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.
Introducción

El síndrome de Klippel-Feil (KFS) ha sido caracterizado como una tríada de hallazgos clínicos, a saber, cuello plano, cuello posterior y reducción de movimiento de la cabeza. A pesar de esta descripción, se ha estimado que aproximadamente 34% a 74% de los pacientes con KFS presentan con esta caracterización y que la asociación de deficiencias congénitas puede ser comitante. También se ha estimado que el KFS ocurre en un rango de 1:40,000 a 42,000 con un predominio femenino; sin embargo, la ausencia de la prueba de screening poblacional ha hecho que la estimación sea provisional.

El reconocimiento que los pacientes con fusiones congénitas de vértebras pueden estar en riesgo aamiento a la degeneración de los segmentos adyacentes se ha propuesto como un hallazgo del KFS. Además, se ha demostrado que la degeneración de los segmentos adyacentes se produce cuando hay una pérdida de la arquitectura vertebral y degeneración neurológica. Con base en este hallazgo, es objetivo de este estudio presentar los hallazgos y compararlos entre pacientes con KFS y sin KFS.

Material y Metodología

Los datos clínicos e imagenológicos se derivaron de una cohorte prospectiva de pacientes en el estudio AO Spine CSM-North America prospectivo y multicéntrico. Los pacientes presentaron con al menos un signo clínico indicativo de CSM y no recibieron previa intervención quirúrgica. Los pacientes con síntomas espinales, enfermedad sistémica activa, artritis reumatoide, anquilosis spondilótica, y concomitante estenosis lumbar fueron excluidos. El comité ético de investigación aprobó la investigación, y el consentimiento del paciente fue obtenido.

Los datos demográficos, clínicos, y radiológicos de estos pacientes fueron analizados. Los parámetros clínicos incluyeron: antecedente personal, antecedente familiar, exploración neurológica, y principales características radiológicas de la columna cervical. A pesar de que todos los pacientes en el estudio experimentaron un tipo de tratamiento quirúrgico según el Arnold’s approach (e.g., anterior/posterior) y método (e.g., corpectomía, laminectomía, y fusión), los resultados del tratamiento fueron comparados con la media del grupo de KFS.

Los datos de los pacientes se analizaron utilizando el método de análisis de datos de la varianza (ANOVA) y la prueba t de Student. Los resultados fueron considerados significativos si la p-value era menor a 0.05.

Resultados

Se evaluaron 131 pacientes con 5 de ellos presentando características radiológicas consistentes con KFS (Fig. 1). En los pacientes presentes con KFS, la edad promedio era de 52 años (rango = 32 a 68) y, aunque ligeramente más joven, son comparables al promedio de pacientes con CSM. De los 5 pacientes, 2 eran mujeres y 3 eran hombres. Todos los pacientes presentaron KFS tipo 1.

Los datos clínicos y radiológicos de los pacientes con KFS se compararon con los de los pacientes sin KFS, y se encontró que los pacientes con KFS tenían peores resultados en la neurología secundaria a la degeneración espinal y degeneración neurológica. Se observó que los pacientes con KFS tenían mayor número de cambios degenerativos en los segmentos adyacentes a la vértebra fusionada.

Discusión

El propósito del estudio multicéntrico prospectivo fue determinar la eficacia del tratamiento quirúrgico en la presencia de KFS. Los resultados publicados por Fehlings et al. mostraron que el tratamiento quirúrgico es efectivo y seguro en pacientes con KFS.
safe. 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., 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%, 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. However, it should be noted that several other modern classifications based on genetic, mobility, and radiographic factors have also been proposed in literature.

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. Sprengel’s deformity and the presence of omovertebral bone may be accompanied associations. In addition to this, several reports have described KFS along with other congenital pathology affecting visceral, musculoskeletal, otolaryngologic, and neurologic systems. 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., 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.

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. More recently, the genes related to MEOX1 and GDF6 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. 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 hypereflexia | 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 paresis, 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.
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.\(^3\) 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.\(^4\) Although the mechanism for the occurrence of neurologic symptoms is likely multifactorial, basilar impression, iniencephaly, intraspinal pathology (including neuroschesis, split cord malformation, and diastematomyelia), and hypermobility of the upper cervical spine have been specifically implicated.\(^5,6\)

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.\(^5\) 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;\(^1,10,21\) 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.

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**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 (cm²) |
|---------|-------------------------|--------------------------|---------|----------|--------------------------------------|-----------------------------|
| 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.
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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