

# Serological profile of John Cunningham virus (JCV) in patients with multiple sclerosis

Perfil sorológico do vírus John Cunningham (JCV) em pacientes com esclerose múltipla

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## ABSTRACT

Treatment options for multiple sclerosis (MS) have changed over the last few years, bringing about a new category of drugs with more efficient profiles. However, these drugs have come with a whole new profile of potential adverse events that neurologists have to learn well and quickly. One of the most feared complications of these MS treatments is progressive multifocal leukoencephalopathy caused by the reactivation of the John Cunningham virus (JCV). Objective: To identify the serologic profile of JCV in patients with MS. Methods: Data on serum antibodies for JCV were obtained using the enzyme-linked immunosorbent assay provided by the STRATIFY-JCV program. Results: A total of 1,501 blood tests were obtained from 1,102 patients with MS. There were 633 patients (57.1%) who were positive for antibodies for JCV and 469 patients who were negative (42.9%). Twenty-three patients became positive after initially having negative JCV antibody status. The rate of seroconversion was 18.5% over 22 months. Conclusion: The JCV serologic profile and seroconversion in Brazilian patients were similar to those described in other countries.

**Keywords:** multiple sclerosis; leukoencephalopathy, progressive multifocal; JC virus; natalizumab.

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## RESUMO

As opções terapêuticas para esclerose múltipla (EM) modificaram-se ao longo dos últimos anos, trazendo uma nova categoria de drogas com melhor perfil de eficácia. No entanto, estas drogas vieram com um novo perfil de potenciais eventos adversos que exigem que o neurologista os reconheça bem e rapidamente. Uma das complicações mais temidas destes tratamentos para a EM é a leucoencefalopatia multifocal progressiva (LEMP), causada pela reativação do vírus John Cunningham (JCV). Objetivo: Identificar o perfil sorológico de JCV em pacientes com EM. Métodos: Dados sorológicos de JCV foram obtidos através do ensaio por enzimas imuno-adsorvidas (ELISA) fornecido pelo programa STRATIFY-JCV. Resultados: Um total de 1.501 testes sanguíneos foram obtidos de 1.102 pacientes com EM. O grupo teve 633 pacientes (57,1%) soropositivos para anticorpos anti-JCV e 469 pacientes negativos (42,9%). Vinte e três pacientes se tornaram positivos após resultados iniciais negativos para anticorpos anti-JCV. A taxa de soroconversão foi 18,5% em 22 meses. Conclusão: O perfil sorológico de JCV e a soroconversão nos pacientes brasileiros foi semelhante àquela descrita em outros países.

**Palavras-chave:** esclerose múltipla; leucoencefalopatia multifocal progressiva; vírus JC; natalizumab.

The John Cunningham virus (JCV) is a ubiquitous polyoma virus that exclusively infects humans<sup>1</sup>. Primary exposure to the JCV is asymptomatic, usually occurring during childhood or adolescence, although the development of anti-JCV antibodies may also occur later in life<sup>2</sup>. The JCV can be found in a latent state in several tissues, including the brain<sup>3</sup>, where it can cause progressive multifocal leukoencephalopathy (PML) in immunosuppressed patients<sup>4</sup>.

The advent of very potent monoclonal antibody immunological treatments for multiple sclerosis (MS) brought about a new category of patients at risk for PML<sup>5</sup>. Whereas, previously, PML was almost exclusively in patients suffering from severe immunosuppression (for example, patients with AIDS), now individuals with MS treated with natalizumab require monitoring of their JCV serum status and proper management of drug withdrawal if necessary<sup>6,7</sup>. The risk of developing PML in MS cases can be stratified, and patients at higher risk may go straight to other therapeutic options or have shorter-term treatment with natalizumab<sup>5</sup>. In the absence of an effective treatment for a devastating disease like PML, patients with MS undergoing treatment with newer drugs must be closely monitored in order to minimize central nervous system injury and to avoid severe disability<sup>6</sup>.

It is essential to ascertain the overall prevalence of the JCV in patients with MS, in order to make better use of recommendations and guidelines regarding the risk of PML. The proportion of the adult population with antibodies for the JCV seems to vary between 50% and 90%<sup>8</sup>. A previous Brazilian study found that 51.2% out of 168 patients with MS were seropositive for the JCV<sup>9</sup>. The objective of the present study was to assess a much larger Brazilian population of patients with MS regarding seropositivity for the JCV.

## METHODS

This study was approved by the Ethics Committee of Universidade Metropolitana de Santos under the number CAAE 05669912.3.0000.5509. Additional approval from other MS centers was obtained, whenever necessary, by the participating neurologists.

Serum antibodies for the JCV were detected using the enzyme-linked immunosorbent assay. This test was always performed by the same laboratory and was done in accordance with the STRATIFY-JCV program (Biogen Idec, Cambridge, MA, USA). The results were analyzed in a descriptive manner and were presented as median values. Fisher's exact test and Pearson's correlation were assessed using SPSS 24.0 software.

## RESULTS

A total of 1,501 blood tests were obtained from 1,102 patients with MS over five years (2012 to 2017). There were 793 women and 314 men (2.5:1); and the patients' median age was 38 years. The patients underwent a variety of therapies and not all of them used (or had previously used) natalizumab for MS control.

In a cross-sectional analysis in October 2017, 633 patients (57.1%) were found to be positive for antibodies for the JCV and 469 patients were negative (42.9%). Twenty-three patients became positive after initially having negative JCV antibody status. Therefore, at the beginning of the assessment (2012), there were 610 JCV-positive patients (55.3%) and 592 patients who had tested negative at least once (54.7%). Men were significantly more prone to having a JCV-positive status ( $p < 0.001$ ), while age did not influence results ( $r = 0.115$ ).

Taking into consideration the 124 seronegative patients who had had more than one JCV test, seroconversion occurred in 23 cases (18.5%) over a median period of 22 months. Seroconversion was not associated with the patient's age or sex. Because the number of patients who were negative for the JCV and converted to positive was small ( $n = 23$ ), it was not possible to conduct further analysis on all factors that might potentially affect seroconversion (for example, previous therapies).

## DISCUSSION

The rate of seropositivity for anti-JCV antibodies in the Brazilian population of patients with MS seems to have

remained stable in relation to a previous study published five years ago<sup>9</sup>. The cross-sectional prevalence of Brazilian JCV-seropositive patients with MS increased from 51.8% (n = 186) in 2012–2013 to 57.1% (n = 1,102). This difference was not significant (p = 0.09), and these prevalence values are in line with those reported by other authors<sup>10,11</sup>. A recent review of the worldwide prevalence of the JCV in patients with MS and neuromyelitis optica included data from 26 countries<sup>11</sup>. The median prevalence around the world was the same as in the present Brazilian study (57.1%) and the range of positive results for JCV antibodies was 40% to 69%<sup>11</sup>. The fact that data on this subject are now being analyzed and reported in so many countries emphasizes the importance of this matter.

The rate of JCV seroconversion in Brazilian patients with MS is similar to that reported in other countries. Seroconversion occurred in 15.9% of the patients over a period of 14.8 months<sup>12</sup>, in 14.5% after 12 months<sup>13</sup>, 17.6% over 18 months<sup>14</sup> and 26.7% over an average period of 43 months<sup>15</sup>. In a recently published review of data in the literature, which included two large cohort studies, the seroconversion rate per year was 10.8%<sup>16</sup>. On the other hand, other researchers have described much lower seroconversion rates: for example, in only 5.8% of the patients in Portugal after five years<sup>17</sup>.

Regarding the correlation between natalizumab use and seroconversion, it has been shown that the serum levels of natalizumab were not associated with the JCV antibody status, JCV antibody index or seroconversion<sup>18</sup>. Other authors

have reported different results and have correlated use of natalizumab with seroconversion to JCV<sup>19</sup>. In fact, a recent longitudinal study showed seroconversion to be 11.5%, but there were also high numbers of intermittently seropositive cases (9.7%) and seroreverters (3.6%)<sup>20</sup>. The JCV serostatus stability was not influenced by age, sex, disease duration or number of natalizumab infusions<sup>20</sup>. The predictive factor for JCV stability was the baseline anti-JCV antibody index<sup>21</sup>. When the index was higher than 0.9, it predicted stable positive serostatus (sensitivity 88.7%, specificity 96.5%), and when it was lower than 0.2, it predicted stable negative serostatus (sensitivity 61.3%, specificity 97.6%)<sup>21</sup>.

The present study did not assess serum levels of natalizumab nor did it obtain detailed data regarding its use as therapy for MS. The potential influence of MS treatments on seroconversion was not considered in the present analyses and will be addressed in further (and larger) population studies. Likewise, the serum index of anti-JCV antibodies will be assessed from now on by the Brazilian group as a potential predictive factor for JCV serostatus stability. These were limitations to our study as a small number of seroconverters were identified, and these could not be studied in further detail.

In conclusion, seropositivity for and seroconversion to JCV in Brazilian patients are similar to those described in other countries. The high number of epidemiological studies similar to ours reinforces the concerns regarding the matter of the JCV, PML and MS.

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