

Original Articles

Series of Patients with Adult-Onset Still's Disease Diagnosed at the Islamic Hospital, Amman, Jordan

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Abstract

Objectives: This study aims at presenting a series of 11 patients diagnosed as an Adult-Onset Still's Disease (AOSD).

Materials and Methods: Clinical and laboratory findings were as follows: fever (100%), arthralgia (81.8%), rash (100%), sore throat (90.9%), arthritis (36.4%), myalgia (54.5%), splenomegaly (36.4%), hepatomegaly (54.5%), lymphadenopathy (54.5%), anaemia (45.4%), neutrophilic leukocytosis (63.6%), increased erythrocyte sedimentation rate (100%).

Results: These clinical and laboratory features of AOSD in present series are more or less similar to that in other reported series.

Conclusion: Half of the cases showed recurrences, but were completely controlled by either adding steroids or a combination of steroids and methotrexate to NSAIDS. A comparison with a Saudi Arabian and other series is given.

Keywords: AOSD, Adult Onset, Still's Disease, Fever.

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Introduction

Adult Onset Still's Disease (AOSD) is a chronic rare systemic inflammatory disorder of unknown aetiology, characterized by quotidian or double-quotidian spiking fevers with an evanescent rash, arthritis, and multiorgan involvement, e.g lymphadenopathy, liver and/or spleen enlargement, and pericarditis, pleuritis or polyserositis.¹ It was first described by Bywaters in 1971,² and many reports then appeared.^{3- 8} Laboratory abnormalities of AOSD include marked leukocytosis with neutrophilia, high C-Reactive Protein (CRP) levels and Erythrocyte

Sedimentation Rate (ESR), abnormal liver function tests and Lactic Dehydrogenase (LDH) levels, and a characteristically pronounced increase in serum ferritin levels.⁹ A recent study has reported that the clinical and laboratory pattern of AOSD in Saudi Arabia is more or less similar to that in other reported series, apart from having lower cardiac and pulmonary involvement than western series. The disease course was relatively benign, with only half the cases showing recurrences, which were controlled by alterations in the dosage of corticosteroid and NSAIDS.¹⁰

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In this study, we present clinical, laboratory parameters and treatment of 11 patients diagnosed with AOSD at our institution, 8 of them were Jordanians, while the other 3 were non Jordanian Arabs. A comparison with international published reports is given.

Methodology

Eleven patients who attended Rheumatology clinic (Department of Medicine) at the Islamic Hospital over the period of the last five years were diagnosed as AOSD. All of them were treated as in-patients:

A typical AOSD is represented by a triad of symptoms that include high-spiking fevers, a characteristic rash, and arthritis/arthralgias. Fever generally exceeds 39° C, and is transient, lasting typically under 4 hours, and is most commonly quotidian or double quotidian in pattern, with the highest temperatures seen in the late afternoon or early evening. Fever can manifest the onset of other symptoms as well, with serositis, sore throat, myalgias, and arthralgias described¹. In this study, the criteria of diagnosis of AOSD described by Al-Arfaj and Al-Saleh,¹⁰ and Cush et al.¹¹ were followed which require the presence of a high spiking fever (≥ 39 C), arthralgia or arthritis, negative Rheumatoid Factors (RF) and an Antinuclear Antibody (ANA) of < 1: 100, and any two of the following four criteria: leukocytosis $> 10000/\text{mm}^3$, evanescent macular or maculopapular rash, serositis (pleuritis or pericarditis), and reticuloendothelial organ involvement (hepatomegaly, splenomegaly, lymphadenopathy).

The clinical presentation of AOSD is heterogeneous, and the spectrum of differential diagnoses is wide, including infectious, neoplastic, and autoimmune disorders, which should be ruled out before the diagnosis of AOSD can be made. Thus, other disorders especially infections, granulomatoses and neoplasms, were excluded by thorough investigation.^{1, 10} The clinical manifestations were recorded, as well as the following laboratory parameters: Full Blood Count (FBC),

Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), liver and renal function tests, ANA, RF, and serum ferritin. The joint X-rays were examined for the presence of periarticular osteopenia, joint space narrowing, erosions and ankylosis. The relevant radiological investigations of lung, heart and abdomen were also examined. Nonparametric statistics Chi-square test and Fischer's exact test for proportion drawn from two different samples were used for comparison of our data with previously reported data.

Results

Eleven patients were diagnosed with AOSD, eight Jordanians (72.7%), and three of other Arab nationalities (27.3%). Among them seven (63.6%) were females and four (36.4%) were males, giving rise to the female: male ratio of 1.75: 1. Eight patients (72.7%) had onset of the disease between 16 and 35 years of age, while two patients (18.2%) showed an onset of the disease between 40 and 60 years of age, one patient had onset of the disease while he was 11 years old. The mean age at diagnosis was 30.5 year (SD ± 12.61) with a range of 11-60 years. All patients showed spiking intermittent fever of more than 39° C with one patient (9.1%). Two patients (18.2%) had pleuritis and one case had pleural effusion (9.1%). Only one patient (9.1%) had pericarditis and pericardial effusion. Arthralgia was common with a score of 81.8% while arthritis was less common with scores of 36.4%. The most commonly affected joint was the small joints of feet in all patients (100%), followed by PIPs (63.6%), MCPs (54.5%), the wrists (54.5%), ankles (45.5%), the knees (36.4%), while shoulders and hips were not affected (0%), ten patients (90.9%) had more than five joints involved during their illness, one (9.1%) had three to five joints involved.

Loss of weight of less than 10% of the original body weight was reported in two (18.2%) cases. Five cases (45.5%) had a weight loss of more than 10% of the original body weight. Skin rashes were associated with fever in all cases.

Enlargement of reticuloendothelial organs were observed at the following frequencies: lymphadenopathy (54.5%), splenomegaly (36.4%), and hepatomegaly (54.5%). Leukocytosis " White Blood Cell count (WBC) $>10000/\text{mm}^3$ ", was present in 7 (63.6%) patients, two (18.2%) had WBC $>15000/\text{mm}^3$, and five (45.4%) had a leukocytosis of $>18000/\text{mm}^3$. The mean WBC of eleven patients was $16891/\text{mm}^3$ (SD \pm 8184), (range 4300-28500/ mm^3), with neutrophil predominance in most cases. A normochromic normocyte anaemia (haemoglobin (Hb) $<10\text{g/dl}$), was found in five (45.4%) patients. Two (18.2%) had haemoglobin levels $<8.5\text{g/dl}$. Thrombocytosis (Platelet count $>400\times 10^9/\text{l}$), was found in six (54.5%) patients. Liver dysfunction were observed in four patients (36.4%). The rise in ALT and AST levels did not exceed five times normal. Hypoalbuminaemia of less than 35g/l was seen in two cases (18.2%), and severe hypoalbuminemia ($<30\text{g/l}$) in one case (9.1%). Acute-phase response was observed in all our patients at the time of diagnosis. Eleven cases (100%) had elevation of ESR ($>40\text{mm/h}$) and CRP (reference values $<1.2\text{mg/dl}$). The mean ESR and CRP were 104.82 mm/h (SD of ± 15.11 , and range of 10-135 mm/h), and 175.0 mg/dl (SD of 68.40 and a range of 78.6-270 mg/dl), respectively.

Ferritin level was measured in 11 patients, all of whom showed hyperferritinemia of more than five times normal (reference value 22-242 pmol/l). Extremely high levels ($>60\text{ X normal}$) of ferritin were observed in 9/11 (81.8%) cases. The mean ferritin level was 15681.44 pmol/l (SD \pm of 22014.86, and a range of 1463-72000 pmol/l). All cases had negative RF and ANA. The recurrence of symptoms was once per year in 2 cases (18.2%), twice per year in one case (9.1%), and three times per year in one case (9.1%), but the others showed no recurrence during the follow-up period.

Treatment

The treatment of AOSD has been centered around the use of NSAIDs, steroids, and antirheumatic agents to control fever, arthritis, and systemic disease.

As a whole, studies indicate the need for steroid treatment in most patients with AOSD. Within this population, disease in the majority of patients is well controlled. Moreover, these studies suggest that the use of antirheumatic drugs like methotrexate should be reserved for cases in which the combination of NSAIDs, and steroids fails, or in which a reduction in the requirement for steroids is desired, either owing to lack of tolerance or adverse events.¹ In our study, all of the patients had been given NSAIDs but failed in six cases (54.5%), and partial response was seen in only two (18.2%) cases which corticosteroid was then added to achieve adequate control. The rest (81.8%) needed corticosteroids for adequate control. Six (54.5%) patients were put on methotrexate to control symptoms and signs in order to taper the corticosteroid dose.

Discussion

Adult Onset Still's Disease (AOSD) is a rare systemic inflammatory disorder of unknown aetiology that is responsible for a significant proportion of cases of fever of unknown origin and can also have serious musculoskeletal sequelae.¹ The diagnosis relies on the presence of a collection of symptoms, signs and laboratory parameters and the exclusion of similar entities.¹⁰

AOSD appears that it occurs worldwide and affects women slightly more often than men. The disease characteristically affects younger people, with three quarters of the patients reporting disease onset between 16 and 35 years of age.^{1, 11, 12} Our study shows age profile similar to the reported data but with a wider range 11-60 years. AOSD affects all ages, and several cases have been reported after the age of 60.¹ However, the age of onset in the Saudi's group of patients was younger than that reported by others, the oldest patient being 35 years old and female.¹⁰ In the Saudi's study,¹⁰ it was reported that the female to male ratio was 1.33:1 among Saudis, which was similar to Caucasians but different from Chinese (2.2:1) and Indian patients (1:2.9). In our study, the female ratio was higher than the male ratio 1.75:1, which was considered slightly higher than the Saudis but not significant ($P>0.05$).

Weight loss of more than 10% of the original body weight was seen in our study (45.5%), but was not seen in the Saudi study.¹⁰

Arthralgia and arthritis are found in the majority of patients with AOSD, with incidences ranging from 64% to 100%. Joints affected most frequently are the knees, wrists, and ankles, although involvement of the elbow, shoulder, proximal and distal interphalangeal joints, metacarpophalangeal and metatarsophalangeal joints, temporomandibular joints, and hip have been described as well.¹

In the current study, the arthralgia was more frequent (81.8%) while arthritis was observed in (36.4%). Involvement of the proximal interphalangeal joints (63.6%), metacarpophalangeal joints (54.5%), wrist (54.5%), and ankle (45.5%) were observed. The small joints of feet were affected in 100% of cases as well, while the number of joints area involved of more than 5 were observed in 90.9% of the cases. The Saudi study reported 100% incidence of arthritis and arthralgia whereas the pattern of arthritis was similar to that reported in the Chinese study, apart from more involvement of the knees and ankles.

The fever and rash were present in 100% of our cases, whereas the incidence of sore throat was present in 90.9% of the cases. Similar to that seen by Pouchot et al.⁷ Furthermore, the incidence of fever and rash was similar to that seen by Al-Arfaj Al-Saleh,¹⁰ while sore throat was lower but not significant ($P>0.05$).

The diagnosis of AOSD remains a clinical one which is not associated with Rheumatoid Factor (RF), or Antinuclear Antibody (ANA) positively, and this fact has been used in various sets of criteria used to define the disease¹ as observed in our study, whereas negative ANA and negative RF were found in all cases (100%). The laboratory parameters of the disease is a reflection of the systemic inflammation. It was reported previously,^{1, 10} that the Erythrocyte Sedimentation Rate (ESR) was raised in virtually all patients and C-Reactive Protein (CRP) may also be found to be raised as seen in our study.

Common haematological abnormalities include leucocytosis, which often accompanies increased disease activity, anaemia, and thrombocytosis.

Furthermore, serum ferritin levels with a five fold increase correlate with disease activity and often normalize when the disease goes into remission thus serum ferritin was suggested to be a useful marker for diagnosis of AOSD. The usefulness of serum ferritin is limited by the fact that very high levels can also be seen in other diseases, however extremely high levels of serum ferritin are diagnostic of AOSD if accompanied by a compatible clinical syndrome.¹ High levels of ferritin in our patients were seen in 100% cases, which were similar to those in the Saudi study and the Chinese study.¹⁰ In our study, serum ferritin levels are more than six folds were seen in 81.8% of the cases which were significantly higher than the ones reported by the Saudi and Chinese studies (40% cases).

Our patients were followed for a mean duration of 2 years. Half of the cases showed recurrences, but was completely controlled by either adding steroids or a combination of steroids and methotrexate to NSAIDS.

Three cases did not show recurrences with a treatment composed of NSAID and steroids, while the other cases were required to add methotrexate to achieve the same response.

The clinical features of our cases were similar to previously published ones (Table 1).^{7, 17- 20} However, the rates of arthralgia, leukocytosis and albumin levels were lower than the rates in the literature review including 303 cases ($P<0.05$).^{7, 17- 19} The difference may be attributed to the number of cases in our series, to geographic area, and to the ethnicity.

Comparing our series with the Saudi Arabian series,¹⁰ the clinical features were similar except in the rate of arthritis, which was lower in our series ($P<0.05$).

In conclusion, AOSD in the present series shows similarities to Saudi Arabian series and international reported series.

In conclusion, for patients presenting with fever of unknown origin, one has to consider AOSD more often. AOSD in present series show similarities to Saudi Arabian series, and international reported theses.

Table (1): Clinical features of our patients with AOSD, compared to reported data in literatures.

No.	Feature	Our series	SA series	P1 Value	LR series		P2 Value
		(n=11)	(n=14)		Ratio	%	
1	Female	63.6%	57%	0.30	157/303	51.8	0.18
2	Beginning between ages (16-35)	72.7%	100%	0.18	192/253	75.9	0.27
3	Fever	100%	100%	1.0	303/303	100	1.00
4	Arthralgia	81.8%	100%	0.18	300/303	99.0	0.01
5	Arthritis	36.4%	100%	0.0007	162/285	56.8	0.10
6	Rash	100%	93%	0.56	265/301	88.0	0.18
7	Sore throat	90.9%	64%	0.12	179/272	65.8	0.06
8	Myalgia	54.5%	71%	0.23	64/182	35.2	0.11
9	Lymphadenopathy	54.5%	43%	0.27	170/284	59.9	0.23
10	Hepatomegaly	54.5%	29%	0.14	113/278	40.6	0.16
11	Splenomegaly	36.4%	50%	0.25	146/285	51.2	0.15
12	Pleuritis	18.2%	21%	0.38	80/259	30.9	0.20
13	Pericarditis	9.1%	14%	0.44	77/274	28.1	0.12
14	Abdominal pain	27.3%	29%	0.34	55/258	21.3	0.24
15	Pneumonia	9.1%	29%	0.21	38/255	14.9	0.33
16	Elevated ESR	100%	86%	0.30	285/287	99.3	0.93
17	Leukocytosis (>10000/mm ³)	63.6%	79%	0.25	246/268	91.8	0.01
18	Anemia (Hb<10g/dl)	45.4%	43%	0.31	172/253	68.0	0.08
19	Thrombocytosis (>400000/mm ³)	54.5%	50%	0.30	164/252	65.1	0.19
20	Albumin level (<3.5g/dl)	18.2%	50%	0.09	160/197	81.2	0.0002
21	Hyperferritinemia (>5 X normal)	100%	100%	1.00	14/16	88	0.34
22	Negative ANA	100%	86%	0.30	272/298	91.3	0.37
23	Negative RF	100%	100%	1.00	279/300	93.0	0.46

*P1 Value: Our series versus Saudi Arabia series (SA), (Reference 10).

*P2 Value: Our series versus collective Literature review (LR) series, (References: 7, 17-19).

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داء ستيل ذو البدء الشبابي لمرضى تم تشخيصهم في المستشفى الإسلامي

حسن النداف، نهله نجم
المستشفى الإسلامي، عمان، الأردن

الملخص

تظهر هذه الدراسة سلسلة من أحد عشر مريضاً شُخصوا بداء ستيل ذي البدء الشبابي، وكانت الموجودات المخبرية والسريرية كالتالي:

ارتفاع درجة الحرارة	100%
ألم مفصلي	81.8%
طفح جلدي	80%
ألم في الحلق	90.9%
التهاب مفصلي	36.4%
ألم عضلي	54.5%
ضخامة طحالية	36.4%
ضخامة كبدية	54.5%
اعتلال عقد لمفية	54.5%
فقر دم	45.5%
كثرة العدلات	63.6%
زيادة معدل التثفل	100%
سلبية العامل الرئوي	100%
سلبية ANA	100%

وجدت هذه الموجودات المخبرية والسريرية لداء ستيل ذي البدء الشبابي بشكل أكثر أو أقل مشابهة في تقارير أخرى. ظهر انتكاس للحالات في نصف المرضى، ولكن تم ضبطها تماماً بإضافة (ستيرويد)، أو (ستيرويد وميثوتركسات) لمضادات الالتهاب اللاستيرويدية. وجدت تقارير مشابهة تمت في المملكة العربية السعودية.

الكلمات الدالة: داء ستيل ذو البدء الشبابي، البدء الشبابي، داء ستيل، ارتفاع درجة الحرارة.