The occurrence of polyomaviruses WUPyV and KIPyV among patients with severe respiratory infections

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Abstract
In 2007, the new polyomaviruses WUPyV and KIPyV were identified in patients with acute respiratory infections. The aim of this study was to investigate these viruses in hospitalized patients with severe acute respiratory infection (SARI). A retrospective study was conducted with 251 patients, from April 2009 to November 2010, using nasopharyngeal aspirates, naso- and oropharyngeal swab samples from hospitalized patients (children < 12 years and adults) who had SARI within 7 days of the onset of symptoms, including fever (> 38.8 °C), dyspnea, and cough. Clinical and epidemiological information was obtained through standardized questionnaire. Enrolled patients were initially suspected to have influenza A(H1N1)pdm09 infections. WUPyV and KIPyV were detected by real-time PCR. Samples were also tested for influenza A and B viruses, human respiratory syncytial virus, rhinovirus, metapneumovirus, coronavirus, adenovirus, and parainfluenza viruses. WUPyV and KIPyV were detected in 6.77% (4.78% and 1.99%, respectively) of hospitalized patients with SARI. All samples from children showed coinfections (rhinovirus was the most commonly detected). Six adults had polyomavirus infection and four (1.6%) had monoinfection. Of them, 3 reported comorbidities including immunosuppression and 1 patient had worse outcome, requiring ICU admission. These preliminary data may suggest a possible role of polyomaviruses in SARI among immunocompromised adult patients.

Keywords Severe acute respiratory infection · Polyomaviruses · WUPyV · KIPyV · Real-time PCR

Introduction
In 2007, the two new polyomaviruses (PyV) KI and WU were described as probable causative agents of respiratory infections in humans [1, 2]. Currently, they are classified in the Polyomaviridae family, Betapolyomavirus genus, Human polyomavirus 3 (KIPyV), and Human polyomavirus 4 (WUPyV) species [3]. These two PyV have been detected globally in children and immunocompetent adults, with detection rates ranging from 1 to 16.4% for WUPyV and 0.45 to 12.14% for KIPyV [4–8].

There has been suggested a role for these viruses on the pathogenesis of respiratory infections in many studies so far demonstrating the presence of WUPyV and KIPyV in the respiratory tract of symptomatic and asymptomatic patients [4–15], although they are also found in other clinical samples such as stool and lymphoid tissue of immunocompromised and immunocompetent individuals [16–20].

Coinfection with other pathogens has been reported in 74% of patients with KIPyV, 68 to 79% of patients with WUPyV, and 10% of coinfection with KIPyV and WUPyV in the absence of other respiratory viruses [21]. In Brazil, KIPyV and WUPyV were found in the saliva of immunocompromised and immunocompetent patients [22, 23]. In this study, we investigated the PyV KI and WU in the occurrence of severe respiratory diseases in hospitalized patients with acute respiratory infection (SARI).
Materials and methods

A retrospective study was conducted from April 2009 to November 2010 (19 months) using samples from hospitalized patients who had presented with SARI within 7 days of the onset of symptoms, including fever (>38.8 °C), dyspnea, and cough. Children (<12 years) and adults were included. The clinical and epidemiological information was obtained through a standardized questionnaire. Informed consent was previously obtained from all enrolled patients initially suspected to have influenza A(H1N1)pdm09 infections. This study was approved by the Ethics Committee of Sao Paulo Federal University (CEP 0090/2016). Nasopharyngeal aspirates were obtained from children under 2 years old. For the other patients, naso- and oropharyngeal swabs were collected, according to the Brazilian Ministry of Health Protocol for management of influenza A (H1N1) 2009 pandemics, and stored in a freezer at −80 °C [24]. Total nucleic acids were extracted using the QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany), according to the manufacturer instructions. The specimens were then tested for the presence of respiratory viruses according to PCR protocols available at our laboratory for influenza A (FLU A) and B (FLU B) viruses [25, 26], human respiratory syncytial virus (HRSV) [27], human rhinovirus (HRV) [28], human metapneumovirus (hMPV) [29], human coronavirus (HCoV) [30], human adenovirus (HAdV) [31, 32], and parainfluenza virus (PIV 1,2,3,4) [33, 34].

For the WUPyV and KIPyV specific detection, qualitative real-time PCR was performed with the primers PyVF (5′-TTGGATGAAAAATTGGCATTGG-3′) and PyVR (5′-TAAACCTCTTTGTCTAAARTGTAGCC-3′), that amplify a fragment of the gene encoding the capsid protein VP1 only common to KIPyV and WUPyV, and two specific probes, WUPyVp (5′-FAM-CATAACTTGTGCTGACCTTTTGGGAGTTAAC-BHQ1-3′) and KIPyVp (3′-VIC-ACATTACTTGTGCAATATGCCTGGAACGAC-BHQ1-3′), both within the VP1 gene, to differentiate the WUPyV and KIPyV viruses [35]. The concentration of primers and probes was 800 nM and 200 nM, respectively, in 25 μL of total reaction volume, with the use of AgPath-ID™ One-Step RT-PCR reagents (Applied Biosystems, Austin, USA) and addition of 5 μL of extracted nucleic acid. In parallel reactions, primers and specific probe were used to amplify a fragment of the gene glycerinaldehyde 3-phosphate dehydrogenase (GAPDH) as endogenous control and to assess the quality of the samples as described by Bergallo et al. [16] Thermocycling conditions were performed in an Applied Biosystems 7500 Real-Time PCR System and involved 10 min at 95 °C followed by 45 cycles of 10 s at 95 °C and 1 min at 55 °C (data collection). For both reactions, the cycle threshold value (Ct) of 39 was adopted as a cut-off. Chi-square analysis and Fisher’s exact test were used to analyze the occurrence of the investigated PyV. Student’s t test for independent samples and analysis of variance (ANOVA) were used to compare the mean ages. All statistical analyses were performed using OpenEpi version 2.3.1 (http://www.openepi.com), and a p value <0.05 was considered statistically significant.

Results

A total of 251 patients presenting with SARI suspected to be due to influenza A (H1N1)pdm09 treated at the Sao Paulo Hospital complex were enrolled; 159 patient samples were obtained in 2009, and 92 in 2010. Among those enrolled, 150 (59.8%) were children, 101 (40.2%) were adults, and (58.16%) were males. The mean age of the children was 2.4 years (median 1 year, range 0–12 years) and the mean age of the adults was 41.4 years (median 40, range 13–91 years). Viral detection was identified in 62.5% (157/251) of the patients, and the detection rate of WUPyV and KIPyV was 6.8% (17/251), with 12 cases of WUPyV and 5 of KIPyV.

The mean Ct value (± SD) for GAPDH endogenous control for all samples was 28.51 ± 3.16 (range 20.44–34.28). All positive samples have shown GAPDH Ct values ≤30.48, except for one sample positive for WUPyV (Ct = 32.46). The mean Ct values for WUPyV and KIPyV (range are shown in brackets) were 32.61 ± 4.86 (24.28–36.94) and 30.52 ± 6.95 (21.96–37.22), respectively.

The single viral detection rates were as follows: 4.78% (12/251) for WUPyV, 1.99 (5/251) for KIPyV, 7.2% (18/251) for FLU A, 4.0% (10/251) for FLU B, 1.6% (4/251) for HAdV, 0.8% (2/251) for HCoV, 8.4% (21/251) for hMPV, 3.6% (9/251) for PIV, 14.7% (37/251) for HRV, and 6.8% (17/251) for HRSV. The WUPyV and KIPyV coinfection rate was 5.2% (13/251). Table 1 compares the viral detection patterns within the 251 patients included in the study. Among the patients with viral infection, 18.5% (29/251) had a coinfection with 2 different viruses and 6.4% (10/157) with 3. Of the population with double viral coinfections, 44.8% (13/29) were also infected with WUPyV or KIPyV and 4 out of the 10 patients with triple coinfections were also positive for WUPyV or KIPyV. However, coinfection with WUPyV or KIPyV and other viruses was not correlated with severity of symptoms.

The proportion of children with WUPyV or KIPyV was 7.3% (11/150), and all samples had multiple detections. The mean age of the children coinfected with polyomaviruses was 1.6 years (median 1 year; range 0–4 years); of these 7 had WUPyV infection and 4 had KIPyV infection. The children coinfected with respiratory viruses other than PyV were younger than those coinfected with PyV, with rates among patients up to 6 months of age being 1/11 (9.1%) and 12/24 (50.0%), respectively (p < 0.027).

Two adults (aged 33 and 91 years) showed coinfections with WUPyV or KIPyV, respectively. Monoinfections were detected in 4 adults, and 3 of them had WUPyV infection (median age
Table 1 Viral detection patterns in patients with SARI (n = 251)

| Viruses               | N = 150 (children) / % | N = 101 (adults) / % |
|-----------------------|------------------------|----------------------|
| Non-detected (%)      | 40 / 26.7              | 50 / 49.5            |
| Detected              | 110 / 73.3             | 51 / 50.5            |
| Monoinfections        | 75 / 50                | 47 / 46.5            |
| Coinfections          |                        |                      |
| HAdV/HCoV             | –                      | 1 / 0.4              |
| HAdV/PIV              | 1 / 0.4                | –                    |
| HAdV/RSV              | 1 / 0.4                | –                    |
| Flu A/HAdV            | 1 / 0.4                | –                    |
| Flu A/PIV             | 1 / 0.4                | –                    |
| HMPV/PIV              | 2 / 0.8                | –                    |
| HMPV/HCoV             | –                      | 1 / 0.4              |
| HRV/HAdV              | 1 / 0.4                | –                    |
| HRV/HMPV              | 3 / 1.2                | –                    |
| HRV/PIV               | 2 / 0.8                | –                    |
| HRV/RSV               | 5 / 2                  | –                    |
| Flu B/HRV/HCoV        | –                      | 1 / 0.4              |
| Flu A/HAdV/HRV        | 1 / 0.4                | –                    |
| HRV/HAdV/PIV          | 1 / 0.4                | –                    |
| HRV/HMPV/HCoV         | 2 / 0.8                | –                    |
| HRV/HMPV/RSV          | 1 / 0.4                | –                    |
| HMPV/WUpyV            | 1 / 0.4                | –                    |
| HAdV/KIPyV            | 1 / 0.4                | –                    |
| HWPyV/KIPyV           | 1 / 0.4                | –                    |
| RSV/WUpyV             | 1 / 0.4                | –                    |
| HAdV/KIPyV            | 2 / 0.8                | –                    |
| HAdV/WUpyV            | 1 / 0.4                | –                    |
| HRV/KIPyV             | –                      | 1 / 0.4              |
| HMPV/KIPyV            | –                      | 1 / 0.4              |
| HRV/RSV/WUpyV         | 1 / 0.4                | –                    |
| HRV/HAdV/WUpyV        | 1 / 0.4                | –                    |
| HAdV/PIV/KIPyV        | 1 / 0.4                | –                    |
| HRV/HCoV/KIPyV        | 1 / 0.4                | –                    |

SARI, severe acute respiratory infection

Table 2 Characteristics of hospitalized patients with single WUpyV or KIPyV infection

| Age (years) | Comorbidity | Hospitalization time (days) | Admission to ICU | Virus          |
|-------------|-------------|-----------------------------|------------------|---------------|
| 28          | _           | 1                           | _                | WUpyV         |
| 21          | Ependymal neoplasm, sarcoma of the scalp | 8               | _                | KIPyV         |
| 32          | HIV, CD4+ count = 8 cells/mm³ | 13              | _                | WUpyV         |
| 51          | Systemic lupus erythematosus* | 20              | Admitted         | WUpyV         |

*Admission to the ICU due to nosocomial pneumonia. ICU, intensive care unit

Discussion

The role of the PyV in the pathogenesis of respiratory infections is not well understood. Some studies have demonstrated the presence of both PyV WU and KI in the asymptomatic population [36, 37]. However, the rate of polyomavirus infection in adult patients hospitalized with SARI has not been established.

The proportion of respiratory samples from hospitalized patients with SARI that were positive for WUpyV or KIPyV was 6.8% with 4.0% (10/251) for WUpyV and 2.8% (7/251) for KIPyV, which is comparable to those obtained by other authors [4–7, 11].

The debate about the role of these viruses in respiratory infections is ongoing because of the high rates of coinfection with other respiratory viruses (approximately 80%) [9, 11, 12, 38, 39]. Recently, high viral loads of KIPyV were observed in children with severe or very severe pneumonia in the absence of other viral or bacterial respiratory infection, suggesting a potential pathogenic role for KIPyV in these patients [12].

A coinfection rate of 76.5% was observed in the present study, mainly among children, with the most common types being WUpyV/HRV in 43% of cases, KIPyV/HRV in 60% and KIPyV/AdV in 67%, which is in accordance with the results by Allander et al. [1] and Gaynor et al. [2] Nonetheless, the frequent coinfections with WUpyV and KIPyV with other respiratory viruses and variations in clinical presentation preclude any conclusion about the association between infection and disease in children. Of interest is the finding of lower rates among very young children that may posit the later acquisition of polyomavirus infection by older children as suggest by serological and molecular studies [19, 40–42].

The finding of monoinfection by polyomaviruses in 4 adult patients hospitalized with SARI may suggest a potential pathogenic role. Moreover, 3 out of these 4 patients were immunocompromised, and one patient with SLE had a severe outcome and required ICU admission and mechanical ventilation. We performed a retrospective study. Therefore, it was not

30 years, range 21–51 years). These 4 patients were admitted with fever, cough, and dyspnea, and the symptoms prevailed for up to 4 days. Radiological chest examination, bacterial hemoculture and systemic antibiotic prophylaxis were conducted according to hospital proceedings for clinical bacterial pneumonia investigation and current guidelines. Three patients reported comorbidities and presented with different states of immunosuppression. The length of the period of hospitalization and ICU admission are shown in Table 2. The patient with systemic lupus erythematosus (SLE) was admitted to the ICU for mechanical ventilation due to nosocomial pneumonia with bacterial coinfection. The 28-year-old patient without comorbidities was hospitalized for 24 h and was discharged upon resolution of the dyspnea.
possible to obtain samples from the lower respiratory tract from the immunocompromised patients for immunohistochemistry or in situ hybridization. Further studies are needed in order to understand the possible role of viral latency and reactivation of these DNA viruses in adult patients, especially among those who are immunocompromised. In this regard, prospective longitudinal studies with large sample sizes, including immunocompetent, immunocompromised, symptomatic, and asymptomatic patients could better answer some of these questions.

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