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CASE REPORT

ANKYLOBLEPHARON-ECTODERMAL DEFECTS-CLEFT LIP-PALATE SYNDROME DUE TO A NOVEL MISSENSE MUTATION IN THE SAM DOMAIN OF THE *TP63* GENE

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ABSTRACT

Ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome is a rare genetic disease with an autosomal dominant transmission, characterized by several congenital anomalies. Clinical features include ectodermal defects affecting the skin, hair, teeth, nails and sweat glands, associated with typical eyelid fusion in addition to a cleft lip and/or palate. The diagnosis is based on clinical criteria and molecular genetic testing of *TP63* gene, the gene related to AEC syndrome. In this context, most reported mutations induce an amino acid change in the sterile alpha motif (SAM) domain, and are predicted to disrupt protein-protein interactions. We here describe the case of a 2-year-old Moroccan girl diagnosed with AEC syndrome on the basis of clinical features. The molecular studies and bioinformatics tools revealed a novel heterozygous missense mutation c.1798G>C (p.Gly600Arg) in exon 14 of the *TP63* gene, that was not found in her parents. The molecular analysis and the early diagnosis of this syndrome are important to offer appropriate genetic counseling and management to patients and their families.

Keywords: Ankyloblepharon; Congenital ectodermal defect and clefting; Hay-Wells syndrome; Sterile alpha motif (SAM) domain; *TP63* gene.

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INTRODUCTION

Ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (MIM number: 106260), also called AEC syndrome and Hay-Wells syndrome [1], is one of the rarest ectodermal dysplasia forms. It is a rare autosomal dominant disorder with an unknown prevalence [2]. The manifestations of AEC syndrome are present at birth. The majority of researchers consider that the phenotype associating ankyloblepharon filiform adnatum (congenital adherences of the eyelids), cleft lip and/or palate and ectodermal dysplasia is the key criterion for the diagnosis of AEC syndrome [2-4]. Ectodermal defects usually consist of sparse wiry hair, skin erosions, onychodystrophy, dental changes and decrease in transpiration capacity.

Subsequent studies showed that this disorder most often results from mutations in the *TP63* gene that affect the sterile alpha motif (SAM) domain in the protein [2-5]. The diagnosis of AEC syndrome is firstly clinical, genetic testing of the causal gene may be useful to ascertain diagnosis and to define the inherited or *de novo* character of genetic abnormality. We report a Moroccan patient with clinical features of AEC syndrome caused by a new mutation in the SAM domain of the *TP63* gene.

MATERIALS AND METHODS

Clinical Report. The proband, a 2-years-old girl, was the third child of no consanguineous Moroccan parents. She was born at term after normal pregnancy and caesarean delivery with a birth weight of 2.5Kg. Congenital diffuse erythroderma was observed. Wiry hair, localized alopecia, scalp dermatitis and erosions, absence of eyebrows and eyelashes, in combination with eyelids fusion (Figure 1) and cleft palate were reported by the treating physician

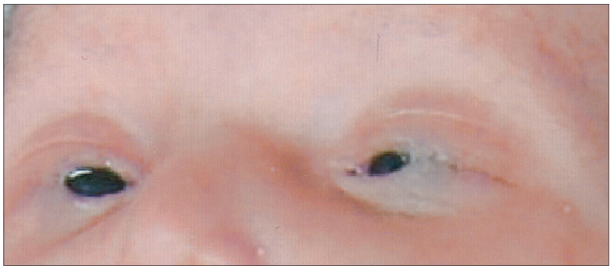

Figure 1. A newborn with ankyloblepharon.

at birth. Her hair started to grow at age of one year and teething began around 18 months of age.

Physical examination findings were characteristic and included dysmorphic features such as hypertelorism, pointed nose, prominent and low set ears in addition to a median cleft palate. The ankyloblepharon was operated at age of 3 months. Dermatological evaluation showed dry skin, sparse and frizzy hair with small areas of alopecia, sparse eyebrows and absent eyelashes. Patient had also oligodontia and dystrophic teeth and nail (Figure 2). The parents report

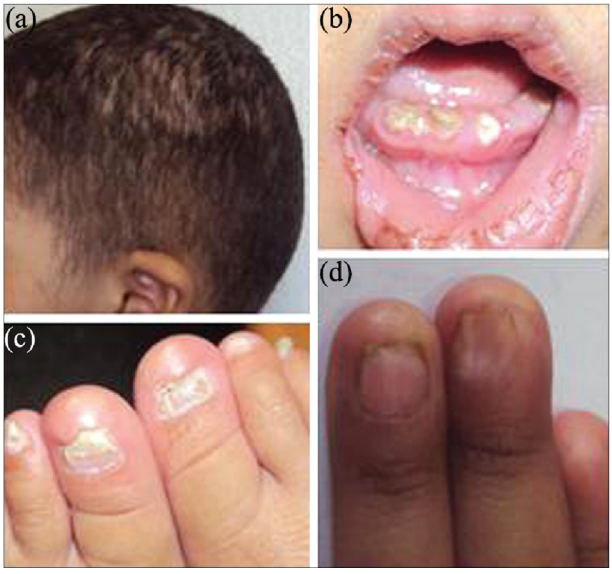

Figure 2. Phenotypic features of patient with AEC syndrome: (a): sparse and frizzy hair with small areas of alopecia; (b): oligodontia and dystrophic teeth (c); (d): dystrophic nails.

that the patient has decreased sweating and heat intolerance. They report also that she has slow growth of the hair, multiple scalp infections treated and constantly watering eyes. Ophthalmological examination revealed obstruction of the lacrymal ducts and normal visual acuity. The patient also has a vaginal atresia discovered during a systematic medical examination. There were no malformations in the hands or feet. The psychomotor development, her weight and height were normal for her age. Cardiac, abdominal and pelvic ultrasonography did not find any malformations.

The parents are healthy, without a positive history for congenital and genetic diseases. There were no similar cases in the family.

Genetic Testing. Informed parental consent was obtained. DNA was extracted from peripheral blood collected from the affected child and his parents. According to the approach described in the literature, we performed sequence analysis of *TP63* gene focusing on exons 13 and 14, which include the SAM domain [2]. *TP63* mutations were identified by bi-directional sequencing of genomic DNA. Alamut interface with Polyphen2 and SIFT softwares were used to perform bioinformatic predictions of mutation effects.

RESULTS

The sequencing of *TP63* gene in the patient DNA has led to the identification of a missense variant in the heterozygous state in exon 14 (c.1798G>C; p.Gly600Arg) (Figure 3). To our knowledge, this variant has never been

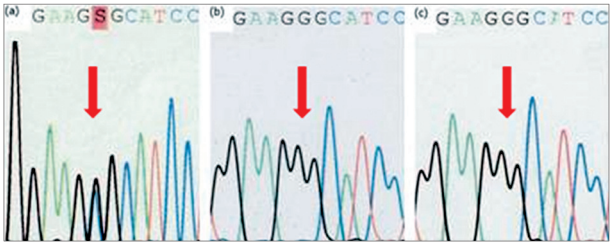

Figure 3. Sequence analysis of the *TP63* gene: (a) the patient DNA shows a heterozygous c.1798G>C mutation encoding a p.Gly600Arg substitution; the mutation is absent in the father's (b) and mother's (c) DNA.

reported in the literature or in the variations databases. Referring to Polyphen2, this amino acid substitution was predicted to be more likely deleterious. In the same context, SIFT predicted a damaging effect. Gly600 is located in the SAM domain of *TP63* gene and its substitution to arginine produces a significant chemical change. According to the standards and guidelines for the interpretation of clinical significance of ACMG sequence variation, the variant c.1798G>C (p.Gly600Arg) in *TP63* gene was in line with the interpretation rule of "likely pathogenic" mutation [PM1+PM2+PM3+PP2+PP3]. This variant was not found in either of the parents (Figure 3) and was therefore treated as the disease-causing mutation.

DISCUSSION

Hay-Wells or AEC syndrome is an autosomal dominant genetic disease characterized the presence of ankyloblepharon, ectodermal abnormalities (including sparse

and frizzy hair, skin defects, nail alterations, dental changes, and hypohidrosis) associated with a clefting of the lip and/or the palate. The majority of authors consider these as the cardinal features suggestive of this syndrome [2-10]. It has been reported that AEC syndrome includes erythroderma at birth with desquamation, superficial erosion and crusting [2]. These clinical manifestations were found in the case reported here. Erosive dermatitis and recurrent scalp infection at birth and during infancy, as present in our case, are major signs that orient differential diagnosis with similar genetic disorders. [11,12]. Eyelids fusion can be partial or complete, this pathognomonic phenomenon is known as ankyloblepharon filiforme adnatum. Lacrymal duct obstruction is a common feature of this syndrome and other eye findings can be observed. Other rare clinical findings include ear canal atresia, supernumerary nipples, heart defects, and genitalia anomalies [11]. Our patient has vaginal atresia, this exceptional finding has been reported in clinical databases as a very rare symptom in this syndrome [2].

The differential diagnoses include ichthyosis and epidermolysis bullosa, but AEC syndrome is distinguished by the type of skin lesions and the associated clefting and eye findings [11]. We have also eliminated other syndromes, especially acro-dermo-ungual-lacrimal-tooth syndrome (ADULT syndrome), ectrodactyly-ectodermal dysplasia-cleft lip/palate syndrome (EEC), split hand/foot malformation (SHFM) and limb-mammary syndrome (LM Syndrome). Although these syndromes present overlapping phenotypes, distinct clinical features may be useful to differentiate them [2,13].

AEC syndrome is due to mutations in *TP63*, an essential gene for the maintenance of progenitor-cell populations that promote epithelial development and morphogenesis [4]. There has been shown that the most cases of this syndrome are caused by heterozygous missense mutations in the SAM domain, corresponding to exons 13 and 14 of the *TP63* gene [3-5]. We have identified in our patient a new heterozygous missense substitution (c.1798G>C) in exon 14 of this gene leading to a p.Gly600Arg substitution in the SAM domain of the protein. The unaffected parents were not carriers of the mutation, which indicated that the mutation is assumed to be *de novo* in our patient (except for a low risk of parental germline mosaicism [14]). Bio-informatics tools predicted the pathogenicity of this mutation.

The genetic testing result of the *TP63* gene supports our clinical diagnosis of AEC syndrome and showed the non-inherited nature of the causal mutation. These clinical and molecular findings are important for genetic counseling to the family. Regular evaluation of the patient with a multidisciplinary team was introduced to ensure adequate management and treatment of disease manifestations.

Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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