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Review Article

KLIPPEL-FEIL SYNDROME AND CONGENTIAL HEART DISEASE PRESENTATION OF CASES AND A REVIEW OF THE LITERATURE

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ABSTRACT

Introduction: Independently described first time in 1912 from two authors: Maurice Klippel and Andre Feil, Klippel-Feil syndrome (synonyms: cervical vertebra fusion syndrome, Klippel-Feil deformity, Klippel-Feil sequence disorder) is a bone disorder characterized by the abnormal joining (fusion) of two or more spinal bones in the neck (cervical vertebrae), which is present from birth. Three major features result from this abnormality: a short neck, a limited range of motion in the neck, and a low hairline at the back of the head. Most affected people have one or two of these characteristic features. Less than half of all individuals with Klippel-Feil syndrome (KFS) have all three classic features of this condition.

Aim of presentation Here, we report five cases in young Kosovars with KFS and heart abnormalities, clinical presentation, diagnosis, management, and outcomes of selected conditions in resources-limited settings.

Methods Retrospectively we analysed medical reports of five our children, diagnosed at different age with congenital disease and clinical and lab signs of Klippel-Feil syndrome.

INTRODUCTION

Klippel–Feil syndrome is a rare disease, initially reported in 1884 by Maurice Klippel and André Feil from France, characterized by the congenital fusion of any two of the seven cervical vertebrae. Since first classification from Feil in three categories (I – III) other classification systems have been advocated to describe the anomalies, predict the potential problems, and guide treatment decisions. Patients with Klippel-Feil syndrome usually present with the disease during childhood, but may present later in life. The challenge to the clinician is to recognize the associated anomalies that can occur with Klippel-Feil syndrome and to perform the appropriate workup for diagnosis [1]. The clinical presentation of Klippel-Feil syndrome is varied because of the different associated syndromes and anomalies that can occur in patients with this syndrome. A complete history and careful physical examination may reveal some associated anomalies.

Klippel-Feil syndrome is a rare skeletal disorder primarily characterized by abnormal union or fusion of two or more bones of the spinal column (vertebrae) within the neck (cervical vertebrae). For the first time, it has been described in 1912, independently from Maurice Klippel and Andre Feil. Three major features result from this abnormality: a short neck, a limited range of motion in the neck, and a low hairline at the back of the head. In some individuals, KFS can be associated with a variety of additional symptoms and physical abnormalities but very rare with structural abnormalities of the heart - congenital heart defects [2].

Klippel-Feil syndrome (KFS) is a congenital anomaly characterized by a defect in the formation or segmentation of the cervical vertebrae, resulting in a fused appearance. The clinical triad consists of short neck, low posterior hairline, and limited neck movement, although less than 50% of patients demonstrate all 3 clinical features [3]. However, despite the lack of accurate epidemiological data from Kosovo, KFS and

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variety are rare in children and adults on this region. KFS is usually non-malignant but causes significant morbidity, especially when is associated with anomalies in vital organs [2]. Discussion of unique aspects of etiology, diagnosis, and management in underserved regions of Kosovo may be important to raise awareness in health professionals, allows timely diagnosis, and improves management and prognosis. Here, we present four cases of patients with KFS and congenital heart disease, diagnosed at different age, surgical treatment and outcomes in Kosovo as a country with limited resources [3,4].

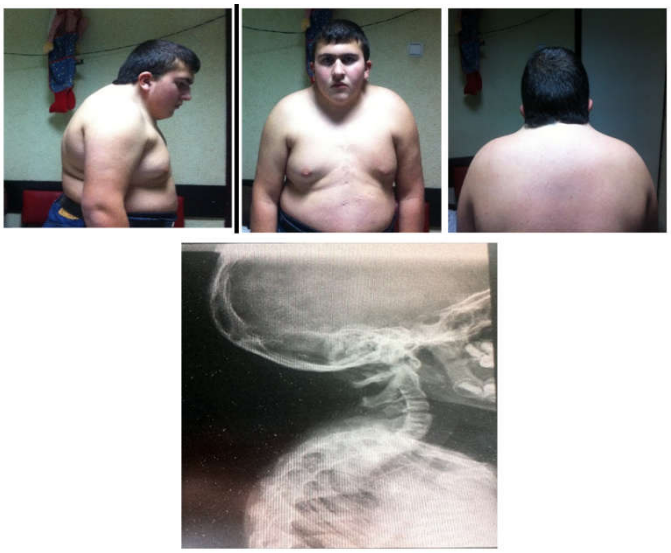

Figure 1 Case 1. A 15-years-old boy diagnosed at delivery with Klippel – Feil syndrome. Note the short neck, low hairline and symmetric shoulders. (Scar on the thorax after surgical repair of total anomalous venous return)

Figure 2 Case 4. A 2-days old neonate with Klippel-Feil syndrome. The image shows an elevated right shoulder due to a Sprengel anomaly, a short, webbed neck, and a low hairline.

Incidence

The actual occurrence for the KFS syndrome is unknown, it is estimated to occur 1 in 40,000 to 42,000 new-borns worldwide. In addition, females seem to be affected slightly more often than males. Mutations in the GDF6 and GDF3 genes can cause Klippel-Feil syndrome. These genes provide instructions for making proteins that belong to the bone morphogenetic protein family, which is involved in regulating the growth and maturation (differentiation) of bone and cartilage. Additional forms of KFS include autosomal recessive KFS2 (214300), caused by mutation in the MEOX1 gene (600147) on chromosome 17q21, and autosomal dominant KFS3 (613702), caused by mutation in the GDF3 gene (606522) on chromosome 12p13. Sometimes this condition is inherited in an autosomal recessive pattern, which means both copies of a gene in each cell have mutations.

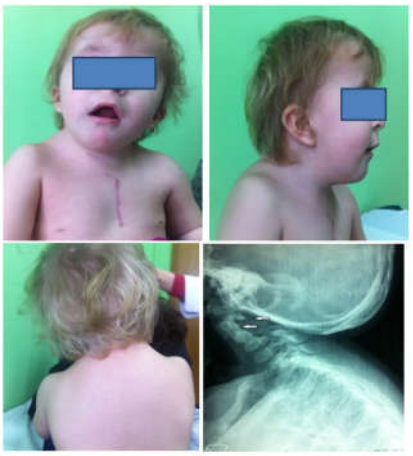

Figure 3 Case 2. Patient with Klippel-Feil syndrome and anomaly of the occipito-cervical junction. The images show an elevated left shoulder due to a Sprengel anomaly, a short, webbed neck, and a low hairline. (Scar on the thorax after surgical repair of nonrestrictive atrial septal defect). X-ray shows occipito-cervical junction

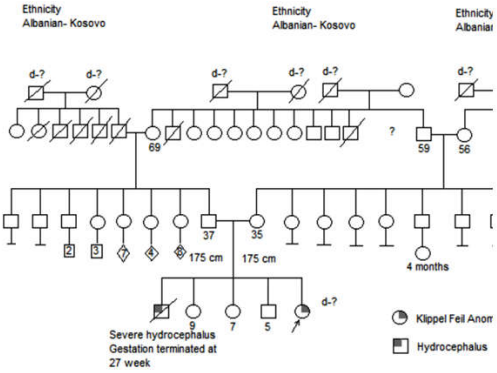

Figure 4 Family tree of Case 2.

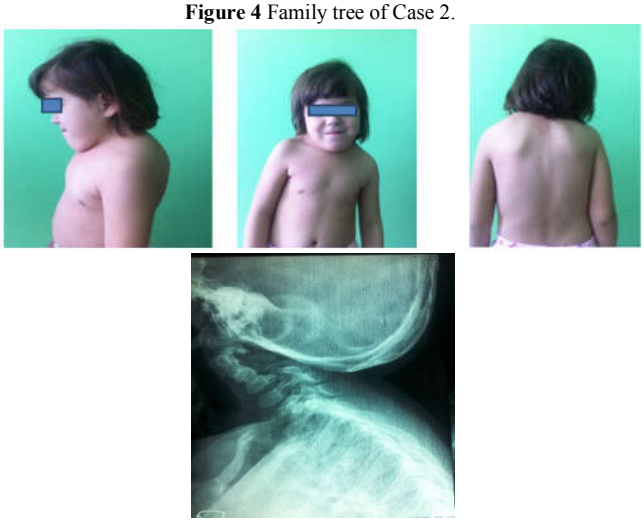

Figure 5 Case 4. A 12-years-old girl with Klippel-Feil syndrome and pulmonary stenosis. Note elevated left shuoldres and thoarx deformity.

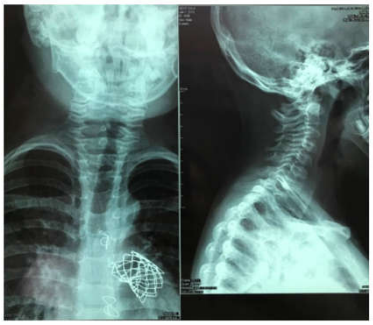

Figure 6 Case 5. X-ray Images show occipito-cervical junction. Note Melody valve implanted as a consequence of pulmonary insufficiency after complete TOF repair.

However, in these cases, the gene involved is unknown. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition [5,6].

Etiology

The etiology of Klippel-Feil syndrome and its associated conditions is unknown. The syndrome can be presented with a variety of other clinical syndromes, including fetal alcohol syndrome, Goldenhar syndrome, anomalies of the extremities etc.[5] The occurrence of KFS in siblimgs and in consanguineous families suggests autosomal recessive inheritance of a form of the disorder. A close evaluation of the immediate family is indicated, because autosomal dominant inheritance with variable expression in affected individuals has been noted, although this is presumably rare. There is a strong association with congenital abnormalities of the genitourinary tract (30 – 40 %), including double collecting systems, renal aplasia and horseshoe kidney [6,7].

Data of our patients are presented on the Table 1.

DISCUSSION

These cases reported show several aspects of KFS in different ages of young Kosovars. They highlight common clinical presentation and etiology, as well as the challenges for the diagnosis and management of these clinical entities resources-poor settings.

KFS has diverse clinical presentation and etiology. The presenting symptoms and signs depend on the age at presentation (at birth – congenital type), on the primary disease (abnormality of the neck and restricted movement of the head and neck) as well as the associated anomalies, especially heart anomalies. Associated anomalies also may include abnormal curvature of the spine (scoliosis) and/or vertebral instability, spina bifida occulta, raised scapula (Sprengel's deformity), absent rib(s) and other rib defects including cervical ribs, other skeletal abnormalities including skeletal malformations of the ear, nose, mouth and larynx including hearing impairment and cleft palate, malformations of the head and facial (craniofacial) area; anomalies of the urinary tract and/or kidney including absent or horse-shoe kidney; or structural abnormalities of the heart (congenital heart defects), mirror movements, webbing of the digits and digital hypoplasia. In addition, in some cases, neurological complications may result due to associated spinal cord injury. The challenge to the clinician is to recognize the associated anomalies that can occur with Klippel-Feil syndrome and to perform the appropriate workup for diagnosis [8,9,10].

Since the first classification from Feil in three categories (I – III) other classification systems have been advocated to describe the anomalies, predict the potential problems, and guide treatment decisions. Patients with Klippel-Feil syndrome usually are presented with the disease during childhood, but may present later in life [11,12].

The disorder can be present at birth (congenital), but mild cases may go undiagnosed until later during life when symptoms worsen or first become apparent. For the first time, it has been described in 1912, independently from Maurice Klippel and Andre Feil. Three major features result from this abnormality: a short neck, a limited range of motion in the neck, and a low hairline at the back of the head [1,13].

Clinical presentation is varied because of the different associated syndromes and anomalies that can occur in patients with Klippel-Feil syndrome. A complete history and careful physical examination may reveal some associated anomalies. Klippel-Feil syndrome involves the congenital fusion (failure of segmentation) of one or more cervical motion segments, and most patients have associated congenital anomalies of the cervical spine or other organs and systems. These anomalies may occur at the craniocervical junction (occipit-C2), the sub axial spine (below C2), or both.[11] Our cases has multiple developmental anomalies of the upper cervical spine consistent with Klippel-Feil syndrome. The posterior skull has a “beaten copper” appearance which may represent a normal variant or less likely reflective of gyral impression from increased intracranial pressure because it is only seen posteriorly [14,15,16].

Associated anomalies occur in the auditory system, neural axis, cardiovascular system, and the musculoskeletal system. Cardiovascular anomalies, mainly septal defects, were found in 7 patients in Hensinger's series, with 4 of these individuals requiring corrective surgery [2,17]. In our presentation all cases have a different CHD including those which from delivery threatening children’s life (first case with total anomalous pulmonary venous return).

People with Klippel-Feil syndrome may have other features in addition to their spine abnormalities. Some people with this condition have hearing difficulties, genitourinary abnormalities such as malformed kidneys, a type of birth defect that occurs during the development of the brain and spinal cord (neural tube defect), an opening in the roof of the mouth (cleft palate), or heart abnormalities [4,6,7]. Consultations from different specialties in Kosovo and in both 1st and 2nd case during the surgical intervention abroad, other anomalies have been eliminated. Careful examinations of specialist exclude anomalies in other organs and systems. Radiographs and MRI of the thoracic and lumbosacral spine are obtained and other anomalies have been excluded.

Affected individuals may have underdeveloped shoulder blades that sit abnormally high on the back, a condition called Sprengel deformity [13]. In three of our cases we have found underdeveloped shoulder where two of them have an elevated left shoulder and the other one has the right.

Lateral flexion-extension radiographs of the cervical spine should be performed on all patients to determine the motion of each open interspace. Clinically, flexion-extension is often maintained if a single functioning open interspace is maintained. Those with hyper mobility of the upper cervical segment are at risk of developing neurologic impairment. Affected individuals with hyper mobility of the lower cervical segment are at increased risk for degenerative disk diseases and should be treated symptomatically [12,16].

In our study all cases are affected from different type of congenital heart disease, starting from easy forms, as a pulmonary stenosis, to life suffering from delivery, as a transposition of the great arteries. To the author's best knowledge our study is the first publication which suggests the

relationship between Klippel-Feil syndrome and different type of CHD, where prognosis is strongly connected with cardiac surgery in a country as a Kosovo where this service is absent.

The authors declare that they have no conflict of interest

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Written informed consent was obtained from the family for participation in this study and any accompanying data.

Table 1 Demographic data of presented patients CHD – congenital heart defect, N of CVF – number of cervical vertebra fusion

Number	Age at diagnosis	Gender	CHD	N of CVF	Actual age	Outcomes
1.	2 days	male	TAPVR	3 (C1, C2, C3)	18 years	alive
2.	28 month	girl	ASD II	3 (C1, C2, C3)	13 years	alive
3.	2 days	male	D-TGA	3 (C1, C2, C3)	0	died
4.	12 years	girl	St AP	5 (C1-C2, C5-C7)	14 years	alive
5.	2 month	male	TOF	2 (C1, C2)	12 years	alive

REVIEW OF LITERATURE

Table 2 Review of literature

Lead author	Year	No.of patients	Siblings
Lubs[18]	1963	2 from11	parents consanguineous
Juberg and Gershanik[19]	1976	1	parents consanguineous
Chemke[20]	1980	1	parents no consanguineous
Da-Silva[21]	1982	4 siblimgs (7f /5m)	parents consanguineous
Fragoso[22]	1982	1	parents no consanguineous
Clarke[23]	1998	Family	autosomal recessive inheritance
Bejiqi[24]	2013	1	parents no consanguineous
Erol[25]	2004	1	parents consanguineous
Ohashi [26]	1992	1	de novo balanced translocation
Bejiqi[27]	2015	4	parents no consanguineous

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