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Research article

Identification of JC polyomavirus in upper respiratory samples from Portuguese children

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ABSTRACT

Background: JC polyomavirus (JCPyV) is ubiquitous in the human population and the causative agent of a rare, fatal and demyelinating disease of the central nervous system named Progressive Multifocal Leukoencephalopathy (PML). The route of JCPyV transmission remains unclear, but high values of seroprevalence suggest an easy and frequent mode, such as respiratory route.
Objectives: The present study aims to investigate the presence of JCPyV in upper respiratory samples and contribute to the elucidation of the JCPyV transmission pathway.
Study design: Nasopharyngeal swabs from 587 Portuguese individuals, including 380 children (≤18 years) and 207 adults (>18 years), collected for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnosis between September and November 2021 were evaluated for the presence of JCPyV DNA.
Results: JCPyV DNA was detected in 3.1 % of the nasopharyngeal swabs analysed, with higher frequency of detection in samples from children (4.5 %) than from adults (0.5 %) ($p = 0.005$). Infection with SARS-CoV-2 does not potentiate the presence of JCPyV in upper respiratory tract, once only one adult of 28 years with confirmed SARS-CoV-2 infection showed detectable JCPyV DNA. JCPyV DNA was more frequently detected in respiratory samples from children without SARS-CoV-2 infection (6.4 %). As for this group, children under six years of age presents the highest frequency of detection (10.3 %).
Conclusions: The present study demonstrates that upper respiratory secretions of children, particularly under the age of six, may be implicated in JCPyV transmission, regardless of SARS-CoV-2 infection.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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1. Introduction

JC polyomavirus (JCPyV) is ubiquitous in the human population, and responsible for a lifelong persistent infection. After asymptomatic primary infection, JCPyV establishes a persistent infection in the kidney, bone marrow and B lymphocytes [1,2]. Low levels of viral replication in renal tubular epithelial cells leads to asymptomatic excretion of the archetype virus in the urine [3–5]. Under profound immunosuppression, viral reactivation can occur and result in the development of Progressive Multifocal Leukoencephalopathy (PML), a rare and often fatal demyelinating disease of the central nervous system [6–8].

JCPyV infection is worldwide distributed. Seroprevalence of JCPyV has been reported to reach 80 % in the adult population [9,10]. In Portugal, seroprevalence from 60.8 % to 91 % [4,11], have been described. Similar seroprevalence values have been reported across Europe: 55.3 % in Spain [12], 80 % in Italy [13], 72 % in Sweden [14], 86 % in Germany [15], and 88.6 % in Croatia [16]. In American continent, values of 32 % in Mexico, 77 % in USA, and 92 % in Brazil are described in the literature [15]. Australia reported 63 % of JCPyV seroprevalence [17].

Nevertheless, data on the JCPyV seroprevalence in children are limited. A study of Italian infants aged one day to three years reported an overall prevalence of 71.8 %, with a lower value observed in infants up to one month of age (46.1 %) [10]. A lower prevalence (13.7 %) was observed in a similar age group of children in USA [18].

Despite the majority of primary infections appear to occur in young children, the increase in seroprevalence with age indicates that JCPyV infection can be acquired throughout life [9,10,18,19]. Although the mode of transmission remains unclear [20], a simple and common mode of transmission appears to be implied as evidenced by the high values of individuals with specific JCPyV antibodies [10]. JCPyV DNA has rarely been reported in respiratory samples, however limitations linked to sample size and the age of the studied individuals [21–26], preclude the exclusion of the respiratory route as a potential mode of transmission.

The restricted sample size used in certain studies represents a limitation of both the research methodology and the resulting conclusions [21,23,24].The majority of studies on the respiratory transmission of JCPyV have not included young children [21–26]. Given that primary infection appears to occur early in life, it is important to consider this age group in studies of respiratory transmission.

The impact of the recent global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), particularly in children, has further highlighted the importance of elucidating the modes of viral transmission in preventing outbreaks and understanding human viral infection [27].

2. Objectives

The main objective of the present study is to evaluate the presence of JCPyV in upper respiratory samples and contribute to the elucidation of the JCPyV transmission pathway. The study was designed aiming to address some limitations of previous studies. Near 600 individuals within a large age range were considered in this study, with particular attention on young children, as it is believed that primary infection occurs mainly in this age group.

3. Study design

3.1. Study population and samples

Nasopharyngeal swabs collected for the diagnosis of SARS-CoV-2 infection between September and November 2021 at the Laboratory of Clinical Analysis of the University of Coimbra (LACUC), were used in the present study. The samples were collected by introducing a nasopharyngeal swab into the nasopharynx and carefully rotating it for approximately 10 s, after which were vortex in 2 mL of inactivation buffer. The study samples were selected using a weighted random sampling procedure based on the age of the individuals, ensuring representativity across different age groups. There was a concern to include a significant number of samples from children with especial attention to those aged below 12 years. The use of samples collected during the COVID-19 pandemic, provided an additional opportunity to investigate the potential influence of SARS-CoV-2 in the presence of JCPyV in upper respiratory tract.

The study group comprised 587 Portuguese individuals, including 380 children (≤18 years) and 207 adults (>18 years). Study

Table 1
Demographic characteristics of the studied population, and detection of JCPyV DNA in respective nasopharyngeal swabs.

Study Group	Nº of individuals (%)	Age range in years (mean age)	Gender		Detection of JCPyV DNA (%)
			Female (%)	Male (%)	
Children (≤18 years)	**380**	**<1–18 (9.4)**	**179 (47,1 %)**	**201 (52.9 %)**	**17 (4.5 %)**
Without SARS-CoV-2 infection	267 (70.3 %)	2-18 (9.1)	127 (47.6 %)	140 (53.0 %)	17 (6.4 %)
Infected with SARS-CoV-2	113 (29.7 %)	<1–18 (10)	52 (46.0 %)	61 (54 %)	0 (0 %)
Adults (>18 years)	**207**	**19-101 (52,29)**	**137 (66,18 %)**	**70 (33.8 %)**	**1 (0.5 %)**
Without SARS-CoV-2 infection	100 (48.3 %)	19-98 (53.3)	71 (71 %)	29 (29 %)	0 (0 %)
Infected with SARS-CoV-2	107 (51.7 %)	19-101 (51.3)	66 (61.7 %)	41 (38.3 %)	1 (0.9 %)
Total	**587**	**<1–101 (24.5)**	**316 (53.8 %)**	**271 (46.2 %)**	**18 (3.1 %)**

individuals were grouped according to age, gender and detection of SARS-CoV-2 genome through real-time reverse-transcriptase (RT) polymerase chain reaction (PCR) in the selected sample (Table 1). This study was approved by the Ethics Committee of the Faculty of Medicine of the Coimbra University, Portugal.

3.2. Nucleic acid extraction and SARS-CoV-2 RNA detection

After viral inactivation, nasopharyngeal samples were submitted to nucleic acids extraction in m2000*sp* (Abbott Molecular®), using the *m*Sample Preparation System$_{DNA}$ reagents (Ref:06K-12–24, Abbot Molecular®, Portugal), according to the manufacturer's instructions. Internal control was added to each sample, and negative and positive controls were included in each extraction batch. Eluted nucleic acids were evaluated for internal control and SARS-CoV-2 RNA by real-time RT-PCR using the Abbott® RealTime SARS-CoV-2 kit (Ref:09N77-095, Abbot Molecular®, Portugal) on *m*2000*rt* equipment (Abbott Molecular®), in accordance with the manufacturer's instructions. After analysis, nucleic acids were preserved at −80 °C.

3.3. Detection of JCPyV DNA

The presence of JCPyV DNA was evaluated on the stored samples, using a previously described real-time PCR with primers and probes directed towards the AgT and NCCR genome regions, which enables the differentiation between archetype and rearranged strains [28]. Briefly, PCR reactions were performed in a total volume of 25 μl containing 7.5 μl of DNA, 12.5 μL of Maxima Probe qPCR Master Mix (2X) (Thermo Fisher Scientific K0232), 300 nM of each primer and 200 nM of TaqMan probe. Amplification was carried out in a CFX96 Real-Time PCR Detection System - C1000 Thermal Cycler (Bio-Rad) under the following conditions: initial incubation of 2 min at 50 °C, 10 min at 95 °C and 45 cycles of 95 °C for 15 s and 60 °C for 60 s. Samples with Ct value lower than 40 were considered positive for the presence of JCPyV genome. Positive and negative controls were included in each amplification batch.

3.4. Statistical analysis

Statistical analysis was performed using the chi-square test for comparisons of categorical variables. Fisher's exact test was applied whenever any cell of the contingency table contained fewer than five expected observations. Statistical analysis was performed using SPSS software (29th version), with p values under 0.05 considered statistically significant.

4. Results

Nucleic acids extracted from 587 nasopharyngeal swabs of 380 children and 207 adults, collected and stored at LACUC during the COVID-19 pandemic, were used to evaluate the presence of JCPyV DNA through real-time PCR, in order to assess its possible transmission by respiratory route. All negative, positive and internal controls rendered the expected results.

JCPyV DNA was detected in 3.1 % of nasopharyngeal swabs, with higher frequency of detection in samples from children (4.5 %) than from adults (0.5 %) ($p = 0.005$) (Tables 1 and 2). All JCPyV genome detected were identified as the archetype strain.

Detection of JCPyV DNA was more frequent in individuals without diagnosis of SARS-CoV-2 infection (4.6 % vs 0.5 %) ($p = 0.003$). The only adult (28 years old) with detectable JCPyV DNA was infected with SARS-CoV-2. In contrast, all 17 children with detectable JCPyV were not infected with SARS-CoV-2 (Tables 1 and 2). When considering only the group of children without COVID-19, JCPyV was detected in 6.4 % of samples. This group of children, without SARS-CoV-2 infection, was further stratified according to age (<6, 6–11 and 12–18 years old, respectively) with the objective of evaluating whether JCPyV detection is consistent across the entire group. Among children without SARS-CoV-2 infection, JCPyV DNA was more frequently detected in those under six years old (10.3 %) ($p = 0.130$), with similar values of prevalence in the other age groups (Fig. 1).

4. Discussion

The present study aims to contribute to the clarification of the route of JCPyV transmission. The high values of JCPyV seroprevalence suggest a common and frequent mode of transmission, such as the respiratory route [9]. Tonsil tissue has been identified as a site of initial viral infection, further suggesting that viral particles could reach the host through the upper respiratory system [29,30].

Table 2
JCPyV DNA detection in nasopharyngeal swabs across different population groups.

	Nº of individuals	JCPyV DNA		
		Detected	Not detected	*p*-value
Age				
Children (≤18 years)	380	17	363	0.005
Adults (>18 years)	207	1	206	
SARS-CoV-2				
Infected	220	1	219	0.003
Not infected	367	17	350	

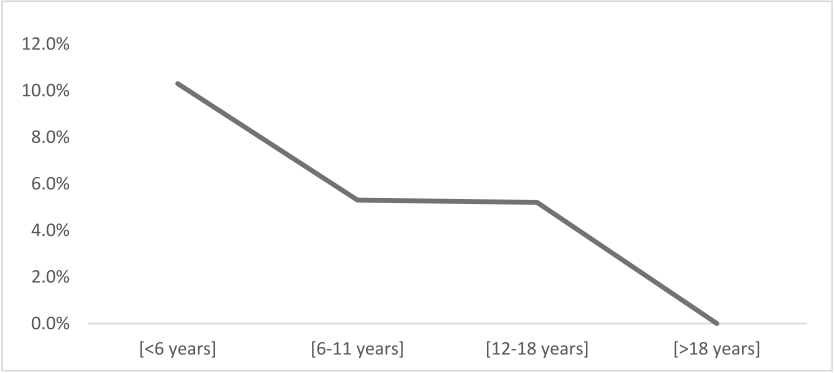

Fig. 1. Detection of JCPyV DNA in nasopharyngeal samples from individuals without SARS-CoV-2 infection.

Infectious virions involved in this type of transmission can result from droplets or aerosols produced by infected individuals [31]. To explore this hypothesis it is important to evaluate the presence of JCPyV in respiratory secretions. Nevertheless, previous studies using respiratory samples, only achieved to detect JCPyV DNA in a low number of individuals [21,23,24]. However, limitations related to the study design, such as the sample type, the studied group size, and the age of included individuals, may bias the results obtained and the conclusions drawn. To overcome some of the limitations in existing research, the present study was designed to evaluate the presence of JCPyV DNA in nasopharyngeal samples and to assess the potential of respiratory secretions as a source of viral transmission.

Nasopharyngeal swabs were selected for the present study due to their established effectiveness in detecting respiratory-transmitted viruses, as well as for its higher cellular content when compared to other samples employed in previous studies, such as saliva or oropharyngeal wash samples [21,24]. The low cellular content of these samples, and consequently the expected low viral load associated with it, may result in an underestimation of the presence of JCPyV [21–26]. In this study, the overall prevalence of JCPyV DNA in nasopharyngeal samples was found to be of 3.1 %, with very low values (0.5 %) observed among adults, which is in line with previous reports [23–25], regardless the type of sample considered. Thus, the initial supposition that samples with low cellular content might impact the study outcomes, may in fact, not be a limitation in this type of study.

The selection of 587 individuals for the present study, spanning a wide age range, from under 1–101 years of age, intended to overcome the restricted sample size and age interval used in some of the previous studies [21,23,24]. The inclusion of a considerable proportion of children (64.7 % of the study population), the majority of whom were below the age of 12 years, represents a distinctive contribution of this study, given that most of previous studies have not included this age group [21–26]. Since primary infection appears to occur early in life, it is crucial to include young children in studies that aim to understand the transmission route [4,8,32,33].

JCPyV DNA was more frequently detected in nasopharyngeal swabs from children (4.5 %) than from adults ($p = 0.005$). As the detection of viral DNA may result from JCPyV replication in the upper respiratory system, these results further support the hypothesis that primary infection mainly occurs at an early age. Moreover, the detection of viral genome in nasopharyngeal samples provides additional evidence that children's respiratory secretions may serve as a source of viral particles involved in transmission.

The samples selected for this study were collected during COVID-19 pandemic and information on SARS-CoV-2 diagnosis was available for the studied patients. Although other polyomaviruses, including KIPyV and WUPyV, have been identified in respiratory samples with SARS-CoV-2 [34], the possible coexistence of SARS-CoV-2 and JCPyV in respiratory samples is unknown. Taking advantage of the availability of those samples and related information, the presence of JCPyV genome in respiratory samples was also assessed in function of SARS-CoV-2 infection. The objective was to ascertain whether the presence of one virus enhances the transmission of the other. In this study and contrarily to what was reported for KIPyV and WUPyV [34], 94 % of the nasopharyngeal samples with detectable JCPyV DNA were from individuals without SARS-CoV-2 infection, suggesting that the coexistence of SARS-CoV-2 and JCPyV in the respiratory tract is not a common occurrence. Thus, it can be hypothesised that SARS-CoV-2 does not increase the likelihood of JCPyV transmission, despite further studies are needed to corroborate these results.

Among the studied population, children not infected with SARS-CoV-2 was the group with more frequent detection of JCPyV DNA (6.4 %) in respiratory samples. Further age stratification of this group revealed that children below the age of six were those with a higher frequency of detection (10.3 %), followed by children aged 6–11 years (5.3 %) and children aged 12–18 years (5.2 %). These findings are consistent with existing literature, which indicates that the primary infection with JCPyV mainly occurs during the first years of life [4,35], and points to the implication of upper respiratory secretions in virus transmission.

The presence of JCPyV DNA in respiratory samples decreases with age until very low values in adult population, irrespectively to SARS-CoV-2 infection. Despite the lack of evidence on JCPyV respiratory transmission among adults, seroepidemiological data indicates that primary infection occurs throughout life [9,18,19]. Therefore, the transmission of JCPyV in adult population is likely to depend on a source of viral particles different from respiratory secretions. This hypothesis is supported by the findings of Vigiser and colleagues (2022), who demonstrated that the seroconversion rates of JCPyV remained stable both before and during the COVID-19 pandemic, despite the implementation of social restrictions designed to prevent respiratory transmission of SARS-CoV-2 [35].

The results of the present study indicate the potential involvement of upper respiratory secretions in the transmission of JCPyV,

particularly among children. However, further studies are needed to confirm whether this virus transmission can occur through the respiratory route. Moreover, the data obtained does not provide any new insights into the mode of transmission among other age groups. Thus, additional studies comprising other virus excretion routes and respective samples, are required to clarify the mode of JCPyV transmission in other population groups, namely among adults.

5. Conclusion

The present study contributes to the clarification of JCPyV transmission, demonstrating that upper respiratory secretions of children, particularly under the age of six, may be implicated in JCPyV transmission, regardless of SARS-CoV-2 infection.

Ethics approval statement

The present study was approved the Ethics Committee of the Faculty of Medicine of the Coimbra University, Portugal (process number: CE_Proc. CE 096/2023). In accordance with resolution 466 of December 12, 2012 of the National Health Council/Ministry of Health, the waiver of the informed consent form was accepted for the submitted project.

CRediT authorship contribution statement

Joana M. Oliveira: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Daniela Veiga:** Writing – review & editing, Methodology. **Helena Martins:** Writing – review & editing, Methodology. **Cristina Luxo:** Writing – review & editing, Investigation, Funding acquisition. **Ana M. Matos:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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