BK VIRUS INFECTION: A REVIEW

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Summary

BK virus (BKV) is omnipresent human polyomaviruses that may happen as a primary infection during childhood that establish persistent asymptomatic infections in immunocompetent individuals, but in a minority of immunocompromised patients, reactivate and cause clinical disease. BKV is associated with BKV nephropathy (BKVN) in kidney transplant. Humoral responses do not appear adequate to protect against reactivation or disease and BKV and appear to be due to a failure of cellular immune responses to control the virus. Among the goals of current research is the identification of the functional correlates of cellular immune protection against these viruses in immunocompetent individuals. In the present review we have focused on transmission, causes, signs and symptoms, pathophysiology and current therapeutic approaches for the treatment of infection produced due to BK virus.

Keywords: Cellular, Immunocompetent, Nephropathy, Polyomaviruses,

Introduction

BK virus (BKV) infection is also called a polyomavirus infection. BKV is an infection that may happen as a primary (first) infection during childhood. The virus may have gone away and you may have never felt sick. The BKV may get into your blood and spread to other body organs. It may stay in your kidneys, brain and other tissues without causing any harm or sickness. If your immune system becomes weak, the virus may become active and cause harm to your organs. The immune system protects your body from infections and diseases.A BKV infection may cause problems for those who have had a kidney transplant. The virus may damage the kidney, or may make your body reject the new kidney. With rejection, your body's immune system does not recognize (know) the new organ and attacks it. Having your BKV infection found and treated early may stop damage to your organs, such as your kidneys[1].

HISTORY

The BK virus was first isolated in 1971 from the urine of a renal transplant patient, initials B.K. The BK virus is similar to another virus called the JCV since their genome sequences share 75% homology. Both of these viruses can be identified and differentiated from each other by carrying out serological tests using specific antibodies or by using a PCR based genotyping approach [2].

BKV EPIDEMIOLOGY [3, 4]

Serological studies indicate that primary BKV infection occurs independently of JCV during childhood at a median age of 4–5 years. The seroprevalence is lowest at the age of 6 months after the loss of maternal antibodies and increases to about 75% among adults worldwide (range 46–94%) except for some remote populations in South America and Asia.After primary infection, BKV persists in the renourinary tract as the principal site. Thus, viraemic spread from the site of entry has to be postulated. BKV genomes were detected in small foci in renal cortex and medulla, ureteric and bladder urothelia, as well as in prostate tissue. Reactivation and urinary shedding in immunocompetent individuals ranges from 0–62%. In some studies, BKV DNA has been described in leucocytes and brain.

PRESENTATION [5, 6]

The BK virus rarely causes disease since many people who are infected with this virus are asymptomatic. If symptoms do appear, they tend to be mild: respiratory infection or fever. These are known as primary BK infections.The virus then disseminates to the kidneys and urinary tract where it persists for the life of the individual. It is thought that up to 80% of the population contains a latent form of this virus, which remains latent until the body undergoes some form of immunosuppression. Presentation in these immunocompromized individuals is much more severe. Clinical manifestations include renal dysfunction (seen by a progressive rise in serum creatinine) and an abnormal urinalysis revealing renal tubular cells and inflammatory cells.

GENOMIC STRUCTURE OF BKV [7, 8]

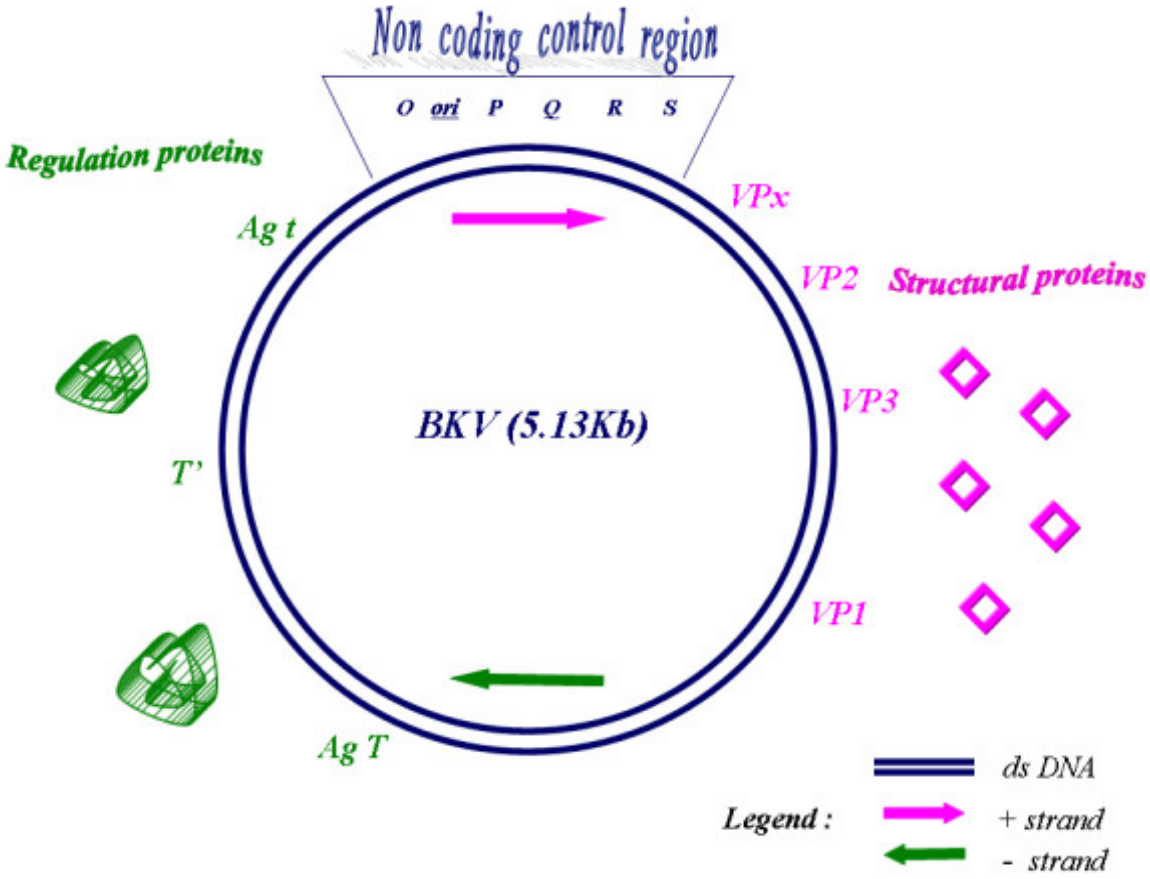

Figure 1: Schematic representation of the gene organization in the BK virus (BKV) genome. The double circle represents the double stranded DNA genomes. The genome is divided into three regions. The early region encodes three regulatory proteins (Agt, AgT, T'). The late region specifies four structural proteins and agnoprotein (VP1, VP2, VP3, VPx). The non-coding control region contains the elements for the control of viral DNA replication (ori) and viral gene expression. The arrows indicate the positive and negative strands according to the direction of viral transcription

IMMUNOSUPPRESSANT-INDUCED SUSCEPTIBILITY

In some renal transplant patients, the necessary use of immunosuppressive drugs has the side-effect of allowing the virus to replicate within the graft, a disease called BK nephropathy [9]. It is thought that 1-10% of renal transplant patients progress to BK virus nephropathy (BKVN) and up to 80% of these patients are reported to have lost their grafts. The onset of nephritis can occur as early as several days post-transplant to as late as 5 years. It is also associated with ureteral stenosis and interstitial nephritis. In bone marrow transplant recipients it is notable as a cause for hemorrhagic cystitis [10].

TRANSMISSION

It is not known how this virus is transmitted. It is known, however, that the virus is spread from person to person and not from an animal source. It has been suggested that this virus may be transmitted through respiratory fluids or urine, since infected individuals periodically excrete virus in the urine. A survey of 400 healthy blood donors was reported as showing that 82% were positive for BK virus.[11]

COMPARISON OF JC VIRUS AND BK VIRUS [12]

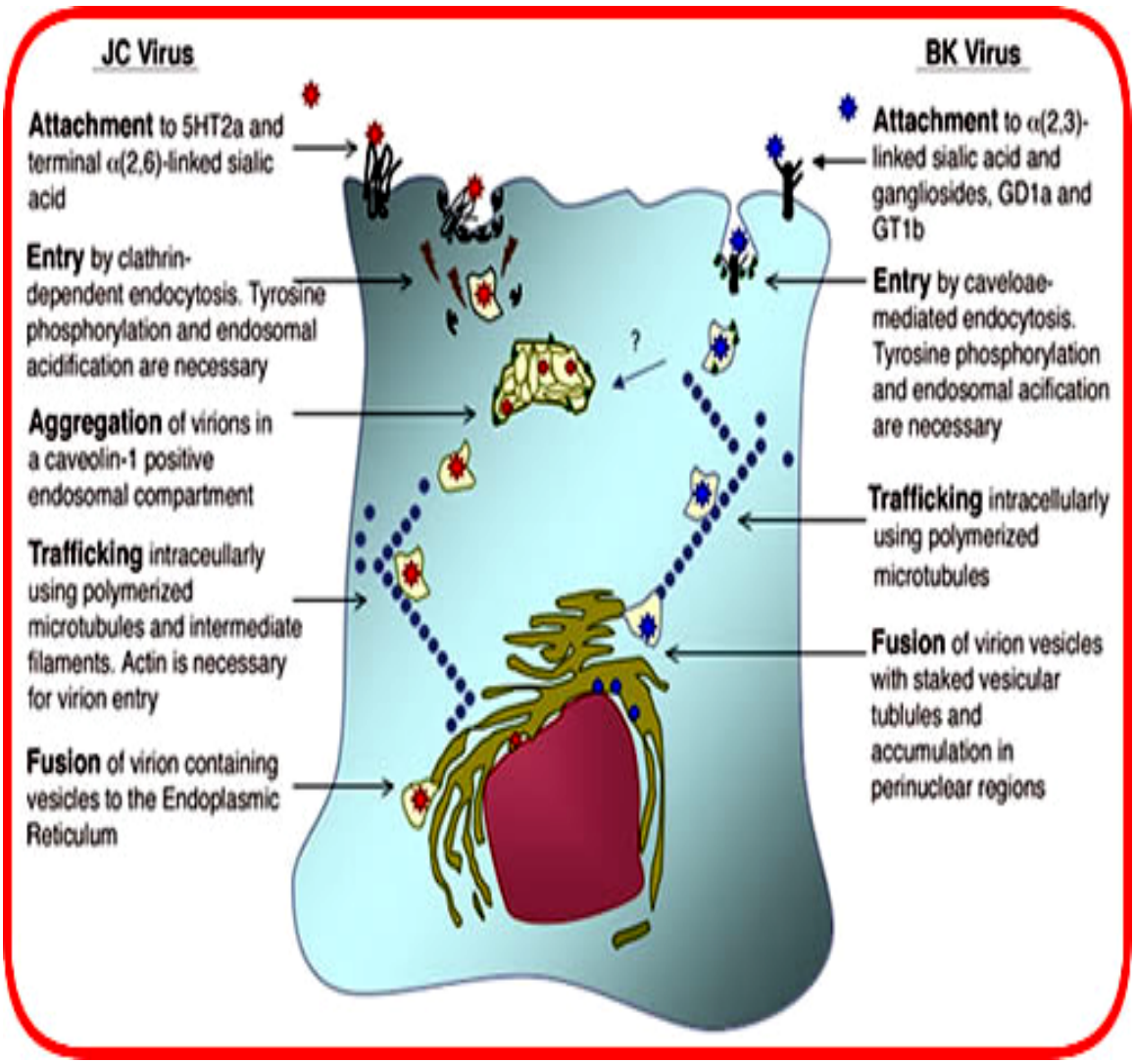

Figure 2: Comparison of Jc Virus and Bk Virus

CAUSES A BKV INFECTION [13, 14]

The infection is caused by a germ called BK virus. You may get the infection from any of the following:

- **Body fluids:** A BKV infection may be spread by breathing in fluid droplets from someone who has the infection. The fluid droplets may come from a sneeze or cough. You may also get BKV from blood transfusions or through semen (fluid containing sperm).
- **During birth:** BKV may be passed on by a mother to her baby during birth.
- **Organ transplant:** This is when your damaged organ is replaced by a new organ. You may get the infection if the kidney that you received has the BKV infection.
- **Unclean food and drink:** This may include drinking liquids or eating foods that have been infected with BKV.

RISK OF HAVING A BKV INFECTION [15, 16]

- **Age:** Elderly people may have a higher risk of having the BKV infection.
- **Gender:** Males are at higher risk of having BKV.
- **Renal injury:** Renal (kidney) injuries may cause the BKV in your body to become active. Examples of injury may be having a stent placed to open your urine passage or renal infections.
- **Weak immune system:** Having a weak immune system commonly causes the virus to increase in number and become active. Your immune system becomes weak when you have a long-term illness. This includes illnesses such as AIDS or diabetes (increased sugar in your blood). Taking antirejection medicines after a kidney or bone marrow transplant may also make your immune system weak. Antirejection medicines help your body accept your new organ and keep your body from rejecting it.

CONDITIONS WITH A BKV INFECTION [17, 18]

A BKV infection may cause any of the following problems:

- **Brain:** Encephalitis (swelling of the brain).
- **Eyes:** Retinitis (swelling of the retina). The retina is the lining at the back of the eye.
- **Lungs:** Pneumonitis (swelling of the lungs) or infection.
- **Urinary:** Swelling and damage of the kidneys, bleeding of the bladder and blockage of urine passageways.

SIGNS AND SYMPTOMS OF A BKV INFECTION [19, 20, 21]

A primary BKV infection may have no symptoms. If your immune system is weak, you may have any of the following:

- Abdominal (stomach) problems.
- Blurry vision or trouble seeing things.
- Brown or reddish-colored urine.
- Burning pain or trouble when passing urine, or passing more urine than usual.
- Cough, colds or trouble breathing.
- Fever, muscle pain, or weakness.
- Seizures (convulsions).

BKV INFECTION DIAGNOSED [22, 23]

You may need tests that will help your caregiver look for BKV in your body. You may need any of the following:

- **Blood tests:** You may need blood taken for tests. The blood can be taken from a blood vessel in your hand, arm, or the bend in your elbow. It is tested to see how your body is doing. It can give your caregivers more information about your health condition. You may need to have blood drawn more than once.

- **Kidney biopsy:** A kidney biopsy is when a very small piece of your kidney is taken out and sent to a lab for tests. For this procedure, you will need to lay face-down and hold very still. You may be given medicine to make the area numb (lose feeling). Your caregiver will put a needle into your back and through to your kidney. The needle may have to be put in two or more times. After the needle is taken out, a bandage will be put to cover the area.
- **Urine sample:** A sample of your urine is collected and sent to a lab for tests. Your caregiver may give you a special wipe and clean cup. Use the wipe to clean your skin around the opening you urinate from. Urinate into the clean cup. Put the lid on the cup. Do not touch the inside of the cup or lid. Give the urine sample to your caregiver.

TREATMENT [24, 25]

The cornerstone of therapy is reduction in immunosuppression. A recent surge in BKVN correlates with use of potent immunosuppressant drugs, such as tacrolimus and mycophenolate mofetil (MMF). Studies have not shown any correlation between BKVN and a single immunosuppressive agent but rather the overall immunosuppressive load.

- No guidelines or drug levels and doses exist for proper reduction of immunosuppressants in BKVN
- Most common methods:

1. Withdrawal of MMF or tacrolimus
2. Replacement of tacrolimus by cyclosporine
3. Overall reduction of immunosuppressive load
4. Some cyclosporine trough levels reported to be reduced to 100-150 ng/ml and tacrolimus levels reduced to 3-5 ng/ml
    - Retrospective analysis of 67 patients concluded graft survival was similar between reduction and discontinuation of agents.
    - Single center study showed renal allografts were preserved in 8/8 individuals managed with reduction in immunosuppression while graft loss occurred in 8/12 patients treated with an increase in therapy for what was thought to be organ rejection.

Other therapeutic options include Leflunomide, Cidofovir, IVIG and the fluoroquinolones. Leflunomide is now generally accepted as the second treatment option behind reduction of immunosuppression.

OTHER TREATMENTS [26, 27]

- **Bladder irrigation:** Your caregiver may need to put a catheter (tube) into your bladder. This is done to rinse your bladder and help you pass urine.
- **Hyperhydration:** You may need to drink more liquids than usual to help flush (wash out) your bladder. Your caregiver may also give you liquids through an IV. An IV is placed in your vein for giving medicine or liquids. This tube is capped or connected to tubing and liquid.
- **Surgery:** You may need surgery if the organs or tissues where your urine passes are damaged. Ask your caregiver for more information about this treatment.

Conclusion

Development of BKV disease is likely to require complementing determinants in the host, the target organ and possibly the virus, which are subject to dynamic modulators. Therefore it is essential to understand and to monitor the delicate balance between viral infection, immune regulation in the transplant population and immunosuppressive therapy in order to minimize viral injury and rejection risk to patients with BKV infection. Despite considerable progress in the past 2 years, present understanding of BKV disease is incomplete and needs further research to ultimately improve patient care. A better definition of risk factors and more effective and less toxic antiviral drugs are paramount. Such insights may help identify the small subset of patients at risk of BKV aid clinical management and permit the development of immunotherapeutic approaches.

References

1. Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet. 1971 Jun 19;1(7712):1253-7.
2. Egli A, Infanti L, Dumoulin A, et al. (2009). "Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors". J Infect Dis 199 (6): 837–846.
3. Fishman, J. A. (2002). "BK Virus Nephropathy — Polyomavirus Adding Insult to Injury". New England Journal of Medicine 347 (7): 527–530.
4. Bista, BR; Ishwad, C; Wadowsky, RM; Manna, P; Randhawa, PS; Gupta, G; Adhikari, M; Tyagi, R et al. (2007). "Development of a loop-mediated isothermal amplification assay for rapid detection of BK virus.". Journa*l of clinical microbiology* 45 (5): 1581–7.
5. Kasiske BL, Vazquez MA, Harmon WE, Brown RS, Danovitch GM, Gaston RS, Roth D, Scandling JD, Singer GG, for the American Society of Transplantation: Recommendations for the outpatient surveillance of renal transplant recipients. J Am Soc Nephrol 2000, 11:S1-S86
6. Jeloka TK, Ross H, Smith R, Huang M, Fenton S, Cattran D, Schiff J, Cardella C, Cole E: Renal transplant outcome in high-cardiovascular risk recipients. Clin Transplant 2007, 21:609-614
7. Matignon M, Dahan K, Fruchaud G, Audard V, Grimbert P, Lang P: Kidney transplantation: indications, results, limitations and perspectives. Presse Med 2007, 36:1829-1834.
8. Foster CE, Weng RR, Smith CV, Imagawa DK: The influence of organ acceptance criteria on long-term graft survival: outcomes of a kidney transplant program. Am J Surg 2007, 195:149-152.
9. Johnston O, O'kelly P, Spencer S, John Donohoe, Walshe JJ, Little DM, Hickey D, Conlon PJ: Reduced graft function (with or without dialysis) vs immediate graft function–a comparison of long-term renal allograft survival. Nephrol Dial Transplant 2006, 21:2270-2274.
10. Sancho A, Gavela E, Avila A, Morales A, Fernández-Nájera JE, Crespo JF, Pallardo LM: Risk factors and prognosis for proteinuria in renal transplant recipients. Transplant Proc 2007, 39:2145-2147.
11. Schaub S, Mayr M, Hönger G, Bestland J, Steiger J, Regeniter A, Mihatsch MJ, Wilkins JA, Rush D, Nickerson P: Detection of subclinical tubular injury after renal transplantation: comparison of urine protein analysis with allograft histopathology. Transplantation 2007, 84:104-112.
12. Braun WE: Renal transplantation: basic concepts and evolution of therapy. J Clin Apher 2003, 18:141-152.

13. Böhmig GA, Regele H, Hörl WH: Protocol biopsies after kidney transplantation. Transpl Int 2005, 18:131-139
14. Goldsmith D, Al-Khoury S, Shah N, Covic A: Anaemia after renal transplantation role of immunosuppressive drugs and a pathophysiological appraisal. Nephron Clin Pract 2006, 104:69-74.
15. Goldfarb S: Update in nephrology. Ann Intern Med 2008, 148:49-54.
16. Shipkova M, Armstrong VW, Oellerich M, Wieland E: Mycophenolate mofetil in organ transplantation: focus on metabolism, safety and tolerability. Expert Opin Drug Metab Toxicol 2005, 1:505-526.
17. Vítko S, Viklický O: Cyclosporine renal dysfunction. Transplant Proc 2004, 36:243S-247S.
18. Scott LJ, McKeage K, Keam SJ, Plosker GL: Tacrolimus: a further update of its use in the management of organ transplantation. Drugs 2003, 63:1247-1297.
19. Drachenberg CB, Hirsch HH, Papadimitriou JC, Gosert R, Wali RK, Munivenkatappa R, Nogueira J, Cangro CB, Haririan A, Mendley S, Ramos E: Polyomavirus BK versus JC replication and nephropathy in renal transplant recipients: a prospective evaluation. Transplantation 2007, 84:323-330.
20. Fishman JA, Emery V, Freeman R, Pascual M, Rostaing L, Schlitt HJ, Sgarabotto D, Torre-Cisneros J, Uknis ME: Cytomegalovirus in transplantation-challenging the status quo. Clin Transplant 2007, 21:149-158.
21. Linares L, Cofán F, Cervera C, Ricart MJ, Oppenheimer F, Campistol JM, Moreno A: Infection-related mortality in a large cohort of renal transplant recipients. Transplant Proc 2007, 39:2225-2227.
22. Schweitzer EJ, Perencevich EN, Philosophe B, Bartlett ST: Estimated benefits of transplantation of kidneys from donors at increased risk for HIV or hepatitis C infection. Am J Transplant 2007, 7:1515-1525.
23. Randhawa P, Vats A, Shapiro R: The pathobiology of polyomavirus infection in man. Adv Exp Med Biol 2006, 577:148-159
24. Knowles WA: Discovery and epidemiology of the human polyomaviruses BK virus (BKV) and JC virus (JCV). Adv Exp Med Biol 2006, 577:19-45
25. Lundstig A, Dillner J: Serological diagnosis of human polyomavirus infection. Adv Exp Med Biol 2006, 577:96-101
26. Ashok A, Atwood WJ: Virus receptors and tropism. Adv Exp Med Biol 2006, 577:60-72.
27. Doerries K: Human polyomavirus JC and BK persistent infection. Adv Exp Med Biol 2006, 577:102-116.