

Positivity Rate of Epstein–Barr Virus Antiviral Capsid Antigen Immunoglobulin M among Children with Infectious Mononucleosis in Diyala

Mohammad Kassem Saleh, Abdulrazak SH. Hasan, Nadhum Gazal Noaman

Department of Community Medicine, College of Medicine, University of Diyala, Baqubah, Iraq

Abstract

Background: Epstein–Barr virus (EBV) is a small double-stranded linear DNA human herpes virus that is transmitted primarily through saliva. Majority of primary EBV infections in infants and young children are clinically silent. Clinically, primary infections by EBV are presented as infectious mononucleosis (IMN) syndrome, which is characterized by pharyngitis, cervical lymphadenopathy, fever, and lymphocytosis. **Objectives:** This study was designed to explore the rate of EBV anti-viral capsid antigen (VCA) immunoglobulin M (IgM) among children who were clinically suspected as having IMN in Diyala province. **Subjects and Methods:** A total of 248 subjects were included; 190 were clinically suspected as having IMN and 58 apparently healthy subjects were included as a control group. The age range of the patients was 9–168 months; 88 of them were males, while 102 were females. Similarly, the age range of the apparently healthy subjects was 9–168 months; 29 of them were males while 29 were females. The anti-VCA IgM antibodies were detected in the serum samples using the VCA IgM enzyme-linked immunosorbent assay technique (DiaPro Diagnostic Bioprobes Srl, Italy). Human privacy was respected by taking the parents' verbal consent. Statistical analysis of the data was carried out using Statistical Packages for the Social Sciences (SPSS), Version 25. Statistical significance was considered whenever the $P \leq 0.05$. **Results:** The results showed that the anti-VCA IgM positivity rate among clinically suspected children with IMN was 24/190 (12.6%), while only 2/58 (3.4%) of the apparently healthy subjects were positive, with a statistically significant difference ($P = 0.046$). Age and gender distribution had no statistically significant effect on the IgM positivity rate ($P = 0.432$ and $P = 0.960$, respectively). Furthermore, most IgM-positive patients had at least three of the main clinical features; however, no statistically significant association was found between the IgM positivity rate and the main clinical features ($P = 0.157$ for headache and $P = 0.692$ for malaise). **Conclusion:** The rate of IMN among clinically suspected patients in Diyala province was 12.6%, the peak age of primary infection was 1–4 years, the male-to-female ratio was 1:1.2, and the main presenting complaints were fever and sore throat.

Keywords: Anti-viral capsid antigen immunoglobulin M, Epstein–Barr virus, infectious mononucleosis

INTRODUCTION

Epstein–Barr virus (EBV) is a small (122–180 nm in diameter) double-stranded linear DNA human herpes virus consisting of a toroid-shaped protein core that is wrapped with the viral DNA inside an icosahedral capsid, with a tegument lining the space between the nucleocapsid and the outer envelope, into which different glycoprotein spikes are inserted. In human, two main types of EBV have been identified: EBV-1 and EBV-2.^[1,2] EBV is transmitted primarily through saliva and is shed intermittently in healthy carriers. Transmission through blood transfusion, genital secretions, and breast milk has also been reported. EBV can also be transmitted as a result of organ transplantation, and primary EBV infection through this route

is a major risk factor for posttransplant lymphoproliferative disease.^[3] EBV can infect both epithelial cells and B cells. The EBV replication cycle can switch between lytic and latent state, and latently infected cells can sometimes be stimulated to reactivate EBV.^[4,5]

Address for correspondence: Dr. Abdulrazak SH. Hasan, Department of Medical Microbiology, College of Medicine, University of Diyala, Baqubah, Iraq.
E-mail: razak1957@yahoo.com

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Over 90% of the population is seropositive for EBV worldwide. Most children are infected by the age of 2 years in developing countries, while in developed countries, EBV infection occurs more often in the late childhood and adolescence.^[6] The majority of primary EBV infections in infants and young children are clinically silent. In older patients, it is accompanied by symptoms of infectious mononucleosis (IMN) in about 50% of cases. The incubation period of IMN in adolescents is 30–50 days. In children, it may be shorter.^[7] IMN is a clinical syndrome characterized by pharyngitis, cervical lymphadenopathy, fever, and lymphocytosis and is most often caused by EBV.^[8] Secondary attack rates of IMN are low (<10%) because most family or household contacts already have antibody to the agent.^[6] Infants coinfecting with HIV acquire EBV infection at an earlier age, have higher EBV plasma loads that are slower to resolve, and more frequently develop pneumonia and hepatosplenomegaly and require hospitalization compared to HIV-negative infants.^[7]

Chen *et al.*, in a study conducted in China, among a total of 761 blood samples from children (22 days to 14 years) with suspected EBV infection, found that 109 were positive for EBV infection with a positivity rate of 14.3%.^[9] Similar studies had yielded comparable results.^[10–12] On the other hand, in the study conducted by Wang *et al.*, in Beijing, China, the positivity rate among suspected IMN patients was higher (59.3%).^[13] Similarly, Saldaña *et al.* observed a high positivity rate in Mexico (57.6%).^[14]

SUBJECTS AND METHODS

This cross-sectional study was carried out in Diyala province, for the period from July 10, to November 5, 2018, to explore the rate of EBV anti-viral capsid antigen (VCA) immunoglobulin M (IgM) among children who were clinically suspected as having IMN.

A total of 248 subjects were included; 190 clinically suspected as having IMN and 58 apparently healthy subjects as a control group. For the clinically suspected patients, the mean age $\pm$ standard deviation (SD) was 57 ± 42 months, the age range was 9–168 months (9 months to 14 years), 88 of them were males, and 102 were females. The mean age $\pm$ SD of the apparently healthy subjects was 57 ± 42.4 months, the age range was 9–168 months, 29 of them were males, and 29 were females. A questionnaire form was preconstructed including information about age, gender, residence, educational status of child, educational status of parents, main clinical features and family history of similar condition (for patients only), and history of previous hospitalization. Blood samples were collected aseptically by venipuncture from the median cubital vein (or some other vein if the former was inaccessible) in Al-Batool Teaching Hospital for Maternity and Children-Consultatory Clinic and Public Health Laboratory in Baquba. Serum was then obtained and preserved in deep freezer (-20°C) until the time of performing the tests. The anti-VCA IgM antibodies were detected in the serum samples

using the VCA IgM enzyme-linked immunosorbent assay kit (from DiaPro Diagnostic Bioprobes Srl, Italy). Human privacy was respected by taking the parents' verbal consent. Statistical analysis of data was carried out using Statistical Package for the Social Sciences (SPSS), version 25 Armonk, NY:IBM. Statistical significance was considered whenever the $P \leq 0.05$.

RESULTS

Results in Table 1 show that 24/190 (12.6%) suspected IMN patients were positive for anti-VCA IgM, while only 2/58 (3.4%) apparently healthy subjects were positive, with a statistically significant difference ($P = 0.046$).

Regarding anti-VCA IgM concentration, Table 2 shows that the mean concentration $\pm$ SD in suspected IMN patients was 6.335 ± 15.061 , which was higher than that in the apparently healthy subjects (4.496 ± 5.568). Similarly, the concentration range in suspected IMN patients (0–100) was wider than that in the apparently healthy subjects (0–28.376). Nevertheless, the difference between the two groups was statistically insignificant ($P = 0.364$).

Table 3 shows that the anti-VCA IgM positivity rate among suspected IMN patients was the highest (20%) among

Table 1: Association of anti-viral capsid antigen immunoglobulin M status with clinical suspicion of infectious mononucleosis

Anti-VCA IgM status	Suspected IMN patients, <i>n</i> (%)	Apparently healthy, <i>n</i> (%)
Positive	24 (12.6)	2 (3.4)
Negative	166 (87.4)	56 (96.6)
<i>P</i>	0.046	

IMN: Infectious mononucleosis, VCA: Viral capsid antigen, IgM: Immunoglobulin M

Table 2: Association of anti-viral capsid antigen immunoglobulin M concentration with clinical suspicion of infectious mononucleosis

Anti-VCA IgM concentration (arbu/ml)	Suspected IMN patients	Apparently healthy
Mean $\pm$ SD	6.335 $\pm$ 15.061	4.496 $\pm$ 5.568
Standard error of mean	1.093	0.743
Range	0–100	0–28.376
Percentile		
5 th	0	0.131
25 th	0.349	0.611
50 th (median)	1.616	2.140
75 th	5.371	8.821
95 th	28.846	9.825
99 th	100	28.376
<i>P</i>	0.364	

IMN: Infectious mononucleosis, VCA: Viral capsid antigen, SD: Standard deviation, IgM: Immunoglobulin M

those <1 year of age. Among the apparently healthy controls, the highest positivity rate (10%) was among those 10–14 years old. No statistically significant association was found in either group ($P = 0.432$ for suspected IMN patients and 0.402 for control subjects).

Results in Table 4 show that there is no statistically significant association between anti-VCA IgM status and gender since the positivity rate is almost the same among males (12.5%) and females (12.7%) of suspected IMN patients, resulting in $P = 0.960$, and the positivity rate is the same (3.4%) in both males and females among control subjects, leaving no chance for statistical comparison (no P value).

The association of anti-VCA IgM status with main clinical features in suspected IMN patients is shown in Table 5. Since all suspected cases had both fever and sore throat (12.6% IgM positive, and the rest negative), no statistical analysis was possible. Only four patients had enlarged lymph nodes (LN) (3, 75% IgM positive and 1, 25% negative); therefore, no statistical analysis could be conducted with such a small number of cases compared to those with no enlarged LN (total of 186 cases). Patients with headache and malaise had a positivity rate of 12.2% and 11.8%, respectively; however, these results did not result in a statistically significant association between IgM status and headache ($P = 0.157$) or malaise ($P = 0.692$).

DISCUSSION

Apart from being the leading study in this field in Diyala province, undoubtedly, the importance of this study manifests through the worldwide dissemination of EBV infection in the community. Furthermore, this virus, as one of human herpes viruses causing early childhood primary infection, has a well-documented role in causing various lymphoid and nonlymphoid malignancies.^[15] Accordingly, this study was designed to figure out the rate of EBV infection among children with clinical suspicion of IMN and to assess the effects of certain demographic factors.

In this study, the positivity rate of anti-VCA IgM among suspected IMN patients was 12.6%, which was significantly higher than its counterpart among apparently healthy subjects ($P = 0.046$). The reason behind such a low positivity rate can probably be explained by the fact that, in developing countries, most children are infected by EBV in early childhood, and in a high percentage of these cases, EBV infection is either completely asymptomatic or presents with atypical clinical picture of IMN or nonspecific constitutional signs and symptoms,^[6] rendering clinical diagnosis of the disease questionable without a high suspicion index and resorting to laboratory tests to fulfill the clinical suspicion. Therefore, laboratory tests are preferably recommended for the final diagnosis of IMN in Iraq, rather than depending on clinical features alone, as these features are common among wide range of infectious and noninfectious illnesses in our community.^[16,17] On reviewing the scientific literature, a good share of the previous studies had yielded similar results.^[10-12]

Table 3: Association of anti-viral capsid antigen immunoglobulin M status with age

Age (years)	Anti-VCA IgM status			
	Suspected IMN patients		Control	
	Positive, n (%)	Negative, n (%)	Positive, n (%)	Negative, n (%)
<1	4 (20.0)	16 (80.0)	-	10 (100)
1-4	13 (14.9)	74 (85.1)	-	23 (100)
5-9	5 (8.8)	52 (91.2)	1 (6.7)	14 (93.3)
10-14	2 (7.7)	24 (92.3)	1 (10.0)	9 (90.0)
<i>P</i>	0.432		0.402	

IMN: Infectious mononucleosis, VCA: Viral capsid antigen, IgM: Immunoglobulin M

Table 4: Association of anti-viral capsid antigen immunoglobulin M status with gender

Gender	Anti-VCA IgM status			
	Suspected IMN patients		Control	
	Positive, n (%)	Negative, n (%)	Positive, n (%)	Negative, n (%)
Male	11 (12.5)	77 (87.5)	1 (3.4)	28 (96.6)
Female	13 (12.7)	89 (87.3)	1 (3.4)	28 (96.6)
<i>P</i>	0.960		-	

IMN: Infectious mononucleosis, VCA: Viral capsid antigen, IgM: Immunoglobulin M

Table 5: Association of anti-viral capsid antigen immunoglobulin M with main clinical features in infectious mononucleosis patients

Main clinical features	Anti-VCA IgM status	
	Suspected IMN patients	
	Positive, n (%)	Negative, n (%)
Fever/sore throat		
Yes	24 (12.6)	166 (87.4)
No	0 (0)	0 (0)
Enlarged LN		
Yes	3 (75.0)	1 (25.0)
No	21 (11.3)	165 (88.7)
Headache		
Yes	11 (12.2)	79 (87.8)
No	13 (13.0)	87 (87.0)
<i>P</i>	0.157	
Malaise		
Yes	13 (11.8)	97 (88.2)
No	11 (13.8)	69 (86.3)
<i>P</i>	0.692	

IMN: Infectious mononucleosis, VCA: Viral capsid antigen, LN: Lymph node, IgM: Immunoglobulin M

Moreover, Chen *et al.*, in a closely similar study to the current one, out of a total of 761 blood samples from children (22 days to 14 years) with suspected EBV infection in China, found out that 109 cases were positive for EBV infection with a positivity rate of 14.3%.^[9] On the other hand, Wang *et al.* found that

the positivity rate among suspected IMN patients was higher than the current study (59.3%).^[13] Similarly, Saldaña *et al.* observed a high positivity rate in Mexico (57.6%).^[14] These inconsistent results can probably be attributed to the larger sample size, as well as the wider age range for the patients included in these studies compared to the current study. In addition, other laboratory criteria were also taken into account for choosing patients for these studies, such as the presence of atypical lymphocytes, whereas the current study's inclusion criteria were based solely on clinical features. Besides that, undoubtedly, the source and type of diagnostic laboratory kits may play a role in the final outcome of results.^[18,19]

The positivity rate of anti-VCA IgM among apparently healthy children in the current study was 3.4%. Such a low positivity rate was also found in most previous studies, despite the fact that some of them had a wider age range for the healthy population included compared to this study.^[11,20-22] The finding of anti-VCA IgM which indicates recent infection in apparently healthy individuals is certainly related to the fact that most primary infections with EBV are clinically silent.^[23]

Results in the present study revealed that the anti-VCA IgM positivity rate has an inverse relation with age, taking into account the total number of suspected IMN patients, with no statistically significant association ($P = 0.432$). However, the age group distribution of IgM positive patients was as shown in the results, indicating a peak in the age group of 1–4 years. These results were strongly consistent with the results of most previous studies.^[10,11,13,24-26] In addition, Devkota *et al.* reported similar results (peak in the age group of 0–<4 years).^[27] However, in another study conducted in Mexico, there was a peak in the number of EBV-positive patients in the age group of 5–7.5 years.^[14] This is most likely due to the superiority of the public health regulations and sanitation in Mexico compared to Iraq, leading to a shift in the peak age of primary EBV infection toward a slightly older age group, or the fact that the study was based merely on the clinical files of patients admitted at National Institute of Pediatrics, Mexico City, making the study group less representative of the general population. Besides the scientific fact that as the age of children progresses, the performance of the immune system becomes more developed and thus the clinical picture of infectees becomes more evident.^[12]

No statistically significant effect of gender on IgM positivity rate was found in this study ($P = 0.960$), and the male-to-female ratio of IgM-positive patients was 1:1.2. Comparative male-to-female ratios were found in many previous studies.^[13,22,28-30] Furthermore, a male-to-female ratio of 1:1.3 was observed in a study conducted in China.^[20] Nonetheless, in other studies, the ratio of males was higher than females among IgM-positive patients; however, as it was found in the current study, no statistically significant effect of gender on IgM positivity rate was found in these studies.^[27,31,32] These slightly dissimilar results are probably due to differences in the male to female ratio of the study group in these studies compared to the present study.

Main clinical features among IgM-positive patients in this study were as follows: 100% had both fever and sore throat (with pharyngitis and/or tonsillitis), this is because the selection of suspected IMN patients was mainly based on having these two clinical features, in addition to other features of IMN, 54.2% had malaise (or fatigue), 45.8% had headache, and 12.5% had enlarged LNs (mainly cervical). No statistically significant association of any of these clinical features with the positivity rate of IgM was found. It is worth mention that only four patients had enlarged LNs, and three of those four tested positive for anti-VCA IgM; however, no statistical analysis could be conducted with this small number of patients with enlarged lymph nodes. Despite the fact that lymphadenopathy is considered a main feature of typical IMN picture, the low percentage of patients with lymphadenopathy in the current study can be attributed to the peak age of primary EBV infection in Iraq (1–4 years as concluded from this study), and IMN only rarely presents in typical picture in this age group. Stock stated that the primary EBV infection in children up to 10 years is usually asymptomatic or shows unspecific courses such as producing flu-like symptoms or symptoms similar to those of common throat infections (mild pharyngitis, with or without tonsillitis).^[33] Wang *et al.* observed similar results concerning fever (96.9%) and sore throat due to tonsillopharyngitis (94.1%), as these were the most common complaints, however, lymphadenopathy was found in 90.2% of patients.^[13] This is probably due to the wider age range of IMN patients (0.6–39 years) included in that study compared to the present study. Similar consistent results were reported by Balfour *et al.*, since 93% of patients had sore throat, 66% had fatigue, and 47% had headache, along with some inconsistent results (76% had cervical lymphadenopathy, and 42% had fever).^[12] Again, the age difference between the study group for that study (included university students) and the present study is the probable reason behind these inconsistent results. Likewise, Macsween *et al.*, in a study targeting university students, reached comparable results concerning sore throat and fatigue, yet again higher percentage of patients had lymphadenopathy (54%).^[30]

CONCLUSION

IMN infection rate among clinically suspected patients in Diyala province was 12.6%, the peak age of primary infection was 1–4 years, the male-to-female ratio was 1:1.2, and the main presenting complaints were fever and sore throat.

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Conflicts of interest

There are no conflicts of interest.

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