Polyomaviruses

Polyomaviruses constitute one genus of the family *Papovaviridae*. The primate polyomavirus SV40 was discovered in 1960 as a passenger virus in cultures of rhesus monkey cells. Poliovirus vaccine produced in monkey kidney cells were contaminated by SV40 which was inadequately inactivated by formalin, and was inadvertently administered to several million people. The 2 human polyoma species, JC and BK, were isolated from patients with the same initials in 1971. BK was isolated from the urine of a person 4 months after renal transplantation. JC was first isolated from the brain from a patient suffering from Hodgkin's disease, and suffering from PML. Previously, it had been shown that PML brain tissue contained virus-like particles in the nuclei of abnormal oligodendrocytes, which is the pathognomonic cell of the disease. The appearance of these particles under EM strongly suggested that they were polyomavirus particles. Strenuous attempts were made to isolate the virus from 1965 onwards but success only came in 1971 with the use of primary human glial cells. A lot of the natural history of human polyomaviruses remain unknown, such as the method of their transmission.

A. Properties

Belong to the family papovaviridae
naked dsDNA viruses with icosahedral symmetry
dsDNA molecule consists of around 5000 bp
5 transcripts are produced, both strands of DNA are used for transcription. 5 proteins are produced
T and t are early proteins, VP1, VP2, and VP3 are the late structural proteins.
The DNA of JC, BK and SV40 exhibit homology
T antigens of JC, BK and SV40 cross-react serologically and functionally, although they are unique and distinct
JC and BK can agglutinate human and guinea pig RBCs
Able to transform certain cells in vitro, and to induce tumours in experimental animals such as newborn Syrian hamsters and adult owl monkeys.

Polyomavirus replication in permissive cells can be detected by observing CPE or plaque production, by identifying virus particles in cell or culture fluid by EM, by detecting virus antigens using IF, or by observing haemagglutination. JC will only grow in a very restricted range of cells, mainly from the brain. BK will grow in a wider range of cells including VERO. It was demonstrated that BK is capable of supplying early gene functions required by a temperature sensitive SV40 mutant for growth at the non- permissive temperature, thus showing that the T antigen of SV40 and BK can cross react functionally. Like many other DNA viruses, JC and BK maintains a latent infection in the body and are reactivated from time to time.

B. Epidemiology

JC and BK viruses are ubiquitous throughout the world, and the 2 viruses circulate independently. Isolated virgin populations exist in remote areas of the world, BKV seems to have penetrated more deeply into remote areas than JC. Antibody titres persist throughout life. For JC, most persons become seropositive by the age of 10, for BK, most persons are seropositive by 5. By adulthood, 70-90% of individuals have antibodies to both JCV and BKV. There is serological evidence for reactivation of JC and/or BK in 5 to 10% of women during pregnancy, and virus can often be isolated from the urine. Whether human intrauterine infection with JC or BK occurs is still unresolved. Virus-specific IgM in cord blood has been found by some workers but not by others. Nevertheless, the possibility that congenital infections occur cannot be excluded. In Germany, it was reported that 17 children with various congenital disorders were found to have BKV-specific IgM. There is no evidence for the existence of animal reservoirs. The exact route of transmission is still unknown. By analogy with murine polyoma virus and with SV40, infection may occur by aerosol inhalation or oral ingestion of virus with excretion occurring via the urinary tract.

C. Association with Disease

Primary polyomavirus infections have not been associated with any specific clinical syndromes. Most infections seem to be subclinical although some children developed mild respiratory symptoms and others had cystitis. It is thought that primary BKV infections may on occasions be associated with either acute respiratory disease or cystitis but further work is required.

1. **Progressive multifocal leucoencephalopathy** - JC virus is now firmly associated with PML. It has not been established whether PML is the result of a primary infection with JCV in a person with impaired immunity or whether it follows reactivation of latent virus. The fact that PML is relatively uncommon in children and young persons and more often develops in people in the fifth and sixth decades of life suggests that latent virus is the more likely cause. The pathogenesis of PML is not fully understood but it is postulated that in patients with disorders of immunoregulation, polyomaviruses are no longer contained in a latent state and replicate within the oligodendrocytes, causing the destruction of the cell and the breakdown of the myelin sheath. PML is a unique demyelinating disease which usually occurs in a person with abnormal immune responses resulting from serious disease, treatment with cytotoxic drugs or irradiation, or long term immunosuppression. The pathology of PML is distinctive and consists of multiple foci of demyelination of varying size from pinpoint lesions to areas of several centimetres. The lesions may occur anywhere but are usually in the cerebral hemispheres, less often in the cerebellum and brain stem and rarely in the spinal cord. The oligodendrocytes in the peripheral zone surrounding an area of demyelination are grossly abnormal. The nuclei of abnormal oligodendrocytes are packed with JC virions. Typically, PML evolves gradually, with impairment of mental function and disturbance of speech and vision. Movement may also be affected. The disease then progresses rapidly and the patient is severely disabled, eventually becoming demented, blind and paralyzed and finally coma and death. PML is frequently associated with lymphoproliferative and other chronic diseases, such as AIDS, Hodgkin's disease, CLL, sarcoidosis, TB, SLE and organ transplantation. Only rarely has PML been reported occurring spontaneously in an apparently healthy person. Occasionally, PML may spontaneously arrest. PML has been reported in children with congenital severe combined immunodeficiency which suggests that a primary JCV infection is responsible.
2. **Ureteric stenosis in renal transplant recipients** - the only other disease with which ureteric stenosis have been associated is ureteric stenosis in renal transplant patients. The polyomavirus infection induces proliferation of the transitional epithelial cells in the ureter and this can lead to partial obstruction or actual stricture formation. The affected cells had inclusion bodies. 9 cases have been recognized and both JC and BK have been implicated. The ureteric obstruction occurred between 50 to 300 days post-transplant.
3. **Other possible associations** - BK virus was associated with cases of acute haemorrhagic cystitis following bone marrow transplantation. However, it is possible that two independent but synchronous events may be taking place - reactivation of BKV and haemorrhagic cystitis. The genomes of JC and BK virus were detected in several tumours, but there is no evidence that human polyomaviruses are associated with the causation of any tumours.

D. Laboratory Diagnosis

1. **PML** - The clinical diagnosis of PML is confirmed by histological and virological examination of brain material obtained by brain biopsy or at postmortem. Before a biopsy is done, both serum and CSF should be examined for antibodies against JCV. A positive result will not confirm PML, but a negative result makes the diagnosis of PML very unlikely. It is rare to detect antibodies against JC in the CSF. When it is detected, it is suggestive of active multiplication of JCV within the CNS. The brain biopsy or autopsy material can be examined by EM or IEM. The specimen can also be examined directly for JCV antigen by immunofluorescence or immunoperoxidase staining. Virus isolation is very difficult for JCV. When attempted, primary human fetal glial cells are used. The presence of the virus in culture is confirmed by EM, IF or haemagglutination. JC is rarely excreted in the urine of patients suffering form PML.
2. **Renal Tract Infections** - the methods generally employed to detect the presence of polyomavirus in urine are cytological examination of the urine for inclusion-bearing cells, EM and virus isolation. The cytology of urine in human polyomavirus infection is quite characteristic. The inclusion-bearing cells have a characteristic appearance and are often present in large numbers. Electron Microscopy of the urinary sediment after centrifugation at 20000 may reveal the presence of polyomavirus particles. It is difficult to isolate JC and BK viruses: Primary PHFG cells must be used for isolation of JCV; BKV have a wider host cell range and HEK cells can be used as well as PHFG cells. More sensitive techniques are

being developed, such as dot- blot and PCR.

3. **Serological Diagnosis** - HAI is the most widely used serological technique for measuring antibodies against the polyomaviruses. CFT, neutralization, ELISA and RIAs have also been used.

E. Management

Because of the invariably fatal outcome of PML, various antiviral drugs have been tried. The only drug that may have had an effect is cytarabine. Reports have been published on 8 laboratory confirmed cases of PML treated with cytarabine. Long-term improvement was seen in 2 patients. In another person, there was a dramatic response to therapy within 24 hours but this was not maintained. The rapid progression of the disease was halted in a fourth patient but the neurological damage was severe. The remaining 4 individuals did not show any improvement. One should also consider relaxing any immunosuppression regimes in such patients.