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Hoarseness as a Presenting Sign in Children with Kawasaki Disease

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Abstract

We noted that many patients with Kawasaki disease (KD) were hoarse at presentation and thus evaluated the frequency of hoarseness in children with acute KD. New onset hoarseness was noted in 86 of 287 (30%) prospectively assessed KD patients. Laryngoscopic examination of three hoarse patients with acute KD revealed edema and erythema of the larynx.

Keywords

Kawasaki Disease; hoarseness; coronary artery dilatation; vasculitis

Introduction

Several lines of evidence suggest a respiratory portal of entry for the agent that triggers KD in genetically susceptible children. These include presentation with enlarged anterior cervical lymph nodes that drain the posterior pharynx in 30% of patients, retropharyngeal edema imaged by computed tomography, and occasional reports of pulmonary nodules during the acute phase of the illness (1–4). We noted that many of our patients were hoarse at the time of presentation, although this finding had not been previously reported in the literature. We therefore added the presence or absence of hoarseness to our standardized admission case report forms for KD patients beginning in 2004. The objective of this study was to determine the frequency of hoarseness in acute KD and to compare the patient characteristics between those with and without hoarseness. Indirect laryngoscopy was performed in a subset of hoarse KD patients.

Materials and Methods

A retrospective review of demographic, clinical, and laboratory data recorded at the time of admission on standardized case report forms was performed on a subset pediatric patients admitted with complete acute KD to Rady Children's Hospital San Diego from January 1, 2007–August 31, 2011. Patients included in the study were evaluated during the first 10

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days after fever onset and met American Heart Association criteria for KD (at least 3 days of fever with 4/5 clinical criteria or 3/5 criteria with abnormalities on echocardiography) (4). Coronary artery Z scores (standard deviation units from the mean normalized for body surface area) were determined for the right coronary artery (RCA) and left anterior descending coronary artery (LAD). Normal was defined as a Z score <2.5 and "Z max" was defined as the highest Z score for the RCA or LAD at any point during the first 6 weeks after disease onset. IVIG resistance was defined as persistent or recrudescent fever (temperature ≥38.0°C) ≥36 hours following completion of IVIG infusion (2 g/kg). Hoarseness was defined as a harsh or raspy quality to the voice or cry that was confirmed by the parents as a change from the patient's baseline. The presence or absence of new onset hoarseness was determined on admission by the KD attending and recorded on case report forms for all KD patients. The protocol for this study was approved by the University of California, San Diego Institutional Review Board and written parent informed consent was obtained for all subjects who underwent laryngoscopy.

Demographic and laboratory data on admission (pre-IVIG) were collected in 287 subjects. Viral respiratory pathogens (adenovirus, parainfluenza 1 and 2, influenza, and respiratory syncytial virus (RSV)) detected by direct fluorescent antibody testing were recorded. Patients who enrolled in an on-going Phase III, randomized, double-blind, placebo-controlled trial assessing the addition of infliximab to primary therapy with IVIG in acute KD were excluded from analysis of coronary artery outcome (95 patients). An additional 12 patients were excluded from the analysis of treatment response because of initial therapy after the 10^{th} day of illness. Indirect laryngoscopy was performed with a flexible fiberoptic laryngoscope *(Olympus ENF-V2 and ENF-XP)*.

Statistical Approach

Frequency of hoarseness during the study period was calculated with 95% confidence intervals. Demographic information, laboratory data, coronary artery status, and treatment response were compared between KD patients with and without hoarseness. Wilcoxon Rank Sum test was used for continuous variables and Fisher's exact test was used for categorical variables, with $p<0.05$ considered to be statistically significant. No adjustments were made for multiple testing. Multivariable models were built to assess whether there was a difference in coronary artery status between patients with and without hoarseness adjusting for age, gender, illness day, and absolute band count. All statistical analyses were performed in R (version 2.14.0).

Results

New onset hoarseness was noted in 86 of 287 (30%, 95% CI: 24.7%–35.6%) of study-eligible patients. The hoarse group was significantly younger than the non-hoarse group (1.9 vs. 3.1 years.), presented earlier in the illness (day 5 vs. day 6), and had a higher absolute band count (1845 vs. 1341). (Table 1) In a multivariable analysis there was no difference in coronary artery Z-max between subjects with and without hoarseness. In this study 43 of 201 (21.4%) of the non-hoarse KD patients had a respiratory screen and 5 (11.6%) of those were positive (2 adenovirus, 1 parainfluenza, and 2 RSV). By contrast 16 of 86 (18.6%) of the hoarse KD patients had a respiratory screen and only 1 (6%) was positive and had RSV. The hoarseness resolved in all patients by their 2-week outpatient clinic visit.

Three acute KD patients with hoarseness underwent flexible fiberoptic laryngoscopy. Of the three, two were female and the ages ranged from 6 to 8 months of age. All three patients had significant erythema and edema of the supraglottic structures. Two patients had edema of the true vocal folds and one patient had small (1 mm) anterior vocal fold nodules as compared with normal subjects of similar age (Fig., Supplemental Digital Content 1, http://

links.lww.com/INF/B628). All patients had normal vocal fold mobility and had resolution of hoarseness by the first outpatient clinic visit between Illness Day 11–21.

Discussion

Hoarseness as a presenting sign of KD and laryngeal involvement documented by laryngoscopy has not been previously reported. At our institution, nearly one-third of patients evaluated in this study were found to have hoarseness as part of their clinical presentation.

Co-infection with a respiratory virus during acute KD has been detected in up to 8.8% of KD patients (5, 6). In our study only one patient (6% of the total hoarse patients) was co-infected with a viral illness in contrast to 11.6% of the non-hoarse KD patients. Thus hoarseness was present even in the absence of viral co-infection.

Our finding that hoarseness was associated with earlier diagnosis and higher band count in a subset of acute KD patients suggests that hoarseness may be a result of more severe systemic inflammation that also involves the larynx. Possible mechanisms for the hoarseness include transient inflammation of the larynx with associated edema of the true vocal folds, the development of vocal fold nodules, and temporary recurrent laryngeal nerve paresis. Inflammation of the larynx as part of the overall systemic inflammation in acute KD is supported by several lines of evidence that suggest entry of the KD pathogen through the mucosa of the upper airway. First, computed tomography has documented diffuse enlargement of multiple lymph nodes most commonly in the anterior cervical chain often associated with retropharyngeal edema during the acute phase KD (7–9). Second, case reports have documented uvulitis, supraglottitis, and pulmonary nodules associated with acute KD.(1, 10, 11) Finally, an oligoclonal IgA immune response suggests entrance of the pathogen through the mucosal surfaces of the oropharynx and upper airway and virus-like inclusion bodies in respiratory epithelial cells may be related to the causative agent.(12, 13) It is also plausible that KD may cause a transient recurrent laryngeal nerve paresis resulting in weakness of one of the vocal folds and associated hoarseness in some patients. Transient paresis of cranial nerves in KD is uncommon but well-reported and may involve cranial nerves VI, VII, and VIII.(14, 15) These palsies are transient and resolve in the subacute phase of the illness. Our limited observations of three patients by laryngoscopy did not suggest recurrent laryngeal nerve paresis as the etiology of the hoarseness in those patients. The laryngoscopic findings suggest that the hoarseness could be due to pathologic changes in the true vocal folds.

We recognize several strengths and weaknesses of our study. A strength of the study is that data were collected prospectively by one of only two clinicians (JCB and AHT) using a standardized data collection form that was completed at the time of admission. Outpatient evaluation was performed at standard intervals for all patients and clinical assessments were performed by the same physicians. Study limitations include the lack of formal voice assessment by a pediatric speech pathologist. The commonly used adult rating scale, GRBAS (Grade, Roughness, Breathiness, Aesthenia, Strain) could not be applied due to the young age of our patients. Finally, the small number of laryngoscopies precludes our ability to make general statements about the mechanism of hoarseness in these patients. Another limitation is that comprehensive viral studies were not performed on the majority of patients so we cannot exclude concomitant viral upper respiratory tract infection as the cause of hoarseness in some of the KD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Clinical and laboratory characteristics of Kawasaki disease patients with and without hoarseness[†]

	Patients with hoarseness	Patients without hoarseness	P
Median age, yrs. (range)	1.9 (0.1–14.7)	3.1 (0.2–14.9)	<0.001
Male, n (%)	56 (65.1)	113 (56.2)	NS
Median illness day at diagnosis (range)[*]	5 (2–9)	6 (2–10)	0.003
White blood cell count/mm^3[**]	13 (10–18)	13 (10–17)	NS
Absolute band count[**]	1763 (1014–2645)	1303 (539–2481)	0.03
Erythrocyte sedimentation rate, mm [**]	61 (37–72)	60 (41–75)	NS
C-reactive protein, mg/dl	9 (5–17)	7 (4–15)	NS
Z worst score[**]	1.53 (0.9–2.66)	1.49 (0.9–2.26)	NS
Coronary artery dilation or aneurysm, n (%)	17 (32.7)	34 (24.3)	NS
Normal coronary artery, n (%)	35 (67.3)	106 (75.7)	NS
IVIG Resistant, n (%)	10 (20.8)	26 (19.7)	NS

[*] First day of fever = Day 1

[**] Laboratory data presented as median (interquartile range)

[†] Demographic and laboratory data on admission (pre-IVIG) were collected and assessed in the entire study cohort (86 and 201 patients with and without hoarseness, respectively); Coronary artery outcome was assessed in patients treated with standard IVIG therapy (52 and 140 patients with and without hoarseness, respectively); IVIG response was assessed in patients treated in the first 10 days of illness (48 and 132 patients with and without hoarseness, respectively)

NS=not significant