Göztepe Tıp Dergisi 29(1):69-72, 2014
doi:10.5222/J.GOZTEPETRH.2014.069

ISSN 1300-526X

OLGU SUNUMU *Genetik*

Split-hand, and split-foot malformations: A family

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SUMMARY

Hand and foot functions of the cases with cleft hand and foot deformities are usually good. Autosomal recessive inheritance is frequently seen in a patient with a family history of cleft hand and foot. However, our cases had autosomal dominant inheritance trait. Herein we have presented the family that had congenital cleft hand and foot deformity.

Key words: *Split-hand/split-foot malformations, autosomal dominant inheritance*

ÖZET

Yarık el/yarık ayak malformasyonlu bir aile

Yarık el ve ayak deformiteleri bulunan olgularda el ve ayak fonksiyonları genellikle iyidir. Ailesinde yarık el ve ayak bulunan durumlarda sıklıkla otozomal resesif geçiş mevcuttur. Ancak, olgularımız otozomal dominant geçişe sahipti. Biz burada doğuştan yarık el ve ayak deformitesi olan bir aileyi sunduk.

Anahtar kelimeler: *Yarık el/yarık ayak malformasyonları, otozomal dominant geçiş*

Split-hand/foot malformation (SHFM) is a congenital limb malformation with median clefts of the hands and feet, and aplasia and/or hypoplasia of the phalanges. The aetiogenesis of SHFM is not well understood, however, defects in the development and/or differentiation of the apical ectodermal ridge (AER) are most probably involved [1,2]. Five different forms of SHFM exist in humans associated with different genetic anomalies [3]. SHFM1 is associated with genomic lesions on chromosome 7q21 in a minimal region, which includes the distal-less-related homeogenes DLX5 and DLX6 [4,5]. The double knockout of Dlx5 and Dlx6 (Dlx5/6 D-KO) in the mouse leads to ectrodactyly in the hind limbs [6,7] with defective development of the middle portion of the AER. Dlx genes code for homeodomain transcription factor homologues to insect distal-less and play a key role in the control of appendage development [8-10]. In mammals, there are six Dlx genes organized into three tail-to-tail bigenic clusters, Dlx1/2, Dlx5/6 and Dlx3/7 [10,11]. Dlx genes are expressed in craniofacial primordia, in the developing brain, ectodermal placodes, and limbs, where they are both expressed in the AER [7,9,12] and in the underlying mesenchyme.

SHFM4 is caused by mutations in p63, a gene coding for a transcription factor homologous to p53 and p73 [13]. Mutations of p63 are also associated with other autosomal, dominant, human syndromes, including ectrodactlyly-ectodermal dysplasia and cleft lip (EEC). p63 plays a major role in the control of epithelial morphogenesis [1,2] controlling the expression of stratification markers. p63 knockout mice (p63 KO) show severedefects affecting their skin, limbs, craniofacial skeleton, hair and mammary gland and in general fail to form normal ectodermal structures with profound defects in squamous epithelial lineages. It has been shown that both p63 and Dlx5 and Dlx6 (Dlx5/6) play a critical role in the control of AER development [1,2,6,7]. We report five cases with ectrodactyly involving hands or feet.

Geliş tarihi: 29.05.2013
Kabul tarihi: 15.07.2013
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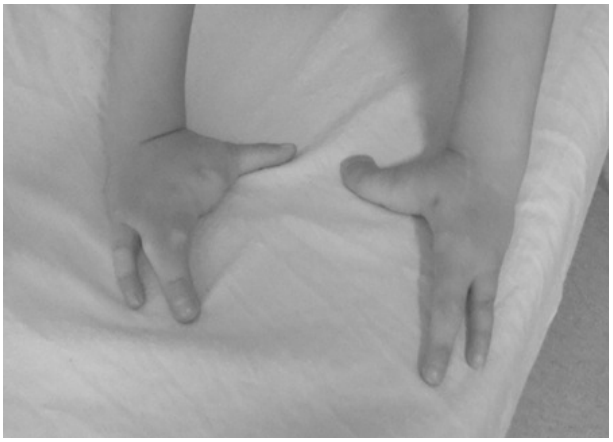

Figure 1a.

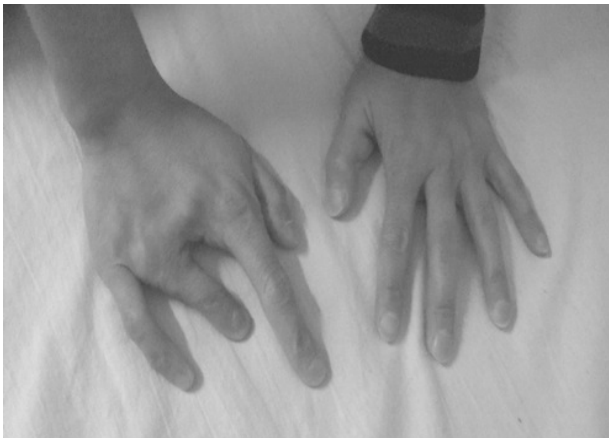

Figure 1c.

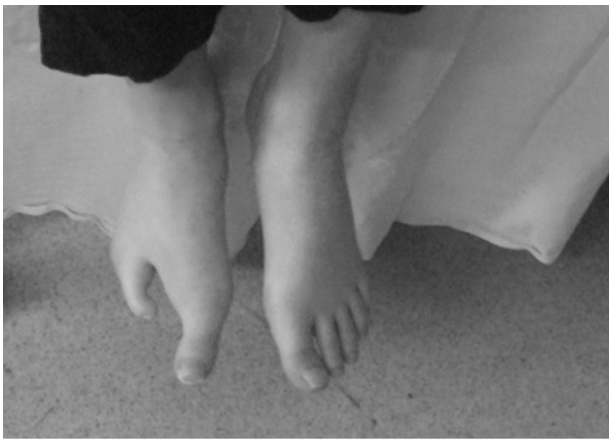

Figure 1b.

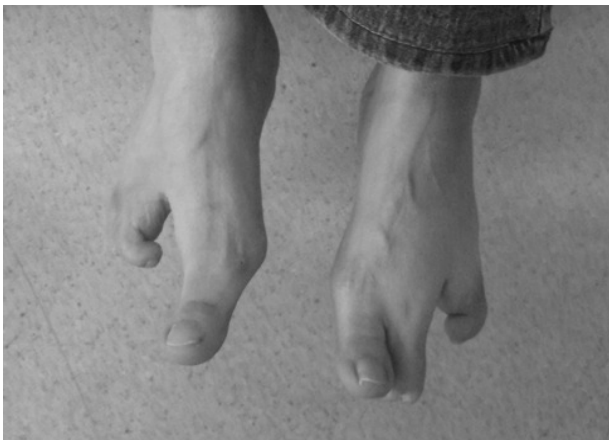

Figure 1d.

CASE REPORT

A 6-year-old boy presented with deformed hands and feet since birth. There were median clefts of both hands and right foot. In the left hand, there was absence of third and fourth fingers and, in the right hand, there was absence of third and fourth fingers (Figure 1a). The right food had a deep midline cleft. In the right foot, there was absence of third and fourth fingers (Figure 1b). There were no other dysmorphic features. The systemic examination was normal. He was a product of non-consanguineous marriage and term normal delivery with no significant perinatal events. The index case was second in birth order. The first sibling was a female baby. This baby also had similar deformed hands (Figure 1c). The mother had median clefts of the feet (Figure 1d). The father did not notice any abnormal features. His aunt had median clefts of the feet (Figure 1e). His maternal grand-father had similar deformed hands and feet. However, there was no history of similar clinical profile in any of the relatives of the father.

DISCUSSION

SHFM involves median clefts of the hands and feet with associated syndactyly, aplasia and/or hypoplasia of the phalanges, metacarpals and metatarsals [14]. Its incidence has been reported to be about 1 in 90,000 babies with no sex predeliction [15]. Two expressions of SHFM occur, one with isolated involvement of the limbs, known as the non-syndromic form, and the second, the syndromic form, with associated anamolies such as tibial aplasia, mental retardation, ectodermal and craniofacial findings,

orofacial clefting and deafness [16]. Our cases belongs to the non-syndromic type of SHFM as there is no associated anomaly. SHFM patients have frequently autosomal recessive inheritance. However, our cases had autosomal dominant inheritance.

The developmental patterning of the limbs results from gradients of signalling molecules in three spatial dimensions:proximo-distal (shoulder-finger direction), antero-posterior (thumb-little finger direction), and dorso-ventral (back-palm direction) (Figure 2). For correct development, three specialized cell clusters are of primary importance: the apical ectodermal ridge (AER), the progress zone (PZ), and the zone of polarizing activity (ZPA). These groups of cells produce signalling molecules that determine the fate of neighbouring cells by instructing them to remain undifferentiated, to proliferate, or to differentiate into a particular cell type.

Failure to initiate the AER leads to truncations of all skeletal elements of the limb (stylopod, zeugopod, autopod). This was first demonstrated by studies in which the AER was surgically excised [17,18]. Since SHFM only affects the autopod, this probably reflects a failure to maintain the normal function of the AER (Figure 2). Genetic defects, as well as environmental factors, may cause ectrodactyly by interfering with AER function or maintenance. For instance, treatment of pregnant rats with retinoic acid induces limb malformations, including ectrodactyly, by inducing AER cell death [19]. Other environmental factors that are known to induce ectrodactyly in rodents include cadmium, hydroxyurea, cytarabine, methotrexate, ethanol, caffeine, cocaine, valproic acid, acetazolamide and methoxyacetic acid [20].

The AER, which is located at the distal rim of the developing limb bud, is crucial for the formation and identity of digits. Signals from the AER allow the underlying mesenchymal cells of the PZ to maintain their proliferative activity [21-25]. A number of key players in the AER are known. These include fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), WNT signalling molecules, and homeobox-containing proteins, such as MSX1 and MSX2. AER formation is induced by mesodermal signalling to the overlying ectoderm. Molecules involved in this process include FGF10, its receptor FGFR2 [26], and BMPs, which control the ectodermal expression of MSX transcription factor genes [27].

FGFs fulfil two major functions. They maintain limb outgrowth by inducing proliferation of mesenchymal cells in the PZ and they maintain Sonic Hedgehog (SHH) expression in the ZPA. Important signalling molecules involved in the latter are BMPs, whose activity is modulated by SHH signalling from the ZPA, through Formin (FMN) and Gremlin (GRE) [28,29]. Several FGFs are restricted to the AER: FGF4, FGF8, FGF9 and FGF17. These AER-FGFs are crucial for limb development. In mice, simultaneous conditional ablation of Fgf4 and Fgf8 is compatible with normal AER initiation, but defective gene expression in the underlying mesenchyme. The AER itself is maintained until embryonic day E11 [29], when it begins to degenerate. The Fgf4 and Fgf8 double knockouts have aplasia of both proximal and distal limb elements, which may be explained by a reduction of mesenchymal cells in the limb bud [23].

Ectrodactyly can be treated surgically in order to improve function and appearance. Prosthetics may also be used. Parents should be counseled regarding the possibility of recurrence of the disease in the future siblings and antenatal diagnosis by ultrasonography should be offered [30,31].

REFERENCES

1. **Yang A, Schweitzer R, Sun D, et al.** p63 is essential for regenerative proliferation in limb, craniofacial and epithelial development. *Nature* 1999;398:714-718. http://dx.doi.org/10.1038/19539
2. **Mills AA, Zheng B, Wang XJ, et al.** p63 is a p53 homologue required for limb and epidermal morphogenesis. *Nature* 1999;398:708-713. http://dx.doi.org/10.1038/19531
3. **Basel D, Kilpatrick MW, Tsipouras P.** The expanding panorama of split hand foot malformation. *Am J Med Genet A* 2006;140:1359-1365.

http://dx.doi.org/10.1002/ajmg.a.31304
4. **Simeone A, Acampora D, Pannese M, et al.** Cloning and characterization of two members of the vertebrate Dlx gene family. *Proc Natl Acad Sci USA* 1994;91:2250-2254. http://dx.doi.org/10.1073/pnas.91.6.2250
5. **Crackower MA, Scherer SW, Rommens JM, et al.** Characterization of the split hand/split foot malformation locus SHFM1 at 7q21.3 – q22.1 and analysis of a candidate gene for its expression during limb development. *Hum Mol Genet* 1996;5:571-579. http://dx.doi.org/10.1093/hmg/5.5.571
6. **Merlo GR, Paleari L, Mantero S, et al.** Mouse model of split hand/ foot malformation type I. *Genesis* 2002;33:97-101. http://dx.doi.org/10.1002/gene.10098
7. **Robledo RF, Rajan L, Li X, Lufkin T.** The Dlx5 and Dlx6 homeobox genes are essential for craniofacial, axial, and appendicular skeletal development. *Genes Dev* 2002; 16: 1089-1101. http://dx.doi.org/10.1101/gad.988402
8. **Panganiban G.** Distal-less function during Drosophila appendage and sense organ development. *Dev Dyn* 2000; 218: 554-562. http://dx.doi.org/10.1002/1097-0177(200008)218:4<554::AID-DVDY1023>3.0.CO;2-#
9. **Merlo GR, Zerega B, Paleari L et al.** Multiple functions of Dlx genes. *Int J Dev Biol* 2000;44:619-626.
10. **Zerucha T, Ekker M.** Distal-less-related homeobox genes of vertebrates: evolution, function, and regulation. *Biochem Cell Biol* 2000;78:593-601. http://dx.doi.org/10.1139/bcb-78-5-593
11. **Ghanem N, Jarinova O, Amores A, et al.** Regulatory roles of conserved intergenic domains in vertebrate Dlx bigene clusters. *Genome Res* 2003;13:533-543. http://dx.doi.org/10.1101/gr.716103
12. **Stock DW, Ellies DL, Zhao Z, et al.** The evolution of the vertebrate Dlx gene family. *Proc Natl Acad Sci USA* 1996; 93:10858-10863. http://dx.doi.org/10.1073/pnas.93.20.10858
13. **Park BK, Sperber SM, Choudhury A, et al.** Intergenic enhancers with distinct activities regulate Dlx gene expression in the mesenchyme of the branchial arches. *Dev Biol* 2004;268:532-545. http://dx.doi.org/10.1016/j.ydbio.2004.01.010
14. **Barsky AJ.** Cleft Hand: Classification, incidence and treatment. *J Bone Joint Surg* 1964;46:1707-1720.
15. **Blauth W, Borisch NC.** Cleft feet. Proposals for a new classification based on roentgenographic morphology. *Clin Orthop* 1990;258:41-48.
16. **Saunders JWJ.** The proximo-distal sequence of the origin of the parts of the chick wing and the role of the ectoderm. *J Exp Zool* 1948;108:363-403. http://dx.doi.org/10.1002/jez.1401080304
17. **Summerbell D.** A quantitative analysis of the effect of excision of the AER from the chick limb-bud. *J Embryol Exp Morphol* 1974;32 651-660.
18. **Sulik KK, Dehart DB.** Retinoic-acid-induced limb malformations resulting from apical ectodermal ridge cell death. *Teratology* 1988;37:527-537. http://dx.doi.org/10.1002/tera.1420370602
19. **Seto ML, Nunes ME, MacArthur C, et al.** Pathogenesis of ectrodactyly in the Dactylaplasia mouse: aberrant cell death of the apical ectodermal ridge. *Teratology* 1997;56: 262-270. http://dx.doi.org/10.1002/(SICI)1096-9926(199710)56:4<262::AID-TERA5>3.0.CO;2-0
20. **Summerbell D, Lewis JH, Wolpert L.** Positional information in chick limb morphogenesis. *Nature* 1973;244:492-496. http://dx.doi.org/10.1038/244492a0
21. **Sun X, Mariani FV, Martin GR.** Functions of FGF signalling from the apical ectodermal ridge in limb development. *Nature* 2002;418:501-508. http://dx.doi.org/10.1038/nature00902
22. **Dudley AT, Ros MA, Tabin CJ.** A re-examination of proximodistal patterning during vertebrate limb development. *Nature* 2002;418:539-544. http://dx.doi.org/10.1038/nature00945
23. **Duboule D.** Making progress with limb models. *Nature* 2002;418:492-493. http://dx.doi.org/10.1038/418492a
24. **Saunders J.** Is the progress zone model a victim of progress? *Cell* 2002;110:541-543. http://dx.doi.org/10.1016/S0092-8674(02)00936-4
25. **Martin GR.** The roles of FGFs in the early development of vertebrate limbs. *Genes Dev* 1998;12:1571-1586. http://dx.doi.org/10.1101/gad.12.11.1571
26. **Pizette S, Abate-Shen C, Niswander L.** BMP controls proximodistal outgrowth, via induction of the apical ectodermal ridge, and dorsoventral patterning in the vertebrate limb. *Development* 2001;128:4463-4474.
27. **Zuniga A, Haramis AP, McMahon AP, et al.** Signal relay by BMP antagonism controls the SHH/FGF4 feedback loop in vertebrate limb buds. *Nature* 1999;401:598-602. http://dx.doi.org/10.1038/44157
28. **Pizette S, Niswander L.** BMPs negatively regulate structure and function of the limb apical ectodermal ridge. *Development* 1999;126:883-894.
29. **Drossopoulou G, Lewis KE, Sanz-Ezquerro JJ, et al.** A model for anteroposterior patterning of the vertebrate limb based on sequential long- and short-range Shh signalling and Bmp signalling. *Development* 2000;127:1337-1348.
30. **Pinette M, Garcia L, Wax JR, et al.** Familial ectrodactyly. J Ultrasound Med 2006;25:1465-1467.
31. **Arbués J, Galindo A, Puente JM, et al.** Typical isolated ectrodactyly of hands and feet: Early antenatal diagnosis. *J Matern Fetal Neonatal Med* 2005;17:299-301. http://dx.doi.org/10.1080/14767050500072839