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CLINICAL CASE

Klippel-Feil autosomal dominant syndrome: a malformation of vertebral segmentation

Síndrome de Klippel-Feil autosómico dominante: una malformación de segmentación vertebral

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Abstract

Klippel-Feil syndrome is a highly heterogeneous complex skeletal disorder characterized by the congenital fusion of two or more cervical vertebrae. The classic clinical triad consists of a short neck, low hairline, and neck movements limitation. The associated mutations are located in the loci of the GDF3 gene (chromosome 12p13.31), GDF6 (chromosome 8q22.1), and MEOX1 (chromosome 17q21.31). **Objective:** To describe the clinical-radiological findings and pedigree of a patient with Klippel-Feil syndrome. **Clinical case:** A 5-year-old patient with short neck, low posterior hairline, and limitation of lateral movements. The cervical flexion and extension radiographs showed fusion blocks between C1-2-3, C4-5, and C6-7. The chest CT scan showed multiple hemivertebrae in the upper third of the thoracic vertebrae corresponding to ribs I-IV. The karyotype was normal, 46, XX. Reduced penetrance was present in five of the family members. The fusion of C2-3 was present in four members and one individual had low fusion in C5-6. Three of the five affected individuals had a fusion between the capitate and the hamate bone. **Conclusion:** The malformation of congenital vertebral segmentation is a case of interest since it is an uncommon diagnosis in the pediatric age and whose clinical suspicion can be generated from the clinical examination, radiological study complemented with the pedigree interpretation in Mendelian inheritance disorders, allowing to provide opportunely genetic counseling to the family.

Keywords:
Klippel-Feil syndrome; congenital abnormalities; cervical vertebrae; scoliosis

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Introduction

Klippel-Feil Syndrome (KFS) (OMIM# 118100) is a highly heterogeneous complex skeletal dysplasia characterized by the congenital fusion of two or more cervical vertebrae[1]. It is caused by a failure in the normal vertebrae segmentation during the fourth week of gestation[2]. The classic clinical triad consists of a short neck, low hairline, and neck movement limitations. Only 34-74% of diagnosed cases have classical clinical manifestations[3]. The estimated incidence is 1 per 40,000 to 42,000 births worldwide and is most prevalent in females with a 1.5/1 ratio[4].

There are four KFS types[5] which are type I, classic single C1 fusion (autosomal recessive); type II, C2-C3 synostosis, cervical, thoracic, and lumbar fusion, and variable expression among a family (autosomal dominant); type III, isolated cervical fusion (recessive), and type IV, fusion in cervical vertebrae (probably linked to the X chromosome) classified according to differences in vertebral synostosis in specific regions and inheritance pattern. In Ecuador, the four described cases were from the Genetics of Paz-y-Miño (2014a) consultation[6].

Mutations associated with autosomal dominant KFS syndrome[7,8] are located in *GDF3*, *GDF6*, and *MEOX1* genes. The *GDF3* gene (is a growth differentiation factor 3) of the family TGF-β/BMP (transforming growth factor-beta/bone morphogenetic protein), and mutations in this gene cause the Klippel-Feil III deformity. *GDF6* (growth differentiation factor 6) is also of the TGF-β/BMP family and mutations in this gene cause KFS I deformity. The protein encoded by the *MEOX1* gene (homeobox protein MOX-1) plays a role in somitogenesis and is specifically involved in the sclerotome formation[9,10].

Pax genes also play an important role during vertebrate embryogenesis, possibly by determining the temporality and place of organs formation such as the brain, eyes, ears, nose, spine, kidneys, and limb muscles.

Considering its genomic organization, domain sequences, and expression patterns, the *Pax* gene family has been classified into four subfamilies; family 1 consists of genes *Pax1* and *Pax9*, family 2 of genes *Pax2*, *Pax5* and *Pax8*; family 3 of genes *Pax3* and *Pax7*; and family 4 of genes *Pax4* and *Pax6*[11].

During the fourth week of embryonic development, the differentiation of somites takes place, where the sclerotome expresses the *Pax1* transcription factor, which initiates the genes cascade that forms cartilage and bone for the formation of vertebrae, ribs, and sternum[2,10]. The hemivertebra is caused by insufficient segmentation of two or more vertebrae[12].

The objective of this research was to describe the clinical-radiological and genealogical findings of a patient with Klippel-Feil syndrome.

Clinical case

Female patient, only child of a couple with no history of consanguinity or endogamy who was referred at age 5 to the genetic service. She had seven prenatal controls, the mother had no history of consumption of alcohol or valproic acid during pregnancy. The patient was born by eutocic delivery of 38 weeks gestation according to the date of last menstruation, with anthropometry corresponded to a small-for-gestational-age term newborn, weight 2.030 g, height 39.5 cm, head circumference 29 cm, Apgar at 9 minutes and at 5 minutes, discharged after two days of life.

At one year of age, she was referred to Neuropediatrics due to right brachial plexus palsy, where she underwent a CT scan of the skull which showed normal results. She had normal progression of developmental milestones, attending preschool education.

The genetic service admission exam highlighted normal intelligence. In the segmental examination, deviation of the head to the left side was observed; skull and face with high and wide forehead; midfacial hypoplasia; slightly arched eyebrows, long eyelashes, white corneas; wide, flattened nose with slight nasal filter; thick cheeks; slightly thick lips, normal occlusion, and crooked teeth; retrognathia; prominent, low set and posteriorly-rotated left ear; short neck, low posterior hairline, and limited neck range of lateral motion. The posterior thorax showed right side scoliosis in the dorsal region, and small and prominent scapulae in high position; the left anterior hemithorax with elevation at the second and third costal cartilage; elbow, wrist, hands, and foot flexion restriction. There were no clinical signs of spinal cord compression (figure 1).

Laboratory tests showed blood count, biochemical profile, and thyroid tests in normal range. Conventional cytogenetic analysis, by lymphocytes culture obtained from peripheral blood with GTG-banding techniques (20 metaphases) showed normal female karyotype 46, XX. Flexion-Extension X-ray of the cervical region showed multiple blocked vertebrae with absence of intervertebral spaces between C1-C2-C3, C4-C5, C6-C7 (figure 2). Wrist X-ray showed fusion between the capitate and the hamate bone (not shown).

The CT-scan volumetric reconstruction findings included costal arches synostosis in the left hemithorax at the back end of I-IV, this one shorter in relation to the adjacent costal arches (Figure 3a); costal arches synostosis in the right hemithorax in the middle third and back end of I-III. There was no difference between them, and to a greater extent in the contralateral side (Figure 3b). III short rib arch in relation to the IV one and absence of the XII rib (figure 3c).

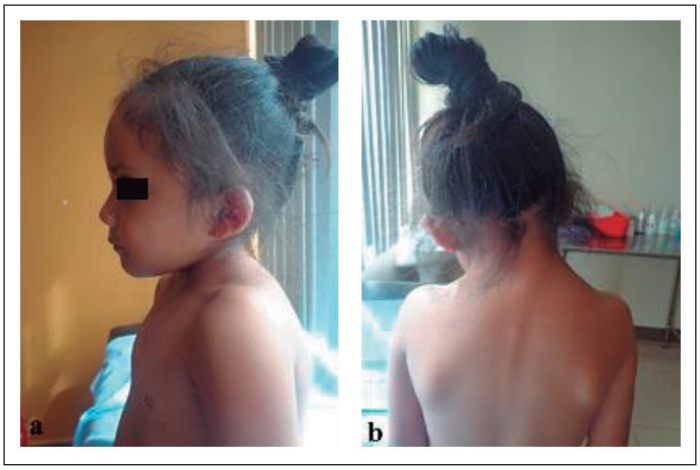

Figure 1. Lateral view of patient with 5 years old that note shortness of neck **(a)**. Posterior view with lower hairline in addition Sprengel's deformity to consist elevation of scapula **(b)**.

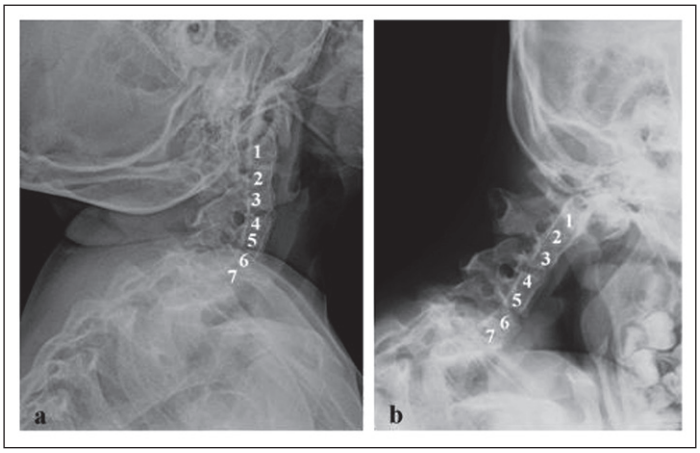

Figure 2. Laterals cervical radiographies (**a** y **b**) showing sinostosis of vertebral bodies C1-2-3, C4-5 and C6-7. **a)** Extension. **b)** Flexion.

In addition, it showed multiple non-segmented hemivertebrae of the thoracic vertebrae in the upper third (T1-T4) corresponding to ribs I-IV and vertebral wedges of T5-T6. Marked right scoliosis (Figure 3c).

Cardiological, ophthalmological, hearing, and abdominal ultrasound evaluations were normal.

In addition to the clinical evaluation, the patient's genealogy was made, defined as case III-5 (Figure 4). When interpreting the family genealogy, it was defined that the individuals (I-5, II-6, II-10, II-14, III-5) presented compatible KFS symptomatology with probable autosomal dominant inheritance pattern, therefore, X-ray of the thoracic cervical spine was indicated.

Considering the decrease in reproductive capacity and also the low prevalence of these defects, it is unlikely that there is a union between parents (II-5 and II-6) affected by a mutation causing the same syndrome. To rule out this possibility, an X-ray of the thoracic cervical spine was performed at II-5, which was normal (not shown).

The I-5 cervical spine radiography showed a spinous process fusion between C2-C3 with partial ossification between the vertebral bodies where the intervertebral space is significantly narrow, with no carpal fusion (Figure 5a).

Patient II-6 (Figure 5d) presented spinous process fusion between C5-C6 and a significant decrease in the intervertebral space, and carpus bones (hamate) are also fused. Abdominal ultrasound showed normal kidney characteristics, as well as ureters and bladder without alterations. Audiological examination reported absence of pathology and conventional cytogenetic analysis, with G-Banding (20 metaphases) showed a karyotype 46, XX.

Patients II-10 and II-14, walked in small steps touching the floor because they cannot lift their legs while keeping them together from the knee up, as a result of the pyramidal tract involvement. Cervical spine radiography identified spinous process fusion between C2-C3 and partial ossification between the vertebral bodies, with significant narrowing of the intervertebral space (Figures 5b and c). The wrist radiography showed fusion between the capitate and hamate bone (Figures 5e and f). They are currently being treated with physiotherapy.

The four maternal relatives (I-5, II-6, II-10, II-14) of the index case (III-5) were examined and evaluated, including II-5 (Figure 4) using thoracic spine and carpal bone radiography, of the eight living maternal individuals. Five of the six evaluated showed at least significant narrowing of the intervertebral space between C2-C3 or C5-C6.

The KFS was present in five members of the family (I-5, II-6, II-10, II-14, III-5). All affected individuals presented cervical spine fusion, four of them (I-5, II-10, II-14, III-5) presented high fusions in C2-C3 and one (II-6), low fusion in C5-C6.

Out of the five individuals with vertebral involvement, in only three (II-10, II-14, III-5) fusion between the capitate and hamate bone was found. None of the affected individuals of the family of patient III-5 in the three generations with this dominant genetic entity, it was observed vocal alteration associated with laryngeal cartilage malformations.

The research protocol was sent to the ethics committee for comment, review, and approval; allowing for the recording of index case data and their relatives with the results subsequently publication.

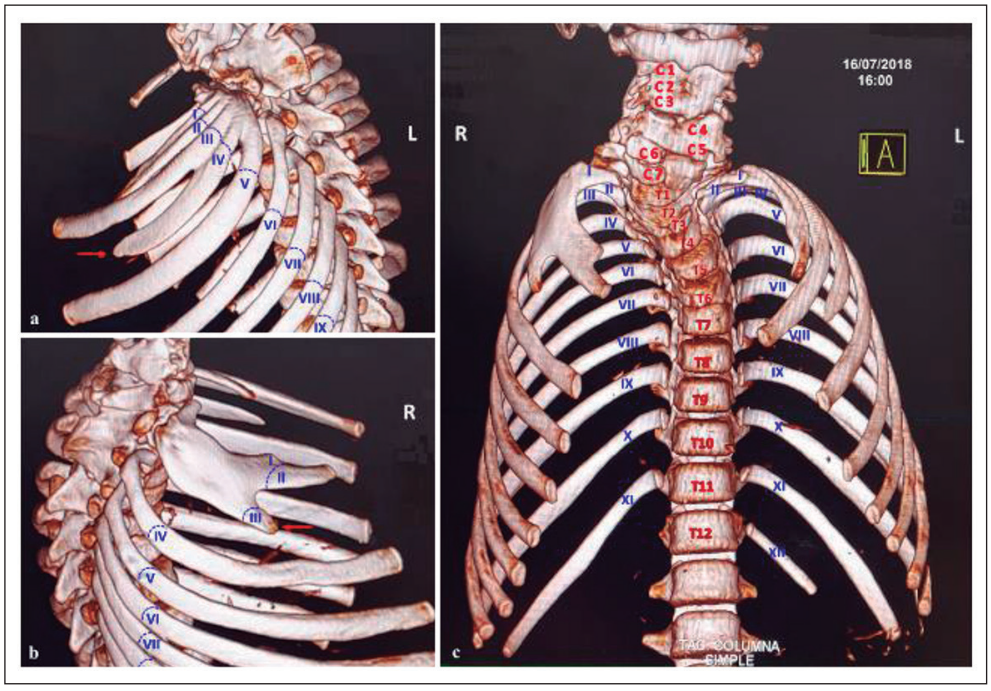

Figure 3. 3D Conputerized Reconstructional format the bones of the thorax, anterior view whith absence of intercostal space back extreme to the costal angle: the left hemithorax I-IV **(a)** and the right hemithorax I-III **(b)** respectively. Shorter costal arches sternales: left IV and right III, whith absence of the XII floatin rib homoside **(c)**. I have far-off electronically the sternum and clavicular.

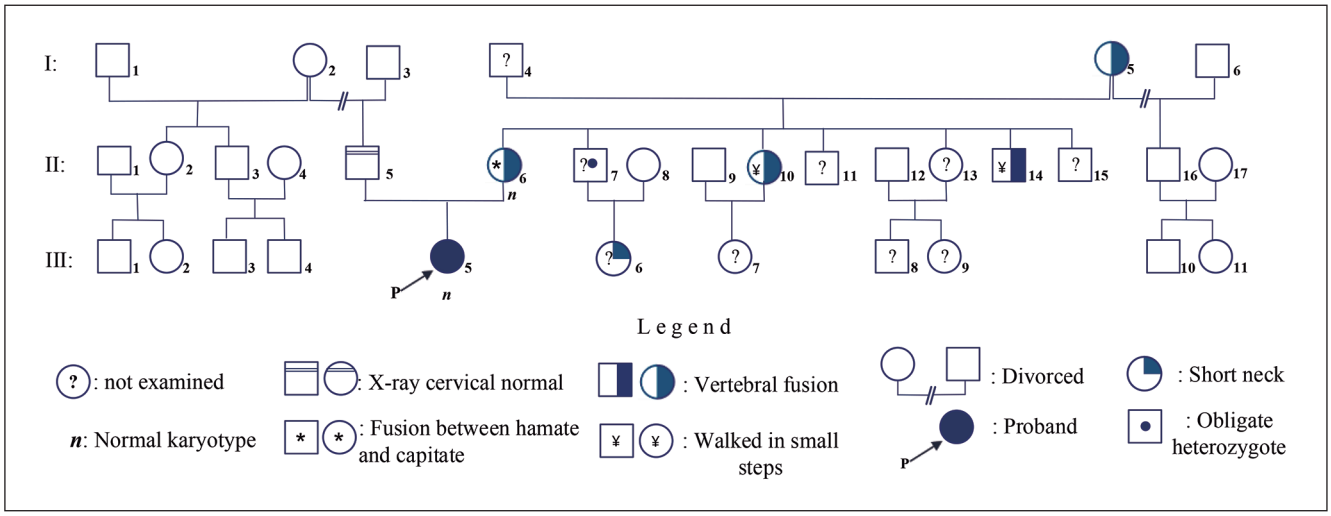

Figure 4. Klippel-Feil syndrome family pedigree.

Discussion

Klippel-Feil syndrome is caused by a failure in the cervical vertebral segmentation with wide phenotypic variability, however, a common characteristic of these patients is the presence of cervical spine fusion in C2-C3 as a universal finding[6].

Patient III-5 presented the classic KFS triad, with cervical spine fusion, short neck, and low posterior hairline, although only 34% of cases present the complete triad, as well as limitation of arm flexion movements. Currently, the patient has no clinical signs of spinal cord compression, with good prognosis. Parents, teachers, and the patient herself must be aware of avoiding trauma, physical activities that could injure the spinal cord with the devastating consequences that would imply[13-15].

In addition to the various vertebral alterations, this is the first case in which synostosis of costal arches with KFS is described, demonstrated with CT scan and vo-

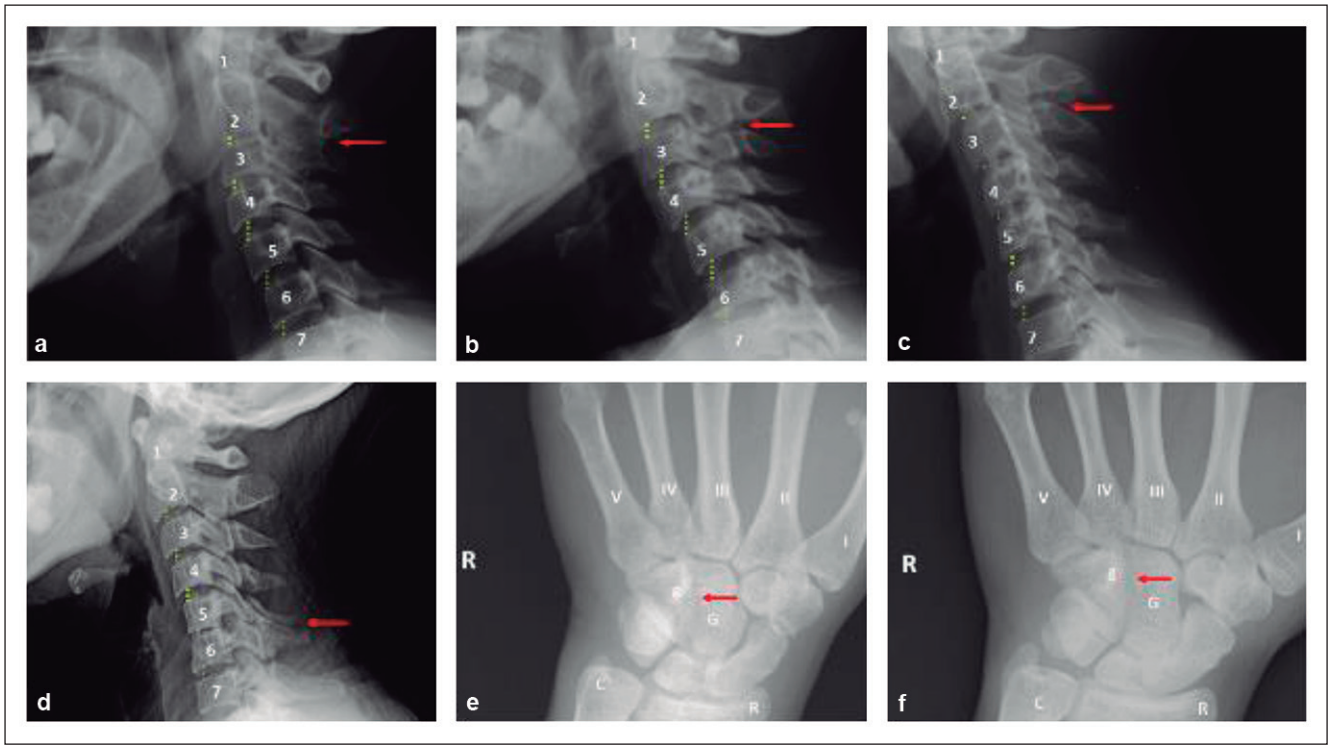

Figure 5. Vertebral cervical radiographs showed the intervertebral space is significantly narrow and spinous process fusion between:C2-3 patient I-5 (a), II-10 (b) and II-14 (c), respectively; C5-6 patiente II-6 (d). X-ray of the carpometacarpal showed fusion between the capitate and hamate bone: The patiente II-10 (e) and II-14 (f), respectively. R, right; G, capitate; g, hamate.

lumetric reconstruction of the thoracic cervical spine, exhibiting the need for imaging and cytogenetic studies in patients with vertebral fusion.

The patient III-5 presented the highest degree of severity, with multiple cervical blocked vertebrae (C1-C2-C3/C4-C5/C6-C7), and wrist radiography showed fusion in the carpus. All of these developmental defects occur due to haploinsufficiency (as a pathological mechanism) possibly in some of the other genes such as *Pax1* during embryogenesis, proposed by McGaughran (2003), by describing the importance in the specific regulation of cell proliferation position[11].

The mother (II-6) had a less severe phenotype than the index case or other relatives, the reduced penetrance could be explained by considering that she has a mutation in one allele and that the other allele (or a mutation in another locus) has a mutation that attenuates the synostosis of the vertebral bodies by interaction between alleles, or if it was in another locus an epistatic effect could have attenuated the phenotype[16,17].

In KFS type II, with autosomal dominant inheritance, variable expressivity has been described in clinical severity[18,19]. Differences in synostosis in specific regions were observed in the cervical spine radiographs of the cases described. Since there was no apparent cause for the pathological gait of II-10 and II-14, it was presumed that it was related to KFS. These patients are highly predisposed to suffer spinal cord compression due to the transfer of mechanical forces through the malformed cervical spine[20].

When interpreting family genealogy, it was defined that individuals (I-5, II-6, II-10, II-14, III-5) had symptoms compatible with KFS and with an autosomal dominant inheritance pattern. Among the identified criteria for this type of inheritance is the phenotype that appears in all generations and one of the parents of each affected individuals is also affected. In an autosomal dominant inheritance pattern, affected individuals of both sexes have the same probability of transmitting the mutated allele and, consequently, also the phenotype to their children of both sexes; the inconspicuous expression of the disorder may give rise to apparent exceptions to this rule (figure 4).

Considering the differences in time and morphology of vertebral bodies synostosis, differences in frequency of fusion in specific regions, the most likely inheritance pattern is autosomal dominant and according to the new KFS classification[6], it is suggested that individuals in the studied family correspond to KFS type II associated with 8q22.1.

In the differential diagnosis approach (table 1), chromosomal pathologies with a higher prevalence,

Table 1. Diagnostic difference of Klippel Feil Syndrome

Features	Turner	Murcs	Klippel Feil*	Wildervanck
Inheritance	Chromosome	Sporadic	Autosomal dominant	Complex inheritance
Short neck	Yes	No	Yes	Yes
Low nuchal hairline	Yes	No	Yes	Yes
Limited neck movement	Normal	Normal	Limited	Limited
Short stature	Yes	Yes	Yes	Yes
Facial asymmetry	No	Rarely	No	No
Oculomotor nerve paralysis	No	No	No	Yes
Low set ears	Low	Normal	Low	Low
Deafness	No	Rarely	No	Sensorineural
Cardiac abnormalities	Yes	No	No	Yes
Kidneys abnormalities	Yes	Yes	No	Yes
Vertebral fusion	No	Thoracic	Cervical	Cervical
Scoliosis	Rarely	Rarely	Cervical-thoracic	Thoracic-lumbar
Sprengel□s deformity	No	Yes	Yes	Yes
Hypoplasia of the thenar muscles	No	Rarely	No	No
Agenesis of the thumbs	No	Yes	No	No
Fusion between hamate and capitate	No	No	Yes	No
Müllerian duct aplasia	Yes	Yes	No	No
Amenorrhea	Yes	Yes	No	No
Second sex characteristics	Absent	Normal	Normal	Normal
LH/FSH level	Low	Normal	Normal	Normal
Karyotype	45,X0	46,XX	46,XX	46,XX

*Description of case

such as Turner syndrome, should be considered among the first options, without forgetting monogenic disorders. KFS has been described as a manifestation of fetal alcohol syndrome and a similar phenotype has been observed in maternal treatment with valproic acid[21].

Aphonia directly related to the malformation of laryngeal cartilages is present in 35% of individuals, Sprengel deformity characterized by scapulae in an unusually high position in 50% of them. Hearing malformations occur most frequently in females with an M:F ratio of 1:1.5; neurosensory impairment is found in less than 30% of KFS cases, followed by mixed deafness and conductive deafness[1].

In the skeletal system, scoliosis or kyphosis is present in 60%, in our cases corresponding to 40% in II-10, III-5 (figure 1), while malformations of the urinary system with horseshoe kidney in 35%, and facial asymmetry and webbed neck with 20%. Among heart malformations, which are present in 4.2 -14%, severe lesions such as aortic coarctation may occur, however, ventricular septal defects are the most frequent[15,22,23].

Mutations in the loci of the *GDF3* gene (chromosome 12p13.1), *GDF6* (chromosome 8q22.1) and *MEOX1* (chromosome 17q21.31) have been shown to be related to KFS[24-26]. In an investigation by Ye M et al., where multiple missense variants were identified in KFS families, it appears to represent one of the few studies reporting on the contribution of bone morphogenetic proteins in heterozygous individuals with alterations in *GDF3* and *GDF6* genes[10]. The patients reported in this research were not subjected to molecular studies, due to the absence of molecular sequencers in Ecuador.

Conclusions

The patient with congenital spinal deformity is a case of interest because it is an infrequent diagnosis in pediatric age and whose clinical suspicion can be generated from a good clinical examination and index case study, complemented with the interpretation of genealogy in Mendelian inheritance disorders, allowing timely genetic counseling.

The described clinical findings could give a pattern of high diagnostic suspicion, where the absence of the molecular study at the moment of establishing a diagnosis is no obstacle. Currently, molecular sequencers are not massively available, a fact that emphasizes the importance of the clinical evaluation described in this research

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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