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# Unravelling the complexity of Klippel-Feil Syndrome: A Comprehensive Review of Etiology, Clinical manifestations and Therapeutic approaches

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## ABSTRACT

Klippel-Feil syndrome (KFS) is a congenital defect that affects the formation or segmentation of cervical spine, which is in the neck region of the spine. This condition can lead to various associated anomalies, meaning that individuals with Klippel-Feil syndrome may have additional abnormalities or differences in their body. The wide spectrum of these associated anomalies adds complexity to understanding genetic causes of the syndrome and poses challenges in managing patients with congenital vertebral fusion, where the vertebrae in neck are fused together. This review provides a comprehensive analysis of the disease Klippel-Feil syndrome.

**KEY WORDS -** Klippel-Feil syndrome, Cervical spine, Sprengel deformity

## INTRODUCTION

Klippel-Feil syndrome, also known as dystrophia brevicolis, was initially documented in 1912 by Maurice Klippel and Andre Feil. This condition is characterized by a set of three main symptoms: a short neck, restricted range of motion in the neck and a low hairline at the back of head which can lead to chronic headaches, limited range of neck motion and neck muscle pain. [1, 2] In addition, Klippel-Feil syndrome can lead to complications such as spinal stenosis, neurological deficits, cervical spinal deformities, instability and spinal stenosis. The patients with this syndrome can also have multiple associated symptoms and

conditions. This syndrome occurs when there are errors in way of embryo develops, leading to its presence at birth. However, if the symptoms are mild, it may remain unnoticed for several years. [3]

The spine consists of 33 vertebrae, the first seven known as cervical vertebrae. Among these, closest to the base of the skull is C1, while C7 is the final vertebrae in this section. Klippel-Feil syndrome commonly affects the C2 and C3 vertebrae. Normally, intervertebral disks and cartilage separate each vertebra, providing cushioning and allowing them to move independently. However, in individuals with Klippel-Feil syndrome, some vertebra fuses together, resembling a single bone. Klippel-Feil syndrome can also be associated with conditions like fetal alcohol syndrome, goldehar syndrome and limb abnormalities. [4] If the spine experiences trauma, like a fall or car accident, it can worsen issues in the fused area. The fusion of vertebrae may result in nerve damage.

Diagnosing KFS can be challenging since it affects a diverse group of patients with various abnormalities. The unifying factor is presence of fused or segmental cervical vertebrae. KFS is not always genetic and may not be recognized at birth. [5]

## EPIDEMOLOGY

Klippel-Feil syndrome (KFS) is quite rare, with an estimated occurrence of 1 in 40,000 to 42,000 newborns worldwide. It tends to affect females slightly more than males. While the exact incidence is unknown, reports suggest it occurs in about 1 in 42,000-50,000 live births. [6]

## SUB-DIVISIONS

- Klippel-Feil syndrome, type I
- Klippel-Feil syndrome, type II
- Klippel-Feil syndrome, type III

## CLINICAL PRESENTATION

Klippel-Feil syndrome, a rare skeletal condition, occurs when two or more vertebrae in the neck fuse together. The spine is made up of 33 bones called vertebrae, with the first seven known as cervical vertebrae. KFS primarily affects the cervical vertebrae and can lead to a range of symptoms that vary from person to person. While the classic symptoms were thought to be a short neck, limited head and neck movement and a low hairline at the back of head, experts have found that these symptoms may only apply to a specific group of people with KFS, accounting for less than half of those affected. [7, 8, 9]

Besides the fusion of specific vertebrae, Klippel-Feil syndrome (KFS) can be associated with a wide range of additional anomalies affecting various organs in the body. The severity and progression of KFS can vary greatly depending on specific complications and class of KFS. It's important for individuals to discuss their unique case, symptoms and prognosis with their doctor and medical team. Approximately 30 percent of people with KFS may have additional skeletal abnormalities, such as rib fusion, scoliosis or sprengel's

deformity. Some individuals may also experience spina bifida occulta, which can lead to symptoms like a tuft of hair or dimple, leg weakness or urinary incontinence.

KFS type II can cause incomplete development of certain vertebrae and fusion of the first neck vertebrae with the skull bone. Hearing impairment is common and it can be conductive, sensorineural or mixed. Eye abnormalities like cross-eye, rapid eye movements and ocular tissue defects may also be present. Some individuals may have craniofacial issues such a facial asymmetry, twisted neck and cleft palate in about 17% of cases. [10] Sometimes, people with KFS may have additional physical issues. This can include heart problems like ventricular septal defects (VSDs), where there's an abnormal opening in the heart's septum. Kidney problems like underdevelopment, absence, abnormal placement or swelling can also happen. Neurological complications can occur due to spinal cord injury from unstable cervical vertebrae. These complications may cause pain, abnormal sensations like tingling or burning or involuntary muscle movements. They usually show up between the ages of 20 and 30. Also, some people with KFS may experience heightened reflex reactions (hyperreflexia), weakness or paralysis on one side of the body (hemiplegia) or in the legs and lower body (paraplegia) or nerve impairments affecting cranial nerves. [11, 12]

## ETIOLOGY

The cause of Klippel-Feil syndrome is not well understood. Some studies suggest that disruptions in blood flow, fetal development issues, neural tube complications or genetic factors may play a role. It can sometimes occur alongside conditions like fetal alcohol syndrome, goldenhar syndrome or sprengel deformity. In certain families, mutations in the GDF6, GDF3 and MEOX1 genes can cause Klippel-Feil syndrome. GDF6 and GDF3 abnormalities are inherited in an autosomal dominant pattern, while MEOX1 mutations are autosomal recessive. [13, 14, 15

## ASSOCIATED ANOMALIES

- SPINAL ANOMALIES – It includes the fusion of neck vertebrae, congenital scoliosis, abnormalities in spinal segmentation and formation, craniovertebral junction anomalies and spina bifida occulta. [16, 17, 18]
- SKELETAL ANOMALIES – Skeletal anomalies like Sprengel deformity, where the shoulder blades are underdeveloped and sit higher on the back. [19, 20, 21]
- OTHER ANOMALIES – It includes torticollis, kidney, rib and heart malformations, respiratory problems, neurological deficits, syndactyly (webbed fingers) and hypoplastic thumb (abnormality of the thumb). [22, 23, 24, 25]

## DIAGNOSIS

Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) myelographic studies are commonly used to determine patterns of associated congenital and acquired abnormalities of the spine and spinal cord. MRI findings shows hydrocephalus and brain stem descent, indicating the presence of Chiari malformations. [26] Chiari malformation is a cranial anomaly, which manifests similar to that of the Klippel

Feil Syndrome. KFS associated with Chiari malformations cause the herniation of any part of the cerebellum through foramen magnum. Among the nonotologic diagnoses, dysphagia was the most common diagnosis. The association of otologic manifestation with KFS has also been reported earlier. [27, 28-35] KFS usually diagnose at the age of birth through observation. An audiological evaluation is evident for testing the hearing ability. AP, lateral, odontoid views in flexion and extension on X ray reveals images of the thoracic and lumbar spine, which illustrates scoliosis, spinal bifida, or hemivertebrae. A wasp- waist sign (anterior-posterior narrowing) illustrates the spinal stability and movement.

## TREATMENT

Surgical treatment was performed for Klippel Feil syndrome with severe basilar invagination. Basilar invagination could not be reduced by halo vest and direct traction. Gentle intraoperative reduction achieves a good spinal alignment and reduction of the basilar invagination. Paralysis was exacerbated immediately after surgery. Nonsurgical massage and therapeutic treatment- surgical options are usually performed. For axial symptoms and radiculopathy, use soft tissue massage and therapeutic treatment including modalities and medications. For transient quadriparesis, soft cerival collars and bracing are recommended. Cervical traction is an option for symptomatic basilar invagination. Aerobic and aquatic exercises improve condition in case of sprengel deformity. Breathing exercises recommended in synkinesia. Neurosurgery with spinal decompression, untethering of the spinal cord and lysis of adhesions with electrophysiological monitoring are also performed. Arnold Chiari malformation and myelomeningocele repair for scoliosis repair and spinal stenosis decompression. For sprengel deformity, performes scapulopathy [36].

## GENETIC CONSIDERATIONS

Mutations in the GDF6 (Growth Differentiation Factor 6) or GDF3 (Growth Differentiation Factor 3) can cause Klippel-Feil Syndrome. KFS is an autosomal recessive disorder which may leads to fused vertebrae limits the movement of the neck and back as well as leads to chronic headaches and muscle pain in the back and neck and back that range in severity. The various classes of FKS (Class 1-4) that addresses the KFS genetic heterogeneity [37]. The most expressed manifestation in patients with KFS is “scoliosis” [38, 39]. KFS is a malformation sequence that starts at the fourth or beginning of the fifth week of fetal life, due to abnormalities in the normal segmentation of mesodermal somites. Embryologically, development control genes (PAX genes) play a significant role in developing the axial skeleton. Studies conducted on mice suggest that, PAX gene is primarily responsible for the anomalies [40]. Abnormalities in such things result in reduced gene expression and complete loss or fusion or both of somites and vertebral bodies with extensive fusions [41]. It was reported by Stallmer et al that cervical ribs were one of the extraspinal abnormalities in KFS [42].

## PROGNOSIS

Klippel-Feil Syndrome presents with an abnormal fusion of 2 or more bones in the cervical spine, thus creates a characteristic appearance of a short neck with facial asymmetry, low hair line and limited neck mobility. The prognosis of Chiari Type III malformation is worse than other types of Chiari. Mirror movement is apparently and normally found on KFS. Mirror movements refer to involuntary movements, which occur in a muscle group or limb on one side of the body in response to an intentionally performed movement in controlateral muscle group or limb [43]. The actual prognosis of the patients with this malformation is not exactly known. Raimond indicated that the presence of the cervical or occipital encephalocele was not associated with a poor prognosis, but the functional prognosis remains severe, and concluded that surgical care should be undertaken if possible [44]. KFS further leads to chronic headaches, limited range of neck movement and neck muscle pain.

## FUTURE DIRECTIONS

Klippel Feil Syndrome is a complex condition presenting the abnormal fusion of cervical vertebrae at C2 and C3, due to abnormality in the segmentation of cervical spine in early fetal development. Patients with KFS can be polysyndromic [45, 46, 47, 48]. The syndrome can be successfully managed non-surgically or surgically, depending on the presence of symptoms. For patients with functional limitations, assisted devices or orthotics may be necessary. Since some of the patients are asymptomatic, a significant number have myelopathy and neuropathy, which may worsen their quality of life [49, 50].

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