

# Infection in childhood sensory hearing loss

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## ABSTRACT

**الأهداف:** من أجل تقييم الدور المحتمل للعوامل المتهبة على الظهور التلقائي لفقدان السمع الحسي لدى الأطفال (SNHL).

**الطريقة:** أجريت هذه الدراسة بمستشفى الرسول - طهران - إيران، خلال الفترة ما بين 2002م وحتى 2003م. قمنا بمقارنة الأجسام المضادة لمصل محدد (IgG, IgM) وتم قياسه بواسطة الإنزيم المرتبط بمعايرة المناعة لدى 95 حالة فقدان السمع الحسي ولدى 63 حالة في مجموعة التحكم.

**النتائج:** تبين وجود التهابات حادة (IgM) في الحالات التي اشتملت على: الحمى الخلوية المعرطلة (34.6% CMV، المقوسات 11.5%، النكاف 8.7%، الروبلا والهربس البسيط كلاً منهما 5.3%. لوحظ وجود التهابات سابقة (IgG) تشمل المعرطلة 72%، الهربس 6.6%، المقوسات 26%، النكاف 23.3%، الروبلا 17.2%. كان التهاب المعرطلة الحاد والمقوسات هما الأكثر شيوعاً بين الحالات. الالتهابات السابقة: المعرطلة، المقوسات، الروبلا، والهربس كانت هي الأكثر شيوعاً في مجموعة التحكم، لم يكن هناك فروقات في التهابات النكاف والروبلا والهربس بين الحالات في مجموعة التحكم.

**خاتمة:** هذه البيانات متقاربة مع العوامل المعدية والتي لها دوراً ملحوظاً في حالات فقدان السمع الحسي التلقائي الذي أجريت له الدراسة في السابق، ولكن اتحادها لا يثبت أي سبب. قمنا بوصف أدوية معينة لإثبات الالتهابات الفعالة (الحمى الخلوية المعرطلة، المقوسات، الهربس) لدى الأطفال الرضع المصابين بفقدان السمع الحسي التلقائي (SNHL)، والذين شخضت حالتهم بالإصابة به قبل أول عام من عمرهم. يحرض النكاف والحصبة فقدان السمع الحسي ويتم الوقاية من ذلك بواسطة التطعيم الروتيني.

**Objectives:** To evaluate the possible role of infectious agents on the occurrence of idiopathic sensorineural hearing loss (SNHL) in children.

**Methods:** This case control study was carried out at Rasul Hospital in Tehran, Iran from 2002-2003. We compared specific serum antibodies (IgG, IgM) measured by

enzyme linked immunosorbent assay in 95 sensory hearing loss cases and 63 controls.

**Results:** Acute infections (IgM) detected in cases included: cytomegalovirus (CMV) 34.6%, toxoplasma 11.5%, mumps 8.7%, rubella 5.3%, and herpes simplex 5.3%. Previous infections (IgG) detected in cases included CMV 72%, herpes 6.6%, toxoplasma 26%, mumps 23.3%, and rubella 17.2%. Acute CMV and toxoplasma infections were more frequent in cases. Previous CMV, toxoplasma, rubella, and herpes infections were higher in controls. There was no significant difference for acute mumps, rubella, and herpes infections between cases and controls.

**Conclusion:** These data are compatible with infectious agents having a significant role in the studied idiopathic SNHL cases, but association does not prove causation. We recommend specific drugs for confirmed active infections (CMV, toxoplasma, herpes) in idiopathic SNHL infants diagnosed before their first birthday. Mumps and rubella induced SNHL are preventable with routine vaccination.

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In developed countries, the incidence of bilateral hearing loss in children is reported at approximately 1-2/1000. Viral infections (mumps, influenza, rubella, measles, cytomegalovirus [CMV]) as well as trauma, drugs, metabolic, viral, or bacterial meningitis are important factors in childhood sensorineural hearing loss (SNHL).<sup>1-5</sup> The hearing impairment was severer

and the prognosis was poorer in children with SNHL than in adults.<sup>1</sup> In 39% of children with SNHL, the etiological factor remained unknown.<sup>2</sup> Of unilateral deaf cases, 7.5% were diagnosed accidentally, most often between the seventh to tenth years of age. Neither children nor their parents can determine the time of its appearance, especially when it is not accompanied by other symptoms such as dizziness or tinnitus.<sup>2</sup> More than 40% of deafness cases with an unknown cause, needing rehabilitation, are caused by congenital CMV. Ten to 17% of congenital CMV infants later may have unilateral or bilateral, usually progressive deafness.<sup>2-5</sup> Congenital CMV infection in children should be treated with ganciclovir. The diagnosis of congenital CMV is by DNA-CMV detection in the urine, and detection of IgM antibody in blood or perilymphatic fluid.<sup>4,6</sup> Detection of serum antibody or virus in urine after the first year of life is not useful as most children develop immunity to the virus.<sup>8-10</sup> Congenital toxoplasma infections may present as a mild or severe neonatal disease with sequelae. The SNHL, both mild and severe, may occur. It is not known whether this is a stable or progressive disorder.<sup>11</sup> Seven to 10% of congenital toxoplasmosis infants will develop SNHL at age 4 or later. Treatment in the first year of life could prevent SNHL.<sup>12-14</sup> Sixty-eight percent of the congenital Rubella infected newborns had subclinical infection during the neonatal period. Seventy-one percent developed manifestations of infection at various times in the first 5 years of life. Deafness is the most common manifestation of congenital rubella, occurring in 80% of those infected. The deafness is usually peripheral (sensorineural) and is more commonly bilateral. Hearing impairment is often the only significant consequence of congenital rubella.<sup>2,3,7</sup> Cord serum can be assayed for the presence of rubella-specific IgM antibody. Detectable IgM antibody is a reliable indicator of congenital infection because IgM is fetally derived. Cerebrospinal fluid may also be examined for the presence of rubella-specific IgM. Virus isolation should be carried out in congenital rubella suspected clinically because viral excretion wanes during infancy.<sup>1,4</sup> Virus can be isolated from the eye and cerebrospinal fluid, or perilymphatic fluid, and can persist for over a year. A reverse transcription-nested polymerase chain reaction has been reported to offer a far more reliable and rapid tool. Acute toxoplasma infection was detected in 30% of pregnant women in Tehran.<sup>10</sup> Cytomegalovirus and toxoplasma were detected as 2 common infections in "TORCH suspected infants" aged less than one year.<sup>11</sup> The CMV infection developed in 2.6% of neonates. The CMV infection was the most common infection in SNHL cases.<sup>11-13</sup> Cytomegalovirus (34.6%) and toxoplasma (11.5%) were the most common active infections observed in

idiopathic SNHL cases in previous reports.<sup>15,16</sup> Mumps meningoencephalitis effects hearing loss. One-sided hearing loss due to mumps infection has been reported in many cases.<sup>17-19</sup> Previous studies in Tehran determined the SNHL prevalence rate as 3/1000 in children. Sensorineural hearing loss is an important complication seen in mumps infected patients.<sup>20,21</sup> The specific IgM antibody for mumps virus is present in more than 75% of mumps infected patients.<sup>17,18</sup> Rubella and mumps hearing loss are preventable with routine vaccination in children.<sup>22</sup> The mumps vaccine has 97% protective efficacy.<sup>22</sup> Mumps infection and its sequels are frequent findings in children where the mumps vaccine is not widely used.<sup>18-20</sup> Our objective was to evaluate the role of infectious agents (CMV, toxoplasma, rubella, herpes, mumps infections) in children with idiopathic SNHL.

**Methods.** This case/control study was carried out in the Ear, Nose, and Throat (ENT) Department of Rasul Hospital in Tehran, Iran between 2002 and 2003. This center is a tertiary care general hospital with 500 active beds and a cochlear implant center. Cases consisted of 95 children with SNHL and 63 children without SNHL (control healthy group). Audiologic screening (auditory brainstem response [ABR], evoked otoacoustic emissions [EOAE], and pure tone audiometry) appropriate for age, was used in all cases and controls. The diagnostic parameters for SNHL were based on the American Academy of Otolaryngology (AAO) criteria. During the study period (2002-2003), children who are suspected to have hearing loss were referred to our auditory department for diagnosis. All children who were diagnosed with idiopathic SNHL in our auditory department were included in this study. The exclusion criteria included all cases with "known" etiology for SNHL (genetic, radiation, drugs, metabolic, trauma, and so forth). The study was approved by the Ethical Committee in the ENT Department of Rasul Hospital. The control group consisted of children who were hospitalized for elective surgery on the general surgery ward (appendectomy and herniorrhaphy). These children were age-matched with the SNHL group. The control group was selected only if they had normal hearing. We used surplus blood drawn from controls, which was obtained during their routine blood tests before their scheduled surgery, for the serologic tests. Initially, a questionnaire was completed by an authorized physician for each case and control, followed by a complete clinical exam. A rather comprehensive audiologic evaluation, including pure tone audiometry (for older children), registration of EOAE, ABR, and tympanometric studies were performed for all cases and controls. Blood samples (2 ml) were centrifuged and transferred to our research laboratory. The serum was

stored in a -20°C temperature freezer until the serologic examination was performed. The centrifuged serum was screened using the ELISA assay for specific IgM and IgG antibodies.

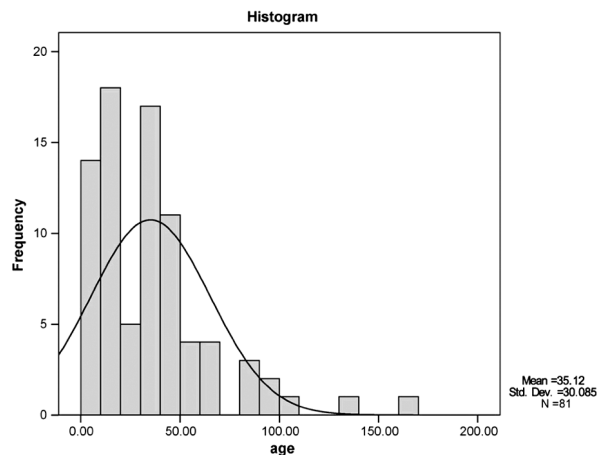
**Serological tests.** The evaluation of specific IgG and IgM antibodies was carried out with commercial kits (Biochem Immuno Systems, Bologna, Italy). Both kits were used and the results were calculated qualitatively. Results were interpreted by cutoff control as suggested by the manufacturer.

**Statistical analysis.** The Student's t test was used to determine significant differences in means for all continuous variables. Chi-square values (confidence interval [CI] 95%;  $p < 0.05$ ) were calculated for all categorical variables. A  $p < 0.05$  had significant value. All analyses were conducted using SPSS, version 13 and EPI, version 6 software.

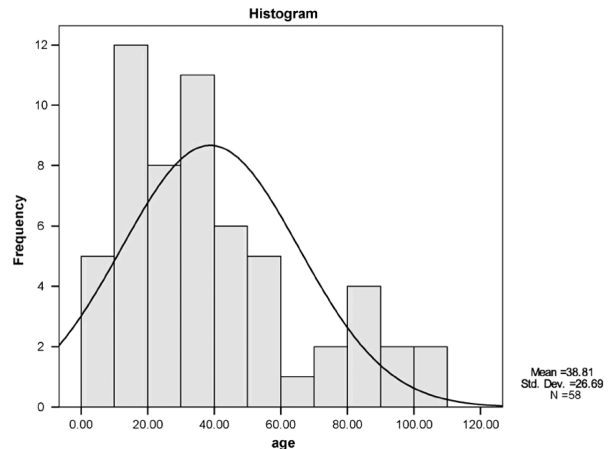
**Results. Demographic pattern.** The age range of the cases ( $n=81$ , missing=14) was 2-168 months, with a mean of  $35 \pm 30$  months (Figure 1). The age and gender distributions were as follows: 23.5% (19/81) were less than one year of age; 64% (52/81) between 1-5 years; 12.5% (10/81) were >5 years of age; 60% (59/94) of patients were males; and 40% (35/94) were females. The severity of SNHL according to American Academy of Otolaryngology (AAO) criteria of the cases included: 80% profound (cochlear implant candidates >95db); 15% moderate; and 5% mild. The proportion of patients with unilateral and bilateral SNHL was 22% (20/95) and 78% (75/95). In children with unilateral SNHL, the average air conduction threshold at 500, 1000, and 2000Hz in the better ear was 15.8 db. The type of progressive or stable type of SNHL was unknown (it was difficult to determine in these children). Other

contaminant abnormalities included: microcephaly and ocular involvement (cataracts and glaucoma) were seen in 3 patients less than one year of age. The age range of the control group ( $n=63$ , missing=9) was 2-106 months with a mean of  $38.7 \pm 27.3$  months (Figure 2). The age and gender distributions in the controls were as follows: 46% (25/54) were less than one year of age; 37% (21/54) were between 1-5 years of age; 17% (8/54) were >5 years of age; 61% (38/63) of the patients were males; and 39% (25/63) were females.

**Serologic results.** In SNHL cases, acute rubella infection (IgM) was detected in 5.3% and previous immunity (IgG) was detected in 7.2%. Acute infection had no significant differences ( $p=0.3$ ) between the cases and controls. Previous immunity was significantly higher in the control group (CI 95%;  $p=0.000$ ). The mean age of children with acute rubella infection in cases showed a significant difference (CI 95%;  $p=0.02$ ) between cases with and without acute infection (6.4 months versus 37.6 months). The mean age of children with previous rubella immunity infection in cases showed a significant difference (CI 95%;  $p=0.05$ ) between cases with and without acute infection (33 months versus 50 months). The most acute and previous rubella infection was seen in infants less than one year old. In SNHL cases, acute herpes simplex infection (IgM) was detected in 5.3% and previous immunity (IgG) was detected in 46.6%. Acute infection showed no significant differences ( $p=0.2$ ) between cases and controls. Previous immunity to herpes simplex was significantly higher (CI 95%,  $p=0.004$ ) in the control group. In SNHL cases, acute mumps infection (IgM) was detected in 8.7% and previous immunity (IgG) was detected in 23.3%. Acute and previous mumps infection did not show significant differences (CI 95%;  $p=1$ ,  $p=0.4$ ) between the cases and controls.



**Figure 1** - Age distribution (in months) in sensorineural hearing loss cases.



**Figure 2** - Age distribution (in months) in the control group.

**Discussion.** Cytomegalovirus (34.6%) and toxoplasma (11.5%) were the most common active infections observed in idiopathic SNHL cases.<sup>15,16</sup> We concluded that both the congenital and acquired form of CMV infection can induce progressive hearing loss in our cases. We preferred at least in our country to consider seropositive (CMV-IgM) SNHL children (less than one year old) as the congenital form and treated them with ganciclovir.<sup>15</sup> We recommended prevention of congenital toxoplasmosis by treatment of toxoplasma infection in pregnant women and treatment of acquired *Toxoplasma gondii* infection after birth to minimize the risk of SNHL in children.<sup>16</sup> Active rubella infection (IgM) showed no significant differences between the SNHL cases and normal children. Rubella infected children had a lower age (mean 6.5 months) in comparison with unaffected ones (37.6 months) [ $p < 0.02$ ]. The rubella infection in the SNHL cases was most likely of a congenital origin. Prior immunity was more frequent in the control group ( $p = 0.000$ ). Immune children had a higher age (mean age = 50 months) compare with non-immune children (mean age = 33 months,  $p = 0.02$ ). Transplacental immunity was seen in infants less than 6 months. Acquired rubella infection occurred postnatally (50 months) in studied children. Therefore, these transplacental antibodies (IgG) were protective in the control group. The rate of acute Rubella infection (IgM) in SNHL cases (5.3%) was mildly less than its rate reported in TORCH suspected cases in Tehran (8%).<sup>11</sup> Previous immunity to rubella (IgG) was detected in 80% of TORCH suspected infants versus 17% in the SNHL cases. These differences are due to lower age and transplacental immunity in TORCH cases. The TORCH cases had a mean age of 4.7 months, compared with 37 months in SNHL cases.<sup>11</sup> Deafness is the most common (80%) manifestation of congenital rubella syndrome, but it has been underestimated because many cases had been missed in infancy and early childhood. Universal immunization of children, with a single dose of vaccine given after the first birthday, and selective immunization of postpubertal and susceptible postpartum women will control rubella and congenital rubella in the future.<sup>22</sup> Acute and previous mumps infection showed no significant differences between SNHL cases and the normal group. Nine percent of SNHL cases had active (IgM) mumps infection. These results are very close to previous studies in Tehran.<sup>20,21</sup> Sensorineural hearing loss developed in 7% ( $n = 94$ ) of mumps infected children (mean age; 4.8 years). The incidence rate for SNHL occurrence (7%) reported (in Tehran) was higher than its incidence in other studies (4.4%).<sup>21</sup> Acute herpes infection (IgM) was seen in 5.3%, and previous immunity (IgG) in 46.6%. Previous immunity to Herpes was protective in the control group

( $p = 0.004$ ). The rate of acute herpes infection (IgM) in SNHL cases (5.3%) is near to the TORCH study (6.7%).<sup>11</sup> Previous immunity to herpes virus (IgG) was detected in 53.3% of TORCH suspected infants in comparison with 46.6% in the SNHL cases. These differences are due to lower age and transplacental immunity in TORCH cases.<sup>11</sup> The incidence rate of deafness due to herpes simplex infection (congenital or acquired); prognosis and treatment in infancy and early childhood are unknown.

**Strengths of the study.** Probably, not only congenital but also the acquired form of many preventable and treatable infectious agents (CMV, toxoplasma, rubella, herpes, mumps) can induce SNHL in children.

**Limitations of the study.** For CMV and toxoplasma infection in studied children, we are not able to differentiate the congenital from acquired infection only by seropositive (IgM) results in SNHL children after the first year of life. The search for etiologic infections in SNHL cases by using a more sensitive method, such as PCR in perilymphatic fluids may elucidate the possible role of infectious agents in the future.

In conclusion, the data presented here is compatible with infectious agents having a significant role in the studied idiopathic SNHL cases, but association does not prove causation. We recommend specific drugs for confirmed active infections (CMV, toxoplasma, herpes) in idiopathic SNHL infants diagnosed before their first birthday. Mumps and rubella induced SNHL are preventable with universal vaccination.

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