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JC virus/human immunodeficiency virus 1 co-infection in the Brazilian Amazonian region

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ABSTRACT

JC virus (JCV) is a member of the *Polyomaviridae* family and is associated to a severe disease known as progressive multifocal leukoencephalopathy, PML, which is gradually increasing in incidence as an opportunistic infection among AIDS patients. The present study aimed to investigate the occurrence of JCV among HIV-1 carriers including their types and molecular subtypes and the possible association with disease. Urine samples from 66 HIV-1 infected subjects were investigated for the presence of the virus by amplifying VP1 (215 bp) and IG (610 bp) regions using the polymerase chain reaction. JCV was detected in 32% of the samples. The results confirmed the occurrence of type B (subtype Af2); in addition, another polyomavirus, BKV, was also detected in 1.5% of samples of the HIV-1 infected subjects. Apparently, there was no significant difference between mono- (HIV-1 only) and co-infected (HIV-1/JCV) subjects regarding their TCD4$^+$/TCD8$^+$ lymphocyte counts or HIV-1 plasma viral load. Self admitted seizures, hearing and visual loses were not significantly different between the two groups.

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Introduction

Polyomaviruses are small agents which infect a variety of species including man, non-human primates, cattle, rodents, rabbits, and birds. Two human polyomaviruses are important pathogens, JC virus (JCV) and BK virus (BKV), as they are able to cause a severe, usually fatal, neurological disease (progressive multifocal leukoencephalopathy, PML) and renal infection in immunosupressed patients, respectively.[1–3] The viruses share approximately 72% of nucleotide homology and a high degree of identity (80%) of amino acid sequence of a capsid protein, VP1.[4,5] JCV infects the human host and establishes a persistent replicative cycle (including latency) following the acute infection, which favors its dissemination within human populations and its carriage through generations.

more than 70% of the Although JCV is found to infect more than 70% of the adult human population as a productively

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persistent infection, PML is a rare disease.[5–9] It is a manifestation that follows malignant conditions, as well as a consequence of primary or secondary immunodeficiencies, particularly in acquired immunodeficiency syndrome (AIDS). The emergence of human immunodeficiency virus 1 (HIV-1) infection elicited an additional interest in JCV with the frequent finding of HIV-1 carriers co-infected with JCV.[10] The incidence of PML is gradually increasing among AIDS patients, initially as a consequence of the increase of HIV-1 infections, and secondly, as an increase in life expectancy as a result of better antiretroviral drugs.[10] JCV infects HIV-1 carriers and is one of the major opportunistic infections of the central nervous system.[11–15] In our previous study we described JCV and BKV infections among Amerindian tribes, Afro-descendant communities, as well as in the urban area of Belém, state of Para, north of Brazil.[16] The results showed a large genetic variability of strains circulating in the region, infecting a large group of individuals. The presence of European, Asiatic, and African subtypes associated to the ethnic origin of the population samples investigated highlighted the idea that JCV is a good marker for studying the early migration of human populations, reflecting their early and late history.

The present study aimed to describe the occurrence of JCV, including their types and molecular subtypes among HIV-1 carriers and the possible association with neurological disease.

Materials and methods

Population examined

A cross-sectional study was performed, using a convenience sample which included 66 HIV-1 infected persons. A single urine sample was obtained from HIV-1 infected persons residing in the city of Belém, attending the University Hospital João de Barros Barreto (HUJBB), for their routine clinical care, and laboratory follow-up determinations of TCD4$^+$/TCD8$^+$ lymphocyte counts and HIV-1 plasma viral load (HPVL). All patients were receiving antiretroviral therapy (ART) at the time of sample collection. The duration of ART ranged from one to seven years. Half of them were on ART for no more than five years, with mean and median values of four years. The project was approved by the Ethics Committee of the University Hospital Joao de Barros Barreto (Protocol Number 2092/05). The participants were briefed about the project and those who accepted to take part signed an informed consent. All patients were adults (18 years or older) and were capable to provide answers to a questionnaire which included questions regarding demographic, social and cultural aspects of their life style. The patients were also asked to inform, over common neurological events which are usually considered as baseline symptoms associated to JCV infection, at least once, since their initial diagnosis of HIV-1 infection.

Quantification of HPVL and TCD4$^+$/TCD8$^+$ lymphocyte counts

HPVL was determined by the bDNA method (VERSANT® HIV-1 RNA 3.0 Assay bDNA "Versant Assay", Siemens, USA) following the manufacturer's directions. Whole blood samples were processed within four hours of collection for the determination of TCD4$^+$ counts by flow cytometry (FacsCount, Becton & Dickinson, San Jose, CA, USA) using the FacsCount™ Reagents immunomonitoring kit, following the protocol recommended by the manufacturer (Becton Dickinson, San Jose, CA, USA). Both procedures were routinely conducted at the Virology Laboratory, which is one of the National Reference Laboratory for the two determinations.

Urine sample collection and DNA extraction

Urine samples (50 mL) were collected in specific vial collectors and transported to the Virology Laboratory of the Institute of Biological Sciences of the Universidade Federal do Para (ICB/UFPA) and stored at −20 °C until assaying for JCV infection. The urine samples were centrifuged at 5000 rpm for 15 min, the urinary sediment washed three times with sterile saline solution and the cell pellet used for DNA extraction according to the protocol using the EZ-DNA kit (Gentra Systems, Inc., Minneapolis, MN, USA), as previously described.[16]

Molecular analysis

Polymerase chain reaction – PCR was performed for amplification of the VP1 gene (215 bp) and the genomic region IG (610 bp) of JCV, using a thermocycler (Mastercycler Personal, Eppendorf, Germany), and the amplified products were subjected to purification for subsequent sequencing analysis of the nucleotide bases, as previously described.[16]

Sequencing and subtype analysis

The amplified products of the IG region were used for determining genetic relationships among the strains detected and those recorded in Genbank database. The amplified fragments were submitted to a direct sequencing assay (both forward and reverse) according to the protocol of the ABI Prism Dye Terminator Cycle Sequencing Ready Kit (Life Technologies, Foster City, CA, USA) and the products were loaded on the ABI Prism 310 DNA Sequencer (Life Technologies, Foster City, CA, USA). The nucleotide sequences were used together with other JCV sequences available in the Genbank as previously described.[16] Nucleotides sequences obtained in the present study are available in the Genbank databases under the accession numbers KR062063, KR062064 and KR062065 and were submitted to Basic Local Alignment Search Tool – Blast (http://blast.ncbi.nlm.nih.gov/Blast.cgi) aiming to identify the virus subtype.

Statistical analysis

The frequency of HIV-1/JCV co-infection was estimated by direct counting. To determine whether the variables TCD4$^+$, TCD8$^+$ and HIV-1 viral load followed a normal distribution, D'Agostino's test was used, and the mean values of the laboratory markers were compared using ANOVA. A p-value <0.05 was considered statistically significant using the BioEstat 5.0 software.[17]

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