Evaluation of Health Status of Children with Autoinflammatory Diseases During COVID-19 Pandemic

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Abstract

Since concerns have been raised that comorbidity is a significant risk factor for Coronavirus Disease-2019 (COVID-19), there is an urgent need to perform studies which evaluate patients with chronic diseases such as autoinflammatory diseases (AIDs). We prepared a web-based survey investigating the clinical findings and contagion histories. Patients with AIDs, were included in the study. Confirmed COVID-19 cases, patients with contact history and patients with symptoms which were highly suggestive of COVID-19 were called via phone or recruited to a video or face to face appointment. Data of AIDs were obtained from their medical records, retrospectively. Laboratory and screening findings were confirmed by using our national health registry website and they were re-examined, if required. There were 404 patients (217 female) eligible for the enrollment. During pandemic, 375 (93%) were on colchicine treatment, and 48 (11.8%) were receiving biologic treatment. 24 out of 404 patients had admission to hospital due to COVID-19 suspicion. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were identified through rhino-pharyngeal swabs in 7 patients, 6 of whom were only on colchicine treatment. Only one patient with no finding of any severe respiratory complications has been hospitalized. All of them recovered completely. Among patients on biologic drugs, neither a symptom nor a positive polymerase chain reaction test was detected that would have been suggestive of COVID-19. In conclusion, pediatric patients with AIDs, those receive either biologic treatment or colchicine may not be at increased risk for either being infected or having worse disease course.

Introduction

A novel coronavirus, named “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2) is responsible for a recently emerged pandemic via causing a disease officially named “Coronavirus Disease-2019” (COVID-19) [1]. At first, the disease has shown itself as a cluster of pneumonia cases with unknown etiology in China, then has spread to other countries with a route which reminds us the ancient silk road in the first sight, and then finally crossed the ocean. Currently, China, the United States of America, Italy and Iran are the most affected countries by COVID-19 [2].

It was suggested that this novel virus tends to infect elder males, particularly with underlying diseases [3]. Older age and to have any comorbidity were also found to be risk factors for intensive care necessity, in a study of Wang *et al* [4]. While, most infected cases are asymptomatic or have mild-moderate symptoms, about %10-20 of them may experience life-threatening events such as multi-organ dysfunction [5]. However, the disease seems to be milder and less often in children compared to adults [6,7]. Although, in the early days of outbreak, pediatric cases were infrequent, we have encountered growing number of children with confirmed COVID-19 by the emerging of familial aggregations [8].

In Italy, Lombardy region and in China, Wuhan are with the highest incidence of COVID-19, as it is well known [9,10]. Likewise, our pediatric rheumatology department is in a tertiary center in Istanbul, which is the most crowded and the most affected city by the current outbreak, in Turkey. We have a significant size of registered pediatric patients with autoinflammatory disease (AIDs), including ones live in distinct cities.

Since, to have comorbidities seems to be a risk for being infected and maybe for worse disease course, as well; it has raised concern that our patients might be more vulnerable to severe COVID-19 compared to general population. Hence, we got hundreds of phone calls from the parents with regard to whether their children are at increased risk of COVID-19 and the necessity of the cessation of their medication. The parents, whose children were on immunosuppressive treatment had more concerns, as expected. Therefore, we purposed to contact with them as much as we can to examine their general health conditions, current outbreak issues and to enlighten them.

Methods

First of all, to conduct this study, we prepared a web-based survey investigating the clinical findings and the presence of contact with subjects affected by COVID-19 of our patients between 11th of March (the day the first case confirmed with COVID-19 in Turkey was reported) and 15th of May 2020. Survey was launched online on 16th of April, 2020. Disease flares, history of contact with confirmed cases, presence of family members confirmed with COVID-19, symptoms resembling COVID-19 such as fever, sore throat, cough, dyspnea, myalgia, diarrhea etc., hospital admission due to suspicion of COVID-19, diagnostic approaches such as performed Polymerase Chain Reaction (PCR) assay in nasopharyngeal swab and chest computed tomography (CT), prescribed medications and hospitalization histories due to COVID-19, and finally current health conditions were questioned in the survey. Data of their AIDs of all of the participants were obtained from their medical records, retrospectively.

Confirmed COVID-19 cases, patients with contact history and patients with symptoms suggestive of COVID-19 were called via phone or recruited to a video or face to face appointment. The communication methods for each one of these were selected according to current curfew conditions which varies day to day and region to region in the country. Laboratory and screening findings were confirmed by using our national health registry website and they were re-examined with paying an extreme attention of personal protective equipment, if required.

The study protocol was approved by the Institutional Ethics Committee of our tertiary center (04/16/20-29430533-604.01-01-54959). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed. Informed consents were obtained from parents/legal guards of children included in the study.

Children with AIDs aged between 1-23 years were included. Patients with an additional rheumatic disease other than AIDs were excluded. To compare the positive PCR test rates for SARS-CoV-2; patients were divided into two groups, patients were on biologic treatment (anti-interleukin-1 (IL-1), anti-interleukin-6 (IL-6) and anti-tumor necrosis factor (TNF) agents) during pandemic and patients were not on biologic treatment.

Statistical Analysis

The statistical analysis was performed using SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL). The distribution of continuous variables was analyzed by the Kolmogorov-Smirnov test. Categorical variables were expressed as numbers (percentages). Continuous variables were given as mean ± standard deviation or median (minimum-maximum) according to their distribution. The comparison of the frequencies of the categorical variables between groups was analyzed by Chi-Square test or Fisher's-Exact test. Statistical significance was defined as $p < 0.05$.

Results

Survey Results

Our web-based survey was launched online, subsequently circulated to 516 parents of children with AIDs, of whom 484 responded. Among the participants, 41 patients were excluded due to their older age (≥23 years old). Another 39 patients were excluded due to presence of another rheumatic disease (n=12), insufficient clinical data (n=25), denial of the informed consent after filling out the survey (n=2).

Finally, 404 patients (217 female) with a median age of 11.1 years (1.1-22.6). were eligible for the enrollment. Surveys were filled out by mothers (n=294, 72.8%), fathers (n=89, 22%), themselves (n=18, 4.5%), and others (n=3, 0.7%) (1 brother, 1 aunt and 1 husband), respectively. 364 (%90) were diagnosed Familial Mediterranean Fever (FMF), 14 (%3,5) were Periodic Fever Aphthous Stomatitis Pharyngitis and Adenitis (PFAPA), 14 (%3,4) were Cryopyrin-Associated Periodic Syndromes (CAPS), 4 (%1) were Chronic Recurrent Multifocal Osteomyelitis (CRMO), 3 (%0,7) were Deficiency of Adenosine Deaminase 2 (DADA2), 3 (%0,7) were Blau Syndrome (BS), 1 (%0,2) was Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), and 1 (%0,2) was Hyperimmunoglobulin D Syndrome (HIDS). For each patient, all of the diagnosis mentioned above were confirmed with clinical and genetic findings.

Treatment Status of the Patients During COVID-19 Pandemic

During pandemic, 375 (93%) (FMF: 364, CAPS: 6, PFAPA: 2, HIDS: 1, TRAPS: 1, DADA2: 1) were on colchicine treatment, and 48 (11.8%) were receiving biologic treatments. Of the patients on biologic agents, 35 were on canakinumab (FMF: 21, CAPS: 13, TRAPS: 1), 6 were on etanercept (DADA2: 3, CRMO: 2, BS: 1), 5 were on anakinra (FMF: 4, CAPS: 1), 1 was on adalimumab (BS) and 1 was on tocilizumab (BS).

COVID-19 Results

Of the 35 (8.6%) patients with a confirmed COVID-19 family member, 14 had reported a contact. Additionally, there were 3 other patients with a history of contact with a known COVID-19 patient who is not a family member. 24 of our patients admitted to hospital due to COVID-19 suspicion, and 23 (FMF: 20, PFAPA: 1, CAPS: 1, DADA2: 1) were tested by using real time PCR for SARS-CoV-2 (Table 1).

The number of patients with positive PCR was 7 (FMF: 6, PFAPA: 1); none of them were receiving biologic treatment, 6 were on colchicine treatment; 5 of them were symptomatic (fever, dry cough, sore throat etc.);

4 of the symptomatic ones were prescribed for COVID-19 and followed-up via outpatient clinic and/or phone, and 1 of the symptomatic ones was hospitalized for 5 days, 2 (FMF: 1, PFAPA: 1) were asymptomatic and were not prescribed medication for COVID-19. Chest CT was performed in 10 patients; 2 were compatible with COVID-19 and both of them had positive PCR. 1 had ground-glass opacities and air bronchograms, and 1 had consolidation surrounded by the ground-glass opacities (Halo sign) in their CT scans (Figure 1). All of the confirmed cases recovered completely (Table 2).

Two patients receiving biologic treatment, had a history of close contact with confirmed COVID-19 family members; 1 with DADA2 was receiving etanercept and 1 with CAPS was receiving canakinumab; both of them were tested by using real-time PCR and were negative. 21 patients not receiving biologic treatment; were tested; 7 were positive as mentioned above (FMF: 6, PFAPA: 1); 6 were on colchicine treatment. Among patients underwent PCR testing; there was no significant difference between patients who were receiving biologic treatment and patients who were not receiving with regard to positive PCR frequency ($p>0,05$).

Discussion

Our planet is suffering from SARS CoV-2 since the first couple of days in 2020. World Health Organization (WHO) declared this novel coronavirus outbreak as pandemic on 11st of March 2020, and the first confirmed case in Turkey was reported on the same day. We have encountered this little-known foe relatively later compared to many other countries. Until that time, many treatment and prevention strategies have been already developed by the health care providers of other countries. Therefore, we were able to make stringent isolation decisions like lockdown promptly and able to establish our national treatment guidelines which contains hydroxychloroquine and other current available options. Hence, even it is early to mention it, numbers of confirmed cases and deaths seem to be moderately low in our country.

However, we have a large number of registered pediatric patients with AIDs, and due to their chronic health conditions and/or immunosuppressive treatment of some of them, parents had concerns for their children regarding the current outbreak. As we got hundreds of phone calls. it was necessity for us to perform this study. Since 11st of March 2020, a total of 7 pediatric patients with AIDs were diagnosed as COVID-19 among the patients we follow-up in regular. None of them were receiving biologic treatment, 6 were on colchicine treatment, 5 were symptomatic; 4 were prescribed and followed-up via outpatient clinic and/or phone, 1 was hospitalized for 5 days, 2 were asymptomatic and were not prescribed, and all of 7 recovered completely. To our best knowledge, this is the first report describing frequency, demographic and clinical findings and outcomes of COVID-19 in pediatric patients with AIDs.

Since stringent isolation measures are widely approved and children be infected mostly via exposure to a known adult case, intrafamilial transmissions merit a special approach [11]. In our study, in 6 of 7 patients with positive PCR, source of infection was a family member. Although, COVID-19 may lead to serious conditions such as multiorgan dysfunction and even death, it seems that children are tend to

have a milder disease course [6]. In the study of Dong *et al* [12] which consist the largest number of pediatric patients up to now, 94% of the patients were asymptomatic, mild or moderate. In another report from Wuhan, there were 1391 children who were tested due to contact with confirmed cases, only 12.3% were positive, and only 1, which one had intussusception, died [13]. Similarly, in our study group, none of the patients required intensive care and/or ventilation support, even the hospitalized one, and all of them recovered completely. Some hypothetical ideas were emerged regarding non-severity of the disease in childhood such as; lower exposure to viruses and air pollution due to being isolated at home mostly thanks to shutting down of the schools, lower smoking rates, higher viral co-infections which may lead to limit replication of SARS CoV-2, and possibly different distribution of ACE2 which acts as a receptor for virus entry into human cells [14].

Although, chronic health conditions such as hypertension and diabetes mellitus were found to be risk factors for worse disease course in COVID-19, immunocompromised situations such as rheumatic diseases requiring immunosuppressive treatment were not [15]. In a report of Monti *et al* [9], 4 of 320 patients with rheumatoid arthritis confirmed with COVID-19 and none of them developed serious pulmonary complications. Although, there is a limited data, there are some suggestions that patients with AIDs may be vulnerable to infections [16,17]. Regarding COVID-19, based on molecular studies, it has been suggested that enhanced innate immune activation may promote a worse disease outcome [5]. However, most of our patients with AIDs are on colchicine treatment, and colchicine is one of the off-label medications used in the treatment of COVID-19, currently [18]. Gandolfini *et al* [19] have noted clinical improvement in their COVID-19 patient by using colchicine. In our study, among 376 patients on colchicine treatment, only 6 were confirmed COVID-19, and all of them recovered completely. To our knowledge, until today, there is no data available describing COVID-19 among pediatric and/or adult patients with AIDs.

Among our patients who had a contact history with confirmed COVID-19 cases, one with DADA2, was receiving etanercept for 2 months and 3 of her family members were confirmed cases (father, brother and grandmother); other one with CAPS, was receiving canakinumab for 2.5 years and 2 of her family members were confirmed cases (mother and father). Compared to other coronaviruses (SARS-CoV and MERS-CoV) which caused outbreaks in the past 2 decades, SARS CoV-2 has a higher capability to infect individuals [20]. Given the immunosuppressive effects of biologic treatment and highly contagious nature of SARS CoV-2, it was striking that these two patients who were receiving biologic treatment and had close contact histories were completely asymptomatic and PCR tests were negative in both. Consistent with our study, none of the patients who received immunosuppressive treatment developed lung disease, even some were confirmed COVID-19 cases, as reported from a liver transplantation unit in Italy [21]. Similarly, Conticini *et al* [22] reported that there were 2 patients with confirmed COVID-19 in their rheumatology department, 1 was a 50-year-old woman affected by rheumatoid arthritis, receiving rituximab, and 1 was an 87-year-old woman affected by giant cell arteritis, receiving tocilizumab; both of them discharged and then remained asymptomatic.

Although serious concerns for patients on immunosuppressive treatment seems reasonable at first, there is no insufficient data in the literature for supporting this. Besides, since it is known that main mechanism of lung injury occurs due to a hyperinflammatory situation resembling cytokine storm syndrome, studies investigating the therapeutic effects of biologic agents on COVID-19 were launched [23]. In hospitalized patients with COVID-19, serum IL-6 levels were found to be elevated, and tocilizumab; an anti-IL-6 agent was found to be effective on the treatment of COVID-19 patients with cytokine storm syndrome [24]. Anakinra, an anti-IL-1 agent has a favorable effect on patients with hyperinflammation, as well [25]. It was shown in a report from France that, anakinra had provided clinical improvement in 8 of 9 patients with COVID-19 [26]. Moreover, as it is known that SARS CoV-2 might induce TNF – alpha converting enzyme for penetration into human cells, a trial evaluating the effects of anti-TNF agents on COVID-19 has been registered in China, currently [27]. Therefore, this relative favorable position of children receiving biologic treatment, may be attributed to that they are unlikely to develop hyperinflammatory conditions resembling cytokine storm syndrome, due to their insufficient immune system.

Since a little percentage of cases may be misdiagnosed by PCR test, many centers in our country launched performing chest CT routinely, particularly in symptomatic ones. In our study, chest CT was performed in 6 of 7 patients with confirmed COVID-19. There were 2 patients with CT findings compatible with COVID-19. One of these two had ground-glass opacities, the most common CT finding in COVID-19 patients [3,4]. The other one had consolidation surrounded by the ground-glass opacities (Halo sign). Although, Halo sign is a rare CT sign in adults, Xia *et al* [8] suggest that it is a typical sign in pediatric patients.

The main limitations of our study were that there were no included otherwise healthy patients who admitted to hospital due to suspicion of COVID-19 as a control group, and we had a short observation period due to that we have encountered the outbreak relatively later compared to many other countries.

In conclusion, further studies including field screenings are required and our finding are insufficient to allow any conclusions. However, our preliminary experience shows that pediatric patients with AIDs, even if they receive biologic treatment may not be at increased risk for either being infected with SARS CoV-2 or having worse disease course. Given that there is no evidence whether colchicine or biologic treatment provides an additional risk for COVID-19, and the disease flares are a great risk for vulnerability to any kind of infections; we rheumatologist, should warn our patients for not withdrawing of their medication unless we advise.

Declarations

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Conflict of interest/Competing interests: None declared.

Ethics approval: The study was approved by Istanbul University-Cerrahpasa Institutional Review Board (29430533-604.01-01-54959).

Informed consent: A written informed consent was obtained from all the participants included in this study and no identifying information of any participant was included in this paper.

Authors' contributions: FH, MY, AA, SS, OK were responsible for data collection and analysis. FH, MY, AA contributed to the writing of the manuscript. OK, AA, KB, OK reviewed and revised the manuscript.

The Patient and Public Involvement statement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data sharing statement: All data relevant to the study are included in the article.

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Tables

Table 1: Demographic and diagnostic variables of the study group.

	Patients not receiving bDMARDs (n=356)	**Patients receiving bDMARDs (n=48)**	***p***
Female	187 (52.5%)	29 (60.4%)	>0,05
Age (Years)	10.9 (1.1-22.6)	13 (2.3-21.9)	>0,05
The person who filled out the survey			>0,05
• *Mothers*	264 (74.2%)	30 (62.5%)	
• *Fathers*	73 (20.5 %)	16 (33.3%)	
• *Herself/Himself*	16 (4.5%)	2 (4.2%)	
• *Others*	3 (0.8%)	-	
Diagnosis			
• *FMF*	339 (95.2%)	25 (52.1%)	
• *PFAPA*	14 (3.9%)	-	
• *CAPS*	-	14 (29.2%)	
• *CRMO*	2 (0.6%)	2 (%4.2)	
• *DADA2*	-	3 (6.3%)	
• *Blau syndrome*	-	3 (6.3%)	
• *TRAPS*	-	1 (2.1%)	
• *HIDS*	1 (0.3%)	-	
Treatment they were on			
• *Colchicine*	342 (96.1%)	34 (70.8%)	
• *Anakinra*	-	5 (10.4%)	
• *Canakinumab*	-	35 (72.9%)	
• *Etanercept*	-	6 (12.5%)	
• *Adalimumab*	-	1 (2.1%)	
• *Tocilizumab*	-	1 (2.1%)	
SARS CoV-2 PCR test performed			
• *Contact history*			
-A family member	12 (3.3%)	2(4.1%)	
-Not a family member	3 (0.9%)	-	
-None	6 (16.8%)	-	
• *Performed CT*			
-Compatible with COVID-19	2 (0.55%)	-	
-Normal	6 (1.65%)	2 (4.1%)	
Positive PCR test	7 (1.9%)	-	>0,05

bDMARDS: biologic Disease Modifying Anti Rheumatic Drugs; CAPS: Cryopyrin-Associated Periodic Syndromes; COVID-19: Coronavirus Disease-19; CRMO: Chronic Recurrent Multifocal Osteomyelitis; CT: Computed Tomography; DADA2: Deficiency of Adenosine Deaminase 2; FMF: Familial Mediterranean Fever; HIDS: Hyperimmunoglobulin D Syndrome; PCR: Polymerase Chain Reaction; PFAPA: Periodic Fever Aphthous Stomatitis Pharyngitis and Adenitis; SARS CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; TRAPS: Tumor Necrosis Factor Receptor Associated Periodic Syndrome

Table 2: *Clinical features of the patients with confirmed COVID-19*

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*	*Patient 7*
Age (years)	18,8	3,8	17,5	17,4	10,9	20,1	18,1
Gender	Female	Male	Male	Male	Female	Male	Female
Diagnosis	FMF	PFAPA	FMF	FMF	FMF	FMF	FMF
Source of contact	Father, mother and two other siblings	Not a family member	Father, mother	Father, mother and one sibling	Father, mother	Father, mother and one sibling	Father, mother
Treatments they were on	Colchicine	None	Colchicine	Colchicine	Colchicine	Colchicine	Colchicine
Number of disease flares during pandemic	6	3	2	1	0	0	0
Symptoms	Fever, dry cough, sore throat, diarrhea	None	Fever, dry cough, sore throat, dyspnea, diarrhea, myalgia	Fever, dry cough, diarrhea	None	Fever, sore throat	Fever, dry cough, sore throat, diarrhea, myalgia
Chest CT	Air bronchograms, ground-glass opacities	Not performed	Normal	Normal	Normal	Halo sign	Normal
Follow-up way	Outpatient clinic and/or via phone	Outpatient clinic and/or via phone	Outpatient clinic and/or via phone	Outpatient clinic and/or via phone	Outpatient clinic and/or via phone	Outpatient clinic and/or via phone	Hospitalized for 5 days
Prescribed medication	Azithromycin Oseltamivir HCQ	None	Azithromycin Oseltamivir HCQ	Azithromycin Oseltamivir HCQ	None	HCQ	Oseltamivir HCQ
Current situation	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic

CT: Computed Tomography, FMF: Familial Mediterranean Fever, HCQ: Hydroxychloroquine, PFAPA: Periodic Fever Aphthous stomatitis Pharyngitis and Adenopathy.

Figures

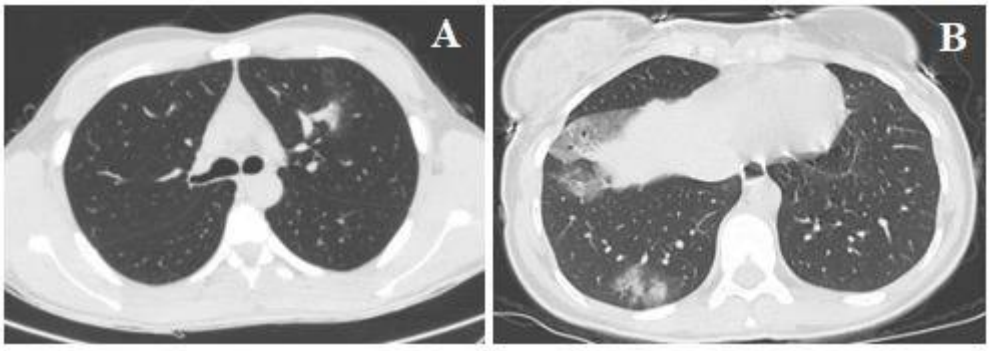

Figure 1

A: On the axial CT image of patient 6, in the upper of left lung, the consolidation surrounded by the ground-glass opacities (Halo sign) is seen. B: On the axial CT image of patient 1, consolidation with air bronchograms on the paracardiac area of the right lung, and ground-glass opacities on the posterosuperior subpleural area of the lower lobe of right lung. CT, Computed Tomography.