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The Rate of Parvovirus B19 Infection among Children with Clinically Suspected Erythema Infectiosumin Diyala Province, Iraq

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Abstract

Background: Parvovirus B19 (PVB19V) infection is widespread and associated with a heterogeneous clinical spectrum, ranging from asymptomatic to potentially life-threatening aplastic crisis in chronic haemolyticanaemia, hydrops fetal is, neurologic diseases and arthroplasty. PVB19 infection usually causes erythema infectiosumin (EI), a benign self-limiting disease characterized by typical cutaneous manifestations (slapped cheek appearance with per oral sparing followed by a diffuse maculopapular rash evolving to a reticular pattern).**Objectives:** The present study was conducted to explore the rate of human PVB19 infection rate among children with fever and skin rash and to figure out the role of attribute factors.**Materials and methods:** The present cross-sectional study was conducted between December 2019 and June 2020 in Diyala province, Iraq. Data and samples were collected from different teaching hospitals and healthcare centers. Sixty apparently healthy children were enrolled as control group and200 patients clinically presented with skin rash and fever. The age group was (1-14) years. A special questionnaire form was pre-constructed for this study including: Sociodemographic factors, clinical manifestation and history of underlining conditions. Blood samples were aseptically drawn from all studied groups. Part of the blood was used for the determination of complete blood count (CBC). The remaining was placed in plane tubes, left at room temperature for 30 minutes. Thereafter, serum samples were separated, labeled and stored at −20°C till use. ELISA technique was used for determination of anti-PVB19 IgM and IgG in serum (DIA-PRO, Italy). Human privacy was respected by obtaining verbal consent from their patents. Statistical analysis was done by SPSS version 25 and P values less than 0.05 were considered significant.**Results:** The anti-PVB19 IgG positivity rate in children with EI patients was 198(95.0%) which is significantly higher compared to that of control (P= 0.0001). The anti-PVB19 IgM positivity rate among children with EI was 907(45.0%), versus 2(3.3%) among healthy control. thus the difference was significantly higher (P= 0.0001). Furthermore, the mean ± SD of the anti-PVB19 IgG as well as anti-PVB19 IgM titers in children with EI were significantly higher than that of children in control (P= 0.0001 and P= 0.0001) respectively. Moreover, the anti-PVB19 IgG and anti-PVB19 IgM titers were insignificantly associated with age, sex, and residence of EI patients. Regarding the blood indices,the PCV (%), WBC (x103), and MCV (fL),MCH (pg/cell).MCHC (gm/dl) and the PLT (x103) were significantly higher in children with EI compared to their counterparts of control.**Conclusion**: The infection rate and seroprevalence of parvovirus B19 among children with fever-rash illness are high suggesting that parvovirus

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B19 should be considered in the differential diagnosis of all children with fever and rash in Diyala province, Iraq.

Keywords: Parvovirus B19, Erythema infectiosumin, Diyala province

INTRODUCTION:

Human parvovirus B19 (hPVB19) is belong to the genus Erythrovirus,*Parvoviridae* family(Cotmore *et al.*, 2014)[1].It has a linear, single-stranded DNA genome packaged into icosahedra capsid,which is composed of 60 capsid proteins, a mixture of VP1 and VP2. VP2 accounts for about 95% of the viral capsid proteins, whereas VP1 accounts for about 5%(Sun *et al.*, 2019)[2]. PVB19V is transmitted mainly by the respiratory route, but prodromal symptoms are fever, malaise, headache, and myalgia rather than respiratory symptoms. The virus can also be transmitted via blood or pooled-blood productsand vertically (Juhl and Hennig, 2018)[3] .Infection of erythroid progenitor cells in bone marrow through the viral cellular receptor P antigen may cause erythema infectiosumin (EI), an entity mainly characterized by fever and skin rash, so historically recognized as the fifth disease, after measles, rubella, Varicella, and scarlet fever of the classical childhood skin rashes or exanthemas in children(Janovitz *et al.*, 2017)[4,5]. PVB19 infection is more common in children than adults; about 20 % of infected are asymptomatic and 50 % are experience non-specific flu-like symptoms. Human PVB19 may cause serious illnesses including pneumonia with diffuse alveolar damage resulting in acute respiratory distress syndrome(Qiu *et al.*, 2017; Das *et al.*, 2019)[6,7].Wawina *et al.*, (2017)[8]found that among children less than 5 years with fever-rash illness, the anti-PVB19 IgM was 61.6% and 51.8% were positive for B19V DNA.Human parvovirus B19 infection is also associated with rheumatoid arthritis and myocarditis (Naciute *et al.*, 2016)[9] and infections in pregnant women which may lead to hydrops fetal is or even fetal loss (Xiong *et al.*, 2019)[10].It can cause severe medical problems if the patient has hematological or immunological deficiencies,as in patients with AIDS or sickle cell disease, in which B19 infection interferes with hematopoisis and causes acute anemia (Regaya *et al.*, 2007; Rastegarpouyani*et al*., 2018)[11,12]. PVB19V infection is common worldwide, with regional epidemiological differences; generally over one-half of the adult population having been exposed. The prevalence of PVB19specific antibodies in the population is age dependent(Qiu*et al.*, 2017)[6]. Erythema infectiosumin is occurring in seasonal outbreaks, being most prevalent in winter and spring in 3 year cycles, with a brief period of incubation, a high infectivity rate, most likely through droplet spread(Servey, Reamy and Hodge, 2007; Wawina *et al.*, 2017)[8,13]. Clinically, prodromal symptoms did not usually precede the rash, which may appear suddenly. The rash appeared firstly as facial erythema (slapped cheek) and then as Erythematous maculopapular eruptions over the trunk and proximal extremities, lasting for weeks or longer(Quattrocchi *et al.*, 2012)[14]. Although the arthralgia and myalgia were more seen in affected adults; However, arthritis and encephalitis were noted as complications of fifth disease (Koliou*et al.*, 2014; Watanabe *et al.*, 2015)[15,16].Parvovirus B19 infection is serologically diagnosed as significant anti-PVB19 IgM positivity which may persist up to 6 months and genotypically by the detection of viral DNA in the serum using PCR which often be detected up to 2 months after onset of illness. The presence of anti-PVB19 IgG in the serum is indicative of an immune response to

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previous viral exposure, while the specific IgA antibodies are too persistent to be a useful indicator of recent PVB19 infection(Erdman *et al.*, 1991; Maple *et al*., 2014)[17,18].Because the primary targets 0f PVB19 infection are erythroid progenitor of the bone marrow leading toErythropoiesis arrest particularly problematic for patients with hematological disorders(Janovitz *et al.*, 2017; Ashaka *et al.*, 2018; Mohamed *et al.*, 2019)[19-21]. HPV-B19 erythema infectiosumin with concomitant leucopenia and low platelet counts were reported even if typical clinical findings are absent(Yaguchi*et al*., 2015)[22]. It has been reported that thrombocytopenia appears earlier than the anemia, because the lifespan of thrombocytosis is considerably shorter than that of erythrocytes, suggest that PVB19 attacks not only "erythropoietin" blast cells but also immature bone marrow cells, which are later responsible for the thrombocytopoiesis (Wiersbitzky, 1991; Wildig et al., 2010)[23,24]. Furthermore, PVB19 infection may be a common cause of leukocytopenia and thrombocytopenia even in adult patients without hematological disorders (Ogata et al., 2000)[25].

MATERIAL AND METHOD

The present study is a cross-sectional conducted between December 2019 and June 2020 in Diyala province, Iraq. Data and samples were collected at AL-Batool Teaching Hospital for Maternity and Children, Baquba Teaching Hospital, Khanqin General Hospital and Jalawla General Hospital.The study was designed to explore the infection rate and seroprevalence ofparvovirus B19 virus among children clinically presented with fever and skin rash. The study was approved by the ethical committee in the college of Medicine/University of Diyala as well as by the scientific committee in the Diyala Directorate of Health.Sixty apparently healthy children were enrolled as control groupand200 patients who were clinically suspected as having erythema infectiosumin. The age range of children was 1-14 years. Special questionnaire was pre-constructed to collect information regarding: age, gender, residence, presence of skin rash, presence of fever, history of underlining disorders. About 4-5 milliliters of venous blood was aseptically drawn from all studied groups. The blood sample was divided into two parts; 1 milliliter was placed in EDTA (Ethylene diamine tetra acetic acid) ant coagulated for the determination of complete blood count (CBC). The remaining of blood was placed in plane tubes, left at room temperature for 30 minutes, and then centrifuged at 3000 rotation /minutes for 15 minutes. The serum samples were separate, labeled and stored at −20°C till use. ELISA technique was used for determination of anti-PVB19 IgM and IgG positivity rate as well as their titers in serum samples (DIA-PRO, Italy). Human privacy was respected by obtaining verbal consent from their patents. Statistical analysis was done by SPSS version 25 and P values less than 0.05 were considered significant.

RESULTS

Table (1) revealed the distribution of age groups. The Mean ± SD of patients with erythema infectiosumin and control groups were 6.5 ± 3.8, and 6.9 ± 3.7 respectively. There was statistically insignificant difference among study groups (P= 0.444).

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Table (1): Age distribution of study groups

Age groups (Ys)	EI patients		Healthy control	
	No.	%	No.	%
1- 4	70	35.0	20	33.3
5- 9	60	30.0	26	43.4
10- 14	70	35.0	14	23.3
Mean ± SD	7.0 ± 4.1		6.9 ± 3.7	
(Range)	(1-15)		(1-14)	
P value	EI patient compared to control = 0.444			

Insignificant difference between percentages of Pearson Chi-square (χ^2-test) at 0.05 levels

Results in table (2) showed that the rate of males in children with erythema infectiosumin was slightly lower than that of controls (40.0% *Vs* 53.3%). Whereas, females of erythema infectiosumin were slightly higher than that of control (60.0% *Vs* 46.7%).The difference was statistically insignificant (P = 0.067). the rate of rural to urban residence in children with erythema infectiosumin compared to that of the control was also statistically insignificant (P= 0.509).

Table (2): Sex and residence distribution of study groups

Gender	EI patients		Healthy control	
	No.	%	No.	%
Male	80	40.0	32	53.3
Female	120	60.0	28	46.7
P value	Thalassemia compared to control = 0.067			
Residence				
Rural	113	56.5	66	48.9
Urban	87	43.5	69	51.1
P value	Thalassemia compared to control = 0.509			

Insignificant difference between percentages of Pearson Chi-square (χ^2-test) at 0.05 level

The distribution of complete blood counts was shown in table (3). The Mean ± SD of hemoglobin concentration Hb (gm/dl) of the children with EI and control groups were 11.3 ± 1.52 and 11.3 ±1.19 respectively, while the range of these groups were (6.3-15.5) and (6.5-13) respectively. The difference was statistically insignificant (P= 0.426). Whereas, the Mean ± SD of Packed cell volume (PCV %) of children with EI and control groups were 35.4 ±4.40 (23.7-50) and 34.8 ± 6.30, while the range of PCV in the same order were (23.7-50) and (4.77-42). Thus, it was significantly lower in RI patients compared to control group (P= 0.0001). The Mean ± SD of mean corpuscular volume (MCV) in the children with EI and control groups were 76.9 ± 8.84, and 73.69 ± 6.16, while their corresponding range in same order were (51.7-101.3) and (52.8-87.3) respectively. Thus thalassemia patients had significantly lower values (P= 0.007). The Mean ± SD of mean corpuscular hemoglobin

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(MCH) in the children with EIand control groups were 24.5 ± 3.4 and 23.5 ± 2.5 with their corresponding range in same order were (16.0-34.6) and (16.2-28.6) respectively. Therefore, EI patients had significantly lower values (P= 0.0001). Concerning the mean corpuscular hemoglobin concentration (MCHC), the results found that the Mean ± SD of mean in the children with EI and control groups were 31.7 ± 2.13 and 31.69 ± 1.52 respectively with their corresponding range in same order were (25.0-38.1) and (26.4-34.7) respectively. Thus children with EI had significantly higher MCHC value (P= 0.003).Regarding the platelets count (PLT $x10^3$), the results showed that the Mean ± SD of mean in the children with EI and control groups were 296.4 ± 102.2 and 317.5 ± 116.2 respectively, with their corresponding range in same order were(118-739) and (34.1-739) respectively. So, the children with EI had significantly higher platelets count (P= 0.0001).

Table (3): comparison of complete blood counts of study groups

CBC values	EI patients	Control	P value
	Mean ± SD (Range)	Mean ± SD (Range)	
Hb (g/dL)	11.3 ± 1.52 (6.3-15.5)	11.3 ±1.19 (6.5-13)	0.426
PCV%	35.4 ± 4.40 (23.7-50)	34.8 ± 6.30 (4.77-42)	0.0001*
WBC ($x10^3$)	9.24 ± 3.38 (3.5-26)	8.89 ± 3.15 (3.5-20.6)	0.0001*
NEU (%)	45.2 ± 19.8 (1.7-88.5)	49.4 ± 13.5 (4.6-74.2)	0.0001*
LYM (%)	33.40 ± 14.12 (7.2-82.8)	39.6 ± 13.98 (13.7-82.8)	0.177
MCV (fL)	76.9 ± 8.84 (51.7-101.3)	73.69 ± 6.16 (52.8-87.3)	0.007*
MCH (pgm/c)	24.5 ± 3.4 (16.0-34.6)	23.5 ± 2.5 (16.2-28.6)	0.0001*
MCHC (gm/dl)	31.7 ± 2.13 (25.0-38.1)	31.69 ± 1.52 (26.4-34.7)	0.003*
PLT ($x10^3$)	296.4 ± 102.2 (118-739)	317.5 ± 116. (34.1-739)	0.0001*

*Significant difference among three independent means using ANOVA-test at 0.05 levels

FL (femtoliters); Pgm/c (pictograms/cell); gm/dl (grams/ deciliters); NEU: Neutrophils; LYM

The anti-PVB19 IgG positivity rate in children with EI patients was 198(95.0%) while the remaining 10 (5.0%) were negative. In the healthy control, the anti- PVB19 IgG positivity rate was 38(63.3%) and the remaining 22 (36.7%) were negative. Again the positivity rate of children with EI was significantly higher compared to control (P= 0.0001). Furthermore, the results also showed that the mean ± SD of anti-PVB19IgG titer of children with EI and controls were 2.400 ±1.590 and 1.434 ±1.220 respectively, and their corresponding range in the same order were (0.147-6.362) and (0.063-3.475) respectively. All these details were shown in table (4).

Table (4): Anti-Parvovirus B 19 IgG positivity rate among study groups

Marker	Status	EI patients		Control	
		No.	%	No.	%
Anti-Parvovirus B 19 IgG	Positive	190	95.0	38	63.3
	Negative	10	5.0	22	36.7
	Mean ± SD	2.400 ±1.590		1.434 ± 1.220	

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	(Range)	(0.147-6.362)	(0.063-3.475)
P value	Thalassemia compared to control =0.0001*		

*Significant difference between two independent means using Students-test at 0.05 levels
The anti-PVB19 IgM positivity rate among children with EI was 907(45.0%), versus 2(3.3%) among healthy control. thus the difference was significantly higher (P= 0.0001). Therefore, the difference between the two groups was statistically significant (P= 0.0001). The results also revealed that the mean ± SD of anti-PVB19 IgM titer among children with EI and healthy control were 0.722 ± 0.541and 0.294 ± 0.267 respectively, and their corresponding range in the same order were (0.044-5.022) and (0.024-1.988) respectively, table (5).

Table (5): Anti-Parvovirus B 19 IgM positivity rate among study groups

Marker	Status	EI patients		Control	
		No.	%	No.	%
Anti-Parvovirus B 19 IgM	Positive	90	45.0	2	3.3
	Negative	110	55.0	58	96.7
	Mean ± SD	0.722 ± 0.541		0.294 ± 0.267	
	(Range)	(0.044-5.022)		(0.024-1.988)	
P value	Thalassemia compared to control =0.0001*				

*Significant difference between two independent means using Students-test at 0.05 levels
Results in table (7) showed the mean ± SD, SE of mean, range, percentile 5,percentile 25, median, percentile 75, percentile 95, percentile 99 of the anti-Parvovirus B19 IgG titer of the study groups. The mean ± SD of anti-Parvovirus B19 IgG titer in children with EI was significantly higher than that of children in control, but the difference was failed to reach the levels of statistical significance (P= 0.0001). Regarding the anti-Parvovirus B19 IgM titer, the mean ± SD of anti-Parvovirus B19 IgM titer in children with EI was significantly higher than that of children in control (P= 0.0001).

Table (6): Anti-Parvovirus B19 IgG and IgM titer among study groups

Details	Anti-Parvovirus B19 IgG titer (IU/L)		Anti-Parvovirus B19 IgM titer (IU/L)	
	EI	Control	EI	Control
Count	200	60	200	60
Mean ± SD	2.400 ±1.590	1.434 ±1.220	0.722±0.541	0.294±0.267
Standard Error of Mean	0.112	0.158	0.038	0.034
Range	0.147-6.362	0.063-3.475	0.044-5.022	0.024-1.988
Percentile 05	0.308	0.116	0.192	0.138
Percentile 25	1.002	0.277	0.448	0.176
Median	2.083	0.981	0.470	0.205
Percentile 75	3.391	2.661	0.903	0.446

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Percentile 95	5.215	3.294	1.612	0.476
Percentile 99	5.876	3.475	1.988	1.988
P value comparing with control	0.0001*		0.0001*	

**Significant difference among three independent means using ANOVA-test at 0.05 levels
*Significant difference between two independent means using Students-test at 0.05 levels

Table (8) showed the association of certain demographic factors with the anti-PVB19 IgG titer. Regarding the age, the mean ± SD of the 1-4 and 5-9 years age groups in children with EI (2.401 ±1.673and 2.626 ±1.580) were significantly higher than their counterparts in control children (1.394±1.166 and 1.413 ± 1.266) (P= 0.0001 and 0.0001) respectively. Whereas, the mean ± SD of the 10-14 years old children (2.136 ±1.485) was higher than that of children in the control (1.528±1.293); However, the difference was failed to reach the levels of statistical significance (P= 0.065). Comparison of mean ± SD of different age groups within the EI patients category had insignificant difference (P= **0.781**), and likewise, the comparison of the mean ± SD of different age groups within the control category (P= **0.690**).Regarding the gender, the results found that the mean ± SD of male and female children with EI (2.332 ± 1.563 and 2.445 ± 1.613) were significantly higher than that of control children (1.485±1.266 and 1.375±1.186), (P= 0.0001 and P= 0.0001) respectively. Vertical comparison between the mean ± SD of male and female in children with EI (2.332 ± 1.563 *Vs*2.445 ± 1.613) were statistically insignificant (P= **0.510**). Likewise, themean ± SD of male versus female children in the control (1.485 ± 1.266 *Vs* 1.375 ± 1.186) were statistically insignificant (P= 0.451). About the residence, the results revealed that the mean ± SD of children reside in the rural areas and those reside in urban areas in the EI (2.292 ± 1.470and 2.541 ± 1.732) and children in the control (1.453 ± 1.294 and 1.413 ± 1.159), (P= 0.0001 and P= 0.001) respectively. However, vertical comparison between the mean ± SD of children reside in rural versus urban areas within EI (2.292 ± 1.470 *Vs*2.541 ± 1.732) were statistically insignificant (P= **0.820**). While, the comparison between rural versus urban children in the control (1.453 ± 1.294 *Vs 1.413* ±1.159) was statistically insignificant (P= 0.390)

Table (7): Association of anti-Parvo B19 IgG titer with demographic variables

Variables	Anti-Parvovirus B 19 IgG titer				P value
	EI patients		Control		
	No.	Mean ± SD	No.	Mean ± SD	
Age					
1--4	70	2.401 ±1.673	20	1.394 ± 1.166	0.0001*
5--9	70	2.626 ±1.580	26	1.413 ± 1.266	0.0001*
10--14	60	2.136 ±1.485	14	1.528 ± 1.293	0.065
P value	0.781		0.690		
Gender					
Male	80	2.332±1.563	32	1.485±1.266	0.0001*
Female	120	2.445±1.613	28	1.375±1.186	0.0001*

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P value	0.510		0.451		
Residence					
Rural	113	2.292±1.470	31	1.453±1.294	0.0001*
Urban	87	2.541±1.732	29	1.413±1.159	0.001*
P value	0.820		0.390		

*****Significant difference among three independent means using ANOVA-test at 0.05 levels
**Significant difference between two independent means using Students-test at 0.05 levels

Table (9) summarizes the association between the anti-PVB19 IgM titer and certain demographic factors. The results showed that the mean ± SD of anti-PVB19 IgM titer in children with EI aged1-4 years, 5-9 years and 10-14 years (0.831 ± 0.711, 0.654 ± 0.378 and 0.673 ± 0.455) were significantly higher than that of the control group (0.337 ± 0.404, 0.311 ± 0.183 and 0.199 ± 0.084), (P= 0.004, 0.0001 and 0.002) respectively. A Comparison of age within the same category, the results found that there was insignificant difference among the EI and control groups (P= **0.110** and P= **0.308**) respectively. The results also found that the mean ± SD anti-PVB19 IgM titer in males (0.699 ± 0.481) and females (0.737 ± 0.579) of children with EI were significantly higher than that of male and female control (0.321 ± 0.330 and 0.262 ± 0.171), (P= 0.0001 and P= 0.0001) respectively. However, a comparison between male and female in the two study groups; EI patients and control were insignificantly different (P= **0.233** and P= **0.396**) respectively.About the residence, the mean ± SD anti-PVB19 IgM titer in children with EI reside in rural areas (0.733 ± 0.612) and those reside in urban areas (0.708 ± 0.435) were significantly higher than that of control children (0.332 ± 0.351 and 0.253 ± 0.121), (P= 0.0001 and P.0001)respectively. Whereas, a comparison between rural and urban participants in the same category; EI, and control were statistically insignificant (P= **0.748** and P= **0.251**) respectively.

Table (8): Association of anti-Parvo B19 IgM titer with demographic variables

Variables	Anti-Parvovirus B 19 IgM titer				P value
	EI patients		Control		
	No.	Mean ± SD	No.	Mean ± SD	
Age					
1--4	70	0.831 ± 0.711	20	0.337 ± 0.404	0.004*
5--9	70	0.654 ± 0.378	26	0.311 ± 0.183	0.0001*
10--14	60	0.673 ± 0.455	14	0.199 ± 0.084	0.002*
P value	0.110		0.308		
Gender					
Male	80	0.699 ± 0.481	32	0.321 ± 0.330	0.0001*
Female	120	0.737 ± 0.579	28	0.262 ± 0.171	0.0001*
P value	0.233		0.396		
Residence					
Rural	113	0.733 ± 0.612	31	0.332 ± 0.351	0.001*
Urban	87	0.708 ± 0.435	29	0.253±0.121	0.0001*
P value	0.748		0.251		

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*****Significant difference among three independent means using ANOVA-test at 0.05 levels
**Significant difference between two independent means using Students-test at 0.05 levels
Results presented in table (3) revealed that all (100%) children with suspected EI has fever and skin rash and on the contrary none of them has concomitant diseases. Face rash was recorded in 25 (12.5%)with significantly higher anti-PVB19 IgM titer (P= 0.0001), while 62 (31.0%) of patients had trunk skin rashwith significantly higher anti-PVB19 IgM titer (P= 0.003). Other site body skin rash was recorded in 113 (56.5%) of the cases with significantly lower anti-PVB19 IgM titer P= 0.049).

Table (9): Association of anti-Parvo B19 IgM titer in EI patients with skin rash

Variables	Anti-Parvovirus B 19 IgMG titer	
	No. (%)	Mea ± SD
Face skin rash		
Yes	25(12.5)	1.133 ± 0.919
No	175 (87.5)	0.663 ± 0.436
P value	0.0001**	
Trunk skin rash		
Yes	62 (31.0)	0.893 ± 0.703
No	138 (69.0)	0.645 ± 0.431
P value	0.003**	
Skin rash on other sites		
Yes	113(56.5)	0.684 ± 0.453
No	87(43.5)	0.870 ± 0.785
P value	0.049**	

**Significant difference between two independent means using Students-test at 0.05 level

DISCUSSION

The anti-PVB19 IgM positivity rate among children with suspected EI (45.0%) was significantly higher versus healthy control (3.3%), (P= 0.0001). Moreover, the mean ± SD of anti-PVB19 IgM titer among children with EI was higher than that of healthy control. Based on the fact that anti-PVB19 IgM was affirmed as a serological markers of primary infection by PVB19 (Jazayer et al., 2013)[26]. The current result in this regard is similar to that conducted by Erdman and his colleagues who reported a specific IgM antibodies were detected in 97% of patients with erythema infectiosumin versus 1% from the control group(Erdman *et al.,* 1991)[17]. Similarly Okabe and his co-workers found a high specific anti-PPVB19 IgM and high concentrations of specificanti-PVB19 IgG among children with EI, but none of control were positive for anti-PVB19 IgM (Okabe *et al.,* 1984)[27]. Additionally, the hPVB19-IgM was detected in 48.97% among 5-52 years old individuals with rash-fever illness in Bulgaria and 56.18% for them were positive for hPVB19-DNA(Toshev*et al.,* 2014)[28]. The variability of anti-PVB19 IgM positivity in different studies may be influenced by age and viral genotypes (Jazayer*et al.,* 2013; Jain and Kant, 2018)[26,29].The 3.3% anti-PVB19 IgM positivity rate among the apparently healthy controls certainly indicate asymptomatic primary infection with PVB19.In this regard, it has been

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documented that about 25%-50% of patients are infected but remain totally asymptomatic although they are still capable of spreading the disease and 50 % of patients are experience nonspecific flu-like symptoms (Woolf *et al.*, 1989; Rogo*et al*., 2014)[30,31].It has been reported that following exposure to PVB19, a rapid viral replication in erythroid progenitor cells results in a high level viremia which is terminated by the production of specific IgM antibody beginning around day 9. High levels of IgM lasting for 1-2 weeks and coinciding with the time of skin rash appearance(Quattrocchi*et al.*, 2012; Qiu *et al.*, 2017)[6,14]. Moreover, it has been found that anti-PVB19 IgM antibody is initially produced at 8 to 12 days post infection, clears viremia, and lasts for 3 to 6 months(Erdman *et al.*, 1991)[17], this relatively long period of persistent of anti-PVB19 IgM may be overlapped by anti-PVB19 IgG which is arise thereafter,meaning that the both markers may be detected simultaneously in same patients. This is true for the present study as 63.3% of healthy controls were positive for anti-PVB19 IgG.On the other hand, The anti-PVB19 IgG positivity rate in children with suspected EI was (95.0%) which was significantly higher compared to that of control (63.3%), (P= 0.0001). Furthermore, the mean ± SD of anti-PVB19IgG titer of children with EI was higher than that of controls. Similar results were found that the prevalence of anti-PVB19 IgG showed a gradual and steady increase from 37% in children aged 1 to 5 years to 87% in people aged >50 years (Heegaard *et al.*, 2002)[32]. The present results also consistent with those assured high seropositivity of anti-PVB19 IgG among children with fever and rash illness (Okabe *et al.*, 2002; Jazayer*et al*., 2013)[26,27]. The existence of circulatory anti-PVB19 IgG undoubtedly indicates past exposure and immunity. The production and rising of IgG antibody follows IgM a few days later, which wanes to an undetectable level thereafter. Whereas the IgG prevails for longer period and probably for the life of individuals (Kurtzman *et al.*, 2008)[33].The seroprevalence of PVB19 among healthy control up to 14 years as represented by IgG was 63.3%. These antibodies, because there was no PVB19 vaccine licensed in the Iraqi Expanded Program of Immunization, are certainly pointing out to past exposure and immunity.The seroprevalence of PVB19 IgG differed between 9.78% and 79.1% among different countries, based on geographical differences, viral genotypes prevailing, sample size enrolled as well as the sensitivity of laboratory kits employed(Juhl and Hennig, 2018)[3]. So, the seroprevalence of anti-PVB19 IgG obtained in this study is either higher or lower than the global studies; for instance, the IgG seropositivity among Chinese blood donors was 24.6% (Ke *et al.*, 2011)[34].The seroprevalence among adults more than 18 years old in Germany was 72.1% suggesting that these individuals were considered as probably immune against a B19V infection (Rohrer *et al.*,2008)[35].Furthermore, the seroprevalence of anti-PVB19 among Indian blood donors was 27.9% (Kumar et al., 2013)[36],among Tunisian blood donors was 65.0% (Letaief et al., 1997)[37], and among Italian was 79.1% (Gallinella *et al.*, 2003)[38]. Since, the blood and its derivatives are among the main routes of PVB19 transmission, almost all studies in regards assure the importance of national screening of blood donors(Li *et al.*, 2020)[39].In the present study and other studies, cases of EI among children were associated with fever, skin rash and anemia. Wawinaa*et al.* (2017)[8] found that among children less than 5 years with fever-rash illness, the anti-PVB19 IgM was 61.6% and 51.8% were positive for B19V DNA. The elevated body temperature is pointing out to the beginning of viremia when there was an elevation of PVB19 levels in the blood circulation. Parvovirus is demonstrable in the bloodstream some 7–10 days after

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exposure and persists for approximately 5 days with viral loads exceeding 10 12 particles/ml of blood. PVB19 IgM antibodies are at a detectable range within 10–12 days and persist for about 3–5 months, while the IgG antibodies are detected 15 days post infection and can persist for long periods and probably confers lifelong immunity(de Jong *et al.*, 2006)[39]. The detrimental effect of PVB19 infection on blood indices particularly the Hemoglobinpathies which are manifested clinically by anemia among patients (Abiodun *et al.*, 2013; Mohamed *et al.*, 2019)[21,40]. Furthermore, Ashaka *et al.*, (2018)[20] in Nigeria, found that the PVB19 IgM was found in 29.8% of anemic children and 15.7% non-anemic children, suggesting that infection with PV B19 is common and screening for the virus during differential diagnosis is recommended. Additionally, Wildig *et al.*, (2010)[24], reported that high PVB19 IgM levels were significantly associated with severe anemia, being found in 2.7% of cases of severe anemia in the population of children, while based on PVB19 IgG about 15% of children were exposed to PVB19. These results support that of the current study in which the Mean ± SD of most blood indices of patients with EI were significantly higher than that of controls.Hematopoisis is the process of the generation of all differentiated blood cells including erythrocytes, which are carried out by a population of hematopoietic stem cells in bone marrow. All blood cells are divided into three lineages; Erythropoiesis, lymphopoiesis and myelopoiesis(Birbrair and Frenette, 2016)[41]. Erythropoiesis is developed from erythropoietin stem cell to mature red blood cell, whereby primitive multiprotein hematopoietic stem cells ($CD34^+$) were committed to the erythroid lineage. PVB19 infection shows a remarkable tropism for earlier and late erythroid progenitor cells in human bone marrow and fetal livers that express the cell surface marker CD36(Ozawa *et al.*, 1986)[42]. It was demonstrated that erythropoietin receptor signaling is absolutely required for PVB19 replication in erythroid progenitor cells from $CD34^+$ hematopoietic cells and at least partly accounts for the remarkable tropism of B19V infection for human erythroid progenitors (Chen et al., 2010)[43]. Actually, the interest in PVB19 has increased because of the burden of anemia among children in developing countries where other multiple causes of anemia abound (Chaparro and Suchdev, 2019)[44]. As PVB19 preferentially targets young erythrocytes and suppresses red blood cell production and contributes to anemia among children with other underlying conditions(Wildig *et al.*, 2007)[24].High PVB19 infection occurs in patients with red cells disorders, the cytopathic effect of the virus on red blood cell progenitors majors; the red cell aplasia leading to a transient aplastic crisis. The most frequent conditions include: sickle cell disease, alpha or beta-thalassemia, enzyme deficiencies (G6PD, pyruvate kinase), hereditary elliptocytosis and Spherocytosis(Arabzadeh et al., 2017; Cilla *et al.*, 2020)[45,46]. The present results also found that neither anti-PVB19 IgM nor IgG titers were associated with age, sex or residence of patients with erythema infectiosumin. In these regards different studies had obtained variable results; for instance, it has been found that rash–fever illnesses in Tunisia were more prevalent in females than males in the age range 19 months to 4 years(Bouafsoun *et al.*, 2016)[47]. Furthermore, there was no significant difference between age groups in children under 5 years of age(Wawina*et al.*, 2017)[8]. However, several studies involving populations with a wider age range have shown that the incidence of PVB19V infection increases significantly with age (Salimi et al., 2008; Rohrer et al., 2008)[35,48].

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CONCLUSION

It can be concluded that the rate of parvovirus B19 infection among children with fever-rash illness as well as the seroprevalence were high in Diyala community beside the presence of asymptomatic infection.

Conflict of interest: No

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