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IMMUNE RESPONSE TO MEASLES-MUMPS-RUBELLA VACCINE IN ASTHMATIC CHILDREN: A CASE CONTROL STUDY

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Abstract

Background: *Asthmatic patients have a TH2-predominant milieu that is associated with humoral immunity. However, little is detected about whether humoral immune responses to viral antigens differ between asthmatic and non-asthmatic children. This study aims to compare the humoral immune response to Measles-Mumps-Rubella (MMR) vaccine in asthmatic children and healthy controls.*
Methods: *This case control study was conducted in Allergy and Immunology Centre; VACSERA. It included 90 children who received two doses of MMR vaccine, aged from 2 to 5 years where 45 asthmatic children were diagnosed using GINA diagnosis & classification criteria and compared to 45 age and sex matched controls. Mean titres of MMR specific IgG levels were determined using an enzyme-linked immunosorbent assay.*
Results*; Lower levels of measles, rubella and mumps were found among asthmatic children than controls but were not statistically significant. Lower level of circulating measles specific IgG correlated with asthma severity. There was statistically significant lower level of circulating mumps specific IgG in preterm children among both cases and controls.*
Conclusion; *Asthmatic children showed lower mean antibody levels for the measles, mumps and rubella vaccination compared to controls.*

Keywords: Asthma, Humoral Immunity, Measles, Mumps, Rubella

INTRODUCTION

Asthma represents a major health problem in the pediatric population worldwide**.** Asthma is a heterogeneous disease that is usually identified by chronic airway inflammation and is also determined by the history of respiratory symptoms such as wheezes, cough, shortness of breath, and chest tightness these respiratory symptoms vary over time and in intensity, associated with variable and/or reversible expiratory airflow limitation, this airflow limitation may become persistent by time **(1,2).**

Asthma has a potential role in increasing susceptibility to viral infections and determination of their severity **(3,13).** At present, the humoral and cell mediated immune responses to MMR vaccine viruses in asthmatic individuals need further investigations.

Measles, mumps, and rubella (MMR) are major diseases which could lead to possibly fatal illnesses and disabilities. MMR is particularly common in low-income developing countries where mortality rates from disease are high and vaccination programs are inconsistent **(4).**

Till date, there is no explanation of increased morbidity and mortality of MMR in previously vaccinated populations. Host factors may play a role in long-term protection against viral infections as no alterations in biological characteristics of the virus have been reported. This case control study aimed to compare the humoral immune response to Measles-Mumps-Rubella vaccine in asthmatic children and healthy controls **(5)**.

SUBJECTS AND METHODS

This study is a case control study that was conducted in the Allergy and Immunology Centre, VACSERA and the samples were analyzed at clinical pathology department, faculty of Medicine, Cairo University. Ninety children aged from 2 to 5years were recruited. Forty- five (29 males and 16 females) were diagnosed with bronchial asthma according to the criteria & classification of bronchial asthma as defined in GINA guidelines, in the duration from December 2019 to August 2020 and forty- five healthy controls who were matched for age and sex. Both groups had documentation of receiving at least two doses of MMR vaccine at the age of 12& 18 months in their medical records, and had no other concomitant chronic diseases nor received medications that might affect immune system or the response of the children to vaccination.

Ethical considerations and approval were obtained from the Research Ethics Committee of the Faculty of Postgraduate Childhood Studies, Ain-Shams University. A written informed consent was obtained from the parents after explanation of the aim of the study and its benefits.

All children were subjected to the following:

1. **Full history taking** with emphasis on personal data (age, sex, history of exposure to smoking, animal contact and residence), history of present illness (onset, course, duration, upper respiratory tract symptoms, chest symptoms, atopic manifestations, seasonal variations, pattern of symptoms, precipitating factors & severity of the disease), family history, vaccination and perinatal history.

2. **Comprehensive clinical examination.**
3. **Detection of IgG levels against measles, mumps and rubella viruses by enzyme-linked immunosorbent assay (ELISA):**

   Fresh serum samples were collected from participants in serum-separating tubes, centrifuged, frozen and stored at -20°C until processing, then they were transported to laboratory of Clinical and Chemical pathology department at Faculty of Medicine, Cairo University where they were analyzed. IgG levels against measles, mumps and rubella viruses were detected using Solid phase enzyme-linked immunosorbent assay, based on the sandwich principle (Measles virus IgG ELISA Kit: IBL INTERNATIONAL GMBH., Hamburg, Germany. Cat. no:RE57141, Mumps virus IgG ELISA Kit: IBL INTERNATIONAL GMBH., Hamburg, Germany. Cat. no:RE56641, Rubella virus IgG ELISA Kit: IBL INTERNATIONAL GMBH.,

Hamburg, Germany. Cat. no:RE57081). Results of samples determined directly using the standard curve**s.**

Statistical analysis Recorded

Data were analyzed using the statistical package for social science (SPSS version 21).

RESULTS

Quantitative mean antibody levels of measles, rubella and mumps were lower among asthmatic children than controls but were not statistically significant **(Table 1).**

Table (1): Mean antibody titres of MMR vaccine among cases and controls.

Mean Antibody titre	**Quantitative immune response**		
	Asthma Cases (n=45)	**Controls (n=45)**	
	Mean (±SD)	**Mean (±SD)**	**P value**
Measles IgG level	1268.736 (±1253)	1340.204 (±1382)	0.798
Mumps IgG level	87.131 (±66)	101.180 (±65.2)	0.313
Rubella IgG level	71.87 (±25.7)	73.14 (±26.9)	0.82

*t-Independent sample t-test; p-value >0.05 NS; *p-value<0.05 S; **p-value<0.001 HS*

Statistically significant lower level of circulating measles specific IgG correlated with asthma severity and nocturnal symptoms **(Table 2).**

Table (2): **Mean IgG levels for MMR in asthmatic cases in relation to degree of severity asthma according to (GINA, 2019a) classification.**

GINA classification		**Measles specific IgG level**		**Mumps specific IgG level**		**Rubella specific IgG level**	
		Mean (±SD)	**P value**	**Mean (±SD)**	**P value**	**Mean (±SD)**	**P value**
Severity of asthma according to GINA classification	**Mild intermittent 9 cases**	1983.800 (±987.6)	0.038*	77.710 (±67.2)	0.741	65.660 (±26)	0.5
	Mild persistent 10 cases	2019.5 (±833.9)		75.8 (±60.8)		70.7 (±24.3)	
	Moderate persistent 14 cases	2048.642 (±1722.6)		80.533 (±61.9)		71.900 (±23.9)	
	Severe persistent 12 cases	985.713 (±896.7)		94.67 (±69.5)		74.565 (±25.6)	

*t-Independent sample t-test; p-value >0.05 NS; *p-value<0.05 S; **p-value<0.001 HS*

Mean level of circulating specific Mumps IgG was higher in urban location than rural (p value = <0.05).

Measles specific IgG was higher in children with positive family history of asthma(p=<0.001). Among controls, mean level of circulating mumps specific IgG was lower in children with positive family history of asthma. Mean level of measles, mumps and rubella IgG were lower in both cases and controls exposed to passive smoking. **(Table 3)**

In both cases &control groups of children; there was statistically significant lower level of circulating mumps specific IgG in preterm children (p=<0.05) and (p=<0.001) respectively. In asthmatic cases there was statistically significant higher mean level of circulating measles specific IgG in Caesarian section delivery (p=<0.01). Children with a history of NICU admission showed lower level of circulating specific rubella IgG among non-asthmatic children (p=<0.03). **(Table 4)**

Table (3): Demographic parameters in cases & controls in relation to specific MMR IgG levels.

Demographic parameters		Asthma Cases						Non-asthma Controls					
		Measles specific IgG level		Mumps specific IgG level		Rubella specific IgG level		Measles specific IgG level		Mumps specific IgG level		Rubella specific IgG level	
		Mean (±SD)	P value	Mean (±SD)	P value	Mean (±SD)	P value	Mean (±SD)	P value	Mean (±SD)	P value	Mean (±SD)	P value
Age cases/ Control	3.5(±1.3)/ 3.2(±1.3)	R-value 0.16	0.27	R-value -0.19	0.2	R-value -0.2	0.1	R-value 0.16	0.2	R-value -0.21	0.15	R-value -0.23	0.1
Sex cases/ Control	Male 29/26	1270.45 (±1184)	0.9	81.29 (±67)	0.4	71.928 (±26.5)	0.9	1525.7 (±1487)	0.2	105 (±67)	0.6	76.7 (±25)	0.3
	Female 16/19	1265.6 (±1408)		97.70 (±64)		71.78 (±24.7)		1086.2 (±1215)		95.1 (±64)		68.2 (±28)	
Location cases/ Control	Urban 23/25	1248.23 (±1030)	0.9	105.7 (±67)	0.05*	70.8 (±23.1)	0.7	1305.9 (±1424)	0.8	101 (±59)	0.9	70.6 (±27)	0.4
	Rural 22/20	1290.2 (±1474)		67.67 (±59)		72.99 (±28.5)		1383.1 (±1362)		101.2 (±67)		76.2 (±26)	
Family History of asthma	Positive 40/19	1373.9 (±1288)	<0.001**	90.97 (±65)	0.2	72.1 (±25.2)	0.8	1096.8 (±1163.4)	0.3	75.2 (±53.3)	<0.01*	67.7 (±26)	0.2
	Negative 5/26	427.240 (±270.4)		56.4 (±72)		70.3 (±32.4)		1518.1 (±1519)		120.2 (±67.6)		77.1 (±26)	
Exposure to passive smoking Cases/ controls	Yes 22/13	1035 (869)	0.2	71.9 (62)	0.1	71.2 (23.9)	0.8	842.8 (708)	0.043*	90.5 (79.7)	0.5	64.4 (28)	0.1
	No 23/32	1491 (±1520)		101.6 (±67)		72.4 (±27.6)		1542 (±1539)		105.5 (±59)		76.6 (±26)	

r-Pearson Correlation Coefficient;<0.5 weak correlation; Between 0.5-0.7 moderate correlation; >0.7 strong correlation

Table (4): Perinatal history in relation to specific MMR IgG levels in cases & controls.

Perinatal history		CASES						CONTROLS					
		Measles specific IgG level		Mumps specific IgG level		Rubella specific IgG level		Measles specific IgG level		Mumps specific IgG level		Rubella specific IgG level	
	No.	*Mean (±SD)*	*P value*	*Mean (±SD)*	*P value*	*Mean (±SD)*	*P value*	*Mean (±SD)*	*P value*	*Mean (±SD)*	*P value*	*Mean (±SD)*	*P value*
Gestational Age	Preterm	1976.3 (±1497)	0.13	79.9 (±66)	0.05*	66.7 (±11)	0.35	1283 (±1683)	0.9	50.7 (±6)	<0.001 **	54.3 (±40)	0.2
	Full term	1159.9 (±1197)		133.9 (±51)		72.7 (±27)		1344 (±1382)		104.8 (±66)		74.5 (±26)	
Mode of delivery	Normal Labor	779.8 (±516)	0.01*	100.7 (±69)	0.35	81 (±24)	0.1	1561 (±1478)	0.5	107.3 (±67)	0.72	71.4 ±29.8	0.8
	CS	1489.6 (±1423)		80.9 (±65)		67.7 (±26)		1269 (±1365)		99.2 (±66)		73.7 (±27)	
NICU Admission	No	1244.1 (±1250)	0.7	88.08 (±69)	0.7	71.5 (±26)	0.8	1317 (±1399)	0.7	97.8 (±65)	0.27	75.8 (±26)	0.03*
	Yes	1465.8 (±1358)		79.54 (±64)		74.6 (±24)		1582 (±1343)		135.9 (±62)		46.6 (±29)	

*t-Independent sample t-test; p-value >0.05 NS; *p-value<0.05 S; **p-value<0.001 HS*

DISCUSSION

Routinely in Egypt, the measles, mumps, and rubella (MMR) vaccine doses are given at 12 &18 months of age, the aim of this study was to detect the humoral immune response to Measles-Mumps-Rubella vaccine in asthmatic group of children versus control non asthmatic group of children and to improve the understanding of factors affecting the immunological specific geometric mean antibody titer (GMT) to MMR vaccine in both groups.

The quantitative immunological data for different study groups showed that, there was no statistically significant difference in mean antibody levels of measles, mumps and rubella specific IgG comparing asthmatic and non-asthmatic groups of children being lower in asthmatic children than control ones.

A retrospective cohort study which investigated the immune response to MMR vaccine in relation to bronchial asthma, showed that the mumps specific IgG level in asthmatic children was lower than controls, However, there were no significant differences in measles and rubella specific IgG levels between subjects with and without asthma **(6).**

The present study showed that there was statistically significant lower level of circulating specific Mumps IgG in the environmental rural location than urban environment with mean difference (67.67(±59.7), 105.7 (±67.6) respectively) (p value = ≤0.05). That may be explained with low sanitation, exposure to environmental hazards, low education or inconsistency to vaccine schedule.

A Nigerian study showed that children living in developing countries have lower antibody responses to measles virus vaccine **(7).**

The present study shows that there was statistically significant higher level of circulating measles specific IgG level compared with positive family history of asthma in cases (p=≤0.001), on the other hand there was statistically significant lower level of circulating mumps specific IgG compared with positive family history of asthma in non-asthmatic control group of children which may be explained by genetic factors and needs further studies.

Among preterm infants; there were statistically significant lower mean level of circulating mumps specific IgG in both cases &control groups of children (p=<0.05), (p=<0.001) respectively.

This may be explained by the concern that premature infants are at major risk of infections as well as the vaccine preventable infections, due to impaired functioning of adaptive and innate immune systems and impaired functioning of external barriers which diminish response to vaccination due to decrease pathogen recognition by dendritic cells and macrophages, decreased T cell activity (especially Th1 activity) and diminished B cell interaction with T cells. However, for similar immunological reasons, variable responses to specific vaccines between full-term and preterm infants have also been reported **(8,9).**

It is reported that humoral antibody response, lymphoproliferation and cytokine responses to vaccines are lower in preterm infants than that of term infants not only after primary immunization but also after booster doses of vaccines as hepatitis B, Hib and poliovirus type 3 vaccination **(10,11).**

Passive smoking is a major problem among pediatric population as it worsens pulmonary functions, affects both adaptive and innate immunity and may be a contributing factor to asthma development **(12)**.

In the present study there was statistically significant decrease in circulating measles specific IgG associated with severity of asthma & nocturnal symptoms (p=<0.03). That may be explained by the chronic psychological stress accompanying chronic illnesses as bronchial asthma, as many studies have reported a negative association between chronic psychological stress and immune response to vaccinations occur **(14).** Moreover, adolescents with stressful life events and a low level of psychological well-being may have lower antibody responses **(15).**

CONCLUSION

-Asthmatic children showed lower mean antibody levels for the measles, mumps and rubella vaccination compared to controls.

-Factors such as prematurity, NICU admission, exposure to passive smoke and severe persistent asthma have a negative influence on the humoral antibody response to MMR virus vaccine in preschool children.

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