

Polyoma BK virus: an emerging opportunistic infectious agent of the human central nervous system

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ABSTRACT

BK virus, a double-stranded DNA virus, is a member of the *Polyomaviridae* family which is known to infect humans. Clinical evidence of disease is mostly encountered in immunosuppressed individuals such as AIDS patients or those who undergo renal or bone marrow transplantation where complications associated with BKV infection manifest commonly as a polyomavirus nephropathy or hemorrhagic cystitis, respectively. Recent evidence suggests that in addition to the JC virus (the other member of the same family known to be strongly neurotropic and responsible for the progressive multifocal leukoencephalopathy), BK virus can infect and cause clinically relevant disease in the human central nervous system. In this mini-review, an analysis of the literature is made. A special focus is given to alert clinicians to the possibility of this association during the differential diagnosis of infections of the central nervous system in the immunocompromised host.

Keywords: BK virus; bone marrow transplantation; AIDS-related opportunistic infections.

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INTRODUCTION

BK virus (BKV), also known as *Polyomavirus hominis 1*, was first isolated in 1971 from the urine of a renal transplant patient, initials B.K. BKV is a non-enveloped encapsulated circular double-stranded DNA virus that belongs to the *Polyomaviridae* family which includes other polyomaviruses that have been found to infect humans namely JC virus (JCV), simian virus 40, KI virus, WU virus and Merkel cell polyomavirus (MCV). BKV is widely distributed in the human population. Primary asymptomatic infection usually occurs during childhood via the respiratory tract. Then, latent infection is established in renal epithelial cells and possibly other tissues (including brain, since BKV-DNA has been detected in the brain tissues from normal subjects) with most individuals having antibodies to BKV. Reactivation may subsequently occur in immunocompromised and healthy individuals, but may be more likely if there is an impairment of the immune function (patients with T-cell deficiencies). Clinical evidence of disease is rare and mostly encountered in patients in

states of relative or absolute immunodeficiency, such as patients with AIDS or transplant recipients where BKV reactivation is associated with diverse entities such as polyomavirus nephropathy (PVN), a form of acute interstitial nephritis and the most frequent BKV-associated disease after renal transplantation, or the hemorrhagic cystitis, a serious BKV-associated complication characterized by dysuria and varying degrees of hematuria that affects up to 10% of the bone marrow transplant (BMT) patients.¹⁻⁴ JCV, one of the other member of the *Polyomaviridae* family that causes human infection, is strongly associated with progressive multifocal leukoencephalopathy (PML), a demyelinating disease of the central nervous system (CNS). Until now, JCV was the only human polyomavirus known to have the ability to infect the CNS. Recently, however, an increasing body of evidence favors the possible neurotropism of BKV, since BKV DNA has been detected in the brain tissue and cerebrospinal fluid (CSF) of both immunocompetent and immunocompromised individuals (mostly adults) with or without neurological symptoms.⁵

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BKV related CNS infection may often be overlooked and under-diagnosed in immunocompromised patients. Only a few cases of neurological disease associated with a possible or proved BKV infection have been reported so far, probably because the clinicians are generally unaware of this association. Herein, a synopsis of all the reported cases in the literature is made, including the clinical and imagiologic manifestations of BKV CNS infection, diagnosis, treatment and outcome.

Since it is an unknown, but emerging infectious disease of the CNS with the advent of more immunosuppressive therapy and procedures, and because in immunocompromised patients is mostly fatal, emphasis will be given to the importance of recognizing this entity and the urgent requirement of new treatments and antiviral drugs.

BKV related CNS infection

To date, since the first report of BKV associated neurological infection almost 20 years ago, only 24 cases have been described so far.⁶⁻²³ Most of them occurred in patients with depression of their immune function (eight cases in AIDS patients; one case in a renal allograft recipient; six cases in the context of hemato-oncological diseases under chemotherapy or bone marrow transplantation, and one case in a patient under long-term steroid therapy). However, eight cases were diagnosed in apparently healthy and immunocompetent individuals, with self-limited clinical manifestations (Table 1). Since clinical manifestations in healthy hosts are benign with rapid resolution of the symptomatology, attention will be given only to the cases of the immunocompromised individuals, mainly AIDS and transplant patients where the clinical picture is more complex and generally devastating, resulting in multi-organ failure and death.

As aforementioned, primary asymptomatic BKV infection usually occurs during childhood via the respiratory tract and after then latent infection is established in renal epithelial cells and possibly other tissues, including the brain, with reactivation in the immunodeficiency states. However, regarding the latent infection in this latter site, there are conflicting data, with some studies supporting a dormant BKV infection in the ependymal cells and astrocytes,^{5,24-28} while others fail to demonstrate that.²⁹⁻³² Peripheral blood leukocytes were postulated as a site of latency. So, one argument against the concept of brain latency that explains the presence of BK virus in the brain of healthy people is that BK viral DNA detected by the PCR method may have been the result of contamination by peripheral blood leukocytes. Hence, further investigation in this area is needed to establish brain as a site of BKV latency.³³⁻³⁵ On the other hand, another study reported that endothelial cells support BKV replication in vitro, which raises the possibility that BKV may cross the endothelial barrier to disseminate from the periphery to its target organs via blood.³⁶

Neurological manifestations of BKV infection

Individuals with CNS involvement by BKV infection, usually show signs and symptoms of acute encephalitis with some cases being accompanied by meningeal involvement.^{6-8,10-23} So far, only two cases presented an ophthalmologic disease manifested as an acute retinitis due to extension of the CNS BKV infection.^{8,9,13} The most common symptom is headache. Other signs of neurological impairment includes seizures, progressive mental deterioration, dysarthria, hallucinations, visual disturbances, and in one case paraplegia. In the pediatric group, irritability and lethargy were the preponderant manifestations.¹⁴ Of particular relevance is the fact that both cases of BKV retinitis occurred in AIDS patients. Thus, when the clinician evaluates this subset of immunocompromised patients with ophthalmologic symptoms, BKV must be included in the differential diagnosis, especially if concurrent CNS and urinary tract involvement by BKV infection is present.^{8,9,13}

Neuroimaging of BKV infection

Some microorganisms have a predilection for particular areas of the brain while others may affect multifocal areas of the cortex. For instance, herpes simplex type I has an affinity for the limbic system, cytomegalovirus favors the periventricular white matter, and *Listeria monocytogenes* is seen on the brain stem and cerebellum.

The CNS infection by BK virus is imagiologically characterized by a preferential involvement of the periventricular and pial surfaces of the brain parenchyma. In fact, magnetic resonance imaging of the cases of BKV meningoencephalitis shows areas of increased signal intensity of the periventricular white matter of brain while the cortex is generally spared. Meningeal contrast enhancement along with increased meningeal thickness also occurs when infection spread to meningitis is present. Deep white matter of the cerebellum is generally spared while deep gray matter structures are compromised.^{6-8,10,11,18,19,21-23} There are two cases, one in a renal transplant recipient and another in a patient under long term steroids, suggestive of PML, but whose PCR for JCV was negative.^{16,17} Instead, BKV DNA of CSF and urine detected by PCR was positive. These cases illustrate and suggest that the etiology of some clinical diagnosis of PML might in fact be BKV and not JCV infection, so a high clinical index of suspicion is necessary in these particular cases.

Diagnostic procedures/tests for suspected BKV infection

The diagnosis of BKV meningitis/encephalitis has usually been established by PCR of the CSF, complemented or not by BKV PCR of the brain biopsy specimen. One report suggested that the presence of BKV with a dominant

Table 1. Patient's characteristics, clinical manifestations, neuro-imagiological findings, diagnostic tests, treatment and outcome of BKV related CNS disease

Reference	Immune status	Gender	Age	Neurological manifestations	Type CNS involvement	Other organ involvement	Neuro-Imaging	Diagnosis	PCR for other micro organisms	Treatment	Outcome
Vallbracht <i>et al.</i> ⁶	AIDS	M	27	Headache, altered mental status	Meningo-encephalitis	Nephritis, pneumonitis	MRI - accentuation of the ventricular and meningeal surfaces of the brain	CSF, brain, lungs, kidneys BKV PCR+	Negative	NA	Dead after 14 weeks
Voltz <i>et al.</i> ⁷	Immuno-competent	M	35	Fever, headache, seizures, hallucinations, delusions	Encephalitis	None	MRI-diffuse, reversible white matter changes, most prominent on long-TR images	CSF BKV PCR+	Negative	Symptomatic	Alive
Bratt <i>et al.</i> ⁸ ; Hedquist <i>et al.</i> ⁹	AIDS	M	26	Progressive hearing loss, visual impairment	Meningo-encephalitis, retinitis	Nephritis	MRI-increased meningeal contrast enhancement and increased meningeal thickness	Eye,brain, kidney, PMN BKV PCR+; IHC+(BKV VPI protein and agnoprotein)	Negative	Antivirals+ steroids	Dead after 8 weeks
Lesprit <i>et al.</i> ¹⁰	AIDS+ NHL (under CT)	M	44	Paraplegia	Encephalitis	Hemorrhagic cystitis	MRI - diffuse areas of increased signal intensity of the periventricular white matter	CSF,blood, bone marrow, kidney, bladder, stomach, mesenteric lymph nodes, lymphoma cells BKV PCR+; IHC+ (ependymal lining, leptomeninges, subpial parenchyma and Choroids plexus); BKV+ in tubular epithelial cells by EM	Negative	Antivirals	Dead after 8 weeks

(Cont.)

Table 1. Patient's characteristics, clinical manifestations, neuro-imagiological findings, diagnostic tests, treatment and outcome of BKV related CNS disease

Reference	Immune status	Gender	Age	Neurological manifestations	Type CNS involvement	Other organ involvement	Neuro-Imaging	Diagnosis	PCR for other micro organisms	Treatment	Outcome
Garavelli and Boldorini ¹²	AIDS	M	37	Fever, headache, altered mental status	Meningo-encephalitis	None	NA	CSF BKV PCR+	Negative	Antivirals	Dead
Stoner <i>et al.</i> ¹¹	Leukemia under CT	M	40	Headache, altered mental status	Meningo-encephalitis	Nephritis, pneumonitis	NA	CSF, brain, kidney, lung, urine BKV PCR+	Negative	Antivirals	Dead
Behzad-Behbahani <i>et al.</i> ¹⁴	BMT	F	5	None	None	NA	NA	CSF BKV PCR+	Negative	NA	Alive
	BMT	M	3	Irritability	Encephalitis	NA	NA	CSF BKV PCR+	Negative	NA	Alive
	Immunocompetent	F	5	Lethargic, irritability	Encephalitis	NA	NA	CSF BKV PCR+	Negative	NA	Alive
	Immunocompetent	M	16	Confusion	Encephalitis	NA	NA	CSF BKV PCR+	Negative	NA	Alive
	Immunocompetent	F	13	Headache, vomiting, diplopia	Meningo-encephalitis	NA	NA	CSF BKV PCR+	Negative	NA	Alive
Behzad-Behbahani <i>et al.</i> ¹⁵	Immunocompetent	F	24	Seizures	Encephalitis	NA	MRI-diffuse white matter lesions, chiefly in the parietal region	CSF BKV PCR+; serum anti-BKV+	Negative	NA	Alive
	Immunocompetent	F	30	Headache, vomiting, lethargy	Meningo-encephalitis	NA	NA	CSF BKV PCR+	Negative	NA	Alive
	Immunocompetent	M	32	Mental status change	Meningitis	NA	NA	CSF BKV PCR+	Negative	NA	Alive
	Immunocompetent	M	29	Fever, headache	Meningitis	NA	NA	CSF BKV PCR+	Negative	NA	Alive
	Immunocompetent	F	26	Headache, left hemiparesis and drowsiness	Meningitis	NA	NA	CSF BKV PCR+	Negative	NA	Alive

(Cont.)

Table 1. Patient's characteristics, clinical manifestations, neuro-imagiological findings, diagnostic tests, treatment and outcome of BKV related CNS disease

Reference	Immune status	Gender	Age	Neurological manifestations	Type CNS involvement	Other organ involvement	Neuro-Imaging	Diagnosis	PCR for other micro organisms	Treatment	Outcome
Jørgensen <i>et al.</i> ¹³	AIDS	M	35	Mental status changes; visual impairment	Meningo-encephalitis, retinitis	Nephritis	NA	CSF, brain PCR BKV+	Negative	NA	Dead
Hix <i>et al.</i> ¹⁶	Renal allograft	M	45	Delirium	PML	Hemorrhagic cystitis	MRI consistent with PML	CSF, urine BKV PCR+	Negative	Stop immuno suppression; leflunomide	Alive
Friedman and Flanders ¹⁸	BMT	M	38	Progressive mental status changes and lethargy; generalized psychomotor slowing and dysarthria	Encephalitis	Hemorrhagic cystitis	MRI-widespread increased signal intensity on T2- and fluid-attenuated inversion recovery-weighted images, with restricted diffusion, in the cerebellum, cerebral white matter, and deep gray matter structures, deep cerebellar white matter and cerebral cortex appeared to be spared	Brain BKV PCR+	Negative	Antivirals; reduction of immunosuppression	Recovery but dead after 5 months
Cabrejo <i>et al.</i> ¹⁷	Long term steroid therapy	F	51	Confusion, dysarthria	PML	None	NA	CSF BKV PCR+	Negative	Stop immunosuppression	NA
Vidal <i>et al.</i> ¹⁹	AIDS	M	43	Headache, speech, gait and memory disturbances	Meningo-encephalitis	None	MRI -increased signal intensity of the periventricular white matter	CSF, brain BKV PCR+	Negative	cART	Alive
Behre <i>et al.</i> ²¹	BMT	NA	NA	Seizures	Encephalitis	Hemorrhagic cystitis	MRI - T2-weighted magnetic resonance imaging showed an edema parieto-occipital in the cerebral white matter and less pronounced in the cerebellum	CSF BKV PCR+	Negative	Antivirals	Dead after few days

(Cont.)

Table 1. Patient's characteristics, clinical manifestations, neuro-imagiological findings, diagnostic tests, treatment and outcome of BKV related CNS disease

Reference	Immune status	Gender	Age	Neurological manifestations	Type CNS involvement	Other organ involvement	Neuro-Imaging	Diagnosis	PCR for other micro organisms	Treatment	Outcome
Ferrari <i>et al.</i> ²⁰	Lymphoma under CT	NA	NA	Confusion	Meningitis	NA	NA	CSF BKV PCR+	Negative	NA	NA
Kinnaird and Anstead ²²	AIDS	M	48	Ataxia, cognitive deficit, dysarthria	Encephalitis	Hemorrhagic cystitis	MRI - multifocal and infratentorial foci of abnormally high T2 and FLAIR signal	urine BKV PCR+; IHC-antibodies against simian virus 40	Negative	cART	Alive
Lopes da Silva <i>et al.</i> ²³	BMT	F	48	Altered mental status, headache, dysarthria	Encephalitis	Nephritis, thrombotic microangiopathy	MRI -predominant involvement of the pons and around the third ventricle. Lesions more expressive in the subcortical region of both cerebral hemispheres	CSF, brain, urine BKV PCR+	Negative	Antivirals, fresh frozen plasma	Dead after 3 weeks

BMT, bone marrow transplant; CT, chemotherapy; M, male, F, female; NA, not available; PML, progressive multifocal leukoencephalopathy; IHC, immunohistochemistry; MRI, magnetic resonance imaging; BKV, BK virus; PCR, polymerase chain reaction

rearranged regulatory region in the CSF may be useful in the diagnosis of BKV meningoencephalitis secondary to BKV nephritis.¹¹ In another report of an AIDS patient with nephritis, retinitis and meningoencephalitis due to BKV, investigators have discovered an undescribed reorganized non-coding control region (NCCR) variant of the virus in the CSF and CNS tissues, completely different from the variants detected in peripheral blood leukocytes and urine, which suggests that rearrangements in the NCCR of the virus led to the appearance of a BKV variant, which is much better adapted to the host cell machinery of the brain tissue and thus, more capable to initiate CNS infection in that particular patient.¹³ In two other reports, apart from PCR of CSF, brain tissue and other involved tissues, diagnosis has been reinforced by immunohistochemical staining for the two BKV proteins, the VP1 and the agnoprotein.⁸⁻¹⁰

In most reports so far, the main limitation to conclude that BKV is the causative agent of the neurological disorders is the lack of demonstration of the virus in the brain tissue sample, either by immunohistochemistry or by *in-situ* hybridization. However, since most cases occur in AIDS and transplant recipients with multi-organ involvement by BKV infection, it is reasonable to assume that if a patient shows neurological symptoms without a positive serology and PCR for other pathogens (namely viral agents such as JCV, herpes simplex virus, cytomegalovirus, etc), while a positive PCR for BKV is present in the CSF/brain tissue, it strongly favors the diagnosis of a BKV meningoencephalitis.

Treatment

Standardized antiviral management for BKV infection has not been established yet and is currently under investigation.

In AIDS patients with BKV encephalitis, immune reconstitution by combined antiretroviral therapy (cART) appears to improve the clinical status, but this needs further evaluation to be validated.^{19,22} In the transplant setting, reduction of immunosuppression is the cornerstone of therapy. However, the implications of this approach clearly has deleterious effects for the success of the transplant. Less immunosuppression combined with antiviral drugs may improve the outcome of these patients.

Cidofovir has shown some efficacy in the treatment of BKV-associated hemorrhagic cystitis, but can be nephrotoxic in renal transplant recipients.³⁷⁻⁴¹ Leflunomide appears to be promising as an adjunctive treatment for BKV induced PVN in renal transplant patients.^{42,43}

Use of quinolone antibiotics has also been advocated in the renal and BMT setting with some success.⁴⁴⁻⁴⁶ However, larger prospective studies are necessary to corroborate these results. New anti-viral drugs are being tested in clinical trials and some have completed the phase I trial in humans.^{47,48}

Outcome

In healthy individuals, BKV CNS infection presents with mild and self-limited manifestations, easily handled by symptomatic approach. In the immunocompromised host, the outcome is often dismal with death occurring due to multi-organ failure or other complications. New antiviral drugs and treatment approaches are currently in progress.

CONCLUSIONS

BKV has recently emerged as an opportunistic CNS infectious agent in the immunocompromised host. Clinical evidence of CNS disease and detection of BKV DNA in the CSF and brain tissue of patients suspected to have either meningitis or encephalitis suggest that this virus has also some neurotropism.

BKV must be considered in the differential diagnosis of CNS disorders in AIDS and transplant patients, particularly those with a coexistent urologic disease and neurological decline.

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