Original Article

The Rate of Anti-measles Immunoglobulin M Positivity among Children with Skin Rash and Fever in Diyala Province

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Abstract

Background: Measles is an extremely contagious disease characterized by generalized maculopapular rash, fever, cough, coryza, and conjunctivitis. It is caused by the measles virus. **Objective:** The objective of this study was to explore the anti-measles immunoglobulin (Ig) M positivity rate among children with clinical suspicion of having measles. **Subjects and Methods:** This is a cross-sectional study carried out in Diyala Province, Iraq, from November/2020 to October/2021. A total of 425 blood samples were collected from children (≤14 years of age): 90 from patients who were clinically suspected as having measles (18 were vaccinated with measles vaccine and 72 were not); 270 from measles-vaccinated children, including those children who received all recommended vaccines in the Iraqi Expanded Program of Immunization (IEPI); and 65 from nonvaccinated children, including those children who received none of the vaccines in the IEPI. Enzyme-linked immunosorbent assay (ELISA) kits for the detection of anti-measles IgM were used. **Results:** The results found that 14 (15.6%) of clinically suspected children were positive for anti-measles IgM antibody versus 76 (84.4%) who were negative. Whereas, only one (1.5%) of the unvaccinated children was positive, and all vaccinated children were negative. Thus, clinically suspected patients had a significantly higher positivity rate compared to other study groups ($P = 0.0001$). Similarly, the mean ± standard deviation of anti-measles IgM concentration was significantly higher compared to other study groups ($P = 0.0001$). **Conclusion:** About one-sixth of patients clinically comparable to measles in Diyala Province actually had measles, most of them were unvaccinated, and the anti-measles IgM ELISA technique was a good marker for exploring measles cases.

Keywords: Anti-measles immunoglobulin M, Diyala, measles

Introduction

Measles is a highly contagious systemic viral illness.[1] The causative agent is measles virus (MeV), which is a member of the genus *Morbillivirus*, within the Paramyxoviridae family. It has a negative-sense, single-stranded RNA genome.[2] The viral genome comprises six genes that encode eight viral proteins: the nucleoprotein (N), phosphoprotein (P), and large protein (L) forming the ribonucleoprotein complex, surrounded by matrix (M) protein. Two of the proteins are nonstructural proteins: MeV envelope glycoproteins and hemagglutinin (H) and fusion (F) proteins.[3] H protein mediates the absorption of virus to receptors on the host cell, and F protein is responsible for the membrane fusion of virus and host cell and for the penetration of virus into the host cell. Transmission of MeV occurs via person-to-person contact, as well as airborne spread droplets from the respiratory secretions.[4]

The incubation period for the disease usually lasts 10–14 days, and symptoms generally consist of fever, cough, conjunctivitis, malaise, and coryza. Usually, patients are contagious from about 4 days before eruption of the rash to 4 days after eruption.[5] Measles remains a common illness in many countries, especially in part of Asia and Africa. People from both developed and developing countries are targets, but measles could be more perilous among children in developing countries, with a potentially increased mortality rate of up to 15%.[6] Several factors can contribute to the severity of measles

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in developing countries, including poor nutrition, exposure to crowded conditions, early age at which infants are exposed to measles, in addition to vitamin A deficiency, poor hygiene, improper immunization, and decreased immunity.[7]

Despite the availability of an effective and safe attenuated measles vaccine for more than 50 years, measles is still a major cause of childhood morbidity and mortality.[8] It has become a global public health problem, attributed to low vaccination coverage observed in different countries.[9] Annual measles outbreaks typically occur in late winter and early spring in temperate climates. Countries with widely used measles vaccine have experienced a marked decrease in the incidence of disease.[10] Measles outbreaks occur predominantly in unvaccinated individuals and are facilitated by low coverage as well as the high transmissibility of MeV. To prevent recurrent outbreaks of measles, 95% of population must be immune. Several attenuated measles vaccines are available worldwide, either as single-virus vaccines or in combination with other vaccine viruses, commonly with rubella and mumps.[11]

Subjects and Methods

This is a cross-sectional study conducted in Diyala Province, Iraq, from November/2020 to October/2021. Blood samples were collected from a total of 425 children (≤14 years of age). Ninety of them were patients clinically-suspected of having measles, they presented with fever and skin rash (18 were vaccinated with measles vaccine and 72 were not). The rest of children had no clinical suspicion of measles, 270 of them were measles-vaccinated, including those who received all recommended vaccines in the Iraqi Expanded Program of Immunization (IEPI), and 65 were non-vaccinated, including those who received none of the vaccines in the IEPI. Patients and controls were enrolled from Al-Batool Teaching Hospital for Children and Maternity as well as other health-care centers belonging to the Diyala Health Directorate. Five milliliters of blood was aspirated aseptically from each subject and 2 mL was placed in ethylenediaminetetraacetic acid tubes for determination of complete blood count (CBC). The remaining 3 mL was placed in plane tubes for separation of serum which were kept frozen at –20°C till tested. Enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource, USA) for quantitative and qualitative detection of anti-measles immunoglobulin (Ig) M were used. A special questionnaire was preconstructed for this study, and it included questions concerning name, age, sex, residence, and vaccination status of the participant, along with notes concerning the clinical features in clinically suspected individuals. The study was ethically and scientifically approved. Informed verbal consent was obtained from all participating children's legal guardians. Statistical analyses were done using the SPSS-27 (Statistical Package for the Social Sciences, version 27, IBM, Armonk, New York, United States). Quantitative data were tested using Student's *t*-test for difference between two independent means or paired two-sample *t*-test for difference of paired dependent means or ANOVA test for difference among more than two independent means. The difference of percentages (qualitative data) was tested using Pearson's Chi-squared test. Statistical significance was considered whenever the $P \leq 0.05$.

Results

The results in Table 1 show that 14 (15.6%) of patient children had positive anti-measles IgM antibody versus 76 (84.4%) who were negative. Whereas, only one (1.5%) of the unvaccinated children was positive for anti-measles IgM. Additionally, all vaccinated children were negative. Thus, the positivity rate of anti-measles IgM was significantly higher in patients compared to other study groups ($P = 0.0001$).

Data in Table 2 reveal that the mean ± standard deviation (SD) of anti-measles IgM concentration in the patient, vaccinated, and unvaccinated groups was 3.328 ± 3.032 mIU/mL, 1.972 ± 0.729 mIU/mL, and 3.628 ± 1.248 mIU/mL, respectively. Therefore, the mean ± SD of anti-measles IgM concentration in patients was significantly higher compared to other study groups ($P = 0.0001$).

Table 3 shows that the anti-measles IgM positivity rate was insignificantly higher among patients in the 1st year of life (28.6%, $P = 0.426$). On the control side, the only child with positive IgM was 6 years of age; therefore, no statistical analysis could be done.

Table 1: Distribution of study groups by anti-measles immunoglobulin M positivity

Anti-measles IgM status	Study groups		
	Vaccinated, *n* (%)	Unvaccinated, *n* (%)	Patients, *n* (%)
Positive	-	1 (1.5)	14 (15.6)
Negative	270 (100.0)	64 (98.5)	76 (84.4)
Total	270 (100.0)	65 (100.0)	90 (100.0)
P	0.0001*		

*Significant difference between percentages using Pearson's Chi-square test at 0.05 level. IgM: Immunoglobulin M

Table 2: Distribution of anti-measles immunoglobulin M concentration in study groups

Measles IgM concentration (mIU/mL)	Study groups		
	Vaccinated, *n* (%)	Unvaccinated, *n* (%)	Patients, *n* (%)
<1.0	-	-	15 (16.7)
1.0	179 (66.3)	11 (16.9)	21 (23.3)
2.0	69 (25.6)	10 (15.4)	18 (20.0)
3.0	13 (4.8)	22 (33.8)	8 (8.9)
4.0	9 (3.3)	17 (26.2)	8 (8.9)
≥5.0	-	5 (7.7)	20 (22.2)
Total	270 (100.0)	65 (100.0)	90 (100.0)
Mean±SD	1.972±0.729	3.62 8±1.248	3.328±3.032
Range	1.040–4.930	1.090–7.80	0.140–18.210
P		0.0001*	

*Significant difference between two independent means using Student's *t*-test at 0.05 level. SD: Standard deviation, IgM: Immunoglobulin M

Results in Table 4 reveal that there was insignificant difference in the anti-measles IgM positivity rate between males and females in the patient group (15.7% vs. 15.4%, $P = 0.969$).

The results in Table 5 reveal that the anti-measles IgM positivity rate was insignificantly higher among patients residing in rural areas compared to those from urban areas (16.7% vs. 13.9%, $P = 0.722$).

The distribution of CBC is shown in Table 6. The mean ± SD of hemoglobin (g/dL) was significantly higher among vaccinated children compared to other groups ($P = 0.0001$). Moreover, the mean ± SD of red blood cell count (cell/cc × 10^6) was significantly higher among vaccinated children compared to other groups ($P = 0.0001$). Furthermore, the mean ± SD of white blood cell count (cell/cc × 10^3) in patients was significantly higher compared to other groups ($P = 0.0001$). Concerning the lymphocyte count (cell/cc × 10^3), the results showed that the mean ± SD was significantly higher among patients ($P = 0.0001$). Regarding the platelet count (cell/cc × 10^3), the mean ± SD was significantly

Table 3: Distribution of anti-measles immunoglobulin M positivity in study groups by age

Age (years)	Study groups - anti-measles IgM					
	Patients (90)			Control (65)		
	Positive, *n* (%)	Negative, *n* (%)	Total, *n* (%)	Positive, *n* (%)	Negative, *n* (%)	Total, *n* (%)
1	2 (28.6)	5 (71.4)	7 (100.0)	-	7 (100.0)	7 (100.0)
2	3 (16.7)	15 (83.3)	18 (100.0)	-	4 (100.0)	4 (100.0)
3	3 (20.0)	12 (80.0)	15 (100.0)	-	4 (100.0)	4 (100.0)
4	2 (18.2)	9 (81.8)	11 (100.0)	-	6 (100.0)	6 (100.0)
5	1 (14.3)	6 (85.7)	7 (100.0)	-	6 (100.0)	6 (100.0)
6 and more	3 (9.4)	29 (90.6)	32 (100.0)	1 (2.6)	37 (97.4)	38 (100.0)
P		0.425*			-	

*Insignificant difference between percentages using Pearson's Chi-square test at 0.05 level. IgM: Immunoglobulin M

Table 4: Distribution of anti-measles immunoglobulin M positivity by gender

Gender	Study groups - anti-measles IgM					
	Patients (90)			Control (65)		
	Positive, *n* (%)	Negative, *n* (%)	Total, *n* (%)	Positive, *n* (%)	Negative, *n* (%)	Total, *n* (%)
Male	8 (15.7)	43 (84.3)	51 (100.0)	-	35 (100.0)	35 (100.0)
Female	6 (15.4)	33 (84.6)	39 (100.0)	1 (3.3)	29 (96.7)	30 (100.0)
P		0.969*			-	

*Insignificant difference between percentages using Pearson's Chi-square test at 0.05 level. IgM: Immunoglobulin M

Table 5: Distribution of anti-measles immunoglobulin M positivity by residence

Residence	Study groups - anti-measles IgM					
	Patients (90)			Control (65)		
	Positive, *n* (%)	Negative, *n* (%)	Total, *n* (%)	Positive, *n* (%)	Negative, *n* (%)	Total, *n* (%)
Rural	9 (16.7)	45 (83.3)	54 (100.0)	1 (2.7)	36 (97.3)	37 (100.0)
Urban	5 (13.9)	31 (86.1)	36 (100.0)	-	28 (100.0)	28 (100.0)
P		0.722*			-	

*Insignificant difference between percentages using Pearson's Chi-square at 0.05 level. IgM: Immunoglobulin M

Table 6: Distribution of complete blood count of study groups

CBC	Vaccinated	Patients	Unvaccinated	*P*
Hb (g/dL)	12.93±0.84	11.83±1.21	12.86±0.90	0.0001*
RBC (cell/cc × 10^6)	4.73±0.45	4.09±0.51	4.49±0.46	0.0001*
WBC (cell/cc × 10^3)	7.10±1.33	7.74±3.46	6.39±1.21	0.0001*
LYM (cell/cc × 10^3)	2.45±0.49	3.59±1.33	2.36±0.52	0.0001*
PLT (cell/cc × 10^3)	255.67±55.38	181.97±53.66	248.06±47.42	0.0001*

*Significant difference among <2 independent means using ANOVA test at 0.05 level. CBC: Complete blood count, Hb: Hemoglobin, RBC: Red blood cell, WBC: White blood cell, LYM: Lymphocyte, PLT: Platelet

higher among vaccinated children compared to other groups ($P = 0.0001$).

Discussion

The anti-measles IgM as a marker of recent infection was affirmed to have high sensitivity and specificity in the serological diagnosis of measles cases.[12,13] The results of this study showed that the rate of anti-measles IgM positivity among patients was 15.6% which was significantly higher compared to that of unvaccinated group (1.5%). This result is comparable with the result of a Turkish study in which ELISA technique was used, and it was found that 11.1% of patients were positive for anti-measles IgM.[14] In another study conducted in Diyala Province, measles was reported in 21.5% of children admitted to hospital.[15]

However, the rate of measles infection in this study is lower compared with the results of several other studies conducted in different cities; for example, using ELISA as a diagnostic method, it was found that the anti-measles IgM was 44.3% in Al-Kadhimiya Teaching Hospital.[16] The anti-measles IgM positivity rate was 71.06% in Beijing, China.[17] A study revealed that 66.7% of patients had positive IgM in Roma.[18] A study reported that the positivity rate of measles IgM was 88.72% in Qinghai Province.[19] It was reported that 62.4% of patients were positive for measles IgM in Nigeria.[20]

Measles infection among previously vaccinated children can probably be attributed to vaccine failure that may arise due to cold chain failure, inadequate viral dose, and host immune factors such as persistence of maternal antibody as well as presence of other underlying illnesses such as HIV.[21] In this context, during an outbreak of measles in a highly vaccinated community of Cameroon, 35% of the cases had not received any measles-containing vaccine.[22] In a study to investigate measles infection in vaccinated and unvaccinated children presenting with fever and maculopapular rash during measles outbreaks in Nigeria, 62.4% had measles IgM, 55.3% of them were vaccinated, while 44.7% were not, affirming that in spite of vaccination program, children were infected with measles, irrespective of their vaccination status.[20] It is worth to mention that among patients included in our study, all 14 (19.4%) who were positive for IgM were unvaccinated, affirming that the appearance of these measles cases was largely or completely due to missed vaccination.

In a large Chinese study, it was found that integration of IgM ELISA, with real-time reverse transcription–polymerase chain reaction (RT-PCR), greatly improved the accurate diagnosis of measles cases, especially during the 1st few days after onset when the patients were highly contagious and in those with secondary vaccine failure, affirming that IgM ELISA is the gold-standard assay for detection of measles cases. However, real-time RT-PCR should be introduced to supplement the laboratory diagnosis, especially in settings of preelimination.[23] In Morocco, it was found that 52% of anti-measles IgM ELISA-negative samples tested positive by RT-PCR.[24]

Additionally, our results found that only 1 (1.5%) of unvaccinated healthy children had positive anti-measles IgM, although those children were basically included as apparently healthy controls. It is important to mention that the majority (95.4%) of those children appeared protected (anti-measles IgG positive). These protective IgG antibodies were most probably induced by clinical or subclinical measles infection, such infection provides lifelong protection against all serotypes of MeV.[25] These naturally derived antibodies were proved to be more durable than vaccine-derived antibodies.[26,27] Of course, due to the high contagiousness of MeV, the existence of subclinical measles cases in the community is very hazardous as it may prime and hasten outbreak occurrence.[20,22]

This study demonstrated that most patients with positive measles IgM were 1 year old and the lowest positivity rate was in children ≥6 years of age. These results are consistent with those of a study that reported that most measles cases were in 1-year-old (27%) and 2-year-old children (19%).[16] Moreover, the present results are consistent with those of a study that showed that the highest incidence of measles was in the age group ≤1 year (52.8%), and the mortality in measles outbreak in Diyala was 17 patients which was also higher among patients aged younger than 1 year.[28] Likewise, in Ethiopia, the rate of measles IgM using ELISA technique was 31.3% among 1- to 4-year-old children regardless of sex.[29]

On the other hand, the current results are inconsistent with several studies such as one study that found that children within 10–12 years of age had the highest seropositivity (88.9%) of measles IgM.[21] Furthermore, another study found that the majority of measles cases (30.0%) appeared in children who were 4 years old.[30]

The 15.6% IgM positivity rate among patients with fever and skin rash is an important outcome which indirectly refers to the fact that MeV still exists and each measles case may herald the onset of an outbreak, especially among unvaccinated children. Whatever the reasons behind the lack of vaccination, the 15.6% infection rate cannot be ignored. Thus, it can be concluded that continuous surveillance system should be monitored and followed up by health authorities, despite the fact that the measles vaccination coverage in the areas under investigation is effective.

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Conflicts of interest

There are no conflicts of interest.

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