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IMMUNITY TO MEASLES, RUBELLA AND HEPATITIS B VIRUSES AMONG IRANIAN MEDICAL STUDENTS IN 2014; A CROSS SECTIONAL STUDY

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ABSTRACT:

BACKGROUND: Measles, Rubella and Hepatitis B are vaccine-preventable infectious diseases that cause several complications and impose a burden on the health systems worldwide. Medical students are exposed to these viruses in their clinical training years and thus are more susceptible to become infected. Therefore, it is rational to assess their immunity against these three viruses.

MATERIALS AND METHODS: In this cross sectional study in 2013, 75 blood samples were collected from medical students of Shiraz University of Medical Sciences. The population under study included 53 females and 22 males with the mean age of 22 years. IgG level against Measles, Hepatitis B and Rubella was measured by ELISA method.

RESULTS: Protective levels of IgG against Measles, Rubella and Hepatitis B were detected in 88%, 97.3% and 94.7% of the students, respectively. There was no significant correlation between gender and immunity against these viruses. We found a significant correlation between positive history of Measles and Hepatitis B vaccination and protection against these two viruses (p value: 0/016 and 0/000 respectively). A significant correlation was detected between the number of hepatitis B vaccination doses and immunity against this virus (p value: 0/016).

DISCUSSION AND CONCLUSION: Immunity of medical students against Measles, Hepatitis B and Rubella is at an acceptable rate, However, it is prudent to address any possible problems in Measles vaccines. It is recommended that health planners evaluate the medical students regarding their immunity to these viruses before they enter their clinical training in hospitals.

INTRODUCTION

Determining antibody titer against vaccine-preventable diseases is crucial to assess the immunity of the people who have been vaccinated against these diseases.

Measles, Rubella and Hepatitis B are among infectious diseases for which vaccines have been available since many years ago.

Measles is a highly contagious disease caused by an RNA virus transmitted by airborne spread or via droplets '[]. Before the advent of measles vaccine, 8 million people died of measles each year[]. Despite significant control of Measles in many parts of the world, Measles was still the most common cause of vaccine-preventable deaths in children in the year 2000 and the fifth leading cause of all deaths in children less than 5 years of age. Outbreaks of measles can occur with increasing ratio of susceptible individuals in the population []. In the year 2012 in Iran, 7 cases of measles were reported in a village in Fars province, southwest of Iran. The primary case was an Afghan refugee and the secondary cases were fully vaccinated except in one case with unknown history of vaccination[]. The probable reasons for lack of immunity to measles in vaccinated individuals include: Drop in the level of antibodies after some years, Improper maintenance of the vaccine cold chain and the inhibitory effect of maternal antibodies on antibody responses in infants .[1]

Rubella is caused by an RNA virus and its major route of transmission in postnatal period is direct contact with nasopharyngeal secretions of the patients. In the first trimester of pregnancy, Rubella infection can have teratogenic effects on the fetus and lead to congenital rubella syndrome with complications ranging from blindness, deafness, heart defects to stillbirth and abortion [7, 8]. The immunity conferred by Rubella vaccine is variable as reported by different studies. In a study ,it is estimated that the vaccine confers immunity against rubella viremia for more than 16 years [9-11] but a small percent of vaccines either do not confer any immunity or produce such low levels of antibodies that the serum titer becomes zero after 5-8 years [12-14]. Just like measles, the reason for vaccine failure in those vaccinated against rubella could be the improper maintenance of vaccine cold chain and the fact that the IgG level starts to decline after a few years.

More than two billion people in the world are infected with Hepatitis B virus; a DNA virus[15] and 350 to 400 million people have Hepatitis B chronic infection[16]. In Iran, data on hepatitis B prevalence are variable[17-19] ,ranging from 1.3% [20, 21] to 2.14% [22] among different provinces. Approximately 5% of those who have been vaccinated with the standard three dose hepatitis B vaccine regimen, display an inadequate response and are thus called non-responders. Some risk factors for vaccine non-response have been proposed, among which are old age, male sex, certain HLA haplotypes, renal failure, immunodeficiency, intragluteal vaccine administration. However, most non-responders are healthy individuals without any known risk factors [23].

OBJECTIVE

Medical students are in close contact with patients who can be infected with these three viruses; Hence evaluating antibody titer against these viruses is a reasonable measure. In this study, we aimed to measure the IgG titer against Measles, Rubella and Hepatitis B in medical students just before they enter their clinical rotations in hospital. In this way, we can assess their immunity status and give them boosters if they have antibody levels below the immunity threshold.

MATERIALS AND METHODS

In this descriptive and analytical cross sectional study, a total of 75 blood samples was collected from medical students of Shiraz University of Medical Sciences in 2013. The subject students were all of the members of the class who were to begin the clinical rotations in the year 2013. Therefore, no inclusion or exclusion criteria were applied. The population under study included 53 females and 22 males with the mean age of 22 years. No missing data were detected in this study. Consent forms were filled by all the students and information regarding the measles, rubella and hepatitis B vaccination status and sociodemographic variables were recorded in a questionnaire that included age, sex, history and place of vaccination and for hepatitis B, the number of vaccines received. If they were not sure about the number of hepatitis B vaccinations, we

considered this as incomplete vaccination.

Serological tests

The sera were centrifuged and stored at -20° and transferred to the virology and bacteriology department of Shiraz university of medical sciences. Then, IgG against rubella, measles and hepatitis B surface antigen were measured by enzyme-linked immunosorbent assay test. In this study, the ELISA reader, stat fax-2100, Awareness technology Inc. was used. The REF number of rubella IgG ELISA kit used was RE58341.For HBsAb, the REF number was 20099.

According to the ELISA kit, antibody titer above 12 IU/ml was considered to be protective for measles and rubella while the titer below 8 IU/ml was considered insufficient. Antibody titer in the range of 8-12 IY/ml was considered equivocal. For hepatitis B, antibody titer below 10 IU/ml and above 20 IU/ml were considered insufficient and protective, respectively. The levels from 10 IU/ml to 20 IU/ml were considered equivocal.

STATISTICAL ANALYSIS

The collected data are analyzed by SPSS 22 software. Descriptive statistics including frequency and mean are described and Chi-square test is used to determine whether a significant correlation exists between the variables. P value less than 0/05 is considered significant.

RESULTS

The participants of this study comprised of 75 medical students. All of them completed the questionnaire and were tested for the presence of antibodies. The mean age of the subjects was 22 years (range: 21-23). Of all the students, 53 (70.7%) were female and 22 (29.3%) were male. The participants originated from diverse regions in Iran. 47 (62.7%) of the students were from Fars province and had received their vaccines there, while 28 (37.3%) were from the other provinces. All of the students with positive history of measles and rubella vaccination had been vaccinated in December of 2003. As for hepatitis B, the vaccinated students had received hepatitis B vaccine in 2009 mass vaccination campaign.

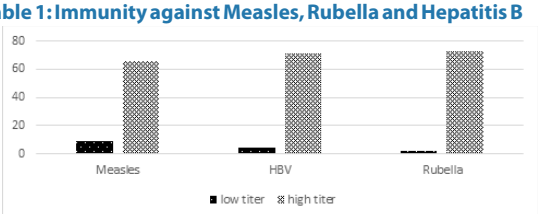
Measles, Rubella and Hepatitis B vaccination status:

Seventy-one (94.7%) of the students had positive history of measles-rubella vaccination and 4 (5.3%) of them either did not receive the vaccine or did not remember their vaccination status. As for hepatitis B, 71 (96%) had received the hepatitis B vaccine. Only 1 (1.3%) of the students had not received the vaccine while 2 (2.7%) of them did not remember their vaccination history. Among those who had received hepatitis B vaccine, 66 (88%) of them had completed the 3 dose regimen while 9 (22%) had received less than 3 doses.

Immunity against Measles, Rubella and Hepatitis B:

Of the 75 students, 66 (88%) had measles IgG titer above 12IU/ml which is considered protective and 9 (12%) of them had IgG level that was insufficient or equivocal. Seventy-three (97.3%) subjects had sufficient anti-rubella IgG and 2 (2.7%) had below 12IU/ml antibody titer which is insufficient. Regarding hepatitis B, 71 (94.7%) had IgG titer above 20 IU/ml which is the used ELISA kit's index of being protective. On the other hand, 4 (5.3%) students did not have protective levels of antibody.

Table 1: Immunity against Measles, Rubella and Hepatitis B



Association between different variables and immunity

We detected no association between gender and immunity against measles (p value: 0/288) while there was a correlation between sex and rubella and hepatitis B serological protection (p values: 0/026 and 0/039 respectively). With regard to measles, 64 students with positive history of vaccination had protective levels of anti-measles IgG while 7 students who were vaccinated against measles had insufficient antibody titers. A positive correlation was found between vaccination history for measles and immunity against measles (p value: 0/016).

Regarding rubella, there were 69 vaccinated students who were immune against measles and 2 students who were vaccinated but did not protective levels of antibody. No correlation was found between positive rubella vaccination history and protection against rubella (p value: 0/734). And as for hepatitis B, there were 70 students who had received hepatitis B vaccine, whether complete or incomplete, and had protective levels of IgG against hepatitis B surface antigen. On the other hand, there were 2 students who had received hepatitis B vaccine but had low antibody titers. We found a significant correlation between receiving hepatitis B vaccination and high IgG titer against hepatitis B surface antigen (p value: 0/000). Since three doses of hepatitis B vaccine are required in order to confer immunity, we investigated the relationship between immunity and the vaccine doses that the subjects had received. There were 64 subjects who had been vaccinated fully and were immune against hepatitis B. There were 7 whose vaccinations were not complete but had sufficient antibody titers while 2 students were not immune despite having received three hepatitis B vaccine doses. A significant correlation was detected between the number of hepatitis B vaccination doses and immunity against this virus. In other words, those with full vaccination history were more likely to be immune to hepatitis B compared with those who had not received the three doses of the vaccine (p value: 0/016).

DISCUSSION

The present study was performed to assess the immunity of medical students against measles, rubella and hepatitis B viruses. This study showed that measles-rubella vaccination rate in Iranian medical students is 94.7%. This is an acceptable coverage and is in accordance with the fact that the national coverage for first and second doses of measles vaccine is 95%(5). Positive vaccination history for measles and rubella were shown to be 49.2%(31) and 55.8%(30) in different studies.

For hepatitis B, vaccination rate in our study was found to be 96% including those who had received less than three doses of the vaccine. This good coverage stems from the hepatitis B mass vaccination campaign that took place in 2009 for the subjects of this study. There was only one student who had received hepatitis B vaccine at birth. In a study in Saudi Arabia by Mosaad M. et al. in medical students, only 36.2% of the students were sure to have received hepatitis B vaccine[24] . In some parts of the world this figure is even less promising; in a study in Cameroon, only 18% of the medical students had completed the three doses of hepatitis B vaccine [25].

Immunity against Measles was the least (88%) among the other two viruses whereas protection against Rubella was the highest (97.3%). This low protection rate of measles in comparison to the other viruses is worrying. Although the incidence of measles has significantly decreased in recent years in Iran [4] and other parts of the world [26], occasional outbreaks occur that can involve the non-immune population [3]. These outbreaks usually happen with the introduction of the infection from abroad, as happened in a village in Fars province in 2012 in which 7 cases of Measles were reported [4] . The Measles immunity rate in our study was in agreement with the study by Wicker S. et al in Germany 2007 in which 91.5% were immune [14]. In the study done by Lewis RF et al. in Uganda in 2005, 100% immunity to measles was detected.

Contrary to the results of the study undertaken in Shiraz University of Medical Sciences two years before our study in which 52% of the

students were immune to measles [27], our rate of 88% seems to be an improvement. However, Attention should be focused on the measles vaccine to address any possible problems in the preservation and administration of the vaccine.

Immunity against Rubella is crucial in women in their childbearing age due to the risk of congenital rubella syndrome with the maternal rubella infection. In our study, 93.3% of the students were serologically protected against rubella. This is in accordance with the previous study in Shiraz University of Medical Sciences that showed the rubella antibody level to be present in 100% of the students [27].

Medical students should be considered as having the same high risk as health care providers for infection with hepatitis B during their clinical training years. In our study, 94.7% of the subjects had protective levels of antibody against hepatitis B virus. In the study undertaken in Shiraz University of Medical Sciences two years before our study, 68% of the students were serologically protected against HBV. In contrast to the results of our study, in the study done by Mosaad M. et al, only 15.2% of the medical students had protective levels of HBsAb [24].

Gender did not seem to play a role in determining the immunity against these three viruses in our study.

Since vaccination is the only means of seroproetction besides natural infection, we investigated the relationship between positive vaccination history and seroprotection. We found a significant correlation between measles and hepatitis B vaccination history and protective levels of antibody; However, no correlation was found between Rubella vaccination history and Rubella seroprotection. This could be explained by either natural infection in those who have not been vaccinated or simply the fact that vaccinated individuals have forgotten their vaccination history.

The low antibody titer in vaccinated individuals in this study can be explained partly by vaccine failure. Primary vaccine failure happens when the body can't mount a protective immune response after vaccination. This can occur when the presence of maternal antibodies to Measles inhibits seroconversion especially in very young aged subjects [26]. Secondary vaccine failure occurs due to the declining levels of antibodies over the years. This mechanism has been proposed for hepatitis B [28] and measles [6] and rubella [12, 13, 29]. It has been shown that approximately 5% of those who have been vaccinated with the standard three dose hepatitis B vaccine, show an inadequate response and are called non-responders. Walayat S. et al. proposed some risk factors for HBV vaccine non-response, among which are old age, male sex, certain HLA haplotypes, renal failure, immunodeficiency and intragluteal vaccine administration [23]. As for Rubella virus, it has been shown that antibodies in the serum can becomes next to zero after 5-8 years[12, 13, 29].

Other causes of vaccine failure may be related to the problems in maintaining the cold chain of the vaccine [5], Improper administration of the vaccine, etc. Interrupted maintenance of the vaccine cold chain especially applies to live attenuated vaccines like measles and rubella vaccines since they are heat sensitive.

That being said, we cannot safely assume that vaccine failure has occurred in all the cases where the students were vaccinated and had low titers. Some studies have shown that despite the low antibody titer against HBs antigen or the non-responder state, in the presence of Hepatitis B surface antibody-producing memory cells, immunity against hepatitis B is at least partially present. According to one study, It is useless or even detrimental to immunize this population with the same vaccine and they may not produce more antibodies this way [30]. Another point to consider is that post-vaccination testing for antibody should be done a few months after vaccination in order to label the subjects as having vaccine failure.

One of the limitations in this study was the small population under study. Since the subjects were all the medical students of a class, no sampling was done. The small sample size makes it difficult to generalize the results of this study. Recall bias could also be present in this study as the students were vaccinated in their childhood and teen years and might not remember their vaccination history completely.

To achieve our goal of maximum protection among medical students, we recommended that the students receive booster doses of hepatitis B vaccine if they had not received the three doses of hepatitis B vaccine and did not have sufficient antibody against hepatitis B. In any case, we advised those who did not receive the hepatitis B vaccine to take the vaccination and test for Hepatitis B surface antibody titer after 4 to 6 weeks.

CONCLUSION

The majority of our medical students in Shiraz University of Medical Sciences had protective levels of antibodies to Measles, Rubella and Hepatitis B. However, due to the constant exposure of the medical students to these infectious agents and the complications and threats imposed by them, It is highly recommended that the university take steps to assess the immunity of these future healthcare providers on a regular basis. Measuring antibody titer to these and possibly other infectious agents before the students enter the hospital for clinical rotations is a prudent action that the health planners in the university can take.

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