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Obstacles in Early Diagnosis of Children With Juvenile Idiopathic Arthritis: A Nationwide Israeli Retrospective Study

Yochai Frenkel[1], Irit Kraushar[2], Mohamad Hamad Saied[3], Ruby Haviv[4], Yosef Uziel[4], Merav Heshin-Bekenstein[5], Eduard Ling[6], Gil Amarilyo[7], Liora Harel[7], Irit Tirosh[8], Shiri Spielman[8], Yackov Berkun[9], and Yonatan Butbul Aviel[10]

ABSTRACT. ***Objective.*** Characterization of the stages that patients with juvenile idiopathic arthritis (JIA) pass until they are diagnosed, and analysis of the different causes that lead to a delay in JIA diagnosis in Israel.

Methods. This is a retrospective cohort study conducted in 8 pediatric rheumatology centers in Israel. All patients diagnosed with JIA between October 2017 and October 2019 were included in the study. Demographic, clinical, and data regarding the referring physicians were collected from hospital and community medical charts.

Results. Of 207 patients included in the study, 201 cases were analyzed, 71.1% of the population were female. Patients, on average, were evaluated during the diagnostic process by 3.1 different physicians. In most cases, they initially met with a pediatrician in the community setting (61.2%), and later, most commonly referred to a rheumatologist by the community pediatrician (27.9%). The median time until diagnosis was 56.0 days (range: 1.0-2451.0 days). Patients diagnosed with polyarticular and spondyloarthritis/enthesitis-related arthritis (SpA/ERA) JIA subtypes had the longest period until diagnosis (median: 115.5 and 112.0 days, respectively). Younger age correlated with a quicker diagnosis, and females were diagnosed earlier compared to males. Fever at presentation significantly shortened the time to diagnosis ($P < 0.01$), whereas involvement of the small joints/sacroiliac joints significantly lengthened the time ($P < 0.05$).

Conclusion. This is the first nationwide multicenter study that analyzes obstacles in the diagnosis of JIA in Israel. Raising awareness about JIA, especially for patients with SpA/ERA, is crucial in order to avoid delays in diagnosis and treatment.

Key Indexing Terms: delay in diagnosis, Israel, juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease, with an estimated incidence of 1:1000 children in Israel.[1] The peak age of incidence differs between JIA subtypes and ranges from 1 to 4 years; sometimes it has a bimodal distribution, with another peak at 6 to 12 years, and with a predominance in females.[2] JIA is a heterogeneous group of chronic joint diseases, which are separated into categories based on the International League of Associations for Rheumatology (ILAR) classification system.[3]

Delay to pediatric rheumatology care is crucial and predicts poorer disease outcomes for patients with JIA.[4] Early and aggressive treatment regimens decrease the frequency of exacerbations, lower complication rates, and improve the physical and functional status of the patients.[5] Left untreated, the disease can potentially cause destruction of the synovial tissue, contracture, permanent skeletal damage, and even blindness. Approximately one-third of patients with JIA remain in high disease activity at 1 year post presentation.[4] According to the 2009 British Society

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[1]Y. Frenkel, MD, Department of Pediatrics A, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa; [2]I. Kraushar, MD, The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa; [3]M.H. Saied, MD, The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, and Department of Pediatrics, Carmel Medical Center and Clalit Health Services, Haifa; [4]R. Haviv, MD, Y. Uziel, MD, Department of Pediatrics, Pediatric Rheumatology Unit, Meir Medical Center, Kfar Saba, and Tel Aviv University, Sackler School of Medicine, Tel Aviv; [5]M. Heshin-Bekenstein, MD, Tel Aviv University, Sackler School of Medicine, and Pediatric Rheumatology Service, Dana-Dwek Children's Hospital, Tel Aviv Medical Center, Tel Aviv; [6]E. Ling, MD, Department of Pediatrics, Pediatric Rheumatology Unit, Soroka University Medical Center, and Faculty of Health Sciences, Ben Gurion University of the Negev, Beer-Sheva; [7]G. Amarilyo, MD, L. Harel, MD, Tel Aviv University, Sackler School of Medicine, Tel Aviv, and Pediatric Rheumatology Unit, Schneider Children's Medical Center, Petah Tikva; [8]I. Tirosh, MD, S. Spielman, MD, Pediatric Rheumatology Service and Pediatric Department, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, and Tel Aviv University, Sackler School of Medicine, Tel Aviv; [9]Y. Berkun, MD, Department of Pediatrics, Hadassah-Hebrew University Medical Center, Mount Scopus, and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem; [10]Y. Butbul Aviel, MD, Department of Pediatrics B, and Pediatric Rheumatology Service, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa, Israel.

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Address correspondence to Dr. Y. Butbul Aviel, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Efron Street 1, Bat-Galim, Haifa 31096, Israel. Email: yonatanbutbul@gmail.com.

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for Pediatric and Adolescent Rheumatology Standards of Care, all children with JIA should be assessed by a pediatric rheumatology team within 10 weeks of symptom onset and 4 weeks of referral.[6] A 2013 study reporting on 10 pediatric rheumatology centers in the United Kingdom that participated in a retrospective review of clinical practice found that 41% of patients were seen within 10 weeks of symptom onset, and 60% had their first pediatric rheumatology appointment within 4 weeks of their initial referral.[7]

A study conducted in France on the time to diagnosis of JIA found that JIA was suspected after a time delay of 3 months.[8] It also pointed out that academic recognition of the pediatric rheumatology subspecialty and opportunities to obtain appropriate medical education are insufficient in many European countries.[8] During that delayed time period, many children were referred to multiple secondary care specialties and subjected to multiple and often invasive procedures, including arthroscopy, synovial biopsy, and synovectomy.[9,10]

In addition, children with systemic JIA (sJIA) seem to experience the shortest delay to diagnosis, whereas total time to diagnosis of enthesitis-related arthritis (ERA) is the longest. Further, general pediatricians almost always consider inflammatory hip pain in children as transient synovitis, even though this diagnosis is limited to younger patients.[11]

In Israel, seeing a rheumatologist is dependent on a referral from another physician. Therefore, the diagnosis of patients with JIA may be delayed by weeks, and even months, though the exact amount of time is unknown.

The aim of our study was to evaluate the time from symptom onset to diagnosis of JIA, and to evaluate the causes for a delay in diagnosis.

METHODS

We conducted a retrospective cohort study among 8 pediatric rheumatology centers in Israel, including all patients who were diagnosed with JIA according to the ILAR criteria between October 2017 and October 2019.[3]

Patients were classified in 5 JIA subtypes: oligoarticular (oligoJIA), polyarticular (polyJIA), ERA, psoriatic arthritis (PsA), and sJIA.

Data collected from hospitals and community medical records included epidemiologic characteristics, documented medical examinations, laboratory tests (C-reactive protein, erythrocyte sedimentation rate [ESR], antinuclear antibodies, rheumatoid factor [RF], and HLA-B27) where available, imaging, empiric treatments, and reference letters. The gathered data included date of the patient's first symptom of JIA, time of diagnosis, time until referral to a rheumatologist, differential diagnoses, number and type of physicians seen before diagnosis, symptoms, and any procedures they underwent prior to diagnosis.

Ethics. The study was approved by the Rambam Health Care Campus clinical studies ethics committee (Helsinki Board; approval no. RMB-0373-19). Due to the retrospective nature of the study, no patient consent was required. Each hospital's local Helsinki Committee approved the study.

Statistical analysis. All statistical analyses were performed using SPSS statistical package version 28 (IBM Corp). All data are expressed as medians, means (SDs), or percentages. Chi-square test, Mann-Whitney *U* test, and *t* test were used, and a P value < 0.05 was statistically significant.

RESULTS

Information was recorded from 207 patients diagnosed with JIA between October 2017 and October 2019. Excluded were 2 patients diagnosed with isolated temporomandibular joint complaints and 3 with extended oligoarticular JIA, due to their small proportion out of the entire cohort population size. One more patient with oligoJIA was excluded due to missing data regarding the date of diagnosis. Of 201 patients included in the analysis, 124 (61.7%) had oligoJIA, 30 (14.9%) had polyJIA (4 were RF positive, 23 RF negative, and 3 did not have a documented test for RF), 21 (10.4%) had sJIA, 19 (9.4%) had ERA, and 7 (3.5%) had PsA. No patients with undifferentiated JIA were diagnosed during the study period. Mean (SD) age at diagnosis was 7.7 (5.4) years and most patients were White (80.6%). Median distance from nearby pediatric rheumatology care center to place of living was 13.0 kilometers. Other demographic and laboratory characteristics of the study population are presented in Table 1.

The most common initial symptoms were limited range of motion (109; 54.2%), limping (103; 51.2%), and morning stiffness (84; 41.8%).

Community clinic pediatricians were most commonly the first physician patients met after symptoms appeared (61.2%). Afterward, as they were referred to other specialists, orthopedists were most commonly encountered as the second (40.3%), and third (19.4%) physicians to examine the patients (Table 2). Therefore, a patient who encountered at least 3 physicians initially was most likely to meet a community clinic pediatrician first, then an orthopedist twice thereafter. On average, patients were seen by 3.1 physicians before being referred to a rheumatologist, though the majority met with a total of 4 physicians (Figure), and the most common referring specialists were community clinic pediatrician (27.9%), in-hospital pediatricians (25.9%), and orthopedists (18.9%). Diagnosis was most commonly made in an outpatient hospital clinic (64.2%), followed by inpatient consultation (26.4%), and outpatient community clinic (7.9%); 99 (49.3%) patients were hospitalized at least once prior to diagnosis.

Table 1. Baseline demographic and laboratory evaluation.

	N = 201
Age, yrs, mean (SD; range)	7.7 (5.4; 0.6-18.2)
Female, n (%)	143 (71.1)
Ethnicity, n (%)	
White	199 (99)
Black	2 (1)
Distance to hospital, km, median (range)	13.0 (0.5-197.0)
CRP[a], mg/dL, mean	5.5
ANA[b], n (%)	
Positive	81 (43.8)
Negative	104 (56.2)
RF positive[c], n (%)	5 (2.5)
ESR[d], mm/h, mean (SD)	34.3 (27.3)
HLA-B27 positive[e], n (%)	6 (2.9)

The following n (%) were evaluated: [a] n = 195 (97%); normal values < 5); [b] n = 185 (92%); [c] n = 134 (66%); [d] n = 129 (64%); [e] n = 30 (5%). ANA: antinuclear antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor.

Table 2. Evaluating physicians prior to a rheumatologist assessment.

	Values
First specialist to evaluate the patient	
Community clinic pediatrician	123 (61.2)
Orthopedic surgeon	22 (10.9)
Emergency physician	27 (13.4)
Family physician	10 (4.9)
General practitioner	11 (5.5)
In-hospital pediatrician	8 (3.9)
Second specialist to evaluate the patient	
Community clinic pediatrician	12 (5.9)
Orthopedic surgeon	81 (40.3)
Emergency physician	48 (23.9)
In-hospital pediatrician	25 (12.4)
Third specialist to evaluate the patient	
Community clinic pediatrician	31 (15.4)
Orthopedic surgeon	39 (19.4)
Emergency physician	30 (14.9)
In-hospital pediatrician	34 (16.9)
No. of physicians evaluating the patient before a rheumatologist, mean	3.1
No. of hospitalizations until given a diagnosis	
0	104 (51.7)
1	74 (36.8)
2	21 (10.4)
3	2 (0.9)

Values are expressed as n (%) unless otherwise indicated.

Overall, the average time to diagnosis was 135.9 (median 56.0, range 1.0-2451.0) days, which, after excluding those diagnosed with sJIA, was increased to 152.1 (median 62.5) days. Eighty-nine (44.3%) patients were diagnosed after more than 10 weeks. PolyJIA was found to have the longest median time (115.5 days) from the presenting symptom until diagnosis, followed by SpA/ERA JIA (112.0 days), PsA (60.0 days), oligoJIA (50.0 days), and sJIA (25.0 days; Table 3). Females were diagnosed significantly sooner (mean 107.2 [SD 175.8] vs 195.2 [361.2] days for males, $P < 0.05$), and younger age at presentation was correlated with shorter time to diagnosis ($r = 0.329$, $P < 0.01$). There was

Table 3. Time (in days) from the first symptom to diagnosis by disease type.

JIA Subtype	Patients, n	Days, median (range)
Polyarticular	30	115.5 (6.0-1442.0)
Oligoarticular	124	50.0 (1.0-782.0)
Systemic	21	25.0 (10.0-370.0)
SpA/ERA	19	112.0 (5.0-2451.0)
Psoriatic arthritis	7	60 0.(24.0-752.0)

ERA: enthesitis-related arthritis; JIA: juvenile idiopathic arthritis; SpA: spondyloarthritis.

no significant difference between the time from first symptom to diagnosis when comparing races and ethnicity (White vs others, mean 118.8 [190.1] vs 197.2 [396.3] days, $P = 0.19$), family history of autoimmune diseases (positive vs negative family history, mean 145.1 [196.1] vs 132.2 [270.3] days, $P = 0.22$), and distance to the hospital from place of living. On the other hand, patients who had higher ESR values at presentation were diagnosed sooner than patients with lower values ($r = -0.207$, $P < 0.05$), and patients who initially presented with fever (median 31.0 days) were diagnosed sooner than patients without fever (median 76.0 days; $P < 0.01$). However, patients who first presented with small joint or sacral joint involvement were diagnosed after a longer period of time compared to those without (median 86.5 vs 46.5 days, $P < 0.01$ for small joint; 226.0 vs. 51.0 days for sacral joint, $P < 0.05$; Table 4).

Morning stiffness was the only symptom to have a significant effect on time to referral to a rheumatologist (median 21.5 vs 36.5 days when stiffness was not present compared to when presented, $P < 0.01$). When inspecting laboratory tests, ESR was the only test found to have an effect on time to referral, shortening this period of time when elevated ($r = -0.196$, $P < 0.05$).

Among the 48 (23.9%) patients in the study population who underwent medical invasive procedures, 2 patients had ≥ 1 procedure. Of the patients who underwent any procedure before JIA diagnosis, the most common operation was joint needle aspiration (95.8%); 2 patients had a synovial biopsy and 1 patient a synovectomy. When analyzing the patients who underwent any

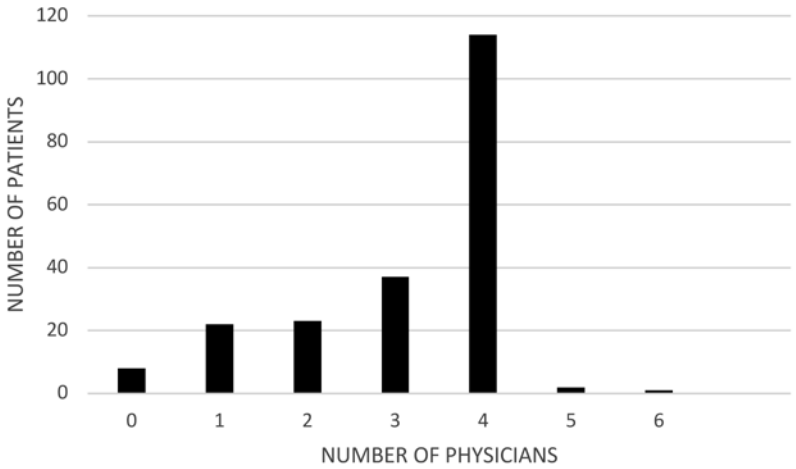

Figure. Total number of evaluating physicians before meeting the rheumatologist.

Table 4. Initial presenting symptom with relation to time until diagnosis.

Symptom at Presentation	Time to Diagnosis, days, median		*P*
	Symptoms Are Present at Presentation	Symptoms Are Not Present at Presentation	
Fever	31.0	76.0	**< 0.01**
Uveitis	36.5	57.0	0.23
Rash	31.5	60.0	0.06
Limited range of motion	50.0	62.0	0.75
Morning stiffness	64.0	53.0	0.34
Small joint involvement	86.5	46.5	**< 0.01**
Large joint involvement	57.0	30.0	0.19
Sacral joint involvement	226.0	51.0	**0.049**

Values in bold are statistically significant ($P < 0.05$).

procedures, 85.4% were eventually diagnosed with oligoJIA, 6.2% with SpA/ERA and 8.3% with polyJIA. Analyzing the initial suspected diagnosis that led to the procedures resulted in 18 (8.9%) patients with suspected infectious etiology, 20 (9.9%) patients with suspected traumatic/orthopedic etiology, and 8 (3.9%) patients with suspected inflammatory etiology.

DISCUSSION

Israel is a relatively small and densely populated country, and its medical care system is very accessible, with every settlement having at least 1 community clinic in and being a relatively short distance to a hospital. This multicenter study retrospectively analyzed the time it took for patients with newly diagnosed JIA in Israel to be referred to a rheumatologist and receive their diagnosis, while describing possible causes for delay in diagnosis over a 2-year period.

In our study, we found that the median time from onset of symptoms to diagnosis of JIA was 56.0 days, with a range of 1.0 to 2451.0 days. In particular, patients with polyJIA and SpA/ERA JIA both demonstrated longer times to diagnosis. Prompt diagnosis of JIA is important to initiate early treatment and avoid long-term complications. In a study by Foster and Rapley, many children with delay in diagnosis (defined as > 10 weeks from symptom onset to first pediatric rheumatology assessment) had prolonged untreated active disease, multiple restricted joints, no eye screening (to detect chronic anterior uveitis), and a median interval from onset of symptoms to starting methotrexate of 10 months.[12] When considering the required waiting time of 6 weeks before JIA diagnosis, our study shows Israel is operating close to the standard, though there is a wide range of observed times to diagnosis and differences among JIA subtypes. Nonetheless, 89 (44.3%) of the patients were diagnosed more than 10 weeks after the beginning of symptoms.

One retrospective study in the UK found that the majority (40%) of patients whose diagnosis was delayed by more than 10 weeks were those with persistent oligoJIA, whereas patients with sJIA were diagnosed in the timeliest manner (1.6% had a delay in diagnosis > 10 weeks).[7] In a study in France, patients with SpA/ERA JIA had the longest time to diagnosis (median 5.5 months), whereas patients with sJIA had the shortest time to diagnosis (median 1.3 months), with a total median time from appearance of symptoms to diagnosis of 3 months.[8]

Patients in the French study were most commonly evaluated by emergency room physicians, followed by general practitioners/pediatricians; most patients saw 2 physicians prior to being referred to a pediatric rheumatologist.[8] In our study, patients were most commonly evaluated by community pediatricians, with the next visit by orthopedists, and 56.7% of the patients were evaluated by a total of 4 physicians prior to referral to a rheumatologist (Figure). Although patients in Israel were seen by more physicians (mean 3.1) prior to referral to a rheumatologist, compared to the French study, the median time to diagnosis was shorter (56.0 days vs 3 months [~90 days]). These data may be explained by a highly accessible and widely affordable medical care to the general population in Israel, leading to frequent visits to medical facilities and greater tendency of administering relatively high volumes of medical exams and tests. Israel, similarly to France and the UK, had the shortest time to diagnosis in patients with sJIA, probably because they are usually admitted quite quickly due to prolonged fever and seen by a rheumatologist early during the course of the disease. Another similarity between Israel and the 2 European countries was the finding that ERA had a significant delay in diagnosis.

In our study, the patients with greatest diagnostic delay were those with SpA/ERA JIA and polyJIA. This may be because the diagnosis of SpA/ERA requires more clinical experience and a high index of suspicion, sacroiliitis may appear later in the course of the disease, and enthesitis may be challenging to diagnose as it presents with symptoms that are common in the general pediatric population, such as in a child with overuse injury.[7] Patients with polyJIA mainly have polyarticular small joint involvement, which may account for the delayed diagnosis, as small joint disease is often missed on physical examination by nonexperienced physicians. JIA, overall, has a broad differential diagnosis that may lead clinicians to think about other possible diseases.[13-16]

Interestingly, younger patients were diagnosed sooner than older patients, and females earlier than males. This may be partly explained by the tendency of SpA/ERA to present in older male patients.[17] JIA is more common in females and, thus, there may be an increased sense of suspicion in this population. Further, diagnosis of racial and ethnic minority groups took almost twice as long than White patients on average, though this finding was not significant. It is already known that sociocultural factors play a role in the diagnosis of JIA, and it is possible that there is a lack of awareness of the condition in racial and ethnic minority populations.[18] Moreover, White patients may have greater accessibility to resources, such as private specialists. In this study, the majority of patients (56.7%) saw 4 physicians prior to their referral to a rheumatologist. In general, the first physician the patients saw was their primary care pediatrician, who most often referred them to an orthopedist. However, even though a large number of patients saw an orthopedist in their course prior to diagnosis, the majority of referrals to rheumatologists were made by pediatricians, either in a community clinic or in hospital, and

not by orthopedists. This raises the concern that orthopedists may not be sufficiently cognizant of JIA.

Finally, 2 more interesting pieces of data should be noted. First, only a minor part of the cases was diagnosed in the community medical system (7.9%). Second, almost half the study population had at least 1 hospitalization before receiving the diagnosis of JIA. Theoretically, a minimal number of hospital admissions is required to achieve a diagnosis within the time frame of 6 weeks (excluding sJIA), so it may be assumed that one would expect a much lower percentage of inpatient admissions in the time between first symptoms until diagnosis. This may point to the need to focus on raising community clinic physicians' awareness of JIA manifestation and the importance of prompt referral to a rheumatologist, to decrease unnecessary admissions and avoid delayed treatment, thus strengthening both the community service and hospital infrastructure.

In our study, distance from the hospital was not associated with longer time to diagnosis, suggesting that the main cause for delay in diagnosis was not the access to pediatric rheumatology service but was mainly due to the delayed diagnosis by primary care physicians and orthopedists in the community.

Our main study limitation is its retrospective nature. In addition, important data (eg, socioeconomic status, cultural association, private clinic visits) are poorly documented, if at all, which could influence the results. Further, because the data were gathered from hospitals, patients who never saw a rheumatologist in the hospital were not included in this study.

In summary, our study demonstrates the importance of increasing the awareness for JIA among general pediatricians and orthopedic surgeons, especially for symptoms of ERA. Efforts should be made to improve the pediatric joint assessment done by primary care physicians and orthopedists in the community health service, which are often the first line of inspection, in order to minimize missing out on overt clinical signs that could hint on JIA. In this way, unnecessary tests and procedures may be avoided and, most importantly, better pediatric joint assessment will allow early introduction of therapy to patients with JIA and prevent long-term complications.

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REFERENCES

1. Uziel Y. Juvenile idiopathic arthritis in the era of international cooperation. Rambam Maimonides Med J 2017;8:3.
2. Macaubas C, Nguyen K, Milojevic D, Park JL, Mellins ED. Oligoarticular and polyarticular JIA: epidemiology and pathogenesis. Nat Rev Rheumatol 2009;5:616-26.
3. Petty RE, Southwood TR, Manner P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton. J Rheumatol 2001;31:390-2.
4. McErlane F, Foster HE, Carrasco R, et al. Trends in paediatric rheumatology referral times and disease activity indices over a ten-year period among children and young people with juvenile idiopathic arthritis: results from the childhood arthritis prospective study. Rheumatology 2016;55:1225-34.
5. Beresford MW, Baildam EM. New advances in the management of juvenile idiopathic arthritis - 1: Non-biological therapy. Arch Dis Child Educ Pract Ed 2009;94:144-50.
6. Davies K, Cleary G, Foster H, Hutchinson E, Baildam E; British Society of Paediatric and Adolescent Rheumatology. BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis. Rheumatology 2010;49:1406-8.
7. Kavirayani A, Foster HE; British Society for Paediatric and Adolescent Rheumatology. Paediatric rheumatology practice in the UK benchmarked against the British Society for Paediatric and Adolescent Rheumatology/Arthritis and Musculoskeletal Alliance Standards of Care for juvenile idiopathic arthritis. Rheumatology 2013;52:2203-7.
8. Aoust L, Rossi-Semerano L, Koné-Paut I, Dusser P. Time to diagnosis in juvenile idiopathic arthritis: a French perspective. Orphanet J Rare Dis 2017;12:43.
9. Foster HE, Eltringham MS, Kay LJ, Friswell M, Abinun M, Myers A. Delay in access to appropriate care for children presenting with musculoskeletal symptoms and ultimately diagnosed with juvenile idiopathic arthritis. Arthritis Rheum 2007;57:921-7.
10. Tzaribachev N, Benseler SM, Tyrrell PN, Meyer A, Kuemmerle-Deschner JB. Predictors of delayed referral to a pediatric rheumatology center. Arthritis Care Res 2009;61:1367-72.
11. Dubois-Ferrière V, Belaieff W, Lascombes P, De Coulon G, Ceroni D. Transient synovitis of the hip: which investigations are truly useful? Swiss Med Wkly 2015;145:w14176.
12. Foster H, Rapley T. Access to pediatric rheumatology care – a major challenge to improving outcome in juvenile idiopathic arthritis. J Rheumatol 2010;37:2199-202.
13. Jones OY, Spencer CH, Bowyer SL, Dent PB, Gottlieb BS, Rabinovich CE. A multicenter case-control study on predictive factors distinguishing childhood leukemia from juvenile rheumatoid arthritis. Pediatrics 2006;117:840-4.
14. El-Hallak M, Giani T, Yeniay BS, et al. Chronic minocycline-induced autoimmunity in children. J Pediatr 2008;153:314-9.
15. Zletni MA, Abeed AM, Kawaja ES. Early-onset childhood sarcoidosis, manifesting as juvenile idiopathic arthritis: a case report. MOJ Orthop Rheumatol 2016;6:234.
16. Yotsumoto S, Takahashi Y, Takei S, Shimada S, Miyata K, Kanzaki T. Early onset sarcoidosis masquerading as juvenile rheumatoid arthritis. J Am Acad Dermatol 2000;43:969-71.
17. Lassoued Ferjani H, Maatallah K, Miri S, et al. Enthesitis-related arthritis: monitoring and specific tools. J Pediatr 2022;98:223-9.
18. Flatø B, Lien G, Smerdel A, et al. Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. J Rheumatol 2003;30:386-93.