The impact of COVID-19 pandemic on pediatric rheumatology patients under immunosuppressive therapy: A single-center experience

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Research Article

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Abstract

Objective: The aim of the research was to further broaden current knowledge of whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (COVID-19) entails a risk for children with rheumatic diseases regarding immunosuppressive treatment.

Methods: Telephone-survey was administered by conducting interviews with the parents. A message containing a link to the actual questionnaire was sent to their phones simultaneously. The medical records of the patients were reviewed for gathering information about demographic data, clinical follow-up, and treatments.

Results: Patients who were followed up with immunosuppressive treatment (n=439) were attempted to be contacted between 1 May 2020 and 15 May 2020. The diagnostic distribution of patients who were accessible and eligible for the study was as follows; juvenile idiopathic arthritis (JIA) (n=243, 58.7%), autoinflammatory diseases (n=109, 26.3%), autoimmune connective tissue diseases (n=51, 12.3%) and vasculitis (n=11, 2.7%). In the entire cohort, the mean age was 12 ± 4.7 years, and 54.1% (n=224) of the patients were female. One patient with seronegative polyarticular JIA, previously prescribed methotrexate and receiving leflunomide during pandemic has been identified to be diagnosed with COVID-19. None of the patients, including the patient diagnosed with COVID-19, had any severe symptoms. More than half of the patients with household contacts required hospitalization as they were asymptomatic.

Conclusion: Although circumstances such as compliance in social distancing policy, transmission patterns, attitude following contact may influence the results, immunosuppressive treatment does not seem to pose additional risk in terms of COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (COVID-19) emerged in the Wuhan region of China in December 2019 swept the world in a few months and became a global health emergency of primary international concern and was officially approved as a pandemic by the World Health Organisation (WHO)[1]. While the repercussions of the coronavirus continue throughout the world, we are faced with devastating impacts on social life, education, and economy. Unfortunately, it also disrupted the health care system by delaying the treatment plans of patients at the stage of diagnosis and causing hitches in the visits of patients struggling with chronic diseases.

The substantial infectivity, source and transmission ways, age and gender-related discrimination, broad clinical spectrum, and complex etiopathogenesis of COVID-19 led to tricky questions and debates worldwide [2]. The similarities at clinical and molecular levels with previously encountered coronavirus types and the published data from severe acute respiratory syndrome (SARS; 2002) and Middle East respiratory syndrome (MERS; 2012) outbreaks acted as a guide in the early periods of the struggle and constituted the backbone of the current therapeutic strategy [3]. However, the growing knowledge about the pathogenesis of COVID-19 and associated cytokine storm syndrome, namely multisystem inflammatory syndrome suggests a new treatment approach with targeted therapy to manage the uncontrolled spread of the infection and inflammation [4, 5].

During the COVID-19 pandemic, several drugs already with essential roles in rheumatology practice emerged as promising treatment alternatives with encouraging results. On the other hand, dysregulation of innate immunity and virus-host interactions in the etiopathogenesis serve a major concern for patients in an immunosuppressive state or under immunosuppressive treatment [6, 7]. In the light of this evidence, several questions raised regarding the management of patients with rheumatic disease in terms of drug selection, initiation, continuation or withdrawal, appropriate dose adjustments and likely problems in drug supply [6-10]. Current guidelines have attempted to draw a common path, but several epidemiological studies are undoubtedly needed. This study set out to determine whether COVID-19 showing a milder course in children entails a risk for patients with rheumatic diseases regarding immunosuppressive therapy, either nonbiologic disease-modifying anti-rheumatic drugs (nbDMARDs) or biologic disease-modifying anti-rheumatic drugs (bDMARDs).

Methods

Study Design

In order to find out how the COVID-19 pandemic influences the patients receiving immunosuppressive therapy for rheumatic diseases, telephone-survey was administered by conducting interviews with the parents. A message containing a link to the actual questionnaire was sent to their phones simultaneously. Only parents were accepted as responders. The medical records of the patients were reviewed for demographic data, clinical follow-up, and treatments.

Subjects and Data Collection

Patients with rheumatic diseases who were between 0-20 ages, under immunosuppressive therapy and followed up at the Pediatric Rheumatology Department in Istanbul Medical Faculty were classified according to their diagnosis and treatment modalities. Patients with incomplete medical data and those whose parents were unable to communicate via phone or refused to participate were excluded from the study.

Patients were called by phone to provide one-on-one communication and be informed about the research. Approval was obtained whether they would participate in the study or not. Sociodemographic data, disease-related information (disease duration, length of the treatment, current medication, disease status at the last visit, comorbidity, and concomitant drugs) were assessed.

The immunosuppressive anti-rheumatic drugs were categorized into the following active ingredient groups:

Nonbiologic DMARDs (methotrexate, leflunomide, mycophenolate mofetil, azathioprine, cyclophosphamide, hydroxychloroquine, sulfasalazine);

Biologic DMARDs (etanercept, adalimumab, infliximab, tocilizumab, anakinra, canakinumab, abatacept, rituximab);

Janus Kinase (JAK) Enzyme Inhibitors (tofacitinib).

Systemic steroids and intravenous immunoglobulin (IVIG) used within the past six months were stated. Comorbid diseases and drugs were noted. Whether the patients required tuberculosis prophylaxis or treatment, status of Bacillus Calmette-Guerin (BCG) vaccination and presence of scar formation were questioned and checked from their medical records.

Content of the Survey

Topics related to the COVID-19 in the survey were:

Symptoms (fever, non-productive cough, sputum production, sore throat, rhinorrhea, fatigue, arthralgia, myalgia, anosmia, dysgeusia, dyspnea, headache, nausea, vomiting, diarrhea, rash),

Attendance at a hospital with a suspicion of COVID-19,

Diagnostic tests or imaging modalities performed for COVID-19 (pharyngeal swab COVID-19 nucleic acid test (PCR), chest X-ray or computed tomography (CT)),

History of contact with confirmed or suspected cases of COVID-19,

A healthcare worker in the family,

Confirmed diagnosis in the patient, family or relatives,

The presence of anti-rheumatic drug interruption during the outbreak and the reason for discontinuation were recorded.

Statistical Analysis

Statistical analyses were performed by using the IBM SPSS Statistics for Windows 21.0 software. Kolmogorov-Smirnov (KS) normality test was used to analyze the distribution of the variables. Mean values with standard deviations (mean±SD) or median (med) with minimum and maximum values (min-max) were given for demonstration of the data according to the distribution. Categorical variables were presented as counts or frequencies.

Ethics

Approval was obtained for the study from the Ethics Committee (approved: May2020-62254).

Results

Demographic and Clinical Characteristics of Patients

Patients followed-up with immunosuppressive treatment (n=439) were surveyed between 1 May 2020 and 20 May 2020. The response rate was 94.3%. In the entire cohort, the mean age (at the study) was 12 ± 4.7 years, and 54.1% (n=224) of the patients were female. The median disease duration was 45 (3-221) months. The diagnostic distribution of patients was as follows; juvenile idiopathic arthritis (JIA) (n=243, 58.7%), autoinflammatory diseases (n=109, 26.3%), connective tissue diseases (n=51, 12.3%) and vasculitis (n=11, 2.7%). In our cohort, two patients had interstitial lung diseases, one with a diagnosis of scleroderma and one with sarcoidosis.

Immunosuppressive treatment was terminated within six months in 14.5% of the patients (n=60). According to their current treatment, 42.3% (n=175) of these patients were receiving bDMARDs, 28.7% (n=119) were on nbDMARDs, 14.5% (n=60) were using both. During the last six months, 18.6% (n=77) of the patients received systemic steroids as a bridging therapy or during a flare combined with other therapies.

The majority of the cohort consisted of patients diagnosed with JIA. Table 1 presents the demographic and clinical characteristics of the patients.

The distribution of the patients with autoinflammatory diseases was as follows; colchicine-resistant familial mediterranean fever (FMF) (n=70, 64.2%), cryopyrin-associated periodic syndrome (CAPS) (n=13, 11.9%), hyper immunoglobulin D syndrome (HIDS) (n=7, 6.4%), tumor necrosis factor receptor associated periodic fever syndrome (TRAPS) (n=6, 5.5%), chronic recurrent multifocal osteomyelitis (CRMO) (n=8, 7.3%), synovitis, acne, pustulosis, hyperostosis, osteitis syndrome (SAPHO) (n=3, 2.8%), juvenile sarcoidosis (n=2, 1.8%). The median age in this group was 11 (4-20) years and 54.1% (n=59) of the patients were female. The median disease duration was 55 (9-173) months. Six (5.5%) had an inflammatory episode in the preceding 6 months. Duration of immunosuppressive treatments was as follows; canakinumab (n=84, 77.1%) for 16 (2-75) months; anakinra (n=81, 74.3%) for 3 (1-24); methotrexate (n=13, 11.9%) for 16 (3-48); etanercept (n=5, 4.6%) for 12 (8-48) and infliximab (n=1, 0.9%) for 9 months. Concomitant use of colchicine was noted in 89 patients (81.7%).

The subgroups of the patients with connective tissue diseases were as follows; systemic lupus erythematosus (SLE) (n=21, 41.2%), scleroderma (n=16, 31.4%), juvenile dermatomyositis (JDM) (n=11, 21.6%), mixed connective tissue disease (MCTD) (n=3, 5.9%). The median age in this group was 13 (4-20)

years and of 76.5% (n=39) were female. The median disease duration was 41 (4-101) months. The duration of immunosuppressive treatments was methotrexate (n=29, 56.9%) for 20 (2-36) months; mycophenolate mofetil (n=24, 47.1%) for 14 (2-48); azathioprine (n=14, 27.5%) for 12 (5-20); tofacitinib (n=3, 5.9%) for 5 (3-10) months. Concomitant use of hydroxychloroquine was noted in 30 patients (58.8%). Three (5.9%) were treated with six cycles of cyclophosphamide in the past year. Five (9.7%) received intravenous immunoglobulin therapy in the past 6 months.

The group of subjects with vasculitis consisted of patients diagnosed with Behçet's Disease (n=8), Takayasu arteritis (n=2), and Polyarteritis Nodosa (PAN) (n=1) with a median age of 16 (11-20) years. Seven (63.6%) were male. The median disease duration was 41 (3-125) months. The duration of immunosuppressive treatments was azathioprine (n=9, 81.8%) for 10 (2-36) months; mycophenolate mofetil (n=1, 9.1%) for 8 months; methotrexate (n=2, 18.2%) for 14.5 (9-20); etanercept (n=1, 9.1%) for 16 months and infliximab (n=2, 18.2%) for 6.5 (5-8) months. Concomitant use of colchicine was noted in 10 patients (90.9%). Four (36.4%) patients had an infusion of cyclophosphamide in the past year.

In the entire cohort, 25.4% (n=105) of the patients had comorbid conditions as uveitis (n=34, 8.2%), proteinuria (n=17, 4.1%), inflammatory bowel disease (n=4, 1%), heart diseases (n=4, 1%), thyroid disease (n=5, 1.2%) and epilepsy (n=1, 0.2%). Forty were concomitantly diagnosed with FMF aside from the rheumatic diseases. Angiotensin-converting enzyme (ACE) inhibitors (n=16, 3.9%), thyroid hormone therapy (n=3, 0.8%), antiepileptics (n=1, 0.2%) were the drugs used concurrently.

In the entire cohort, 366 patients (88.4%) have been BCG vaccinated, and scar formation was present. Ninety-six patients (23.2%) have received prophylactic tuberculosis therapy.

The Survey Results

All subjects who consented completed the survey and answered all questions accurately on the phone. Table 2 details the survey results. In our cohort, we identified one confirmed case of COVID-19. Medical records of the patient during the pandemic period were examined. Nine patients attended to the hospital for COVID-19 evaluation, 6 of whom were in close contact with confirmed cases (Table 3).

Case Description

The case with COVID-19 was a 14-year-old female diagnosed with seronegative polyarticular JIA nine months ago. Initially, she received methotrexate for 3 months and due to gastrointestinal adverse reactions, leflunomide was introduced for the past 8 months. Active joint involvement or articular damage was not present at the last appointment. There was no history of bDMARD use or comorbid disease. She was vaccinated with BCG during childhood and had no history of treatment or prophylaxis for tuberculosis.

In the 3rd week of April, her father and uncle had a diagnosis of COVID-19 requiring hospitalization. On the 4th day of household contact, she developed sudden onset of fever up to 38°C, non-productive cough, and fatigue. She also complained of anosmia and dysgeusia. On hospital admission, she was well-appearing with normal vital signs. Laboratory evaluation revealed slightly elevated inflammatory markers. Chest X-ray showed minimal pulmonary infiltrates within the lung parenchyma, chest CT was normal. The diagnosis of COVID-19 was confirmed by a history of contact, consistent clinical features, and a positive PCR test. She was treated with hydroxychloroquine and a 5-day course of azithromycin for potential respiratory tract infection. She fully recovered after the treatment and control PCR turned negative.

Discussion

In our cohort, consisting of patients who received nbDMARDs and bDMARDs for various rheumatic diseases, one patient who had a history of household exposure had been diagnosed with COVID-19. In the pandemic period, none of the patients in our cohort have experienced a severe health condition, including the one diagnosed with COVID-19 who recovered with an uncomplicated course.

Similar to the previous coronavirus outbreaks, SARS-CoV-2 infection seems to influence children less prevalently, and the course of the disease appears to be milder as compared with adults [11-14]. Although there is no clear-cut explanation, some relevant speculations have been asserted. Since children are different from adults in several aspects, such as immune defense functions against viruses, they have a distinctive feature of eliminating the viral disease [12]. Differences in expression and function of ACE-2 receptor, playing a crucial role in the invasion capacity of COVID-19, sets precedent relevancy to the issue [12, 14-16].

Another point is that children do not seek medical attention as they overcome the disease, usually without demonstrating any sign or symptom [13, 17]. Correspondingly, more than half of our patients with household contacts were not brought to a hospital as they were asymptomatic. Unfortunately, given its spreading potential, this may hinder the detection and management of the disease and thereby promote the spread of the infection. During the interview, when this point was mentioned, parents stated that they strictly adhered to home-based quarantine rules and social distancing policy. Psychosocial distress, the fear of social stigma, or lack of awareness of the possible consequences of the pandemic may be the other likely reasons keeping them from seeking medical help.

In epidemiological studies, sample size is small due to the rarity of the infection in children, but the data presented is mainly parallel. The most common symptoms are fever and dry cough, as in adults [11, 13, 18, 19]. Gastrointestinal symptoms may also accompany mostly in children [7, 20]. When our patients were asked about the complaints, it was noticed that the musculoskeletal system symptoms were in the foreground. Since similar complaints are met in the course of rheumatic diseases, the hospital attendance rate was low among patients who had complaints such as arthralgia, myalgia, and fever during the pandemic process and without history of contact.

The current epidemiological studies show that children primarily contract the disease through household exposure, but rarely vice versa [19-21]. The incubation period may differ in adults and children, making it challenging to identify the primary source [22]. In our case, the virus was transmitted from father or uncle. The prevalence of the disease in adults seems to be a significant reason for the parents being the index case of the infection in the family. On the other hand, children's social ecologies and the probability of contact with contamination sources can concretize the difference. They generally grow and develop within a familiar circle nested by their family and relatives. In our cohort, the disease was not detected in other households contacted patients supporting the claim that children are less likely to become infected. On the contrary, several sources suggest children are just as likely as adults to become infected but are less likely to be symptomatic or develop severe symptoms [12, 17, 19]. Further research is required to better understand notable differences observed by age.

In general, as still developing organisms, children may be more susceptible to some infections. Especially those with immunocompromised states are vulnerable to various viral or bacterial agents (such as tuberculosis) and may encounter a more severe disease course [23, 24]. Hence, the screening of the patients, particularly those receiving nbDMARDs and bDMARDs, for such common infections is a part of a routine in pediatric rheumatology practice. Novel coronavirus demonstrating high morbidity and mortality worldwide has raised substantial concern for the patients with immune-related conditions and subspecialties as rheumatology dealing with their management [24, 25]. In our cohort, 14.3% of the patients interrupted their medications during the pandemic period. The conspicuous reason was that patients treated with infusion therapy or who used drugs in subcutaneous form could not provide access to health institutions. Noteworthy was the concern that treatment would increase the risk, as expected. These results underline the importance of patient-doctor communication throughout the patient's entire treatment process. Current evidence suggests not withdrawing the immunosuppressive treatment and no need for additional dose adjustment during the pandemic process unless physician indication or presence of specific symptoms [7, 8, 15, 24-26]. Although current guidelines, yet available online, relevant to the topic are mostly based on adult series, they served as an essential guide to elucidate multiple issues yet not resolved in this field [9, 27, 28]. However, considering the mentioned differences between children and adults, there is a need for evidence focusing primarily on pediatric rheumatology patients and identifying high-risk individuals.

Some preliminary work was carried out in the early period of the pandemic from jeopardous regions to investigate the association between SARS-CoV-2 and immunosuppressive drugs. In a report from Italy on adult patients with chronic arthritis treated with DMARDs, there was no increased risk of respiratory or life-threatening complications among the confirmed and suspected cases [29]. Another report presented from one of the most affected regions in Italy reported that there were no confirmed or suspected cases of COVID-19 in 123 children with rheumatic diseases (the majority of JIA) on bDMARDs treatment [30]. In another report from the same region of Italy, among 530 patients, 54 of whom were children, three confirmed cases with mild symptoms were notified, and it was underlined that the compliance of the social distancing might be reflected in the results [31]. Among the patients in our cohort, 18 were close contacts who have been socially interacted with the confirmed cases of whom 17 were with household members. Of the patients with a history of contact, three developed symptoms, and only one was diagnosed with COVID-19. Because all of the contact patients had not been tested, a definite ratio of the diagnosis was hard to be given, still it was obvious that the infection has not caused any severe symptoms or complications in any patient. The limited resources available indicate that rheumatic diseases, generally heterogeneous and associated with immune dysregulation, and various immunosuppressive drugs used in the treatment do not pose a risk for COVID-19. Our study supported this issue.

Another link between the field of rheumatology and the current pandemic is the shared drugs commonly used in rheumatology and recently included in the management of COVID-19 [25, 32]. Novel researches, presenting a better understanding of the immune mechanisms with cytokine networks in the process of SARS-CoV-2, started to illuminate the etiopathogenetic patterns as well as the treatment [4, 16, 33]. In the light of in vivo and in vitro studies, antiviral effects of some antirheumatic drugs came to the fore in the process [33-36]. In our patients receiving hydroxychloroquine therapy, we neither encountered an exacerbation associated with current autoimmune diseases nor a severe impact of the pandemic. However, in other respects, the alliance caused a shortage of drug supply for rheumatology patients within the early period of the pandemic [37, 38] also for 14 patients of our cohort. Comparative studies with large populations are needed to mention its potency and protective role in the pandemic.

The only case diagnosed with COVID-19 in our cohort has been using leflunomide, which is another nbDMARDs that have been demonstrated to have antiviral capacity, particularly against *cytomegalovirus* and *herpes simplex-1* [36, 39]. Nevertheless, leflunomide is not one of the drugs shining in the strategy against COVID-19 [36].

Glucocorticoids and IVIG, which are used in many fields of medicine and are frequently used in rheumatology, are the first remedies for COVID-19, but have failed to take part in routine use [6, 25]. The fact that glucocorticoids may increase virus replication on one hand, and have potent anti-inflammatory effects, on the other hand, led to a contradiction in pandemic and this controversy extends to the management of chronic patients already under glucocorticoid therapy [25, 36]. When we go back over our data, there were no active usages of steroid or IVIG among the contacted patients. More studies related to the follow-up and management of these patients are required.

Biologic DMARDs selectively blocking inflammatory cytokines, such as TNF- α inhibitors, anti-IL6, anti-IL1, and JAK inhibitors, represents a milestone in the treatment of inflammatory rheumatic disorders. Given the similarities of the cytokine storm syndromes, these drugs gained prominence in the era of SARS-CoV-2 [24, 36, 40, 41]. Particularly tocilizumab is a candidate to be indispensable treatment approach in the management of severe disease [25, 42]. In our cohort, an 11-year-old male patient with sJIA under tocilizumab treatment who had a history of contact with a confirmed case remained asymptomatic, and the PCR result was negative. At a large adult cohort from Italy, one of the two cases with COVID-19 was using tocilizumab. In this report, the role of biological agents in acute respiratory distress syndrome was emphasized, and it was pointed out that this patient might lack immune triggers [43]. Even though the experiences from rheumatology patients on tocilizumab therapy have been a guide, it has not yet been possible to consider their place in the risk cluster.

The countries with the inclusion of BCG vaccination in their national vaccination programs were considered to be shown a lower contagion and mortality rate, suggesting that the vaccine may induce trained immunity for SARS-CoV-2 [44]. Since our country is one of the regions where BCG is routinely administered,

most of the patients in our cohort (88.4%) were vaccinated. Besides, the patients are regularly screened for tuberculosis before and throughout biological treatment. There is no definitive proof of causality that justifies the protective role of BCG vaccination [45]. Moreover, one should not overlook the differences in demographic, social and genetic structure of the populations while assessing the link to BCG and COVID-19.

Comorbid conditions such as diabetes mellitus and cardiovascular diseases have been associated with an increased risk in the course of SARS-CoV-2 [13]. Although rarely seen in children, we questioned comorbid conditions and drugs in our patients to evaluate our results justly. Close contacts in our cohort had no comorbid conditions in addition to rheumatic diseases. ACE inhibitors were used concurrently with antirheumatic drugs in some of our patients. Select hypothetical claims have been mooted considering the role of ACE-2 enzyme in the etiopathogenesis of SARS-CoV-2. Patients with diabetes mellitus or hypertension using ACE-inhibitors or angiotensin receptor blockers have been found to have an increased risk regarding the severity of COVID-19 [46]. The assertion was not supported as it was based on incomplete experimental evidence, and it was strongly emphasized that patients using these drugs should continue their treatment [47].

Conclusion

While the link between anti-rheumatic drugs and SARS-CoV-2 was on the table, we presented our experience by in-depth research with the largest cohort yet reported, consisting of children with rheumatic diseases under immunosuppressive therapy. Although circumstances such as compliance in social distancing policy, transmission patterns, attitude following contact may influence the results, immunosuppressive treatment does not seem to pose an additional risk. On the contrary, abrupt withdrawal of these drugs may lead to clinical instability, exacerbation of the underlying disease, and worse consequences. Moreover, one should be alert in terms of triggering disease exacerbations related to COVID-19. What is now needed is a cross-national study involving larger populations and assessing the long-term effects and safety profiles of the mentioned drugs on agenda topics.

Tables

TABLE 1. Demographic and Clinical Manifestations of Patients with Juvenile Idiopathic Arthritis

Age at the study (years), med (min-max)	12.5 (2-20)	
Gender, n (%)		
Female	124 (51)	
Male	119 (49)	
Disease duration (months), med (min-max)	42 (4-221)	
Subtype of JIA, n (%)		
Oligoarthritis	82 (33.7)	
Seronegative Polyarthritis	50 (20.6)	
Seropositive Polyarthritis	12 (4.9)	
Psoriatic Arthritis	12 (4.9)	
Enthesitis-Related Arthritis	62 (25.5)	
Systemic-onset JIA	25 (10.3)	
Disease activity state according to JADAS-27 at the last visit (mean $\pm$ SD) (range)	2.2 $\pm$ 4.9 (0-20)	
Nonbiologic DMARDs		
Type n (%), Duration med (min-max) (months)		
Methotrexate	226 (93),	18 (2-114)
Leflunomide	41 (16.9),	12 (5-60)
Sulfasalazine	53 (21.8),	6 (1-24)
Hydroxychloroquine	3 (1.2),	4 (3-4)
Biologic DMARDs		
Type n (%), Duration med (min-max) (months)		
Etanercept	97 (39.9),	14 (2-60)
Adalimumab	54 (22.2),	12 (2-36)
Infliximab	4 (1.6),	11 (3-24)
Tocilizumab	35 (14.4),	14 (3-76)
Anakinra	12 (4.9),	4 (1-8)
Canakinumab	8 (3.3),	24 (6-36)
Abatacept	4 (1.6),	16 (9-18)
JAK enzyme Inhibitors		
Type n (%), Duration med (min-max) (months)		
Tofacitinib	1 (0.4),	3 months

DMARDs: Disease-Modifying Anti-rheumatic Drugs, JAK enzyme Inhibitors : Janus Kinase Enzyme Inhibitors, JADAS:Juvenile Arthritis Disease Activity Score
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TABLE 2. Telephone Survey Results Related COVID-19 Pandemic

Analyzing Survey Data	Results, n(%)
COVID-19 related symptoms	
Fever	20 (4.8)
Non-productive cough	8 (1.9)
Sputum production	-
Sore throat	9 (2.2)
Rhinorrhea	3 (0.7)
Fatigue	8 (1.9)
Arthralgia,	49 (11.8)
Myalgia	15 (3.6)
Anosmia/dysgeusia	3 (0.7)
Dyspnea	1 (0.2)
Headache	-
Nausea/vomiting	2 (0.5)
Diarrhea	8 (1.9)
Rash	4 (1)
A healthcare worker in the family (household contact)	9 (2.2)
Confirmed diagnosis in the family (household contact)	17 (4.1)
Confirmed diagnosis in relatives or neighbors living in the same apartment	63 (15.2)
History of contact with confirmed cases of COVID-19 (clearly stated)	18 (4.3)
Attendance at a hospital emergency department with suspicion of COVID-19	9 (2.2)
History of contact	6
Chest X-ray performed for COVID-19	6 (1.4)
History of contact	4
Consistent with COVID-19	1
Computed tomography performed for COVID-19	4 (0.9)
History of contact	3
Consistent with COVID-19	-
Pharyngeal swab COVID-19 nucleic acid test	9 (2.1)
History of contact	6
Positive for COVID-19	1
Treatment interruption during the outbreak	59 (14.3)
Reason for discontinuation of treatment	
Inadequate Access to Health Care	29 (49.2%)
Concern about increased risk	16 (27.1%)
Shortage of medication	14 (23.7%)

TABLE 3. Patients attending at a hospital emergency department with suspicion of COVID-19

Attendance at a hospital (n=9)	Rheumatic Disease	Disease Duration (months)	Comorbid Diseases	Current Treatment	BCG Status	Treatment Interruption	Symptoms	Contact History	Chest X - ray (n=6)
15-y M	oJIA+FMF	41	–	Methotrexate, Etanercept, Colchicium	neg	no	asymptomatic	Mother	–
16-y M	ERA+FMF	85	–	Adalimumab, Colchicium	pos	no	fever,arthralgia,myalgia	no	normal
11-y M	SoJIA	54	–	Tocilizumab	pos	no	asymptomatic	cousin	normal
16-y F	RF+PoJIA+FMF	90	–	Abatacept, Leflunomide	pos	no	cough	no	normal
17-y M	ERA	64	–	Adalimumab	pos	no	fever, sore throat	father	normal
14-y F	RF-PoJIA+FMF	9	–	Leflunomide	pos	no	fever,cough,fatigue, anosmia,dysgeusia	father,uncle	suspicious infiltrates
13-y F	FMF	77	–	Canakinumab	pos	yes, inadequate access to health care	fever, arthralgia	no	–
10-y M	CAPS	89	–	Canakinumab	pos	no	arthralgia	mother	–
12y-F	FMF	78	–	Canakinumab	pos	yes, inadequate access to health care	asymptomatic	father,brother	normal

BCG: Bacillus Calmette-Guerin, CT: computed tomography, PCR: pharyngeal swab COVID-19 nucleic acid test, oJIA:oligoarthritis juvenile idiopathic arthritis, FMF: familial mediterranean fever, Enthesitis-related arthritis, SoJIA: Systemic-onset arthritis, RF+ PoJIA: Rheumatoid factor -positive Polyarthritis, RF- PoJIA: RF-negative Polyarthritis, CAPS: cryopyrin-associated periodic syndrome, neg:negative, pos:positive

Declarations

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Conflict of interest statement

Author O.K, Author F.D, Author G.K, Author F.C, Author A.T, Author S.K, Author E.S, Author R.O and Author N.A declare that they have no conflict of interest including specific financial interests, relationships and/or affiliations relevant to the subject matter or materials.

Availability of data and material (data transparency): Not applicable

Code availability (software application or custom code): Not applicable

Compliance with ethical standards:

Ethical approval

Approval was obtained for the study from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (approved: May2020-62254).

Informed consent was obtained from the legally authorized representatives of our patients.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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