CASE REPORT

Recep Eroz[1]
Mustafa Dogan[1]
Semih Bolu[2]
Hüseyin Yuce[1]

[1]Duzce University Medical Faculty, Department of Medical Genetics, Duzce, Turkey
[2]Duzce University Medical Faculty, Department of Pediatric Endocrinology, Duzce, Turkey

Corresponding Author:
Recep Eroz
Duzce University Medical Faculty, Department of Medical Genetics, Duzce (81820),Turkey
Phone: +90 380 5421128,
Email: eroz38r@hotmail.com

Received: 27.03.2017
Acceptance: 15.06.2017
DOI: 10.18521/ktd.300827

Konuralp Medical Journal
e-ISSN1309–3878
konuralptipdergi@duzce.edu.tr
konuralptipdergisi@gmail.com
www.konuralptipdergi.duzce.edu.tr

A Seven Years Old Girl with Klippel-Feil Syndrome, Bilateral Sprengel Deformity, Congenital Unilateral Renal Agenesis and A Heterozygous Mutation M680I(G>C) in The MEFV Gene

ABSTRACT

KFS is characterized by fusion of cervical vertebrae that restricts the range of motion of the neck, short neck and low posterior hairline. We presented at a female KFS case within bilateral Sprengel deformity, congenital unilateral renal agenesis and correlation by MEFV gene mutation.

Physical examination, routin biochemical evaluation, radiological evaluation of the case were performed and family history was taken. Additionally, chromosomal analysis, complete exom sequencing analysis of MEFV gene and the sequencing analysis of GDF6 gene were conducted.

She had short neck, limitation of the movement of head and neck and a low posterior hairline, bilateral sprengel deformity, mild scoliosis and congenital unilateral renal agenesis. Also, she had partial vertebral body fusion. She had cervical kyphosis, the fusiform enlargement of the spinal canal, increased thickness of the cervical spinal cord, cystic enlargement, which reached about 1.5cm long in central of the spinal cord and normal caryotype. She had M680I(G>C) mutation. The patient analysis result was normal for GDF6 gene.

To our knowledge, this is the first reported case together with KFS, bilateral Sprengel deformity, congenital unilateral renal agenesis and FMF mutation. Due to neurological deficits can be seen after minor trauma in cases with KFS, she should be careful and avoid from heavy exercise. She had cysts in her liver and spleen and had renal failure her family history. Thus the case has been evaluated for policystic kidney disorder. Additionally, she had MEFV gene mutation, she should be followed for kidney failure during her life for amyloidosis risk.

Keywords: Klippel-Feil Syndrome, FMF, Bilateral Sprengel Deformity, Fusion of Cervical Vertebrae, GDF6 Gene

Bilateral Sprengel Deformite, Konjenital Tek Taraflı Böbrek Agenezisi, MEFV Geninde M680İ (G>C) Heterozigot Mutasyonu Olan Klippel-Feil Sendromlu Yedi Yaşında Bir Kız Olgu

ÖZET

KFS, kısa boyun, düşük arka saç çizgisi ve boyun hareketlerini kısıtlayan servikal vertebraların füzyonuyla karakterizedir. Biz bilateral Sprengel deformiteli, konjenital tek taraflı böbrek agenezisi ve MEFV gen mutasyonu olan bir bayan KFS'li vakayı sunduk.

Hastanın fizik muayenesi, rutin biyokimyasal, radyolojik değerlendirilmesi yapıldı ve aile öyküsü alındı. İlaveten, kromozomal analiz, MEFV geninin tüm ekzom sekans analizi ve GDF6 geninin sekans analizi yapıldı.

Hastada kısa boyun, baş ve boyun hareketleri kısıtlanmış, düşük posterior saç çizgisi, bilateral Sprengel deformitesi, hafif skolyoz ve konjenital tek taraflı renal agenezisi vardı. Ayrıca hastanın parsiyel vertebra füzyonu vardı. Hasta, servikal kifoz, spinal kanalın füziform genişlemesi, servikal spinal kordun artmış kalınlığı, spinal kordun merkezinde yaklaşık 1.5 cm'ye ulaşan kistik genişlemeye ve normal karyotipe sahipti. Vakanın M680I(G>C) mutasyonu vardı. Vakanın GDF6 geni analiz sonucu normaldi.

Bildiğimiz kadarıyla bu; KFS, bilateral Sprengel deformite, konjenital tek taraflı renal agenezi ve FMF mutasyonunun birlikte olduğu ilk vakadır. KFS'li olgularda nörolojik defisitlerin minör travma sonrası görülmesi nedeniyle hasta, dikkatli olmalı ve ağır egzersizden kaçınmalıdır. Hastanın karaciğerinde ve dalağında kistler ve aile geçmişinde böbrek yetmezliği vardı. Bu nedenle hasta polikistik böbrek rahatsızlığı açısındanda değerlendirilmektedir. Bunlara ilaveten, vaka MEFV geninde mutasyona sahip olduğundan, amiloidozis riski için hasta yaşamı süresince böbrek rahatsızlığı açısından takip edilmelidir.

Anahtar Kelimeler: Klippel-Feil Sendromue, FMF, Bilateral Sprengel Deformitesi, Servikal Vertebranın Füzyonu, GDF6 Geni

INTRODUCTION

Klippel–Feil syndrome (KFS) was firstly reported by Maurice Klippel and Andre Feil in 1912. It is described by fusion of cervical vertebrae that restricts the range of motion of the neck, low posterior hairline and short neck (1). KFS was anatomically classified as three type. Type I is described by fusion of numerous cervical and upper thoracic vertebrae. Type II is characterized by fusion of one or two cervical vertebrae and Type III cases have fused cervical vertebrae in conjunction with fusions in the lower thoracic or lumbar spines (2,3).

Cases with KFS may have a higher risk for mechanical spinal cord injury as a result of unstable cervical segments. It was thought that KFS mostly occur as sporadic, also there are autosomal recessive, autosomal dominant and X-linked forms (4). Autosomal dominant (GDF6 and GDF3) and recessive (MEOX1 and RIPPLY2) inheritance patterns were described in families with Klippel–Feil (5).

FMF (OMIM #249100) is a hereditary autosomal recessive genetic disorder, which is characterized by short, self resolving recurrent attacks of fever, acute abdominal, joint pain, synovitis, myalgia and erythema. Renal failure and renal amyloidosis are the most severe complication of Familial Mediterranean Fever (FMF). MEFV gene mutations are responsible for the disease (6). It is mainly seen in eastern Mediterranean populations including Armenians, non-Ashkenazi Jews, Turks, and Arabs (7,8,9).

Herein, the case with KFS, congenital unilateral renal agenesis, bilateral Sprengel deformity and a heterozygous mutation M680I(G>C) in the MEFV gene is presented. To the best of our knowledge this is the first case together with KFS, congenital unilateral renal agenesis, bilateral Sprengel deformity and FMF mutation until now, never been reported.

CLINICAL REPORT

A girl 7 years old was presented with growth retardation and congenital unilateral renal agenesis. There was no relationship between parents. The parents have not chronic diseases. She was from Turkish ethnic group. Her mother's and father's age were 40 years old. Her mother has not been used cigarette and alcohol. The mother had used antibiotics under medical supervision because of the bronchitis during pregnancy. She was born at 38 weeks gestation with a birth weight of 2.4 kg by cesarean section due to fetal distress. There was no asphyxia story and admission in an couveuse at birth.

The head circumference was 48 cm <3p (lower than -2.362 SD). Her length was 109.2 cm <3p (lower than -2.397 SD) and her weight was 15.5 kg <3p (lower than -2.651 SD). She had a healthy sister at 14 years old. She was able to walk (1.5 year), onset sit unsupported (6 month), to keep her head (3 month) and onset of speech (1 year). Her mental level is normal. She had upslanting palpebral fissures, flat face, malar hypoplasia, prominent forehead, brachycephaly, facial asymmetry, low set posteriorly rotated ears, thin lips, short webbed neck, limitation of the movement of head and neck and a low posterior hairline, bilateral sprengel deformity (also known as High scapula or Congenital high scapula), mild scoliosis and congenital unilateral renal agenesis (Figure 1). Routine serum and urine biochemical analysis were in the normal range.

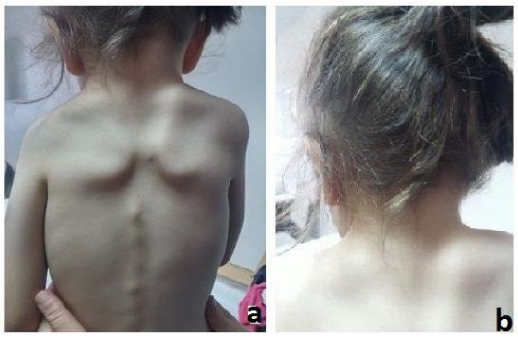

Figure 1: Characteristic features of the proband

She has strabismus and amblyopia. Her hearing and pediatric echocardiography examination were normal. According to abdominal ultrasonography, the cysts were seen in liver (7x4mm in size) and spleen (11mm in size). In addition to this, two uncle of her mother died of kidney failure (at 45 years old and 63 years old). The uncle of her mother, who died at 63 years old, lived with renal transplant during 20 years. Also her two aunts have FMF and one of them had amyloidosis due to late diagnosis of FMF (Figure 2).

Cervical MR showed partial vertebral body fusion associated with C7-T1 and also observed that spinous process fusion at C5-T1 and T3-T5. Cervical spine curve to the right (rotoscoliosis), cervical kyphosis, the fusiform enlargement of the spinal canal between C6-T2, increased thickness of the cervical spinal cord at C5-T1 level, cystic enlargement in 1.5 mm diameter, which reached about 1.5 cm long in central of the spinal cord at the C6-C7-T1 level (Figure 3). According to chest computed tomography, there was wide flat costa, intercostal herniation, mild scoliosis, azygos lobe variations.

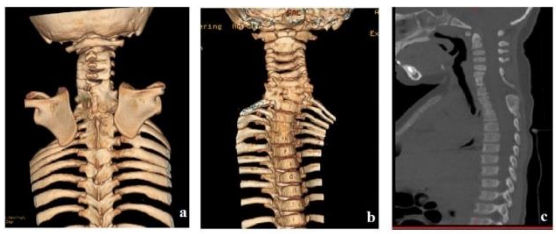

Figure 3: Cervical MR pictures of proband

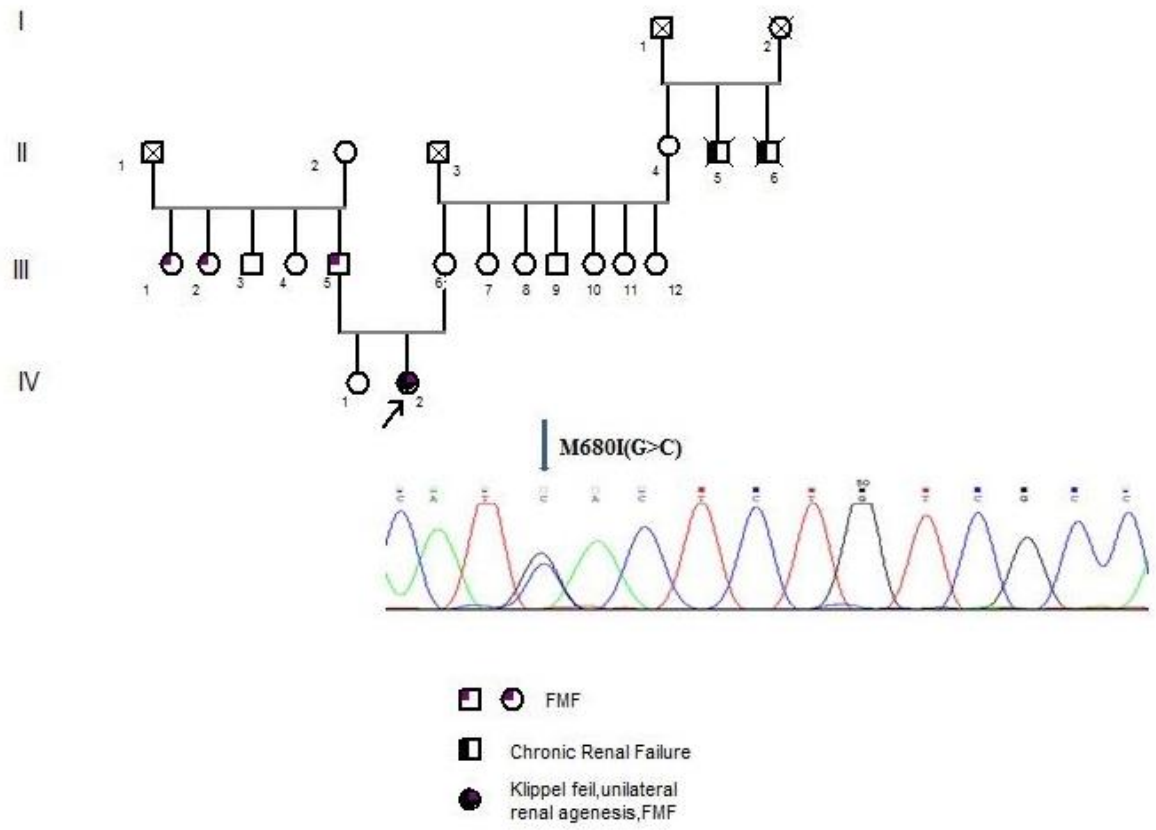

Figure 2: Family pedigree and sequence analaysis results of the proband

Both kidneys were not untracked in the slot of kidney. The parenchymal echogenicity and thickness were normal. According to dimercaptosuccinic acid scan, one kidney that show ectopic location and has normal cortical function was observed on superior of the bladder in the pelvic area. Also MURCS association, in which Klippel-Feil anomalyis associated with urogenital anomalies. But mullerian structures of our case were normal in pelvic ultrasonography.

She had normal caryotype (46, XX). Because she had abdominal pain and recurrent fever, all exons of MEFV gene (1,2,3,4,5,6,7,8,9,10) were amplified and complete exom sequencing analysis was performed. Analysis of MEFV gene was showed that she had M680I(G>C) mutation. Therefore complete exom sequencing analysis of MEFV gene was performed for other members of the family. The father has the same mutation (M680I(G>C)) for MEFV gene and has used colchicine but the mother and sister have not a mutation (Figure 2). So, she has used colchicine. Also she has asthma and hypothyroidism, thus she has used to ventolin, fluxotide and levatron. The sequencing analysis was performed for GDF6 gene and detected as normal.

DISCUSSION

KFS are characterized by the triad of short neck, low posterior hairline, and limited motion of the head and neck due to two or more congenitally fused cervical vertebrae (2,10). According to cervical MR, our case had various vertebral body fusion, fusiform enlargement of the spinal canal, increased thickness of the cervical spinal cord, cystic enlargement. Her neurological examination was normal and there was not sensorimotor loss. She has also low posterior hairline, short neck and limitation of the movement of head and neck. In cases with KFS, neurological deficits can be seen after minor trauma. Therefore, the case should be careful and avoid from heavy exercise.

These cases may have pulmonary, cardiovascular, and renal abnormalities along with scoliosis, cervical ribs anomalies and Sprengel's deformity (1,2). The mental level, routine serum and urine biochemical analysis and mullerian structures of our case were normal. She had strabismus and amblyopia. Her hearing and pediatric echocardiography examinations were normal. But she had bilateral sprengel deformity, which is rare condition among the cases with sprengel deformity.

It was reported that the M680I mutation, that markedly rare among Jews and relatively more prevalent in Armenians and Arabs, was the second most common mutation in Turks (7). Also Cases with p.M694V, p.M694I, or p.M680I mutations are tend to have a more severe disease, more joint involvement, and a greater chance of developing

amyloidosis (11). Our case had congenital unilateral renal agenesis. Both kidneys were not untracked in the slot of kidney. One kidney, which showed ectopic location and had normal cortical function was observed on superior of the bladder in the pelvic area. Additionally, there were cysts in her liver and spleen. Also she had renal failure her family history. Two uncle of her mother died because of kidney failure. Therefore the cases should be taken into consideration for policystic kidney disorder. In addition to these, our case and her father had MEFV gene mutation (M680I(G>C)). To our knowledge this is the first case together with KFS, congenital unilateral renal agenesis and FMF mutation. Due to she had familial mediterranian fever, she has used colchicine. Because of the amyloidosis risk, she should be monitored for kidney failure during her life.

REFERENCES

1. Thomsen MN, Schneider U, Weber M, et al. Scoliosis and congenital anomalies associated with Klippel-Feil syndrome types I-III. Spine J 1997;22(4):396–401.
2. Tracy MR, Dormans JP, Kusumi K. Klippel–Feil syndrome: clinical features and current understanding of etiology. Clin Orthop Relat Res 2004;2:183–90.
3. Gunderson CH, Greenspan RH, Glaser GH, et al. The Klippel–Feil syndrome: genetic and clinical reevaluation of cervical fusion. Medicine 1967;46:491–512.
4. Giampietro PF, Raggio CL, Blank RD, et al. Clinical, genetic and environmental factors associated with congenital vertebral malformations. Mol Syndromol 2013;4:94 – 105. doi: 10.1159/000345329.
5. Karaca E, Yuregir OO, Bozdogan ST, et al. Rare variants in the notch signaling pathway describe a novel type of autosomal recessive Klippel–Feil syndrome. Am J Med Genet Part A 2015;9999A:1–5. doi: 10.1002/ajmg.a.37263.
6. Konstantopoulos K, Michael S, Kanta A, et al. Renal amyloidosis as a first manifestation of Familial Mediterranean Fever. Scand J Rheumatol 2000;29(2):129–130
7. Tunca M, Akar S, Onen F, et al. Turkish FMF Study Group. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 2005;84(1):1-11.
8. Eroz R, Dogan M, Yuce H, et al. A Turkish Family with A89T (p. Ala89Thr, c.265G>A) Mutation on The MEFV Gene, Their Clinical Findings and Review of The Literature. F.Ü.Sağ.Bil.Tıp Derg. 2016; 30 (2): 67-70. http://www.fusabil.org
9. Eroz R, Dogan M, Yuce H, et al. A Family From Turkey With 761_764dupCCGC p.Asn256Argfs70,c.761_764dupCCGC MEFV Gene Mutation, Their Clinical Features and Review of The Literature. Konuralp Tıp Dergisi 2016;8(3): 214-217.
10. Patel PR, Lauerman WC. Klippel Maurice. Spine J 1995;20:2157–60.
11. Ben-Chetrıt E and Touıtou I. Familial Mediterranean Fever in the World Arthritis & Rheumatism (Arthritis Care & Research). American College of Rheumatology 2009;61(10):1447–1453. doi: 10.1002/art.24458.