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RESEARCH ARTICLE

The prevalence of sensorineural hearing loss in patients with Kawasaki disease after treatment

Khadije Toomaj[1], Parvin Akbariasbagh[1], Alireza Karimi Yazdi[2]*, Yahya Aghighi[1], Seyyed Reza Raeeskarami[1], Fariba Eslambol Nassaj[3], Shahnaz Alamdari[3]

[1]- Department of Pediatrics, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

[2]- Otorhinolaryngology Research Center, Tehran University of Medical Sciences, Tehran, Iran

[3]- Department of Audiology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

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Abstract

Background and Aim: Kawasaki disease (KD) is an acute childhood febrile illness with world-wide incidence and the highest incidence occurs in Asian children, with coronary arteritis being the main complication. Sensorineural hearing loss (SNHL) has also been described as a complication of KD in several articles. The aim of this study was to evaluate the prevalence of SNHL in patients with KD treated with intra vein immunoglobellin (IVIG).

Methods: In this cross sectional study, we evaluated 56 patients who received KD treatment between 2011 and 2015 by auditory brainstem evoked response (ABR), pure tone audiometry (PTA), and tympanometry. Also, we evaluated the prevalence of coronary arteritis, the time of beginning IVIG treatment from the onset of fever, the prevalence of thrombocytosis, and erythrocyte sedimentation rate (ESR) in acute or subacute phases of their disease.

Results: During audiological evaluation, we found SNHL in one (2.6%) of the 36 patients. Other findings in the acute and subacute phases of KD included: 8 patients (22%) had coronary aneurysm, 17 (47%) thrombocytosis, 25 (69%) had elevated ESR, and the treatment with IVIG within 10 days of fever was done in 19 patients (53%).

Conclusion: SNHL is a complication of KD which could extend beyond the treatment time. In this study, the patient with SNHL was treated with KD two years before the study and in the acute phase of KD, he had thrombocytosis > 500,0000, ccoronary artery aneurysm, ESR > 40. The treatment with IVIG was done within the first 10 days of fever onset.

Keywords: Kawasaki disease; sensorineural hearing loss; auditory brainstem evoked response; intra vein immunoglobellin

* **Corresponding author:** Otorhinolaryngology Research Center, Tehran University of Medical Sciences, Tehran, 1145765111, Iran. Tel: 009821-66760269, E-mail: Karimiya@sina.tums.ac.ir

Introduction

Kawasaki disease (KD) is a systemic vasculitis that predominantly occurs in children younger than five years of age. Although epidemiologic aspects strongly suggest an infectious agent, its etiology remains unknown [1,2]. KD is characterized by fever, nonexudative bilateral conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash and cervical adenopathy. The classic diagnosis of KD has been based on the presence of five or more days of fever and at least four of the five principle clinical features [3]. More recently proposed criteria include perineal rash in the criterion for

changes in the extremities. In the presence of fever and coronary artery changes demonstrated by echocardiography, less than the four criteria are sufficient for KD diagnosis [3,4]. Cardiac involvement is the most important manifestation of KD. Coronary artery aneurisms develop in up to 25% of the untreated patients. The intra vein immunoglobellin (IVIG) administration over the 10 first days of the disease leads to a reduced coronary artery impairment of 3% to 8% and a mortality rate of up to 0.2% [1,3]. Because of significant morbidity and mortality potential, all children should receive a screening echocardiogram as a component of their treatment [5,6].

The first description for hearing loss in KD was made by Suzuki et al. in Japan in 1988 [7]. Since 1988, few research have been published on the possible relationship and the results of the studies suggest that KD is associated with SNHL, but with varying degrees of severity and persistence [8-14]. Normal hearing is an essential component of speech and language development, especially from birth to five years of age. Even mild SNHL may cause problems with normal speech and language development [15].

The main aims of this study were: 1) to evaluate the prevalence of SNHL in patients who had KD and received IVIG treatment and 2) to find the prevalence of coronary arteritis, the time of beginning IVIG treatment from the onset of fever, the prevalence of thrombocytosis, and serum elevated ESR in acute or subacute phases of their disease. The evaluation was done six months or more after the treatment in patients with or without SNHL.

Methods

This cross sectional study was conducted to evaluate the patients with KD diagnosis, who were admitted to the pediatric ward of the Imam Khomeini Hospital between 2011 and 2015 and received IVIG treatment. Totally, archive files of 59 KD patients in accordance with the American Heart Association (AHA) criteria were studied. Data of the acute phase of KD was collected using questionnaire forms. Three patients were excluded from the study because of having other probable reasons for SNHL.

Table 1. Interpeak interval values for 80 dB nHL click auditory brainstem response for ages above three years

	I-III	III-V	I-V
Mean	2.4	1.86	4.00
SD	0.23	0.14	0.20

SD; standard deviation

Then, we called all of the patients to evaluate them by auditory brainstem evoked response (ABR), tympanometry, and pure tone audiometry (PTA). In the ABR test we used click stimuli and tone burst stimuli (80 dB) to evoke responses from the auditory pathway.

The normal ABR test discloses six distinct waves: I, II, III, IV, V, VI. The ABR neurophysiologic evaluation of the auditory nervous impulse was performed considering 2 milliseconds as the normal conduction time between waves I and III (from cochlea to the superior olivary complex, SOC, of the pons) and waves III and V (pons to the inferior colliculus, IC, of the mesencephalon) [11]. However abnormal findings in our study were defined as ABR waves interpeak interval (IPI) values for an 80 dB nHL click more than normal ranges standardized by the manufacturer factory (ICS Charter, Madsen, Denmark) for our patients (Table 1).

We used clinical acoustic impedence audiometer ZA86/B to measure the changes in the acoustic impedence of the middle ear system in response to changes in air pressure by tympanometry. According to classification of Jerger-Liden, we considered type An with physical volume 0.8-1.0 ml as normal tympanogram; and types B, C, As and Ad as abnormal tympanograms [16].

In this study we used Orbiter 922 as clinical audiometer.for pure tone audiometry to evaluate hearing in frequencies 250, 500, 1000, 2000, 3000, 4000 and 8000 Hz. According to classification of Goodman-Clark we considered normal hearing: -10 to +15 dB, slight hearing loss: 16 to 25 dB, mild hearing loss: 26 to 40 dB, moderate hearing loss: 41 to 55 dB, severe hearing loss: 71 to 90 dB; and profound hearing loss > 90 dB.

The threshold for each tone was determined by finding the intensity level at which the child could detect the tone 50 percent of the time [17].

Of the 56 patients, 36 completed the audiological evaluations and were examined in the ear, nose, throat, and cardiac by specialist physicians. A questionnaire assessing possible risk factors for hearing loss was also administered. The study was approved by the Ethics Research Committee from the Tehran University of Medical Sciences (IR.TUMS.REC.1394.2065) and an informed consent was obtained from all the parents of the children included in the project.

The data collected from archive files included: complete blood count, platelet count, ESR, reports of the echocardiography at the acute phase of KD, and the time of administration of IVIG within the onset of KD. All the patients had been treated with IVIG soon after the confirmation of their KD diagnosis. All the 36 patients underwent the audiologic evaluations, echocardiogram, careful examinations.

To analyze the data we used the SPSS 20, since only one patient had SNHL, we could not compare the two groups of patients with and without SNHL. We used means for continuous variables, and frequency for discontinuous variables and reported the result of echocardiography and other variables at the acute phase of the disease (during the admission in the hospital) for the patient with SNHL.

Results

In total, of the 56 patients, 36 completed the audiologic evaluations. The patients were 22 boys (61%), and 14 girls (39%). The median age of the participtants at the time of KD diagnosis was 4 years (ranged from 9 months to 11 years). All of the patients were older than three years at the time of audiologic evaluation. Of the 36 patients, IVIG treatment was done in 19 (53%) within the first 10 days of their disease, and in 17 (47%) after 10 days of the onset of their disease. All the patients were treated with IVIG and aminosalisylic acid (ASA) at the time of the KD diagnosis. At the acute and subacute phases of the disease, coronary artery aneurysms were developed in 8 patients (22%); 25 patients (69%) had high ESR (>40 mm/hr); 17 patients (47%) had thrombocytosis (Platelet > 500,000) in the acute phase of the disease; and 35 patients (97%) had normal audiologic evaluation including normal, Table 2 shows results of ABR, PTA, and tympanogram. Only one patient (2.8%) shows SNHL with abnormal ABR (increased interpeak interval I-III, and I-V), and, abnormal PTA (hearing loss was shown in 10-20 dB), and normal tympanogram (Figures 1, 2 and 3). Other probable reasons for SNHL in this patient were ruled out through getting the case history, careful physical examination by specialists and normal PTA screening test at the neonatal period. The patient was a four year old boy at the time of treatment for KD. We evaluated him two years later by the audiologic tests. At the acute and subacute phases of KD, he had coronary artery aneurism, thrombocytosis (Platelet>500,000), high ESR level (>40 mm/hr), and his IVIG treatment was done within the first 10 days of the onset of KD (Table 3). The coronary artery aneurism was resolved at the fallow up echocardiograms.

Discussion

The most significant and characteristic complication of KD, the development of coronary aneurysms in up to 25% of the untreated patients, makes KD the leading cause of acquired heart disease among children in the developed world [18]. Although neurologic symptoms in KD are very rare, extreme irritability, possibly due to aseptic meningitis, is common in KD. Seizures, involvement of cranial pairs and hemiparesis caused by thrombosis or infarction have rarely been reported in the literature [8,19].

Several articles have documented the association between SNHL and KD [7-13,20,21] and SNHL in KD is possibly irreversible [11,13]. An early treatment initiated during the first week of the disease and including the use of systemic steroids, is thought to possibly prevent this complication [22]. The pathogenesis of SNHL associated with KD is unknown. The hearing loss may be associated with

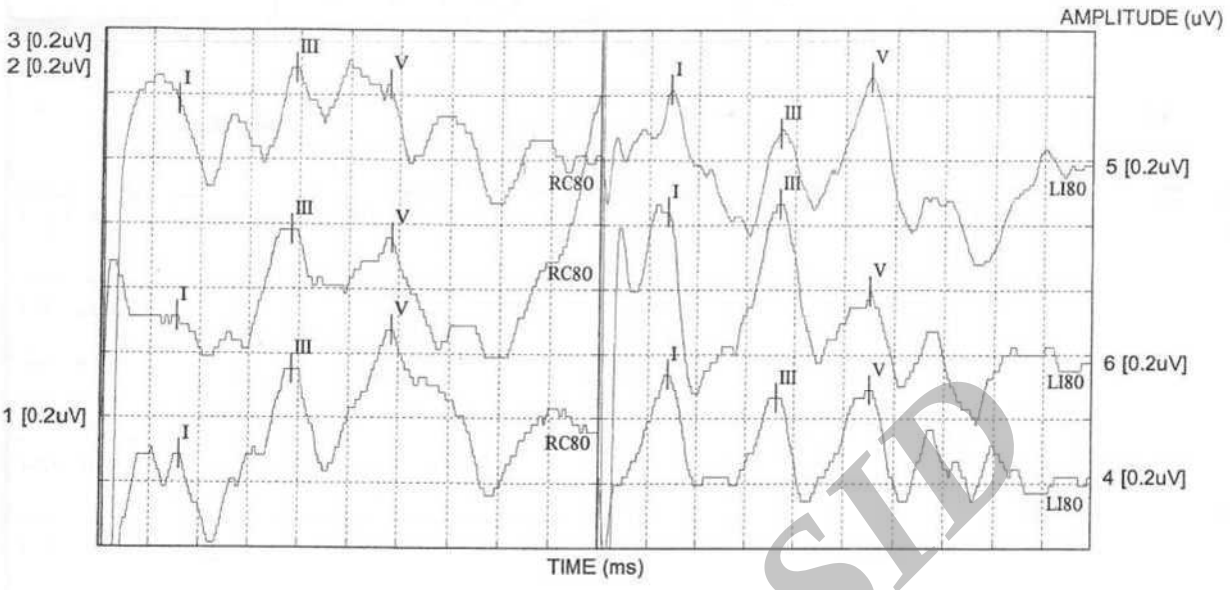
Table 2. The prevalence of variables in the patients

	Frequency	Percent
Male	22	61
Female	14	39
Normal ABR	35	97
Abnormal ABR	1	3
ESR>40	25	69
ESR<40	11	31
Plt>500,000	17	47
Plt<500,000	19	53
With coronary aneurism at the acute and subacute phases of KD	8	22
Withoutcoronary aneurism at the acute and subacute phases of KD	28	78
IVIG treatment within the first 10 days	19	53
IVIG treatment after the first 10 days	17	47

ABR; auditory brainstem response, ESR; erythrocyte sedimentation rate, Plt; Platelet, KD; Kawasaki disease, IVIG; intra vein immunoglobulin

the inflammatory process, owing to the intense immune activation observed in the acute phase, and this can affect the membranes of the labyrinth and the osmotic balance in the fluid inside the compartments of the inner ear or in the cochlear vessels, leading to hearing loss [20,23-25]. The relative rarity of KD in the perinatal period and adulthood suggests that KD may be caused by an agent, to which virtually all adults are immune, and 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 cytopatic effects on the labyrinth and cochlea, which occurs by certain viral illnesses, such as mumps and rubella [26]. Although there is a potential role of salicylate ototoxicity in the genesis of the hearing loss seen in KD, salicylate ototoxicity is reported to be reversible within 72 hours after cessation of therapy and ototoxicity by salicylate occurs when used in high doses (80-100 mg/kg) [27,28]. The SNHL pattern in patients with KD differed from the salicylate ototoxicity patterns, in which binaural flat or high frequency deficits are predominant. In addition, SNHL associated with KD has been reported in Japan, where the high dose ASA is never used because of concerns regarding hept-otoxicity of salicylates in the population [13]. In our patient, SNHL persisted about three years after the cessation of the ASA, and the SNHL pattern in our patient was different from the salicylate ototoxicity patterns.

Our patient had thrombocytosis (Platelet >500,000), high ESR (ESR > 40), and coronary artery aneurysm in the acute phase of KD. IVIG plus ASA were used within the first 10 days of fever and coronary aneurysm was resolved at the follow up echocardiograms. Two studies in Brasilia showed an association between thro-mbocytosis (Platelet > 500,000), high ESR level and IVIG administration after 10 days of fever with the prevalence of SNHL in KD. In these studies, the prevalence of SNHL in KD was higher than three from our finding [10]. The prevalence of SNHL in our study is more simi-lar to another study by Knott et al., reporting a lower SNHL prevalence than the study by



LATENCIES (ms)
ABR

Waveform	Ear	I	II	III	IV	V	VI
1	Right	1.60	***	3.91	***	5.97	***
2	Right	1.60	***	3.98	***	5.90	***
3	Right	1.67	***	3.93	***	5.97	***
4	Left	1.46	***	3.69	***	5.59	***
5	Left	1.48	***	3.74	***	5.59	***
6	Left	1.45	***	3.74	***	5.59	***

INTERPEAK INTERVALS (ms)
ABR

Waveform	Ear	I-III	III-V	I-V
1	Right	2.31	2.06	4.37
2	Right	2.38	1.92	4.30
3	Right	2.26	2.04	4.30
4	Left	2.23	1.90	4.13
5	Left	2.26	1.85	4.11
6	Left	2.29	1.85	4.15

WAVEFORMS
ABR

#	Date	Record	Transducer	Intensity	Ear	Rate	Stimulus	Gain	High	Low	Acc	Rej	Epoch
1	2014/09/27	5.1	Headphones	80dB nHL	Right	21.1/s	Click-A	50k	100 Hz	3 kHz	2000	1	10ms
2	2014/09/27	6.1	Headphones	80dB nHL	Right	21.1/s	Click-R	50k	100 Hz	3 kHz	2000	0	10ms
3	2014/09/27	9.1	Headphones	80dB nHL	Right	21.1/s	Click-R	50k	100 Hz	3 kHz	2000	0	10ms
4	2014/09/27	12.1	Headphones	80dB nHL	Left	21.1/s	Click-A	50k	100 Hz	3 kHz	2000	32	10ms
5	2014/09/27	16.1	Headphones	80dB nHL	Left	27.7/s	Click-A	100k	100 Hz	3 kHz	1667	59	10ms
6	2014/09/27	14.1	Headphones	80dB nHL	Left	21.1/s	Click-C	50k	100 Hz	3 kHz	2000	10	10ms

WAVEFORM COMMENTS
ABR

Waveform	Comments
1	(Smooth: 5.1 - 7 points)
2	(Smooth: 6.1 - 7 points)
3	(Smooth: 9.1 - 7 points)
4	(Smooth: 12.1 - 7 points)
5	(Smooth: 16.1 - 7 points)
6	(Smooth: 14.1 - 7 points)

Fig. 1. Waves of ABR in the patient with abnormal ABR. Interpeak interval I-III, and I-V was increased in the right ear.

Magalhães et al. and Alves et al.in Brasilia. SNHL in our patient was persistent as reported by Magalhães et al., but the study by Knott et al. showed that SNHL could be reversible and its prevalence within 30 days of the onset of fever was near to our finding [10,11,13]. Parents frequently fail to identify the problem, and conventional audiometry is generally difficult to perform in younger children, especially in those younger than two years. In addition to the irritability that is usually associated with both acute and subacute phases of the illness [20]. In our study, the parents failed to identify the SNHL, maybe because it was the mild,

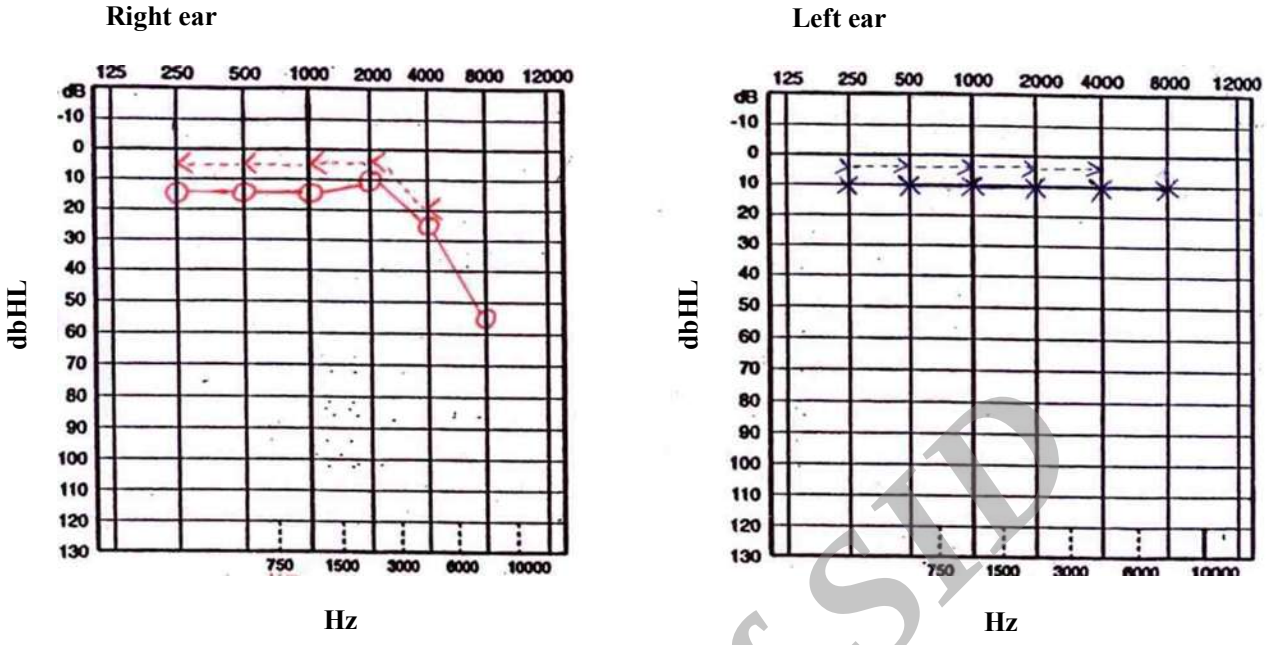


Fig. 2. Sensorineural hearing loss in a 6 year old boy.

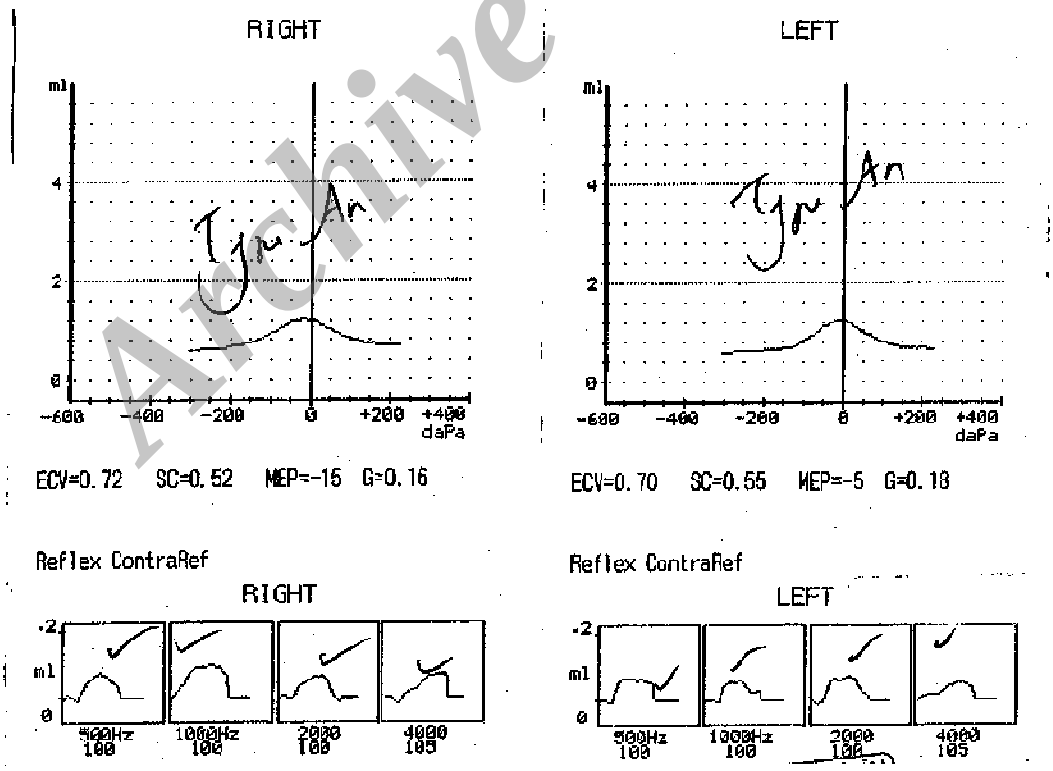


Fig. 3. Tympanogram in the patient with sensoryneural hearing loss.

Table 3. Results of the variables in the patient with SNHL

	Abnormal ABR
Sex	Male
Age	4 years
Aneurism in the acute and subacute phase of KD	Yes
ESR	>40
IVIG treatment within the first 10 days	Yes
Plt	>500,000

ABR; auditory brainstem response, KD; Kawasaki disease, ESR; erythrocyte sedimentation rate, IVIG; intra vein immunoglobulin, Plt; Platelet

unilateral SNHL.

Normal hearing is an essential component of speech and language development, especially in the first five years of life. Even mild SNHL may cause problems with normal speech and language development [15]. Affected children who are identified earlier have also been shown to have better outcomes than children with delayed diagnoses [29].

Conclusion

This study suggests that there is an association between KD and SNHL. Our conclusion is that routine exams suitable to the patient's age should be performed to assess hearing function in KD. However, parents should be educated on the possible sequelae of unrecognized hearing loss in this age group.

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