

## AUDIOLOGIC PROFILES OF CHILDREN WITH KAWASAKI DISEASE

*Robert P. Sundel, M.D.,\* Sandra S. Cleveland, M.Ed.,\* Alexa S. Beiser, Ph.D.,†  
Jane W. Newburger, M.D.,\* Trevor McGill, M.D.,\* Annette L. Baker, R.N., M.S.N.,\*  
Gideon Koren, M.D.,‡ Robert E. Novak, Ph.D.,§ Jeffrey P. Harris, M.D., Ph.D.,#  
and Jane C. Burns, M.D.#*

### ABSTRACT

Kawasaki disease (KD) is an idiopathic vasculitis associated with systemic inflammation and profound immunoregulatory changes. Recent reports from Japan and the United States have documented the association of sensorineural hearing loss (SNHL) with acute KD. To further characterize the nature and prevalence of this complication, we prospectively evaluated the hearing of 40 consecutive patients with acute KD at a single institution. Standard audiometric procedures were used, including visual reinforcement audiometry and play audiometry. Auditory brainstem response (ABR) testing using clicks and tone pips (1000–4000 Hz) was performed in patients with abnormal or unreliable results on behavioral audiometry. Acoustic immittance measurements were obtained on all patients. Of the 23 males and 17 females (mean age  $3.2 \pm 2.3$  years, range 0.6–11.1 years), all but three were evaluated and treated with aspirin and intravenous gamma globulin within 1 month of onset of fever. Seven children had test results suggesting sensorineural threshold shifts, 16 had normal hearing, and 14 had inconclusive hearing evaluations. Laboratory data in patients with hearing threshold shifts revealed significantly longer duration of fever ( $4.1 \pm 1.0$  versus  $1.9 \pm 0.5$  days), and a tendency for higher temperatures and white blood cell counts at diagnosis compared to those with normal hearing. Results suggest that transient as well as persistent SNHL may be associated with the acute vasculitis of KD, and may be associated with laboratory markers indicating more severe systemic inflammation. Audiologic screening should be considered for all patients following KD.

Kawasaki disease (KD) is a self-limited acute vasculitis of infants and children that affects predominantly medium-sized extraparenchymal muscular arteries. Manifestations of the disease are protean and may include nondeforming arthritis, aseptic meningitis, hepatitis, and sterile pyuria. Coronary artery abnormalities occur in approximately 20 percent of untreated patients and are the major cause of morbidity in KD.<sup>1</sup> Administration of high dose intravenous gamma globulin (IVGG) and aspirin during the acute phase of the illness decreases the prevalence of coronary artery aneurysms and reverses the signs of systemic inflammation and immunoregulatory changes associated with KD.<sup>2</sup>

Recent reports from Japan<sup>3</sup> and the United States<sup>4</sup> have documented the association of sensorineural hearing loss (SNHL) with acute KD. To fur-

ther characterize the nature and prevalence of this complication, we prospectively evaluated the hearing of 40 children with KD at a single pediatric hospital during a period of 20 consecutive months.

### PATIENTS AND METHODS

#### Patients

Forty patients treated for KD between February 1989 and September 1990 at Children's Hospital, Boston, MA, formed the basis of this study. All patients met standard clinical criteria for KD, with 5 or more days of fever and at least four of five markers of mucocutaneous inflammation (nonexudative conjunctivitis, cervical lymphadenopathy, oropharyngeal

\*Departments of Medicine, Otolaryngology, and Cardiology, Children's Hospital, and the Department of Pediatrics, Harvard Medical School, Boston, Massachusetts

†Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, Massachusetts

‡Division of Clinical Pharmacology, Hospital for Sick Children, and Pharmacology and Research Institute, University of Toronto, Toronto, Ontario, Canada

§Department of Communicative Disorders, San Diego State University, San Diego, California

#Departments of Pediatrics and Surgery/Otolaryngology, School of Medicine, University of California San Diego, San Diego, California

Reprint requests: Robert P. Sundel, Division of Immunology (Rheumatology), Children's Hospital Medical Center, 300 Longwood Avenue, Boston, MA 02115

erythema, indurated erythema of the hands or feet, and polymorphous rash (Table 1).<sup>5</sup>

### Treatment

All patients received intravenous gamma globulin, 2 g/kg, within 14 days of onset of fever, plus aspirin 80 to 100 mg/kg per day.<sup>6</sup> When the child had been afebrile for 48 hours, the salicylate dose was decreased to 3 to 5 mg/kg per day. No patient received other medications known to be ototoxic, including diuretics or aminoglycoside antibiotics.

### Methods

#### Laboratory Studies

Blood samples for complete blood count, C-reactive protein, platelet count, alpha-1-antitrypsin, albumin, and immunoglobulin levels were obtained at the time of enrollment (prior to infusion of IVGG). Sera were obtained in six children 4 days after beginning aspirin therapy, for measurement of salicylate levels and protein binding of salicylate using radiolabeled salicylate and ultrafiltration, as previously described.<sup>7</sup>

#### Hearing Evaluations

Patients were included in the study if they had a hearing evaluation performed within 1 month following onset of Kawasaki disease. Audiologic evaluations were performed in a sound-treated booth that met current American National Standards Institute (ANSI) specifications.<sup>8</sup> Manual pure-tone air- and bone-conduction thresholds were obtained using a standard descending procedure for the frequency range of 0.25 or 0.5 to 8 kHz. Evaluations were conducted on a model GSI-10 or GSI-1704 audiometer (Grason-Stadler, Inc., Littleton, MA) meeting ANSI specifications for audiometers.<sup>9</sup> Audiologic methods included either a conventional hand-raising technique, play audiometry task, or visual reinforcement audiometry, depending on the age and developmen-

tal level of the patient. All evaluations were performed by a single experienced audiologist who classified as "indeterminate" any unreliable results; a second audiologist assisted for sound-field tests. Auditory brainstem response (ABR) threshold measures using click stimuli and tone bursts of 2 and 4 kHz were used to assess the hearing in those patients with abnormal or unreliable results on behavioral audiometry. Measurements were made with surface electrodes placed on the forehead and in each mastoid region. Acoustic immittance measurements were performed in all patients.

#### Statistical Methods

We used two sample t-tests to compare groups with respect to all continuous variables at enrollment. Results are expressed as mean plus or minus standard error.

### RESULTS

Of the 40 patients with KD evaluated during the study period, 17 were excluded from analysis:

1. Test results or otologic examination were consistent with otitis media in seven.
2. Behavioral audiometric tests were unreliable in seven. These included results felt to be adversely affected by the patient's age or state, or by the test procedure, such that small response threshold shifts could not be analyzed with confidence.
3. Time constraints of the study were not fulfilled in three, with late hearing evaluations in two patients and late IVGG therapy in one.

Twenty-three children, 13 males and 10 females, were thus available for analysis. Sixteen children were found to have normal hearing. Seven others, five girls and two boys, had test results suggesting a transient hearing threshold shift of 10 to 25 dB between initial and final hearing evaluations. In three of these patients, bone-conduction testing could not be completed, though there was no evidence of middle-ear pathology suggesting a conductive component to the threshold shift. Six of the seven children with threshold shifts were retested at varying intervals. In all six, thresholds improved 10 to 25 dB during the ensuing 8 days to 4 months.

The threshold hearing levels of these seven patients are summarized in Table 2. On initial evaluation, patient 1 demonstrated thresholds of 25 to 30 dB HL at 6 and 8 kHz in both ears. Two weeks after the acute illness, reevaluation revealed a 10 dB improvement in hearing threshold at 6 kHz in the right ear, but otherwise no change. Four months later, follow-up testing revealed normal hearing (5–10 dB HL) bilaterally at 0.5 to 8 kHz.

Patient 2 also demonstrated significantly decreased thresholds: 35 dB HL at 6 and 8 kHz, and 20 to 25 dB HL at 0.5 to 4 kHz, in her right ear. Hearing

**Table 1. Diagnostic Criteria of Kawasaki Disease\***

Fever lasting 5 days or more without any other explanation and at least four of the following criteria:
1. Bilateral conjunctival injection
2. Changes of the peripheral extremities, including the following:
Erythema of palms or soles, edema of hands or feet (acute phase)
Periungual desquamation (convalescent phase)
3. Mucous membrane changes, including the following:
Injected or fissured lips
Injected pharynx
Strawberry tongue
4. Polymorphous rash
5. Acute nonpurulent cervical lymphadenopathy (at least one lymph node 1.5 cm or greater in diameter)

\*Adapted from Rauch Am: Adv Pediatr Infect Dis 1989; 4:164.

in the left ear was within the normal hearing range (5–15 dB HL), with thresholds of 20 dB HL at 6 and 8 kHz. One week later, thresholds were slightly improved, and final evaluation 3 weeks after the illness revealed normal hearing (5–15 dB HL) bilaterally at 0.5 to 8 kHz.

Four patients had threshold shifts that produced a flat audiometric configuration. Patients 3, 5, and 6 demonstrated thresholds of 15 to 25 dB HL across most of the frequency range from 0.5 to 4 kHz (except for thresholds of 5–10 dB HL at 4 kHz in patient 3, and thresholds of 10 dB HL at 2 kHz in patient 5). Patient 4 showed threshold shifts at 0.5 to 4 kHz, but his responses reached the mild hearing loss range, with thresholds of 30 to 35 dB HL at 0.5 to 1 and at 4 kHz. Reevaluation of these patients showed improvement of thresholds to within the normal hearing range (0–15 dB HL) during a period ranging from 8 days to 1 month. Patient 4 remained with 20 dB HL thresholds at 8 kHz.

Patient 7, a 10-month-old girl, was evaluated using ABR potentials to click and tonal signals. Results revealed hearing thresholds of 15 to 25 dB HL for clicks and a 4 kHz tone burst. A threshold of 25 dB HL at 2 kHz was measured in her left ear, but the right ear was not assessed at this frequency. The patient did not return for follow-up testing.

Children with hearing threshold shifts did not differ significantly from those with normal hearing

with respect to age at onset of KD ( $3.4 \pm 0.5$  versus  $4.0 \pm 0.6$  yr,  $p > 0.05$ ), days until treatment ( $6.1 \pm 0.8$  versus  $7.4 \pm 0.7$ ,  $p > 0.05$ ), or days until initial hearing evaluation ( $9.1 \pm 0.9$  versus  $12.3 \pm 1.7$ ,  $p > 0.05$ ). There was a tendency for children who developed hearing threshold shifts to display evidence of greater inflammation at enrollment, though, in the case of most variables, this did not reach statistical significance in this small sample. Thus, children with threshold shifts had higher white blood cell counts ( $16.3 \pm 1.6$  versus  $12.7 \pm 1.5 \times 10^3/\text{mm}^3$ ,  $p > 0.05$ ), and higher temperatures ( $39.4 \pm 0.5$  versus  $38.9 \pm 0.3^\circ\text{C}$ ,  $p > 0.05$ ) at enrollment, and they had a significantly longer duration of fever ( $>38.0^\circ\text{C}$ ) after hospitalization for treatment ( $4.1 \pm 1.0$  versus  $1.9 \pm 0.5$  days,  $p < 0.04$ ). One child in each group developed coronary artery aneurysms.

Six of the 40 children enrolled in the study, including two with hearing threshold shifts, had total and free (unbound) salicylate levels determined. Levels of unbound salicylate greater than 0.2 mM/L correlate with total salicylate levels greater than 28 mg/dl, which have been associated with ototoxicity. Patient 3, with transient bilateral upsloping borderline hearing loss, had a salicylate level of 0.63 mM/L and 70 percent protein binding (free salicylate = 0.189 mM/L). Patient 7, on the other hand, had a salicylate level of 1.95 mM/L with 57 percent protein binding (free salicylate = 0.837 mM/L) at a time that ABR

Table 2. Audiologic Profiles of Children with Kawasaki Disease

Patient Number	Age (yr/mo)	Test	Results	
			Initial	Final
1	3/11	Play Audiometry	R: *10–15 dB HL @ 0.5–4 kHz 25–30 dB HL @ 6, 8 kHz L: *10–15 dB HL @ 0.5–4 kHz 30 dB HL @ 6, 8 kHz	R: 5–15 dB HL @ 0.5–8 kHz L: 5–15 dB HL @ 0.5–8 kHz
2	5/1	Play Audiometry	R: 20–25 dB HL @ 0.5–4 kHz 35 dB HL @ 6, 8 kHz L: 5–15 dB HL @ 1–4 kHz 20 dB HL @ 0.5, 6, 8 kHz	R: 5–15 dB HL @ 0.5–8 kHz L: 5–15 dB HL @ 0.5–8 kHz
3	3/5	Play Audiometry	R: 20–25 dB HL @ 0.5–2 kHz 10 dB HL @ 2 kHz L: 15–20 dB HL @ 0.5–2 kHz 5 dB HL @ 4 kHz	R: 0–10 dB HL @ 0.5–8 kHz L: 0–10 dB HL @ 0.5–8 kHz
4	3/5	Play Audiometry	SF: 30–35 dB HL @ 0.5–1, 4 kHz 20 dB HL @ 4 kHz	R: 10–15 dB HL @ 0.5–6 kHz 20 dB HL @ 8 kHz L: 10–15 dB HL @ 0.5–6 kHz 20 dB HL @ 8 kHz
5	2/11	Play Audiometry	SF: 20 dB HL @ 0.5–1, 4 kHz 10 dB HL @ 2 kHz	SF: 0–5 dB HL @ 0.5–4 kHz
6	1/7	Behavioral observation and visual reinforcement audiometry and play audiometry	SF: 20–25 dB HL @ 0.5–4 kHz	R: 5–15 dB HL @ 0.5–8 kHz L: 5–10 dB HL @ 0.5–8 kHz
7	10 mo	ABR <sup>†</sup>	R: 20–25 dB HL @ 4 kHz & clicks L: 15–25 dB HL @ 2, 4 kHz & clicks	—

\*Did not test <10 dB HL; <sup>†</sup>Auditory brainstem response; R = right ear; L = left ear; SF = sound field

revealed a threshold for clicks of 20 to 25 dB HL. Four other children with free salicylate levels of 0.209 to 0.354 mM/L had normal hearing.

## DISCUSSION

Previous reports have documented 13 children with sensorineural hearing loss associated with KD; in 10 patients, some degree of hearing loss was permanent.<sup>3,4</sup> No systematic study of hearing loss in KD has been reported. We therefore initiated a pilot study to determine prospectively the prevalence of hearing loss following acute KD. We observed hearing threshold shifts of 10 to 25 dB in 7 of the 23 patients who could be tested reliably. The threshold shifts appeared to be sensorineural in nature in view of the absence of middle ear dysfunction, and in view of concomitant shifts in bone-conduction thresholds in the three patients so evaluated. Among those children with hearing threshold shifts, hearing returned to normal 8 days to 4 months after the illness in six children; one girl was not retested.

The mechanism of sensorineural hearing loss associated with acute KD remains to be determined. Epidemiologic data suggest that KD may have an infectious etiology.<sup>10</sup> If this is the case, hearing loss may be a manifestation of infection of the inner ear, analogous to direct cytopathic effects on the labyrinth and cochlea seen in certain viral illnesses. Alternatively, hearing loss may be associated with the intense immune activation or elevated levels of circulating immune complexes<sup>11</sup> seen in patients with acute KD.

In collagen-vascular diseases, hearing loss has been ascribed to numerous autoimmune mechanisms, including anticochlear antibodies, lymphocytes reactive to inner ear antigens, and immune complex deposition within the otic capsule.<sup>12</sup> The possibility that more severe KD—manifested by trends toward higher fevers and more intense leukocytosis at presentation—predisposes to SNHL suggests that hearing loss is a reflection of the underlying disease process. The preponderance of affected girls, despite an overall male to female ratio in KD of 1.6:1, must be confirmed in future studies; earlier reports did not demonstrate a similar tendency. Over-representation of females in the group with SNHL might suggest an autoimmune basis for the hearing loss, in view of the increased tendency of females to develop autoimmune phenomena.<sup>13</sup>

The potential role of aspirin toxicity in the sensorineural hearing loss associated with KD requires further study. Free drug levels account for the therapeutic effects and the toxicity of salicylates. As a result of hypoalbuminemia, free salicylate levels are significantly elevated during the acute phase of Kawasaki disease.<sup>7</sup> Only two of the patients with hearing loss had salicylate levels measured, and in one case a supratherapeutic level was noted. On the other hand, four of the children without hearing threshold shifts had potentially toxic calculated free salicylate levels. Further, salicylate ototoxicity in adults is reported to

be reversible within 72 hours,<sup>14</sup> yet permanent hearing loss has been associated with KD in the past. Based on these data, we cannot exclude a contribution of aspirin toxicity to the hearing threshold shifts we observed in one patient. Further studies of the mechanism of hearing loss in KD, including possible roles of aspirin toxicity or of autoimmunity, are needed.

Whatever the mechanism, these results, in conjunction with those of previous reports, suggest that transient hearing threshold shifts as well as persistent SNHL are associated with the acute vasculitis of KD. Female gender and laboratory values indicative of more severe systemic inflammation may be markers of increased risk for developing SNHL. A large percentage of patients were excluded from this study because small threshold shifts could not be analyzed with confidence using behavioral audiologic test procedures, because of patient age and state. Future test protocols should thus include objective audiometric test procedures, such as ABR, whenever possible. Until further data are available, however, audiologic screening should be considered for all patients presenting with Kawasaki disease.

## REFERENCES

1. Suzuki A, Kamiya T, Kuwahara N, et al: Coronary arterial lesions of Kawasaki disease: cardiac catheterization findings of 1100 cases. *Pediatr Cardiol* 1986; 7:3.
2. Newburger JW, Takahashi M, Burns JC, et al: The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986; 315:341.
3. Suzuki H, Yanagawa T, Kihira S, et al: *J Clin Pediatr (Jpn)* 1988; 41:167-172.
4. Sundel RP, Newburger JW, McGill T, et al: Sensorineural hearing loss associated with Kawasaki disease. *J Pediatr* 1990; 117:371-377.
5. Kawasaki T, Kosaki R, Okawa S, Shigematsu I, Yanagawa H: A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* 1974; 54:271-276.
6. Newburger JW, Takahashi M, Burns JC, et al: A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991; 324:1633-1639.
7. Koren G, Silverman E, Sundel R, et al: Decreased protein binding of salicylates in Kawasaki disease. *J Pediatr* 1991; 118:456-459.
8. American National Standards Institute. American National Standard for permissible ambient noise during audiometric testing. New York: American National Standards Institute, 1977.
9. American National Standards Institute. American National Standard specifications for audiometers. New York: American National Standards Institute, 1970.
10. Sundel R, Leung DYM: Kawasaki Disease. *Curr Opin Rheumatol* 1990; 2:81-86.
11. Leung DYM, Siegel RL, Grady S, et al: Immunoregulatory abnormalities in mucocutaneous lymph node syndrome. *Clin Immunol Immunopathol* 1982; 23:100-112.
12. Harris JP: Immunologic mechanisms in disorders of the inner ear. In: Cummings CW, ed. *Otolaryngology: head and neck surgery*. St. Louis: CV Mosby, 1986.
13. Lahita RG: Sex and age in systemic lupus erythematosus. In: Lahita RG, ed. *Systemic lupus erythematosus*. New York: Churchill Livingstone, 1987.
14. Myers EN, Bernstein JM: Salicylate ototoxicity. *Arch Otolaryngol Head Neck Surg* 1965; 82:483-493.