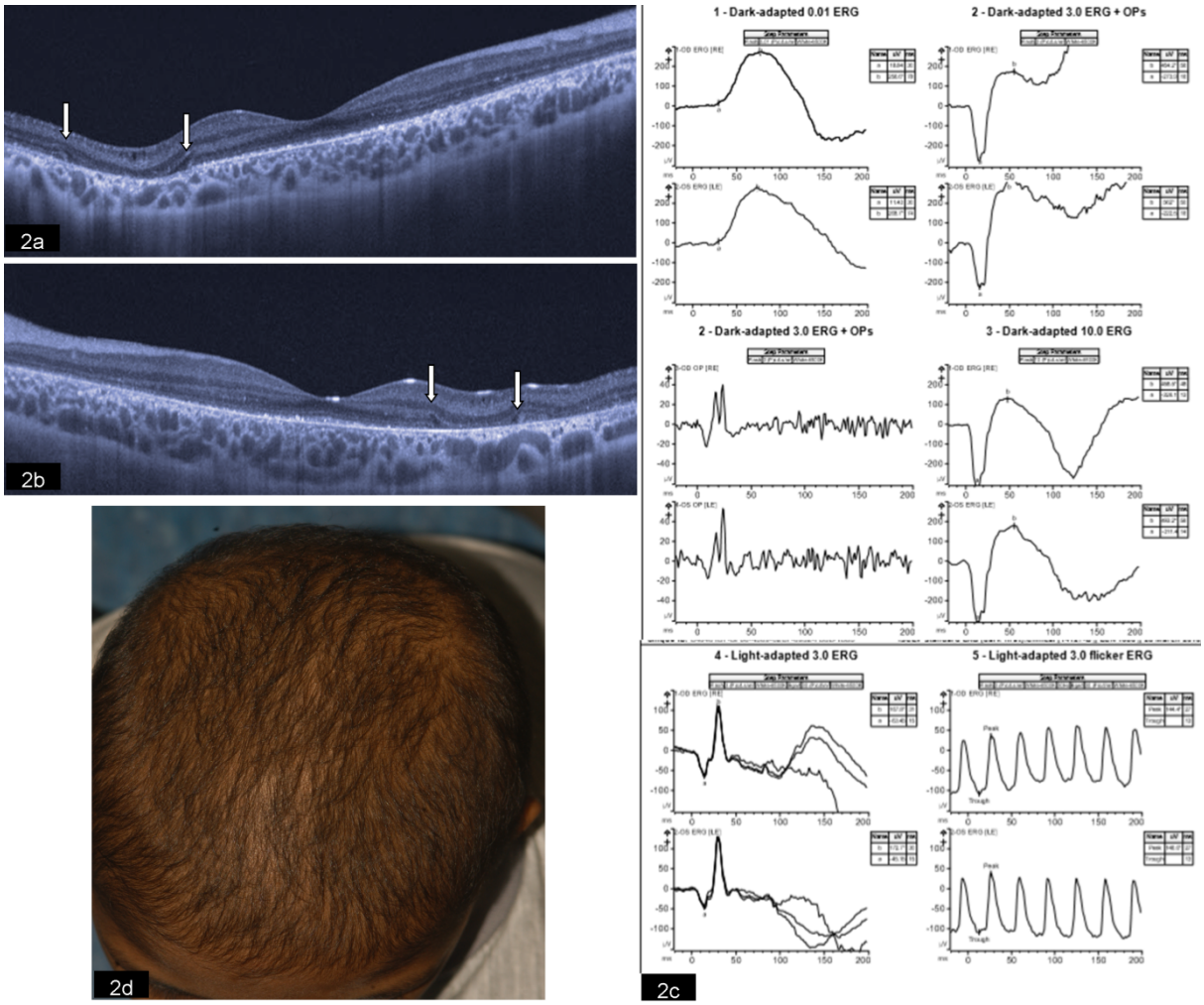

Figure 2: SDOCT (2a and 2b) of both eyes showing subfoveal retinal pigment epithelium irregularities with segmental atrophy of outer retina (white arrows) and choriocapillaris. Electroretinogram (2c) showing normal a wave but a slight reduction of b wave amplitude in both eyes. External photograph of head (2d) with sparse scalp hair.

and 1d) showed central hypo autofluorescence with surrounding hyper autofluorescence corresponding to RPE atrophy and a faint hypo autofluorescence at the junction of normal retina. Spectral domain optical coherence tomography (Figures 2a and 2b) of both eyes showed segmental outer retinal and choriocapillaris atrophy temporal to fovea with interdigitation zone and ellipsoid zone loss and RPE irregularities with hyperreflective subretinal deposits at the fovea. Electroretinogram (ERG) (Figure 2c) showed normal a wave but a slight reduction of b wave amplitude in both eyes. Electro-oculogram measurements were within normal limits. Fields were unreliable and acute zonal occult outer retinopathy (AZOOR) was a

probable diagnosis looking at the loss of outer retinal layers. His sparse scalp-hair (Figure 2d) forced us to search the literature and helped in clinching the clinical diagnosis of HJMD. There were no systemic changes noted on skin and complete pediatrician check-up was done. Genetic testing of the whole genome was done using next generation sequencing. It showed a homozygous single base pair deletion in exon 13 of the CDH3 gene (chr16:g.68725765delC) that results in a frameshift and premature truncation of the protein 31 amino acids downstream to codon 647 (p.Cys647.AlafsTer31; ENST00000264012.4). Fundus evaluation of both the parents and the younger sister were within normal limits and the family history was unremarkable other than consanguinity. The patient was referred to a Pediatric geneticist for further evaluation.

DISCUSSION

Mutations in the cadherin 3 gene are associated with HJMD and it is a critical mediator of cell-cell adhesion which is expressed in human RPE (Sprecher et al, 2001; Balarin Silva et al, 1999; Singh et al, 2016). Abnormal or absent CDH3 expression can cause progressive macular degeneration and visual loss. With evidence of extramacular retinal involvement and full-field ERG showing generalized cone-rod dysfunction, it has been suggested that the condition be renamed as hypotrichosis with cone-rod dystrophy (Leibu et al, 2006). The coding sequence of CDH3 is small and can be tried for recombinant AAV vector transmission and thereby can be a disease candidate for gene therapy (Singh et al, 2016). Patients with HJMD can show progressive decline over time leading to blindness during the second or third decade of life. There have been approximately 50 reports of HJMD described in the literature. Gene therapy may be a treatment option in future.

Our patient had no teeth or skin abnormality. People have tried scalp biopsies and histopathologic examination with reduced number of terminal hair follicles revealing mostly vellus and catagen hair follicles. Scalp biopsy corroborates the clinical diagnosis. Sparse hair in hypotrichosis results from a hair regeneration defect with impairment in hair cycling and anchoring of the hair shaft in the skin. Non-syndromic as well as syndromic forms can occur with different mutations resulting in hypotrichosis simplex, HJMD, Marie Unna hypotrichosis, and autosomal recessive wooly hair/ hypotrichosis simplex. Electron microscopy of the hair may show pseudomonilethrix, pili torti, longitudinal ridging, scaling and folding of the hair shaft (Sprecher et al, 2001).

The hair is less pigmented and the anomaly does not improve with age. Some children may have ectodermal dysplasia, limb anomalies, ectrodactyly and macular dystrophy thereby requiring a complete systemic evaluation to differentiate them from HJMD (Balarin Silva et al, 1999). The ERG findings have been found to be normal or show subnormal rod and/or cone

responses (Leibu et al, 2006). ERG changes with subnormal responses are described specifically in the scotopic part similar to our patient (Sprecher et al, 2001; Singh et al, 2016).

The hypo autofluorescence is reported but a trizonal pattern as seen in our patient similar to AZOOR has never been described before. The OCT features of outer layer disruption is discussed but reports focussed more on pigments and scars on RPE (Sprecher et al, 2001; Singh et al, 2016). Present report focuses more on segmental outer layer atrophy along with choriocapillaris atrophy which may progress to more diffuse change and pigment clumping over a period of time.

Stargardt disease due to biallelic mutations in ABCA4 is the most common cause of juvenile-onset macular dystrophy and it may be one of the differential diagnoses for HJMD (Hwang et al, 2009). Children with Stargardt disease may not have flecks at the presentation. HJMD can be distinguished by examination of the sparse scalp hair with normal eyebrows or eyelashes. Sparse scalp hair from birth is the first sign of HJMD. Macular atrophy with Stargardt disease is less extensive and spares the peripapillary region in most patients with ABCA4 retinopathy (Hwang et al, 2009).

HJMD has no specific treatment at present. Children with reduced vision not falling into a typical macular degeneration should be examined systemically and may just have sparse scalp hair and still have a genetic disease. Ophthalmologists should take help from pediatricians and geneticists to diagnose and prognosticate conditions like HJMD. A regular follow-up should be emphasized in view of progressive nature of the disease.

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