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ORIGINAL ARTICLE

EPIDEMIOLOGICAL PROFILE OF HOSPITALIZED HUMAN METAPNEUMOVIRUS IN A CAPITAL OF CENTRAL-WEST OF BRAZIL FROM 2017 TO 2019: HIGH LETHALITY AT EXTREMES OF AGE

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ABSTRACT

Human metapneumovirus (hMPV) is a paramyxovirus that causes airway infections. hMPV symptoms range from mild infections of the upper respiratory tract to infections as serious as bronchiolitis and pneumonia. From 2018 to 2019, there was a high incidence of severe acute respiratory syndrome (SARS) in the State of Goiás with a relative increase in hMPV incidence. This study aimed to assess the hMPV epidemiology of cases treated at tertiary hospitals of Goiás, as there are not significant published data from hMPV infection in Brazil. We performed a retrospective and descriptive analysis of a case series of patients infected with hMPV diagnosed by PCR (16 individuals), through medical records review from 2017 to 2019. The observed age distribution was bimodal, with the disease affecting individuals at extremes of age (median of 3.5 years old in the first stratum and median of 52 years in the second stratum). The time between the onset of flu-like symptoms and the first medical assessment had an average of 5 days. The most frequent severe symptoms were respiratory distress/dyspnea and oxygen saturation <95% (93.7% as media), even in patients without comorbidities. The most frequent complications were acute renal failure (18.7%) and healthcare-associated infections (43.7%). Death occurred in 37.5% of patients. hMPV may cause upper and lower respiratory tract infections in patients of all age groups, but the symptomatic disease occurs more frequently at extremes of age. In the pandemic caused by a new coronavirus (SARS-CoV-2), which is known to lead to influenza-like and SARS, the differential diagnosis of the etiologic agent becomes paramount.

KEY WORDS: Respiratory tract infections; paramyxoviridae infections; acute disease.

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INTRODUCTION

Identified in 2001, human metapneumovirus (hMPV) is a paramyxovirus that causes airway infections in adults and children with a clinical course similar to the respiratory syncytial virus (RSV) (Ravindranath et al., 2018; van den Hoogen et al., 2002). Seroprevalence studies demonstrate that primary infection occurs in children under five years-old, with individuals being reinfected throughout life (Schuster & Williams, 2014). A Japanese study published in 2003 found a 76% hMPV seroprevalence among children aged two to five years and 87% of RSV in the same age group (Ebihara et al., 2003). hMPV appears to have a similar seasonal distribution to RSV and influenza viruses, occurring mainly during the winter (Bastien et al., 2003; van den Hoogen et al., 2002).

In Brazil, few studies addressed epidemiology profile and lethality rates in different age groups (Cuevas et al., 2003; Gregianini et al., 2018). In 2018, there was a high incidence of severe acute respiratory syndrome (SARS) in the State of Goiás, Central-West Brazil (SES/GO, 2020), with a relative increase in hMPV incidence, despite the small absolute number of cases. Table 1 details the cases and deaths from influenza , RSV and hMPV from 2017 to 2019 in Goiás State (van den Hoogen et al., 2001). The real time polymerase chain reaction (RT-PCR) in nasopharyngeal samples is the most sensitive diagnostic methodology (Jeong at al., 2020) and was implemented at Central Public Health Laboratory in January 2017 (Respiratory Viruses - CDC/ Atlanta/US protocol).

Table 1. Total cases and deaths of confirmed severe acute respiratory syndrome (SARS) in the State of Goiás, 2017-2019

Year	Total Cases	Total deaths		Influenza	Influenza Deaths		hMPV	hMPV Deaths		RSV	RSV deaths	
		n	%		n	%		n	%	n	n	%
2017	729	130	4.1	108	26 (14 H3N2)	24	33	1	3	98	10	10.2
2018	1672	247	14	481	81 (68 H1N1)	16.8	96	18	18.7	278	15	5.4
2019	1366	192	14	193	41 (35 H1N1)	21.2	32	2	6.2	277	12	4.3

hMPV: metapneumovirus; RSV: respiratory syncytial virus.
Source: Epidemiological report of SARS of Goiás State Health Department (Goiás, 2020)

The most common symptoms range from mild infections of the upper respiratory tract to infections as serious as bronchiolitis and pneumonia, with sneezing, coughing, fever, and dyspnea frequently observed (van den Hoogen et al., 2002). A Canadian study found that the hospitalization rate for hMPV was 33%, with risk factors being age less than five years-old and more than 50 years old (Principi & Esposito, 2014). This study aimed to assess the epidemiological profile of PCR-confirmed hospitalized hMPV cases at three tertiary hospitals in a capital of the Centre-West region of Brazil, as there are not significant published data on this specific respiratory viral infection in Brazil.

MATERIAL AND METHODS

It is a retrospective analysis obtained by notification forms and medical records review from 2017 to 2019. During the study period, the State of Goiás notified 161 cases of flu-like or respiratory distress syndrome with hMPV detected in nasopharyngeal swab specimes by RT-PCR. Our sample consists of all those notified as SARS and hospitalized at three tertiary hospitals located in the city of Goiânia: Dr. Anuar Auad State Hospital for Tropical Diseases (HDT), Clinical Hospital of the Federal University of Goiás (HC-UFG), and Emergency Hospital of the Northwest Region of Goiânia - Governor Otávio Laje de Siqueira (HUGOL) in these three years The exclusion criteria was presenting unavailable epidemiological and clinical data during the medical record review. Ethical approval obtained from local committees are CAAEs 07612919.9.0000.0034, 07612919.9.3001.5078 and 07612919.9.3002.5082 respectively.

Descriptive analysis included clinical and epidemiological data as signs and symptoms, comorbidities, treatment performed, radiological findings, date of diagnostic hypothesis, the time elapsed between hypothesis and result of the collected nasopharynx specimens, need for intensive care treatment, Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, need for mechanical ventilation and length of hospital stay.

RESULTS

Sixteen individuals with SARS caused by hMPV were admitted to study settings, been 62.5% (10) females, with bimodal age distribution, affecting individuals at extremes of age [median 3.5 years old (2 months to 16 years) in the first stratum and a median of 52 years (27 - 81 years) in the second stratum]. Most of them were from the capital [Goiânia (50%; 8) and the metropolitan region (43.8%; 7)]. The case distribution was more

frequent between epidemiological weeks 5 and 19, generally compatible with the circulation of respiratory viruses in our region, as described in Figure 1 (Openshaw et al., 2003). The availability of the PCR-multiplex technique since 2017 allowed the identification of this infection in SARS cases in Goiânia, although with a significant delay to results of more than one week.

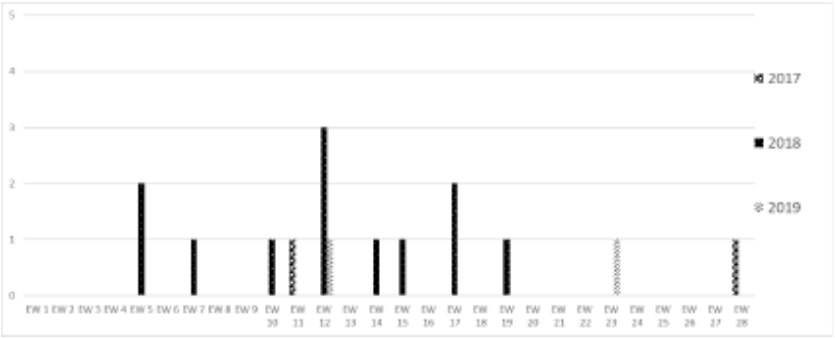

Figure 1. Distribution of metapneumovirus cases according to epidemiological week (EW), Goiás, 2017-2019.

The time between the onset of flu-like symptoms and the first medical assessment had an average of 5 (1-15) days and 2.1 days for diagnostic suspicion after hospital admission (Table 2). One of the patients developed in-hospital, symptoms 21 days after the initial hospitalization for another disease.

Among flu-like illness symptoms, the most prevalent were fever (87.5% n=14), cough (87.5% n=14), respiratory distress/dyspnea (93.8% n=15), oxygen saturation <95% (93.8% n=15), in addition to typical upper airway symptoms such as a runny nose (50% n=8).

The main comorbidities in this sample, considered as risk factors for complications in respiratory infections, were chronic lung disease (25%; n=4), cardiovascular disease (18.8%; n=3), and hematologic malignancy, chronic neurological disease, chronic kidney disease, HIV infection, all accounting for 12.5% (n=2), in addition to diabetes and pregnancy accounting for 6.2% (n=1) each. None of the patients were obese.

As the influenza virus still is the main flu-like syndromic agent and has an available antiviral treatment, 87.5% (14) of patients received oseltamivir for an average of 6 (1–10) days. Almost 70% of patients received corticosteroids, such as hydrocortisone (37.5%; n=6), dexamethasone (25%; n=4), or prednisone (6.2%; n=1) and there was concomitant use of bronchodilators in 56.3% (n=9).

Table 2. Clinical and laboratory characteristics of patients with human metapneumovirus infection treated at referral hospitals in Goiás, 2017-2019.

Variables	
Age (average in years, minimum - maximum)	23.75 (2m-81y)
Women	62.5% (10)
Municipality of residence	
Capital of state (Goiânia)	50% (8)
Metropolitan Region	43.8% (7)
Result release time (median, days – IQR)	8 (4-12)
Time of onset of symptoms (median, days – IQR)	4 (3-7)
Time between admission and diagnostic hypothesis (average in days, minimum - maximum)	2.13 (0-21)
Signs and symptoms	
Fever	87.5% (14)
Runny nose	50% (8)
Cough	87.5% (14)
Respiratory distress	93.7% (15)
Chest pain	18.7% (3)
Sore throat	6.2% (1)
Dyspnea	100% (16)
Myalgia	6.2% (1)
Saturation <95%	93.7% (15)
Abdominal pain	12.5% (2)
Comorbidities	
Chronic lung disease	25% (4)
Chronic neurological disease	12.5% (2)
Cardiovascular disease	18.7% (3)
Chronic kidney disease	12.5% (2)
Obesity	0
HIV	12.5 % (2)
Hematologic neoplasm	12.5% (2)
Diabetes	6.2% (1)
Pregnancy/puerperium	6.2% (1)

Treatment performed	
Antimicrobial	
Macrolide	56.2% (9)
Ceftriaxone	62.5% (10)
Cefepime	18,75% (3)
Amoxicillin/clavulanate	18.7% (2)
Meropenem	25% (4)
Duration of antibiotic therapy (median, days – IQR)	10 (5-17)
Corticosteroids	68.8% (11)
Hydrocortisone	37.5% (6)
Dexamethasone	25% (4)
Prednisone	6.2% (1)
Bronchodilator	56.3% (9)
Oseltamivir	87.5% (14)
Duration of oseltamivir (median, days – IQR)	5 (5-7,7)
Admission to the ICU	62.5% (10)
Length of stay in the ICU (median, days – IQR)	10 (6-17)
SOFA	5.4 (0-11)
APACHE II	18.3 (4-40)
Laboratory tests on hospital admission (median, IQR)	
Hemoglobin (g/L)	10 (9-11)
Hematocrit (%)	29.5 (27-33)
Total leukocytes	10,115 (3,300-15,560)
Rods	349 (75-645)
Segmented	7,222 (1,624-10,928)
Lymphocytes	1,492 (904-2,706)
Platelets	161,500 (58,475-234,000)
Creatinine (mg/dL)	0.7 (0.4-1.48)
CRP (mg/L)	44 (30-101)
PaO2/FiO2 Ratio	274 (108-556)
Changes in chest X-ray	
Interstitial infiltrate	75% (12)
Consolidation	81,3% (13)
Pleural effusion	37.5% (6)

Complications in hospitalization	
Mechanical Ventilation	68.75% (11)
Duration of mechanical ventilation (median, days – IQR)	8 (6-9.5)
ARDS	56.25% (9)
Hospital infection	43.75% (7)
Acute renal failure	18.75% (3)
Death	37.5% (6)
Deaths by age group	
0-5 years	2/7
6-10 years	1/2
10-50 years	0/3
51-70 years	2/3
>70 years	1/1
Length of hospital stay until death (median, days – IQR)	8 (6-26)
Average length of hospital stays (median, days – IQR)	14 (6-25)

APACHE: Acute Physiology and Chronic Health Evaluation (severity-of-disease classification system for ICU mortality); ARDS: Acute Respiratory Distress Syndrome; CRP: C reactive protein; ICU: intensive care unit; IQR: interquartile range; SOFA: Sequential Organ Failure Assessment (severity of illness score for hospital mortality).

Furthermore, the use of corticosteroids may be justified in cases of sepsis and septic shock, as a complement to intensive care. In this context, 68.7% (n=11) of the patients underwent mechanical ventilation and 62.5% (n=10) were admitted to the intensive care unit, with a mean SOFA of 5.4 (0 - 11) and an APACHE II of 18.3 (4 - 40). Criteria for adult respiratory distress syndrome (PaO2/FiO2 < 300) (Ranieri et al., 2012; Riviello et al., 2016) were noted in 56.2% (9) of cases, with radiological findings being compatible with interstitial infiltrate in 75% (n=12), pulmonary consolidations in 81.3% (n=13), and pleural effusion in 37.5% (n=6). The mean duration of mechanical ventilation was 7.7 (5 - 12) days.

The main complications were healthcare-associated infections (43.8%; n=7) and acute renal failure (18.7%; n=3). Death occurred in 37.5% (n=6) of patients, 33% (3/9) in the pediatric age group from 0 to 10 years and 75% (3/4) in adults ageing > 50 years. After binary logistic regression, cardiovascular diseases, mechanical ventilation, and acute renal failure were associated with death as a major outcome ($p<0.05$). Available at supplementary material.

DISCUSSION

In accordance to previous hMPV literature data, it may cause upper and lower respiratory tract infections in patients of all age groups, but the symptomatic disease occurs more frequently in young children or older adults. Among patients requiring hospitalization, clinical manifestations may range from bronchiolitis or asthma exacerbation to severe pneumonia and ARDS (Boivin et al., 2002; Jallow et al., 2019; Vidaur et al., 2019), as seen here. hMPV incidence varies seasonally: late winter and early spring in other countries, which is probably also the case in Brazil (van den Hoogen et al., 2002). According to local epidemiological data, in 2018 hMPV infection accounted for 5.7% of SARS cases, with a mortality rate of 18.7% (Table 1). Our findings confirm that hMPV may be associated with severe lower respiratory tract infections in very young children, elderly and immunocompromised patients, as described in the literature (Hilmes et al., 2017). In hospitalized Canadian children, the most frequent diagnosis were pneumonitis (66.7%) and bronchiolitis (58.3%), whereas bronchitis and/or bronchospasm (60%) and pneumonitis (40%) were more commonly observed in the elderly (Haas et al., 2013).

In 2003, a capital from northeast of Brazil reported 27 hMPV infections in children from 6 to 24 months-old, being 8 coinfected with hRSV. Hospitalization was required in average 25% of hMPV patients (Cuevas et al., 2003). In southern Brazil, from 109 children with identified hMPV infections, the prevalence was similar between males and females, and greater on those under 6 years-old, particularly under 1 year (39.4%). They occurred more frequently during epidemiological weeks (EW) 26 to 38. There were only five cases aged > 20 years and the overall lethality rate was 2.7% (3/109), one immunosuppressed adult and 2 children ≤ 6 months-old (Gregianini et al., 2018).

Upper respiratory tract infection by hMPV occurs in adults, but its frequency as a cause of acute lower respiratory illness appears to be lower than in children (Stockton et al., 2002; Walsh et al., 2008). In the United States, hMPV has been detected in about 4% of hospitalized adults with community-acquired pneumonia, primarily as a single pathogen. Frail elderly patients with hMPV infection are more likely to need medical assistance (Jain et al., 2015; Stockton et al., 2002).

The use of corticosteroids was high, although there is no existing consensus on its use in viral pneumonia. Recent systematic reviews contraindicate their use in influenza cases due to the lack of evidence for them reducing mortality (Arabi et al., 2018; Stockman et al., 2006). A possible explanation for both could be the presence of wheezing and bronchoconstriction. Wheezing is frequent during viral infections, especially in bronchiolitis-like conditions (Openshaw et al., 2003). The requirement for bronchodilators in the context of bronchoreactivity and wheezing in children

and adults has been described as an important characteristic of hMPV infection in hospitalized patients (Williams et al., 2005). This has been associated with mucus hyperproduction and hyperplasia of the respiratory epithelium, resulting in airway obstruction and bronchial hyperresponsiveness. These data are consistent with studies of other respiratory viruses, suggesting that the pathogenesis of severe respiratory infections in childhood may be associated with the development of or susceptibility to asthma (Openshaw et al., 2003).

Chest radiographic findings are not specific in the setting of hMPV infection, usually showing perihilar opacities, hyperinflation, atelectasis, and occasionally consolidation, but usually, pleural effusion or pneumothorax is absent in children according to the literature (Hilmes et al., 2017). Our study findings are consistent with those already described; however, the presence of pleural effusion in 37% differs substantially and may correspond to bacterial complications or clinical comorbidities of adults.

Treatment is supportive and varies according to clinical manifestations. There are no clinical data on the efficacy of antiviral therapy for hMPV infections, but in periods of influenza virus co-circulation, the use of empirical oseltamivir is encouraged. Especially if we considered the long average time to laboratory results, as we can see here.

This study has several limitations including the reduced sample size and incomplete or missing information in retrospective analysis. In a pandemic caused by a new coronavirus (SARS-CoV-2), which is known to lead to influenza-like and SARS, the differential diagnosis of the etiologic agent becomes paramount, as coinfections may occur. Therefore, the PCR-multiplex technique that identifies the main respiratory viruses is of great value to define the real epidemiology and the main outcomes of these infections in different age groups, but the time of results release should be improved.

The epidemiological profile of metapneumovirus cases in three tertiary centers located in a capital in the center-west of Brazil was composed predominantly of female patients, at extremes of age, presenting with fever, wheezing, hypoxemia, and respiratory distress. The main therapies included bronchodilators and corticosteroids to control bronchial hyperresponsiveness, and antibiotics to treat secondary bacterial infection or healthcare-associated infections.

hMPV infection can be severe and needs to be remembered as a cause of upper and lower respiratory tract infection in patients of all age groups, although the symptomatic disease occurs more frequently in young children or older adults. Among patients requiring hospitalization, clinical manifestations can range from bronchiolitis or asthma exacerbation to severe pneumonia and SARS, and lethality is high markedly in extremes of age with comorbidities.

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CONFLICTS OF INTEREST

We have no conflicts of interest to disclose.

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