CDH3 mutation associated with ectodermal dysplasia and hair abnormalities

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Abstract

Background: Hypotrichosis with juvenile macular dystrophy (HJMD) is a rare autosomal recessive disorder characterized by impaired hair growth and progressive macular degeneration, leading to blindness.

Objectives: The aim of this study is to present a case of HJMD from Saudi Arabia.

Methods: We present a six-year-old Saudi girl who was referred to the Dermatology Clinic at King Faisal Specialist Hospital and Research Center (General Organization) in Jeddah, Saudi Arabia because of sparse hair with no other phenotypic abnormalities. She had multiple short sparse, lusterless hair appearance with a few alopecic patches and plaques. Her macula exhibited retinal and choroidal dystrophy with parapapillary retinal pigmentation. Genetic test showed positive homozygous pathogenicvariant in the CDH3 gene, which is linked to HJMD.

Results: Hair examination revealed multiple short, sparse and lusterless appearance with few alopecic patches and plaques. The skin was dry with normal temperature. The Macula exhibited retinal and choroidal dystrophy with parapapillary retinal pigmentation with no decrease of the retinal nerve fiber layer in both eyes. Hair biopsy was taken, and it showed trichorrhexis nodosa. The genetic test showed a positive homozygous pathogenic variant in the CDH3 gene, which is linked to autosomal recessive congenital hypotrichosis and macular dystrophy syndrome.

Conclusion: HJMD is a rare genetic cause of hypotrichosis that should be considered when assessing patients with abnormal hair growth. Fundus examination is important in suspected cases even with no visual symptoms. Further molecular DNA analysis is needed to identify the type of mutation in our patient.

Key words: CDH3, mutation, ectodermal, dysplasia, hair, abnormalities

Introduction

Ectodermal dysplasia (ED) comprises a group of rare inherited disorders characterized by defects in the development of two or more of ectodermal derived tissues. The involved tissues include hair, nail, teeth, and sweat glands, as well as parts of the eyes, ears, neural and adrenal tissues to various degrees [1]. The estimated prevalence of ED is approximately 7 cases in every 100,000 live births [2]. There are primarily two forms of ED, i.e. hypohidrotic type and hydronic type based on the role of the sweat gland. Hypohidrotic / anhidrotic ED means defects in the sweat glands [3].

Hypohidrotic-shaped individuals typically show heat intolerance. Diagnosis is sometimes made during infancy because the baby seems to have a fever of unknown origin [4]. Other features are fine sparse hair and decreased density of eyebrows and eyelashes [5]. The mid-face shows hypoplasia which results in protuberant lips, and periorbital area may show wrinkling and increased pigmentation. Nails may also appear dystrophic and brittle [6].

In 1935, Wagner first described congenital hypotrichosis with juvenile macular dystrophy (HJMD; OMIM 601553), a rare autosomal recessive disorder characterized by sparse scalp hair and progressive macular degeneration resulting in severe visual impairment and early blindness in childhood [7]. HJMD is caused by loss-of-function mutations in the cadherin-3 (CDH3) gene [8,9].

The CDH3 gene, located on chromosome 16q22.1, encodes for P-cadherin, which is expressed in a variety of tissues including retinal pigmented epithelial cells and hair follicles. P-cadherin is a transmembrane glycoprotein that is responsible for adherents junctions (calcium-dependent cell-cell adhesion) in these and other epithelial tissues [10,11]. Ectodermal dysplasia, ectrodactyly and macular dystrophy (EEM) is also caused by mutations in the CDH3 gene and is associated with hypotrichosis and macular dystrophy with the additional features of ectrodactyly with split hand/foot malformations [12]. The exact prevalence of HJMD is unknown, however, worldwide around 50 cases of HJMD have been described [13]. The aim of this study is to present a case of HJMD from Saudi Arabia.

Case report

A six-year-old Saudi girl was referred to the Dermatology Clinic at King Faisal Specialist Hospital and Research Center (General Organization) – Jeddah, Saudi Arabia with a chief complaint of fine sparse hair since birth. The patient was given several shampoos and multi-vitamins which did not help. She is the second in order of birth of first cousin consanguineous parents. There was no history of perinatal complications and no other live family member with the same condition. She is thriving well with no history suggestive of developmental delay. On clinical examination, patient's vitals and systemic examination were within normal according to her age.

Hair examination revealed multiple short, sparse and lusterless appearance with few alopecic patches and plaques (Figures 1). There was no evidence of scalp scarring and no follicular tufting was seen either. Eye and ear examination revealed no abnormality with no associated dysmorphic features. Bilateral hand examination revealed normal shaped fingers with no abnormality (\Figure 2). The skin was dry with normal temperature. She has no missing or abnormally shaped teeth. No evidence of gingivitis or involvement of the mucous membrane was seen (Figure 2).

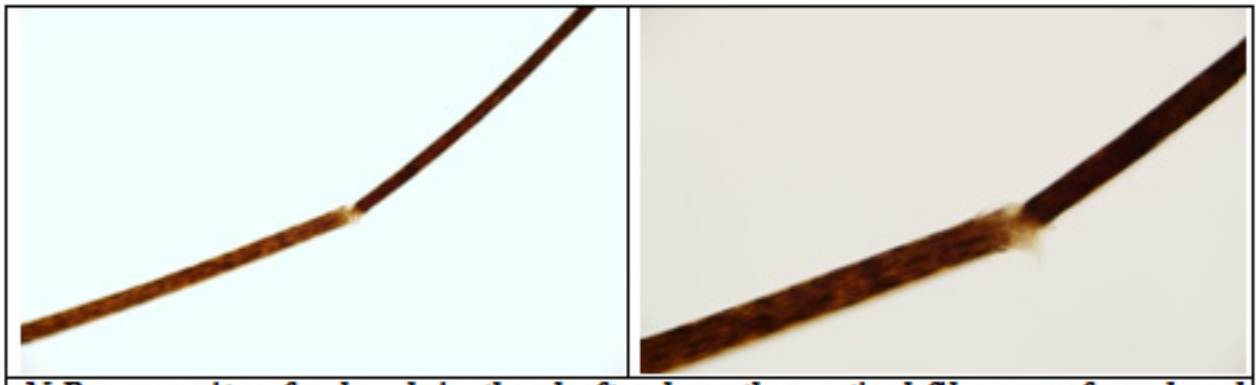
The ophthalmological exam was done with Fundus examination and Optical Coherence Tomography (OCT). The Macula exhibited retinal and choroidal dystrophy with parapapillary retinal pigmentation with no decrease of the retinal nerve fiber layer in both eyes. The patient's complete blood count (CBC), comprehensive metabolic panel, and urine analysis reports were normal. Hair biopsy was taken and it showed trichorrhexis nodosa. The parents were informed that they needed further genetic testing to rule out Menkes kinky hair versus Netherton syndrome. The genetic test showed a positive homozygous pathogenic variant in CDH3 gene, which is linked to autosomal recessive congenital hypotrichosis and macular dystrophy syndrome.

Parents were counseled about this finding. We explained to them that the recurrence risk of this disorder in each future pregnancy is 25%, which can be reduced by preventive measures such as prenatal pre-implantation genetic diagnosis or antenatal molecular testing for this gene. Unfortunately, there are no good treatment options for this entity. Further research is needed in this area.

Figure 1: different views of the head of the subject

Figure 2: Feet, hands, mouth and teeth views of the subject

Figure 3: Microscopic hair shaft examination



N.B.: rare site of a break in the shaft, where the cortical fibers are frayed and splayed, but remain largely attached. (200x) (inset: 400x)

Discussion

We present a case of Hypotrichosis with juvenile macular dystrophy (HJMD) from Saudi Arabia. This is the fifth case to be reported from Saudi Arabia. HJMD is a rare inherited disorder caused by mutations in the CDH3 gene (MIM 114021), encoding the classical cadherin molecule P-cadherin [9]. Cadherins are integral membrane glycoproteins expressed in a variety of tissues, including hair follicles and retinal pigment epithelium [14]. HJMD is mainly found in the Drouze population of Northern Israel and some Mediterranean areas [15].

In 2001, Sprecher et al. [9] studied the molecular background of HJMD, and they presented the first mutation in the CDH3 gene causing HJMD in a Druze-origin family. They indicated that HJMD is caused by the loss of function of P-cadherin resulting from a frameshift mutation in CDH3. Later on, several studies identified around 19 different CDH3 mutations in 28 separate families of different ethnic origins who have HJMD [5,9,16,17,18,19,20,21,22,23]. However, Kjaer et al. [12] found that mutations in the CDH3 gene also caused ectodermal dysplasia, ectrodactyly, and macular dystrophy (EEM syndrome; OMIM 225280).

Moreover, Basel-Vanagaite et al. [24] suggested that these syndromes act as a continued phenotypic spectrum that is linked to mutations in the CDH3 gene; therefore, they might be classified as CDH3-related syndromes instead of other genetic syndromes. Hypotrichosis and macular dystrophy are common features that exist over these two overlapped syndromes. Although EEM syndrome thought to be different from HJMD due to limb anomalies presence, genetic analysis report found these abnormalities in both syndromes [5].

Our six-year-old female patient presented with fine, short, sparse and lusterless hair since birth. The skin was dry with normal temperature. No other phenotypic abnormalities were noted on clinical examination. She had no visual complaints, however, fundus examination showed macular retinal and choroidal dystrophy with parapapillary retinal pigmentation and no decrease of the retinal nerve fiber layer in both eyes.

Khan and Bolz [25] presented four affected individuals from three consanguineous Saudi families (two sisters, 17 and 13 years old, and two unrelated males, 5 and 26 years old). They had visual loss since birth or early childhood. All had circumscribed central macular dystrophic changes that did not respect the horizontal arterioles, and associated with polygonal pigment clumps. One of the affected patients did not have frank hypotrichosis but had relatively slow hair growth. None had dental or digital abnormalities.

Saeidian et al., 2019 [26] found no systematic correlation between phenotypic findings and the type (missense vs. nonsense and/or frameshift) or location of the CDH3 mutations among the affected members of an Iranian family and the 19 previously reported mutations. Phenotypic heterogeneity of the disorder and absence of genotype-phenotype correlations were also observed among the studied family members. They found variations in the severity of alopecia with or without nail dystrophy. Also, they found variation in the age of onset and degree of visual disabilities. Singh et al. [7] presented the case of an 11-year-old boy who developed blurred vision in his right eye for one year duration and was found to have sparse hair.

Fundus examination revealed features of macular dystrophy including symmetrical areas of retinal pigment epithelium (RPE) hypopigmentation extending from the optic discs to the temporal maculae in the right and left fundi and similar to our study there were no other affected family members. Another report described an 11-year-old Iranian boy born with a missing left index fingernail and sparse scalp hair; the hair follicles were examined dermato-pathologically and no abnormalities were found, and there were no other dermatologic conditions, except for mild eczema. The dilated fundus examination at that time showed stable primarily macular pigmentary changes [27]. Jelani et al. [21] studied another large consanguineous pedigree from Pakistan with nine affected individuals. They were born with sparse scalp hair but otherwise normal integumentary and teeth. Examination showed degeneration of the macular pigmented epithelium. Electroretinogram (ERG) testing of two of the affected individuals showed severe retinal dysfunction. A 13-year-old Turkish girl was clinically diagnosed with congenital hypotrichosis, and was

presented with progressive deterioration of vision since the age of 8 years. Clinical examination revealed she had short, sparse and slow-growing hair without scalp erythema or scales. However, no abnormalities in eyebrows, eyelashes, nails, teeth, and limbs were reported. [28].

Conclusion

HJMD is a rare genetic cause of hypotrichosis that should be considered when assessing patients with abnormal hair growth especially when no other cause of hair loss could be detected. Fundus examination is important in suspected cases even with no visual symptoms. Further molecular DNA analysis is needed to identify the type of mutation in our patient.

Declaration of patient consent
This research was approved by the local ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms for pictures and clinical information to be reported in the study. The patient understands that her name and initials will not be published, and due efforts will be made to conceal their identity.

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