Nationwide Israeli Study: Obstacles in Early Diagnosis of Children with Juvenile Idiopathic Arthritis (JIA) - A Retrospective Study

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ABSTRACT

Objectives: Characterization of the stages that patients with JIA pass until diagnosis, and analysis of the different causes that lead to a delay in JIA diagnosis in Israel.

Methods: The study is a retrospective, cohort study that was done in eight 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 referral's 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 three (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 (27.8%). The median time until diagnosis was 56.0 days (range: 1.0-2451.0 days). Patients diagnosed with polyarticular and enthesitis related-/spondyloarthritic (ERA/SPA) 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 ($P<0.05$).

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

1. Introduction[1]

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease, with an estimated incidence of 1:1,000 children in Israel (1). The peak age of incidence differs between JIA subtypes and mostly ranges around 1-4 years and sometimes has a bimodal distribution with another peak at 6-12 years, and with a predominance of 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 JIA patients (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, skeletal permanent 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 for Pediatric and Adolescent Rheumatology (BSPAR) 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 ten UK pediatric rheumatology centers that participated in a retrospective review of clinical practice found that 41.0% of patients were seen within 10 weeks of symptom onset, and 60.0% had their first pediatric rheumatology appointment within 4 weeks of their initial referral (7).

[1] Abbreviations:
Oligoarticular JIA (OAJIA), polyarticular JIA (POJIA), enthesitis-related arthritis (ERA), systemic onset JIA (sJIA), temporo-mandibular joint (TMJ), rheumatoid factor (RF).

A study on time to diagnosis of JIA, conducted in France, found that JIA was suspected after a time delay of 3 months. 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-onset JIA seem to experience the shortest delay to diagnosis, whereas, total time to diagnosis of enthesitis-related arthritis is the longest. Furthermore, 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 suffering from 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 symptoms onset to diagnosis of JIA, and to evaluate the causes for a delay in diagnosis.

2. Materials and Methods

We conducted a retrospective cohort study among eight 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 five JIA subtypes: oligoarticular onset (OAJIA), polyarticular onset (POJIA), enthesitis-related arthritis (ERA), psoriatic arthritis, and systemic JIA (sJIA).

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

The study was approved by the author's institution's clinical studies' ethics committee (Helsinki board); the approval number is RMB-0373-19.

Due to the nature of the study as a retrospective cohort study, no patient consent was required.

2.1 Statistical analysis

All statistical analyses were performed using SPSS statistical package (SPSS, Chicago, IL, USA). All data is expressed as median, mean +/- standard deviation or as percentages. A Chi-square test, Mann-Whitney U-test, and student's t-test were used, and a p-value of less than 0.05 was accepted as statistically significant. Each hospital's local Helsinki Committee approved the study.

3. Results

Information was recorded from 207 patients diagnosed with JIA between October 2017 and October 2019. Excluded were two patients diagnosed with isolated TMJ complaints

and three with extended oligoarticular JIA, due to their small proportion out of the entire cohort population size. One more patient with oligoarticular JIA was excluded due to missing data regarding the date of diagnosis. Of 201 patients included in the analysis, 124 (61.7%) had OAJIA, 30 (14.9%) POJIA (4 were RF positive, 23 RF negative and 3 did not have a documented test for RF), 21 (10.4%) sJIA, 19 (9.4%) ERA, and 7 (3.5%) psoriatic arthritis. No undifferentiated JIA patients were diagnosed during the study period. Mean age (±SD) at diagnosis was 7.7±5.4 years and most patients were Caucasian (80.6%). Median distance from nearby pediatric rheumatology care center to place of living was 13.0 kilometers. Other demographic characteristics of the study population and laboratory tests evaluation 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%). Afterwards, as they were referred to other specialists, orthopedists were most commonly encountered as the second (40.3%), and third (19.4%) physicians in line to examine the patients orderly (Table 2). Meaning, a patient who encountered at least 3 physicians initially, was most likely to meet a community-clinic pediatrician first, and an orthopedist thereafter, twice. On average, patients were seen by three physicians (3.1) before being referred to a rheumatologist, though the majority met with a total of four (Figure 1), 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.

Overall, the average time to diagnosis was 135.9 days (median: 56.0, range 1.0-2451.0 days), which after excluding those diagnosed with sJIA was increased to 152.1 days (median: 62.5 days). 89 (44.3%) patients were diagnosed after more than 10 weeks. Polyarticular JIA was found to have the longest median time (115.5 days) from the presenting symptom until diagnosis, followed by ERA/SPA JIA (112.0 days), psoriatic arthritis (60.0 days), oligoarticular JIA (50.0 days), and systemic JIA (25.0 days) (Table 3). Females were diagnosed significantly sooner (mean 107.2±175.8, for females 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 no significant difference between the time from first symptom to diagnosis when comparing ethnicities (Caucasians vs. non-Caucasians, mean 118.8±190.1 vs. 197.2±396.3 days, respectively, $P=0.19$), family history of autoimmune diseases (positive vs. negative family history, mean 145.1±196.1 vs. 132.2±270.3 days, respectively, $P=0.22$), 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, as compared to those without (median: 86.5 vs. 46.5 days, $P<0.01$; 226.0 vs. 51.0 days, $P<0.05$, respectively) (Table 4).

Morning stiffness was the only symptom to have a significant impact on time to referral to a rheumatologist (median 21.5 vs. 36.5 days when stiffness was not present compared to when presented, respectively, $P<0.01$). 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, two had more than one procedure. Of the patients who underwent any procedure before diagnosed with JIA, the most common operation was joint needle aspiration (95.8%), while two patients had a synovial biopsy and one a synovectomy. When analyzing the patients who underwent any procedures, 85.4% were eventually diagnosed with OAJIA, 6.2% with ERA/SPA and 8.3% with POJIA. Analyzing the initial suspected diagnosis which 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.

4. Discussion

Israel is a relatively small and densely populated country, and its medical care system is very accessible, with at least one community clinic in every settlement and relatively short distance to a near hospital. This multicenter study retrospectively analyzed the time it took for newly diagnosed JIA patients 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 1.0-2451.0 days. In particular, patients with POJIA and ERA/SPA JIA both demonstrated longer times to diagnosis. Prompt diagnosis of JIA is important in order to initiate early treatment and avoid long-term complications.

In a study by Foster et al, many children with delay 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 the median interval from onset of symptoms to starting methotrexate was 10 months (12). When considering the required waiting time of 6 weeks before diagnosing JIA, 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 Britain found that the majority (40.0%) of patients whose diagnosis was delayed by more than 10 weeks were those with persistent OAJIA, whereas patients with sJIA were diagnosed in the timeliest manner (1.6% had a delay in diagnosis more than 10 weeks) (7). In a study in France, patients with ERA/SPA JIA had the longest time to diagnosis (median: 5.5 months) while 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 two physicians prior to being referred to a pediatric rheumatologist. 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 four physicians prior to referral to a rheumatologist (Figure 1). Although patients in Israel were seen by more physicians (mean: 3.1 physicians) 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], respectively). These data items 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 great tendency of going through relatively high amounts of medical exams and tests. Israel, similarly to France and Great Britain, 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 two 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 ERA/SPA JIA and POJIA. This may be because the diagnosis of ERA/SPA 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, as in a child with overuse injury (7). POJIA patients mainly suffer from polyarticular small joint involvement, which may account for the delayed diagnosis, as small joint disease is often missed on physical examination by non-experienced 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 ERA/SPA 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. Furthermore, diagnosis of non-Caucasian patients took almost twice as long as for Caucasian 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 non-Caucasian populations (18). Moreover, Caucasian patients may have greater accessibility to resources, such as private specialists. In this study, the

majority of patients (56.7%) saw four 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 enough of JIA.

Finally, two 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 one hospitalization before receiving the diagnosis of JIA. Theoretically, minimal amount 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, in order to decrease unnecessary admissions and avoid delayed treatment, thus strengthening both the community service and hospital infrastructure.

In our report distance from the hospital was not associated with longer time to diagnosis, this finding suggest that the main cause for delay in diagnosis wasn’t the access to pediatric rheumatology service but was mainly due to delayed diagnosis by primary care physician and orthopedics in the community.

Our main study limitation is its retrospective nature. In addition, important data (e.g., socioeconomic status, cultural association, and private clinic visits) are poorly documented, if at all, which could influence the results. Furthermore, because the data was 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.

An effort should be done to improve the pediatric joint assessment done by primary care physician and orthopedics 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, thus, avoiding unnecessary tests and procedures, and most importantly, allowing early introduction of therapy to JIA patients, preventing long term complications.

Author contributions: Yochai Frenkel wrote the first draft of the manuscript, collected and analyzed the data. Irit Kraushar collected and analyzed the data. Yonatan Butbul Aviel initiated the study, and contributed to the research design, data collection, and writing of the manuscript. All authors contributed to data collection and read, repaired and approved the final submitted manuscript.

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Figure 1: Number of total evaluating physicians before meeting the rheumatologist

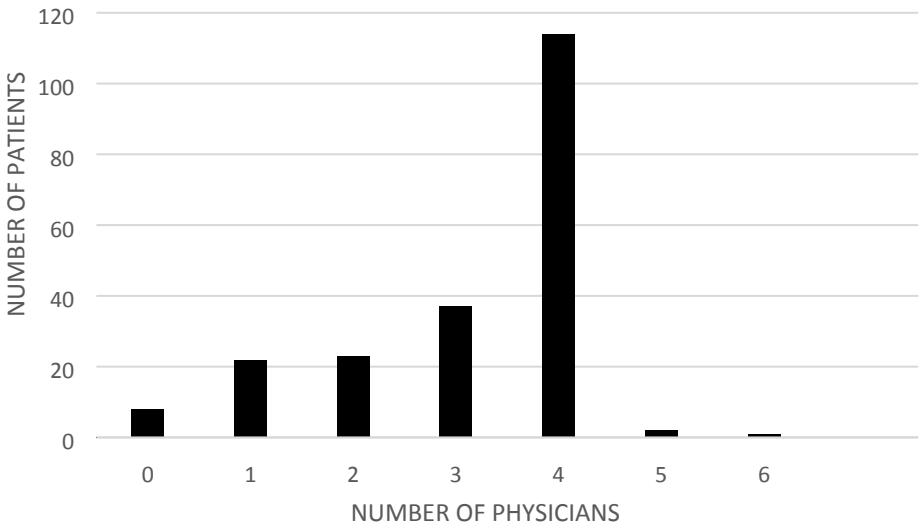

Table 1: Baseline demographic and laboratory evaluation.

Demographic Characteristics	
Age in years, mean+SD (range)	7.7±5.4;(0.6-18.2)
Female, N (%)	143 (71.1%)
Ethnicity, N (%)	
Caucasian	162 (80.6%)
Other	39 (19.4%)
Distance to hospital in kilometers, median (range)	13.0 (0.5-197.0)
Mean C-reactive protein [mg/dl] (195;97% evaluated, normal values <5)	5.5
Anti-nuclear antibody (185;92% evaluated), N (%)	
Positive	81 (43.8%)
Negative	104 (56.2%)
Positive Rheumatoid factor (134;66% evaluated), N (%)	5 (2.5%)
Erythrocyte sedimentation rate [mm/hour] (129; 64% evaluated), mean±SD	34.3 ±27.3
Positive Human leukocyte antigen B27 (30;15% evaluated), N (%)	6 (2.9%)

Table 2: Evaluating physicians prior to a rheumatologist assessment.

First specialist to evaluate the patient, N (%)	
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, N (%)	
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, N (%)	
Community-clinic pediatrician	31 (15.4%)
Orthopedic surgeon	39 (19.4%)
Emergency physician	30 (14.9%)
In-hospital pediatrician	34 (16.9%)

Number of physicians evaluating the patient before a rheumatologist, Mean	3.1
Number of hospitalizations until given diagnosis, N (%)	
0	104 (51.7%)
1	74 (36.8%)
2	21 (10.4%)
3	2 (0.9%)

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

Juvenile idiopathic arthritis type	Number of patients	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)
Enthesitis related arthritis	19	112.0 (5.0-2451.0)
Psoriatic Arthritis	7	60.0 (24.0-752.0)

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

Symptoms at presentation	Median time until diagnosis when symptoms are present at presentation (days)	Median time until diagnosis when symptoms not present at presentation (days)	P-value
Fever (median)	31.0	76.0	P<0.01*
Uveitis (median)	36.5	57.0	P=0.23
Rash (median)	31.5	60.0	P=0.06
Limited range of motion (median)	50.0	62.0	P=0.75
Morning stiffness (median)	64.0	53.0	P=0.34
Small joint involvement (median)	86.5	46.5	P<0.01*
Large joint involvement (median)	57.0	30.0	P=0.19

Sacral joint involvement (median)	226.0	51.0	P<0.05*

*Statistical significance P<0.05