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Original Article

Sero-Prevalence of Antibodies against Varicella Zoster Virus in Children under Seven-Years Old in 2012 in Tehran, Iran

Yasaman VOJGANI [1,2], Saeed ZAREI [1], Samira RAJAEI [3], Leili CHAMANI-TABRIZ [4], Fatemeh GHAEMIMANESH [1], Nematallah MOHAMMADINIA [5], *Mahmood JEDDI-TEHRANI [1]

1. *Monoclonal Antibody Research Center, Avicenna Research Institute, ACECR, Tehran, Iran*
2. *Islamic, Azad University, Science and Research Branch, Arak, Iran*
3. *Lab Sciences Department, School of Allied Medicine, Tehran University of Medical Sciences (TUMS), Tehran, Iran*
4. *Reproductive Biotechnology Research Center, Avicenna Research Institute, ACECR*
5. *East Health Center, Shahid Beheshti University of Medical Science, Tehran, Iran*

***Corresponding Author:** Tel: +982122432020, Email: mahjed@yahoo.com

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Abstract

Background: Varicella zoster virus (VZV) is a member of herpes family viruses, which causes varicella (chickenpox) after primary infection and herpes zoster (shingles) because of latent virus reactivation from dorsal root ganglia. Generally, prevalence of varicella antibodies increases with age. We aimed to compare the prevalence of anti-VZV antibody in children under seven years old, in order to obtain a preliminarily picture of general presence of these antibodies to design an immunization plan.

Methods: In this cross-sectional study, performed from September 2011 to September 2012 in Tehran , Iran, 267 serum samples including sera from 7 month old infants, n= 87; 18 month old children**,** n= 86; and 6 year old children, n= 94 were assessed for the presence of specific IgG antibodies against VZV, using ELISA technique.

Results: 4.6% of 7 month, 12.8% of 18 month and 21.3% of 6-year-old children were seropositive. No relation was found between demographic variables (e.g. age and birth weight) and seropositivity in these age groups. VZV antibodies increased with age. Serum levels of varicella antibodies were elevated in 18 months old compared to 7 months old children**,** significantly ($P < 0.001$).

Conclusion: In view of the significant elevation of VZV antibodies in children from 7 months to 18 months of age and rate of seronegative children, our results support the necessity of varicella immunization between 7 and 18 months of age in order to prevent viral infection.

Keywords: Antibody, Children, Prevalence, Varicella-zoster virus

Introduction

Primary infection with varicella zoster virus (VZV) which is a mild to moderate self-limited disease causes varicella (chickenpox) in children (1). Because of the waning VZV specific cell mediate immunity, virus reactivation in relation to suppressed immune conditions or elder people, could induce herpes zoster (2, 3). Varicella zoster is accompanied by serious complications such as post-herpetic neuralgia, viral pneumonia and encephalitis (4, 5). Herpes zoster frequency and its most common complications are likely to increase with age (6). The virus is usually transmitted 1-2 days before appearance of rashes via respiratory droplets, vesicle fluid, direct contact or aerosol

exposure to the vesicular lesions of a patient with varicella. Also, in hospital setting, airborne transmission has been described (7, 8).

Following VZV exposure (primary infection or vaccination), VZV antibodies appear in serum. Different studies have confirmed the increasing trend in VZV seroprevalence parallel to aging (9, 10). One survey that was conducted before VZV mass vaccination during 1988-1994, demonstrated a high VZV seroprevalence ranging from 86% in 6-11 years old children to 99% in ≥30 years old individuals(6). Another study reported that 49% of 2 years old and 93% of 5 years old children were VZV seropositive before VZV vaccination (11). VZV seroprevalence is diverse in different studies depending on race, gender, country and number of siblings in a household (6, 12, 13).

A highly efficient strategy to eliminate VZV-infection and its related complications is the routine varicella vaccination (14). Since 1974 a live-attenuated varicella vaccine has been proven safe and effective and universal childhood immunization has been implemented in several countries(15). It is well documented universal vaccination of children would increase the prevalence of VZV protective antibodies in the population (16, 17). A number of studies on the prevalence of antibodies against this virus have been conducted in different countries (18-20). In France, general vaccination against varicella zoster indicated at least 80% efficacy in reduction of VZV infection (21). Besides, a survey in Brazil in 2006 reported that varicella immunization developed 70-90% protection against any form of varicella zoster infection (22). Although varicella immunization schedule has been well established in health care systems of many countries (23, 24), immunization against this virus, has not been included in official vaccination program in Iran.

The present study aimed to compare the prevalence of anti-VZV antibody in three groups of children under 7 years old in Tehran, Iran, in order to obtain an informative picture of general presence of these antibodies for designing a comprehensive immunization plan.

Material and Methods

Study population

This cross-sectional study was conducted between October 2011 and July 2012 at Avicenna Research Institute, Tehran, Iran. The study population included 7 months, 18 months and 6-year-old healthy children who attended to health care centers for routine vaccinations. These health care centers provide general vaccination services to children and adults with different socio-demographic status representative of an ordinary population. Written informed consents were obtained from the parents of children after declaring the process of the study. The parents completed the questionnaires containing general information such as age, birth weight, and previous history of VZV infections in children.

The subjects were categorized in three age groups consisting of 7 month, 18 month and 6-year-old children. It is important to note that the 7 months old children were bled again at the age of 18 months; Thus, the corresponding 7 and 18 months old children blood samples were taken from the same individuals.

An approval for the study was obtained from the local Ethical Committee.

Serological assessments

Two and a half milliliters of venous blood sample were taken from each person. Serum samples were separated and stored at -20 ºC until used.

Serological tests were conducted by ELISA kit (Euroimmune anti-varicella-zoster virus IgG ELISA medizinische labor diagnostka AG, Lubeck, Germany). Serum antibody levels were defined according to the manufacturer`s instructions as follows: <80 IU/L: Negative, 80-110 IU/L: Borderline and >110 IU/L: positive. The test was defined to have a specificity of 100% and a sensitivity of 100%, according to the manufactures instructions.

Statistical analyses

Statistical analyses were performed using statistical package for the social sciences SPSS version 13.0

(SPSS Inc, Chicago, IL, USA). The prevalence rates of VZV antibodies were calculated for the different age groups. Differences in antibody titers for the different age groups were assessed using chi-square, independent t-test and Paired T-test. Gender and age were included in the multi-variant logistic regression analyses. *P*-values < 0.05 were considered statistically significant.

Results

Participants' characteristics

In this study totally 86 boys and 95 girls were included. 267 serum samples were collected from September 2011 to September 2012. From these specimens, 87 were taken from 7 month old infants, 86 of whom come back again for sampling at the age of 18 months and 94 serum samples belonged to 6 year old children. According to the filled questionnaires, none of the parents reported past history of VZV infection in their children. Mean birth weights and visited-day weights of subjects in different age groups were 3.2 ± 0.3 kg, and 5.0 ± 0.9 kg (7 months), 3.2 ± 0.3 kg and 11.0 ± 1.1 kg (18 months) and 3.2 ± 0.4 kg and 20.3 ± 2.7 kg (6 years), respectively. No significant difference was found between birth weights and visited-day weights with gender ($P > 0.05$) (Table1).

Table 1: Birth weights and visited- day weights in different age groups of Iranian children

Age	Gender	Birth weight Mean± SD (kg)	Visited- day weight Mean± SD (kg)	*P*-valued* (birth weight)	*P*-value * (visited-day weight)
7 months	Male (n=39)	3.03 ± 0.4	4.9 ± 0.7	0.158	0.592
	Female (n=48)	3.1 ± 0.3	4.8 ± 0.6		
18 months	Male (n=38)	3.3 ± 0.4	11.1 ± 0.7	0.158	0.638
	Female (n=48)	3.1 ± 0.3	11.0 ± 1.2		
6 years	Male (n=47)	3.3 ± 0.3	20.3 ± 2.0	0.746	0.576
	Female (n=47)	3.2± 0.4	20.7 ± 2.3		

*Evaluated by independent t- test

Seroprevalence of anti-VZV in the study population

The Mean antibody concentrations against VZV were 183 ± 781 IU/L, 327 ± 878 IU/L and 425 ± 107 IU/L in 7 months, 18 months and 6 years old subjects, respectively. The seropositive rates were 4.6%, 12.8% and 21.3% for 7 month, 18 month and 6-year-old individuals, respectively. Table 2 shows antibody titers against VZV and seropositive rates of subjects in each age group and their distribution according to the gender. Our findings showed no significant difference in anti-VZV antibody concentrations and seropositive rates related to gender in each of age groups ($P > 0.05$) (Table2). This study also demonstrated the increasing trend of prevalence of seropositivity (Fig. 1).

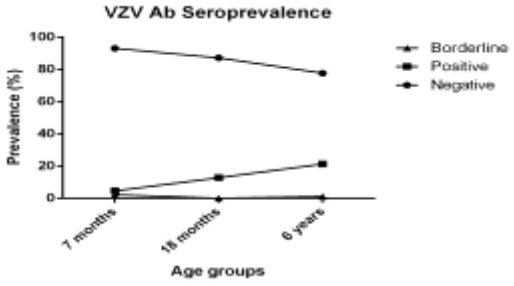

Fig. 1: VZV antibody prevalence was shown in three age groups. Positive seroprevalence rates were increased along with age increasing (difference was not statistically significant)

Comparison of antibody titers against VZV in 6 year old children with that in 7 months age (*P*=0.086) and 18 months age (*P*=0.506) groups showed no significant differences, but the rates of seropositive subjects were significantly higher in 6 year old children compared to 7 months old infants (*P* = 0.001, chi-square). Anti-VZV antibody titers increased significantly by age when they were measured in the same individuals at 7 months and 18 months of age (*P*< 0.001, Paired *t*-test). Multiple linear regression did not show any significant correlation between demographic characters (gender, birth weight, visited-day weight) and anti-VZV antibody titers in different age groups (Table 3).

Table 2: Mean antibody titers against VZV and seropositive rates in different age groups of Iranian children

Age	Gender	No. of subjects	Anti-VZV (IU/L) Mean ± SD	Seropositive > 110 IU/L n (confidence interval of 95% for prevalence)	*P*- value* (Anti- VZV relative to gender)	*P*- Value** (seropositive relative to gender)
7 months	Male	39	125 ± 678	1(-0.03-0.8)	0.540	0.390
	Female	48	229 ± 860	3 (-0.01-0.13)		
	All	87	183±781	4(0.0-0.09)		
18 months	Male	38	380 ± 933	6 (0.04-0.28)	0.623	0.337
	Female	48	286 ± 840	5 (0.01-0.19)		
	All	86	327±878	11(0.06-0.20)		
6 years	Male	47	430 ± 1109	10 (0.09-0.33)	0.969	0.599
	Female	47	421 ± 1047	10 (0.09-0.33)		
	All	94	425±107	20(0.13-0.30)		

*Evaluated by independent *t*- test/** Evaluated by Chi-squre

Table 3: Multiple linear regressions between demographic characters (gender, birth weight, visited- day weight) and anti-VZV antibody titers in different age groups of Iranian children. Values show *P*-values of multiple linear regression

Age	variables	B	Beta	p-value
7 months	Gender	-120.898	-.126	.281
	Birth weigh	.047	.033	.790
	Visited-day weight	-.042	-.079	.532
18 months	Gender	60.962	.035	.768
	Birth weigh	.244	.096	.423
	Visited-day weight	.060	.079	.512
6 years	Gender	92.612	.039	.748
	Birth weigh	.065	.022	.858
	Visited-day weight	.111	.252	0.051

Discussion

This study was conducted to generate data on the epidemiology of VZV infection in a limited population of Iranian children with the aim to establish a preliminary report as a basis for larger studies for health system improvement in varicella vaccination strategies.

Protection against VZV in neonates is dependent on maternal immunity until they are 6 months old when the production of antibody by their own immune systems begins (19, 25). Since we did not have access to confirmed history of immunity in mothers, we selected 7 months old infants to determine their seroprevalence of anti-VZV antibodies. Our results regarding similar anti-VZV prevalence rates in different genders are confirmed by previous reports (10, 26-28). The age group specific prevalence in our survey suggests that the seropositivity of antibodies against VZV increases with age. The prevalence of VZV antibodies were 7.1% , 5.6% and 18.2% in 9 , 15 and

24 months old subjects, respectively(10). Also, 16% of 1 year old children and 25.1% of children between 2-3 years old were seropositive in a cross-sectional study in Cyprus(9). In Thailand, seropositivity rate increased from 15.5% in children (between 9 months and 4 years old), to 75.9% in adults (20-29 years old) (29). Thiry et al. reported 29-35% seropositivity in 1-year-old, 80.19% in 5 year old and 84.78% in 6-year-old individuals in Flanders (30). Similarly, in Italy, seroprevalences of varicella were reported to be 32.9%, 67% and 84% in the age classes: 2-4, 5-9 and 10-14 years, respectively (31). It could be noticeably deduced that the increasing trend in prevalence of anti-VZV antibodies with age is evident (27), however the prevalence rates may be different from our results (32, 33). The elevated levels of prevalence in these countries may be related to increased exposure to virus after natural infection, since all these studies were conducted before their vaccination plans started.

The elevation in VZV antibody titers following vaccination causes diminishing impact on incidence of chickenpox and zoster infection. Findings of a survey demonstrated varicella vaccination could induce 34.7% decrease in the incidence of varicella among 0-14 year old children and 51% reduction in the number of complications associated to varicella (3, 34). In addition, another study reported of 55% reduction in varicella cases in the studied population that included 63% and 38% reduction in 0-4 and 5-9 years old children, respectively (35). Similar results were also reported in other studies (36, 37). Besides, in France, seropositivity was reported in 15% of 1-2 year and 89% of 7-8 year old children (20). In a similar trend, in Malaysia 25.6% of 1-5, 47.2% of 6-10 and 50.8% of 11-15 old children were reported as seropositive (38). This increasing pattern was also observed in India, Canada and other countries (18, 31, 39-42). The unique characteristic of our study has been the provision of an opportunity to investigate the association between antibody titers within a person at different ages that revealed a significant increase by age. Protective role of maternal antibody against VZV is durable up to 6 months (19). With the advent of VZV vaccine, the incidence of VZV infection in children and adults has decreased and the breakthroughs are minimizing. This vaccine is not routinely used in Iran, however this important subject was considered from 1988 to 1995 in Japan, Turky and The United States. In The USA, the combination of MMR and Varicella Zoster Vaccine (MMRV) was allowed for children between 12 months and 12 years of age in 2005(42, 43).

According to our results, we suggest usage of MMRV vaccine to be administered in children.

Conclusion

Our findings that, significant elevation of VZV antibodies occur from 7 to 18 months of age and rate of seronegative children support the necessity of varicella immunization at this age range in order to prevent virus infection. Since serious complications and long-lasting sequels have been reported after VZV infection, it may be recommended that VZV vaccination be integrated in the Iran national vaccination program. In this regard, larger and more comprehensive studies need to be conducted to warrant information required for decision-making.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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