Parvovirus B19 status in liver, kidney and pancreas transplant candidates: A single center experience

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Observational Study

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Abstract

BACKGROUND
Parvovirus B19 (B19V) is associated with a wide range of clinical manifestations. The major presentation is erythema infectiosum. However, a persistent infection may cause pure red cell aplasia and chronic anemia in immunocompromized patients. The B19V seroprevalence varies with age and geographical location.

AIM
To determine the B19V serological status and DNAemia in kidney, liver, and pancreas transplant candidates.

METHODS
Patients who underwent kidney, liver, or simultaneous kidney and pancreas/liver

transplantation between January 2021 and May 2022 were included in the study. The serum samples were collected before transplantation. For detection of B19V DNA, a LightMix Kit B19V EC (TIB MOLBIOL, Berlin, Germany) was used. B19V IgM and IgG antibodies were detected using a commercial ELISA test (Euroimmun, Lübeck, Germany).

RESULTS
One hundred and thirty-one transplant candidates were included in the study, 71.0% male, with an average age of 53.27 years ± 12.71 years. There were 68.7% liver, 27.5% kidney, 3.0% simultaneous pancreas/kidney transplant (SPKT), and 0.8% simultaneous liver/kidney transplant recipients. No patients had detectable B19V DNA. B19V IgG seroprevalence was 77.1%. No acute or recent infections were detected (IgM antibodies). There was no difference in the mean age of seronegative and seropositive patients (51.8 years ± 12.9 years *vs* 53.7 years ± 12.7 years, t = -0.603; P = 0.548). Although seropositivity was lower in patients aged less than 30 years (66.6%) compared to the patients aged 30-59 years and > 60 years (80.4% and 78.1%, respectively), this difference was not significant. In addition, there was no difference in seropositivity between male and female transplant candidates, 76.3% and 78.9% (χ^2 = 0.104; P = 0.748). The seroprevalence did not differ among organ recipients, with 77.8%, 80.6%, and 50.0% for liver, kidney, and SPKT, respectively, (χ^2 = 5.297; P = 0.151). No significant difference was found in the seroprevalence in kidney transplant patients according to dialysis modality. Seroprevalence was 71.1% in hemodialysis patients, and 100% in peritoneal dialysis patients (χ^2 = 0.799; P = 0.372).

CONCLUSION
The B19V seroprevalence is expectedly high among kidney, liver, and pancreas transplant candidates, but there are still 22.9% of seronegative individuals who remain at risk for primary disease and severe manifestations. Further research should elucidate the necessity of B19V screening in peri-transplant management.

Key Words: Parvovirus B19; Seroprevalence; DNA; Kidney transplantation; Liver transplantation; Pancreas transplantation

Core Tip: Many liver, kidney, or pancreas transplant recipients are parvovirus B19 seronegative and at risk for primary disease and severe manifestations. Serological studies on pretransplant could simplify the diagnostic work-up of anemia after transplantation in these complex patients.

INTRODUCTION

Parvovirus B19 (B19V) is a small non-enveloped single-stranded DNA virus of the family *Parvoviridae*, genus *Erythroparvovirus*[1]. It was first discovered in a healthy blood donor[2] and then linked to aplastic crises in children with sickle cell anemia[3]. Subsequently, the major presentation, erythema infectiosum (fifth disease), was described[4]. B19V mainly infects the human erythroid progenitor cells [5]. The cellular receptor is globoside (erythrocyte P antigen), found on erythroid cells, erythroid precursors and red cells of the placenta and fetal myocardium, fetal liver, and some megakaryocytes and endothelial cells[6]. Rarely, individuals may lack blood group P antigen, which confers resistance to B19V infection[7].

In healthy individuals, the disease is often asymptomatic or occurs as a two-phase illness: Fever and non-specific influenza-like symptoms during the early phase of viremia, followed by erythema, arthralgia, or both, at the time of appearance of specific antiviral antibodies[8,9]. The cutaneous manifestations of B19V infection vary. Four basic patterns have been reported: exanthema, gloves-and-socks, periflexural, and palpable purpura[10]. A robust humoral immune response is required to control B19V infection and clear DNAemia. Neutralizing antibodies to B19V structural proteins appear to confer life-long protective immunity[11]. Therefore, in immunocompromised patients unable to mount

sufficient antibody response, the infection may persist and cause pure red cell aplasia and chronic anemia[12,13]. More recently, other disease manifestations have been reported, ranging from hepatitis and myocarditis to meningoencephalitis[14-17].

In the transplant setting, B19V is long known to cause persistent anemia and pure red cell aplasia due to the inability of the immunosuppressed host to clear the virus[18-20]. The epidemiology of B19V infection in solid organ transplant (SOT) recipients is unknown, with wide variances of rates reported in different studies, from 0% to 58%[21-24]. Some recent studies report a much lower rate, under 15%[23, 25]. It is noteworthy that the immune response mediates non-hematological manifestations of B19V infection; thus immune-mediated symptoms may be absent or blunted in transplant recipients. Therefore, a high level of suspicion should be present to diagnose the infection.

Serology may not reliably establish the diagnosis in the transplant population due to the inability to produce a sufficient antibody response, and polymerase chain reaction (PCR) should be used to detect viral DNA in this population[11]. High-level viremia is more likely associated with symptomatic disease [11]. Conversely, if detected at low levels, persistent DNAemia after infection may not be clinically significant[11]. Despite the lack of robust data, intravenous administration of immunoglobulins (IVIg) and decrease of immunosuppression levels are the mainstay of treatment of SOT recipients with symptomatic B19V infection[11,19]. Although IVIg's optimal dosage and duration are unknown, most patients respond well to treatment. Unfortunately, recurrence of anemia is common[26-28]. There are preliminary reports of foscarnet being used for treatment[29]. Cidofovir has shown *in vitro* efficacy, but further research is needed[30]. Also, the conversion from calcineurin inhibitor-based immunosuppression to everolimus has been described[31].

Currently, routine screening of donor and recipient serostatus for B19V is not recommended; there have been research efforts[24,32]. There is also a lack of epidemiologic data, including the seroprevalence in transplant candidates, depending on the region or organ type[11,33].

This study aimed to determine the B19V serological status and active viral replication by B19V DNA quantification in kidney, liver, and pancreas transplant candidates at a large national transplant center.

MATERIALS AND METHODS

Patients who were transplanted (kidney, liver, or simultaneous kidney and pancreas/liver) at Merkur University Hospital from January 2021 to May 2022 were included in the analysis. The hospital is a high-volume transplant center with approximately 110 liver and 50 kidney transplants performed yearly, representing over 90% of the liver transplantation program in the country and the only institution performing simultaneous transplantations. This was a single-center, prospective study.

The serum samples were collected before the transplantation. Data about the patients were collected prospectively using the hospital's electronic medical record.

Viral DNA was extracted from blood samples using a High Pure Viral Nucleic Acid Kit (Roche Applied Science, Penzberg, Germany). For quantification of B19V DNA in nucleic acid extracts, a LightMix Kit Parvovirus B19 EC (TIB MOLBIOL, Berlin, Germany) was used.

B19V IgG and IgM antibodies were detected using a commercial enzyme-linked immunosorbent assay (ELISA; Euroimmun, Lübeck, Germany). Results were interpreted according to the manufacturer's recommendations as follows: IgM ratio < 0.8 negative, 8.8-1.1 borderline, > 1.1 positive; IgG RU/mL < 4 negative, 4.0-5.5 borderline, > 5.5 positive.

Statistical analysis

Statistical analysis was performed using SPSS version 25 (Armonk, NY, United States, IBM Corp). A $P <$ 0.05 was considered to be significant. The data are expressed as the median and interquartile range (IQR), or mean ± SD, as appropriate. Categorical variables are presented as frequency counts and percentages. The normality of the data distribution was tested using the Shapiro-Wilks test. The categorical values were compared using the χ^2 test. In cases with less than 5 outcomes, Fisher's exact test was used. For continuous variables, a parametric (Student's *t*-test, ANOVA) or nonparametric test (Mann-Whitney *U*, Wilcoxon, Kruskal-Wallis) was used, depending on the distribution.

RESULTS

A total of 131 transplant candidates were included in the study, with 70.9% being male. The average age was 53.27 years ± 12.71 years. The median age was 57 years, IQR 43-63 years. The age distribution of patients is presented in Figure 1.

There were 68.7% liver, 27.5% kidney, 3.0% simultaneous pancreas-kidney transplant (SPKT) and 0.8% simultaneous liver-kidney transplant (SLKT) recipients (Table 1).

None of the tested patients had detectable B19V DNA. IgG seroprevalence was 77.1%. No recent infections (IgM antibodies) were detected.

Table 1 Study population characteristics (*n* = 131)	
Item	**Value**
Age, yr (mean ± SD)	53.27 ± 12.71
Gender	
Male	93 (70.9%)
Female	38 (29.1%)
Transplant type	
Liver	90 (68.7%)
Kidney	36 (27.5%)
SPKT	4 (3.0%)
SLKT	1 (0.8%)
Virology results	
B19V DNA positive	0 (0%; one-sided 97.5% CI: 0-2.8)
B19V IgM positive	0 (0%; one-sided 97.5% CI: 0-2.8)
IgG B19V positive	101 (77.1%; 95% CI: 68.9-83.9)

SPKT: Simultaneous pancreas/kidney transplantation; SLKT: Simultaneous liver/kidney transplantation; CI: Confidence interval.

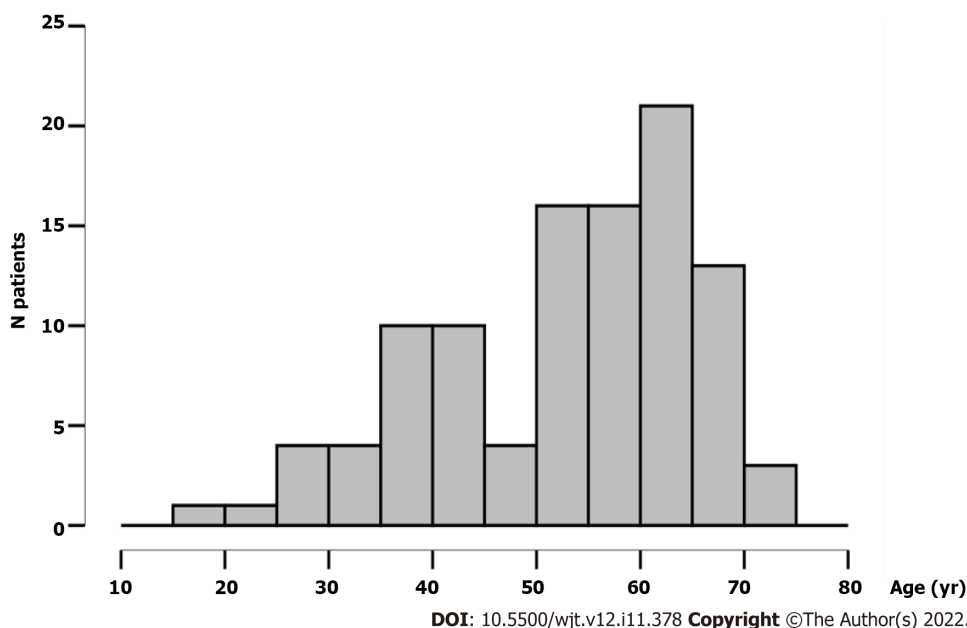DOI: 10.5500/wjt.v12.i11.378 Copyright ©The Author(s) 2022.

Figure 1 Distribution of transplant candidates according to age.

There was no difference in the mean age of seronegative and seropositive patients (51.8 years ± 12.9 years *vs* 53.7 years ± 12.7 years, t = -0.603; P = 0.548). In addition, there was no difference in seropositivity between male and female transplant candidates, 76.3% *vs* 78.9%, respectively (χ^2 = 0.104; P = 0.748). When divided into age groups, the seroprevalence was 66.7% in those under 30 years, 80.4% in those aged 30 to 59 years, and 78.1% in patients over 60 (χ^2 = 0.619; P = 0.734) (Table 2).

The seroprevalence did not differ significantly among different organ recipients, with 77.8%, 80.6%, and 50% for liver, kidney, and SPKT, respectively, (χ^2 = 5.297; P = 0.151). There was only one SLKT recipient who was seronegative. The recipients of SPKT were significantly younger than kidney or liver recipients (36.0 years ± 6.8 years, 52.6 years ± 11.6 years and 54.8 years ± 12.9 years, respectively, P = 0.014).

There was no association between immunosuppression prior to transplantation and seropositivity. B19V seroprevalence was 81.3% in the subgroup which received immunosuppression prior to transplantation and 76.4% in the subgroup that did not (χ^2 = 0.176; P = 0.675).

Table 2 Parvovirus B19 IgG seroprevalence rates in transplant candidates

Characteristics	Tested, *n* (%)	IgG positive, *n* (%)	χ^2	*P* value
Gender			0.104	0.748
Male	93 (71.0)	71 (76.3)		
Female	38 (29.0)	30 (78.9)		
Age, yr			0.619	0.734
< 30	6 (5.8)	4 (66.6)		
30-59	56 (54.4)	45 (80.4)		
> 60	41 (39.8)	32 (78.1)		
Transplant type			5.297	0.151
Liver	90 (68.7)	70 (77.8)		
Kidney	36 (27.5)	29 (80.6)		
SPKT	4 (3.0)	2 (50.0)		
SLKT	1 (0.8)	0 (0)		
IS before transplantation			0.498	0.780
Yes	16 (18.2)	13 (81.3)		
No	72 (81.8)	55 (76.4)		
Dialysis modality				0.372[1]
HD	38 (95)	27 (71.1)		
PD	2 (5)	2 (100)		

[1]Fisher's exact test. SPKT: Simultaneous pancreas/kidney transplantation; SLKT: Simultaneous liver/kidney transplantation; IS: Immunosuppression; HD: Hemodialysis; PD: Peritoneal dialysis.

No significant difference was found in the seroprevalence in kidney transplant candidates according to the dialysis modality. Seroprevalence was 71.1% in hemodialysis patients, and 100% in peritoneal dialysis patients (χ^2 = 0.799; *P* = 0.372). In addition, there was no association with dialysis duration (40.1 mo ± 25.4 mo in seropositive *vs* 37.4 mo ± 17.6 mo in seronegative, *t* = -0.288, *P* = 0.775).

DISCUSSION

Our results show a high seroprevalence of B19V among transplant candidates. The seroprevalence of 77.1% was higher compared to a large previous study in the general Croatian population, where a seroprevalence of 64.1% was found[34]. Surprisingly, the seroprevalence did not differ with age, which is commonly reported. However, although not significantly, seropositivity was lower in patients aged less than 30 years (66.6%) compared to patients aged 30-59 and 60 years (80.4% and 78.1%, respectively). The transplant population tested in this study was skewed to slightly older recipients, as shown in the age distribution. This could partly explain the inability to detect the expected difference in seroprevalence with age. In the Croatian general population, seroprevalence in the matching age group 50-59 years was 69.1%[34], which is concordant to our findings. However, it is important to note that the seroprevalence in transplant patients younger than 30 years was higher (66.6%) compared to the same age group in the general population (53.2%)[34].

Additionally, it is important to emphasize that our study investigated transplant candidates, not recipients. The candidates, contrary to the recipients, have not yet received immunosuppression. The data on transplant candidates is even scarcer in literature than on SOT recipients[11]. A German study reported a similar seroprevalence rate of 82% in transplant candidates (kidney, liver, heart, and bone marrow)[35]. Moreover, no difference was found in seroprevalence between various organ recipients, but with a trend toward lower seroprevalence among simultaneous kidney and pancreas candidates. All kidney transplant candidates in our study were patients on dialysis. Few studies analyzed the B19V seroprevalence in hemodialysis or peritoneal dialysis patients. Prevalence rates of 67.5% and 54% were reported from Brazil and Iran, respectively[36,37], which is similar to our result of 71.1% in hemodialysis patients. In our study, we found no association of seroprevalence with the duration of hemodialysis (40.1 mo ± 25.4 mo in seropositive *vs* 37.4 mo ± 17.6 mo in seronegative, *t* = -0.288, *P* =

0.775). Due to better treatment of anemia today, most dialysis patients do not receive transfusions. Therefore, the duration of dialysis does not appear to be a risk factor. The lower prevalence in SPKT candidates was not statistically significant. The SPKT candidates were significantly younger than other transplant candidates, which could explain the trend. Moreover, although there is a paucity of data in the literature on B19V infection in SPKT recipients, the cases presented[38-40] imply a more severe course. We hypothesize that pancreas candidates may be at higher risk for infection given a larger proportion of seronegative recipients due to the immunosuppressive nature of diabetes[41] and the younger age of the recipients. The possible difference among various organ type recipients includes not only age as seen in SPKT recipients but also different numbers of blood transfusions due to bleeding events in cirrhotic patients. Interestingly there was no association between immunosuppression prior to transplantation (*e.g.*, for glomerulonephritis or autoimmune liver disease) and seropositivity.

Following acute infection in immunocompetent individuals, viral genomes may persist in various tissues for life. However, acute B19V infection can lead to severe complications in immunocompromized patients. In our study, no B19V DNA was found. In a German study, B19V DNA was detected in 4.0% of patients. Whereas DNAemia was found in 5.5%, 6.7%, and 5.7% of liver, heart, and bone marrow recipients, and viral genomes were found in only 1.4% of kidney recipients[35]. In a large recent Chinese study, a B19V DNA positive rate of 1.9% was reported in transplant candidates[25].

In addition, a large proportion of patients are still seronegative at the time of transplant and remain at risk for severe disease manifestations. Currently, there is no specific prevention of B19V disease. There is also no routine screening of donor and recipient serostatus for B19V. The true incidence of parvovirus infection in SOT recipients is unknown, with rates varying considerably across different studies[21-25]. There have been efforts in prospective routine monitoring of B19V in the first 6 mo after transplantation in seronegative SOT recipients. The findings showed low incidence rates (1.2% recipients per month) and even lower clinically significant events[24]. In another recent study, prospective monitoring revealed a higher incidence of B19V (10.17%), all infections occurred in seronegative recipients and were deemed clinically significant[42]. To conclude, large prospective data series on B19V disease in transplant recipients are lacking, but in our opinion, at the moment there is no rationale for routine B19V testing. However, pretransplant serostatus could be cost-efficient given the lower cost of a serological test than PCR testing and could potentially reveal patients at high risk. Post-transplant anemia is prevalent and often multifactorial. Serostatus could potentially hasten the diagnosis of B19V infection in selected patients and thus help avoid diagnostic delay and unnecessarily broad testing.

Moreover, B19V has also been implicated as a trigger for thrombotic microangiopathy[43,44], especially in the transplant setting[45-48]. These implications warrant additional research, but the information on serostatus could be beneficial during thrombotic microangiopathy workup, which is expensive and usually long-lasting. A large number of post-transplant thrombotic microangiopathies are regarded as secondary, either to immunosuppressive drugs or transplant itself; thus, B19V infection as a possible causative agent is probably underdiagnosed[49]. Identifying high-risk individuals pretransplant could be beneficial and help elucidate this pathophysiologically complex state[50].

Our study has limitations. Firstly, it is a single-center study with low numbers of rare transplant-ations, *e.g.*, SPKT and SLKT. Secondly, the incidence of clinical B19V infection was not reported in the post-transplant follow-up of these patients, reflecting the clinical significance of the serological status detected pretransplant. We plan to prospectively evaluate DNAemia and serostatus post-transplant as well as clinical manifestations to establish the clinical significance and epidemiology of B19V disease post-transplant. In addition, blood samples from control subjects were unavailable; therefore, it was not possible to compare the prevalence of B19V DNA in healthy individuals.

CONCLUSION

The B19V seroprevalence is expectedly high among kidney, liver, and pancreas transplant candidates, but 22.9% of seronegative individuals remain at risk for primary disease and severe manifestations. Further research should elucidate the utility of B19V screening in peri-transplant management.

ARTICLE HIGHLIGHTS

Research background

Parvovirus B19 (B19V) is an important pathogen in transplant settings. The epidemiology of B19V infection in solid organ transplant (SOT) recipients is not well studied, and reported prevalence rates vary greatly.

Research motivation

Data on B19V infection in transplant settings are scarce.

Research objectives

To analyze the prevalence of B19V antibodies and DNA in SOT candidates (kidney, liver, or simultaneous kidney and pancreas/liver) at a large national transplant center.

Research methods

Serum samples collected before transplantation were tested for the presence of B19V IgM and IgG antibodies and B19V DNA. Patients' data were collected using the electronic medical record.

Research results

A total of 131 transplant candidates were included in the study, with 70.9% being male. The average age was 53.27 years ± 12.71 years. None of the tested patients had detectable B19V DNA and IgM, while IgG seroprevalence was 77.1%. There was no difference in seropositivity between males and females (76.3% *vs* 78.9%). According to age, the seroprevalence was 66.7% in those under 30 years, 80.4% in those aged 30-59 years, and 78.1% in patients over 60. The seroprevalence did not differ significantly among different organ recipients, with 77.8%, 80.6%, and 50% for liver, kidney, and simultaneous pancreas-kidney transplant, respectively. There was no association between immunosuppression prior to transplantation and B19V IgG seropositivity.

Research conclusions

The B19V seroprevalence is high in transplant candidates, but 22.9% of seronegative individuals remain at risk for primary disease and severe manifestations.

Research perspectives

Further studies on large samples as well the B19V prevalence during the post-transplant period are needed to determine the clinical significance of B19V infection in transplant patients**.**

FOOTNOTES

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