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A Single-Center Experience of Systemic Onset Juvenile Idiopathic Arthritis at a Tertiary Hospital in Jeddah, Saudi Arabia

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Abstract

Background and Objective: Systemic-onset juvenile idiopathic arthritis (JIA) is a major and prevalent subset of arthritis among children and it has a broad spectrum of clinical presentation, course and prognosis. This study described the clinical presentation of systemic-onset JIA in a Saudi-based cohort. Methods: A retrospective chart review was performed of the medical records of children with systemic-onset JIA who were followed up at King Abdul Aziz University Hospital, Jeddah, between January 1997 and December 2013. Patients' files were reviewed for demographic, clinical, and paraclinical data, which were analyzed using the statistical Package for the Social Sciences. Results: We included 20 patients of both genders (8 boys and 12 girls). The mean age of disease onset was 7 (4.5) years. The most common presenting symptoms were fever (100%), arthritis (100%), and rash (55%). Hepatomegaly (5%), abdominal (5%) and pulmonary manifestations (3%) were less frequent manifestations. Most patients had high white blood cell counts (50%), elevated erythrocyte sedimentation rates (80%) and C-reactive protein levels (90%). The interval between onset of symptoms and diagnosis was 9.4 (12.5) weeks. Patients were treated with non-steroidal anti-inflammatory drugs, methotrexate, steroids, anti-tumor necrosis agents, and disease-modifying anti-rheumatic drugs. Bone marrow biopsy was conducted to exclude malignancy in 20% of the patients. Conclusion: Saudi children with systemic-onset JIA present with prolonged fever and arthritis (mainly oligoarticular rather than polyarticular). Physicians should be aware of the presentation of systemic-onset JIA in our setting in order to make prompt diagnosis and treatment decisions as early as possible. Carful follow-up of febrile patients is paramount to reaching the diagnosis early and initiating treatment.

Keywords

SO-JIA, Systemic Onset Juvenile Idiopathic Arthritis, Clinical Presentation, Saudi Arabia

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1. Introduction

In 1897, Sir George Fredrick Still described three patterns of arthritis in 19 patients [1] [2]. One of these three patterns was known as Still's disease, which is currently known as systemic-onset juvenile idiopathic arthritis (JIA) [3].

Systemic-onset JIA is classified as a subset of JIA, which constitutes 10% - 15% of all JIA cases [4]. It is characterized by a spectrum of clinical presentation, which in the initial stage can be misleading to the physician and be easily misdiagnosed before the full picture of the disease becomes apparent [5]. Therefore its definition was supplanted by the International League of Associations for Rheumatology (ILAR). Diagnosis of systemic-onset JIA requires the presence of quotidian fever in addition to arthritis, rash, lymphadenopathy, organomegaly, or serositis if disease onset occurs before the age of 16 years [1] [6] [7]. Recently, there was an emerging consensus that systemic JIA should be viewed as an auto-inflammatory syndrome [8].

The course of systemic onset JIA is variable. It can involve many organ systems, and disease activity changes with time [9]. Delays in diagnosis worsen outcome and increase disease morbidity [10]. Furthermore, extensive investigations, prolonged hospitalizations and treatments of patients with systemic-onset JIA have placed substantial cost on hospitals, health staff, and families of patients, which could be minimized by better understanding of the nature of the disease.

The purpose of this review was to describe the clinical presentation of systemic-onset JIA in a Saudi-based cohort. To the best of our knowledge, only one study were reported the clinical presentation of Saudi patients with systemic-onset JIA [10].

2. Methods

A retrospective chart review was performed of the medical records of all cases of systemic-onset JIA that were diagnosed at the Pediatric Department of King Abdulaziz University Hospital between January 1997 and December 2013. Patients were included provided they had a diagnosis of systemic JIA diagnosed as per the criteria of the ILAR (**Table 1**) [5]. Patients who had other conditions that may present with fever and arthritis, such as infections, malignancies, and other inflammatory diseases (Kawasaki disease and systemic lupus erythematosus) were excluded [4]. Permission to conduct the study was granted by the Biomedical Ethics Committee of King Abdulaziz University.

For all patients included in this study, we documented the following data: gender, age of presentation, family history, clinical manifestations, physical findings, laboratory data, results of imaging studies, treatment received, and complications.

Statistical Analysis

The data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, US), version 20. Descriptive statistics were computed for all variables. Results are expressed as frequencies, percentages, means and (standard deviation (SD)).

Table 1. Classification criteria for systemic-onset juvenile idiopathic arthritis.

Arthritis with or preceding daily fever with a duration of at least two weeks accompanied by at least one of the following symptoms during the first six months.
– Erythematous rash;
– Lymphadenopathy;
– Hepatomegaly and/or splenomegaly;
– Serositis.
Exclusion criteria
– Psoriasis or history of psoriasis in the patient or first degree relative;
– Arthritis in a boy (six year-old or more) positive for HLA-B27;
– Ankylosing spondylitis, enthesitis with arthritis, sacroiliitis and inflammatory bowel disease, Reiter syndrome or acute anterior uveitis in a first degree relative;
– Presence of rheumatoid factor type IgM confirmed in an interval of at least three months apart.

Abbreviations: HLA: Human leukocyte antigen; Ig: Immunoglobulin.

3. Results

We enrolled 20 patients aged 3 to 12 years (mean, 11.25 years). Females comprised a larger proportion of the sample (n = 12; 60%). The mean (SD) age of disease onset was 7 (4.5) years (range, 112 years). The mean interval between the onset of symptoms and diagnosis was 9.2 (12.5) weeks (range, three weeks to one year).

The clinical manifestations of systemic-onset JIA in our patients are summarized in **Table 2**. Of the 20 patients, three females had a family history of rheumatic diseases. One patient had a sister with JIA; among the other two patients, one had a sister and a mother with JIA, while the other had a grandmother who was a rheumatoid arthritis patient.

The most commonly encountered features of systemic-onset JIA in our cohort were fever (n = 20; 100%), rash (n = 11; 55%) and arthritis (n = 20; 100%). The average duration of fever in the sample was 5 (10.6) months. Patients developed arthritis either early in the course of the disease or within a few weeks from the onset of fever. Most of the patients (n = 16; 80%) had an oligoarticular pattern; only four patients (20%) had a polyarticular pattern. The most frequently involved joints were the knees (n = 16; 80%), ankles (n = 14; 70%), and wrists (n = 8; 40%). Shoulder and interphalangeal joint involvement accounted for three cases (15%) each.

Lymphadenopathy was detected in four patients (20%). Cervical, inguinal, and axillary lymph node groups were involved. Splenomegaly was documented in four patients (20%), while hepatomegaly was reported in one case (5%). Four patients (20%) had experienced pericarditis during the course of their illness.

Regarding the patients' laboratory results, hemoglobin levels were low for age in 85% of the patients (**Table 3**). Fifty percent of the patients had leukocytosis. Similarly, 50% had thrombocytosis (mean, 518 K/μL); a

Table 2. Frequency of clinical manifestations of systemic onset juvenile idiopathic arthritis in the sample.

Case	Sex	Age of Onset	Duration from Onset to Diagnosis (wks)	Family History	Fever (month)	Joint Involvement	Rash	Hepatom-egaly	Splenome-galy	Lymph Nodes	Co-Morbidity
1	Male	11.0	48	−	48.00	+	−	−	−	−	−
2	Female	5.0	3	−	0.75	+	+	−	−	−	−
3	Male	13.0	12	−	3.00	+	−	−	−	−	−
4	Male	13.0	4	−	0.75	+	−	−	−	−	−
5	Female	1.0	16	−	0.50	+	−	−	−	−	−
6	Male	1.5	5	+	0.75	+	−	−	−	−	−
7	Female	10.0	40	−	7.00	+	−	−	−	−	−
8	Male	7.0	4	−	0.54	+	−	−	+	−	−
9	Male	2.0	3	−	0.54	+	+	−	+	+	−
10	Female	10.0	4	−	0.50	+	+	−	+	+	Pericarditis
11	Female	4.0	7	−	7.00	+	+	−	−	+	−
12	Female	2.0	12	+	12.00	+	+	+	+	−	−
13	Female	2.0	4	+	2.00	+	+	−	−	−	−
14	Female	7.0	3	−	0.75	+	+	−	−	−	−
15	Male	3.0	5	−	5.00	+	−	−	−	−	−
16	Male	3.0	3	−	0.25	+	+	−	+	+	Pericarditis
17	Female	15.0	2	−	0.50	+	−	−	−	−	Pericarditis
18	Female	7.0	3	−	0.50	+	+	−	−	−	Pericarditis
19	Female	8.0	6	−	6.00	+	+	−	−	−	−
20	Female	12.0	3	−	2.00	+	+	−	−	−	−

Table 3. Summary of the patients' laboratory data.

	Hemoglobin g/dl	WBC (4.5 - 13.5 K/UL)	Neut (35% - 65%)	PLT (150 - 450 K/UL)	ESR (1 - 20 mm/H)	CRP (0 - 3 mg/l)	RF (0 - 20 IU/L)	ANA	Anti MCV	C3 (0.75 - 1.65 g/L)	C4 (0.2 - 0.6 g/L)	ALT (30 - 65 U/L)	AST (15 - 37 U/L)	Albumin (34 - 50 g/L)	Ferritin (30 - 400 ng/ml)
1	low	5.8	54.2	590	78	119	<9.8	mildly positive	-	1.9	0.231	21	21	21	873.8
2	low	10.9	69.4	478	101	79.6	<9.6	negative	-	-	-	51	26	24	none
3	low	15.05	68	489	88	171	10.1	negative	-	2.22	-	7	26	26	14
4	low	10.2	71.5	425	18	3.41	10	not done	-	-	-	22	35	35	none
5	normal	6.03	43.5	345	6		-	negative	-	-	-	19	38	38	none
6	low	8.4	41.2	458	99	174	<7.3	negative	-	-	-	29	25	25	none
7	low	21.22	87.6	401	45	17.6	10.1	negative	14.7	-	-	16	36	36	311.8
8	low	18	69	990	66	104	0	-	-	-	-	25	22	29	34.8
9	low	21.5	17	597	117	222	negative	mildly positive	-	1.71	0.289	50	27	23	none
10	low	27.25	94.3	352	79	298	10.6	negative	-	1.86	0.42	41	20	20	2000
11	low	10.2	49	726	81	70	-	negative	-	-	-	19	26	26	505
12	low	11.9	20.8	382	16	3.3	<8.7	negative	-	1.71	0.266	29	33	33	24.5
13	low	16.7	45	973	64	120	-	negative	-	1.16	0.193	38	36	28	none
14	low	16.3	81.7	420	91	118	0	negative	-	0.76	0.46	16	27	27	none
15	low	21.3	66.3	623	53	198	10.1	negative	22	-	-	19	33	33	736.6
16	low	11.3	73	358	110	97.4	<9	negative	-	1.78	0.374	192	31	19	none
17	low	12	40	234	40	30	negative	negative	-	-	-	34	33	29	none
18	normal	12	10	261	66	166	negative	negative	-	1.92	0.28	24	31	30	none
19	low	14.17	85	334	99	164	<10	negative	-	1.92	0.28	24	31	27	4295
20	normal	18.3	81	922	not done	not done	<10	negative	-	1.34	0.2	24	12	34	none

Abbreviations: ALT: Alanine transaminase; ANA: Anti-nuclear antibody; AST: Aspartate aminotransferase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MCV: Modified citrullinated vimentin; Neut: Neutrophils; PLT: Platelet; RF: Rheumatoid factor; WBC: White blood cell; -: Not done.

platelet count of 990 K/µL was documented in one of the patients. Inflammatory markers were high in most patients, and up to 18 patients (90%) had high levels of C-reactive protein (range, 3.4 to 298 mg/L). The erythrocyte sedimentation rate was elevated in 16 patients (80%; range, 6 - 117 mm/ hour). Only one patient (5%) had impaired liver function tests, while low albumin levels were documented in 13 patients (65%). Ferritin levels were high in four (44.4%) of the patients who did the test.

Antinuclear antibody titer was positive in two patients (10%). Rheumatoid factor was negative in all the patients. Two patients who were tested for antibodies against a modified citrullinated vimentin (anti MCV) had positive results. There was no decrease in C3 and C4 levels in our cohort. The mean serum C3 concentration was 1.73 (0.42) g/dL (reference range, 0.75 - 1.65 g/L), while mean C4 concentration was 0.30 (0.1) g/dL (reference range, 0.2 - 0.6 g/L).

Bone marrow aspiration was done to exclude malignancy in four patients (20%).

Imaging studies, including magnetic resonance imaging (MRI), X-rays, and abdominal ultrasound were performed in six patients (30%). One patient had multiple gallstones on ultrasound examination. Three patients

showed evidence of joint damage, as demonstrated by the presence of lumbar lordosis, acetabular dysplasia, and severe narrowing of the hip joint on MRI and X-ray images.

Table 4 shows the frequency of complications of systemic-onset JIA in the cohort. One patient with the most severe disease course had limb discrepancy. Short stature complicated the course of disease in six patients (30%). One patient had avascular necrosis. Three patients had psychological disorders. None of the patients had uveitis. Cushingoid features were documented in 40% of the patients.

Regarding treatment, all the patients received non-steroidal anti-inflammatory drugs (NSAIDs). Steroids were also prescribed in cases where NSAIDs were ineffective (n = 15; 75%). Methotrexate was also administered in 17 cases (85%). Four patients received etanercept, an anti-tumor necrosis factor agent. Three patients were started on tocilizumab (a humanized anti-interleukin 6 receptor antibody). Six patients were treated with adalimumab (a tumor necrosis factor inhibitor).

4. Discussion

Systemic onset JIA is becoming more recognized among the Saudi society. Its diagnosis is based on clinical presentation, which makes it difficult for physicians to recognize the disease early. The variability and overlap of disease symptoms as well as lack of specific biomarkers pose an additional challenge to physicians [1].

In our study, we found that the main presenting symptoms, namely fever, rash, and arthritis, were similar to those reported in studies conducted abroad [1] [5] [6].The mean age of onset in our study is similar to 7.4 (5.5)

Table 4. Complications in patients with systemic onset juvenile idiopathic arthritis[1].

	Articular Deformity	Articular Damage	Limb Discrepancy	Short Stature	Bone Fracture	Avascular Necrosis	Liver Damage	Anemia	Psychological Disorders	Uveitis	Cushingoid Features
1	+	+	−	+	−	−	−	−	−	−	−
2	+	+	−	−	−	−	−	−	−	−	−
3	−	−	−	−	−	−	−	−	−	−	+
4	−	−	−	−	−	−	−	−	−	−	−
5	−	−	−	−	−	−	−	−	−	−	−
6	−	−	−	−	−	−	−	−	−	−	+
7	−	−	−	−	−	−	−	−	−	−	−
8	−	−	−	+	−	−	−	−	−	−	+
9	−	−	−	−	−	−	−	−	−	−	−
10	−	−	−	−	−	−	−	+	+	−	+
11	−	+	−	+	−	−	−	+	+	−	+
12	−	−	−	−	−	−	−	−	−	−	−
13	−	−	−	+	−	−	−	+	−	−	+
14	−	−	−	−	−	−	−	−	−	−	−
15	−	−	−	+	+	−	−	+	−	−	+
16	+	+	+	+	+	+	−	+	+	−	+
17	−	−	−	−	−	−	−	+	−	−	−
18	−	−	−	−	−	−	−	−	−	−	−
19	−	−	−	−	−	−	−	+	−	−	−
20	−	−	−	−	−	−	−	+	−	−	−

[1]Only cushingoid features and short stature are considered complications due to steroid use; all other complications could be caused by both the disease and steroids. Abbreviations: +: Positive; −: Negative.

years reported by Yeh *et al.*, who investigated the clinical investigations in 16 Taiwan children [1]. Another study conducted in Taiwan reported that the age of disease onset was 8.7 years. Contrary to our findings, other authors reported a lower age of disease onset. In the United States, the most common age of onset was reported to be two years [3], while another study conducted in Saudi Arabia found that patients were 5.3 years at disease onset [10].

The pattern of arthritis was predominantly oligoarticular in our patients (80%). Tsai *et al.* [2] reported that the pattern of arthritis was oligoarticular in 50% of their patients with systemic-onset JIA. In the literature [5] [6] [11] [12], however, joint involvement is predominantly polyarticular in systemic-onset JIA, contrary to our finding. In addition, while we found that most (60%) of our patients were females, there was no predilection for sex in studies conducted aboard [5] [6]. The laboratory profile of our patients is similar to that reported by other authors [2] [5] [10], who documented leukocytosis, anemia, thrombocytosis, and elevated inflammatory markers in patients with systemic-onset JIA. Thrombocytosis is an important variable that should be determined early in the course of the disease, as it is a predictor of disease severity [13].

The prevalence of multiple diseases that could present initially with fever only might be an important factor in delaying the diagnosis in many patients. Most probably this cause lie behind the prolonged time between onset and diagnosis as many investigation are undertaken to exclude other differentials, for example, bone marrow aspiration, which is an invasive procedure, had to be performed in most of our patients to rule out malignancy. Further, the evolutional nature of disease symptoms contributes to this delay [3] [5] [6].

Systemic-onset JIA is a subset of JIA that is common in Saudi Arabia. In 1997, Baharbi *et al.* [10] described the clinical characteristic of JIA based on disease onset and found that 44% of the cases were of systemic onset.

Although our study provides an insight into the clinical presentation of systemic-onset JIA in our patients, its limitations cannot be overlooked. First, it is limited by its retrospective design. Second, it was a single-center hospital based study, and the findings cannot be therefore extrapolated to the population of Jeddah.

5. Conclusion

Overall, while our patients have arthritis with a predominantly oligoarticular pattern contrary to those in studies conducted abroad, the clinical presentation of the disease is similar. A high index of suspicion should be considered in order to identify patients with systemic-onset JIA and consequently initiate treatment as early as possible. Careful follow-up of febrile patients is paramount to making a prompt diagnosis and initiating treatment.

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