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The Seropositivity Rate of Human Parvovirus-B19 Infection in Children with Skin Rash and Thalassemia in Diyala Gavernarate

A Thesis

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Chapter One

Introduction

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1. Introduction

1.1. Background

The first identified human virus of *Parvoviridae*, genus *Erythroparvovirus*, was the parvovirus B19, also called *erythrovirus B19*. The Australian virologist Yvonne Cossart discovered the virus by chance in 1975. It gained the B19 name because it was discovered in well B19 of a large series of microtiter plates as well as from the Latin word parvum, meaning small, reflecting the fact that Parvo B19V ranks among the smallest DNA viruses (Cossart *et al*., 1975). Parvo B19V is a non-enveloped, icosahedral virus measuring 23–26 nm in diameter, which contains a linear single - stranded DNA genome with a length of approximately 5600 base pairs (bp). The infectious particles may contain either positive or negative strands of DNA. The icosahedral capsid consists of 60 capsomeres, consisting of two structural proteins, VP1 (83 kDa) and VP2 (58 kDa), which are identical except for 227 amino acids at the amino-terminal of the VP1-protein, the so-called VP1-unique region. VP2 is the major capsid protein, and comprises approximately 95% of the total virus particle (Callaway *et al.*, 2017; Sun *et al.*, 2019).

Like other non-enveloped DNA viruses, the pathogenicity of Parvo B19V involves binding to host cell receptors, internalization, translocation of the genome to the host nucleus, DNA replication, RNA transcription, assembly of capsids and packaging of the genome, and finally cell lysis with release of the mature virions. In humans, the P antigen (Globoside) is the cellular receptor for Parvo B19V (Servant-Delmas and Morinet, 2016). Furthermore, erythropoietin signals have been shown to be completely important in the erythroid progenitor cell replication of Parvovirus B19V by disrupting human genomes and facilitating the incorporation of erythroid progenitor cell viral DNA (Chen *et al.*, 2010; Janovitz *et al.*, 2017). Affirming that the induction of inflammatory cytokines gene expression in parvo B19V -infected marrow mesenchymal stem cells might influence on bone marrow microenvironment and hematopoiesis (Behzadi *et al.*, 2019).

The virus is primarily spread by infected respiratory droplets; blood-borne transmission, however, has been reported. The secondary attack risk for exposed household persons is about 50%, and about half of that for classroom contacts (Juhl and Hennig, 2018). Parvo B19V can also be transmitted from the mother to the fetus, through bone marrow and organ transplantations, and via transfused blood products

(Qiu *et al*., 2017; Jain and Kant, 2018). It has been reported that 5.3% of parvo B19V infection is transfusion transmitted, suggesting an implementation of screening assays for blood and blood products (Byaene *et al*., 2020). A significant increase in the number of cases is seen every three to four years; the last epidemic year was 1998. Outbreaks can arise especially in nurseries and schools. Parvo B19V causes an infection in humans only. Cat and dog parvoviruses do not infect humans. As of 2017, no approved human vaccine existed against parvo B19V (Enders *et al.*, 2006; Qiu *et al.*, 2017).

A variety of diseases is related to parvo B19V, including erythema infectiosum in children (fifth disease), acute or chronic arthropathy in adults, transient aplastic crisis in patients with chronic hemolytic anaemia, persistent anaemia in immunocompromised patients, and fetal hydrops in pregnant women. Many genotypes of parvo B19V (genotypes 1-3) are circulating with wide variability in their geographic distribution and their association with different clinical manifestation as well as childrens age at infection (Türk Dağı *et al*., 2010; Jain and Kant, 2018). However, parvo B19V is known as the classic cause of the childhood rash called fifth disease, erythema infectiosum, or slapped cheek syndrome (Young and Brown, 2004; Qiu *et al.*, 2017).

The Fifth disease of parvo B19V is associated with bright red rash of the cheeks which gives it the nickname slapped cheek syndrome. Any age may be affected, although it is most common in children aged 6-10 years. It is so named because it was the fifth most common cause of a pink-red infection associated rash (Bokalanga *et al.*, 2017). Once infected, patients usually develop the illness after an incubation period of 4-14 days. The disease commences with mild fever and malaise, when the virus is most abundant in the bloodstream, and patients are usually no longer infectious once the characteristic rash of this disease has appeared (Servey *et al.*, 2007; Qiu *et al.*, 2017). Symptoms begin some 6 days after exposure and last about a week. Infected patients with normal immune systems are contagious before becoming symptomatic, but probably not after. Individuals with parvo B19V IgG antibodies are generally considered immune to recurrent infection, but reinfection is possible in a minority of cases. About half of adults are parvo B19V-immune due to a past infection (Lehmann *et al.*, 2003; Wawina *et al.*, 2017).

Human Parvovirus B19 is a cause of chronic anemia in individuals with acquired immunodeficiency syndrome (AIDS) and kidney transplant patients (Doldan *et al.*, 2009; Hai *et al.*, 2019). Furthermore, there is evidence that parvo B19V is a cause of acute and chronic persistent hepatitis, which is considered to be an exceptional etiology in case other causes of chronic hepatitis were ruled out (Mogensen *et al.*, 2010). In adults and perhaps some infants and arthritis are frequently recorded in connection with parvo B19V infection. The occurrence of the viral structural proteins (VP1 and VP2)

coincides with the initial identification of circulating IgM and IgG antibodies. This is could be due to parvovirus does not progress to other forms of arthritis up to 15% of all new cases of arthritis. Joint symptoms usually last one to three weeks but can last from 10% to 20% of people affected (Caliskan *et al.*, 2005; Weissbrich e*t al.*, 2007; Watanabe and Kawashima, 2015). Parvo B19V infection was also shown to include rheumatoid arthritis pathogens in at least some patients (Naciute *et al.*, 2016).

Human parvovirus B19 infection in pregnant women is associated with hydrops fetalis due to severe fetal anemia, sometimes leading to miscarriage or stillbirth. The risk of fetal loss is about 10% if infection occurs before week 20 of pregnancy. Maternal parvo B19V infection during pregnancy increased the risk of fetal loss, spontaneous abortion, and stillbirth. A high incidence of fetal loss and fetal hydrops were observed in pregnant women with placental villitis (Abiodun *et al.*, 2013; Oliveira *et al.*, 2019; Xiong *et al.*, 2019). To the best of our knowledge, only one study was conducted in Diyala province on Parvovirus B 19 focusing on the infection in pregnant women (Hasan *et al.*, 2013). Therefore, this study was suggested to be carried out.

1.2. Aims of the study

The present study was conducted to achieve the following goals:

1. To explore the Parvovirus B19 infection rate among children clinically presented with fever and rash in Diyala province through detection of anti-parvovirus B19 IgM and IgG.

2. To Figure out the Parvovirus B19 Infection rates in Thalassemia patients as a risky group through dectection of anti-parvovirus B19 IgM and IgG.

3. To determine the effect of certain socio-demographic factors.

SUMMARY

Human parvovirus B19 (parvo B19V) is the only member of *Parvoviridae* family, genus of *Erythrovirus*, pathogenic to humans. It is a non-enveloped, icosahedral virus containing single-stranded linear DNA genome. VP2 is the main capsid protein and forms 95% of the impact of the virus particle size. It is composed of two structural proteins, (VP1 and VP2) incorporated with VP1 proteins to make the capsid structure. This is graded as erythrovirus but has a distinct tropism for human erythroid progenitor cells and triggers apoptosis in compromised erythroid progenitors, contributing to acute and chronic anemia. Parvo B19V infection is common worldwide, transmited by respiratory droplets, contaminated blood products which is transplacentaly from an infected mother to the fetus. The most common clinical manifestation of parvo B19V during childhood is erythema infectiosum (Fifth disease or slapped cheek) which is mainly characterized by fever and rash, Arthralgia and arthritis particularly in adults.

The objectives of this study are to explore the prevalence of Parvo B19V IgG and IgM antibodies among children with fever and skin rash, and to figure out the Parvo B19V infection in children with thalassemia and to determine its ratio of association with socio-demographic factors.

This is across‑sectional study conducted in Diyala province from December 2019 to August 2020. The study population included children from AL-Batool Teaching Hospital for Maternity and Children, Baquba Teaching Hospital, Khanqin General Hospital, Jalawla General Hospital and Central Blood Bank.This study enrolled 395 participants. The following categories were grouped; 60 children apparently healthy as control; 200 children presented skin rash and fever as clinically suspected erythema infectiosum and 135 children with laboratory confirmed thalassemia. The age range was from 1 to 14 years. A questionnaire form was preconstructed for this purpose. ELISA Anti-HEV IgM and IgG (DIA-PRO, Italy) antibodies and titer were calculated. Human privacy was respected by obtaining the verbal consent of the parents of selected children. Statistical analysis was done via SPSS version 26 and P values less than 0.05 were considered significant.

It was found that anti-parvovirus B19 IgG rate of positive between children with clinically suspected erythema infectiosum was (**95.0%**), in the children with thalassemia, it was (**89.6%**), and among healthy children, it was (**63.3%**) a statistically insignificant difference (**P= 0.062**). The anti-parvovirus B19 IgM rate of positive among children with clinically suspected erythema infectiosum was (**45.0%**), in children with thalassemia it was

(**34.8%**), while among healthy children it was (**3.3%**) a statistically insignificant difference (**P= 0.063**).

The Mean ± SD of anti-Parvovirus B19 IgG titer of children with clinically suspected erythema infectiosum, children with thalassemia and healthy children were 2.400 ±1.590 IU/L, 1.929 ±1.955 IU/ L and 1.434 ±1.220 IU/L respectively with high significance in clinically suspected children with erythema infectiosum (P= 0.0001). Whereas, the Mean ± SD of anti-Parvovirus B19 IgM titer of children with clinically suspected erythema infectiosum, children with thalassemia and healthy children were 0.722±0.541 IU/L, 0.621±0.449 IU/L and 0.294±0.267 IU/L respecrtively, with high significance in clinically suspected erythema infectiosum (P= 0.0001). However, there was insignificant correlation between other variables; age, residence, gender and clinical signs with Parvo B19V IgM titers and IgG titers.

The analysis found that the hemoglobin level was also presented insignificantly different among the study groups. In thalassemia patients there were a significantly lower values in the level of PCV (P=0.0001); mean corpuscular volume (MCV) (P=0.007); mean corpuscular hemoglobin (MCH) (P=0.0001). Therefore, thalassemia patients had significantly higher MCHC value (P=0.003) compared to other groups.

The result of the correlation of anti-parvovirus B19 IgG titer with different variables showed that the platelets count was significantly correlated with the anti-parvovirus B19 IgG titer in children with erythema infectiosum (r = 0.182, P= 0.010), but not in other groups. Other variables were insignificantly correlated with the IgG titer. The correlation between anti-parvovirus B19 IgM titer and other different variables such as the hemoglobin concentration, PCV%, WBC count in children with erythema infectiosum were significantly correlated with the anti-parvovirus B19 IgM titer (r=-0.203, P= 0.004; r= -0.184, P= 0.009; r= 0.154, P= 0.030) respectively. Other variables in erythema infectiosum and other groups were insignificantly correlated with the Parvo B19V IgM titer.

In conclusion, the seroprevalence of parvo B19V as detected by anti-parvovirus B19 IgG among children in Diyala province was high. Asymptomatic infection among children was recorded (3.3%). Anti-parvovirus B19 IgM as a marker of recent infection was high among children with erythema infectiosum as well as thalassemia patients. The parvo B19V was associated with severe anaemia particularly among childrens with thalassemia, suggesting that in these risky children. This virus should be considered as an etiological agent.