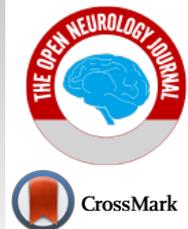


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RESEARCH ARTICLE

Cytomegalovirus and Toxoplasma Gondii: Common Causes of Profound Sensori Neural Hearing Loss in Children with Cochlear Implant Surgery in a Highly Immune Population: Tehran; Iran

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Abstract:

Background:

Iranian population is highly immune from *T.Gondii* and CMV infection.

Objective:

To determine the immunity to *T.Gondii* and CMV in children with the cochlear implant surgery accompanied with the profound Idiopathic type of SNHL

Methods and Materials:

We studied 45 cases with the cochlear implant surgery (Idiopathic profound SNHL) and 30 controls with the normal OAEs in a cross-sectional study in Rasoul Akram Hospital in Tehran (2010 -2012). Blood samples (2 ml) were centrifuged and were kept frozen at -20°C. Sera searched for the specific antibodies against CMV and *T.Gondii*. The enzyme-linked immunosorbent assay (ELISA; BioChem Immune System) was calculated qualitatively. (*P* value< 0.05)

Results:

Range of age in cases with profound SNHL (<95 dB) was 6 months- to-14 years; mean=3.4+3.16 y; Idiopathic type of SNHL children diagnosed in 45 cases were younger than cases with non-Idiopathic SNHL (mean age=20 months; *PV*=0.05). Positive *T.Gondii* - IgM was found in 8 /45 (17.7%) and also one of these cases (2.2%) had positive *T.Gondii* -IgG test. Positive CMV- IgM & IgG were determined in 23% and 51% of cases, respectively. Positive *T.Gondii* -IgG was observed in 60% (18/30) of controls but none of them had positive *T.Gondii* - IgM. Positive CMV- IgM & IgG in controls was 3.3% and 90%, respectively.

Conclusion:

CMV infection is one of the most common infections found in profound idiopathic SNHL children especially in younger cases (< 2 years) even in highly immune Iranian populations. Probably, *T.Gondii* infection has a relative role in younger cases with profound SNHL but a higher role in mild to moderate SNHL in our pediatric population. Most of the *T.Gondii* infected SNHL cases never require cochlear implant surgery.

In future, a cohort study for prenatal diagnosis of the intrauterine infection and the role of infection in producing SNHL would be very helpful. It has been recommended to search the specific antibodies against these two common infections in all types of SNHL in pediatric groups which are treatable especially in younger cases (<2 year).

Keywords: Sensory Neural Hearing Loss (SNHL), Cochlear implant, CMV (Cytomegalovirus), *T.Gondii* (Toxoplasma Gondii), ELISA (Enzyme-Linked, Immunosorbent Assay), Idiopathic.

Article History

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1. INTRODUCTION

Sensor Neural Hearing Loss (SNHL) is a type of hearing loss in which the root cause lies in the vestibulocochlear nerve

(cranial nerve VIII), the inner ear or the central processing centres of the brain [1]. The ethology of SNHL is unknown in near about 40% of children which may be viral in origin [1]. Idiopathic (unexplained) hearing loss may be the result of an infectious disease or an injury [1]. Cytomegalovirus is the most common cause of congenital infection, 40% of the unknown cause of deafness cases are due to congenital CMV [2].

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Gancyclovir treatment is recommended for diminishing the SNHL-induced congenital CMV [3, 4]. Asymptomatic infected neonates might have SNHL, vision loss and mental retardation and development delay [3, 4].

Many studies proved the significant role for the congenital CMV in children with SNHL [2 - 4]. Yamamoto *et al.*, confirmed the prominent role for the congenital CMV in children with SNHL even in a country with high immunity to CMV. They determined the rate, risk factors, and predictors of SNHL in CMV-infected neonates identified by newborn screening in a highly immune maternal population [4].

First Siadati *et al.*, reported the CMV infection in primiparous pregnant women in Tehran [5]. Sotoodeh *et al.*, described the CMV in South of Iran [6]. Bagheri *et al.*, study showed the seroprevalence of CMV infection (IgG and IgM) among 240 pregnant women in East of Iran [7] CMV was reported to be the common cause of intrauterine infection in Iran [8, 9]. Congenital CMV infection was developed in 2.6% of neonates in Tehran [9]. CMV infection was reported as one of the most common infectious agents in SNHL children [10 - 12]

Congenital toxoplasmosis is a mild or severe neonatal disease during the first months of life, or with sequels or relapse of a previously undiagnosed infection at any time during infancy or later in life [13, 14]. 10-17% of infants with congenital toxoplasmosis developed SNHL at the age of 4 months or later [14, 15]. Treatment of Active *T.Gondii* infection in pregnant women can prevent congenital toxoplasmosis from occurring in infants [16 - 20].

Screening for intrauterine infections during pregnancy or in neonates is not available in Iran [21 - 23]. The prevalence of antibodies to *T.Gondii* ranges from 24% to 57.7% in Iran [19, 20]. Acute *T-Gondii* was reported in 9.8% of TORCH suspected infants (< 2 y old) which had no significant difference with controls but in contrast, the previous immunity was higher in the control group [21].

All the above studies determined that the adult Iranian population is highly immune to CMV infection. The burden of congenital CMV associated Sensor Neural Hearing Loss (SNHL) in populations with 100% CMV seroprevalence is unknown [5].

Previous immunity from *T.Gondii* in adult Iranian population is varied between 24%- 57.7% [19, 20] which causes congenital infection in about 10% of all intrauterine infection in our country. (21) CMV and *T.Gondii* infection may play a major role in children with congenital or acquired forms of SNHL in our country [10 - 12, 24, 25].

The main goal of study was to determine the immunity to *T.Gondii* and CMV in children with cochlear implant surgery (Idiopathic SNHL; < 95 db) in comparison with normal children.

2. METHODS & MATERIALS

We studied that 117 children were diagnosed as profound SNHL; < 95 dB (according to AAO; American Academy of Otolaryngology) criteria in cochlear implant center at Rasoul

Akram Hospital Tehran in the duration of 2 years (2015 – 2017). This cross-sectional study was approved by the Ethical Committee in Research Center of Pediatric Infectious Diseases affiliated with Iran University of Medical Sciences. The consent letter was obtained from all persons (or parents).

2.1. Data Collection

All children with profound SNHL were referred to the selected cochlear implant surgery department. From 117 cases who were the candidates for cochlear implant surgery, 58.1% were male and 49.1% were female. The range of age was: 6 months to 14 years; mean age = 3.4 ± 3.16. The Non-idiopathic type of SNHL (Infection, familial, kernicterus, hypoxia, prematurity, convulsion, mental retardation, malformation *etc.*) was diagnosed in 39.5% of cases; Idiopathic type of SNHL was determined in 28.8% (47/117) of cases. Children with idiopathic type were younger than those in the cases with non-Idiopathic (mean age = 20 months; $PV=0.05$). The controls (n = 30) had normal OAEs in screening test at birth, and were healthy in pediatrician visit before elective surgeries. The controls (n = 30) aged between 2-106 months, mean age = 38.7 - 27.3 months.

2.2. Lab Test

We used the extra blood of routine tests in cases and controls. Sera was kept frozen in our research laboratory. In frozen sera, specific antibodies (IgG, IgM) against CMV, *T. Gondii* were determined by Enzyme-linked immunosorbent assay (Bio Chem Immune Systems). Antibodies were calculated qualitatively by cut-off controls according to the manufacturer's instructions

2.3. Statistical Analysis

SPSS version 13 was used. All continuous variables evaluated by Student t-test. Chi-square values (CI: 95%; $P < 0.05$) were calculated. P value < 0.05 was significant.

3. RESULTS

Positive *T.Gondii* - IgM was found in 60% (18/30) of cases and none of the controls (0/30). Positive *T.Gondii* -IgG was detected in 2.2% (1/45) of cases and 60% (18/30) of controls. Comparison of the serologic results between cases and controls is showed in Table 1. The correlation between age and serologic results in cases showed in Table 2

4. DISCUSSION

Here, we studied 45 children with implant surgery due to the Idiopathic type of SNHL. Cases with the Idiopathic SNHL include younger children than non-Idiopathic type (mean age = 20 months). We observed recent CMV infection (positive IgM) in 23% of cases (*vs* 3.3% controls); and previous immunity (positive IgG) in 51% of cases (*vs* 90% controls).

Present findings are very close to other studies upon SNHL children (and normal controls) in our center (11, 25); positive CMV-IgM & IgG was observed in 23% of cases *vs* 34.7% of controls; and 51% of cases *vs* 72.6% controls, respectively. Recent CMV infection was higher in the SNHL cases (P -value = 0.000) but previously, there was higher immunity (CMV-

Table 1. Comparison the serologic results between cases and controls.

	Age (Mean±SD)	Positive Toxo- IgM	Positive Toxo- IgG
Cases	20±3.47months	17% (8/45)	2.2% (1/45)
Normal Controls	38.73±27.3 months.	none (0/30)	60% (18/30)
	Age (Mean±SD)	Positive CMV- IgM	Positive CMV- IgG
Cases	20±30.47 months	23% (11/45)	51% (23/45)
Normal Controls	38.73±27.3 months.	3.3% (1/30)	%90% (27/30)

P value<0.05 considered significant

Table 2. Correlation of age and serologic results in cases.

Serologic results	Mean age	Value
Positive –Toxo IgM	4.7 months	0.5
Negative –Toxo IgM	5.8 months	--
Positive –Toxo IgG	5.7 months	0.9
Negative –Toxo IgG	5.8 months	--

IgG) in controls (P value = 0.001). Mean age of cases with recent infection (positive IgM) was 40 months; and 35 months for cases with previous immunity (positive IgG) probably due to the transplacental immunity which waned after 4 months [11]. These results differ from the previous (2006-2008) serological study in 11 idiopathic type of SNHL (mean age; 32 +28 months) [12] and positive CMV- IgG in 100% of cases (previous immunity), none had recent infection (positive, IgM) [12]

Yamamoto *et al.*, described newborns with positive saliva CMV-DNA in the first 2 weeks of life, a prospective follow-up study was conducted to monitor hearing outcome [5]. Out of 12,195 infants screened, 1% were infected with CMV while 10% had a symptomatic infection at birth. SNHL was observed in 9.8% in 12 months age.

Profound SNHL (>90 dB) was observed in 4/5 children with bilateral SNHL while all 5 children with unilateral SNHL had moderate to severe loss [5]. Symptomatic CMV infection is not related to intrauterine growth retardation, gestational age, gravidity, and maternal age [5].

Some Iranian authors reported the seroprevalence of CMV infection in Iranian pregnant women [5 - 7]. Bagheri *et al.*, described the seroprevalence of CMV (IgG and IgM) among 240 pregnant women in Eastern part. The IgG avidity test was used for all patients who were CMV-IgM⁺ and CMV-IgG⁺ to distinguish between primary and recurrent CMV infection [7]. All CMV- IgM⁺ were monitored until labor. The CMV seroprevalence rate was 72.1%, 69.6% had a previous CMV infection, 27.9% had never been infected with CMV, 2.5% were CMV-IgM⁺, 1.66% had recurrent CMV infection (IgM⁺ and high IgG avidity) and 0.84% had primary CMV infection (IgM⁺ and low IgG avidity) [7]. Indeed, CMV was reported to be the common cause of intrauterine infection in Iran [8, 9]. Congenital CMV infection was developed in 2.6% of neonates [9]

Here, as detailed above, the rate of recent *T.Gondii* infection (IgM) was higher in the cases (17.7% vs. 0% con-

rols); but in previous cases, the immunity (IgG) was very low (2.2% vs. 60% controls). The previous immunity in the controls (probably Trans placental origin) might prevent the neonates against *T.Gondii* intrauterine infection. The present study is very close to other reports in our country [22 - 24]. At least 2 studies confirm these results [22, 24].

The study to search the congenital toxoplasmosis in 51 cases (mean age = 4.7 months + 3.7 month), and 30 controls in our center had been published recently [22]. It showed recent *T.Gondii* infection (IgM) in 10% of cases but none of the controls; previous immunity (IgG) was found in 18% cases and 60% of controls [22]. Like here, previous immunity (IgG) was significantly higher in the control healthy group (P value =0.00) [22]. Similar results were presented in our previous studies. None of the controls were detected in the recent *T.Gondii* infection (IgM) in comparison with 12% of SNHL cases (P value =0.00). Previous immunity (IgG) against *T.Gondii* infection was significantly higher in the control healthy group (48% vs. 21%; P value < 0.001) [24, 25].

All results confirmed the relative role for *T.Gondii* in studied cases.(19,24) The rate of seropositivity in severe SNHL which is 4 fold lower than the previous study (63.6%) had applied upon all type of SNHL in our center. 2.2% of cases with severe SNHL had recent *T.Gondii* infection (vs. 10% previous study) [24]. It means that *T.Gondii* infection might have a higher role in mild to moderate SNHL in our pediatric population. Most of the infected SNHL cases never require cochlear implant surgery.

The prevalence of *T.Gondii* antibodies ranges from 24% to 57.7% in Iranian population [19, 20]. One study determined the previous and acute *T.Gondii* infection in 34.7% and 7.1% of young pregnant women in Tehran [19]. Recent infection observed in 9.8% of TORCH suspected infants (<2y old) in Tehran; but previous immunity(positive IgG) was higher in normal children [8]. So, the congenital toxoplasmosis can be prevented by the treatment of Active *T.Gondii* infection in pregnant women [13 - 15]. Treatment of congenital toxo-

plasmosis in the first year of life could prevent this late sequel [16 - 20]. In our opinion, the neonatal screening test (Guthrie cards) might be helpful to detect at least 2 common treatable infections (; CMV / *T.Gondii*) in our country.

We observed recent CMV infection (positive IgM) in 23% of cases (*vs* 3.3% controls); and previous immunity (positive IgG) in 51% of cases (*vs*. 90% controls).

So, we recommend rapid diagnosis and suitable treatment of the indolent infections in SNHL children to decrease the requirement of cochlear implantation surgery.

At least 1-year treatment is required in infants (positive IgM) for the prevention of its sequels [10, 13]

CONCLUSION

CMV infection is one of the most common infection found in profound idiopathic SNHL children especially in younger cases (< 2 years) even in highly immune Iranian populations. Probably *T.Gondii* infection has a relative role in younger cases with profound SNHL but a higher role in mild to mode-rate SNHL in our pediatric population. Most of the *T.Gondii* infected SNHL cases never require cochlear implant surgery.

In the future, a cohort study for prenatal diagnosis of intrauterine infection and the role of infection in producing SNHL would be very helpful. We recommend to search the specific antibodies against these two common infections in all type of SNHL in pediatric groups, which are treatable especially in younger cases (< 2 year).

LIMITATIONS OF THE STUDY

This study followed the known cases of SNHL for intrauterine infection after birth. This time of diagnosis is late for specific treatment. In contrast to the developed countries, the prenatal /perinatal screening for intrauterine infection is not available in Iran. We should diagnose the indolent (intrauterine) infections in SNHL children and treatment should be started as soon as possible to decrease the need of the cochlear implantation surgery

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical Committee in the Pediatric Infectious Diseases (affiliates by Iran University of Medical Sciences) has reviewed and approved the Waiver of Authorization for use of protected health information (PHI) for research purposes for this study.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all individual parents of the participants.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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