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Clinico-epidemiological characteristics of acute respiratory infections by coronavirus OC43, NL63 and 229E☆

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Abstract

Background and objectives: Acute respiratory infection is a very common condition in the general population. The majority of these infections are due to viruses. This study attempted to determine the clinical and epidemiological characteristics of adult patients with respiratory infection by the coronavirus OC43, NL63 and 229E.

Patients and methods: Between January 2013 and February 2014, we prospectively studied all patients with suspected clinical respiratory infection by taking throat swabs and performing a reverse transcription polymerase chain reaction in search of coronavirus.

Results: In 48 cases (7.0% of the 686 enrolled patients; 12.6% of the 381 in whom a virus was detected) the presence of a coronavirus demonstrated. In 24 cases, the virus was OC43 (50%); in 14 cases, the virus was NL63 (29%); and in 10 cases, the virus was 229E (21%). The mean age was 54.5 years, with a slight predominance of men. The most common clinical presentations were nonspecific influenza symptoms (43.7%), pneumonia (29.2%) and chronic obstructive pulmonary disease exacerbation (8.3%). Fifty-two percent of the patients required hospitalization, and 2 patients required intensive care. There were no deaths.

Conclusion: Acute respiratory infections caused by coronavirus mainly affect middle-aged male smokers, who are often affected by previous diseases. The most common clinical picture has been nonspecific influenza symptoms.

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Características de las infecciones respiratorias agudas causadas por los coronavirus OC43, NL63 y 229E

Resumen

Antecedentes y objetivos: Las infecciones respiratorias agudas son una entidad muy frecuente en la población general. La mayoría de ellas son debidas a infecciones víricas. Este estudio pretende precisar las características clínicas y epidemiológicas de los pacientes adultos con infección respiratoria por los coronavirus OC43, NL63 y 229E.

Pacientes y métodos: Entre enero del 2013 y febrero del 2014 se estudió prospectivamente a todos los pacientes con sospecha clínica de infección respiratoria mediante la toma de un frotis faríngeo y la realización de una reacción en cadena de la polimerasa en transcripción reversa en tiempo real en búsqueda de coronavirus.

Resultados: En 48 casos (7,0% de los 686 pacientes incluidos; 12,6% de los 381 en los que se detectó algún virus) se pudo demostrar la presencia de algún coronavirus. En 24 casos se trataba del OC43 (50%), en 14 del NL63 (29%) y en 10 del 229E (21%). La edad media fue de 54,5 años, con un ligero predominio de varones. Las presentaciones clínicas más frecuentes fueron el cuadro gripal inespecífico (43,7%), la neumonía (29,2%) y la agudización de enfermedad pulmonar obstructiva crónica (8,3%). El 52% de los pacientes precisaron ingreso hospitalario, en 2 ocasiones en cuidados intensivos. No se produjo ningún fallecimiento.

Conclusión: Las infecciones respiratorias agudas causadas por coronavirus inciden preferentemente en varones fumadores en la edad media de la vida, frecuentemente afectados de enfermedades previas. La sintomatología clínica mas frecuente ha sido el cuadro gripal inespecífico.

Background

Acute respiratory tract infections affect the general population. However, these infections have a higher incidence in the early and late ages of life and in immunosuppressed patients, in whom the infections can be more severe.[1] These respiratory infections are frequently caused by viruses, especially the respiratory syncytial virus (RSV) in children and the adenovirus and influenza viruses in adults.[2] However, the growing use of molecular diagnostic techniques has broadened the spectrum of viruses involved.[2,3]

Human coronaviruses are RNA viruses that taxonomically belong to the *Coronavirinae* subfamily and are classified into 3 distinct genera. The genus *Alphacoronavirus* includes the coronaviruses 229E and NL63, while the genus *Betacoronavirus* contains the coronaviruses OC43 and HKU1.[1] The latter genus also includes the coronavirus that causes severe acute respiratory syndrome[4] and the recently described MERS-CoV, which causes Middle East respiratory syndrome, although its definitive taxonomic position has not yet been established.[5]

There are few studies that have focused on defining the virus' role in acute respiratory infections in adults, and those that have analyzed the role of the coronavirus are even scarcer.[2,6] We therefore believe that our experience with this type of viral respiratory infection is of interest.

Material and methods

This was a series of prospective cases between January 2013 and February 2014, which included all patients with acute respiratory infections caused by coronavirus in a population over 18 years of age. Throat swabs were taken and assessed for the presence of the coronaviruses OC43, NL63 and 229E. These swabs were used as the only respiratory sample to avoid potential difficulties in the interpretation of the results based on the sample type. The throat swabs were sent to the laboratory in a viral transport medium (MTV, Vircell, Granada, Spain). Only one sample per patient was considered. The samples were processed to detect the various respiratory viruses using a real-time genomic amplification technique (commercial real-time reverse transcription polymerase chain reaction kit), which provides simultaneous and differential detection of 16 different respiratory viruses (Anyplex RV16, Seegene, South Korea). Blood cultures were performed for patients with suspected pneumonia, and serological determinations for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were conducted. The medical records and epidemiological data of the patients with coronavirus were reviewed. The statistical analysis was performed using the chi-squared test and Student's *t*-test for paired data. Values of $p < .05$ were considered significant.

Results

The study took place on the island of Mallorca, with patients with no history of trips abroad in the last 15 days and no known contact with farm or wild animals. A total of 686 patients older than 14 years with suspected viral respiratory infection were included. The presence of a virus was detected in 381 (55.5%) of these patients. In 48 cases (7.0%

What we know?

Respiratory infections are frequently caused by viruses. The use of molecular techniques helps us better understand the etiological spectrum of the viruses involved. This study attempts to determine the involvement of the human coronavirus OC43, NL63 and 2229E in our community.

What this article provides?

The presence of a virus was demonstrated in 55.5% of the included patients, 12.6% of which involved the coronavirus, affecting mostly middle-aged smokers with underlying diseases. The most common clinical presentation was catarrhal syndrome and pneumonia. Fifty-two percent of the patients were hospitalized and had good outcomes, with no case ending in death.

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of the 686 enrolled patients; 12.6% of the 381 in whom a virus was detected), the presence of a coronavirus was demonstrated. In 24 cases, the virus corresponded to OC43 (50%); in 14 cases, the virus was NL63 (29%); and in 10 cases, the virus was 229E (21%). In these 48 patients, the blood cultures were negative, and the serologies did not indicate any other diagnosis.

The main characteristics of each patient with acute human coronavirus infection are listed in Table 1. The mean patient age was 54.5 years (range, 18–85 years); the mean ages of the patients infected by coronavirus OC43, NL63 and 229E were 49 years (range, 18–84 years), 63.5 years (range 33–84 years) and 55.3 years (range 39–85 years), respectively ($p > .05$). Twenty-six patients (54.1%) were men and 22 (45.9%) were women ($p > .05$). A predominance of men (60%) was observed in the coronavirus 229E infections. Although cases of coronavirus infection were detected over the entire course of the year, 58.3% of the cases occurred between January and March. In 36 cases (75%), the coronavirus was detected as the only virus, and in 12 cases (25%) it was detected as a coinfection with other viruses (7 cases of rhinovirus, 3 cases of influenza virus, 1 case of RSV and 1 case of bocavirus). The coronavirus 229E had the lowest frequency of mixed infection (10%).

Twenty-three patients (47.9%) were smokers. Only 15 (31.2%) had been vaccinated for seasonal influenza. Eleven patients (22.9%) were infected with the human immunodeficiency virus (HIV). The main respiratory syndromes associated with the coronaviruses were catarrhal syndromes (fever, general discomfort, pharyngitis, adynamia) (occurring in 21 patients, 43.7%), pneumonia (occurring in 14 patients, 29.1%) and exacerbation of chronic obstructive pulmonary disease (COPD) (occurring in 4 patients, 8.3%). Twenty-five patients (52%) were hospitalized, 2 of them (8%) in the intensive care unit. Thirty-nine patients (81.2%) underwent antibiotic treatment (21 patients were treated with amoxicillin/amoxicillin, and 18 were treated with

levofloxacin), which typically was maintained despite the viral diagnosis. There were no deaths.

Discussion

Acute respiratory infections caused by coronavirus in the general population represent 2–18% of cases, depending on the geographical area, type of population studied and viral detection technique employed.[7] In a large 4-year study performed in France, Lepiller et al.[8] found that coronaviruses represented 11.7% of the analyzed cases. However, in Brazil, these viruses only represented 1.2% of the cases studied from 2009 to 2010,[9] while in China, the rates were 4.4%[10] and 11.7%[11] for a pediatric population and an adult population, respectively. In a study performed in Canada,[12] coronaviruses only represented 2% of the respiratory samples from adults, which is consistent with that observed by Gaunt et al.[13] in Great Britain (2.3%). However, all of these estimates generally refer to the rate of positivity for a total number of samples analyzed. Thus for the Gaunt et al. study,[13] the rate of etiologic participation of the coronaviruses rose to 8.1% of all the samples positive to any virus. In our study, we detected coronaviruses in 6.9% of the enrolled patients and in 12.6% of those in whom a virus was demonstrated, with readings very close to those measured in neighboring countries, such as France.[8]

The distribution of the various types of coronavirus varied widely according to the geographical area. Thus, while only NL63 and OC43 were detected in Brazil,[9] Lepiller et al.[8] observed a predominance in France of the coronavirus 229E (53%) compared to the others (36% for NL63 and 11% for OC43). However, Gaunt et al.[13] observed in their series of 221 cases in Edinburgh that the most common coronavirus was OC43 (50.2%), followed by NL63 (33.9%) and 229E (15.8%). In our study, which was shorter and had fewer cases of infections, the coronavirus OC43 (50%) was also predominant, followed by NL63 (29%) and 229E (21%).

One of the common characteristics of most respiratory viruses is that they usually cause mixed infections, in conjunction with other respiratory viruses.[14] The rates of coinfection vary from 30 to 70%[3,14]; patients with mixed infections do not have higher rates of morbidity or mortality.[8,13] The detection of probable mixed infections should be assessed with caution because they can reflect respiratory infections prior to the acute process that motivated the study. The simultaneous detection of several viruses through genomic tests also establishes the possibility that some patients are carriers of any of the detected viruses without them having a direct pathogenic role in the current infection.[3,14]

In our study, the rate of coinfection was not very high (25%). Gaunt et al.[13] reported a 35% coinfection rate, with rhinovirus the most frequent companions (65%); in our study, this virus represented 58.3%. Coinfections with the influenza virus have been described mainly in children, representing 5–10% of the cases.[10] Twenty-five percent of coinfection cases in our series corresponded to the influenza virus, probably coinciding with the seasonal flu epidemic. The detection of a case of RSV coinfection is noteworthy, given that a previous study on RSV did not detect any cases of this type of coinfection.[15]

Table 1 General characteristics of patients with respiratory tract infections in whom coronavirus was detected.

Sex	Age	History	Admission	Clinical Presentation	Diagnosis	Antibiotic Treatment	Smoker	Other Virus
Coronavirus OC43 (24 cases)								
M	61	AHT, MM	No	Fever, myalgia	CS	A–Cl	No	No
F	22	None	No	Fever, pharyngitis	CS	None	No	No
M	74	Ischemic heart disease	Yes	Pneumonia	ARI	A–Cl/LV	Yes	No
F	48	HIV-C3; HCV	No	Sore throat, cough, fever	ARI	LV	No	No
F	60	Kidney transplantation	Yes	Fever, sore throat	ARI	A–Cl	No	No
M	38	HIV-	No	Fever, expectoration	CS	A–Cl	Yes	No
M	60	HIV-B1	Yes	Dyspnea, cough	Exacerbated COPD	LV	Yes	No
F	52	DM	No	Catarrhal symptoms	CS	None	Yes	No
F	41	HIV-C3; HCV	UCI	Fever, cough, distress	ARI	LV	Yes	No
F	40	BMT	No	Catarrhal symptoms	CS	A–Cl	No	No
M	47	HIV-C3; HCV	Yes	Fever, expectoration	Pneumonia	A–Cl/CTX	Yes	No
M	50	None	No	Catarrhal symptoms	CS	None	Yes	No
F	45	Sarcoidosis	Yes	Fever, expectoration	CS	None	No	No
F	55	MM	Yes	Catarrhal symptoms	CS	A–Cl	No	No
F	85	AHT, COPD	Yes	Fever, chest pain	Pneumonia	A–Cl	Yes	No
M	18	None	Yes	Fever, chest pain	Myopericarditis	A–Cl	Yes	No
M	84	AHT, DM	No	Catarrhal symptoms	CS	LV	Yes	No
F	32	None	No	Catarrhal symptoms	CS	None	No	No
M	54	AHT, DM, kidney transplantation	UCI	Fever, dyspnea, expectoration	Pneumonia	P–TZ	No	RSV
F	44	HIV-B3	Yes	Fever, cough	CS	A–Cl	Yes	RV
F	39	None	Yes	Fever, dyspnea	Pneumonia	LV	No	RV
M	53	HIV-C3; HCV	Yes	Dyspnea, fever	Pneumonia	A–Cl/AZ	No	RV
M	33	DM	No	Catarrhal symptoms	CS	None	No	RV
M	41	COPD	No	Fever, cough	CS	A–Cl	Yes	RV
Coronavirus NL63 (14 cases)								
M	42	HIV-A1	No	Catarrhal symptoms	CS	A–Cl	Yes	No
M	84	HCV/AHT	No	Fever, expectoration, diarrhea	ARI	A–Cl	Yes	No
F	84	Chronic lung disease	Yes	Dyspnea, fever, chest pain	ARI	LV	No	No
M	66	Thalassemia minor, COPD, AHT	Yes	Dyspnea, fever	Exacerbated COPD	A–Cl	Yes	No
M	74	Lung cancer, AHT, DM	Yes	Dyspnea, fever, expectoration	Pneumonia	A–Cl/LV	Yes	No
F	80	COPD, DM	No	Catarrhal symptoms	Pneumonia	LV	Yes	No
F	53	Scleroderma, AHT, DM	Yes	Chest pain, fever	Pneumonia	A–Cl	No	No
M	72	COPD, AHT	No	Fever, cough	Exacerbated COPD	LV	Yes	No
M	65	Asthma, bronchiectasis, colon cancer	Yes	Fever, expectoration, chest pain	ARI	LV	No	No
F	33	DM	No	Catarrhal symptoms	CS	None	No	IF-A
M	79	DM, AHT, Nephropathy	No	Fever, dyspnea, cough, myalgia	Exacerbated COPD	LV	Yes	IF-B
F	74	DM, AHT	No	Catarrhal symptoms	CS	A–Cl	No	IF-B
F	40	HIV-C3; HCV	Yes	Respiratory distress, fever	Pneumonia	A–Cl/AZ	No	RV

Table 1 (Continued)

Sex	Age	History	Admission	Clinical Presentation	Diagnosis	Antibiotic Treatment	Smoker	Other Virus
M	43	BMT, AML	No	Fever, cough, expectoration	CS	LV	No	RV
Coronavirus 229E (10 cases)								
F	53	Hodgkin's disease, BMT	Yes	Fever, expectoration, chills	CS	LV	No	No
M	39	HIV-C3	Yes	Fever, expectoration, dyspnea	Pneumonia	A–Cl/AZ	No	No
M	49	DM, AHT	No	Catarrhal symptoms	CS	None	No	No
M	43	AML, BMT	Yes	Fever, cough, chest pain	CS	LV/CTX	No	No
M	53	COPD	No	Cough, expectoration	Exacerbated COPD	LV	Yes	No
F	85	AHT	No	Fever, rhinorrhea, rales	Pneumonia	A–Cl/AZ	No	No
F	47	Bronchial asthma	Yes	Fever, expectoration, dyspnea, diarrhea	Pneumonia	LV	Yes	No
M	64	ALL	Yes	Fever, cough	CS	LV	Yes	No
M	77	AHT	No	Catarrhal symptoms	CS	None	Yes	No
F	43	HIV-C3	Yes	Catarrhal symptoms	ARI	A–Cl	No	BV

General characteristics of the patients enrolled in this study with respiratory tract infections in whom the presence of coronavirus OC43, NL63 or 229E was detected.

A–Cl: amoxicillin–clavulanate; AHT: arterial hypertension; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ARI: acute lower respiratory tract infection; AZ: azithromycin; BMT: bone marrow transplantation; BV: bocavirus; CA: cancer; COPD: chronic obstructive pulmonary disease; CS: catarrhal syndrome; CTX: cotrimoxazole; DM: diabetes mellitus; F: female; HCV: liver disease due to hepatitis C virus infection; HIV: human immunodeficiency virus; IF: influenza; LV: levofloxacin; M: male; MM: multiple myeloma; P–TZ: piperacillin–tazobactam; RSV: respiratory syncytial virus; RV: rhinovirus.

Although they can be detected over the course of the year, the incidence of coronavirus infections adjusts to a seasonal pattern, occurring predominantly in winter months.[2,6,13] A number of studies have observed that OC43 presents a pattern with a biannual variation, with a predominance in the first quarter of the year.[13,16] We detected the incidence of respiratory infections by coronavirus over the course of the year, although the majority (58.3%) occurred between the months of January and March.

The mean age of our patients was 54.5 years, with a range of 18–85 years and the infections mainly affecting middle-aged individuals. There are few studies that reflect middle age in adult patients. Bastien et al.[12] measured a mean age of 72 years for patients infected by NL63. We observed no significant variations in patient age depending on the type of coronavirus, although the mean age of the patients with NL63 was somewhat higher (63.5 years). We also observed no significant differences in terms of the sex of the patients with infections; however, Gaunt et al.[13] reported a somewhat higher rate in men infected by OC43 and NL63.

The coronavirus, as with most other respiratory viruses, causes acute infections in both the upper and lower respiratory tract; the clinical spectrum is therefore difficult to differentiate from other viruses.[2,8,13,17] In our study, as in previous studies, the most common respiratory disease was nonspecific catarrhal syndrome.[3,8,13,16,18]

Pneumonia constitutes another of the typical clinical presentations of coronaviruses; thus, 10–18% rates have been reported.[19,20] Lepiller et al.[8] found that the clinical presentation of coronavirus infection was pneumonia in 14% of their patients, with values of 26% for 229E, 25% for OC43 and 0% for NL63. In our series, 29.1% of the patients were diagnosed with pneumonia, with a greater rate in infections from coronavirus 229E (40%).

Coronavirus 229E has been described as the predominant causal agent in immunosuppressed patients.[21] Eleven patients in our study (22.9%) were infected with HIV; coronavirus 229E was involved as the pathogen in only 2 cases (18%), while OC43 was involved in 7 (64%) and NL63 in 2 (18%). We have found no data referring to the potential implications of coronavirus infections in patients with HIV infection.

Respiratory virus infections can also cause COPD exacerbations, although the coronavirus appears to be less involved than other viruses.[8,13,16] Nevertheless, our study detected NL63 in 14.2% of the infected patients, and Lepiller et al.[8] found them to be involved in 6% of their patients. These viruses should therefore be considered potential etiologic agents in these processes.

Most of the patients enrolled in our series had an underlying disease (43 patients, 89.6%), which might explain the high rate of empiric antibiotic treatment, which was employed for 38 patients (81.2%), mainly amoxicillin/clavulanic acid (21 patients, 53.8%) and levofloxacin (18 patients, 46.1%). Sixty-six percent of the patients underwent antibiotic treatment even after the presence of coronavirus was detected. At present, there is no antiviral drug that has been proven effective against the human coronavirus.[7]

Smoking is one of the main predisposing factors for numerous respiratory diseases and, among others, viral infections. Twenty-three of our patients (47.9%) were

smokers. Only 15 of the patients in our series (31.2%) had been vaccinated against seasonal influenza.

The hospitalization of patients with acute respiratory infection often depends on the symptoms and severity of the respiratory clinical picture or of the patient's underlying disease. Twenty-five of the patients (52%) in our series were hospitalized, but only 2 (4%) were admitted to the ICU, 1 of whom was a patient infected with HIV and in respiratory distress and the other was a patient with a kidney transplant and bilateral pneumonia. Both of the patients had favorable outcomes. Of the 50 cases described by Lepiller et al.,[8] 4% were admitted to the ICU, consisting of a case of NL63 infection and a case of 229E infection. Our 2 cases were infected by the coronavirus OC43 (8.3% of the total). As with the study by Lepiller et al.,[8] none of our patients died during the coronavirus infection episode.

We can conclude that acute respiratory infections by human coronavirus mostly affect middle-aged men who smoke and have underlying diseases. The predominant clinical presentation is a lower respiratory tract infection, with general malaise, which usually has a favorable outcome.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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