Acta Scientific Orthopaedics

Volume 2 Issue 2 February 2019

Case Study

An Unusual Combination of Klippel Feil Syndrome and Morquio's Disease in Siblings of Second Degree Consanguineous Couple – A Rare Case Report

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Received: January 16, 2019; **Published:** January 24, 2019

Abstract

Autosomal recessive disorders are common in consanguineous marriage couples. Horizontal transmission of disease is seen among the siblings with 25% affected, 50% carriers and 25% normal individuals. Klippel-Feil syndrome (KFS) is a rare, congenital syndrome complex of osseous and visceral anomalies with a clinical triad of short neck, limitation of head and neck movements and low posterior hairline. It follows various autosomal dominant and recessive mutations with reduced penetrance and variable expression. Morquio's disease is a rare autosomal recessive lysosomal storage disorder due to deficiency of N-Galactosamine-6-sulphate sulphatase (MPS IV-A) and beta galactosidase (MPS IV-B). MPS – IV is characterised by short trunk dwarfism, fine corneal deposits and skeletal dysplasia (Dysostosis multiplex) that is distinct from other MPS syndrome with preservation of intelligence. In our article, we present both siblings with Klippel Feil syndrome and Morquio's syndrome born out of second degree consanguineous marriage couples. Both the siblings were managed conservatively and symptomatically with regular follow-ups. The primary genetic counselling is addressed for future pregnancy.

Keywords: Autosomal Recessive; Klippel-Feil Syndrome; Morquio's Disease; Second Degree Consanguineous; Genetic Counselling

Introduction

Autosomal recessive disorders are common in consanguineous marriage couples. Horizontal transmission of disease is seen among the siblings with 25% affected, 50% carriers and 25% normal individuals.

Klippel-Feil syndrome (KFS) is a rare, congenital syndrome complex of osseous and visceral anomalies with a clinical triad of short neck, limitation of head and neck movements and low posterior hairline [1]. It follows various autosomal dominant and recessive mutations with reduced penetrance and variable expression [2].

Morquio's disease is also known as type IV mucopolysaccharidosis, a rare autosomal recessive lysosomal storage disorder which is due to deficiency of N-Galactosamine-6-sulphate sulphatase (MPS IV-A) and beta galactosidase (MPS IV-B). Both MPS – IV-A and IV-B results in defective degradations of keratan sulphate and chondroitin sulphate [3]. MPS – IV is characterised by short trunk dwarfism, fine corneal deposits and skeletal dysplasia (Dysostosis multiplex) that is distinct from other MPS syndrome with preservation of intelligence [4].

In our article, we present an elder sibling with Klippel Feil syndrome and younger sibling with Morquio's syndrome born out of second degree consanguineous marriage couples. Both the siblings were managed conservatively and symptomatically with regular follow-ups and multi-disciplinary modality is used to improve the quality of life. Once the diagnosis is made, one should closely investigate for other anomalies for better, early management and rehabilitation. And further primary prevention were done through genetic counselling regarding future pregnancy.

Case 1

A 14 years old female patient brought by parents, born to first issue of second degree consanguineous couple with a chief

complaints of restricted movements of neck since birth, swelling in the lower part of back of head since birth and headache since past 5 years. The patient was developmentally normal who attained all developmental milestones at appropriate age and with immunisation status up-to date. No significant family history was noted.

On examination, the patient had swelling in occipital region of 3 x 3 cm which cystic and non-translucent in nature, short neck with global restriction of neck movements and short trunk dwarfism (disproportionate short stature). The patient had pallor, knuckle and perioral hyperpigmentation.

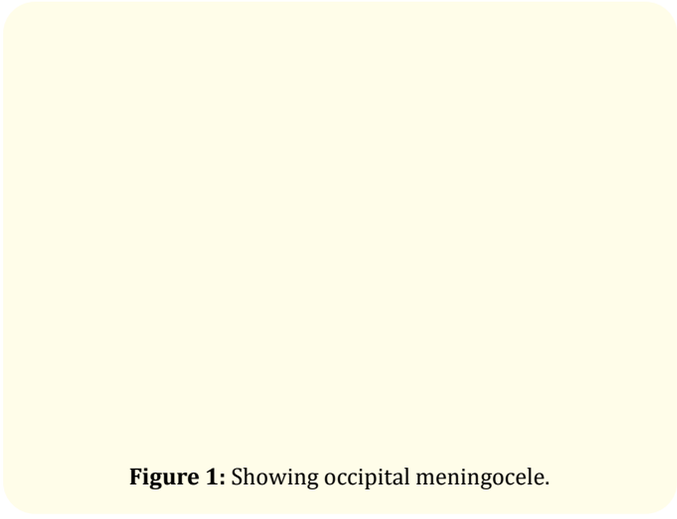

Figure 1: Showing occipital meningocele.

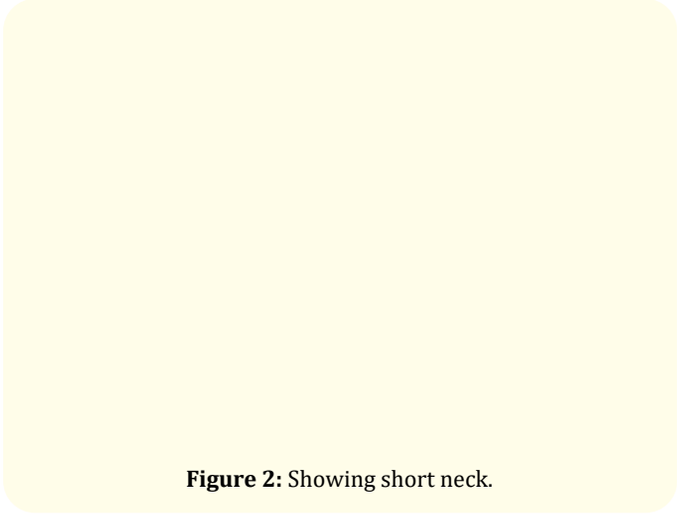

Figure 2: Showing short neck.

Investigations were as follows:

a) Hb – 7.6 gm/dL

b) Normal renal and liver function tests

c) Ultrasound neck and abdomen revealed normal status

d) 2D ECHO revealed no defects

e) Peripheral smear showed microcytic hypochromic anemia

f) X ray cervical spine showed fusion of C1 – C6 vertebrae with fusion of spinous process with normal atlanto dens interval, exaggerated lordosis, normal anterior posterior ligaments, normal dens and normal tracheal shadow (as shown in figure 3)

g) CT brain revealed 11 mm midline occipital bone defect noted with herniation of meninges with CSF flow through it which is suggestive of occipital meningocele; 10 mm defect also noted in frontal bone on left side with underlying gliosis in left frontal lobe and ex-vacuo dilatation of frontal horn of left lateral ventricle (as shown in figure 4).

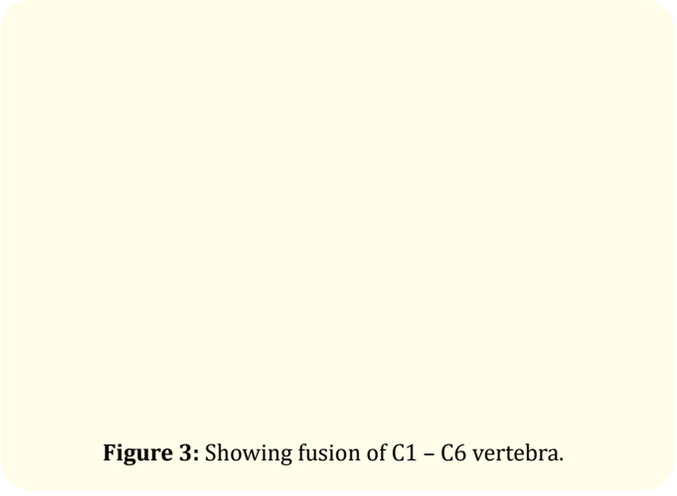

Figure 3: Showing fusion of C1 – C6 vertebra.

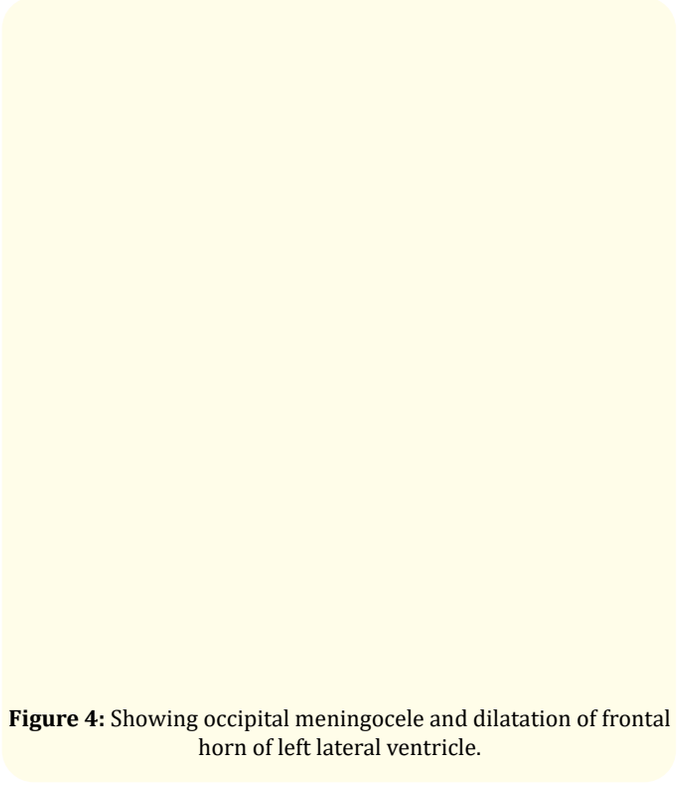

Figure 4: Showing occipital meningocele and dilatation of frontal horn of left lateral ventricle.

Discussion

Klippel-Feil syndrome (KFS) is a rare combination of congenital osseous and visceral anomalies leading to fusion of 2 segments or the entire cervical spine. KFS appears to be a failure of the normal segmentation and fusion processes of the mesodermal somites, which occur between the third and seventh week of embryonic development. Pathogenesis of the KFS involves various autosomal dominant and recessive genetic mutations including *GDF6, GDF3, MEOX1,* and *RIPPLY2* which are responsible for transcription regulation and signalling pathways involved in somite development during embryogenesis [2,5-7]. Webbing of the neck, elevation of the scapula and congenital heart defects are frequently associated with this spinal anomaly [1,8,9].

Gunderson., *et al.* [10] distinguished 3 types of cervical vertebral fusion defect related to Klippel-Feil anomalies

- Type I – Massive fusion of many cervical and upper thoracic vertebrae into bony blocks
- Type II – Fusion of only 1 or 2 interspaces, usually C2-C3 or C5-C6, but there can be intrafamilial variability
- Type III – Both cervical fusion and lower thoracic or lumbar fusion, often associated with multiple organ anomalies and subsequent neurologic compromise.

A fourth type of Klippel-Feil anomaly has been suggested to be associated with sacral agenesis [8].

Our patient presented with a short neck, limited neck movements and a low-set posterior hairline. This patient has fusion of the C1 – C6 vertebrae without elevation of the scapula. With these features, our patient fit the type I category of KFS.

Several authors report the association of partial or complete conductive hearing impairment, underdeveloped low-set ears and facial asymmetry in patients with type II KFS [11]. Clinicians should be aware of the characteristics of KFS when making an oral diagnosis and planning treatment. Our patient had no dental complaints with moderate oral hygiene.

No surgical intervention, such as disc arthroplasty or fusion of unstable adjacent spine levels, were indicated for our patient, since neurologic symptoms to suggest radiculopathy or myelopathy were not evident. Type III KFS patients do have increased risk of developing radiculopathic or myelopathic symptoms when compared to Type I and II patients [12]. Rarely, breathing disorders in sleep, such as fatal obstruction sleep apnea, stridor or bradypnea, are seen and all children diagnosed with KFS should be regularly followed for these problems [13]. Mouth breathing and facial asymmetries are frequently observed in patients with KFS. Special precautions should be taken when considering sedation or anesthesia in the pediatric dental office as these patients should not be intubated [14].

Our patient had a classical triad of short neck, limitation of head and neck movements and low posterior hairline which is supplemented by radiograph of cervical spine shows fusion of C1 – C6 vertebrae along with fusion of spinous process. All these findings confirm a diagnosis of Klippel Feil syndrome – Type I. Our patient was managed symptomatically and with physiotherapy in the form of short wave diathermy, interferential therapy and cervical spine strengthening exercises.

Case 2

1 year 6 months old male child brought by mother born to second issue of second degree consanguineous couple with a chief complaints of bony prominence in lower part of back and prominent anterior chest. On examination, the case presented with florid ricketic features such as frontal bossing, short neck, dental malocclusion, widened wrist, pectus carinatum, harrison sulcus, disproportionate short stature (short trunk dwarfism), kyphosis, gibbus deformity of lumbar spine, pes planus, double malleoli and genu varus were noted (as shown in figure 5a and 5b). Developmentally normal child with no organomegaly and no coarse facies were noted.

Figure 5: A Showing prominent anterior chest wall, frontal bossing, short neck, Harrison sulcus and pectus carinatum and figure B Showing gibbus deformity of lumbar spine.

Investigations were as follows:

a) Normal serum calcium, phosphorus, alkaline phosphatase and PTH levels
b) Renal parameters and USG abdomen were normal.
c) Plain radiograph of wrists showed widened joint space and bullet shaped metacarpals (as shown in figure 6)

d) Plain radiograph of spine showed anterior beaking of vertebra with posterior scalloping and thoraco-lumbar kyphosis (as shown in figure 7)

e) Plain radiograph of bilateral hip joint showed rounded iliac wings, dysplastic acetabuli and small femoral heads and cox valga (as shown in figure 7).

f) Urine analysis showed elevated levels of keratan sulphate and chondroitin sulphate.

g) Enzyme analysis revealed reduced fibroblast N-Galactosamine-6-sulphate sulphatase enzyme activity.

Figure 6: Showing bullet shaped metacarpals in bilateral wrist radiograph.

Figure 7: Showing anterior breaking of vertebra with posterior scalloping in spine radiograph and rounded iliac wings, dysplastic acetabuli and small femoral heads and cox valga in pelvis radiograph.

Discussion

Morquio's syndrome is a member of a group of inherited metabolic disorders collectively termed mucopolysaccharidosis (MPSs). It is estimated to occur in 1 in 2, 00,000 live births [15]. Morquio syndrome is divided into two subtypes; Type A and Type B which result from the deficient enzymes N-acetylgalactosamine 6-sulfatase (Type A) or beta-galactosidase (Type B) needed to break down the keratan sulfate.

Patients with Morquio's syndrome usually can be clinically distinguished from patients with other mucopolysaccharidosis as they do not have coarse facial features or mental retardation and they have additional skeletal manifestations (Dysostosis multiplex) derived from a unique spondyloepiphyseal dysplasia and ligamentous laxity.

Clinical manifestation of Morquio's disease are as follows [16-18]

a. Skeletal manifestation – Genu valgus, kyphosis, waddling gait, dwarfism, pectus carinatum, platyspondylysis, odontoid hypoplasia, hyperlordosis, osteoporosis, ulnar deviation, spondyloepiphyseal dysplasia and widening of metacarpals with proximal pointing

b. Extra skeletal manifestation – Mild corneal clouding, progressive deafness, cardiac valvular lesion, small teeth, thin enamel, dental caries.

In our case, clinical findings of frontal bossing, short neck, dental malocclusion, widened wrist, pectus carinatum, harrison sulcus, disproportionate short stature (short trunk), kyphosis, gibbus deformity of lumbar spine, pes planus, double malleoli and genu Varus were noted with normal intelligence and without dental caries, organomegaly and coarse facies. Radiologically, X ray of spine showed anterior beaking of vertebra with posterior scalloping and thoraco-lumbar kyphosis, X ray pelvis with bilateral hip joint showed rounded iliac wings, dysplastic acetabuli widened joint space, small femoral heads and cox valga, X ray bilateral wrists show bullet shaped metacarpals and X ray skull showed J shaped sella in skeletal survey. Urine analysis showed elevated levels of keratan sulphate and chondroitin sulphate. Enzyme analysis revealed reduced fibroblast N-Galactosamine-6-sulphate sulphatase enzyme activity. The treatment options for patients with MPS were hematopoietic stem cell transplantation and recombinant intravenous enzyme replacement therapy. Early diagnosis and treatment can improve patient outcome and prolong survival [19]. Our case has been managed conservatively and symptomatically with regular follow-ups and multi-disciplinary modality is used to improve the quality of life. And further primary prevention was done through genetic counselling.

Conclusion

Though genetic parental counselling has been given about autosomal recessive disorder for first child, the parents got conceived for second pregnancy which led to genetic abnormality (25%) in the second child. Strict compliance to genetic counselling is not adhered by the parents. Both the siblings were managed conservatively through multidisciplinary approach and followed up once in 2 months for the progression of disease. A genetic work up should be done but due to non-availability of facilities further genetic analysis could not be done.

Conflicting Interest

Nil

Acknowledgement

Nil

Funding Sources

Nil

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