ORIGINAL ARTICLES

Assessment of the outcomes of SARS-CoV-2 infection in children and young people followed at Portuguese pediatric rheumatology clinics

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ABSTRACT

Introduction: Coronavirus Disease 2019 (COVID-19) generally appears to have milder clinical symptoms and fewer laboratory abnormalities in children. It remains unknown whether children and young people with inflammatory chronic diseases who acquire SARS-CoV-2 infection have a more severe course, due to either underlying disease or immunosuppressive treatments.

Objectives: To assess the epidemiological features and clinical outcomes of children and young people with inflammatory chronic diseases followed at Pediatric Rheumatology Clinics who were infected with SARS-CoV-2. Methods: A multicentric prospective observational study was performed. Data on demographic variables, clinical features and treatment were collected between March 2020 and September 2021, using the Rheumatic Diseases Portuguese Register (Reuma.pt) and complemented with data from the hospital clinical records.

Results: Thirty-four patients were included, 62% were female, with a median age of 13 [8-16] years and a median time of inflammatory chronic disease of 6 [3-10] years. The most common diagnoses were juvenile idiopathic arthritis (n=22, 64.7%), juvenile dermatomyositis (n=3, 8.8%) and idiopathic uveitis (n=3, 8.8%). Twenty patients were on conventional synthetic disease modifying drugs (csDMARDs) and 10 on biologic DMARDs (bDMARDs). Five patients had an active rheumatic disease at the time of infection (low activity). Sevenpatients had asymptomatic infection while 27 (79%) patients had symptoms: cough (n=12), fever (n=11), rhinorrhea (n=10), headache (n=8), malaise (n=8), fatigue (n=7), anosmia (n=5), myalgia (n=5),dysgeusia (n=4), odynophagia (n=4), chest pain (n=2), diarrhea (n=2), arthralgia (n=1), vomiting (n=1) and conjunctivitis (n=1). No patient required hospitalization or directed treatment, and all recovered without sequelae. In 8 patients there was a change in the baseline medication during the infection: suspension of bDMARDs (n=4), reduction of bDMARDs (n=1), suspension of csDMARDs (n=4) and reduction of csDMARDs (n=2). Only in one patient with JDM (who discontinued bDMARDs and csDMARDs), the underlying disease worsened.

Conclusions: This is the first study involving children inflammatory chronic diseases followed at Rheumatology Clinics and SARS-CoV-2 infection in Portugal. In our cohort, mild illness was predominant, which is consistent with the literature. There was no need for hospitalization or specific treatment, and, in most cases, no worsening of the underlying disease was identified.

Keywords: Juvenile idiopathic arthritis; Viruses; Paediatric/Juvenile rheumatology.

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INTRODUCTION

The outbreak of SARS-CoV-2 infections has spread all over the world, establishing a major global health concern and the World Health Organization (WHO) declared it a global pandemic on March 11, 2020.

Children are usually more susceptible to infectious diseases due to their developing immune system. However, the susceptibility to severe COVID-19 seems to be lower, with less probability of developing serious illness and only rare cases of death[1–3]. Estimates of asymptomatic infection range from 13% to 50% of cases[4]. In symptomatic cases, fever and cough are the most common[3,5,6]. Only 1% to 5% of pediatric cases qualify as severe versus 10% to 20% in adults[4]. SARS-CoV-2 infections comprise only approximately 1% of pediatric admissions to hospitals[7] and only a minority of infected children require hospitalization[6]. Several reasons could account for the low severity and mortality of COVID-19 in children. Some studies have suggested that the expression of the ACE-2 receptor, the primary binding site for SARS-CoV-2, may be less developed in children[4,8]. Globally, the milder illness is attributed to a healthier respiratory tract (not exposed to cigarette smoke and air pollution), and fewer chronic diseases[6].

Patients with rheumatic and musculoskeletal diseases (RMD) are characterized by an overall increase in risk of infection due to the immune-mediated disease itself and to the immunomodulatory drugs used for its control[5,9]. A high RMD disease activity was identified as an independent risk factor for hospitalization and death in adults[9–11]. There is also an association with a worse prognosis with the use of certain drugs, including glucocorticoids (GC), rituximab and sulfasalazine[10]. Several studies focused on whether disease-modifying anti-rheumatic drugs' (DMARDs) use in adult patients with rheumatic diseases might change the course of infection. (12) Data about the additional risk associated with DMARDs have not been reported in pediatric rheumatic diseases yet.

Children with comorbidities and young age, particularly infants, had a higher risk of severe COVID-19[13]. Common underlying conditions associated with severe disease were chronic pulmonary disease (including asthma), immunosuppression (e.g., related to cancer, hematopoietic cell or solid organ transplant, high doses of GC), endocrine disorders (e.g., diabetes mellitus) and neurologic and neurodevelopmental conditions (e.g., cerebral palsy, spinal cord injury)[6].

It remains unknown whether children and young people with inflammatory diseases who acquire COVID-19 have a more severe course and if there is an additional risk due to either underlying diseases or its treatment. Besides, the COVID-19 pandemic may have consequences on the course of RMD in pediatric patients, concerning the follow-up of these patients and the possible worsening of the underlying diseases. Thus, the Paediatric Rheumatology European Association (PReS) recommends that pediatric rheumatic patients should be vaccinated against COVID-19 using vaccines approved for children in this age group[14].

In Portugal, the Covid-19 vaccination started in December 2020. Vaccination for adolescents aged 12 or more years under immunosuppression with biologic therapy or therapy equivalent to prednisolone >20mg/day started in April 2021 (second phase of vaccination). For all the other adolescents, the Covid-19 vaccination started in August 2021. Children with 5-11 years started being vaccinated in December 2021, with priority for children with increased risk pathologies, like immunosuppression. Due to high vaccination rates in adults, the highest COVID-19 incidence is now seen in children and adolescents.

We intended to assess the epidemiological features and clinical outcomes of Portuguese children and young people followed in pediatric rheumatology clinics who had a SARS-CoV-2 infection.

METHODS

A multicenter prospective observational study including 10 Portuguese centers was performed.

Data regarding children and young people <19 years of age with inflammatory chronic diseases and evaluated at pediatric rheumatology clinics at the time of detection of SARS-CoV-2 infection was obtained between March 2020 and September 2021, using the Rheumatic Diseases Portuguese Register (Reuma.pt) and complemented with data from the hospital clinical records. Patients' information including gender, age, inflammatory disease diagnosis, disease activity before and after the infection and comorbidities was collected. Physicians indicated the diagnostic method and the transmission mechanism. The definition of the disease activity was defined by patients attending physician. Medications before the infection were categorized as conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologic DMARDs (bDMARDs). The patients' symptoms and SARS-CoV-2 infection evolution were registered. COVID-19 disease severity was classified as mild (no hospitalisation required), moderate (required hospitalisation) or severe (required admission at Intensive Care Unit or mechanical ventilation support).

Categorical variables were presented by their absolute and relative frequency, while continuous variables were presented using the median and quartiles of distribution.

The Reuma.pt registry requires signed informed consent/assent. The registry was approved by the Portuguese Data Protection Authority (CNPD) and by the

ethics committees of the participating institutions. This study was approved by the ethics committee of Lisbon Academic Medical Centre.

RESULTS

The demographic and clinical characteristics of patients are shown in Table I.

Thirty-four patients were included, 21 (62%) were female, with a median age of 13 [8-16] years and a median time of the inflammatory disease diagnosis of 6 [3-10] years.

The most common diagnoses were juvenile idiopathic arthritis (n=22, 64.7%), juvenile dermatomyositis (n=3, 8.8%), idiopathic uveitis (n=3, 8.8%) The other diagnoses were undefined auto-inflammatory syndrome (n=2, 5.9%), IgG4-related disease (n=1, 2.9%), Kawasaki disease (n=1, 2.9%), chronic nonbacterial osteomyelitis (n=1, 2.9%)and rheumatic fever (n=1, 2.9%).

Five patients were considered in low disease activity by their attending physician: 2 with Juvenile idiopathic arthritis (JIA), 1 with Juvenile dermatomyositis (JDM), 1 with auto-inflammatory syndrome and 1 case of uveitis and all the other patients were considered in remission at the time of the infection.

The COVID-19 diagnostic test more commonly used was polimerase chain reaction (PCR) (n=28, 82%), 1 patient had a positive antigen test, 1 other patient had a positive serology test and 4 patients had a presumptive diagnosis based on symptoms and epidemiological context. Regarding transmission pathway: twenty-one patients had a relative or a friend infected (62%), in 1 cases, the transmission occurred in the healthcare setting (3%) and 12 (35%) had an unknown transmission mechanism.

Seven patients were asymptomatic, and 27 patients had symptoms (79.4%). All symptomatic patients had mild symptoms and those are shown in Figure 1.

As expected, cough was the most frequent symptom reported followed by fever.

Non-specific symptoms like headache, fatigue and malaise were common. Gastrointestinal symptoms were rarer but also described.

JDM patients did not report myalgias. The patient that reported arthralgias had a JIA diagnosis and low disease activity at the time of the infection, so we cannot be sure about the etiology of the joint pain. No patient reported dyspnea.

Twenty patients were on csDMARDs and 10 were on bDMARDs. In 8 patients there was a change in the baseline medication during the infection: 4 patients suspended and 1 reduced bDMARDs, 4 suspended and 2 reduced csDMARDs.

One patient with JDM, receiving prednisolone 5mg/day, mycophenolate mofetil, hydroxychloroquine, intravenous immunoglobulin, and adalimumab, discontinued all medication for almost one month, without clinical indication. He had a mild SARS-CoV-2 infection and there was an exclusive worsening of the cutaneous disease activity. All the other patients returned to the usual medication at the usual dosage and there was no other record of a further worsening of underlying diseases.

Most patients did not have blood tests at the time of the infection. Of those who had (n=12), only 3 patients had abnormalities. Two cases of alanine aminotransferase (ALT) mild elevation (41 and 52, Reference value (RV) <33U/L) and one case of lymphopenia ($0.81x10^9$/L, RV 1-5 $x10^9$/L) and LDH elevation (309 U/L, RV 100-250 U/L). The analytical changes were clinically not significant.

There were no severe cases registered like pneumonia, Multisystem Inflammatory Syndrome (MIS-C) and

Table I. Demographic and clinical characteristics of patients with an inflammatory disease and SARS-COV-2 infection evaluated at pediatric rheumatology clinics

Demographic data	N (%)
Female	21 (62%)
Caucasian	33 (97%)
Age (years) Median (IQR)	13 [8-16]
Time of inflammatory chronic disease diagnosis (years) Median (IQR)	6 [3-10]
Inflammatory chronic disease diagnosis	
Juvenile idiopathic arthritis (JIA)	22 (64.7%)
Juvenile dermatomyositis (JDM)	3 (8.8%)
Idiopathic uveitis (IU)	3 (8.8%)
Undefined auto-inflammatory syndrome	2 (5.9%)
IgG4-related disease	1 (2.9%)
Kawasaki disease	1 (2.9%)
Chronic nonbacterial osteomyelitis	1 (2.9%)
Rheumatic fever	1 (2.9%)
Comorbilities	
Asthma	1 (2.9%)
Allergic rhinitis	1 (2.9%)
Celiac disease	1 (2.9%)

IQR: interquartile range; JIA: Juvenile idiopathic arthritis; JDM: Juvenile dermatomyositis; IU: Idiopathic uveitis

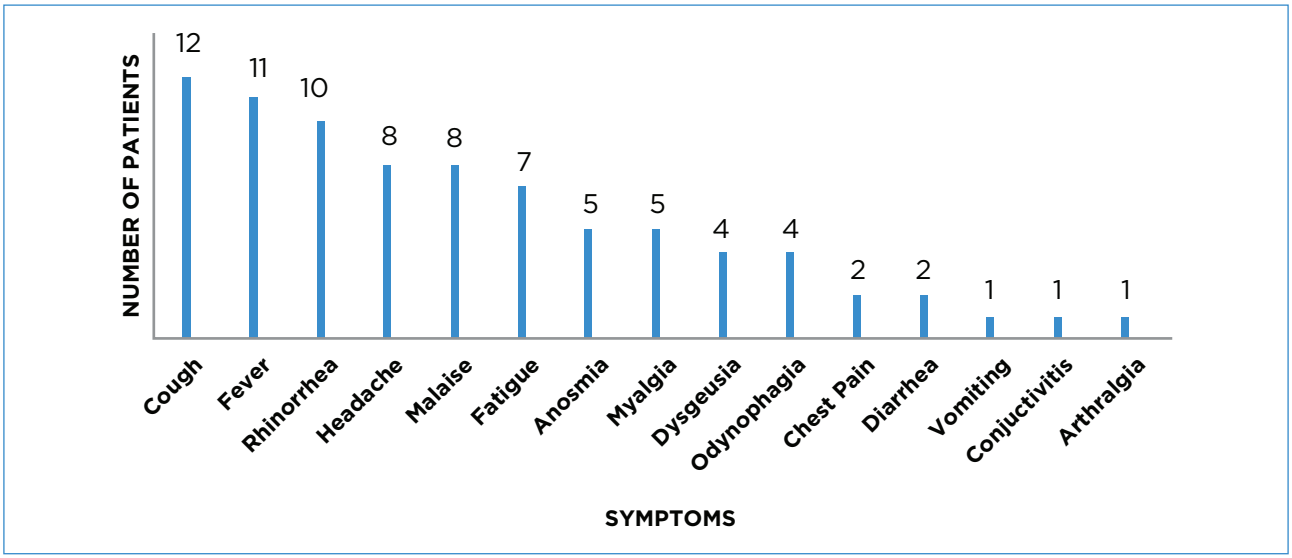

Figure 1. Symptoms identified in patients with inflammatory disease and COVID-19 infection

long Covid during the time of follow-up (median time of 8 [6-10] months). No patient required hospitalization or directed treatment and all patients recovered without sequelae.

DISCUSSION

We report a cohort of 34 children and young people with RMD or uveitis and with SARS-CoV-2 infection. JIA was the most frequent diagnosis. The majority of this population had a well-controlled disease before the SARS-CoV-2 infection.

Seventy-nine percent of patients were symptomatic and all reported mild symptoms. The percentage of symptomatic patients was similar to other cohorts[15,16]. The most frequent symptoms found were cough and fever, similar to several meta-analyses in adults and children[6,16,17]. Upper airway symptoms, as rhinorrhea, were also common. According to literature, despite being predominantly a respiratory virus, unlike adults, SARS-CoV-2 causes gastrointestinal symptoms in approximately 10% of infected children (18). Although less frequently our patients also reported diarrhea and vomiting. Anosmia, fatigue and headache were more frequent in our patients than expected and reported in other cohorts[18]. Arthromyalgias described don't seem to relate to RMD. Most patients had epidemiological contact history, mostly with family members, which is also predominant in other cohorts[6,19].

In the general pediatric population white blood cell count is normal, but leukopenia may be seen, with decreased lymphocyte count. C-reactive protein (CRP) may be increased and Procalcitonin (PCT) > 0.5 ng/mL might be a sign of secondary bacterial infection. Elevation of liver enzymes, muscle enzymes and increased level of D-dimer can be seen in severe cases[20]. However, these clinical markers alone are non-specific. In our study, most patients had no blood tests at the time of the infection and of those who had most did not present significant alterations.

Although the pandemic may have contributed to a less regular follow-up, our pediatric patients kept their underlying inflammatory disease under control, as we can see with most patients at remission at the time of the infection.

The American College of Rheumatology (ACR) published recommendations for the management of pediatric rheumatic diseases during the pandemic. The recommendations were selected by a task force based on their clinical expertise and review of the available literature[21]. According to the ACR task force, in symptomatic disease, csDMARDs and bDMARDs should be temporarily withheld, except hydroxychloroquine and IL-1 inhibitors that may be continued to control underlying disease, and glucocorticoids should be continued, with an effort to reduce the dose to the lowest dose possible. All our patients who changed the baseline medication had symptomatic disease, but most symptomatic patients didn't change the usual medication and no severe cases were registered. Reinitiating medication in severe cases of COVID-19 should be determined on a case-by-case basis, but in mild disease, therapeutics with csDMARDs and bDMARDs may be restarted 7-14 days after resolution of fever and respiratory symptoms to avoid the worsening of the underlying disease. Patients with asymptomatic SARS-CoV-2 infection may continue therapeutics with csDMARDs and bDMARDs and glucocorticoids should be continued, using the lowest dose possible to control RMD. Like previous registries of SARS-CoV-2 infections (22), in our cohort, pediat-

ric patients had a good prognosis. There was no need for hospitalization or specific treatment and the maintenance of their usual therapeutics does not seem to have influenced the outcome. This study supports the idea that in, mild infections, the maintenance of usual therapy should be considered, and, in asymptomatic disease, keeping the usual therapeutics could be the best option.

This study has limitations related to the small number of patients included. Comorbidities such as obesity could have been underreported and there were few laboratorial tests in most cases.

We had no data regarding the vaccination status of our patients. We also didn't have information about possible SARS-CoV-2 variants involved, but at the time of this study, four variants classified by the WHO as of concern (Alpha, Beta, Gamma and Delta) were present in Portugal with community transmission and there were still no cases of the Omicron variant.

A long-term follow-up of these patients may reveal sequels associated with the infection and changes in the activity of theinflammatory disease, especially to those who had an infection at the end of the cut-off date.

CONCLUSIONS

Understanding the impact of a SARS-CoV-2 infection on children and young people with inflammatory chronic diseases is essential for their clinical management, including recommendations regarding medication and the prioritization for vaccines. Knowing the risks can also define the best way to manage their school and social life.

This manuscript describes the first collection of SARS-CoV-2 infection among Portuguese pediatric patients with RMD and uveitis. Mild illness was predominant in our patients, which is consistent with the literature.

Additional studies are needed on this topic to corroborate findings and establish the individual risk associated with the use of the various classes of DMARDs, as well as the long-term effects of SARS--CoV-2 in a pediatric population.

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