Prevalence of Klippel-Feil Syndrome in a Surgical Series of Patients with Cervical Spondylotic Myelopathy: Analysis of the Prospective, Multicenter AOSpine North America Study

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Abstract

Study Design Prospective study.

Objective To evaluate the prevalence of Klippel-Feil syndrome (KFS) in a prospective data set of patients undergoing surgical treatment for cervical spondylotic myelopathy (CSM) and to evaluate if magnetic resonance imaging (MRI) features in patients with KFS are more pronounced than those of non-KFS patients with CSM.

Methods A retrospective analysis of baseline MRI data from the AOSpine prospective and multicenter CSM-North American study was conducted. All the patients presented with at least one clinical sign of myelopathy and underwent decompression surgery. The MRIs and radiographs were reviewed by three investigators. The clinical and imaging findings were compared with patients without KFS but with CSM.

Results Imaging analysis discovered 5 of 131 patients with CSM (~3.82%) had single-level congenital fusion of the cervical spine. The site of fusion differed for all the patients. One patient underwent posterior surgery and four patients received anterior surgery. Postoperative follow-up was available for four of the five patients with KFS and indicated stable or improved functional status. All five patients demonstrated pathologic changes of adjacent segments and hyperintensity signal changes in the spinal cord on T2-weighted MRI. Multiple MRI features, most notably maximum canal compromise ($p = 0.05$) and T2 signal hyperintensity area ($p = 0.05$), were worse in patients with CSM and KFS.

Conclusions The high prevalence of KFS in our surgical series of patients with CSM may serve as an indication that these patients are prone to increased biomechanical use of segments adjacent to fused vertebra. This supposition is supported by a tendency of patients with KFS to present with more extensive MRI evidence of degeneration than non-KFS patients with CSM.

Keywords
- congenital anomaly
- degenerative cervical myelopathy (DCM)
- fusion
- magnetic resonance imaging (MRI)
- radiograph
- spine

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Introduction

Klippel-Feil syndrome (KFS) has been characterized as a triad of clinical findings encompassing a short neck, low posterior hairline, and restriction of neck motion.[1,2] Despite this description, it has been estimated that only 34 to 74% of patients with KFS present with this collective manifestation and that additional associated congenital defects may present concomitantly.[1] It has been estimated that KFS occurs in 1:40,000 to 42,000 births with a slight female predominance; however, the absence of population screening leaves such estimation provisional.[3]

The relationship between KFS and degenerative cervical myelopathy (DCM) has not been well described despite reports of segmental hypermobility and a predisposition to degenerative changes in the cervical spine of patients with KFS.[4,5] The recognition that patients with surgical fusion of vertebrae may be at risk for adjacent segment pathology further supports that patients with KFS should be investigated for an increased propensity to develop neurologic sequelae resulting from the degenerative changes.[6]

In the recent AOSpine-North America prospective and multicenter study on patients with cervical spondylotic myelopathy (CSM) undergoing surgical decompression, a review of magnetic resonance imaging (MRI) resulted in the discovery of five patients with congenital cervical fusion, considered to be the "hallmark" of KFS.[1] Given the finding that these patients may be predisposed to spinal degeneration and neurologic disease, it is the objective of the present study to assess whether patients with KFS demonstrate more pronounced features of degenerative spine disease using quantitative MRI analysis than patients without KFS but with CSM.

Materials and Methods

Clinical and imaging data were derived from a prospective cohort of patients enrolled in the AOSpine CSM-North American prospective and multicenter study. Patients presented with at least one clinical sign indicative of CSM and had not received prior spine decompression surgery. Patients with asymptomatic CSM, active infection, neoplastic disease, rheumatoid arthritis, ankylosing spondylitis, and concomitant lumbar stenosis were excluded. The research ethics board approved the study, and patient consent was obtained.

The general demographic, clinical, and radiologic features of these patients were analyzed. Clinical parameters included medical history, neurologic examination, and modified Japanese Orthopedic Association (mJOA) evaluation at baseline and 6, 12, and 24 months. Patients were evaluated using radiographs and MRIs of the cervical spine. Although all patients in the study underwent spinal cord decompression surgery, the surgical approach (e.g., anterior/posterior) and method (e.g., corpectomy, laminectomy, and fusion), as is the case in clinical practice, was left at the discretion of the surgeon.

The radiologic criteria for KFS diagnosis were congenitally fused vertebrae and a wasp-waist sign. Further quantitative imaging analysis was conducted using MRI.

MRIs were obtained using 1.5-T magnets. Image analysis of DICOM (Digital Imaging and Communications in Medicine) file formats was performed using OsiriX (open access, available at: http://www.osirix-viewer.com). The evaluation of presence or absence of signal change on T1- and T2-weighted MRI was performed by three investigators, and any disagreement was resolved with consensus. The measurements for maximum spinal cord compression, maximum canal compromise (MCC), area as well as sagittal extent of T2 hyperintensity signal change were conducted by the primary author using methods previously described by Nouri et al and Fehlings et al.[7,8]

The frequencies of categorical variables were compared between KFS and non-KFS groups using the Fisher exact test. The means of continuous variables were compared between patients with KFS and patients without KFS using the appropriate one-tailed *t*-test (depending on the parametric properties).

Results

Five of a total 131 patients had radiologic features consistent with KFS (►**Fig. 1**), translating to a prevalence of ~3.82% (5/131). The mean age of patients with KFS was 52 years (range = 32 to 68) and, although slightly younger, is comparable to the average age reported in the greater AOSpine-NA study cohort (56.33 ± 11.71 years).[9] Of the 5 patients, 2 were women and 3 were men. All patients had Samartzis type I KFS.[1] The clinical features varied depending on the level of compression but numb, clumsy hands and impaired gait were seen in all the patients. Patients with mJOA scores of 15 to 18 were classified as mild, 12 to 14 as moderate, and less than 12 as severe CSM based on the classification outlined by Fehlings et al.[9] One patient had mild CSM, two patients had moderate CSM, and one patient had severe CSM based on their preoperative mJOA scores (mJOA scores were not available for one patient). Four patients underwent anterior cervical decompression and instrumented fusion, and one patient underwent laminectomy and instrumented fusion. Four of the five patients with follow-up data had stable or improved mJOA scores. The clinical and surgical details are described in ►**Table 1**.

All five patients with KFS demonstrated pathologic changes in the segments adjacent to the fused vertebrae as well as hyperintensity signal changes in the spinal cord on T2-weighted MRI. With the exception of the presence of T1 hypointensity signal change, which was comparable to patients without KFS, all MRI features demonstrated a consistent tendency to be more pronounced in patients with KFS (►**Table 2**). Additionally, patients with KFS had worse MCC as well as larger T2 hyperintensity area, which were statistically significant ($p = 0.05$).

Discussion

The purpose of the prospective multicenter cohort was to determine the efficacy of decompressive surgery for the treatment of CSM. The results published by Fehlings et al showed that surgical intervention is indeed effective and

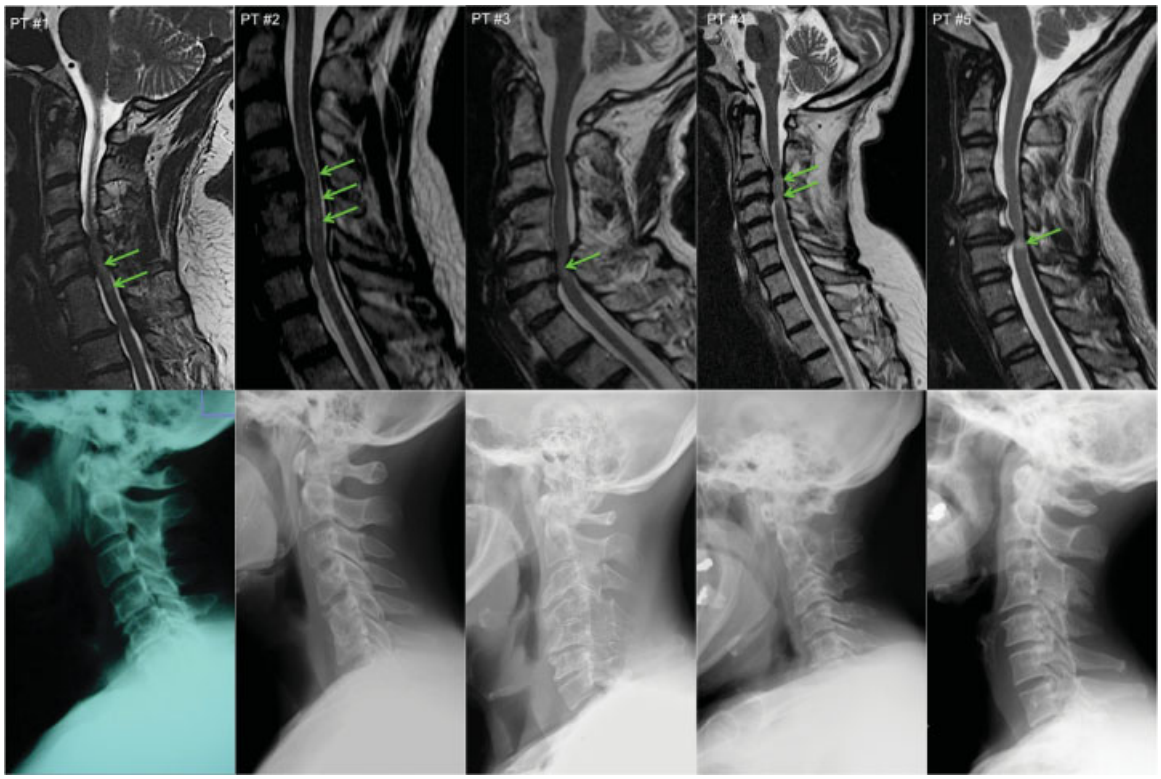

Fig. 1 T2-weighted magnetic resonance images as well as radiographs for all five patients are presented. Patient numbers correspond with those provided in ►**Table 1**.

safe.[9] Though it is difficult to make the same determination for the subset of patients with KFS given our small series, functional assessment via the mJOA from baseline was maintained or improved in all four of the five patients with outcome data. Given these findings and those reported by Fehlings et al,[9] it seems reasonable to assume that, for the majority of patients with KFS, surgical decompression for CSM should offer comparable efficacy.

The finding of KFS within the surgical cohort of patients with CSM also provided an opportunity to assess the prevalence of KFS in this population. Interestingly, although it has been previously reported that the population prevalence of KFS is 0.71%,[10] we found a prevalence of 3.82% in our series. It is possible that the prevalence of KFS among patients with CSM may be even higher if one includes patients with craniovertebral junction anomalies; however, this was out of the scope of our work.

All patients presented with a single fusion, or type I KFS based on the classification by Samartzis et al.[1] However, it should be noted that several other modern classifications based on genetic, mobility, and radiographic factors have also been proposed in literature.[5,11,12]

KFS represents a relatively rare kind of congenital malformation of the cervical spine where appropriate segmentation of vertebrae during the second to eighth week of gestational development is interrupted.[1,4,13,14] Sprengel's deformity and the presence of omovertebral bone may be accompanied associations.[14] In addition to this, several reports have described KFS along with other congenital pathology affecting visceral, musculoskeletal, otolaryngologic, and neurologic systems.[1,13,15–17] It is unclear if these reported associations are extraordinary cases, are different variations of KFS, or rather represent one of the large number of other conditions described by Giampietro et al,[18] which have been identified to entail congenital cervical segmentation defects. Varying genetic and prenatal factors are likely to contribute to the spectrum of manifestations. Indeed, although most occurrences of KFS have been suggested to appear sporadically, there are reports of autosomal dominant, autosomal recessive, and X-linked forms.[15,18] It has been shown that disruption of the Notch pathway genes impact somite segmentation in mice, and additionally, that PAX as well as SGM1 may present potential candidate genes responsible for KFS development.[3] More recently, the genes related to MEOX1[14] and GDF6[19] have been associated with KFS in humans as well. With regards to prenatal factors, cervical spine malformations in general have been linked to maternal alcohol use, anticonvulsant medications (e.g., valproic acid), hyperthermia, maternal insulin-dependent diabetes mellitus, and gestational diabetes.[18] Ultimately, however, specific etiologic factors for KFS have not been well defined. Unfortunately, because patients in the original AOSpine-NA study cohort were not specifically screened for KFS, a tailored clinical history to investigate etiologic factors surrounding the condition was not performed.

From a clinical perspective, the ramifications of KFS are largely dependent on the extent of fusion and the number of segments involved. Clinically relevant symptoms of fusions,

Table 1 Baseline general characteristic, clinical findings, surgical summary, and mJOA scores from the follow-up of patients with KFS are described

Patient no. and gender	Age (y)	Comorbidities	Symptom duration (mo)	Signs and symptoms	Baseline severity (mJOA)	Klippel-Feil level and type	Spinal cord signal change on T2 MRI	Surgical summary	Outcome (mJOA)
1 (female)	55	Mild respiratory dysfunction, mild psychiatric disorder	3	Numb and clumsy hands, positive Hoffmann's sign, broad-based unstable gait	Moderate (14)	C6–C7, type I	C5–C7	C3–C7 posterior laminectomy and instrumented fusion	6 mo (NR); 12 mo (18); 24 mo (NR)
2 (male)	32	Mild hypertension, psychiatric comorbidity	3	Numb and clumsy hands, positive Hoffmann's sign, generalized weakness and hyperreflexia	N/A	C5–C6, type I	C4–C6	C5-C7 anterior corpectomy and C4–T1 instrumented fusion (mesh cage and plate)	N/A
3 (male)	61	Mild angina/coronary artery disease, mild hypertension, mild respiratory dysfunction	12	Numb and clumsy hands, impaired gait, bilateral arm paresthesia, weakness, atrophy of intrinsic hand muscles, hyperreflexia, positive Hoffmann sign	Severe (11)	C4–C5, type I	C6–C7	C6 anterior corpectomy and C5–C7 instrumented fusion (bone graft and plate)	6 mo (17); 24 mo (NR); 24 mo (NR)
4 (male)	68	None	13	Numb and clumsy hands, impaired gait, weakness, corticospinal distribution motor deficits, hyperreflexia, positive Hoffmann sign	Moderate (14)	C2–C3, type I	C3–C5	C4 anterior corpectomy and C3–C5 instrumented fusion (bone graft and plate)	6 mo (14); 12 mo (14); 24 mo (17)
5 (female)	44	None	18	Numb and clumsy hands, impaired gait, weakness, corticospinal distribution motor deficits, atrophy of intrinsic hand muscles hyperreflexia, positive Hoffmann sign, upgoing plantar responses, lower limb spasticity, broad-based unstable gait	Mild (17)	C3–C4, type I	C5–C6	C5 anterior corpectomy and C4–C6 instrumented fusion (mesh cage and plate)	6 mo (18); 12 mo (17); 24 mo (18)

Abbreviations: mJOA, modified Japanese Orthopedic Association score; MRI, magnetic resonance imaging; N/A, not available; NR, not rated.

Table 2 MRI quantitative analysis of patients with KFS compared with the findings of the non-KFS cohort

Patient	T1 signal hypointensity	T2 signal hyperintensity	MCC (%)	MSCC (%)	T2 hyperintensity sagittal extent (cm)	T2 hyperintensity area (cm^2)
1	Absent	Present	59.9	36.1	2.13	0.383
2	Absent	Present	40.7	23.4	2.70	0.470
3	N/A	Present	67.6	47.1	1.27	0.232
4	Present	Present	65.4	50.4	3.17	0.697
5	Absent	Present	61.8	54.6	0.68	0.183
Patients with KFS	25.0% ($n = 4$)	100% ($n = 5$)	59.1 ($n = 5$)	42.3 ($n = 5$)	1.99 ($n = 5$)	0.393 ($n = 5$)
Patients without KFS	27.6% ($n = 116$)	65.3% ($n = 118$)	48.8 ($n = 115$)	33.7 ($n = 115$)	1.36 ($n = 77$)	0.281 ($n = 77$)
Statistical significance (p value)	0.73	0.13	0.05	0.10	0.06	0.05

Abbreviations: KFS, Klippel-Feil syndrome; MCC; maximum canal compromise; MSCC, maximum spinal cord compression; MRI, magnetic resonance imaging; N/A, not available.

Note: Statistical analysis: Frequencies of categorical variables (i.e., T1 hypointensity signal change; T2 hyperintensity signal change) were compared between KFS and non-KFS groups using the Fisher exact test. Means of continuous variables (i.e., MSCC, MCC) were compared between patients with KFS and patients without KFS using a one-tailed t tests.

such as the restricted movement of the neck, are largely contingent upon which levels are involved. The observations that many patients with KFS have lower posterior hairlines and shorter necks can be fundamentally attributed to the absence of complete vertebral disks, which would normally contribute to the height of the cervical spine, and therefore may be more pronounced in patients with fusion of multiple levels. Additionally, many younger patients have been reported to present with late neurologic symptoms upon follow-up that has frequently necessitated surgical intervention.[11,20–22] It has also been reported that patients with KFS are predisposed to synkinesia (mirror movement disorder), which may be the consequence of incomplete decussation of the pyramidal tract in the cervical spinal cord.[23] Although the mechanism for the occurrence of neurologic symptoms is likely multifactorial, basilar impression, iniencephaly, intraspinal pathology (including neuroschisis, split cord malformation, and diastematomyelia), and hypermobility of the upper cervical spine have been specifically implicated.[5,23]

The long-term biomechanical sequelae of KFS has not been thoroughly investigated. However, there are indications that an "adaptive hypermobility" of nonfused segments occurs and that when focused in lower cervical segments, patients are at greatest risk for degenerative changes.[5] Both degenerative changes and hypermobility can contribute to the development of myelopathy, and thus it is not surprising that patients with KFS in our series presented with a more severe constellation of findings on MRI. In particular, it was interesting to note the difference in MCC and T2 signal hyperintensity area as well as the sagittal extent between patients with KFS and patients without KFS given our small series.

It has also been recognized that the fusion of vertebrae both congenitally and through surgical means alters the biomechanics of the spine. In terms of surgical fusions, it has been postulated that this may result in an increased propensity for the development of adjacent segment pathology; however, a systematic review by Riew et al has been unable to conclusively answer the question as to whether adjacent segment pathology is a natural degenerative process or an iatrogenic one.[6] This conclusion was largely based on a general dearth of literature on the topic. Ultimately, there needs to be more investigation on the biomechanical effects of fused vertebrae, possibility with the use of dynamic/kinematic MRI techniques, to provide more clarity regarding the effects on the adjacent segments.

Substantiating an etiologic relationship in patients with KFS between the degenerative changes arising from biomechanical alterations and myelopathy is also complicated by several factors, including: (1) the reports of neurologic abnormalities unrelated to congenital vertebral fusions as described earlier; (2) the reports indicating a potential relationship between KFS and congenital stenosis[11,17,23]; and (3) the recent findings demonstrating that patients with KFS may have a smaller cross-sectional area of the spinal cord than patients without KFS, potentially increasing the risk of neurologic sequelae in the setting of extrinsic compression.[23]

Ultimately, however, the predominant finding of disk pathology immediately adjacent to fused vertebrae in our series supports that these changes may be a response to altered biomechanics of the spine and potentially the development of myelopathy. However, because signal changes on T2-weighted MRI may appear above or below the site of greatest compression, and because adjacent levels did not always represent the level of greatest canal compromise, it is challenging to definitively attribute a biomechanical etiology to myelopathy development. Thus, the underlying mechanism behind a potentially increased prevalence of KFS in patients with CSM remains to be fully elucidated. Having said this, it seems most plausible that combinations of aberrant neurologic and anatomical manifestations are likely responsible.

Limitations

There are a few limitations to our findings that have to be considered. Our ability to diagnose patients with KFS was dependent on the retrospective analysis of medical imaging. As well, these images were static and not dynamic in nature. Additionally, evidence in the form of prior imaging of the cervical spine, a tailored medical history, or genetic studies was not available and would have been valuable additional information. Furthermore, the significant heterogeneity of the patient characteristics makes it difficult to extrapolate our findings. And last, we have described a small series of only patients with clinically confirmed CSM; therefore, larger studies comprising of both symptomatic and asymptomatic patients with KFS are necessary to substantiate our findings.

Conclusion

Despite the suggestion that cervical spine degeneration can be expected in patients with KFS, we are not aware of any other study that has evaluated the prevalence of KFS in CSM patients. The relatively high prevalence of KFS in our surgical series and their more pronounced MRI findings support that these patients may be at greater risk for CSM development than the general population. However, whether biomechanically derived degenerative changes are culpable for myelopathy development remains to be substantiated. Accordingly, our findings underscore the need for further research to evaluate the extent of the association between KFS, the natural progression of cervical spine degeneration, and the possibility for an increased susceptibility for this subset of patients to develop myelopathy.

Disclosures
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