

Patients Without a Rheumatic Disease Diagnosis in a Pediatric Rheumatology Unit: Retrospective Analysis and Comparison Between Pre-pandemic and Pandemic Periods

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What is already known on this topic?

- Rheumatic diseases can lead to a wide variety of symptoms.
- Pediatric rheumatology departments receive a large load of consultations.
- The Coronavirus disease 2019 pandemic has a significant impact on our daily lifestyle as well as pediatric rheumatology practice.

What this study adds to this topic?

- Prolonged or recurrent fever, anti-nuclear antibody positivity, arthralgia, and skin findings were the most frequent complaints of the referrals in patients who did not have a rheumatic disease diagnosis.
- The number of patients referred to the pediatric rheumatology unit decreased during the pandemic period.
- During the pandemic year, the number of patients referred for back pain increased significantly while the number of patients admitted with the presence of heterozygous mutations in the MEFV gene and complaints of leg pain decreased.

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ABSTRACT

Objective: Children with suspicious complaints of rheumatic diseases are generally referred to a pediatric rheumatologist. We aimed to evaluate the profile of patients referred to the pediatric rheumatology unit and were not diagnosed with a rheumatic disease and to assess the impact of the coronavirus disease-2019 pandemic on referral complaints.

Materials and Methods: All new outpatients who applied to the pediatric rheumatology department between March 2019 and February 2021 and were not diagnosed with rheumatic disease were included. We also compared the frequency of admission symptoms during the pre-pandemic (March 2019–February 2020) and pandemic periods (March 2020–February 2021).

Results: A total of 1089 patients without a rheumatic disease diagnosis (568 female, 52.2%; median age 10.0 years) were included in this study. The most common complaint for referral was prolonged or recurrent fevers (13.4%) followed by anti-nuclear antibody positivity (13.1%), arthralgia (13.0%), skin findings (7.5%), and the presence of heterozygous mutations in the Mediterranean fever gene (6.9%). During the pandemic year, the number of patients referred for back pain increased significantly ($P = .028$). A total of 682 of 1089 patients were consulted from other departments in our center (62.6%). Of these, the most frequent consultation request was from general pediatrics (43.6%). The rheumatic disease was excluded in 11.3% of the patients.

Conclusion: Prolonged or recurrent fever and anti-nuclear antibody positivity were the most frequent complaints of referrals to a pediatric rheumatology unit in patients who did not have a rheumatic disease. The rate of back pain was more common in children during the pandemic period.

Keywords: Referral symptoms, rheumatic disease, children, COVID-19

INTRODUCTION

Pediatric rheumatology is a department that focuses on autoimmune and autoinflammatory diseases. The prevalence of pediatric rheumatic diseases is not known exactly and may differ between geographical regions.¹ The overall incidence of rheumatic disease in children was reported as 8.6 per 100 000 children in a study from Eastern Austria.² As for Turkey, pediatric rheumatology is a growing discipline with increasing numbers of centers and specialists. Its geographical location also leads to a suitable basis, especially for auto-inflammatory disease.³

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Patients with rheumatic diseases may present with a wide variety of symptoms, and thus pediatric rheumatology departments receive a large load of consultations. The median annual referral rate to a pediatric rheumatology center was reported as 26 per 100 000 children at risk in Canada.⁴ Children with suspicious complaints of rheumatic diseases are generally referred to a pediatric rheumatologist. Approximately half of these patients are diagnosed with rheumatic disease.⁵⁻⁷

Musculoskeletal complaints are among the most common problems experienced by 10%-20% of children.⁸ The most common musculoskeletal complaints in primary pediatric care were reported in descending order of frequency: arthralgias of the knees, other joints (e.g., ankles, wrists) arthralgias, soft tissue pain, heel pain, hip pain, and back pain.⁹ The differential diagnosis is extensive such as infections, trauma, orthopedic, rheumatic disease, and malignancy. A statement issued by the American College of Rheumatology was published to inform primary care physicians about indications for referral to a pediatric rheumatology center.¹⁰ Pediatric rheumatology is a subspecialty of pediatrics dealing with childhood arthritis and joint pains as well as vasculitis, connective tissue diseases, autoimmune, and rare inflammatory disorders. It is essential to raise awareness among pediatricians and other physicians about rheumatic diseases.

Coronavirus disease 2019 (COVID-19) infection emerged in December 2019 and spread all over the world in a short time.¹¹ The first confirmed case of COVID-19 in Turkey was recorded on March 11, 2020.¹² The COVID-19 pandemic has brought tremendous challenges for healthcare providers. Delays in appointments and concerns about using immunosuppressive therapies were yielded.¹³ Several complications closely related to rheumatic diseases have been noted in patients with COVID-19, such as multisystem inflammatory syndrome in children, COVID-19-related vasculitis, and Kawasaki-like disease.¹⁴⁻¹⁸ On the other hand, a decrease in the diagnosis rate of some rheumatological diseases such as acute rheumatic fever, IgA vasculitis, classic Kawasaki disease, and macrophage activation syndrome was reported in the pandemic period compared

to previous years.¹⁹ The COVID-19 pandemic had a significant impact on pediatric rheumatology practice.

In this study, we aimed to evaluate the demographic and clinical characteristics of patients who were referred to a tertiary pediatric rheumatology outpatient clinic and were not diagnosed with rheumatic disease. We also investigated how the COVID pandemic affected the admissions to the pediatric rheumatology outpatient clinic and its effect on referral symptoms or complaints.

MATERIALS AND METHODS

Study Population

A total of 11 792 patients applied to our pediatric rheumatology department between March 2019 and February 2021 (Figure 1), 7702 of which were between March 2019 and February 2020, and 4090 were between March 2020 and February 2021. Excluding the recurrent visits (n = 9750), there were 2042 new patient referrals. Out of 2042 patients, 953 were diagnosed with rheumatic disease (46.6%). The remaining 1089 patients without a rheumatic disease diagnosis were included in this study. Patients were excluded from this study if they had a diagnosis of rheumatic disease at admission and/or in the follow-up period.

In our healthcare system, primary care clinicians evaluate the patient first and refer patients with complaints or symptoms suggestive of rheumatic disease to the pediatric rheumatology center. In addition, some patients are referred from other departments of our hospital for outpatient consultation.

The patients were divided into 2 groups according to the year of referral to pediatric rheumatology (March 2019-February 2020 and March 2020-February 2021). The first period was defined as the pre-COVID-19 pandemic period while the second period was defined as the COVID-19 pandemic period.

Data Collection

All patients were evaluated by the pediatric rheumatology team. A comprehensive medical history and physical

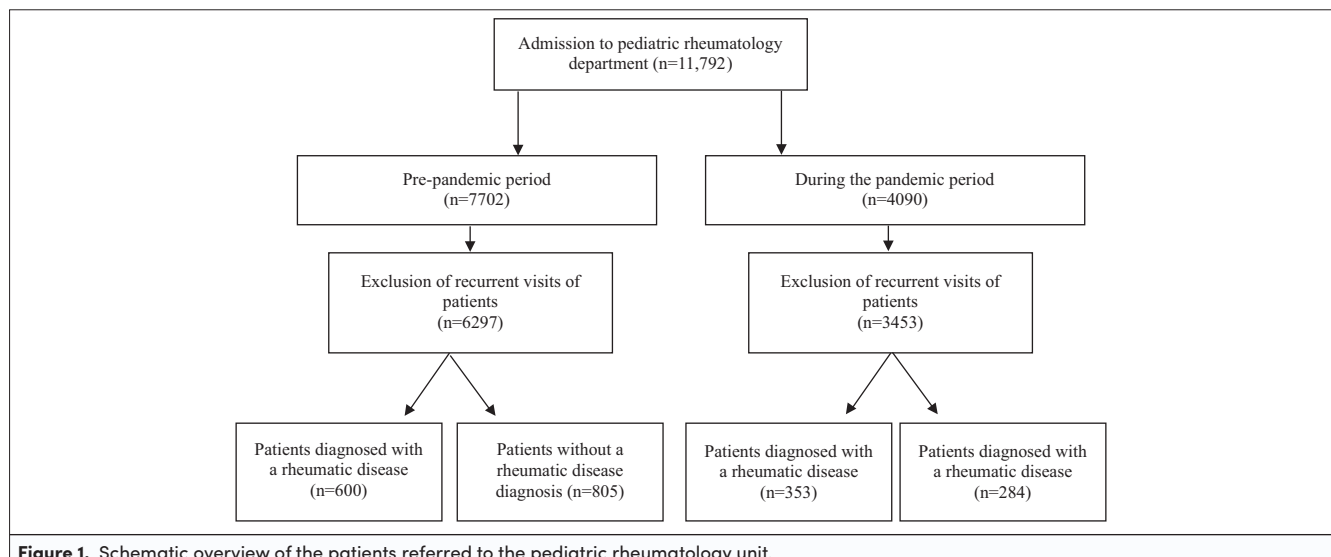


Figure 1. Schematic overview of the patients referred to the pediatric rheumatology unit.

examination were performed. Appropriate laboratory and/or radiological investigations were also carried out. In addition, patients who require a multidisciplinary approach were evaluated by an interdisciplinary team for diagnosis. The medical records of patients were assessed retrospectively for the following variables: sex, age at symptom onset and pediatric rheumatology assessment, the distribution of the consultation requests for patients referred with a consultation form, the referral symptoms or complaints, and any diagnosis of non-rheumatic disease in the follow-up.

Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences software version 20.0. Descriptive statistics such as frequency, median, and percentiles were used for description. The normality of the variable's distribution was investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test). The chi-square test or Fisher's exact test (when the values observed in cells did not meet chi-square test assumptions) was used for the comparison of categorical variables between the groups. Mann–Whitney *U*-test was used for the comparison of continuous data that were not normally distributed. A *P*-value of less than .05 was considered statistically significant.

Ethics Statement

This study has been approved by the ethics committee of Hacettepe University (approval number: GO 21/670) and was conducted according to the guidelines of the Declaration of Helsinki.

RESULTS

Evaluation of Symptoms in Children Referred to Pediatric Rheumatology Unit

A total of 1089 patients (568 female, 52.2%; median age of 10.0 years) were included in the study (Table 1). The most common complaints of referring patients to pediatric rheumatology center were prolonged or recurrent fevers (*n* = 147, 13.4%) followed by anti-nuclear antibody (ANA) positivity (*n* = 143, 13.1%), arthralgia (*n* = 142, 13.0%), skin findings (*n* = 82, 7.5%), and the presence of heterozygous mutations in the MEditerranean FeVer (*MEFV*) gene (*n* = 75, 6.9%) (Table 2). Other indications for referral are summarized in Table 2. The median (25th–75th percentile) time period between symptom onset to application to the pediatric rheumatology department was 6 (1.0–24.0) months for patients without a rheumatic disease diagnosis. There was no significant difference between the time interval from initial symptom onset to the date of admission in the comparison of the pre-pandemic and pandemic period (median time of 6.5 vs. 6.0 months, respectively, *P* = .779).

Distribution of the Referral Departments to the Pediatric Rheumatology Unit

Of 1089 patients, 682 were consulted from other departments in our center (62.6%) (Table 1). Of these, the most frequent consultation request was from general pediatrics (*n* = 298, 43.6%) followed by 77 from the pediatric allergy and immunology department (11.2%), 69 from the pediatric hematology unit (10.1%), 37 from the pediatric emergency department (5.4%), and 26 from the orthopedics (3.8%).

Table 1. Demographic Characteristics of the Patients Referred and Distribution of the Referral Departments to the Pediatric Rheumatology Unit

	Patient Number (n = 1089)
Sex (female), n (%)	568 (52.2)
Age at study, years, median (25th–75th percentile)	10.0 (6.0–13.9)
Age at symptom onset, years, median (25th–75th percentile)	8.0 (3.7–11.9)
Age at pediatric rheumatology assessment, median (25th–75th percentile)	9.5 (5.5–13.3)
Interval between symptom onset to pediatric rheumatology assessment, months, median (25th–75th percentile)	6.0 (1.0–24.0)
Consultation form, n (%) in-hospital consultation	682 (62.6)
The distribution of the consultation requests, n (%)	
General pediatrics	298 (43.6)
Pediatric allergy and immunology department	77 (11.2)
Pediatric hematology unit	69 (10.1)
Pediatric emergency department	37 (5.4)
Orthopedics	26 (3.8)
Pediatric infectious diseases unit	22 (3.2)
Pediatric pulmonology department	19 (2.8)
Dermatology	18 (2.6)
Pediatric endocrinology department	18 (2.6)
Pediatric neurology department	17 (2.5)
Pediatric gastroenterology department	16 (2.3)
Pediatric cardiology department	16 (2.3)
Pediatric nephrology department	11 (1.6)
Pediatric oncology department	8 (1.2)
Department of ophthalmology	6 (0.9)
Department of adolescent medicine	6 (0.9)
Department of pediatric surgery	5 (0.7)
Department of otolaryngology	4 (0.6)
Department of genetics	2 (0.3)
Department of sports medicine	2 (0.3)
Department of pediatric metabolism	2 (0.3)
Department of physical medicine and rehabilitation	2 (0.3)
Department of plastic and reconstructive surgery	1 (0.1)

Impact of the Coronavirus Disease 2019 Pandemic on Patient Characteristics and Referral Symptoms

The number of patients during the COVID-19 pandemic year (March 2020–February 2021) was lower than in the pre-pandemic period (854 patients/year vs. 235 patients/pandemic year). There was no significant age difference between patients admitted in the pre-pandemic and those in the pandemic period (median age of 9.8 years vs. 10.5 years, respectively, *P* = .814). The sex distribution of the groups was also similar (444 females, 51.9% vs. 124 females, 52.7%, *P* = .833). The median (25th–75th percentile) time period between symptom onset to admission to the pediatric rheumatology department was 6.5 (2–23) months in the pre-pandemic period and 6.0 (1–25) months in the pandemic period (*P* = .779). During the pandemic year, the number of patients referred for back pain

Table 2. Complaints or Symptoms of Patients Referred to the Pediatric Rheumatology Unit

	Patient Number (n = 1089)	Patient Number/Year 2019-2020 (n = 854)	Patient Number/Year 2020-2021 (n = 235)	P
Prolonged or recurrent fever, n (%)	147 (13.5)	111 (13.0)	36 (15.3)	.356
ANA positivity, n (%)	143 (13.1)	111 (13.0)	32 (13.6)	.803
Arthralgia, n (%)	142 (13.0)	106 (12.4)	36 (15.3)	.241
Skin findings, n (%)	82 (7.5)	63 (7.4)	19 (8.1)	.716
Presence of heterozygous mutations in the <i>MEFV</i> gene, n (%)	75 (6.9)	66 (7.7)	9 (3.8)	.037
Arthritis, n (%)	68 (6.2)	51 (6.0)	17 (7.2)	.479
Recurrent aphthous stomatitis, n (%)	66 (6.1)	50 (5.9)	16 (6.8)	.587
Abdominal pain, n (%)	63 (5.8)	54 (6.3)	9 (3.8)	.147
Leg pain, n (%)	55 (5.1)	50 (5.9)	5 (2.1)	.021
Neurological findings, n (%)	25 (2.3)	16 (1.9)	9 (3.8)	.076
Ocular manifestations, n (%)	23 (2.1)	20 (2.3)	3 (1.3)	.444*
Back pain, n (%)	19 (1.7)	11 (1.3)	8 (3.4)	.028
Swelling of fingers or hands, n (%)	19 (1.7)	14 (1.6)	5 (2.1)	.579*
Presence of thrombus, n (%)	18 (1.7)	14 (1.6)	4 (1.7)	1.000*
Deformity of the hands or feet, n (%)	14 (1.3)	13 (1.5)	1 (0.4)	.324*
Low serum complement, n (%)	13 (1.2)	13 (1.2)	-	
Elevated ASO level, n (%)	12 (1.1)	9 (1.1)	3 (1.3)	.729*
Erythema nodosum, n (%)	11 (1.0)	10 (1.2)	1 (0.4)	.473*
Cardiac manifestations, n (%)	11 (1.0)	6 (0.7)	5 (2.1)	.066*
Discoloration of the hands or fingers, n (%)	10 (0.9)	8 (0.9)	2 (0.9)	1.000*
Recurrent parotitis, n (%)	9 (0.8)	7 (0.8)	2 (0.9)	1.000*
Gait abnormality, n (%)	8 (0.7)	8 (0.7)	-	
Elevated CK levels, n (%)	8 (0.7)	6 (0.7)	2 (0.9)	.685*
Heel pain, n (%)	7 (0.6)	6 (0.7)	1 (0.4)	1.000*
Interstitial lung diseases, n (%)	6 (0.6)	3 (0.4)	3 (1.3)	.119*
Muscle weakness, n (%)	6 (0.6)	4 (0.5)	2 (0.9)	.615*
Renal manifestations, n (%)	6 (0.6)	4 (0.5)	2 (0.9)	.615*
Unexplained high levels of acute phase reactants, n (%)	5 (0.5)	4 (0.5)	1 (0.4)	1.000*
Hemoptysis, n (%)	4 (0.4)	4 (0.5)	-	
Neck pain, n (%)	4 (0.4)	4 (0.5)	-	
Hypertension, n (%)	4 (0.4)	2 (0.2)	2 (0.9)	.205*
Cytopenias, n (%)	3 (0.3)	3 (0.4)	-	
Granulomatous lesion, n (%)	2 (0.2)	2 (0.2)	-	
Swelling of the cartilage of ears, n (%)	1 (0.1)	1 (0.1)	-	

ANA, anti-nuclear antibody; ASO, anti-streptolysin O; CK, creatine kinase; *MEFV*, Mediterranean Fever gene.
Chi-square test was used unless otherwise stated.
*Fisher's exact test was used.

increased significantly ($P = .028$) while the number of patients admitted with the presence of heterozygous mutations in the *MEFV* gene and complaints of leg pain decreased ($P = .037$ and $P = .021$, respectively) (Table 2).

Outcome of Patients Referred to Pediatric Rheumatology Unit and Not Diagnosed with Rheumatic Disease

Twenty-six patients (2.3%) were diagnosed with a non-rheumatic disease (Table 3). Infections, hematologic malignancies, and celiac disease were the most commonly diagnosed non-rheumatic diseases. A rheumatic disease was excluded in a total of 124 patients (11.3%) and follow-up was stopped. The remaining patients continue to follow up.

DISCUSSION

In this study, we evaluated the complaint profile of patients who were referred to the tertiary pediatric rheumatology unit

and were not diagnosed with rheumatic disease. Although prolonged or recurrent fever, ANA positivity, and arthralgia were the most common reasons for referrals, patients were referred with a wide range of complaints. Our results demonstrated that pediatric rheumatology is a department that deals with a wide variety of symptoms. We also found that the number of patients referred for back pain increased significantly during the pandemic year.

About half of the patients (46.6%) admitted were diagnosed with rheumatic disease. The rheumatic disease diagnosis rate was reported as 51% in Israel, 40.5% in the USA, and 50.9% in Canada.^{6,7,20} The diagnosis rate in the patient population referred to the pediatric rheumatology unit in Southeast Asia was found to range from 51.2% to 73%.²¹ As stated, the difference in the diagnosis rate may be related to awareness of the rheumatic disease, socioeconomic characteristics

Table 3. Pediatric Patients Diagnosed with a Non-Rheumatic Disease

Diagnosis with a non-rheumatic disease, n	26
Infections, n (%)	4 (15.3)
Hematologic malignancies, n (%)	3 (11.5)
Celiac disease, n (%)	3 (11.5)
Osteoblastoma, n (%)	1 (3.8)
Immunodeficiency, n (%)	1 (3.8)
Becker's muscular dystrophy, n (%)	1 (3.8)
Non-ossifying fibroma, n (%)	2 (7.6)
Pigmented purpuric dermatitis, n (%)	1 (3.8)
FARSB mutation, n (%)	1 (3.8)
Patellar dislocation, n (%)	1 (3.8)
Stress fracture, n (%)	1 (3.8)
Inflammatory bowel disease, n (%)	1 (3.8)
Leber hereditary optic neuropathy, n (%)	1 (3.8)
Atopic dermatitis, n (%)	1 (3.8)
Tarsal coalition, n (%)	1 (3.8)
Osteogenesis imperfecta, n (%)	1 (3.8)
Atlantoaxial dislocation, n (%)	1 (3.8)
Tubulointerstitial nephritis, n (%)	1 (3.8)

of the community, and accessibility to pediatric rheumatology centers.²¹

The most common symptom for referral was prolonged or recurrent fever. Infection, malignancy, and rheumatic inflammatory diseases are included in the etiology of fever of unknown origin. Autoinflammatory diseases also cause recurrent fevers. Children with periodic (episodic) fever and accompanying elevation of acute phase reactants are highly suspect for autoinflammatory diseases, especially in the presence of symptoms such as arthralgia and abdominal pain. The prevalence of autoinflammatory diseases varies between geographical regions. Familial Mediterranean fever (FMF) is the most common hereditary monogenic autoinflammatory disease.²² The prevalence of FMF in Turkey is approximately 1/1000, and the carrier rate is 1 : 5.²³ Therefore, FMF should be kept in mind in the differential diagnosis of patients with recurrent fever. Meanwhile, approximately 7% of patients were referred to our department for the presence of heterozygous mutations in the *MEFV* gene. Although FMF is an autosomal recessive disease, some carriers of one *MEFV* mutation may have an FMF phenotype.^{24,25} Also, evidence of subclinical inflammation was demonstrated in these patients.^{26,27} Heterozygous carriers of *MEFV* mutations should be followed up for clinical phenotype of FMF and signs of subclinical inflammation.

Anti-nuclear antibody positivity was the second most common reason for referral, accounting for 13.1% of all referrals. A result of a web-based survey of primary pediatricians revealed that the most common reasons for referral to pediatric rheumatologists were high suspicion of rheumatic disease (88%), chronic arthritis of uncertain etiology (64%), musculoskeletal pain with a normal examination (44%), and positive ANA tests (44%).²⁸ Positive ANA results can be found in rheumatic diseases such as systemic lupus erythematosus (SLE), mixed connective tissue disease, and other overlap syndromes.^{29,30} However, its specificity is low.³¹ Haslak et al³² evaluated 358 patients referred

for ANA positivity to the pediatric rheumatology department. After a median follow-up of 4.8 years, they showed that none of the patients developed any ANA-associated rheumatic disease. The prevalence of ANA positivity was also reported as 15% in healthy children.³³ Anti-nuclear antibody positivity would be more valuable in the presence of signs and symptoms of rheumatic disease, or suggestive laboratory tests such as elevated erythrocyte sedimentation rate or proteinuria. Moreover, the titer of ANA is significant. The European League Against Rheumatism/American College of Rheumatology classification criteria of SLE require the presence of ANA with a titer of 1:80 or higher as an "entry criterion."³⁴ However, the use of a cut-off titer at 1 : 160 to distinguish healthy controls from those with connective tissue disease was suggested in some studies.^{35,36}

Arthralgia was the third most common clinical feature for the referral. In a study from Turkey, the most frequent reason for referral was stated as arthralgia in 21.9%, followed by recurrent fever and abdominal pain in 10.6% of patients.⁵ The list of differential diagnoses of joint pain is large including orthopedic, infectious, inflammatory conditions, and malignancies.³⁷ The character of the pain should be evaluated to understand whether it is an inflammatory type of pain. Diseases such as juvenile idiopathic arthritis, vasculitis, and SLE are included in the differential diagnosis of inflammatory joint pain.^{38,39} A comprehensive medical history and physical examination are key to the appropriate management of these patients and their combination with laboratory investigation may point to one or a few diagnoses. For instance, in a child with generalized joint pain, constitutional symptoms, and lymphadenopathy or organomegaly, the assessment for malignancy should be given priority, while FMF should first come to mind in a patient with a history of recurrent fever and concurrent short-term joint swelling.

The COVID-19 pandemic has a significant impact on our daily lifestyle as well as pediatric rheumatology practice.^{13,19,40} Physical inactivity, increased television viewing, and computer/tablet use during the pandemic were found to be related to a higher frequency of back pain in adults.⁴¹ In the evaluation of screen and digital game playing time in children, Ofli et al⁴² found that the proportion of children with screen time of ≥ 1 hour and playing digital games during the pandemic period increased significantly compared to the pre-pandemic era. Also, severe acute respiratory syndrome coronavirus 2 infection itself may lead to prolonged myalgia which could also contribute to the increased frequency of back pain during the pandemic. An online survey completed by 388 adults revealed that 30% of participants experienced back pain before the onset of COVID-19 while 49% had low back pain since the onset of COVID-19. More than half of the participants (53.4%) who had suffered from back pain since the onset of COVID-19 reported that they had never experienced chronic back pain before.⁴³ We also found that the number of patients referred for back pain increased significantly in children during the pandemic year. Another major effect of the pandemic was the decrease in the number of patients in the outpatient pediatric rheumatology clinic because of postponed or missed appointments.¹³ A 57.7% reduction in pediatric admissions was reported in the first year of the COVID-19 pandemic.⁴⁴ The number of patients had decreased during the pandemic in our study, as well.

One limitation is the retrospective nature of the study. Another is that it can take time to go from symptoms to a rheumatic disease diagnosis and long-term follow-up may be needed. Some of these patients may be diagnosed in the long-term follow-up. We evaluated the patients without a rheumatic disease diagnosis in a pediatric rheumatology unit. Despite these limitations, the strength of our study was that we evaluated the symptom profile of patients referred to a tertiary pediatric rheumatology unit and the impact of the pandemic on reasons for referral.

In conclusion, rheumatic diseases can lead to a wide variety of symptoms. Prolonged or recurrent fever, ANA positivity, arthralgia, and skin findings were the most frequent complaints of referrals to a pediatric rheumatology unit in patients who did not have a rheumatic disease. Documenting the diversity and frequency of referral symptoms will raise awareness among physicians. Also, a comprehensive medical history, physical examination, and the correct use of laboratory tests are required to reach a correct diagnosis and reduce unnecessary referrals. In addition, the rate of back pain was found to be more common in children during the pandemic period. Physical activity may help to reduce the negative effects of a sedentary lifestyle during the COVID-19 pandemic.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Hacettepe University (Approval No: GO 21/670, Date: 26.05.2021).

Informed Consent: Informed consent was not obtained from patients due to its retrospective nature.

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