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ORIGINAL ARTICLE

The impact of COVID-19 on clinical course and treatment among patients with juvenile systemic sclerosis

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ABSTRACT

Objectives: This study aimed to explore the influence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic among patients with juvenile systemic sclerosis (JSS).

Patients and methods: Twenty-seven patients (22 females, 5 males; mean age: 20 years; range, 17 to 22 years) diagnosed with JSS and followed up at the department of pediatric rheumatology were included in the cross-sectional study. A web-based survey was performed by focusing on patients' complaints, accessibility to health care, and compliance with routine treatment from January 1, 2021, to January 10, 2021.

Results: Five (18.5%) patients had deterioration of the disease, while six (22.2%) patients reported irregular usage of their routine scleroderma treatment during the last six months. Nine (33.3%) patients had missed their routine clinic control since the proclamation of the SARS-CoV-2 pandemic. Seven (25.9%) patients had household contact with coronavirus disease 2019 (COVID-19). Four (14.8%) patients were diagnosed with COVID-19, and only one (3.7%) was hospitalized. Nine patients were under biological treatment (tocilizumab); however, only one of them was diagnosed with COVID-19.

Conclusion: The COVID-19 pandemic has not significantly disrupted the medical care of JSS patients. Telemedicine could be an acceptable option for JSS patients disenabled to come to the hospital.

Keywords: Coronavirus disease 2019, interstitial lung disease, juvenile systemic sclerosis, SARS-CoV-2, tocilizumab.

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), made a sustainable impact on health care worldwide. The COVID-19 pandemic had a significant effect on different aspects of health care systems globally, including the management and treatment of patients with a variety of chronic diseases.[1]

All chronic conditions, including rheumatologic diseases, represent a possible risk of infection and a more severe clinical course. Considering the well-known susceptibility of patients with autoimmune conditions to infections due to both altered immune systems and the usage of immunosuppressive treatment, the concerns regarding the impact of COVID-19 in these

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patient populations are raised. At the same time, COVID-19 had a certain impact on the management and treatment of patients with chronic conditions.[1-3]

Juvenile systemic sclerosis (JSS) is an extremely rare condition in which disease nature by itself, as well as the used immunosuppressive treatment, create the appropriate ground for viral infections, including SARS-CoV-2.[4-7] Till recently, there had been limited data regarding the impact of the SARS-CoV-2 pandemic on patients with systemic sclerosis.[8]

In this study, we aimed to explore the influence of the SARS-CoV-2 pandemic among patients with JSS. In this context, we performed a web-based survey among JSS patients by focusing on patients' complaints, accessibility to health care, and compliance with routine treatment. In this way, we sought to explore the possible interruption of routine medical care and psychological aspects, including fear of isolation and risk of infections, among patients with JSS.

PATIENTS AND METHODS

In the cross-sectional study, a web-based survey was delivered to 35 patients diagnosed with JSS according to the Pediatric Rheumatology European Society (PReS)/American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) provisional classification criteria for juvenile systemic sclerosis criteria[9] and followed up at the Department of Pediatric Rheumatology of Cerrahpaşa Medical School. The survey was sent to the patients via smartphone or electronic mail, obtained from the hospital database. The eligible patients were given 10 days to complete the questionnaire from January 1, 2021, to January 10, 2021. Thirty-three patients responded to the survey, and six were excluded from the evaluation since three responded incompletely and three responded twice. Finally, responses of 27 patients (22 females, 5 males; mean age: 20 years; range, 17 to 22 years) were accepted and evaluated further.

The questionnaire consisted of 28 questions. The first part of the form included questions regarding the demographic characteristics of the patients. The second part included multichoice questions regarding the clinical characteristics of patients, the treatment they used for JSS, and the continuation or discontinuation of regular follow-up during the pandemic. Patients were asked for the reason if they missed a routine follow-up or treatment. The questionary included questions regarding contact with COVID-19 and the presence of the infections among them.

One junior and one senior pediatric rheumatologist evaluated the answers and decided on validity. Questionnaires that were not fully completed were excluded from the evaluation.

Statistical analysis

Data were analyzed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Due to the limited sample size, nonparametric tests were used. Categorical variables were reported as median (interquartile range) according to their distribution. The frequencies were reported as numbers and percentages.

RESULTS

The median age at the time of diagnosis was 11 (range, 9 to 13) years. The demographic features of patients are shown in Table 1. At the time of the study, four (14.8%) patients were under treatment with glucocorticoids, 10 (37%) with mycophenolate mofetil, six (22.2%) with methotrexate, one (3.7%) with cyclophosphamide, eight (29.6%) with subcutaneous tocilizumab, one with intravenous tocilizumab, eight with bosentan, nine (33.3%) with nifedipine (Table 1).

The impact of the COVID-19 pandemic on disease status

Six (22.2%) patients responded that they had deterioration in disease during the last six months. Among these patients, six reported increased intensity of Raynaud's phenomenon, five (18.5%) had an increase in the number of digital ulcerations, five (18.5%) had dysphagia, four (14.8%) reported increased stiffness of the skin, two (7.4%) had arthralgia, one (3.7%) had dizziness, and one (3.7%) had myalgia (Figure 1).

The SARS-CoV-2 infections among JSS patients

Seven (25.9%) patients reported irregular usage of their routine scleroderma treatment

Table 1. Demographic and clinic characteristics of patients with JSS at the time of the survey (n=27)

	n	%	Median	IQR
Sex				
Female	22	81.5		
Mean age at the study (year)			20	17-22
Mean age at diagnosis (year)			11	9-13
Mean disease duration (year)			7	4.5-10
Previous lung involvement due to JSS	11	39.3		
Glucocorticoids	4	14.8		
Mycophenolate mofetil	10	37		
Methotrexate	6	22.2		
Cyclophosphamide	1	3.7		
Tocilizumab	9	32.1		
Nifedipine	9	32.1		
Bosentan	8	29.6		

JSS: Juvenile systemic sclerosis; IQR: Interquartile range.

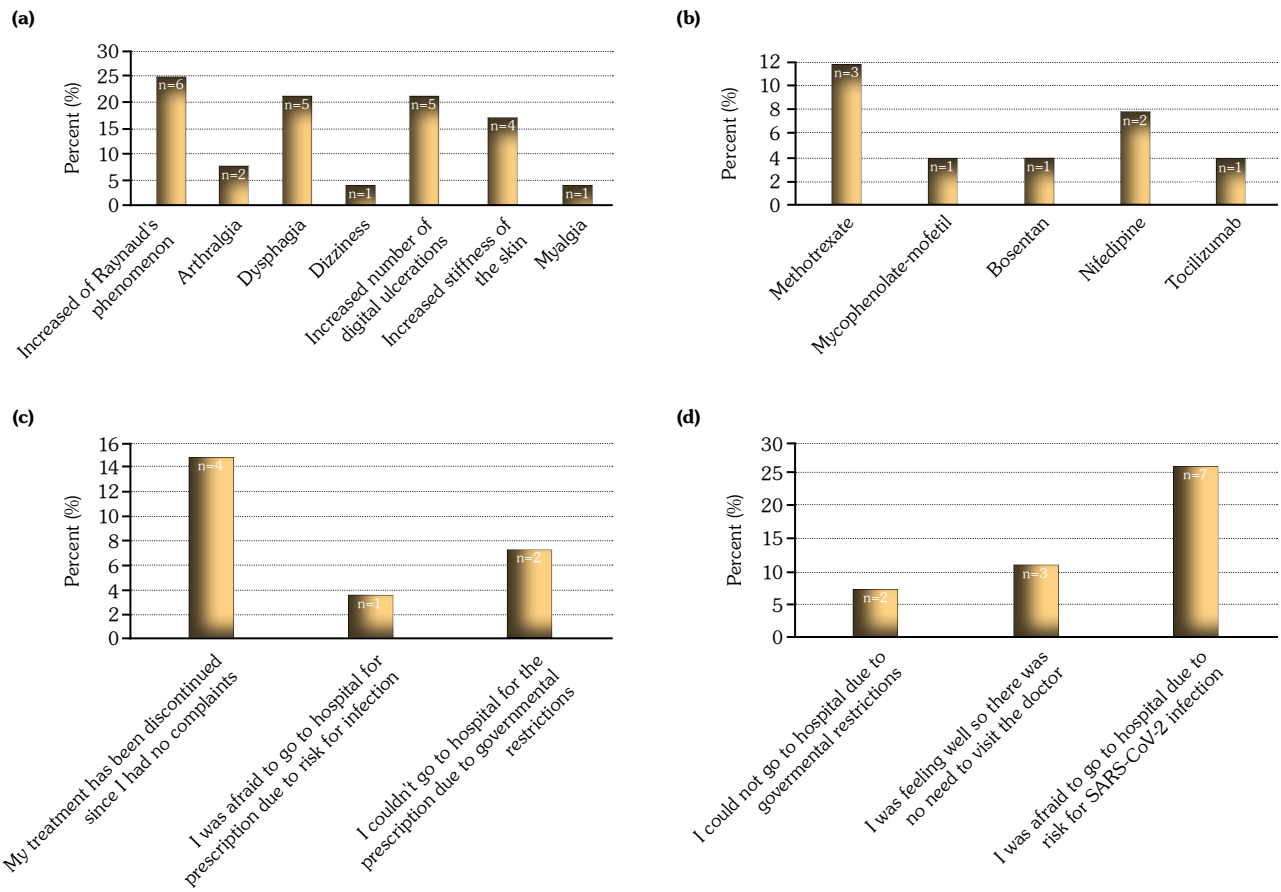

Figure 1. Treatment and follow-up of JSS patients during the COVID-19 pandemic. **(a)** Deterioration of the primary disease during the COVID-19 pandemic. **(b)** Interruption of the routine medical treatment. **(c)** The reason for the interruption of routine treatment. **(d)** The disruption of the routine follow-up.

JSS: Juvenile systemic sclerosis; COVID-19: Coronavirus disease 2019.

during the pandemic. The most common reason was that patients had no complaints; thus, they decided to discontinue the routine treatment. Twelve (44.4%) patients reported that they missed their routine clinic controls after the proclamation of the SARS-CoV-2 pandemic (March 11, 2020). The most common reason was that patients were afraid to go to the hospital due to the risk of SARS-CoV-2 infection (Figure 1). Results regarding the deterioration of the primary disease during the COVID-19 pandemic and interruption of routine medical treatment are better reported in Figures 1a-d.

Seven (25.9%) patients reported that they had contact with a family member diagnosed with COVID-19, and two of them tested positive for SARS-CoV-2. Five (18.5%) patients visited the physician and were tested with a suspected diagnosis of COVID-19; four (14.8%) tested positive for SARS-CoV-2 by PCR, and a thorax high-resolution computed tomography was performed in only one of them. The patient who had a confirmed SARS-CoV-2 infection and signs of viral pneumonia on thorax computed tomography was hospitalized due to COVID-19. The patient was treated with favipiravir and supportive treatment. Among four patients diagnosed with COVID-19, all of them reported that they had symptoms of fever, fatigue, myalgia, and headache, but their symptoms completely resolved.

DISCUSSION

As far as we know, this is the first study evaluating the impact of the SARS-CoV-2 pandemic on patients with JSS. When the pandemic emerged, there were major concerns for the pediatric patients with connective tissue disorders, including systemic sclerosis. There were questions on whether pediatric patients with connective tissue disorders are under increased risk for the SARS-CoV-2 infection and if the infected patients were under increased risk of more severe clinical course.[10-13]

The World Scleroderma Foundation reported the preliminary advice on the management of systemic sclerosis patients at the start of the COVID-19 pandemic.[10] According to recommendations, patients with systemic sclerosis should continue their immunosuppressive treatment during the pandemic to avoid disease relapses. In the case of symptoms suggestive of COVID-19 or if someone in the household develops COVID-19, immunosuppression should be halted.[10]

Therefore, we decided to perform the survey to analyze the impact of COVID-19 on patients with JSS by concentrating on the continuation of medical treatment and the clinical course of the primary disease during the pandemic. The survey was prepared by one specialist and two fellows in pediatric rheumatology and approved by a senior pediatric rheumatologist with years of experience in the field). The survey used in this study was primarily prepared for all patients with pediatric rheumatologic diseases, including autoinflammatory disease and juvenile idiopathic arthritis, and performed among patients other than JSS. The survey showed a satisfactory performance in a study published recently. Furthermore, the survey, previously used to evaluate patients with autoimmune diseases in our hospital,[14,15] was adopted for patients with JSS and delivered via smartphone or electronic mail, obtained from the hospital database of patients followed up at our department.

Till recently, there had been limited data regarding the effects of the SARS-CoV-2 pandemic on patients with JSS. Some reports from adults suggest that systemic sclerosis does not represent a significant risk for the severe form of COVID-19.[11-13]

In a study by Bellan et al.[11] performed on 164 adult systemic sclerosis patients, 17 patients reported a worsening of Raynaud's phenomenon, and nine reported the onset of new ulcers. Only one patient was referred to the emergency department and diagnosed with COVID-19-related pneumonia. The patient completely recovered without additional complications. In another study on 526 adult systemic sclerosis patients, two were hospitalized due to COVID-19-related pneumonia, while 11 had a mild clinical course.[12] One of two patients with pneumonia died due to respiratory failure. The patient was previously diagnosed with interstitial lung disease and treated with methotrexate and rituximab. In a study by Gupta et al.[8] on 291 adult systemic sclerosis patients,

119 (40.9%) experienced problems related to the COVID-19 pandemic. Among these patients, 46 (38.7%) required an increase in medicine, and 12 (10.1%) needed hospitalization due to complications of the primary disease.

In our cohort, four (14.8%) patients were diagnosed with COVID-19. All had disease symptoms, with three of them having mild disease, and only one patient was hospitalized due to COVID-19 with a diagnosis of viral pneumonia. The patient had moderate disease severity without the need for intensive care unit treatment and mechanical ventilation. The mentioned patient was under continuous treatment with mycophenolate mofetil, subcutaneous tocilizumab (162 mg/day every two weeks), nifedipine, and bosentan. During the SARS-CoV-2 infection, the mycophenolate mofetil was interrupted while the tocilizumab treatment was continued, which is in concordance with the recommendations of the World Scleroderma Foundation.[10] The patients completely recovered without any disease complications or sequelae. The other three JSS patients diagnosed with COVID-19 were biologic naive.

The Centers for Disease Control and Prevention does not recommend the usage of glucocorticoids during the critical phase of the infection, particularly at a dose >20 mg/day, since it could prolong the elimination of the virus and modulate the immune response.[16,17] Our patient was treated with intravenous methylprednisolone (32 mg/day), which is in accordance with the recommendations of the National Institute of Health COVID-19 treatment guidelines.[18] Corticosteroids are indicated in the severe hyperinflammatory phase of COVID-19 itself.[2] It is important to mention that in some cases it is hard to make a distinction between SARS-CoV-2-related pneumonia and interstitial lung disease due to some similar radiological signs. Since a significant number of systemic sclerosis patients have interstitial lung disease, in the case of SARS-CoV-2-related pneumonia, the differentiation between the lung involvement related to underlying disease and secondary infection is challenging. Moreover, the SARS-CoV-2 superinfection can be a reason for worsening in patients with underlying interstitial lung disease. Consequently, the corticosteroids' initiation or cessation among rheumatic patients with COVID-19 is left to the decision of experienced clinicians, with a need for more precisely defined criteria.[19]

Among our patients, three of nine who were under continuous treatment with tocilizumab had household contact with COVID-19; however, only one was diagnosed and hospitalized due to SARS-CoV-2-related pneumonia. According to the EULAR recommendations, patients under interleukin-6 inhibitor treatment are advised to continue taking them.[20] The ACR recommends that the immunosuppressive treatments should be temporarily interrupted and restarted 10 to 14 days after in cases without symptoms (even in the case of PCR positivity).[21] Similarly, it is suggested to postpone the initiation of the immunosuppressant in case of suspected or confirmed COVID-19. There is evidence that some biologics (e.g., tocilizumab and Janus kinase inhibitors) may be useful in preventing the development of cytokine storm in patients with systemic sclerosis and COVID-19.[22]

In our study, seven (25.9%) patients disrupted the routine disease follow-up and missed the clinic control with the fear of being infected by the SARS-CoV-2. Similarly, in a study by Gupta et al.[8] on 291 patients, contracting COVID-19 was the most prevalent concern. In the same study, 119 (40.9%) patients experienced worsened health, with 12 (10.1%) requiring hospitalization. Among our patients, 6 (22.2%) reported increased symptoms related to primary disease; however, none of our patients required hospitalization, unlike in the study of Gupta et al.[8] The difference could be explained by the comorbidity being more prevalent among adults compared to JSS patients.

Among our patients, three (11.1%) reported that they could not go to purchase the drug prescription, and therefore, they could not obtain the medicine. Similarly, 197 out of 291 (67.7%) adult patients could not go to purchase their drugs during the pandemic in the study by Gupta et al.[8] Additionally, more than half of patients preferred electronic consultations (n=162, 55.7%) for continuous medical care, while 43 (14.8%) preferred personal interactions by visiting the physician themselves.[8] In our study, only one

(3.7%) patient benefited from telemedicine. Electronic consultations and telemedicine should be encouraged, particularly among patients with chronic diseases who are more prone to frequent hospital visits. Face-to-face rheumatologic consultations should be preferred among patients with unstable, progressive diseases and those with comorbidities and possible disease complications.

This study has some limitations. The number of evaluated patients is limited due to the rarity of JSS. The nasopharyngeal swab was not obtained from all patients. Therefore, those with mild clinical form and those who were symptomatic could be missed by the survey. The study was performed by telephone or electronic mail; consequently, the objective state of the patients' conditions could not be obtained. The governmental regulations and restrictions during the pandemic could be a reason for uncommon SARS-CoV-2 infections among all chronic patients, including JSS).

In conclusion, COVID-19 does not have a considerable effect on the clinical management of patients with JSS. Since the COVID-19 pandemic is still not over, future studies with a higher number of patients and longer follow-up duration would provide more relevant data.

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Ethics Committee Approval: The study protocol was approved by the Istanbul University-Cerrahpaşa, Cerrahpaşa Medical School Ethics Committee (date: 04.05.2021, no: 29430533-903.99-83219). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient before participation in the survey.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Made a design of the paper: O.K.; Provided the search of the literature and wrote the paper: A.A., M.Y., F.H., O.K., and A.G.; Made a critical evaluation of the data collection and interpretation: S.S., K.B., and O.K.; Designed a figure: M.Y.; All authors revised the final version of the manuscript.

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