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ORIGINAL ARTICLE

Clinical and epidemiological features of SARS-CoV-2 infection in children under 16 years of age

Caracterización clínica y epidemiológica de la infección por SARS-CoV-2 en menores de 16 años

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What do we know about the subject matter of this study?

To date, there is little information on the behavior of SARS-CoV-2 in the pediatric population, while studies and publications in adults are far more numerous.

What does this study contribute to what is already known?

This study provides further data on the clinical and epidemiological characteristics of patients under 16 years of age diagnosed with SARS-CoV-2 infection, through a series of 165 pediatric patients with a confirmed diagnosis.

Abstract

During the SARS-CoV-2 pandemic, efforts have focused on trying to identify the routes of transmission of the virus, characterize its symptoms and signs, and investigate the best diagnostic and therapeutic methods. There are fewer published data and series in the pediatric population than in adults. **Objective**: To analyze the clinical and epidemiological characteristics in children under 16 years of age diagnosed with SARS-CoV-2. **Patients and Method**: Descriptive study carried out on children who underwent SARS-CoV-2 RNA testing due to compatible symptoms, close contact, or requiring hospitalization or surgery, in the Emergency Department of a hospital in Madrid, Spain. 30 variables were collected including epidemiological data, symptoms, and signs of infection. **Results**: Out of 1378 patients, 12% were positive (165). There was a higher proportion of patients of North African origin in the positive group than in the negative one ($p < 0.01$). Of all patients, 35.6% reported close contact with a confirmed case, which was more frequent in the positive group. 75.8% of the positive patients had some symptoms, most frequently fever, runny nose, and cough, followed by digestive symptoms. There was one case of COVID-19 pneumonia and two patients with MIS-C, one of which had SARS-CoV-2 infection. Eight of the positive patients (4.8%) required hospitalization due to SARS-CoV-2 infection. **Conclusion**: Although SARS-CoV-2 infection is milder in the pediatric population, almost 5% will require hospitalization. No close contact was identified in a high percentage of patients (61%). Further studies are needed at all levels of care to characterize the infection in children and adolescents.

Keywords:
COVID-19;
Coronavirus;
SARS-CoV-2;
Emergency Room;
Children;
Symptoms

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Introduction

In December 2019, a novel coronavirus capable of infecting humans, SARS-CoV-2[1-5], was identified in Hubei, China. Since then, the infection has been spreading around the world, being declared a pandemic in March 2020[2,4,6], with more than 113 million people infected worldwide and more than 2.5 million dead at present, according to the World Health Organization (WHO)[7].

Spain is one of the countries most affected by SARS-CoV-2, with more than 3,000,000 people infected and more than 69,000 dead, according to data from the Ministry of Health.

Since the beginning of the pandemic, all efforts have been focused on trying to identify the routes of transmission of the virus in order to curb its spread, define the clinical characteristics of the infection, find the best diagnostic methods, and the most appropriate treatment. There are numerous publications, mainly focused on adults, with fewer data published in the pediatric population[1,6,8].

Infection in adults typically presents with respiratory symptoms and pneumonia[2] which, in some cases, causes an acute respiratory syndrome and an excessive inflammatory response, with high mortality. In the pediatric age group, the infection has a milder course[1] and, therefore, the prognosis is more favorable[6,9].

The main routes of transmission are through contact and inhalation of droplets and respiratory aerosols[10-12]. In most publications, infected children have had contact with a family member[1,2,13] or with a sick caregiver[11], so it seems that children do not play a fundamental role in its transmission[14], unlike other infections, such as those caused by the respiratory syncytial virus (RSV), rotavirus, scarlet fever, erythema infectiosum, or hand-foot-and-mouth disease.

During the first months of the pandemic, diagnostic testing to confirm infection was exceptional, especially in pediatric patients, who presented a milder clinical picture. Currently, diagnostic tests for acute infection are much more widely available and their performance is indicated in the presence of compatible symptoms and/or close contact, as well as in cases in which it is necessary to know the patient's condition for the performance of different invasive techniques or to carry out specific isolation in the case of hospitalization.

As it is a new, unknown virus with such a different behavior in children and adults, it is essential to adequately define the characteristics of this infection in the pediatric population, in order to improve our actions against this disease.

The objective of this study is to analyze the clinical and epidemiological characteristics of patients diagnosed with SARS-CoV-2 infection in our center from July 15 to September 30, 2020, during the second epidemic wave.

Patients and Method

Retrospective descriptive study in a second-level hospital in Madrid, Spain. We included all patients under 16 years of age who were screened for SARS-CoV-2 infection in the Pediatric Emergency Department between July 15 and September 30, 2020.

The microbiological test performed for the detection of SARS-CoV-2 infection was an RNA-SARS-CoV-2 test, from a sample of oropharyngeal and nasopharyngeal exudate.

During the study period, this test was performed on all pediatric patients with compatible symptoms, on all close contacts (according to the definition established in the Protocol for the strategy of early detection, surveillance, and control of COVID 19 developed by the Ministry of Health, in force at that time[15]), whether or not they had symptoms, and on all patients who required urgent surgery or hospital admission, in order to carry out isolation measures if necessary.

30 variables were collected, including epidemiological data (age, sex, ethnicity) and clinical data (symptoms and signs). The symptoms recorded were fever (days of fever and maximum temperature), low-grade fever, cough, rhinorrhea, dyspnea, chest pain, odynophagia, headache, vomiting, diarrhea, abdominal pain, syncope, anosmia, ageusia, myalgia, skin lesions, and days of evolution since the onset of symptoms. The signs collected were oxygen saturation, respiratory distress, pathological pulmonary auscultation, presence of exanthema, and tonsillar exudate. In addition, we recorded whether they had had close contact with a confirmed case, whether they required hospitalization, or if the SARS-CoV-2 RNA test had been requested because of the need for urgent surgery or because they required hospitalization for causes unrelated to COVID-19.

For statistical analysis, Excel and SPSS Statistics 25 software were used. Quantitative variables were expressed as mean, median, standard deviation, and interquartile range (IQR). Qualitative variables were expressed as frequency and percentage. Quantitative variables were compared in the univariate analysis using Student's t-test. Qualitative variables were compared using the chi-square test, applying Fisher's exact test when required. A $p < 0.05$ value was considered statistically significant.

Results

During the study period, RNA-SARS-CoV-2 tests were requested for 1,378 patients. Of these, 12% were positive (165 patients) and 88% were negative (1,213 patients).

Epidemiology

The median age of the overall sample was 4.6 years (IQR: 2.05-8.35) and that of the positive group was 4.4 years (IQR: 1.74-8.28). The distribution by sex was 52.3% males in the total sample and 49.7% males in the group with a positive test.

If we analyze the percentage of positivity by age group, 1.8% were patients under 1 month of age; 2.4% in the group aged 1 to 2 months; 11% patients aged 3 to 11 months; 12.1% patients aged 1 year; 31.5% patients aged 2 to 4 years; and 41.2% those patients aged 5 to 15 years (table 1).

Of the patients of Caucasian origin, 74.4% presented a positive test and 88% presented a negative one ($p < 0.001$); patients of North African origin presented 11% and 4.5%, respectively ($p = 0.001$); and sub-Saharan African patients presented 7.9% and 1.9%, respectively ($p < 0.001$). There were no significant differences in other ethnicities (table 1).

35.6% (490/1378) reported close contact with a confirmed case; 45.5% (75/165) in the group with positive test and 34.2% (415/1213) among the negative ones ($p < 0.05$) (table 1). No history of contact was recorded in 47 patients (3.4%), with a similar distribution between positive and negative tests.

23.6% of patients (325/1378) were asymptomatic; 24.2% were in the group with positive test and 23.5% among the negative ones (figure 1). Of the total number of asymptomatic patients, 94.2% were tested due to close contact and the remainder due to scheduled admission or invasive complementary tests.

Of the positive patients, 75.8% were symptomatic. Of the patients who were tested due to compatible symptoms, the history of close contact was more frequent in the positive patients (28%) than in the negative patients (16%) ($p < 0.001$) (figure 1).

Signs and symptoms

At the time of diagnosis, the mean number of days after symptoms onset was 1.6 (IQR: 1-2). The most frequent symptom was fever (54.4%), with 75% presenting a temperature between 38ºC and 39ºC; 15.2% presented low-grade fever. Following fever, the most frequent symptoms were upper airway infection (52.8% rhinorrhea and 52% cough). Table 2 details the remaining symptoms and their frequencies.

On the physical examination, 7.2% presented pathological pulmonary auscultation, with the most frequent findings being crackles and wheezing. Signs of respiratory distress were present in 3.2% and mean oxygen saturation was 97 ± 1.8%. The presence of skin lesions was 2.4% and tonsillar exudates 1.6%.

During the study period, two patients with a radiological diagnosis of pneumonia were identified, and SARS-CoV-2 infection was confirmed in only one of them.

Of all the patients included in the study, 8 (4.8%) required admission due to COVID-19 infection. Three of them were infants under 3 months of age with febrile syndrome, three patients were admitted due to bronchitis requiring oxygen support, one patient due to pneumonia requiring oxygen support, and a patient with sickle cell disease due to febrile syndrome.

There were two cases of Multisystem Inflammatory Syndrome in children (MIS-C) related to SARS-CoV-2, who required referral to the PICU for treatment, aged 12 and 13 years. The SARS-CoV-2 RNA test was positive in only one of them, with positive IgG serology. The first IgG serology performed on the patient with a negative test was also negative.

Discussion

We present a series of 165 pediatric patients with a confirmed diagnosis of SARS-CoV-2 infection, representing one of the series with the largest number of patients published in our country. In addition, both hospitalized patients and those with outpatient follow-up were included.

The age of the patients with a positive test does not differ from that of the negative ones, and it does not appear that there is an age group that is more affected by the infection, in relation to the number of cases. However, if we compare the percentage of positivity with negativity in children under 3 months of age, it does seem significantly higher when compared with the percentages presented by older patients. This may be of interest if we consider that in children under 3 months of age the test is performed mainly due to clinical compatibility or close contact and, exceptionally, due to the need for surgery or admission for other reasons.

In our series, we found significant differences in the frequency of positives regarding ethnicity, which coincides with the largest cohort study carried out to date by Goyal et al[16], in which minority ethnicities seem to be at higher risk of infection. We have not collected data on the socioeconomic status of the patients, but the same study shows that a low socioeconomic level is also associated with a higher risk of infection. The causes are probably multiple such as lower availability of resources, overcrowded housing, jobs with little social distance, and greater use of public transport, thus increasing exposure to the virus[16].

In some of the published review studies, between 70 and 80% of pediatric patients reported previous close contact, most of the time in the family setting[1,2,9,11,13]; however, only 35.6% of our cases have this history, which may be due, in part, to the retrospective collection of data, but also the high percentage of asympto-

Table 1. Epidemiological data

	Total patients (n = 1378) n (%)	Patients with a positive test (n = 165) n (%)	Patients with a negative test (n = 1213) n (%)	p
Age				
< 1 month	8 (0.6%)	3 (1.8%)	5 (0.4%)	ns
1-2 months	18 (1.3%)	4 (2.4%)	14 (1.1%)	ns
3 months -11 months	122 (8.8%)	18 (11%)	104 (8.6%)	ns
1 year	187 (13.6%)	20 (12.1%)	167 (13.8%)	ns
2-4 years	406 (29.5%)	52 (31.5%)	354 (29.2%)	ns
5-15 years	637 (46.2%)	68 (41.2%)	569 (46.9%)	ns
Ethnicity distribution				
Caucasian	1.191 (86.4%)	123 (74.4%)	1.068 (88%)	p < 0.001
North Africa	73 (5.3%)	18 (11%)	55 (4.5%)	p = 0.001
Sub-Saharan Africa	36 (2.6%)	13 (7.9%)	23 (1.9%)	p < 0.001
South America	53 (3.8%)	9 (5.5%)	44 (3.6%)	ns
Eastern	8 (0.6%)	0 (0%)	8 (0.7%)	ns
Not stated	17 (1.2%)	2 (1.2%)	15 (1.2%)	ns
Close contact	490 (35.6%)	75 (45.5%)	415 (34.2%)	p = 0.005

ns: not significant

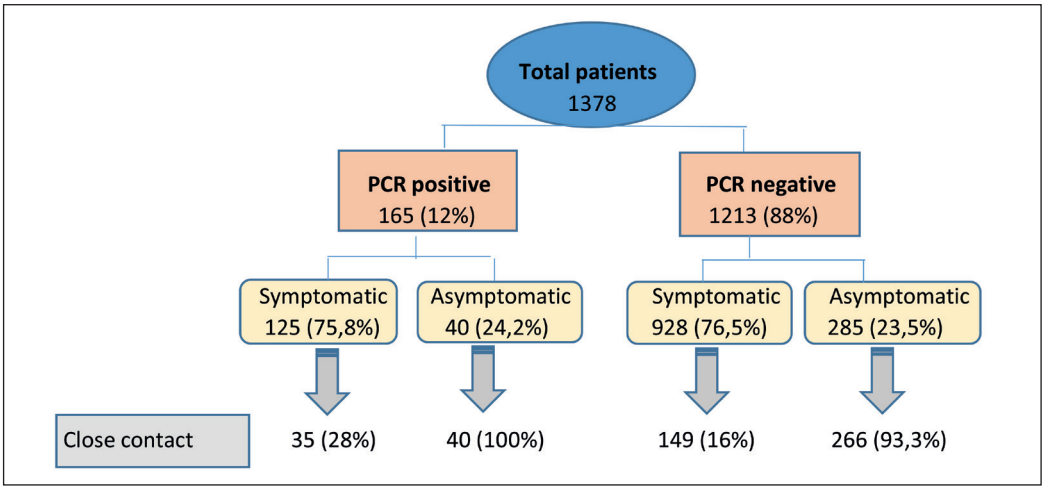

Figure 1. Flow diagram

matic cases and the epidemiological situation of community transmission. In any case, these data highlight the role of the pediatric population in transmission.

In our study, the most frequent symptoms were fever, rhinorrhea, and cough, which is in line with published reports[3,9,17]. Furthermore, as Yoldas et al[2], we found that there are present gastrointestinal symptoms, such as vomiting or diarrhea, much more often than adults[4,13,14]. On the other hand, unlike them, the occurrence of anosmia and ageusia is exceptional[11,14]. However, we must consider that the exploration of these symptoms in children is more complicated, especially in the youngest, and their main manifestations are usually more nonspecific, such as refusal of food. Curiously, Jeng reports the absence of anosmia and ageusia in the Chinese population, which was only been detected in European and American patients[11].

As published by several authors, up to 24% of infected patients were asymptomatic[8-10], therefore, the total number of infections may be underestimated which could be hindering transmission control[4].

According to WHO definitions, the pediatric population usually presents mild or moderate infection symptoms, with a very good prognosis, which coincides with the findings of our study and with most of the literature reviewed. Thus, unlike in adults, there

Table 2. Symptoms in patients with a positive test

Fever	54,4%
Rhinorrhea	52,8%
Cough	52%
Diarrhea	20%
Low-grade fever	15,2%
Odynophagia	15,2%
Abdominal pain	9,6%
Headache	7,2%
Myalgia	4,8%
Dyspnea	4,8%
Chest pain	0,8%
Anosmia	0%
Ageusia	0%

are few cases of severe pneumonia in children[2,10], and deaths are rare[9,13,17]. In addition, in our series, the patients who required admission had an adequate clinical evolution, which agrees with the preliminary results of the EPICO-AEP study.

Different theories attempt to explain why the disease is less severe in children such as that with age the immune system deteriorates, thus reducing its capacity to protect against infection[2]; children have fewer comorbidities than adults[6] and lower expression of the ACE receptor[25,14], and that previous exposure to other human coronaviruses could generate protection by cross-reaction[19]. However, the exact reasons for this are currently unknown.

In adults, the presence of comorbidities further worsens the prognosis[4,20], a fact that is not so clear in the pediatric population since there are not as many specific data[3,6]. However, recent studies had reported that the presence of underlying diseases increases the risk of admission to the PICU[14,17]. Although this variable was not specifically analyzed in our study, we did note that the only patient with underlying disease (sickle cell disease) in our series presented an adequate clinical course. In any case, due to the greater vulnerability of these patients, they should be given special attention[19,20].

Two patients were diagnosed with MIS-C requiring treatment in the PICU, with a favorable evolution. This agrees with the data known so far, which indicate a major complication, but without high mortality[5,14,21]. Some authors have published that a high percentage of patients with this syndrome present negative SARS-CoV-2 RNA test with positive IgG serology, suggesting that it could be a post-infectious inflammatory syndrome[5,19], as is the case of one of our patients.

In relation to admissions, in our study, less than 5% of patients required admission. The increased knowledge of SARS-CoV-2 infection has allowed the discharge of those with mild symptoms, who are closely followed up by telephone until the symptoms are resolved, thus reducing the number of hospital admissions[12].

SARS-CoV2 infection appears to be milder in the pediatric population than in adults. For this reason, we believe that it is essential to share all the data obtained since greater knowledge will allow us to make better decisions about the most appropriate management, both diagnostically and therapeutically.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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