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BKV AND JCV VIRUSES OF POLYOMAVIRUS FAMILY INVOLVED IN HUMAN DISEASES

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S u m m a r y. Infections with polyomaviruses are *widespread.* The number of identified polyomaviruses has grown radically over the last 10 years to more than 35 subtypes, including 13 typical of humans. The work is based on a review of the literature of the last 5 years available in PubMed, concerned with selected polyomaviruses involved in human diseases, e.g. nephritis caused by BK virus (BKV), or encephalitis caused by JC virus (JCV). Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the CNS.

K e y w o r d s: infection, polyomavirus, BK virus, JC virus, progressive multifocal leukoencephalopathy

INTRODUCTION

Infections with polyomaviruses are *very widespread***.** The number of identified polyomaviruses has grown radically over the last 10 years to more than 35 subtypes, including 13 typical of humans [5]. Although polyomaviruses do not typically cause illness in healthy individuals, several polyomaviruses may produce catastrophic results in immunocompromised hosts [7]. Polyomavirus-related diseases can occur among immunosuppressed individuals, including post-transplantation and AIDS patients [25].

MATERIALS, METHODS AND AIM OF THE STUDY

The work is based on review of the literature of the last 5 years available in PubMed on selected polyomaviruses. The review includes reports on viruses of polyomavirus family involved in human diseases. In this study, we discuss selected polyomaviruses, BK virus (BKV) and JC virus (JCV).

RESULTS

BKV

In 1971 BKV and JCV were first isolated human polyomaviruses [9]. BKV infection usually occurs in early childhood [29]. Robaina *et al.* noticed that BKV infection was observed most frequently in thirty-year-old people [26]. BKV was isolated from the urine sample collected from a kidney allograft recipient with chronic pyelonephritis and advanced renal failure [9, 11]. This opportunist agent is associated with nephropathy in 1-10% of kidney transplant recipients [33]. BKV genotype-specific neutralizing antibody NAb titers may be a good predictive marker that allows patient stratification by BKV disease risk before and after transplant [30]. Solis et al. measured BKV DNA load and

Nab titers in the graft for 24 months after kidney transplantation. After transplant, 52 (31%) patients displayed BKV replication: 24 (46%) patients were virulic and 28 (54%) patients were viremic and patients with high NAb titers against the replicating strain had a lower risk of developing BKV viremia. Genotype mismatch between recipients' neutralization profiles before transplant and their subsequently replicating strain significantly increased the risk of developing viremia [30].

The United States Transplant Cancer Match Study of 2003-2013 found 2,015 (3,6%) patients with BKV among 55,697 graft recipients [12]. Gupta *et al.* showed similarly increased incidence in cases of kidney cancer in the recipients with or without BKV infection and invasive bladder cancer compared to those with BKV infection [12]. Jarzyński *et al.* analyzed the incidence of BKV in the tissue samples of colorectal cancer in order to determine the relationship between the presence of these viruses and the development of cancer [16]. BKV DNA was detected by PCR using specific primers and differentiated by digestion with BamHI enzyme in 50 colorectal cancer samples collected from histological sections. The presence of BKV was confirmed in 30% cases. Jarzyński *et al.* conclude that BKV infections seem to contribute to neoplastic process , however that requires further studies and a larger group of patients.

In the study by Swedan *et al.,* BKV viremia was observed among 19% hemodialyzed patients and 3% controls [16]. The authors conclude that hemodialyzed patients may be at increased risk of nephropathy due to increased incidence of BKV reactivations, and may require optimization of immunosuppressive therapy.

JCV

BKV and JCV are named after patients' initials the viruses were first isolated from [29]. JCV, isolated almost half a century ago, was identified from the brain sample of a patient with progressive multifocal leukoencephalopathy (PML) [9, 21, 30]. JVC has a small circular DNA genome of about 5 kb and generates two primary transcripts, producing several products alternatively predicted mainly by Cis-splicing [30]. Genome of JVC comprises 5,130 bp [29]. This polyomavirus causes asymptomatic infection in the kidney. In the majority of population it is rarely the causative agent of transplant-related kidney disease, but in immunosuppressed individuals this pathogen can become reactivated and spread to the brain [5, 19]. JCV could also infect oligodendrocytes and astrocytes in the CNS [23, 30]. JCV has been strongly associated with the development of a fatal brain disease known as progressive multifocal leukoencephalopathy (PML) [5]. JCV is the cause of PML, a rare demyelinating disease in immunocompromised individuals, especially in AIDS sufferers [2, 10, 30, 35]. PML is an opportunistic infection of the CNS [20].

Sierra Morales *et al.* discuss the difficulty in diagnosing PML. They present a case of HIV-2 infected patient who developed PML in immune reconstitution inflammatory syndrome (IRIS). MRI showed a single lesion in the facial colliculus, initially considered to be ischemic in nature [31].

We can observe that the incidence of PML has decreased in developing countries after the introduction of combined antiretroviral therapy (cART) [17]. Lima *et al.* described the epidemiological and clinical profile of a group of 27 HIV-infected patients of whom 44% patients developed motor deficits which are most common early manifestations. Seizures occurred in 37% patients and 9 (33.3%) patients had PML associated with IRIS, with 33% mortality rate reported. Genetic background, death from other diseases and underdiagnosis may explain low prevalence of reported PML cases in developing countries [17].

Cases of PML are observed in immunosuppressed patients. Immunosup-pressed group also includes patients treated with monoclonal antibody therapies for autoimmune diseases, e.g. systemic lupus erythematosus, rheumatoid arthritis or multiple sclerosis (MS) [5]. The diagnosis of PML could base on MRI scan of the brain and the detection of JCV in the cerebrospinal fluid [3]. Natalizumab, a humanized IgG4 monoclonal antibody could be used to treat individuals with Crohn's disease but their use was limited due to increased risk of PML [10]. Therefore, it is important to monitor the presence of serum anti-JCV antibodies.

PML is also a serious complication in patients treated with a number of disease-modifying therapies (DMTs) in treating MS [35]. It mainly occurs in MS patients on natalizumab [2]. Therefore, to reduce the risk of PML patients suffering from MS should have serum anti-JCV antibodies monitored. Anti-JCV index is used to

help decide whether to start treatment with natalizumab, continue or stop treatment in cases of seroconversion in MS patients. Patients treated with natalizumab, who were initially JCV-antibody negative, seroconverted at a significantly higher rate than patients naïve to natalizumab. Thus, the therapy with natalizumab was likely to be associated with higher rates of seroconversion [22]. Ho PR. et al. found that156 (<1%) patients had PML out of 37,249 natalizumab-treated patients with MS,. They estimated PML risk as less than 0.07 per 1,000 in anti-JCV antibody-negative patients, but in anti-JCV antibody-positive patients they estimated cumulative PML probability over 6 years in 2-7% patients on immunosuppressants, and 1.7% in patients without previous immunosuppressants [19].

Barry A. Singer *et al*. investigated a group of ca. 167,300 patients on natalizumab, and reported a total of 714 cases of PML, among them 711 patients with MS and 3 with Crohn's disease. The diagnosis of PML based on MRI scan of the brain and JCV detected by PCR in the CSF. However, 23% patients with PML treated with natalizumab died. The authors conclude that for patients with MS without immunosuppressant medication exposure, the median anti-JCV antibody index is higher for patients with PML than those without PML [3]. The patients with MS who are anti-JCV antibody negative also have a risk of seroconversion to become anti-JCV antibody positive, according to some studies it is 3-8 % [3, 14, 34]. Another important risk factor for PML is natalizumab treatment duration [3, 15]. The disadvantageous functional outcome was linked to more advanced age, higher initial JCV copy number in the CSF and advanced stage of PML on the MRI scan of the brain. Moreno-Estébanez *et al*. present a study on jcv-miR-J1-5(5p miRNA) expression found in 102 plasma samples from 25 healthy individuals, 49 patients with relapsing-remitting MS treated with natalizumab and 28 patients on interferon-beta (IFN-ß) [20]. They observed the overall detection rate of 5p miRNA was 92% among heathy persons, 84% among patients treated with natalizumab, and 75% among patients treated with interferon-beta. 5p miRNA expression inversely correlated with ant-JCV antibody index among JCV-seropositive long-term patients treated with natalizumab [20]. Relative 5p miRNA expression levels were lower in the patients treated with natalizumab compared to the patients with interferon-beta. Hence, it is important to monitor antibody index in patients with MS in order avoid the risk of developing PML.

PML is rarely detected in patients after transplantation but may occur either way. Avsenik *et al.* reported a case of a 65-year-old liver transplant recipient with PML who developed left-side hemiplegia and drowsiness. MRI revealed enlargement of PML lesions with contrast enhancement and ongoing edema, consistent with IRIS [2]. Moreno-Estébanez A. *et al.* reported a case of PML with characteristic clinical symptoms and MRI scan of the brain, but with an atypical late onset, developed 11 years after liver transplantation, and after single-drug, long-term (8 years) and low-dose immunosuppression with mycophenolate mofetil (MMF) [20].

DISCUSSION

Polyomaviruses could be transmitted via respiratory, fecal-oral and also with blood as well as transplanted organs. BKV and JCV mainly lodge in the urinary tract tissues [29]. Robaina *et al.* analyzed polyomaviruses such BKV, JCV, Washington University virus (WUV) and Karolinska Institute viruses (KIV) DNA by real-time PCR in 291 saliva samples of healthy individuals [26]. They showed that 71 (24.3%) samples were positive for at least one of the screened polyomaviruses; in particular 37 were WUV-positive, 21 (7.2%) BKV-positive, 7 (2.4%) KIV-positive, and 1 (0.3%) JCV-positive. The only co-infection with BKV and WUV was found in 5 healthy individuals. Robaina *et al.* concluded that saliva may be a route for BKV transmission, and that the oral cavity is a likely site of virus replication. JCV, WUV, and KIV may be transmitted in a similar fashion to BKV transmission [26].

Although these viruses generally do not cause illness in healthy individuals, several polyomaviruses can result in catastrophic diseases in immunosuppressed individuals, including post-transplantation and AIDS patients [7, 25]. BKV may cause BKV nephropathy and hemorrhagic cystitis [29]. It is estimated that over 80% of the adult population has detectable antibodies against polyomaviruses BKV and JCV [1, 18, 29]. PML is an example of a catastrophic disease due to polyomaviruses. JCV is likely to cause PML [29]. At present there are limited treatment options for PML [19]. PML is a rare infection, which may occur in people with decreased immunity, especially in untreated HIV-infected persons and

in immunosuppressed patients [2, 5]. PML is caused by JCV infection of particular brain cells, i.e. oligodendrocytes [23]. In patient with MS, anti-JCV index values are used to help decide whether to start treatment with natalizumab. Previous estimates of PML risk in patients with MS on natalizumab could be stratified by serum anti-JCV antibodies. For anti-JCV antibody-negative patients, estimated PML risk was smaller than for anti-JCV antibody-positive patients. In patients with MS, anti-JCV index values are used to help decide whether to continue or stop treatment in cases of seroconversion in patients with MS. Plavina T. *et al.* noticed that median index values in individuals suffering from MS with prior immunosuppressant medication exposure was the same despite PML status ($p = 0.82$), but median anti-JCV antibody index appeared to be higher in patients without immunosuppressant medication exposure with PML than those without PML ($p < 0.0001$). Previous assessment of PML risk in patients with MS on natalizumab could be stratified by previous use of immunosuppressants [3, 24]. The major risk factors for PML on natalizumab therapy include anti-JCV-positive status and prior immunosuppressant medication [3].

Polyomaviruses are likely to cause damage in patients after transplantation. Following primary infection with polyomaviruses, BKV and JCV persist latently in different sites, particularly in the reno-urinary tract. Reactivation from latency might take place not only in individuals in good health with asymptomatic viruria, but also in those with nephropathy after kidney transplantation. BKV could cause renal allograft dysfunction, and is associated with nephropathy. Nephropathy may be common in 1-10% of renal transplant patients with loss of the transplanted organ in 30% up to 80% of the cases [6, 30, 33]. Some authors conclude that patients on hemodialysis may be at increased risk if nephropathy due to increased incidence of BKV virus reactivation has developed, and may require optimization of immunosuppressive therapy. PML caused by JCV is rarely detected in patients after transplantation, it can occur though.

The review of literature revealed a few epidemiologic studies that examined correlations between human polyomaviruses and the risk of cancer, however numerous scientific studies appear contradictory. Some authors present BKV as a possible carcinogen [13, 32]. Jarzyński *et al.* conclude that BKV infections contribute to neoplasmatic process, however a further study on a larger group is necessary [16]. Other authors present JCV as a possible carcinogen, too [13, 32]. Engels EA. *et al.* concluded that these results provide an opportunity to consider the possibility that JVC could be involved in the etiology of NHL, but more laboratory research is needed to verify this hypothesis [8]. In the study of Teras *et al.* an inverse trend was proposed for trichodysplasia spinulosa-associated polyomavirus (TSV) antibody level and NHL risk, but there were no other links observed between the risk of BKV, JCV polyomaviruses and non-Hodgkin lymphoma (NHL) [32]. Rollison D.E. *et al.* observed that JCV- and BKV-seropositivity was not associated with the increased risk of NHL [28]. In the study of Robles C.*et al.* no association between seroprevalence of BKV and JCV and diffuse large B-cell lymphoma (DLBCL) was found [27]. Human polyomaviruses antibody levels do not facilitate higher NHL risk in immunocompetent individuals [32]. Future research into the relationship between polyomaviruses and cancers is definitely needed.

CONCLUSIONS

The first two human polyomaviruses discovered, BKV and JCV are the causative agents of transplant-related kidney disease, common in case of BKV, but rare for JV [5]. Although polyomaviruses typically do not cause illness in healthy individuals, reactivation from latency of several polyomaviruses can cause catastrophic diseases in immunosuppressed individuals, including post-transplantation and AIDS patients. Nephritis could be caused by BKV [11], and encephalitis by JCV [21]. PML is an example of a catastrophic disease developed due to infection with JCV which can cause death of patients within a few weeks. The reactivation of JCV is the cause of PML, a rare demyelinating disease [2, 10]. It is important to examine anti-JVC index in immunosuppressed patients. In MS patients, anti-JCV index values are used to help decide whether to start treatment with natalizumab, continue or stop treatment in cases of seroconversion. It is necessary to understand individual risk factors for PML in relapse-remitting MS patient in order to promptly treat symptoms. Some polyomavirus act as respiratory pathogens. Polyomaviruses could be damaging in patients after transplantation, e.g. renal transplantation. Nephropathy may be common in

1-10% renal transplant patients with loss of the transplanted organ in 30% up to 80% of the cases [6]. There are a few epidemiologic studies that examined association between human polyomaviruses and the risk of cancer, but that requires further investigations.

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