Sensorineural Hearing Loss and Kawasaki Disease: A Prospective Study

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Purpose: Kawasaki disease (KD) is an acute, self-limited vasculitis of infants and children that is now the most common cause of acquired heart disease in the pediatric age group in the United States and Japan. Reports have documented the association of acute KD with sensorineural hearing loss. To assess the prevalence of hearing loss following acute KD in a geographically and ethnically diverse population, a prospective, multicenter study of hearing loss in patients with KD was conducted.

Materials and Methods: Patients with acute KD were enrolled in 7 clinical centers and underwent a primary audiologic evaluation within 30 days of the onset of fever. Patients were subsequently reevaluated after resolution of the acute phase of the disease. A questionnaire assessing risk factors for hearing loss was also administered.

Results: A total of 62 patients were evaluated during the 29-month study period. At the first audiologic evaluation, 19 patients (30.6%) had sensorineural hearing loss, 6 patients (9.7%) had conductive hearing loss, 17 patients (27.4%) had normal hearing, and 20 patients (32.3%) had inconclusive studies. Overall, 2 of 36 patients (5.5%) had sensorineural hearing loss documented on their second audiologic evaluation. No risk factors for hearing loss were identified by the questionnaire.

Conclusions: Transient sensorineural hearing loss (20 to 35 dB) is a frequent complication of acute KD and may be related to salicylate toxicity in some patients. Persistent sensorineural hearing loss is uncommon. Parents and primary care providers should be made aware of the potential for persistent sensorineural hearing loss following resolution of KD, but routine audiologic screening of this patient population does not appear to be warranted.
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Kawasaki disease (KD) is an acute systemic vasculitis of children characterized by fever, rash, conjunctival hyperemia, oropharyngeal erythema, edema and erythema of the hands and feet, and cervical adenopathy.[1] A variety of other features are also characteristic of this syndrome, including coronary artery aneurysms, aseptic meningitis, arthralgia and arthritis, urethritis, anterior uveitis, mild hepatobiliary dysfunction, and gallbladder hydrops.[2]

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The course of KD may be divided into 3 clinical phases.[3] The acute phase, which is associated with fever, may last 1 to 3 weeks in the absence of treatment, and is characterized by clinical signs of inflammation. Coronary arteritis is present at this time, and coronary artery dilatation may occur. The subacute phase begins after resolution of the fever and lasts 1 to 3 weeks. The development of coronary artery aneurysms and the risk of sudden death are highest during this phase. During the convalescent stage, the erythrocyte sedimentation rate returns to normal, typically 6 to 8 weeks after fever onset.

Approximately 20% to 25% of untreated patients with KD develop coronary artery abnormalities, including diffuse dilatation and aneurysms.[4] Treatment of patients within the first 10 days of illness onset with 2 g/kg of intravenous gamma globulin (IVIG) and high-dose aspirin (ASA) at 80 to 100 mg/kg/d reduces the prevalence of coronary artery abnormalities to 2% to 4%.[5] ASA is used at this

high dose for its anti-inflammatory effects. After the acute phase, the ASA dosage is reduced to 3 to 5 mg/kg for its antiplatelet effect.

Histopathologic features of vasculitis involving medium-sized, extraparenchymal arteries appear in the earliest phase of the disease and widely affect organ systems.[6] Reports from Japan and the United States have documented the association of sensorineural hearing loss (SNHL) with acute KD.[7-9] These reports document 20 patients in whom hearing loss ranged from mild and transient to profound and permanent. In patients for whom an onset of hearing loss could be ascertained, deficits occurred in the second week of illness and were associated, in some cases, with prolonged fever and seventh nerve palsy.

Although all of the previously reported patients were receiving ASA at variable dosages, the pattern of the audiograms and the occurrence of unilateral hearing loss in some patients were not consistent with salicylate toxicity. Hypotheses regarding the pathophysiology of the hearing loss in these patients included autoimmune mechanisms, damage to the microvasculature of the inner ear, or cochlear hydrops secondary to inflammation with altered production or flow of endolymph.

To further characterize the nature and prevalence of SNHL in patients with acute KD, we conducted a prospective multicenter study. We examined risk factors for the development of hearing loss and formulated recommendations for audiologic screening of patients after acute KD.

METHODS

Patients

Patients were enrolled from February 1989 through June 1991. Cases of KD were defined according to the standard clinical criteria (Table 1). Eligible patients had fever plus 4 of 5 clinical criteria, were treated with IVIG and ASA within 14 days after onset of fever, and had no previous history of hearing loss.

Clinical Centers

Patients were enrolled from 7 clinical centers across North America: University of Hawaii, University of Southern California, University of California at San Diego, University of Colorado, Northwestern University, University of Toronto, and Tufts University.

TABLE 1. Diagnostic Criteria for Kawasaki Disease

Fever ≥5 days
Bilateral conjunctival hyperemia
Changes of the mucous membranes of the upper respiratory tract; injected pharynx; injected, fissured lips; strawberry tongue
Changes of the peripheral extremities; edema and/or erythema of hands and feet; periungual desquamation
Polymorphous rash
Cervical adenopathy >1.5 cm

NOTE. The diagnosis of KD is confirmed by the presence of fever and 4 of the remaining 5 criteria and in the absence of other known disease processes.

Procedures

After parents gave informed consent, the first audiologic assessment was scheduled within 30 days after the onset of fever. A second audiologic assessment was attempted in all patients at least 10 days after the first evaluation. Patient hearing and middle ear function were assessed by visual reinforcement, play audiometry, tympanometry, and brainstem auditory evoked response (BAER) testing in patients less than 1 year of age, or in patients for whom the results of behavioral audiometry were deemed unreliable. All audiologic assessments were reviewed and classified by a single audiologist (R.E.N.). A questionnaire was administered to all subjects; it documented pre and postnatal risk factors for hearing loss.

Abnormal studies were defined as follows; audiogram pure tone thresholds greater than 15 dB, tympanogram peak 4 amplitude or width outside the established normal range, or an absent wave V on BAER testing at stimulus levels less than or equal to 20 dB.

Patients were classified as having probable conductive hearing loss if they had an elevated pure tone air conduction threshold with normal unmasked bone conduction thresholds or elevated soundfield thresholds with abnormal tympanograms. Patients were classified with probable SNHL if they had elevated pure tone air conduction, soundfield, or BAER thresholds with normal tympanograms or with abnormal unmasked bone conduction thresholds.

Statistical Analysis

We compared the groups with and without SNHL by using paired Student's *t*-tests, two-tailed, for comparison of means for continuous variables, and χ^2 tests for dichotomous variables. Responses to the questionnaire were compared between the groups with and without hearing loss by analysis of variance (ANOVA).

TABLE 2. Results of First and Second Audiologic Evaluations of 62 Patients with Acute Kawasaki Disease

First Evaluation		Second Evaluation				
Result	No. of Patients (%)	SNHL	CHL	Normal	Inconclusive	Not Studied
SNHL	19 (30.6)	1	1	9	1	7
CHL	6 (9.7)	1	0	2	0	3
Normal	17 (27.4)	0	0	10	0	7
Inconclusive	20 (32.3)	0	1	5	5	9
Total	62 (100.0)	2	2	26	6	26

Abbreviations: SNHL, sensorineural hearing loss; CHL, conductive hearing loss.

RESULTS

Over the 29-month study period, 82 eligible subjects were enrolled. Of these 82 patients, 20 could not be scheduled for their first audiologic evaluation within 30 days after fever onset, and were therefore excluded from the study. The study sample of 62 patients included 33 boys (53.2%), and the median age of the study participants was 3.7 years (range 0.4 to 12.5 years).

On the first audiologic assessment of these 62 patients, 19 patients (30.6%) had SNHL, 6 patients (9.7%) had hearing loss associated with middle ear dysfunction, and 17 patients (27.4%) had normal hearing. Hearing evaluation was inconclusive in 20 patients (32.3%) because of suprathreshold screening procedures or failure to obtain a BAER in patients with unreliable behavioral testing (Table 2).

The pattern of hearing loss in patients with abnormal audiograms on their first evaluation was variable (Fig 1). To address the potential role of ASA toxicity in the genesis of hearing loss, we evaluated the exposure to high-dose ASA in the 15 patients with binaural high frequency, soundfield high frequency, and binaural flat losses. Of 8 patients, 5 (62.5%) with binaural or soundfield high frequency loss, and all of 7 patients (100%) with binaural flat losses, were exposed to high-dose ASA at the time of their initial audiologic evaluation. Thus, ASA toxicity alone could have been the cause of hearing loss in 12 of these 15 patients (80.0%).

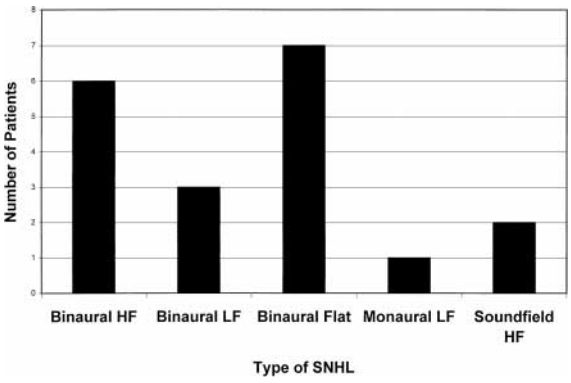

Fig 1. Patterns of SNHL on initial audiologic evaluation of 19 patients with acute KD. (HF, high frequency; LF, low frequency.)

Follow-up audiologic evaluation was successfully completed in 36 patients (56.4%), or approximately half of each patient group; 12 of the 19 patients with SNHL (63.1%), 10 of the 17 patients with normal hearing (58.8%), 3 of the 6 patients with a conductive hearing loss (50.0%), and 11 of the 20 patients with inconclusive first evaluations (55.0%) (see Table 2). The second audiologic evaluation was performed at a mean of 41.4 days after disease onset (range 19 to 80 days) and at least 10 days after the first evaluation. None of the patients were on high-dose ASA at the time of the second audiologic evaluation.

Of the 12 patients with SNHL on their first evaluation who were restudied, 9 (75.0%) had normal hearing on their second assessment, 1 (8.3%) had conductive hearing loss, 1 (8.3%) had an inconclusive study, and 1 (8.3%) showed persistent SNHL. This patient, a 7-year-old boy, had mild hearing loss documented on illness days 8 and 20 and was subsequently lost to follow-up (Fig 2). A second patient, a 1.75-year-old boy, had evidence of conductive hearing loss on impedance audiometry on his first evaluation on illness day 6 and a 20- to 30-dB hearing loss on soundfield testing. On his second evaluation on illness day 19, middle ear function was normal,

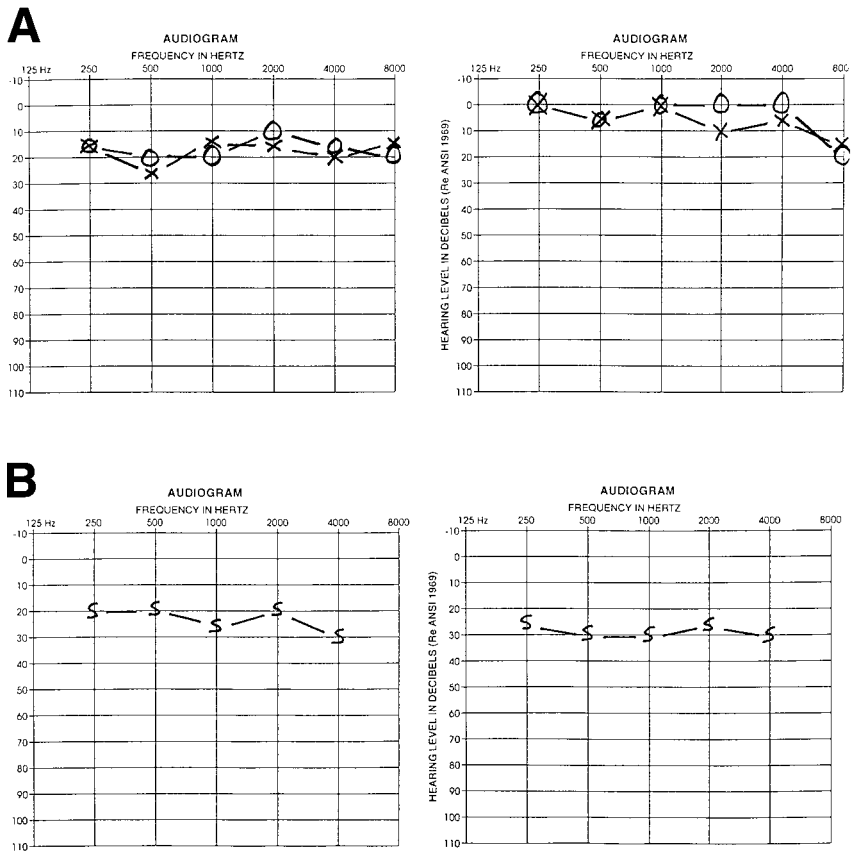

Fig 2. Audiograms of 2 patients with sensorineural hearing loss. (A) Pure tone thresholds in a 7-year-old boy studied 8 and 20 days after onset of fever. Although the hearing loss shown on both studies was mild, the persistence of a bilateral 20-dB loss at 8,000 Hz suggests that this result was not an artifact. (B) Soundfield testing on a 1.75-year-old boy studied 6 and 19 days after onset of fever. (S, soundfield; O, unmasked right ear; X, unmasked left ear.)

but a 25- to 30-dB hearing loss persisted (see Fig 2).

Univariate analysis showed that groups with and without hearing loss on their first evaluation did not differ significantly with respect to mean age at onset of KD (4.8 versus 4.1 years, $P = .36$), and illness day at first audiologic evaluation (11.1 days versus 10.6 days, $P = .72$).

Patients with and without hearing loss were classified with respect to treatment with high-dose ASA at the time of initial audiologic evaluation. Of 19 patients with SNHL, 16 (84.0%), and 8 of 17 with normal hearing (47.0%), were exposed to high-dose ASA. The relative risk of SNHL for patients on high-dose ASA was 1.79, which did not reach statistical significance (95% confidence interval 0.37-8.5).

Parents of patients were interviewed with a standard questionnaire that collected information regarding prenatal history, family history, drug exposure, past medical history, and otologic medical history. The group with SNHL was compared with the remaining study population for each of the variables by ANOVA. No risk factors for SNHL were identified, although the small sample size limited our power to detect a difference.

DISCUSSION

Reports from Japan and the United States have previously documented 20 children with SNHL of varying degrees after KD.[7-9] A prospective, multicenter study was warranted to systematically investigate this phenomenon and estimate the prevalence of SNHL associated with KD. Approximately one third of the study population had some degree of SNHL

documented on initial evaluation within 30 days of fever onset.

The precise etiology of the hearing loss remains to be explained. Although a causative agent has not been identified, epidemiologic data suggest that KD has an infectious etiology.[3] The relative rarity of KD in the perinatal period and among adolescents and adults suggests that KD may be caused by an agent to which virtually all adults are immune, and from which most very young infants are protected by maternal antibodies. The SNHL associated with acute KD might then reflect infection of the inner ear, analogous to the direct cytopathic effects on the labyrinth and cochlea, which occur with certain viral illnesses, such as mumps and rubella.[10]

Alternatively, the SNHL may be associated with aberrant immune activation with antibody complexes directed against elements of the membranous portion of the cochlea, or to specific proteins within the hair cells.[11] The vasculitis associated with KD is most severe in the medium sized arteries, although arterioles and venules may be affected early in the illness. Multiple mediators of inflammation are elevated during the acute phase of the disease,[12-14] and expression of cellular adhesion molecules is increased.[15-18] These processes may potentiate the damage to vascular tissue, particularly the media and intima. This widespread vasculitis could affect the membranes of the labyrinth or the osmotic balance within the fluid compartments of the inner ear.

The potential role of salicylate ototoxicity in the genesis of the hearing loss in acute KD patients deserves further comment. Many studies have shown that salicylates in high doses cause a flat 20- to 30-dB SNHL, or a loss shifted towards the higher frequencies.[19] Higher doses tend to cause more severe hearing losses, although a precise dose-response relationship cannot be shown.[19] Free drug levels are responsible for the therapeutic effects and ototoxicity of salicylates. Hypoalbuminemia, which occurs during the acute phase of KD, causes a higher level of free salicylate in the serum.[20] It is unlikely, however, that the SNHL experienced by patients in our study was caused by ASA ototoxicity alone. The patterns of hearing impairment in 4 patients differed from the patterns characteristic of salicylate ototoxicity, in which binaural flat or high-frequency deficits predominate (see Fig 2). Of 19 patients, 15 (78.9%) had a pattern consistent with ASA ototoxicity. Furthermore, salicylate ototoxicity in adults is reported to be reversible within 72 hours after cessation of therapy. However, 2 patients in our study showed hearing impairment that persisted beyond the period of their ASA treatment, consistent with earlier reports of SNHL associated with KD. In addition, SNHL associated with KD has been reported in Japan, where high-dose ASA is never used because of concerns regarding hepatotoxicity of salicylates in that population. Based on these data, a role for ASA toxicity in the SNHL seen in our study population is postulated, but is unlikely to explain all of the hearing loss.

Children with KD may be referred to the otolaryngologist for a variety of signs and symptoms during their acute illness. Consultation may be sought for evaluation of cervical adenopathy, airway obstruction, hoarseness, torticollis, and retropharyngeal soft tissue swelling.[21-27] In contrast, referral for evaluation of hearing loss may occur long after signs and symptoms of acute KD have disappeared. Because KD is a self-limited illness that resolves even in the absence of treatment, the diagnosis may be missed and the illness forgotten. Therefore, a history of an illness compatible with KD should be sought in all children who are being evaluated for hearing loss. Any suspicion of missed KD should precipitate referral for echocardiogram to detect possible coronary artery abnormalities.

Based on current information, it is recommended that primary care providers and parents of patients with KD be counseled regarding the possibility of SNHL after acute KD. Routine audiologic evaluation does not appear to be warranted. However, parents should be educated with respect to the possible sequelae of unrecognized hearing loss in this age group, which can include speech and language delay, behavioral and social adjustment difficulties, and poor academic performance. Health care providers should refer patients for audiologic evaluation should any of these sequelae develop after acute KD.

APPENDIX

Members of the Kawasaki Disease Multicenter Hearing Loss Study Group are as follows (from west to east):

University of Hawaii, Marian E. Melish; University of Southern California, Wilbert H. Mason; University of California San Diego, John F. Bastian; University of Colorado, Mary P. Glode; Northwestern University, Stanford T. Shulman; University of Toronto, Ronald M. Laxer; Tufts University, H. Cody Meissner; Harvard University, Robert P. Sundel; Boston University, Alexa S. Beiser; Coordinating Center, Jane C. Burns, UCSD, Jeffrey P. Harris, UCSD, Robert E. Novak, San Diego State University, Jane W. Newburger, Harvard University.

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