Medical Genetics
Official Journal of Turkish Society of Medical Genetics

Case Report

A FAMILY FROM TURKEY WITH HAY WELLS SYNDROME RESULTING FROM HETEROZYGOUS MUTATION OF P63 GENE

Türkiye'deki bir ailede heterozigot p63 mutasyonunun neden olduğu Hay Wells sendromu

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ABSTRACT

Objective: Hay Wells syndrome, also known as ankyloblepharon–ectodermal dysplasia–clefting (AEC) syndrome, is a rare autosomal dominant genetic syndrome. Its major features are ankyloblepharon (fusion of the eye lids), ectodermal dysplasia and orofacial clefting. It is known that heterozygous mutations of the p63 gene cause this syndrome. A two-month-old boy was referred to our clinic with ankyloblepharon, cleft palate and a dysmorphic facial appearance reminiscent of this syndrome.

Results: When we observed the findings of ectodermal dysplasia on the physical examination, we made the prediagnosis of Hay Wells syndrome. It was learned from the family history that the father of the baby was mentally retarded with clefting of the feet. P63 gene sequence analysis was performed on the boy and the father in Turin. A heterozygote c.1553G>T mutation was found at both father and child.

Conclusion: It is important, in the family history, if one of the parents has mild findings of autosomal dominant diseases it should not be missed and should be considered in the diagnosis of rare genetic diseases. We re-emphasized the fact that some similar syndromes may be caused by mutations of the same gene.

Key words: AEC, ectodermal dysplasia, autosomal dominant, p63 gene

ÖZET

Amaç: Ankyloblepharon–ectodermal dysplasia–clefting (AEC) sendromu olarak da bilinen Hay Wells nadir bir otozomal dominant genetik sendromudur. Başlıca özellikleri ankiloblefaron (Göz kapaklarının füzyonu), ektodermal displazi ve örofasiyal yarıklanmadır. P63 geninin heterozigot mutasyonlarının bu sendroma yol açtığı bilinmektedir. Bu sendromu hatırlatan ankiloblefaron, yarık damak ve dismorfik yüz görünümüyle bu sendromu hatırlatan 2 aylık bir erkek çocuğu kliniğimize danışılmıştır.

Bulgular: Fizik muayenede ektodermal displazi bulgularını gözlemlediğimizde Hay Wells sendromu ön tanısını koyduk. Aile öyküsünde bebeğin babasının ayaklarında yarıklanma ve mental retardasyonu olduğunu öğrendik. Baba ve oğlunun DNA sekans analizi Turin'de yapıldı. Her ikisinde de heterozigot bir c.1553G>T mutasyonu bulundu.

Sonuç: Aile öyküsü alındığında ebeveynden birinde de hastalığın hafif bulgularının olabileceği gözden kaçırılmamalı ve nadir genetik hastalıkların tanısında akla gelmelidir. Yazıda bu gendeki mutasyonların bazı benzer sendromlara da yol açabileceğini vurguladık.

INTRODUCTION

Hay Wells syndome, also known as ankyloblepharon–ectodermal dysplasia–clefting (AEC) syndrome, is one of the ectodermal dysplasia syndromes. It is an autosomal dominant disorder characterized by findings of ectodermal dyplasia including alopecia, scalp infections, dystrophic nails, hypodontia, ankyloblepharon and cleft lip-palate (1). It was first described by Hay and Wells in 7 individuals with different familial penetrance (2). Sporadic cases have also rarely been described (3). Ectrodactyly, also known as split hand/foot malformation, is a central reduction defect of the hand and foot, frequently accompanied by syndactyly (4, 5).

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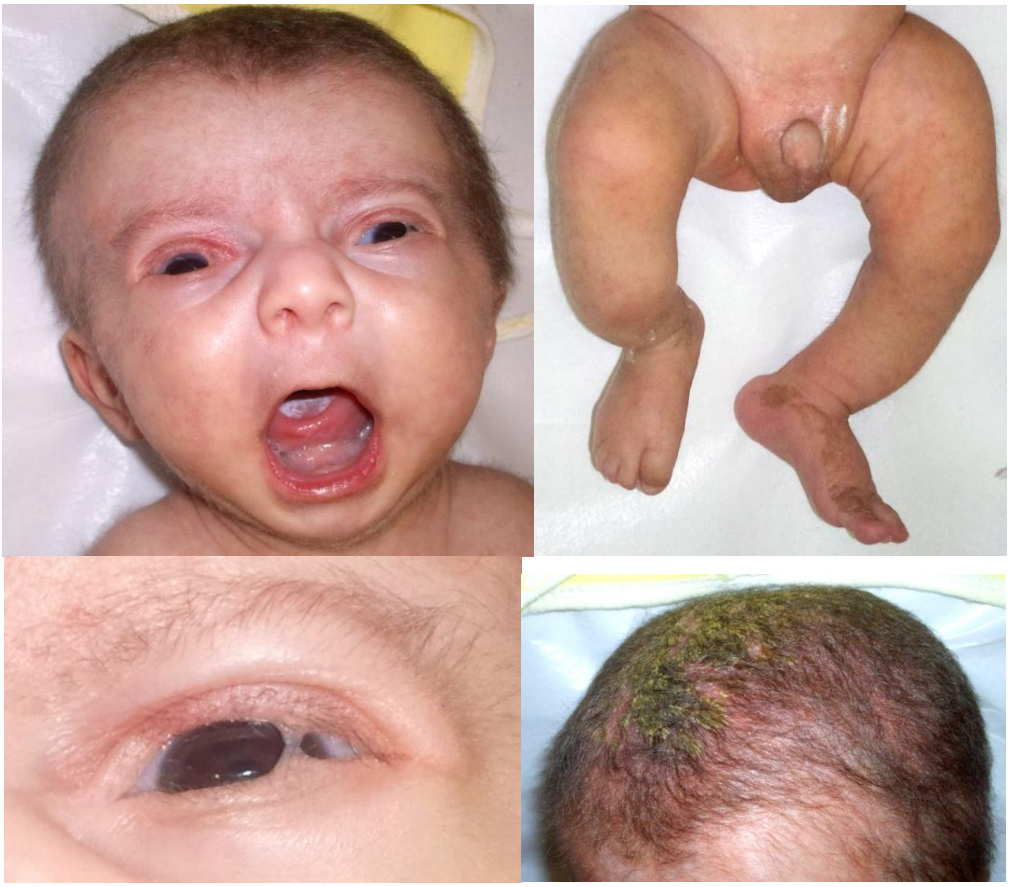

Figure 1. Physical appearance of the patient

Ectodermal dysplasia may present as dry skin, scarce hair, dystrophic nails, hypoplastic teeth and lacrimal duct obstruction. There may be lip and/or palate clefting (6). Advanced studies have demonstrated that mutations in the p63 gene cause this pathology. The P63 gene, also known as p51 or KET, is homologous to the tumor supressor gene (TP53) (1). Heterozygous mutations of the p63 gene cause 6 different syndromes with various combinations of ectodermal dysplasia, orofacial clefting and skeletal malformations: Hay Wells syndrome, Rapp-Hodgkin syndrome, Bowen-Armstrong (EEC) syndrome ADULT (acro–dermato–ungual- lacrimal-tooth) syndrome, LADD (lacrimo-auricular-dental-digital) syndrome and Isolated Split Hand/Foot Malformation (SHFM) type 4. The P63 protein has 4 protein motives, namely the transactivation domain (TA), the DNA-binding domain, the tetramerization domain, and the sterile alpha domain (SAM) (1). It was shown that mutaions in the DNA-binding domain cause EEC syndrome, and mutations in the SAM domain cause Hay Wells syndrome (1, 7, 8). The Hay Wells syndrome and the Rapp Hodgkin syndrome are similar and share different findings of the same clinical entity (8, 9). These two syndromes are characterized by ankyloblepharon filiforme adnatum (fusion of the eye lids), severe skin erosions, abnormal hair structure (pili torti/pili canaliculi, scarce hair) and cleft palate (may be combined with cleft lip). Severe skeletal malformations such as ectrodactyly are rarely seen with these syndromes (10). Alopecia and absence of eyelashes and eyebrows are frequently observed in Hay Wells syndrome. Clefting is present in 80% of the cases, frequently in the form of cleft palate or cleft lip-palate. Ankyloblepharon is observed in 44% of the cases, and hearing loss has been reported as 40%. Nail and teeth deformities are seen in 75-80% of AEC patients and half of the patients have lacrimal duct atresia. Sweating problems and mammary gland and/or nipple hypoplasia have rarely been reported. Mutations causing AEC and RHS are on the 3’ end of the p63 gene and they are missense or frameshift mutations usually on exon 13 and 14 affecting the SAM and the TI domains. Although mutations causing AEC and RHS Syndromes are on the alpha end of the p63 gene, Rinne et al. described new mutations on the 5’ end of the p63 gene (11).

In this paper, we present a family in which the father and the son were affected by heterozygous mutation of the TP63 gene. The family is originally from the city of Mardin in Turkey. The significant phenotypical expressivity difference in the affected father and the child has also been observed in this syndrome of autosomal dominant inheritance.

CASE REPORT

A two-month-old male infant, who had been followed-up in the neonatal intensive care unit was

referred to our clinic due to the presence of multiple anomalies. The prenatal history was not clear and the baby had a healthy 4-year-old brother. There was no consanguinity between the mother and the father, and the father had scarce hair, mild mental retardation and ectrodactyly of the feet.

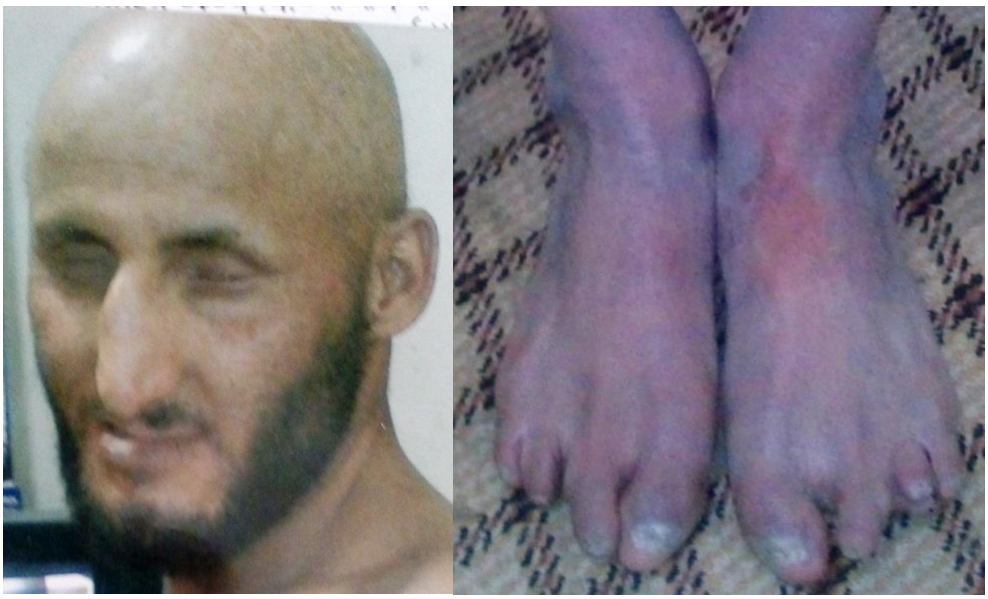

Figure 2. Physical appearance of father

On physical examination, the height and the weight were close to the lowest limit (3p), the hair was coarse, sparse, dry and thin, the eyebrows were scarce; he had a large scalp erosion, bilateral ankyloblepharon, blurry corneas and hypertelorism (Figure 1). The nasal tip was prominent and pointing downward, the ears pointed downward. He had retro-micrognathia, cleft palate, hypoplasic nails, inclination of the tibia and the femur bilaterally (o'bain deformity), right foot 2nd and 3rd toe partial skin syndactyly and shortness. The left testis was in the inguinal canal. We could not perform the physical examination on the father; we could only see the photos that we obtained from the family. The photos of the father revealed alopecia, scarce eyebrows and eyelashes, small and closed eyes resembling ankyloblepharon, prominent and downward pointing nasal tip, prognatic big chin and ectrodactyly of the feet (Figure 2). Furthermore, it was stated that the father had mild mental retardation.

In the laboratory tests, the results of the complete blood count and biochemical tests were normal.
TORCH serology tests were also normal. Abdominal USG was normal. Pelvic USG revealed bilateral hypoplastic femoral heads. Trans-fontanelle US and echocardiography were normal. There was no problem in the neonatal hearing test. The X-ray showed a deformity of the tibia and the femur, forming a square appearance. The karyotype analysis was normal 46, XY.

In the light of above findings, the patient was pre-diagnosed with Hay Wells syndrome. We thought that the father could also be affected in accordance with the autosomal dominant inheritance pattern. The p63 gene analysis was performed from peripheral blood leukocytes in Turin University Pediatrics and Adolescents Clinic. A heterozygous c.1553G>T (p.Gly518Val) mutation on exon 13 of the p63 gene was determined in both the father and the son, which confirmed the diagnosis of Hay Wells syndrome.

CONCLUSION

It is well known that c.1553G>T (p.Gly518Val) mutation on exon 13 of p63 gene causes Hay Wells syndrome, which also happened in our family. Ectodermal dysplasias are a heterogenous disease group affecting the hair, nail, skin, tooth and the sweat glands, which are frequently accompanied by deafness, skeletal anomalies, mental retardation, ichthiosis, palmoplantar keratoderma, eye anomalies, facial deformities, cleft lip-palate and other systemic findings (2, 12, 13). Hay Wells syndome is a rare autosomal dominant syndrome characterized by ankyloblepharon filiforme adnatum, ectodermal dysplasia and cleft lip-palate (14). Cases with Hay Wells syndrome may have alopecia of varying degrees, scarce hair, onicodystrophy, palmoplantar hyperkeratosis, pigmentation changes of the skin, hypohydrosis, hypodontia, tooth malformations and ear deformities (2, 14). Lacrimal duct obstruction is also frequently observed. Ankyloblepharon is the complete or partial fusion of the eyelids and it is mostly reported to be sporadic. Moreover, ankyloblepharon is also described in trisomy 18 and CHAND (Curly Hair, Ankyloblepharon-Nail Dystrophy) (15). All of these described findings were present in our case.

The P63 protein, coded by the p63 gene, has four domains: the transactivation domain (TA), the DNA-binding domain, the tetramerization domain, and the

sterile alpha domain (SAM). It was shown that missense mutations on exon 13 and 14 causing Hay Wells syndrome include the SAM domain (1). Mutations on the DNA-binding domain cause EEC syndrome and this domain includes all the p53 isotypes (1, 7, 8). The SAM domain includes the dominant-negative isotypes of p63. Investigators emphasize that disruption of the interaction between the SAM domain and other proteins causes Hay Wells syndrome. This interacting protein may be an important modulator for the transcriptional activity of p63, and this may play a role in ankyloblepharon and scalp dermatitis in Hay Wells syndrome and ectrodactyly in EEC syndrome; ectrodactyly is seen less frequently in Hay Wells syndrome (1).

Our patient's father was described as mentally retarded, although it has been reported as a rare feature in Hay Wells syndrome.

The variable expressivity in autosomal dominant syndromes is also seen in our case and his father. Genetic counselling should be provided and, prenatal diagnosis or preimplantation genetic diagnosis should also be offered.

Acknowledgements: This case report was supported with the family's help. The data presented, the statements made, and the views expressed are solely the responsibility of the author. The permissions were gotten from the family for publish the photographs and information.

Consent Section: Written informed consent was obtained from the patient for publication of this case report and any accompanying images/photos. A copy of the written consent is available for review by the Editor of this journal. Ethical approval of this manuscript was given by Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee for use the patients' results of genetic analysis.

REFERENCES

1. McGrath JA, Duijf PH, Doetsch V, Irvine AD, de Waal R, Vanmolkot KR, et al: Hay-Wells syndrome is caused by heterozygous missense mutations in the SAM domain of p63. Hum Mol Genet 2001;10(3):221-9.
2. Hay RJ, Wells RS: The syndrome of ankyloblepharon, ectodermal defects, and cleft lip and palate: an autosomal dominant condition. Br J Dermatol 1976;94:277-89.
3. Payne AS, Yan AC, Ilyas E, Li W, Seykora JT, Young TL, et al: Two novel TP63 mutations associated with the ankyloblepharon, ectodermal defects, and cleft lip and palate syndrome - a skin fragility phenotype. Arch Dermatol 2005;141:1567-73.
4. Jones KL: Smith's recognizable patterns of human malformation. 4th ed. New York: Harcourt Brace Jovanich, WB Saunders 1988:252-3.
5. Jorgenson RJ: Ectrodactyly-ectodermal dysplasia-clefting syndrome. In: Buyse ML, ed. Birth defects encyclopedia. 1st ed. Dover: Center for Birth Defects Information Service 1990:607-8.
6. Gorlin RJ, Cohen MM, Levin LS: Syndromes of the head and neck. 3rd ed. New York: Oxford University Press 1990:716-19.
7. Celli J, Duijf P, Hamel BC, Bamshad M, Kramer B, Smits AP, et al: Heterozygous germline mutations in the p53 homolog p63 are the cause of EEC syndrome. Cell 1999; 99:143-153.
8. Rinne T, Hamel B, Bokhoven HV, Brunner HG: Pattern of p63 mutations and their phenotypes-update. Am J Med Genet A 2006; 140A: 1396-1406.
9. Bertola DR, Kim CA, Albano LM, Scheffer H, Meijer R, vanBokhoven H: Molecular evidence that AEC syndrome and Rapp-Hodgkin syndrome are variable expression of a single genetic disorder. Clin Genet 2004. 66(1):79-80.
10. Rinne T, Bolat E, Meijer R, Scheffer H, van Bokhoven H: Spectrum of p63 mutations in a selectedpatientcohortaffectedwithankyloblepharon-ectodermaldefects-cleftlip/palatesyndrome (AEC). Am J Med Genet A 2009;149A(9):1948-51.
11. Rinne T, Clements SE, Lamme E, Duijf PH, Bolat E, Meijer R, et al: A novel translation re-initiation mechanism for the p63 gene revealed by amino-terminal truncating mutations in Rapp-Hodgkin/Hay-Wells-like syndromes. Hum Mol Genet 2008; 17(13):1968-77.
12. Itin PH, Fistarol SK: Ectodermal dysplasias. Am J Med Genet C Semin Med Genet 2004;131:45-51.
13. Visinoni AF, Lisboa-Costa T, Pagnan NAB, Chautard-Freire-Maia EA: Ectodermal Dysplasias: Clinical and Molecular Review. Am J Med Genet A 2009;149A:1980-2002.
14. Macias E, de Carlos F, Cobo J: Hay-Wells syndrome (AEC): a case report. Oral Dis 2006;12:506-8.
15. Sharkey D, Marlow N, Stokes J: Ankyloblepharon filiforme adenatum. J Pediatr 2008;152:594.