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ORIGINAL ARTICLE

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A multicenter study of patients with adult-onset Still's disease compared with systemic juvenile idiopathic arthritis

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Abstract Adult-onset Still's disease (AOSD) has often been regarded as the adult spectrum of systemic juvenile idiopathic arthritis (sJIA). The present study aims to compare the clinical and laboratory features, the disease course and the response to treatment in patients having AOSD with those having sJIA. Retrospective review of all available data that were filled out by adult and paediatric rheumatologists from six centers using a standard data extraction form was performed. A total of 95 patients with AOSD and 25 patients with sJIA were recruited for the study. The frequency of fever, rash, myalgia, weight loss and sore throat was higher in patients with AOSD. The pattern of joint involvement differed slightly. Laboratory findings were similar in both groups, except that liver dysfunction and neutrophilia were more common among adults. A multiphasic pattern dominated the childhood cases, whereas the most frequent course was a chronic one in adults. Corticosteroids and methotrexate were the most commonly employed therapy; however, chloroquine was another popular therapy in the adult group. We showed a difference in the rate of clinical and laboratory features between patients with AOSD and those with sJIA. AOSD and sJIA may still be the same disease, and children may simply be reacting differently as the result of the first encounter of the putative antigens with the immune system.

Keywords Adult-onset Still's disease · Systemic juvenile idiopathic arthritis

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Introduction

It has been more than a century since systemic juvenile idiopathic arthritis (sJIA) was defined as a distinct clinical entity [1]. However, adult-onset Still's disease (AOSD) was first described by Bywaters only in 1971, based on the clinical similarities it shared with sJIA and an age of onset of greater than 16 years [2]. Features common in both clinical entities include acute febrile syndrome, typical multiorgan involvement and association of several clinical and laboratory findings.

The precise pathogenesis of AOSD remains to be defined, and it is unknown whether sJIA and AOSD share the same pathogenesis. The resemblance of clinical and laboratory

features of both diseases has implied that similar pathogenetic mechanisms might operate in the development of these entities.

Both diseases have no specific laboratory criteria, and the diagnosis usually remains a clinical one requiring the exclusion of other diseases. Despite several studies comparing the clinical and laboratory features of AOSD with that of sJIA, only a limited number of comparative studies addressing the prognosis and response to treatment exist. Although some of the patients respond to treatment with non-steroid anti-inflammatory drugs (NSAIDs) or corticosteroids, a substantial number of patients may require more aggressive treatment with immunosuppressive drugs or even biological agents in order to achieve remission.

The present study aims to compare the clinical and laboratory features, the disease course and the response to treatment in patients having AOSD with those having sJIA followed up by six rheumatology centers that serve as tertiary referral centers for arthritis care.

Patients and methods

The Ankara Rheumatology Study Group consists of six centers located in Ankara serving mainly the region of central Anatolia as referral hospitals. These centers are Ankara University School of Medicine, Ankara Numune Education and Research Hospital, Baskent University School of Medicine, Gazi University School of Medicine, Gulhane Military School of Medicine and Hacettepe University School of Medicine. The data of 95 patients with AOSD from five centers and 25 paediatric patients with sJIA from the Department of Pediatrics, Hacettepe University School of Medicine, were included in the study. A medical record room search of all adult and paediatric patients discharged with a diagnosis of AOSD and sJIA, respectively, during the last 10 years was conducted at each center. All patients with AOSD and sJIA fulfilled the definition criteria proposed by Yamaguchi et al. [3] and the Durban criteria [1], respectively. In order to reach standardization, the data at presentation, clinical course, laboratory features, response to treatment and treatment-related complications of all subjects were filled out by a single investigator from each center using a standard data extraction form. Identities of the patients were also included in the data extraction form in order to prevent duplication.

Remission was defined as the absence of articular, systemic and laboratory evidence of disease activity noted during chart review, for at least 2 consecutive months, regardless of the current therapy. A *disease flare* was used to refer to an event that required therapy and was not readily explained by an alternative diagnosis. *Resistance to treatment* was defined as the persistence of articular or systemic evidence of disease activity noted during chart review, for at least 2 consecutive months, regardless of the current treatment protocol. *Mean delay in diagnosis* was used to refer to a mean time elapsed from the onset of symptoms to diagnosis. *Weight loss* was defined as the loss of 5% of body weight after the onset of symptoms.

With respect to the disease course, patients were classified into four groups. *Monocyclic disease* was defined as a single episode of less than 1 year followed by a prolonged remission throughout the whole follow-up period. *Polycyclic disease* was characterized by recurrent systemic or articular flares in the absence of any treatment. The flares had to have persisted for less than 1 year and always had to have been followed by a complete remission. *Chronic disease* was defined as the persistence of articular symptoms in the absence of systemic features lasting longer than 1 year. Patients who have been followed up for less than a year or patients in whom the immunosuppressive treatment could not be discontinued during the whole follow-up period were defined as having *unclassified disease*. *Joint involvement* denotes joints in which objective findings of the arthritis were observed by the physician both at the onset and during the course of the disease. *Radiological involvement* was defined as either the presence of ankylosis or joint space narrowing detected in plain radiographs. Statistical analysis was carried out by using Fisher's exact test. A p value of <0,05 was considered to be statistically significant.

Results

Demographic features

Sex distributions, median age at onset, median delay in the diagnosis and median follow-up duration for both groups of patients were compared and summarized in Table 1. The median age at the disease onset of AOSD and sJIA were 27 (16–82) and 6 (1–15) years, respectively. Fifty of the 95 adults (53%) and 13 of the 25 children (52%) were female. There was no difference in the median time in delay for diagnosis. The median follow-up duration was longer among sJIA than AOSD patients (44 vs 12.5 months).

Clinical features

The clinical features of the AOSD and sJIA patients were compared in Table 2. The frequency of fever (98.9 vs 84%; $p<0.05$), skin rash (82.1 vs 64%; $p<0.05$), myalgia (69.5 vs 20%; $p<0.001$), weight loss (17.9 vs 0%; $p<0.05$) and sore

Table 1 Demographic features

	AOSD (n=95)	sJIA (n=25)
Male/female	45/50	12/13
Median age at onset (years)	27 (16–82)	6 (1–15)
Median delay in diagnosis (months)	3 (0.5–84)	1.5 (0.25–48)
Median follow-up duration (months)	12.5(1–120)	44 (3–148)
Monocyclic course (n, %)	20 (21.1)	5 (20.8)
Polycyclic course (n, %)	16 (16.8)	10 (41.7)*
Chronic course (n, %)	39 (41.1)	7(29.2)
Unclassified course (n, %)	20 (21.1)**	2 (8.3)

*$p<0.001$; **$p<0.05$

Table 2 Clinical features in 95 patients with AOSD and 25 patients with sJIA

	AOSD *n*=95 (%)	sJIA *n*=25 (%)
Fever	94/95 (98.9)*	21/25 (84)
1 spike/day	78/94 (82.9)	17/21 (81)
2 spikes/day	16/94 (17)	5/21 (23.8)
Fever at night	79/94 (84)	16/21 (76.2)
Fever in the morning	15/94 (15.9)	16/21 (28.6)
Skin rash	78/95 (82.1)*	16/25 (64)
Macular	75/78 (96.1)	16/16 (100)
Urticarial	4/78 (5.1)	0/16 (0)
Trunk/upper extremity	70/78 (89.7)	16/16 (100)
Face	3/78 (3.8)	3/16 (18.8)
Arthralgia	95/95 (100)	22/25 (88)
Arthritis	81/95 (85.3)	20/25 (80)
Myalgia	66/95 (69.5)**	5/25 (20)
Sore throat	63/95 (66.3)**	6/25 (24)
Weight loss	17/95 (17.9)*	0/25 (0)
Lymphadenopathy	35/95 (36.8)	13/25 (52)
Splenomegaly	40/95 (42.1)	10/25 (40)
Hepatomegaly	43/95 (45.3)	11/25 (44)
Pleural effusion	21/95 (22.1)	5/25 (20)
Pericardial effusion	8/95 (8.4)	4/25 (16)
Sicca	3/95 (3.2)	0/25 (0)
Orbital pseudotumour	2/95 (2.1)	0/25 (0)

*$p<0.05$; **$p<0.001$

throat (66.3 vs 24%; $p<0.001$) was found to be significantly higher in patients with AOSD as compared to the patients with sJIA.

There were no significant differences in the pattern of fever, type of skin rash or its localization between the groups. The fever was typically spiking once a day, usually in the evening or night, while the skin rash was frequently macular and commonly found on the trunk and proximal extremities. The pattern of joint involvement was also different between the two groups (Table 3). The most commonly affected joints were the wrists, knees and ankles (in order of frequency) in adult patients and the ankles, knees and wrists in patients with sJIA. Furthermore, the involvement of knee (80 vs 55.8%; $p<0.05$), ankle (88 vs 38.9%; $p<0.001$), elbow (56 vs 28.4%; $p<0.05$), metatarsophalangeal (25 vs 6.3%; $p<0.05$), hip (32 vs 2.1%; $p<0.001$) and cervical joints (24 vs 1.1%; $p<0.001$) was more prevalent in sJIA patients.

Laboratory and radiological findings

Liver dysfunction and neutrophilia were more common among adults (64.1 vs 18.2%; $p<0.001$ and 78.9 vs 36,8%; $p< 0.05$, respectively). Comparison of bone marrow examination disclosed a higher rate of granulocytic hyperplasia (95.2 vs 44.4%; $p<0.001$) and hypercellularity (81 vs 11.1%; $p<0,001$) in patients with AOSD (Table 4). As to the radiological findings, no difference was observed between the groups. Radiographs showed evidence of involvement in 26 of the adults (27.3%) and six of the paediatric patients (24%) at various localizations. The most common region of the radiological involvement was the wrist joint.

Table 3 Articular characteristics

	AOSD *n*=95 (%)	sJIA *n*=25 (%)
Knee	53 (55.8)	20 (80)*
Wrist	64 (67.4)	16 (64)
Ankle	37 (38.9)	22 (88)**
Elbow	27 (28.4)	14 (56)*
MCP	21 (22.1)	4 (16)
PIP	17 (17.9)	8 (32)
Shoulder	14 (14.7)	8 (32)
MTP	6 (6.3)	5 (25)*
DIP (hand)	1 (1.1)	1 (4)
Hip	2 (2.1)	8 (32)**
Cervical spine	1 (1.1)	6 (24)**
TMJ	3 (3.2)	1 (4)

MCP Metacarpophalangeal, *PIP* proximal interphalangeal, *MTP* metatarsophalangeal, *DIP* distal interphalangeal, *TMJ* temporomandibular joint
*$p<0.05$; **$p<0.001$

Disease course and treatment

The patterns of disease course were significantly different between the two groups (Table 1), in part possibly related to the difference in duration of follow-up.

The majority of the adult patients had an unclassified course (21.1 vs 8.3%; $p<0.05$), whereas children predominantly had a polycyclic disease pattern (41.7 vs 16.8%; $p<0.001$). Among the patients with AOSD, only one patient responded to NSAIDs alone and 13 patients achieved a clinical response with steroids only. However, this particular group of patients was characterized by a shorter duration of follow-up and unclassified disease course when analysed individually. The first choice of treatment was a combination of steroid plus methotrexate or hydroxychloroquine, which was associated with a high response rate. Likewise, both newly diagnosed patients and patients who had been resistant to previous treatment responded well to the regimen consisting of steroids, methotrexate and hydroxychloroquine (96% response rate).

Four patients with AOSD required a second immunosuppressive drug or an increase in the dosage of steroids due to the lack of response to their primary treatment. Treatment regimens of nine patients were changed after the development of relapse. Two patients out of four treated with sulfasalazine discontinued therapy due to toxicity. A patient with AOSD diagnosed as having haemophagocytosis was treated successfully by the combination of methotrexate, hydroxychloroquine, steroid and intravenous immunoglobulin (Table 5).

Table 4 Laboratory findings

	AOSD (%)	sJIA (%)		AOSD (%)	sJIA (%)
ESR (<30 mm/h)	6/95 (6.3)	0/25 (0)	Elevated ferritin	81/91 (89)	4/5 (80)
ESR (≥30 mm/h)	89/95 (93.7)	25/25 (100)	Ferritin>×5[a]	57/91 (62.6)	1/5 (20)
CRP (<6 g/dl)	3/90 (3.4)	2/23 (8.7)	Elevated transaminase	59/92 (64.1)*	4/22 (18.2)
CRP (≥6 g/dl)	87/90 (96.6)	21/23 (91.3)	GGT	44/87 (50.6)**	2/12 (16.7)
Hb (<12 g/dl)	70/94 (74.5)	22/25 (88)	Hypoalbuminemia (<3.5 g/dl)	36/85 (42.4)	13/22 (59.1)
Hb (≥12 g/dl)	24/94 (25.5)	3/25 (12)	Neutrophilia (≥80%)	60/76 (78.9)*	7/19 (36.8)
WBC<15,000/mm^3	45/94 (47.9)	12/25 (48)	BM, granulocytic hyperplasia	20/21 (95.2)*	8/18 (44.4)
WBC≥15,000/mm^3	49/94 (52.1)	13/25 (52)	BM, hypercellularity	17/21 (81)*	2/18 (11.1)
Plt (<400,000/mm^3)	47/91 (51.6)	8/24 (33.3)	BM, haemophagocytosis	1/21 (4.8)	1/18 (5.6)
Plt (≥400,000/mm^3)	44/91 (48.4)	16/24 (66.7)			

ESR Erythrocyte sedimentation rate, *CRP* C-reactive protein, *Hb* haemoglobin, *WBC* white blood cell count, *Plt* platelet count, *GGT* gamma glutamyl transpeptidase, *BM* bone marrow microscopy
[a]Elevated ferritin levels higher than five times of normal
*p<0.001; **p<0.05

With respect to the patients with sJIA, none of them achieved a remission with NSAIDs alone. Eight patients were treated successfully with only steroids. Of the ten patients who received steroid and methotrexate, seven responded well. On the other hand, treatment with steroid and cyclosporine resulted in remission in only two out of six patients. Only one patient received sulfasalazine under close supervision, in whom the drug was tolerated without toxicity. Steroid and azathiopyrin were given to one patient and the patient failed to achieve a remission.

Thus, a total of six patients were defined as resistant and received anti-tumour necrosis factor (anti-TNF) agents as a second-line therapy. Response to this treatment was successful in five of them. In two of the patients, the aforementioned treatment protocols and thalidomide failed to produce any substantial improvement (Table 6). One patient with sJIA developed haemophagocytosis during the follow-up and was treated with pulse steroids and cyclosporine successfully.

It was noted that the overall steroid dose was less in children as compared to adults. The mean number of drugs given to a patient during activation was higher in the AOSD patients as compared to sJIA patients.

Table 5 Treatment of the patients with AOSD

Treatment protocols	Number of patients (new/resistant)	Success ratio of the treatment (n, %)
NSAID	1	
Corticosteroids only	13	
Corticosteroids and single immunosuppressive drug (total)	65/2	53/67 (79.1)
Corticosteroids and chloroquine	27/1	21/28 (77.7)
Corticosteroids and methotrexate	35/1	30/36 (83.3)
Corticosteroids and azathiopyrin	2/0	2/2 (100)
Corticosteroids and sulfasalazine	1/0	0/1 (0)
Corticosteroids and combined immunosuppressive drugs (total)	16/13	27/29 (93.1)
Corticosteroids and methotrexate and chloroquine	15/10	24/25 (96)
Corticosteroids and methotrexate and sulfasalazine[a]	1/1	0/2 (0)
Corticosteroids and methotrexate and chloroquine and sulfasalazine	0/1	1/1 (100)
Corticosteroids and etanercept	0/1	1/1 (100)

[a]Sulfasalazine was discontinued due to toxicity in these two patients

Table 6 Treatment of the patients with sJIA

Treatment protocols	Number of patients (new/resistant)	Success ratio of the treatment (n, %)
NSAID	–	
Corticosteroids only	8	
Corticosteroids and single immunosuppressive drug (total)	13/4	9/17 (52.7)
Corticosteroids and methotrexate	7/3	7/10 (70)
Corticosteroids and cyclosporine	5/1	2/6 (33.3)
Corticosteroids and azathiopyrin	1/0	0/1 (0)
Corticosteroids and leflunomide	0/1	1/1 (100)
Corticosteroids and combined immunosuppressive drugs (total)	2/4	6/7 (85.7)
Corticosteroids and methotrexate and anti-TNF	1/5	5/6 (83.3)
Corticosteroids and methotrexate and sulfasalazine	0/1	1/1 (100)
Unresponsive patients	2	2/25 (8)

Discussion

There have been a number of studies comparing the clinical features, laboratory findings, disease course and response to treatment of AOSD with that of sJIA in which the results were almost equivocal. Some authors proposed that these two entities had many characteristics in common and that they may actually represent a clinical spectrum. In support of this view, Tanaka et al. compared 26 Japanese patients of sJIA with 19 patients of AOSD and found no difference in clinical and laboratory features, prognosis and response to treatment except for sore throat, which was more frequently observed in adult patients [4]. A similar conclusion was reached in a few other studies as well [5, 6]. Similarities in the clinical features of AOSD and sJIA were also emphasized in a recent study by Luthi et al. comparing ten patients with AOSD and nine patients with sJIA [6]. Unlike the previous studies, these authors included only patients presenting during adolescence (13–18 years old) with sJIA in order to address the question of whether adolescents presenting with sJIA and patients with AOSD represent the same spectrum of disease.

Cabane et al. compared the long-term outcome of sJIA and AOSD in ten and nine patients, respectively [7]. They showed that articular prognosis in both groups of patients was poor in 50% of patients (in each group) suffering from severe joint destruction after 10 years of disease onset. Although no significant difference was observed between the groups with respect to articular prognosis, it was interesting to note that all three patients who developed amyloidosis were from the adult-onset group. Contrary to this data, a study from China compared the outcome of 24 patients having sJIA with 21 patients having AOSD and found that patients having sJIA had a worse functional outcome than those having AOSD [8]. Furthermore, several studies investigating the pathogenic mechanisms underlying AOSD and sJIA suggest that despite the similarities in their clinical features and cytokine profiles, these two entities may be different from each other with respect to the pathogenesis [9–12].

Although rare, several ocular manifestations have been described in patients with AOSD [13]. It is of interest that three of our adult patients and two others developed sicca syndrome and inflammatory orbital pseudotumour, respectively. In one of those patients, orbital pseudotumour was the initial manifestation of the disease, in which the treatment with steroids was successful.

The results from our current study showed significant differences in the frequencies of clinical manifestations between the two groups. Indeed, fever, skin rash, sore throat (as in the series of Tanaka et al.), myalgia and weight loss occurred more frequently in adult patients. The frequencies of the clinical features of adult patients were in accordance with the previous reports [14]. On the other hand, the pattern of joint involvement differed between the two groups. Enrollment of more adult patients in our study than those of the previous ones and ethnical differences in the clinical expression of the disease might account for the observed discrepancies.

In addition to the clinical features, some laboratory abnormalities were also more common in patients with AOSD. The frequency of liver dysfunction, neutrophilia, granulocytic hyperplasia and hypercellularity of the bone marrow was significantly higher in AOSD patients. Bone marrow examination disclosed haemophagocytosis in one patient, while none of the patients had histiocytosis.

Due to the relatively lower number of paediatric patients in whom the ferritin analysis was requested, no comparison was made between the adult and paediatric patients with regard to serum ferritin levels. Nevertheless, the proportion of adult patients who had increased serum ferritin levels was found to be comparable with those of the previous studies [6, 8]. With regard to the disease course, adult and paediatric patients were also different. Patients with sJIA tended to have polycyclic course, while patients with AOSD have had an unclassified course. Because of the relatively shorter follow-up period, 21% of the adult patients were labelled as having an unclassified course. However, this pattern of distribution might change with time as these patients may be reclassified as chronic, monocyclic or polycyclic during the follow-up.

There has been no double-blind, well-controlled study that attempted to evaluate the effect of different treatment regimens on the outcome of patients with either AOSD or sJIA. Non-steroid anti-inflammatory drugs, steroids, methotrexate and hydroxychloroquine, either alone or in combination, are frequently used in the treatment of AOSD. In recent years, alternative therapies including intravenous immunoglobulin (IVIG), cyclosporine-A, leflunomide, azathiopyrin and anti-TNF agents (infliximab and etanercept) have become increasingly used in the treatment of refractory cases [15–18].

Of our patients with AOSD, one went into remission taking NSAIDs alone, 13 were treated with only steroid monotherapy and the remaining 81 were given steroids in combination with immunosuppressive agents.

Steroids in combination with either methotrexate or hydroxychloroquine were instituted in 65 patients as a first-line treatment and in two patients resistant to previous regimens; 53 of these patients responded to this course of therapy. With respect to the combinational treatment, 21 out 28 of the patients responded to a combination of steroids and hydroxychloroquine, while 30 out 36 of them responded to steroids and methotrexate. These results suggested that both of these combinations can be used successfully (especially) as a first-line regimen in the treatment of AOSD. Of the 29 patients (16 newly diagnosed, 13 non-responders) that were treated with a combination consisting steroids and two different classes of immunosuppressive agents, 27 achieved a remission. The most commonly used combination in this group of patients was steroids, methotrexate and hydroxychloroquine, with a 96% response rate. In light of these findings, we propose that clinical response can be obtained in most patients by the combination of disease modifying anti-rheumatic drugs (DMARDs) that are commonly used in our daily practice.

Among the sJIA patients, steroids and methotrexate were the first choice of therapy. The response rate to this therapeutic regimen was 77.7%, which was better than the

rates obtained for the other combinations, which were of limited number. On the other hand, anti-TNF agents may be regarded as useful tools in the treatment of disease refractory to conventional therapy. Although anti-TNF agents have a good effect on disease activity, long-term safety and sustained improvement after cessation of the therapy remain the major concerns [19]. Overall, the remission rate was very good in our cohort of sJIA patients. This is in accordance with the recent favourable rates reported for sJIA [20]. We have had only one patient with amyloidosis, whereas this complication was more common before the 1990s [21]. Haemophagocytosis was observed in only one patient and this patient was treated with success. We may thus suggest that recent treatment strategies are improving the outcome and decreasing the frequency of major complications.

It was noted that paediatricians were inclined to give less steroids and kept the daily dose lower as compared to their colleagues treating adult patients. Paediatricians were hastier in lowering the steroid dose and adding other immunosuppressive drugs. However, the average number of drugs prescribed at a given time was lower in sJIA patients. This "undertreatment" may be reflective of the worries of paediatricians for their growing patients who have a longer life expectancy than their adult counterparts.

In conclusion; we have confirmed that there are a number of differences in clinical and laboratory features.

AOSD and sJIA may still be the same disease, and children may simply be reacting differently as a result of the first encounter of antigens with a more naive immune system.

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