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Otolaryngologic Manifestations of Klippel-Feil Syndrome in Children

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IMPORTANCE Children with Klippel-Feil syndrome (KFS), characterized principally by abnormal fusion of 2 or more cervical vertebrae, may have many additional congenital anomalies. The overall prevalence of otolaryngologic manifestations among patients with KFS has not been previously characterized.

OBJECTIVE To define the otolaryngologic diagnoses made and procedures performed in 95 patients with KFS, which, to our knowledge, is the largest series of this challenging patient population published to date.

DESIGN, SETTING, AND PARTICIPANTS For this retrospective review, all patients with KFS who underwent otolaryngology consultation at our institution over a 26-year period (January 1989 to December 2015) were included. Patients were identified using *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes and were confirmed through individual medical record review. Relevant otolaryngologic diagnoses and procedures were extracted using *ICD-9* and Current Procedural Terminology codes, respectively. Selected demographics included age, sex, number of clinic visits, and number of procedures.

MAIN OUTCOMES AND MEASURES The primary outcomes were the otolaryngologic diagnoses and procedures associated with the KFS patient population; the secondary outcome was Cormack-Lehane classification documented during airway procedures.

RESULTS Overall, 95 patients with KFS were included in this study (55 males [58%] and 40 females [42%]); mean (range) age at time of presentation to the otorhinolaryngology clinic was 5.8 (birth-23.0) years. Each patient with KFS averaged 8 visits to the otorhinolaryngology office and 5 otolaryngologic diagnoses. The most common diagnosis was conductive hearing loss (n = 49 [52%]), followed by sensorineural hearing loss (n = 38 [40%]), and dysphagia (n = 37 [39%]). Sixty-two (65%) patients underwent otolaryngologic procedures, with 44 (46%) undergoing multiple procedures. The most common procedure was tympanostomy tube placement (n = 36 [38%]), followed by office flexible endoscopy (n = 23 [24%]). Twelve of the 20 patients who underwent direct laryngoscopy had documented Cormack-Lehane classification; 5 of 12 patients (42%) had a compromised view (grade 2, 3, or 4) of the larynx. Three patients required tracheotomies at this institution for airway stabilization purposes; each had severe upper airway obstruction leading to respiratory failure.

CONCLUSIONS AND RELEVANCE Patients with KFS require consultation for a variety of otolaryngologic conditions. Among these, hearing loss is the most common, but airway issues related to cervical spine fusion are the most challenging. Formulating an appropriate care plan in advance is paramount, even for routine otolaryngology procedures.

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Klippel-Feil syndrome (KFS) involves a congenital deformity of the cervical spine characterized by abnormal fusion of 2 or more vertebrae resulting from abnormal vertebral formation or segmentation.[1-3] The first 3 cervical vertebrae are fused in approximately 75% of patients with KFS.[4] Klippel-Feil syndrome affects approximately 1 in 40 000 live births and is considered the most common congenital malformation of the cervical spine.[1-3,5,6] There is significant variability in the phenotypic manifestations of KFS, and the classic KFS triad of a short neck, low posterior hairline, and limited neck mobility is present in fewer than 50% of affected individuals.[5] Associated anomalies may be skeletal or extraskeletal. Additional skeletal anomalies often found together with KFS include Sprengel deformity and limb-length discrepancy. Extraskeletal manifestations include otologic abnormalities, genitourinary and cardiovascular anomalies, neural tube defects, and palatal clefting. Klippel-Feil syndrome is 1 of 3 defining features of Wildervanck syndrome, which also includes Duane syndrome (abducens nerve palsy with retraction bulbi), and hearing loss.[1-3,7-9] Klippel-Feil syndrome results from the abnormal expression of a variety of genes responsible for sclerotomal segmentation during embryologic development.[10,11]

The overall prevalence of otolaryngologic manifestations among patients with KFS has not been previously characterized. Otologic anomalies have been reported in up to 60% of patients with KFS, including a variety of unilateral and bilateral external, middle, and inner ear pathologies.[12] Additionally, several case reports[13-15] discuss challenges in airway management due to the skeletal abnormalities associated with KFS. The objective of this study is to more comprehensively define otolaryngologic diagnoses and procedures in, to our knowledge, the largest series of patients with KFS published to date.

Key Points

Question What are the otolaryngologic manifestations among pediatric patients with Klippel-Feil syndrome (KFS)?

Findings The most common diagnosis in 95 patients included in this study was conductive hearing loss, and the most common procedure is tympanostomy tube placement. Airway evaluation of patients with KFS can be particularly challenging; of 12 KFS patients who underwent direct laryngoscopy with documented Cormack-Lehane classification, 5 had a compromised view (grade 2, 3, or 4) of the larynx.

Meaning Patients with KFS require consultation for a wide variety of otolaryngologic conditions, with airway issues related to cervical spine fusion being the most challenging.

Methods

A multiple-source search using (1) an Informatics for Integrating Biology and the Bedside (i2b2) database; (2) an institution-specific Childrens360 database; and (3) a subsequent 26-year retrospective medical record review (January 1989 to December 2015) was performed on all pediatric patients with KFS who were examined by an otolaryngologist at our institution. The National Institutes of Health–funded scalable informatics framework i2b2 enables the use of existing clinical data for discovery research (https://www.i2b2.org/about/index.html). Childrens360 is a data extraction tool linked to the electronic medical record database at our institution. Within this identified cohort of patients with KFS, a list of 38 *International Classification of Diseases, Ninth Revision* codes and 43 Current Procedural Terminology codes deemed relevant from an otolaryngology standpoint by the authors were searched. Data including age, sex, number of clinic visits, and number of procedures were extracted. Diagnoses and procedures were confirmed through individual medical record review.

Airway procedure notes were thoroughly reviewed for laryngeal view grade using the modified Cormack-Lehane classification system: grade 1 (full view of the glottis); grade 2a (partial view of the glottis); grade 2b (partial view with only the arytenoids or posterior aspect of the vocal folds visible); grade 3 (only epiglottis visible); and grade 4 (neither glottis nor epiglottis visible).[16]

Descriptive statistics were performed using IBM SPSS Statistics version 23.0 for Macintosh (International Business Machines Corp). The study was approved by the Boston Children's Hospital institutional review board.

Results

The i2b2 and Childrens360 database searches initially identified 120 patients with a potential diagnosis of KFS who were also evaluated by an otolaryngologist. Subsequent medical record review confirmed 95 of these patients met the criteria for KFS. The remaining 25 patients did not did not have an explicit diagnosis of KFS or Klippel-Feil anomaly mentioned in their medical records and were excluded from further analysis. The study group included 55 males (58%) and 40 females (42%). Mean (range) age at time of first assessment by an otolaryngologist was 5.8 (birth-23.0) years. Otolaryngology clinic visits totaled 752 with a mean (range) of 7.9 (1.0-45.0) visits per patient.

Eighty-two of the 95 patients with KFS (86%) were identified as having at least 1 of 22 otolaryngology diagnostic codes, with 73 patients (77%) having more than 1 diagnosis (**Table 1**). Mean diagnoses per patient was 4.8. The most common diagnosis was hearing loss: conductive (n = 49 [52%]), sensorineural (n = 38 [40%]), or mixed (n = 34 [36%]). The severity of hearing loss is summarized in **Table 2**. The multiple otological diagnoses listed in Table 1 indicate a variety of potential conductive and mixed hearing loss etiologies.

Among the nonotologic diagnoses, dysphagia was most common diagnosis, affecting 37 patients (39%). Among sleep-related diagnoses, polysomnography-confirmed obstructive sleep apnea (n = 15 [16%]) and sleep apnea not otherwise specified (n = 15 [16%]) were the most frequent, most probably related in part to the relatively high prevalence of adenotonsillar hypertrophy (n = 28 [29%]). Sinus disease (n = 17 [18%]) and laryngotracheal anomalies (n = 16 [17%]) were also common. Obstructive sleep apnea severity is further summarized in Table 2.

Table 1. Distribution of Otolaryngologic Diagnoses in 95 Patients

Diagnosis	Diagnoses, No.
Otological	
Conductive hearing loss	49
Sensorineural hearing loss	38
Mixed hearing loss	34
Otitis media with effusion	28
Eustachian tube dysfunction	20
Ossicular malformation	11
Hemifacial microsomia	8
Stenotic/atretic external auditory canal	6
Cerumen impaction	4
Cholesteatoma	2
Sinonasal	
Acute sinusitis	7
Chronic sinusitis	10
Chronic rhinitis	5
Aerodigestive	
Dysphagia	37
Dysphonia	2
Stenosis of larynx	3
Laryngotracheal anomaly (not otherwise specified)	16
Vocal cord disease (not otherwise specified)	4
Bilateral vocal cord paralysis, partial	1
Unilateral vocal cord paralysis, partial	1
Unilateral vocal cord paralysis, total	1
Hypertrophy adenoid (only)	6
Hypertrophy tonsils and adenoid	19
Hypertrophy tonsils (only)	3
Sleep related	
Obstructive sleep apnea	15
Primary central sleep apnea	2
Primary apnea of newborn	2
Sleep apnea (not otherwise specified)	15
Sleep related non-obstructive hypoventialtion	3
Sleep related hypoventilation/hypoxemia	1

Sixty-two patients with KFS (65%) underwent an otolaryngologic procedural intervention (**Table 3**). Eighteen patients (19%) underwent a single procedure, and 44 patients (46%) underwent multiple procedures, with a mean of 3 procedures per patient. Tympanostomy tube placement was most common (n = 36 [38%]), followed by fiberoptic endoscopic examination performed in the office (n = 23 [24%]).

Twenty (21%) patients underwent direct laryngoscopy in the operating room. The procedure notes and intraoperative anesthesia records of these 20 patients were reviewed for grading of laryngeal view using the modified Cormack-Lehane classification system, of which 12 had such documentation (**Table 4**). These 12 patients underwent a total of 15 endoscopic airway procedures. A grade 1 view was documented for 10 operative examinations (67%); grade 2 view, 2 procedures (13%); grade 3 view, 1 procedure (7%); and grade 4 view, 2 procedures (13%). Following unsuccessful direct laryngoscopy, flexible endoscopic airway examinations were performed at the time of the 2 grade 4 operative assessments. One patient required intubation with an endotracheal tube loaded on a flexible bronchoscope advanced through an laryngeal mask airway. The other patient had a tracheostomy tube placed at an outside hospital and required flexible fiberoptic laryngoscopy and bronchoscopy for evaluation of tracheal granulation tissue and mucosal ulceration.

Three tracheotomies were performed at this institution for the purpose of airway stabilization. One 20-year-old patient with Jarcho-Levin syndrome in addition to KFS underwent tracheostomy tube placement for chronic respiratory failure. Another 6-year-old patient required ongoing ventilator support following cervical fusion and spica cast placement. Operative notes reported difficulty visualizing the larynx in both these patients on subsequent rigid endoscopy examinations; however, no Cormack-Lehane classifications were listed. The third patient had Crouzon syndrome with multiple maxillofacial anomalies including nasal aperture stenosis in addition to Klippel-Feil anomaly. He underwent a tracheostomy at 1 month of age due to respiratory difficulties, nasal obstruction, and feeding issues; subsequent direct laryngoscopies documented either a grade 1 or grade 2 laryngeal view.

Discussion

Klippel-Feil syndrome was first described by Maurice Klippel and Andre Feil in 1912.[17,18] The original classification reported 3 types based on the degree of cervical fusion: type I, fusion of the cervical and upper thoracic vertebrae; type II, fusion of 2 or 3 cervical vertebrae with associated hemivertebrae, occipitoatlantoid fusion, or other cervical spine abnormalities; and type III, cervical fusion with lower thoracic or lumbar vertebral fusion.[2]

An additional classification schema, the Clarke classification, has been proposed which is not based solely on the extent of cervical fusion but also addresses differences in fusion patterns, timing, incidence, mode of inheritance, and associated anomalies.[1] The derivation of the Clarke classification was based on the evaluation of several large families with KFS, while the original description by Klippel and Feil was based primarily on sporadic cases. In the Clarke system, KFS is subdivided into 4 types. In KF1, C1 fusion is most common, and these children often present with severe associated anomalies, including a shortened or nonexistent neck. In KF2, C2-3 fusion is most common and is always the most rostral fusion; many children with KF2 also have laryngeal cartilage malformations. KFS3 is characterized by isolated cervical fusions such as C2-3, C3-4, or C5-6 (but not C1-2). In KFS4, fusion of cervical vertebrae in addition to ocular, hearing, or cardiac anomalies may be present; KFS4 is frequently associated with Wildervanck syndrome, also known as cervico-oculo-acoustic syndrome, which is characterized by Klippel-Feil anomaly, Duane retraction syndrome, and congenital deafness.[19]

Several genes are associated with KFS, although there is considerable clinical heterogeneity, and each gene does not necessarily correspond to a particular Clarke classification. Klippel-Feil syndrome 1 (KFS1), and many of the sporadic forms, are associated with autosomal dominant heterozygous muta-

Table 2. Severity of Hearing Loss and Obstructive Sleep Apnea

Diagnosis	Frequency of Diagnosis
Hearing Loss Severity (PTA, by Ear)[a]	
Low-normal (18-20 dB)	2
Mild (21-40 dB)	44
Moderate (41-55 dB)	24
Moderately severe (56-70 dB)	16
Severe (71-90 dB)	10
Profound (>91 dB)	11
Unknown	10
Obstructive Sleep Apnea Severity[b]	
Mild	4
Moderate	2
Severe	9

Abbreviations: dB, decibel; PTA, pure tone average.

[a] Hearing loss severity is defined based upon the audiology results on the initial date the hearing loss was identified.

[b] Severity of obstructive sleep apnea is based upon polysomnography data.

Table 3. Distribution of Otolaryngologic Procedures

Procedure	Times Procedure Was Performed, No.	Patients Who Underwent Procedure, No.
Otological		
Tympanostomy tubes	93	36
Myringotomy (no tubes placed)	6	5
Tympanoplasty	5	2
Tympanoplasty with canalplasty	1	1
Cholesteatoma removal	3	2
Ossicular chain reconstruction	1	1
Ossicular mobilization with excision of tympanosclerosis	1	1
Exploratory tympanotomy	1	1
Canal wall-up tympanomastoidectomy	1	1
Sinonasal		
Septoplasty	3	1
Inferior turbinate reduction	1	1
Choanal dilatation	6	1
Endoscopic sinus surgery	1	1
Nasal reconstruction	1	1
Aerodigestive		
Flexible fiberoptic endoscopic examination in operating room	30	16
Flexible fiberoptic endoscopic examination in office	99	23
Rigid endoscopic operative examination	55	20
Nasal endoscopy in operating room	4	3
Nasal endoscopy in office	13	7
Adenoidectomy	21	15
Tonsillectomy	12	12
Tracheostomy	3	3
Supraglottoplasty	1	1

tions in the *GDF6* gene on chromosome 8q22. Additional forms of KFS include autosomal recessive KFS2 caused by mutations in the *MEOX1* gene on chromosome 17q21, and autosomal dominant KFS3 caused by mutations in the *GDF3* gene on chromosome 12p13. Klippel-Feil syndrome 4 results from homozygous mutations in the *MYO18B* gene and is associated with nemaline myopathy and facial dysmorphism. Klippel-Feil syndrome may also present as part of another disorder or syndrome, including Goldenhar syndrome, Wildervanck syndrome, hemifacial microsomia, or fetal alcohol syndrome. Inheritance in these cases is determined by the gene associated with the constellation of symptoms rather than with the KFS manifestations alone.[11,20,21]

The association of otologic manifestations with KFS has been previously reported.[12,22-29] Deafness was first described in association with KFS in 1936.[30] Subsequent studies similarly documented hearing loss in approximately one-third of patients with KFS.[31,32] In the most comprehensive series reported to date,[22] 35 of 44 patients (80%) had some form of hearing loss on audiologic testing. Sensorineural loss was the most common, affecting 15 patients (43%), followed by mixed hearing loss in 10 patients (23%), and conductive hearing loss in 7 patients (16%). Common causes of hearing loss in this population include major anatomical malformations such as microtia, external ear canal stenosis, ossicular deformities, and cochlear defects.

In the current study, 52% of patients had conductive hearing loss, followed by 40% with sensorineural hearing loss, and 36% with mixed hearing loss. While these percentages are higher than some previous reports, it is important to note patients were included in this study only if they underwent otolaryngology consultation. Comparative rates were reported in another study that similarly assessed patients with KFS referred to an otolaryngology department for otologic and audiologic evaluation, with 65% affected by some form of hearing loss and 60% having associated anomalies of the external, middle, and/or inner ear.[12]

Congenital cervical fusion can cause pain and additional neurologic symptoms. Most importantly, with respect to airway intervention, there are limitations of cervical rotation, flexion, and extension. Cervical spine instability, hypermobility, and symptomatic stenosis at the interspaces between the fused segments may develop. There have also been multiple reports of mandibular abnormalities in patients with KFS including retrognathia,[33] duplication of the mandibular rami,[34-36] and extra-articular ankylosis of the temporomandibular joint.[37]

Progressive cervical instability or neurological compromise attributable to cervical instability is usually managed with surgical stabilization.[5] The combination of congenital fusion and subsequent surgical stabilization poses significant potential challenges with respect to airway management, both in terms of laryngeal visualization as well as the possibility of morbidity secondary to neck manipulation. The development of an appropriate care plan for intubation and routine otolaryngologic procedures is essential in these patients.

From a procedural standpoint, 62 of the 95 patients with KFS (65%) required operative intervention, the most common procedure being tympanostomy tube placement, and the most challenging being intraoperative rigid bronchoscopy. Of

Table 4. General Anesthesia Laryngeal Airway Evaluation Details

Patient No.	Procedure	Age at Time of Procedure, y	Grade View of Larynx
1	DLB	25.3	1
2	DLB	21.5	1
3	Attempted DLB unsuccessful due to severe trismus; flexible laryngoscopy/bronchoscopy performed	15.2	4
4	DLB	8.9	1
5	DLB	7.1	2b
6	DLB	4.5	1
7	DLB	4.2	1
8	DLB	3.1	1
9	Attempted DLB unsuccessful; flexible bronchoscopy performed through LMA	1.6	4
10	DLB	4.2	1
	DLB	1.3	2
	DLB	0.5	1
	DLB	0.3	1
11	DLB	0.4	1
12	DLB	0.2	3

Abbreviations: DLB, direct laryngoscopy and bronchoscopy; LMA, laryngeal mask airway.

the 93 tympanostomy tube placement procedures, the majority (58%) were able to be performed using mask anesthesia technique. Thirty-six procedures required endotracheal intubation, with all but 2 having concurrent additional procedures. The most common concurrent surgeries were adenoidectomy (n = 9), cleft palate and/or lip repair (n = 6), tonsillectomy (n = 5), and dental rehabilitation (n = 4).

Several case reports with respect to difficult intubations in patients with KFS exist in the otolaryngology literature.[13-15,38-43] A useful strategy, as used in one of our patients with a grade 4 view on direct laryngoscopy, is to perform intubation with an endotracheal tube loaded on a flexible bronchoscope advanced through an laryngeal mask airway.[14,39,40,42] Under such circumstances, it is imperative to maintain spontaneous ventilation, as even this intubation technique may not prove successful. A tracheotomy is the ultimate airway stabilization procedure if more conservative airway management strategies fail.

Limitation of neck range of motion also has implications for otolaryngology procedures distinct from airway access issues. When placing tympanostomy tubes, the patient's head is usually rotated away from the surgeon. In patients with KFS, this is often not possible. Both the plane of the bed and the entire patient may need to be turned, and the microscope appropriately manipulated, due to the limitations of neck rotation. Similarly, tonsillectomy and adenoidectomy may need to be performed without neck extension with mouth gag suspension modification.

Limitations

There are several limitations of the current study. Foremost are the limitations inherent to the study design of a database search with retrospective review. Additionally, some patients may have had otolaryngology diagnoses established or procedures performed by an otolaryngologist outside our institution. We are also fortunate to work with a highly skilled group of pediatric anesthesiologists. As a result, we may not be called for assistance with intubation even in patients with known difficult airways due to their experience and competence with alternative intubation techniques.

Conclusions

Patients with KFS may manifest a variety of otolaryngologic issues. Among these, hearing loss is the most common, but airway issues related to their cervical spinal fusion are the most challenging. Formulating in advance an appropriate care plan is paramount even for routine otolaryngology procedures.

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Study concept and design: Kenna, Strychowsky, Cunningham.
Acquisition, analysis, or interpretation of data: Kenna, Irace, Strychowsky, Kawai.
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