CHAPTER 7

Serological Diagnosis of Human Polyomavirus Infection

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Abstract

Measurement of antibody titres to the human polyomaviruses BK and JC has for many years had to rely on Hemagglutination inhibition. In recent years, viral serology based on virus-like particles (VLPs) in enzyme immunoassays (EIAs) has become widely used for a variety of viruses. We sought to establish a modern method for serological diagnosis of BK and JC viruses, by using purified VLPs containing the VP1 major capsid proteins. Antibody titres in assays based on VLPs of BKV (strain SB) showed no correlation to the titres in similar JCV assays. BKV (SB) seropositivity increases rapidly with increasing age of the children and reaches a 98% seroprevalence at 7-9 years of age, whereas JCV seroprevalences increase more slowly with increasing age reaching 51% positivity among children 9-11 years of age. The antibody levels are almost identical in serial samples taken up to 5 years apart, suggesting that both BKV and JCV VLP seropositivities are usually stable over time and can be used to measure cumulative exposure to these viruses.

Serology using SV40 VLPs showed strong cross-reactivity with human polyomaviruses, in particular with BKV strain AS, and establishing a specific VLP-based serology assay for SV40 required blocking with several hyperimmune sera to the human polyomaviruses. SV40-specific seropositivity also increased with increasing age of children, reaching 14% seroprevalence among children 7-9 years of age, but had limited stability over time in serial samples.

Introduction

Different serological methods have been used over the years to measure antibodies to the Polyomaviruses. Hemagglutination inhibition (HI) assay has been the standard method for this purpose because of the ease and rapidity with which it could be performed. Neutralization test and plaque reduction assay, where cell culture is required as neutralization of virus infectivity has also been described for SV40 and BKV antibody detection.

In recent years enzyme immunoassays (EIAs) has become widely used. A modern EIA based on virus-like particles (VLPs) has been established to assess polyomavirus antibodies in serum samples. The Polyoma VLPs are based on the major capsid protein, VP1 and produced in yeast cells from Saccharomyces cerevisiae.

Four antigenic variants of BKV have been described: the BKV prototype, BKV AS, BKV SB and BKV IV. These BKV strains were isolated from urine specimens from several patient groups. Each strain has been characterized by nucleotide sequencing of the VP1 region, which encodes the major capsid protein of BKV. Specific variations correlate with serological typing by Hemagglutination inhibition.

Infection with BKV occurs at an earlier age than does JCV infection. In the United States antibodies to BKV are acquired by 50% of the children by the age of 3-4 years, whereas antibodies to JCV are acquired by 50% of the children by the age of 10-14 years. The antibody prevalence to BKV reaches nearly 100% by the age of 10-11 years and then declines to around 70-80% in older age groups. The antibody prevalence to JCV reaches a peak of about 75% by adult age.9

In a recent study, serum samples from 290 children and 150 pregnant women stratified by age of first pregnancy were analysed for antibodies to polyomaviruses in a VLP-based antibody assay. Samples from 290 Swedish children aged 1-13 years, stratified in age groups with 2 year intervals demonstrated that BKV seropositivity increased rapidly with increasing age of the children, reaching 98% seroprevalence at 7-9 years of age, followed by a minor decrease.4,10

JCV seroprevalence increased only slowly with increasing age and reached a 51% positivity among children 9-11 years of age4 (Fig. 1).

Simian Virus 40

Antibodies against SV40 have been reported to be present in about 5% of healthy individuals from the US and India. Most reactivities are low-titered, but occasionally humans with neutralizing antibody titers of very high magnitude are found (similar titers as in experimentally infected monkeys). In the few and limited surveys that have been performed, there has been no correlation of SV40 seroprevalences with history of poliovirus vaccination. This has been interpreted as showing that SV40 is now circulating in human populations.11

It is possible that the antibodies reacting with SV40 are induced by the human polyomaviruses and cross react with SV40. It is suggested that SV40 antibodies are cross-reactive BK antibodies and significant correlations have been reported between SV40 and BKV antibody levels, as well as with JCV antibody levels.4,12 In our studies SV40 antibodies were most closely related to BKV strain AS antibodies (correlation coefficient = 0.70).4 Sensitive and specific reagents are needed to establish exposure to SV40 infection.13 Only after blocking SV40 VLPs with high-titered hyperimmune sera against both BKV and JCV were we able to establish an SV40 serological assay devoid of cross-reactivity with BKV and JCV (unpublished observations). The SV40 seroprevalences increased with age of the children in a similar manner, as does BKV, with the peak being reached at 7-9 years of age with a 14% seroprevalence. SV40-specific antibodies appear to be less stable over time than BKV and JCV antibodies (unpublished observations).