



Investigation of BK/JC Polyomavirus Presence in Infertile Male Patients

İnfertil Erkek Hastalarda BK/JC Polyomavirüs Varlığının Araştırılması

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ABSTRACT

Introduction: Infertility is a common medical condition that is frequently encountered worldwide. The most common diagnosis of male infertility is idiopathic, accounting for 30% of the cases. Worldwide, infections are another important cause of infertility. The present study aimed to investigate whether BK polyomavirus (BKV) and JC polyomavirus (JCV) are associated with male infertility.

Materials and Methods: From a university hospital, 80 semen and 80 urine samples were collected from men who applied to the infertility clinic and diagnosed as idiopathic infertility. As a control group, 60 semen and 60 urine samples were taken from healthy males who had fathered children. The detection of BKV and JCV was performed by multiplex real-time PCR.

Results: JCV positivity was 62.5% (50/80) for urine and 40% (32/80) for semen in the infertile group. In the control group, JCV positivity was 38.3% (23/60) for urine and 35% (21/60) for semen. Only one patient of the control group had BKV positivity in urine and semen. The difference of JCV positivity in urine between infertile males and control group was statistically significant ($p= 0.005$). In addition, mean viral DNA load of JCV was found significantly higher compared to the control group in both urine and semen samples ($p< 0.0001$ and $p= 0.002$, respectively).

Conclusion: These results can be an important finding in elucidating the etiology of idiopathic infertility.

Key Words: Polyomavirus; Male infertility; PCR; JC virus

ÖZ

İnfertil Erkek Hastalarda BK/JC Polyomavirüs Varlığının Araştırılması

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Giriş: İnfertilite, tüm dünyada sıklıkla karşılaşılan yaygın bir medikal durumdur. İdiopatik infertilite, erkek infertilitesinin en sık karşılaşılan sebebi olup, tüm vakaların %30'nu oluşturmaktadır. İnfeksiyonlar ise infertilitenin diğer önemli sebeplerindendir. Bu çalışmada BK polyomavirüs (BKV) ve JC polyomavirüs (JCV)'ün erkek infertilitesi ile ilişkisinin araştırılması amaçlanmıştır.

Materyal ve Metod: Bir üniversite hastanesi infertilite kliniğine başvuran ve idiyopatik infertilite tanısı alan erkeklerden, 80 idrar ve 80 semen örneği toplandı. Kontrol grubu olarak çocuk sahibi olmuş 60 sağlıklı erkeğe ait idrar ve semen örnekleri çalışmaya dahil edildi. BKV ve JCV varlığı, klinik örneklerde gerçek zamanlı polimeraz zincir reaksiyonu ile araştırıldı.

Bulgular: İnfertil hasta grubunda JCV pozitifliği; idrar için %62.5 (50/80), semen için %40 (32/80) olarak bulundu. Kontrol grubunda, idrardaki JCV pozitifliği %38.3 (23/60) iken, semende JCV pozitiflik oranı %35 (21/60) olarak tespit edildi. BKV pozitifliğine ise sadece kontrol grubundaki bir hastanın idrar ve semeninde rastlandı. İdrardaki JCV pozitifliği açısından infertil grup ve kontrol grubu arasındaki fark istatistiksel olarak anlamlı bulundu ($p=0.005$). Ayrıca JCV'nin ortalama viral DNA yükü, infertil hastaların hem idrar hem de semen örneklerinde kontrol grubuna kıyasla anlamlı oranda yüksek tespit edildi (sırasıyla $p<0.0001$ and $p=0.002$).

Sonuç: Bu sonuçların idiyopatik infertilite etyolojisini aydınlatmada önemli bulgular olabileceği düşünüldü.

Anahtar Kelimeler: Polyomavirüs; Erkek infertilitesi; PCR; JC virüs

INTRODUCTION

Infertility is a common medical condition, with a prevalence of around 15% in couples worldwide. Male infertility accounts for around 50% of the cases. After varicoceles, the most common diagnosis of male infertility is idiopathic, accounting for 25% of the cases^[1,2]. Worldwide, infections are another important cause of infertility. Bacteria that affect the reproductive system can cause infertility by a number of methods^[3,4]. Male infertility associated with *Chlamydia trachomatis* infection may be caused by sperm tract obstruction, epididymitis, prostatitis or orchitis. In a similar way, it has been reported that *Neisseria gonorrhoeae* may cause male infertility with disseminated gonococcal infection^[4,5].

Viral infections as a case of male infertility have been less well-studied. An impact on fertility is suggested, but not well understood^[3,6]. Many viruses, including Epstein-Barr virus, human papillomavirus, cytomegalovirus, hepatitis B and C virus, human immunodeficiency virus (HIV), herpes simplex virus type 2, human herpes virus type

6 are frequently present even in asymptomatic males, and they are often associated with poor sperm quality. The role of chronic viral infections as an etiologic factor of male infertility is not clear^[7,8].

Human papillomaviruses are one of the most highly studied viruses as a cause of infertility. Some studies have reported that human papillomaviruses induce abnormal sperm count, low capacity for fertilization and production of anti-sperm antibodies^[9]. On the other hand, the relationship between sperm parameters and the presence of cytomegalovirus DNA is unresolved, with some studies reporting no association, and other findings that sperm parameters and function are impaired by cytomegalovirus infection, and that a high concentration cytomegalovirus in ejaculate correlates with a transient decrease in spermatozoa motility. Herpes simplex virus has been associated with impaired semen quality and functions of the prostate and epididymis. HIV, hepatitis B and hepatitis C viruses in semen impair DNA integrity and sperm parameters (and

in particular reduce forward motility). In some studies, azoospermia or oligozoospermia, hypogonadism, and orchitis have been noted in HIV-positive men^[7,9,10].

BKV and JCV are the original members of the human polyomaviruses family and ubiquitous among humans. Primary infections of BKV and JCV are usually asymptomatic and rarely seen as a distinct clinical disease. However, in immunosuppressed patients these viruses can cause serious morbidity and mortality. BKV is associated with nephropathy after kidney transplantation and also associated haemorrhagic cystitis in allogenic stem cell recipients. JCV causes a fatal neurodegenerative disorder of the brain called the progressive multifocal leukoencephalopathy only in immunosuppressed individuals^[6,11,12].

BKV and JCV are viruses commonly found in the population. Therefore, general seroprevalence rates are high in societies. The prevalences of BKV and JCV vary, depending on demographic factors such as geographical region, age, sex, concomitant infection and immunity status. JCV exposure among different populations was reported to be 33% - 91%, in various geographies and using different methods^[13-15].

In Turkey, Us et al. have investigated BKV antibody levels in 1123 healthy humans belonging to different age groups by a hemagglutination inhibition test. BKV seropositivity was found 61.4% in infants aged 0-11 months, 65.3% in children aged 1-5 years, and over 80% in the ≥ 6 years age group^[16]. In a multinational study, Olsson et al. have found overall prevalence of anti-JCV antibody as 57.6% in 10280 multiple sclerosis patients and the highest prevalence rates are reported for Turkey with 67.7%. In the same study, the prevalence of JCV in Turkey was reported to be significantly higher in comparison to other countries^[17]. Egli et al. have found BKV and JCV IgG seroprevalences of 82% and 58% in healthy blood donors by ELISA, while asymptomatic urinary shedding of these viruses has been detected in 7% for BKV and in 21% for JCV by molecular assays^[15]. Sroller et al.^[14] have reported anti-JCV and anti-BK seroprevalences of 57% and 69% in the general Czech population by ELISA.

The aim of this study was to investigate the frequency of BKV and JCV in infertile male patients by real time PCR in comparison with the control group and to determine whether there may be an association between polyomaviruses and infertility.

MATERIALS and METHODS

The study was approved by our university ethical committee with 2013/416 number, and informed consent was obtained from all participants. A long-term prospective study was undertaken in infertile men and a control group of healthy males. For the study, 80 semen and 80 urine samples were collected from infertile males who were attending the infertility clinic of our university hospital with low sperm concentration, decreased motility and abnormal sperm morphology. Control samples were 60 semen and 60 urine from healthy males who had fathered children.

Inclusion criteria were man aged 25-45 years living in rural and urban centers of Konya in the Internal Anatolia region of Turkey, who were non-smokers and who had not had previous urinary tract surgery. Men who were in the other age groups, from different geographical regions, or who had malignancy or were receiving immunomodulatory or immunosuppressive treatment were excluded. All patients in the study group had a diagnosis of idiopathic infertility; none had sexually transmitted infections, epididymitis, prostatitis, urinary tract infections or male accessory gland infection. Full urine analysis was normal in all infertile patients in the study group. Semen analysis of infertile patients was evaluated based on the WHO laboratory manual on the examination and processing of human semen. Oligoasthenospermia was detected in all of the infertility cases^[18].

The presence of BKV and JCV was investigated by real-time polymerase chain reaction on clinical samples. DNA was isolated from 200 μ L of semen and 200 μ L of urine samples, using a commercial kit (High Pure Viral Nucleic Acid Kit, Cat- No. 03-003-248-001, Roche Applied Science, Mannheim, Germany) according to the manufacturer's instructions. DNA was stored at -20°C until processing. In order to detect JCV

and BKV; a LightMix® kit was used for the polyomaviruses JC and BK (Cat.No-40-0203-32, Roche Diagnostics, Tibmolbiol) multiplex PCR in real-time was performed on the Roche Diagnostic LightCycler 2.0 Instrument.

Descriptive statistics were given for all variables. Chi square test was used when comparing categorical variables between the groups. T- test was used to compare means of age between the groups. Analysis was performed using SAS University Edition 9.4. A p value <0.05 was considered significant.

RESULTS

A total of 140 patients consented to participate in the study, 60 of them were in the control group consisting of fertile males, and the experimental group consisted of 80 infertile males. The median age of the 80 infertile males was 35 years (median 34.47 years), and that of the control group was 34 years (median 33.98). These differences were not statistically significant (p= 0.6). The distribution of two groups according to age is shown in Figure 1.

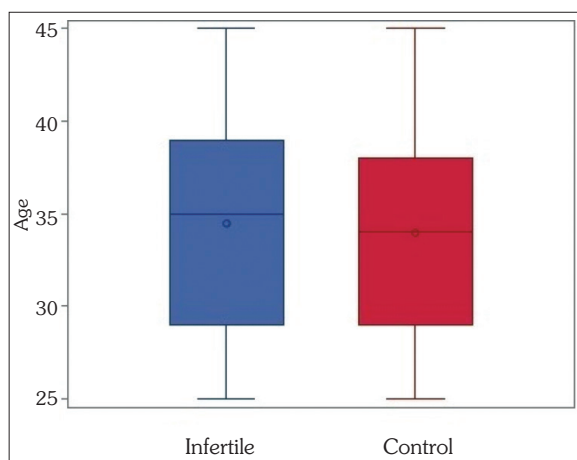


Figure 1. Distribution of age for infertile and control groups.

JCV positivity in urine was significantly higher in the infertile group (62.5%) than in the control group (38.3%) (χ^2 (1, n= 140)= 8.0932, p= 0.005). However, there was no significant difference in the rates of JCV positivity in semen between the infertile (40%) and control (35%) groups (p= 0.55).

In the infertile group, none of the samples were positive for BKV DNA. Only one patient of the control group was BKV positive in urine and semen. Among the patients (infertile and control fertile patients), JCV prevalence was found 52.1% (73/140) in urine and 37.8% (53/140) in semen samples. The majority of the JCV positivity in urine [68.5% (50/73)] and in semen [60.4 (32/53)] belonged to infertile patients (Table 1).

Viral DNA load of JCV in urine and semen from infertile males was found 3.5×10^6 copies/mL and 2.6×10^4 copies/mL, respectively. However, in the control group, viral load rates in positive patients were very low in both urine and semen with a value of 1.1×10^5 and 1.5×10^3 , respectively (p< 0.0001 and p= 0.002, Mann Whitney U test).

DISCUSSION

Male infertility is a big problem globally that is not always openly discussed. It is therefore important to determine the underlying etiology in the idiopathic infertility group. With a prevalence of 6% to 10%, infections and the resulting inflammatory reactions within the male genital tract are among the main causes for male infertility. Chronic inflammation in the male reproductive system can affect spermatogenesis by reducing the number and motility of the sperm^[19,20].

The possible association between male infertility and polyomaviruses is largely unknown, with there

Table 1. Prevalence of JCV and BKV positivity

Polyomavirus	Infertile males		Control group		Total positivity (Infertile and control)	
	Urine (n= 80)	Semen (n= 80)	Urine (n= 60)	Semen (n= 60)	Urine (n= 140)	Semen (n= 140)
JCV positive sample number (%)	50 (62.5%)	32 (40%)	23 (38.3%)	21 (35%)	73 (52.1%)	53 (37.8%)
BKV positive sample number (%)	0 (0%)	0 (0%)	1 (1.7%)	1 (1.7%)	1 (0.7%)	1 (0.7%)

having been almost no studies on this topic. In this study, we investigated the presence of BKV and JCV DNA in sperm and urine of infertile male patients compared to healthy fertile males.

BKV and JCV are common viruses in the population. They generally infect the children in early years and remain latent in kidneys, urinary tracts and lymphoid tissues for long years. Reactivation and urinary shedding in immunocompetent individuals ranges from 0-62%. Asymptomatic shedding of these viruses in the urine can be seen in both healthy subjects and immunosuppressed patients^[21-23].

Rota et al. from Turkey have investigated BKV and JCV positivity rate in a group of at-risk patients in Central Anatolia region that is same region with this study and reported respectively as 20% and %11^[24]. Çağlı et al. have tested for Polyomavirus DNA in renal transplant recipients and healthy blood donors. BKV DNA and JCV DNA were found in 23.5% and 47.1% of transplant recipients at months 12 post-transplant, respectively. In healthy blood donors BKV DNA was not found, and JCV DNA was positive in 30%^[25]. In another study from Turkey, BKV and JCV positivity rates have been found as 33.4% and 4.3% respectively in immunosuppressive patients by multiplex real-time PCR^[26].

In the general population, JCV viruria is more common than BKV viruria. In contrast, in immunosuppressed patients, BK viruria is more common^[27]. However in the literature, different rates have been reported in different studies. JCV seropositivity was higher in males, as previously reported although the reason behind this remains unknown. In a previous Turkish study, the prevalence of anti-JCV antibodies in multiple sclerosis patients has been found as 78.6% in males and 64.1% infemales^[28]. In a study conducted in India, the prevalence of JCV has been confirmed significantly higher in males^[29]. In another multicenter study from different countries, the prevalence of JCV in patients with multiple sclerosis has been determined significantly higher in men (61.9% in men and 55.8% in women). Looking at the data from Turkey in the same study, JCV prevalence rates have been reported as 80% in men and 63% in women^[17].

The clinical state caused by virus reactivation is often associated with the immune status of the person. However, Enam et al. have reported that JCV can cause distinct morphological changes, rapid division and prolonged life in cells. In some studies, it has been reported that JCV genomic sequences are detected in various tumors, particularly colon cancer and several types of brain tumor^[26,30,31]. Polyomavirus infections have been proposed as candidate etiological agents in some of diseases with unknown etiologies, and there have been few studies of these viruses as a cause of infertility^[26].

Seroprevalence rates in adult populations vary widely, from less than 20% to up to 90%, depending on the demographic characteristics, the geographic area, ethnic groups, age groups and polyomaviruses strains^[21]. In a multicenter study involving several countries from Europe, Asia and Africa, JCV sequences in semen have been investigated by PCR and the overall prevalence of JCV in semen samples have been found to be 27.6%. In that study, which does not have any data from our country, it has been emphasized that the prevalence rates of JCV in semen and virus genotype vary according to geographical regions^[13].

We chose to investigate patients and controls resident in one region, Konya, in the internal Anatolia region of Turkey. However, the ethnic origins of the patients and controls were not fully analyzed. In this study, in order to test for possible infection of male genital system with BKV and JCV, 80 urine samples and 80 semen samples from infertile males were analyzed, also control group was created from fertile men. Patients in the study group were previously analyzed for sexually transmitted infections. Infertile patients with sexually transmitted infections were excluded from the study. BKV DNA was not found in any infertile male samples, only one patient of the control group had BKV positivity. The prevalence of JCV was higher in urine samples from infertile men (62.5%) than in the control group (38.3%, $p=0.005$), but there was no statistically significant difference in the prevalence of JCV in semen. In this regard, it is thought that our commercial PCR kit is produced for blood and urine samples and there may be standardization and optimization problems

related to the study in semen. In addition, the mean viral load of JCV was higher in both the urine and semen of infertile men. When all samples were taken into consideration, both the mean viral load and the positivity rate in the semen were found to be lower than the urine. However, we believe that the detection of JCV DNA in semen is important for infertility.

Many microorganisms have been reported to bring about adverse changes in sperm parameters in vitro, but their in vivo potential to cause infertility is still controversial. In a study similar to ours, Comar et al. have found JCV positivity as 43.4% in urine and 24.5% in semen of infertile men, compared with 28% and 11% in controls. They have also found similar to ours that the prevalence of JCV in the semen was lower than that of the urine. They speculated that the presence of JCV DNA in sperm may affect egg fertilization and embryo development stages^[6].

When the literature is reviewed, it is reported that most microorganisms cause negative changes in sperm parameters in vitro, but their potential for causing infertility in vivo is still controversial. In their retrospective study, Garolla et al. have investigated the effects of HPV vaccine on fertility in infertile couples admitted to the infertility clinic and those who accepted and did not accept the HPV prophylactic vaccine. In the results of the study, it was reported that sperm motility and antisperm antibodies ameliorated in the vaccinated group and pregnancy and live birth rates were significantly higher in this group during the follow-up period. At the end of the study, it was suggested that HPV prophylactic vaccine increases the reproductive potential of infertile patients^[32].

In conclusion, using sensitive molecular assays, we detected an unexpectedly high prevalence of JCV from asymptomatic infertility patients compared to the control group. Furthermore, our finding that the JCV viral load was significantly higher in the study group than in the control group suggests that infertility may be associated with JCV. The possible role of JCV in the etiology of male infertility needs large multicenter studies. Furthermore, detailed cytological studies of the effect of JCV on the semen and urinary tract are needed at the cellular level. Certain studies on the presence of

JCV in the etiology of infertility will also guide the treatment of infertility, perhaps paving the way for JCV vaccine studies.

ETHICS COMMITTEE APPROVAL

The approval for this study was obtained from Necmettin Erbakan University, Clinical Research Ethics Committee (Decision No: 2013/416, Date: 17.05.2013).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: MÖ, FET, HHT

Data Collection or Processing: FET, HHT

Analysis/Interpretation: MÖ, FET, HHT, BF

Literature Search: MÖ, HHT, BF

Writing: FET

Final Approval: MÖ, BF

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