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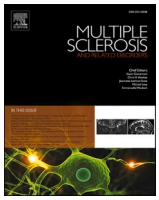

Original article

JCV seroconversion rate during the SARS COVID-19 pandemic

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ABSTRACT

The transmission route of the John Cunningham virus (JCV) is not clearly understood. The high prevalence of JCV in urine and sewage and the stability of the viral particles observed suggest that contaminated water, food, and fomites could be the vehicles of JCV transmission through the oral route. Multiple Sclerosis (MS) patients treated with Natalizumab are at risk of developing progressive multifocal leukoencephalopathy (PML), and hence, JCV serology is monitored for risk stratification. Social restrictions introduced in 2020 which intended to limit the transmission of SARS-CoV-2 are associated with decreased rates of other communicable diseases, as has been shown in recent observational studies. We evaluated the prevalence of seroconversion prior to and during the coronavirus disease (COVID -19) pandemic based on clinical records of JCV serology status in a single-center cohort of Natalizumab-treated Multiple Sclerosis patients. We hypothesized that seroconversion rates would decrease due to behavioral changes. However, seroconversion rates were stable during the COVID-19 pandemic compared to the pre-pandemic. These findings support the notion that JCV is transmitted via the GI tract rather than the respiratory system.

1. Introduction

The majority of the primary JCV infections occur early in childhood and are asymptomatic however the virus persists in the kidneys and is excreted in the urine (Kitamura et al., 1990, Agostini et al., 1996). Human infections with JCV seem to be associated with ethnicity; the JCV genotype excreted by individuals of different ethnicities is determined by the geographical origin of the ethnic group rather than the JCV genotypes prevalent in their current location (Agostini et al., 1997).

JVC's presumed transmission route is not yet clear. A common theory is that oral transmission, probably including both the tonsil and gastrointestinal tract, could be a route of entry of JCV into the body (Bofill-Mas and Girones, 2003). Previous studies concluded that JC virus was rarely present in oropharyngeal fluid and blood samples but it was commonly detected in urine samples, suggesting that urine contributes to transmission. (Cortese et al., 2021, Berger et al., 2006).

Annual seroconversion rates among healthy people are estimated at approximately 1% per year with 70% seropositive by the sixth decade of life (Kean et al., 2009, Hirsch et al., 2013)

Latent infection with JCV increases the risk of PML in patients undergoing MS-specific disease-modifying therapy, particularly Natalizumab. Natalizumab is a monoclonal antibody that binds α4β1 and α4β7 integrins located on the surface of lymphocytes preventing them from adhering to the endothelium of the blood-brain barrier thereby decreasing their infiltration of the CNS. The subsequent amelioration of T-cell mediated inflammatory demyelination makes it a highly effective treatment for relapsing-remitting forms of MS (Dwyer et al., 2021).

Determination of antibodies against the JCV is essential for risk stratification in Natalizumab-treated MS patients. Six-monthly testing has been suggested for anti-JCV antibody-negative patients and for patients with low antibody index to detect serostatus changes.

Epidemiological data from registration studies note annual JCV seroconversion rates of approximately 4% in patients treated with Natalizumab (Plavina et al., 2014, Bozic et al., 2014).

As has been observed in recent observational studies, social distancing, masks, and other behavioral factors introduced during the COVID -19 pandemic may influence the risk of various infectious diseases. A recent study showed a concomitant decrease in influenza, enterovirus, and all-cause pneumonia during the COVID-19 pandemic (Chiu et al., 2020).

In this study, we aimed to evaluate the rate of JCV seroconversion

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among Natalizumab-treated patients during the first 12 months of the COVID-19 pandemic compared to the 12 months prior to the pandemic outbreak.

2. Methods

Study population: The registry of the Neuroimmunology and Multiple Sclerosis Unit at the Tel Aviv Sourasky Medical Center was browsed for patients who attended the clinic between the years 2019-2021 and met the following criteria: confirmed diagnosis of MS according to 2017 McDonald's criteria, disease duration of at least one year, Natalizumab treated patients and recorded JCV serology status every six months.

The Institutional Review Board approved the study (No. 0597-17-TLV).

Sampling: We used the sampling kits provided by Unilabs, Copenhagen. Anti-JCV antibodies were measured by a two-step ELISA (14). Qualitative (negative/positive) and, for anti-JCV antibody-positive patients, semi-quantitative results (i.e., anti-JCV antibody index, which is the OD value of the ELISA) were obtained.

Statistics: Statistical analysis was performed using R-studio 4.0. Descriptive statistics were presented with mean and standard deviation.

Fisher's exact test was used to compare categorical variables between the pandemic / pre-pandemic JCV conversion rates.

3. Results

Overall, 96 patients met the defined criteria between February 2019 and January 2021. Demographic variables as gender and age did not differ between groups (prior to and during the COVID -19 pandemic).

Between February 2019 and January 2020, the rate of seroconversion was 0.04%. Between February 2020 and January 2021 seroconversion rate was 0.12 %. This increase in seroconversion during the COVID outbreak was not statistically significant (Fisher exact test statistic value= 0.2714. The result is *not* significant at $p < .05$).

4. Discussion

JCV can cause PML, a fatal progressive neurological disorder, however a solid understanding of the virus transmission mechanism has not yet been elucidated. Understating the JCV transmission mechanism can help at-risk populations reduce the risk of infection, potentially by behavioral modifications.

The COVID-19 pandemic led governments to enforce policies to reduce transmission of the corona virus, including social distancing and facial masks. These policies led to a concomitant decrease in other communicable diseases such as influenza, enterovirus, and all-cause pneumonia.

In this study, we evaluated JCV seroconversion rates during the first year after the COVID-19 outbreak and compared it to seroconversion rates the year prior. We assumed that if JCV is transmitted via direct contact with a carrier or through aerosol, rates of seroconversion would have decreased; interestingly and as opposed to our initial hypothesis, we have observed a non-statistically significant but notable 3-fold increase in seroconversion post-pandemic. This data may suggest that masking had no impact on JCV transmission. This observation reinforces prior assumptions that JCV primary infection occurs most likely as a result of urine-oral transmission, however, hand washing is probably not an effective preventive method.

The limitations of this study include its retrospective nature, limited sample size, and unknown variables such as compliance with COVID-19 restrictions. Nevertheless, this is the first report indicating that the JCV transmission pattern is not modified by population behavioral changes aimed at reducing viral spread.

Ethics approval and consent to participate

The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Tel Aviv Sourasky Medical Center Institutional Review Board (Helsinki Committee). (No. 0597-17-TLV). The need for consent was waived by the IRB due to the retrospective nature of the study.

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Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by IV, AK, HK, TS, IK, YP and KR. The first draft of the manuscript was written by IV and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no conflict of interest. None of the authors reports conflicts of interest related to this work. Dr. Karni Arnon received research support from Stem Cell Medicine Ltd, Medison Pharma Ltd and from Novartis Pharmaceutical Ltd.

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