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Anti-rubella, Mumps and Measles IgG Antibodies in Medical Students of Tehran University

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ABSTRACT

Measles, mumps and rubella are viral infectious diseases that may result in serious complications. Since the production of vaccines, the number of cases of these diseases has been dropped. Nevertheless, these infectious diseases are still one of the major health problems in developing countries.

In this study, in order to evaluate the protective responses against measles, mumps and rubella, the level and avidity of virus-specific IgG antibodies were measured in 53 medical students of Tehran University, aged between 20-30 years. Except for mumps vaccine, all the students had been vaccinated against measles and rubella according to Iran's nationwide mass vaccination protocol for all persons aged 5–25 in 2003. Our results showed that 96.2% of the volunteers had a protective level (>15 IU/ml) of IgG against rubella, 79.2% had a protective level (>11 IU/ml) of IgG against measles and 64.16% had a protective level (>11 IU/ml) of IgG against mumps.

Over ten years after nationwide measles-rubella vaccination campaign, most young adults aged 20-30 had protective levels of humoral immunity against measles and rubella. However, Iranian young population is still unvaccinated against mumps, and therefore relatively large number of young adults had no protective level of IgG against it.

This finding may be due to reduction in circulating of wild strain. We recommend screening of medical students for immunity against infectious agents such as measles, mumps, rubella, because they are at a high risk of these infectious agents.

Keywords: Measles; Mumps; Rubella

INTRODUCTION

Measles, mumps and rubella are contagious viral diseases that may result in serious complications or death. In 2012, due to measles infection, 122,000 deaths were recorded worldwide. Mumps is a causative agent of deafness in childhood and also is associated with aseptic meningitis and encephalitis. Rubella infection, especially during the first trimester of pregnancy, can cause congenital rubella syndrome

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(CRS) associated with serious abnormalities. Measles, mumps and rubella vaccination have remarkably reduced the incidence of these diseases in the world.[1-6]

Despite the availability of safe and effective vaccines; measles, mumps and rubella are still one of the major concerns of health in developing countries[7-11] and associated outbreaks continue to occur worldwide.

In Iran, two doses of measles vaccine were assigned in Expanded Program on Immunization (EPI) schedule in 1988.[12] Despite the high vaccination coverage, the incidence of the disease increased in older individuals during 1996–2002.[12] In order to eliminate measles from the East Mediterranean Region (EMR) including Iran by 2011[13] and to control measles incidence in older individuals, the Ministry of Health and Medical Education performed a nationwide mass vaccination campaign in 2003. All persons aged 5–25 years received one dose of measles-rubella (MR) vaccine.[12] After the campaign, two doses of measles, mumps, and rubella (MMR) vaccines were incorporated to Iran's EPI program, the first dose at 12 months of age and the second dose at 18 months of age.[14]

Specific antibody titers have been conventionally used to assess protective immunity to measles, mumps, and rubella viruses.[15,16] In addition, the avidity of IgG has been used for evaluation of immunization success, distinguishing primary from secondary immune responses and to study the immunity status.[17,18] In primary responses, B cells produce IgM more than IgG antibody with low avidity whereas in secondary immune response, memory B cells produce the higher level IgG antibody with higher avidity.[19] After a reinfection with a wild or attenuated live virus an increased level of high avidity IgG is usually detected. Thus, measurement of avidity for IgG antibodies could be used to evaluate the memory immune response and vaccination efficacy[12]. After nearly ten years of the MR mass vaccination campaign, significant variations of humoral immunity against measles and rubella in adults who were vaccinated in the nationwide campaign are unclear. We also know that mumps is endemic in Iran and immunity against mumps in adults was resulted from experiencing the natural infection. Therefore, avidity of anti–mumps IgG was estimated to distinguish mumps reinfection cases with high-avidity IgG antibodies from primary infections with low-avidity response. Moreover, avidity of anti-measles and anti-rubella IgG antibodies were evaluated to recognize secondary vaccine failure with low-avidity response. The findings of present study may help to manage future strategies for screening of immunity level against measles, mumps and rubella and appropriate vaccination for all young adults.

MATERIALS AND METHODS

Study Population

Fifty three volunteers of medical students from Tehran University, aged 20–30 years old (29 male and 24 female) were included in this study. 36 Participants (20–27 years old) were born after the introduction of two doses of live attenuated measles vaccine in Iran's expanded program on immunization (EPI) in 1988.[12]

All volunteers had a history of MR vaccination (measles, rubella) during nationwide mass vaccination camping in 2003. Therefore every person had received one dose of rubella vaccine and according to her/him age 2 or 3 doses measles vaccine.

None of volunteers had been vaccinated against mumps virus because MMR vaccine has enrolled in routine childhood immunization program since 2003.

We divided the participants into three age subgroups of 20-23, 24-27 and 28-30 and evaluated immune responses against measles, mumps and rubella viruses. The volunteers were also divided into two categories according to the number of measles vaccine dose (Table 1).

All participants filled in a questionnaire about their age, taking immune-suppressive drugs, and history of measles, mumps and rubella infection. Sera of volunteers were isolated and stored at -20°C until the time of tests. The study was performed at the Immunology department of Tehran University of Medical Sciences, Iran (2014-2015). The method of the research was approved by the ethical committee of Tehran University of Medical Sciences.

Serological Analysis

Specific immunoglobulin G (IgG) antibody levels against measles, mumps and rubella were measured in serums using enzyme-linked immunoassay kit (GenWay, USA), according to the manufacturer's instructions. The specificity and sensitivity of the kits were more than 95 %.

In accordance with the kit protocol, IgG antibody levels against mumps or measles were categorized into two groups: non-immune (<11 U/mL) and immune (>11 U/mL). IgG antibody levels against rubella also

Table 1. Geometric mean value of IgG titer in young adults

		Geometric Mean Titer IgG					
		Measles(IU/ML)		Mumps(IU/ML)		Rubella(IU/ml)	
	n	CI 95%,IU/ML	SE	CI 95%,IU/ML	SE	CI 95%, IU/mL	SE
Total	53	16.82 (13.8–19)	1.53	16.45 (13.7–19.2)	1.41	65.6 53(59.8–72.3)	3.19
Gender							
Male	29	16.18(8.20-24.16)	3.63	14.32(7.89-20.75)	2.92	63.09(48.38-77.80)	6.68
Female	24	17.68(10.43-24.93)	3.29	19.38(12.37-26.39)	3.18	79.78(63.66-89.91)	5.96
Age group							
G1:20-23	20	14.69(9.21-20.17)	2.49	10.97(5.29-16.65)	2.58	56.98(37.46-76.50)	8.87
G2:24-27	16	14.42(8.82-20.14)	2.54	18.91(14.87-22.93)	1.83	75.70(61.80-89.61)	6.32
G3:28-30	17	20.68(13.59-27.77)	3.35	20.03(12.16-27.91)	3.58	68.75(58.34-79.17)	4.73
Measles vaccination history							
Two doses	36	15.04(11.89-18.19)	1.55				
Three doses	17	20.68(13.59-27.77)	3.35				

were divided into two groups: non-immune (<15 IU/ml) and immune (>15 IU/ml).

Avidity Measurement

Avidity testing was based on the strength of antigen –antibody interaction. The avidity of IgG antibody against Measles, mumps, and rubella viruses were measured using IgG EIA kits (measles, mumps, and rubella EIA; GenWay, USA) with some modification. Briefly, serum was diluted 1:100 with ready-to-use sample diluents and was added to virus antigen coated wells at 2 replicates. During incubation time, virus specific IgGs bound to virus antigens. Wells were washed three times by buffers with or without protein denaturing agents such as urea and diethylamine. The interaction between IgG antibody and the antigen was denatured by chemical protein denaturing agents. We used 6M urea (Amresco, USA)[17,18] for denaturating anti-measles and mumps IgG and 35 mM diethylamine[20] for anti-rubella IgG antibodies. Low avidity IgGs were separated faster than the high avidity IgGs. Therefore, optical density readings of wells treated with protein denaturing agents is less than wells treated with usual buffers.

Avidity index (AI) was calculated as the following: (Urea or EDA treated OD / untreated OD)×100

The secondary immune response against mumps was defined by IgG antibody (high avidity) with an avidity index over 32%, while a primary immune response was identified by IgG antibody (low avidity) with an avidity index less than 32%.[21] Avidity index less than 60% (low avidity IgG) indicated a primary immune response against measles or rubella,[22] while avidity index over 60% (high avidity IgG) indicated secondary immune response.[18]

Statistical Analysis

All statistical analyses were performed with SPSS version 20 software (SPSS, Chicago, USA) for Windows. We used student's unpaired T test or Fisher's exact test for comparison data between groups and considered *p* values less than 0.05 as significant.

RESULTS

Measles, Mumps and Rubella IgG levels

The geometric mean concentration of anti-rubella IgG was 65.6 IU/mL (CI 95%,59.8–72.3), anti-measles IgG was 16.8 IU/mL (CI 95%, 13.8–19), and anti-mumps IgG was 16.4 IU/mL (CI 95%, 13.7–19.2). Protective serological levels of measles- specific IgG (>11 IU/mL) was detected in 42 (79.2%) of the volunteers compared to 11(20.8%) who had a nonprotective (<11 IU/mL) level of antibody. Thirty four (64.16%) of the volunteers had a protective level (>11IU/mL) of anti-mumps IgG and 19 (35.84%) had a nonprotective (<11 IU/mL) level of IgG antibody. Fifty one (96.2%) of the volunteers were immune against rubella and had a protective level (>15 IU/ml) of anti-rubella IgG. Every volunteer was immune against at least one type of viruses. Some of the volunteers had a protective level of antibody against more than one type

Table 2. Geometric mean of IgG avidity in young adults

Characteristics	numbers	IgG avidity					
		Measles: AI≥60		Mumps: AI≥32		Rubella: AI≥60	
	n	*CI 95%	SE	CI 95%	SE	CI 95%	SE
Total	53	71.6 (68–75)	1.76	41.4 (35.9–46.8)	2.72	73.7 (71.1- 76.3)	1.29
Gender							
Male	29	66.53 (57.47-75.58)	4.12	43.85 (30.41-57.29)	6.11	74.43 (68.35-80.50)	2.76
Female	24	74.73 (64.85-84.61)	4.49	34.21 (25.29-43.12)	4.05	73.36 (67.06-79.66)	2.86
Age group							
G1:20-23	20	67.78 (59.11-76.46)	3.94	49.15 (34.73-63.59)	6.55	75.32 (68.27-82.38)	3.21
G2:24-27	16	73.92 (65.61-82.23)	3.78	42,50 (29.01-55.99)	6.13	72.91 (66.00-79.81)	3.14
G3:28-30	17	70.89 (66.63-75.16)	2.10	36.95 (29.56-44.33)	3.36	73.74 (67.99-79.47)	2.61
Measles vaccination history							
Two doses	36	73.05 (66.12-79.98)	3.27				
Three doses	17	70.89 (66.63-75.16)	2.10				

* CI: confidence interval

of virus. Twenty four (45.28%) of the volunteers had a protective level of IgG against measles, mumps, and rubella. A summary of the results is shown in Table 1. There was no difference in anti-measles, anti-rubella, and anti-mumps IgG levels by age and gender. No significant differences were observed between anti-measles IgG levels and the number of vaccine doses (Table 3).

IgG Avidity

The mean avidity of anti-rubella IgG is presented in table2. Fifty (94.3%) volunteers had anti-rubella high avidity IgG (AI≥60%), which confirmed that they had a secondary immune response. Three volunteers showed low-avidity (AI<60%) IgG antibody and were at risk of rubella infection. Forty three (81.1 %) volunteers had high avidity anti-measles IgG (AI≥60%), it means that 18.9% of the cases had a secondary vaccine failure. Thirty three (62.26%) of the volunteers had high avidity anti-mumps IgG (AI≥32%), which confirmed that they had a secondary immune response, whereas twenty cases had low-avidity antibody indicating a primary response to mumps infection. Secondary immune response against measles and mumps were detected in 45.28% of cases, whereas thirty four of the volunteers had high avidity immune response against rubella and measles. Twenty three of the volunteers had secondary immune response against measles, rubella, and mumps. A summary of the results is shown in the Table 2.

There was no significant correlation between anti-measles, anti-rubella, and anti-mumps IgG avidity with age and gender. No statistically significant difference was found between anti-measles IgG avidity and the number of vaccine doses. There was a significant correlation between IgG level and avidity to measles, mumps, and rubella viruses (Table 3).

Table 3. Comparison of demographic characteristics and avidity or concentration of IgG in young adults (independent samples T test).

Item	Measles		Mumps		Rubella	
	Titer	Avidity	Titer	Avidity	Titer	Avidity
sex	0.669	0.145	0.251	0.230	0.444	0.062
Age group(G1,G2)	0.566	0.215	0.127	0.464	0.075	.951
Age group(G1,G3)	0.238	0.307	0.851	0.185	0.201	0.804
Age group(G2,G3)	0.107	0.859	0.149	0.585	0.347	0.854
Avidity	0.000		0.000		0.001	
The number of measles vaccine doses	0.140	0.573				

DISCUSSION

More than a decade after the 2003 campaign, significant variations in protective levels of IgG antibody against measles, mumps and rubella were found in adults who were vaccinated during the Iran's nationwide campaign. The evidences of the post-campaign study performed in 2004 indicated that 97.4% and 94.6% of the population aged between 5 and 40 years had immunity to measles and rubella, respectively.[13]

In the present study, 79.2% of the volunteers had a protective level of anti-measles IgG. The presence of high avidity IgG antibody is an indicator of secondary immune response resulted by a natural infection or vaccination. High avidity anti- measles IgG observed in 81.1 % of the cases, which identified secondary immune response against measles, whereas 18.9% of the volunteers showed low avidity IgG which indicated a secondary vaccine failure. According to previous studies, most of the target population were protected against measles infection[23,24], however, Iran is located in the neighborhood of countries with high measles mortality and insufficient coverage of measles vaccination.[25] Therefore, in order to control measles outbreak occurrence, all measles doubtful cases should be checked at Iran's national measles laboratory.[12]

In agreement with previous study in Iranian populations, there was no significant correlation in concentration and avidity of anti-measles, anti-mumps and anti-rubella IgG by age and gender.[23,24,26] No significant differences were also observed between individuals regarding the number of measles vaccine doses.

We found a positive correlation between IgG antibody level and IgG antibody avidity against measles, mumps and rubella, similar to the study reported by Sanz-Moreno, et al.[27] Additionally, vaccinated individuals and persons with a history of natural infection had a protective level of high avidity IgG antibody.

Before worldwide rubella vaccination, the prevalence of congenital rubella syndrome (CRS) was approximately 0.1-0.2/1000 live births in non-epidemic years in developing countries.[28] The prevalence of CRS in Iran was estimated approximately 0.2/1000 live births before rubella vaccination. After the mass vaccination, the incidence of the disease decreased to <1 case per 1,000,000.[29]

In the present study, 96.2% of the volunteers had a protective level of anti-rubella IgG. 94.3% of the volunteers had high avidity anti-rubella IgG, suggesting that they had experienced natural infection before or after vaccination. Most of the population (83% to 94.6%) had a secondary immune response against rubella. Therefore, mass MR vaccination camping in Iran was successful.[13,30,31] Women of childbearing age with low avidity anti-rubella IgG antibody are at risk of rubella infection during pregnancy and CRS. In Iran, human populations have often experienced subclinical natural infection which induced high level of IgG antibody against rubella. Before introduction of mumps vaccine, over 90% of population showed serological evidence of mumps virus infection for about 15 years.[32,3] Mumps infection is endemic among Iranians[33] like other unvaccinated populations. Although about 30% of cases may be subclinical, mumps infection in 10% of patients may develop to aseptic meningitis. Mumps infection can cause deafness in children infected with mumps and impaired fertility of males that experienced mumps infection in childhood.

The most common complication of mumps infection in childhood is Meningoencephalitis [7,8] and in Iranian children, mumps virus is one of the causes of Meningoencephalitis.[34,35]

Several mumps vaccine strains have been introduced. The most commonly used strain is Jeryl Lynn.[36] The use of other mumps vaccine strains has been limited to one or two countries. Hoshino is a mumps vaccine strains that has been used in Iran and Japan.[37]

Immunity to measles, mumps and rubella has been decreasing over the years. However, seropositive response against measles, mumps and rubella in children that received the first dose of MMR vaccine have been 99%, 86%, and 100% respectively.[38]

Mumps seroconversion rate in Iranian volunteers who received MMR vaccine containing Hoshino strain was 86.1% which decreased to 75% during 24 months.[39] Although mumps vaccine introduced in 1960 and mumps vaccine as MMR vaccine introduced in Iranian EPI, none of Iranian young adults including medical students are vaccinated.

In present study, 64.16% of the volunteers had a protective level of anti-mumps IgG, and 62.26% had high avidity IgG. Secondary immune response to mumps is often identified by the presence of high avidity IgG, therefore the evidence showed 62.26% of

the volunteers experienced a mumps reinfection, whereas 35.84% of the cases were seronegative. These results showed that a large number of adults (aged 20-30 years) were at a risk of mumps infection. In other survey performed in different age groups of Iranian population, a large number of nonimmune persons were reported.[26]

Although the sample size was small in the present study, the results may highlight the existence of nonimmune persons against measles, mumps and rubella in young adult populations. Correct evolution of our results needs studying on a large size of Iranian young adults.

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