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Research Article

Prognostic Factors In Adult Onset Still's Disease

Karima Abbaci Daghor[1,2]*, Amel Otmane[2], Mohamed Makrelouf[2], Karima Belatar[2], Nadia Ait Hamadouche[3], Chafia Dahou-Makhloufi[4], Farida Mechid[4] , Fifi Otmani[5], Zohra Lerari[5], Chafika Haouichet[6], Fella Hanni[7], Salima Lefkir Taffiani[8], Bilel Bengana[8], Nacera Benfenatki[9], Smail Nourredine[10], Rafika Bougherarou[11], Mounir Tabouche[11], Fatma Zohra Aissat[12], Nadia Boukheris[13], Amar Tebaibia[14], Baya Taharbouchet[15], Soraya Ayoub[16], Brahim Benziane[17], Nadia Oumnia[18], Djennete Hakem[19], Malika Boucelma[20], Nazim Laraba[1] and Abdelkrim Berrah[1]

[1]*Department of Internal medicine, Bab El Oued University Hospital center, University of Algiers 1, Faculty of Medical sciences, Benyoucef Benkhedda, Algeria, North Africa*

[2]*Department of Biochemistry, Hemotology and genetics laboratory of research, Algeria, North Africa*

[3]*Department of Epidemiology, Bab El Oued University Hospital center, Algeria, North Africa*

[4]*Department of Rheumatology, Bab El Oued University Hospital center, Algeria, North Africa*

[5]*Department of Internal medicine, Mustapha Bacha University Hospital center, Algeria, North Africa*

[6]*Department of Rheumatology, Douera University Hospital center, Algeria, North Africa*

[7]*Department of Rheumatology, Benaknoun University Hospital center, Algeria, North Africa*

[8]*Department of Rheumatology, Benimessous University Hospital center, Algeria, North Africa*

[9]*Department of Internal medicine, Rouiba University Hospital center, Algeria, North Africa*

[10]*Department of Epidemiology, Mustapha Bacha University Hospital center, Algeria, North Africa*

[11]*Department of Radiology, Bab El Oued University Hospital center, Algeria, North Africa*

[12]*Department of Infectious diseases, El Hadi Flici University Hospital centre, Algeria, North Africa*

[13]*Department of Internal medicine, Annaba University Hospital centre, Algeria, North Africa*

[14]*Department of Internal medicine, Birtraria University Hospital centre, Algeria, North Africa*

[15]*Department of Internal medicine, Bouloughine University Hospital centre, Algeria, North Africa*

[16]*Department of Internal medicine, Benimessous University Hospital centre, Algeria, North Africa*

[17]*Department of Internal medicine, Laghouat University Hospital centre, Algeria, North Africa*

[18]*Department of Internal medicine, Zmirli University Hospital centre, Algeria, North Africa*

[19]*Department of Internal medicine, Mostaghanem University Hospital centre, Algeria, North Africa*

[20]*Department of Internal medicine, Kouba University Hospital centre, Algeria, North Africa*

***Corresponding author:** Karima Abbaci Daghor, Department of Internal medicine, Bab El Oued University Hospital center, University of Algiers 1, Faculty of Medical sciences, Benyoucef Benkhedda, Algeria, North Africa. **Email:** daghor23dz@yahoo.fr; abbacidaghor@gmail.com

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Abstract

Background: The severity of Adult Onset Still's Disease (AOSD) can be attributed to its life-threatening complications with organ damage, the chronic course with high rate of relapses and the occurrence of erosive arthritis.

Objective: To identify the prognostic factors in AOSD

Methods: We conducted a multicenter prospective longitudinal nationwide study in tertiary rheumatology and Internal Medicine departments (16 departments) to enroll successively patients with established AOSD diagnosis who fulfilled either Yamaguchi or Fautrel criteria with the exclusion of any cause that can explain the clinical picture. All clinical and biological data were collected in a consensual and standardized clinical assessment at baseline and during follow up. The different clinical and biological features at diagnosis were compared to the clinical course and the complications of AOSD.

Results: 80 patients with AOSD were included. Life-threatening complications with organ damage occurred in 11 patients who presented 14 complications. 56 (70 %) patients had a chronic course with 23.7% erosive arthritis. A third of patients relapsed at 3 months, 6 months and 12 months. Low Glycosylated Ferritin (GF≤ 10%) is a predictive factor of life threatening complications (p= 0.001), corticosteroid dependence and early relapses at 3 months (p=0.02). Prognostic factors of erosive arthritis are polyarthritis (p=0.006), chronic course (p=0.02) and relapses at 6 months (p=0.02).

Conclusion: Lower glycosylated Ferritin (GF≤ 10%) was predictive of life-threatening complications, corticosteroid dependence and high rate of relapses in Adult Onset Still's Disease. Polyarthritis, chronic course and high rate of relapses were predictive of erosive arthritis.

Keywords: Adult Onset Still's Disease; Prognostic Factor; Glycosylated Ferritin; Polyarthritis; Chronic course; Relapses; Erosive arthritis

Introduction

The severity of AOSD can be attributed to its life-threatening complications with organ damage, the chronic course with high rate of relapses and the occurrence of erosive arthritis [1-5]. Few prognostic factors have been reported in AOSD. Particularly, persistent polyarthritis and high ferritin exposed to the chronic course of the disease [6]. We need to identify factors, which predict the severity of AOSD and specify the group of patients that requires special monitoring and possibly more intensive treatment. To our knowledge, data about the predictive value of the glycosylated ferritin in the occurrence of chronic course, erosive arthritis and some complications such myocarditis are not available.

Methods

Study design

We conducted a multicenter prospective longitudinal observational nationwide study in tertiary rheumatology and Internal Medicine departments. Seventeen tertiary centers (5 Rheumatology and 11 Internal medicine, 1 Infectious diseases) participated to the study between December 2016 and December 2019 for recruitment. The follow-up was carried out by 16 departments from December 2016 to December 2020 (5 Rheumatology and 11 Internal medicine). The study protocol was approved by the Ethics committee of the University of Algiers 1, Benyoucef Benkhedda.

Patients and Data collection

Patients with established AOSD diagnosis according to the referring physician were successively included. Patients fulfilled Yamaguchi classification 1992 [7] or Fautrel classification 2002 [2] with the exclusion of any cause that can explain the clinical picture.

All clinical and biological features were collected in a consensual and standardized clinical assessment at baseline and during follow up.

The principal investigator (A.D.K) gathered subsequently all data in a unique database to conduct the statistical analysis. We excluded patients who were less than 18 years, those who did not consent or those who had missing data and insufficient follow-up. Written informed consent was obtained from each patient for the participation in the study.

Definitions

Life-threatening complications were defined by the presence of Reactive Hemophagocytic lympho-Histiocytosis (RHL), coagulation disorder, myocarditis, heart failure, tomponade, pulmonary arterial hypertension, acute respiratory distress syndrome, pancreatitis and fulminant Hepatitis [5].

Three different clinical patterns were considered: the monocyclic or self-limited course defined as a single period (less than 12 months) followed by persistent remission, the polycyclic or intermittent course is considered if recurrent relapses occurred between complete remissions and the chronic course if the symptoms persist more than a year. The chronic course was subdivided on systemic and articular form [8, 9].

Erosive arthritis was defined by the presence of erosion and or ankylosis on articular radiographs attested by senior rheumatologist or radiologist (authors of this article) [6].

Relapses were defined by the presence of two or more criteria of Yamaguchi classification and high fever or high CRP (> 10 mg/l). Assessment of relapses included Fever, rash, swollen joints count, tender joints count, physician global assessment on visual analogue scale (VAS), patient global assessment on VAS, pain assessment on VAS, pharyngitis, pleuritis, pericarditis, abdominal pain, C reactive protein, erythrocyte sedimentation rate, neutrophils, liver enzymes, serum ferritin and therapeutic modification [10].

Variables

The clinical variables were defined as present or absent: spiking fever (≥ 38 C°), joint symptoms (arthralgia, Arthritis, number of affected joints), myalgia, skin rash, lymphadenopathy, splenomegaly, pharyngitis, pleuritis, pneumonia, acute respiratory distress syndrome, pericarditis, tamponade, myocarditis, heart

failure, Hepatitis, hepatomegaly, abdominal pain, pancreatitis kidney failure and neurological involvement.

The biological variables were defined as normal or abnormal according to their predefined threshold: leukocytosis (≥ 10 000/ mm), agranulocytosis (≥ 80%, ≥ 75%, mean granulocytes), lymphopenia (lymphocytes < 1500/ mm), mean Hemoglobin and platelets (normal range: 150 000 -450 000 platelets/millimeter), Neutrophils To Lymphocytes Ratio (normal range: 0.78 to 3.53).

We have also tested liver enzymes (Alanine aminotransferase, Aspartate aminotransferase, Lactates dehydrogenase, Gamma glutamyl Transferase) C reactive protein (normal value < 6mg/l), mean erythrocyte sedimentation rate and increased serum ferritin (higher than the upper normal value and higher than 5-fold the upper normal value, normal range: 50- 200 µg/l)

Reactive Hemophagocytic lympho-Histiocytosis (cytopenia, increased liver enzymes, hypertriglyceridemia, elevated LDH level, hemophagocytosis in bone marrow smear) and disseminated intravascular coagulation (thrombocytopenia, prolongation of prothrombin time, decreased fibrinogen, increase of fibrin degradation products).

The different levels of glycosylated ferritin were classified as follow: < 5%, 5-10%, 11- 20%, 21- 25%, > 25% (normal range: 50-80%). The glycosylated ferritin was not measurable or not interpretable when the serum ferritin was low or in normal range [2].

Statistical analysis

In the descriptive study, qualitative variables were described with counts (percentage) and quantitative variables with mean +/- standard deviation.

To identify the variables that predict the outcomes of the disease, the different clinical and biological variables collected at diagnosis were compared to the disease course (group with chronic pattern and self-limited or polycyclic pattern), the relapses (group who relapsed and who did not relapse), the occurrence of complications (group with or without life-threatening complications) and the occurrence of erosive arthritis (group with or without erosive arthritis) during follow up.

The searches for associations between the different variables were performed using Pearson's chi-square test for qualitative variables, when the conditions for applying the test are not met Yates' correction is applied and Fisher's exact test for small samples. A $p < 0.05$ was considered statistically significant. The Data analysis was performed with SPSS software (version 23).

Results

Main clinical features

Eighty patients with AOSD were included. Seventy-five patients were followed up for 12 months, 50 patients for 24 months and 35 patients for 36 months. Only 5 patients were lost to follow-up. The main clinical characteristics were a mean age of 33,76 +/- 13 years with 61.2% (n=49) female. The most frequent clinical features were fever (n=80, 100%), arthralgia (n=75, 93.7%), skin rash (n=70, 87.5%), deterioration of general condition (n=67, 83.7%) and pharyngitis (n=66, 82.5%).

The association fever, arthralgia and rash was present at the diagnosis in 65 (81%) patients while only 16 patients (20%) had lymphadenopathies and splenomegaly.

Main laboratory findings

The most frequent laboratory findings were: high CRP (n=80, 100%), leukocytes > 10 000 (n=67, 83.7%), anemia (n=71, 88%), high ferritin (n=70, 87.5%) and granulocytosis (neutrophils ≥ 80% in 51, 63.7%). Furthermore, 36 % (n=29) of patients had a high level of serum ferritin greater than 10-fold the upper normal value.

The Neutrophils To Lymphocytes Ratio was ≥ 4 in 75 (93.7%) patients with mean NLR of 10+/-10.24. Thirty-seven (78.7%) among 47 patients with available glycosylated ferritin had low glycosylated ferritin ≤ 20 % while 42 (89.3%) patients had a glycosylated ferritin ≤ 25%.

Treatment and relapses

All patients received corticosteroid whereas seven of them received Non-steroidal Anti-inflammatory drugs as the first line of treatment particularly diclofenac. Forty-eight patients (60%) required a second line of treatment with sDMARD specially Methotrexate (46, 57.5%).

Treatment with biologic agents was prescribed 20 times in 16 patients (20%). Anakinra was the most prescribed (n =7) and effective biologic therapy (n= 5).

The relapses rate was high and concerned (28/80, 35%) patients at 3 months, (28/76, 36.8%) patients at 6 months, (26/75, 34.6%) patients at 12 months, (18/50, 36%) patients at 24 months and (9/35, 25.7%) patients at 36 months.

Disease course and complications

The chronic pattern concerned 56 patients (70%) among them 19 (34%) had articular form and 37 (64%) had systemic form while the polycyclic pattern concerned 15 patients (18.7%) and the self-limited pattern concerned 9 patients (11.3%). Erosive arthritis was noted in 19 (23.7%) patients or one third of the chronic pattern (19/56: 33.4%).

Life-threatening complications with organ damage occurred in 11 patients who presented 14 complications. These complications were: 6 Reactive Hemophagocytic lympho-Histiocytosis, 2 disseminated intravascular coagulation, 3 Myocarditis, 1 acute respiratory distress syndrome, 1 pancreatitis and 1 fulminant Hepatitis.

Prognostic value of Glycosylated Ferritin

Forty-seven patients had available glycosylated Ferritin and were considered for further analysis of the predictive value of GF. Low glycosylated ferritin less than 20% concerned 37 (78.7%) patients. However, 42 (89.2%) patients had a GF level less than 25 % (Table 1).

In this group (n=47), the chronic pattern concerned 36 patients with 22 systemic form and 14 articular forms, among them 10 patients developed erosive arthritis. The relapses rate was high and affected one-third of patients during the disease course.

Comparative analysis

Low glycosylated ferritin level less than ≤ 10 % was more frequent in patients with life threatening complications (n=12/14, 85.7%) compared to higher level of GF (n=2/14, 14.2%) or greater than 10% (p= 0.001). Moreover, low glycosylated ferritin (GF ≤ 10%) was more frequent in patients with early high relapses rate at 3 months compared to higher level of GF or greater than 10% (73.3%, 26.6%, p=0.02) (Table 2). Furthermore, urticarial skin rash and arthritis was associated to higher rate of relapses at 12 months respectively (p= 0.02, p= 0.05).

Table 1: Levels of glycosylated ferritin.

Glycosylated ferritin	n=47	Percentage %
< 5 %	5	10.60%
5-10 %	19	40.40%
11-20%	13	27.60%
21-25%	5	10.60%
> 25 %	5	10.60%
Total	47	100%

Table 2: Correlation between relapses, chronic course, complications and glycosylated ferritin level.

	GF ≤ 10%	GF >10%	p
Relapses	n=24	n=23	
3 Months (n= 15)	11 (73.3)	04 (26.7)	p=0.02
6 Months (n= 17)	9 (53)	8 (47)	p=0.6
12 Months (n= 18)	9 (50)	9 (50)	p=0.6
24 Months (n= 16)	10 (62.5)	06 (37.5)	p=0.2
Chronic course	GF ≤ 10 %	GF > 10 %	p
Chronic course (n=36)	18 (50%)	18 (50%)	p = 0.7
Complications	GF ≤ 10%	GF >10%	p
Patients with Complications (n=11)	9 (81.8)	2 (18.2)	p=0.01
All Complications (n=14)	12 (85.7)	2 (14.3)	p=0.001

However, lower GF (GF ≤ 10%) was not associated to chronic course when compared to higher level (50%, 50%, p=0.7). Moreover, there was no correlation between the occurrence of erosive arthritis and GF level. Lower glycosylated ferritin (GF ≤ 10%) was not more frequent in the group of patients with erosive arthritis (5/10) compared to the group of patients without erosive arthritis (19/37), (50%, 51.3%, p=0.7).

Prognostic factors of chronic course

Chronic course versus monocyclic course

High persistent fever versus nocturnal fever (33.9%, 0 %, p= 0.03), alteration of general condition (94.6%, 44.4%, p=2.10-4), abdominal pain (32.1%, 0%, p=0.04), liver abnormalities (75%, 22.2%, p=0.003), anemia (9.30+/-1.46, 11+/-1.9, p=0.001), high disease activity evaluated by physician (6.33+/-1.22, 4.88+/-1.05, p=0.001) and patient (6.33+/-1.22, 4.88+/-1.05, p=0.001) were predictive of chronic course.

Chronic course versus polycyclic course

Arthralgia (98.2%, 80%, p=0.02), abdominal pain (32.1%, 0%, p=0.01), high disease activity evaluated by physician (6.33+/-1.22, 4.93+/-1.48, p=2.10-4) and patient (8.60+/-1.53, 6.8+/-2.14, p=3.10-4) were predictive of chronic course.

Complications with organ damage were more frequent in patients with chronic course (n=10/56) than in monocyclic or polycyclic course (n=1/24) without significant difference (p= 0.1). Moreover, Antinuclear Antibodies with low titer (n=8) were present only in the chronic course group.

Prognostic factors of erosive arthritis

Several variables tested were more frequent in the group with erosive arthritis such long diagnostic delay (27.4+/-61.2, 8.13+/-27.97, p= 0.2) and a higher dose of prednisone (30.88+/-25.69, 12.61+/- 11.05, p= 0.1) but without significant difference. The disease activity at the diagnosis evaluated by the Disease Activity Score DAS28 was not higher in erosive arthritis group (5.9+/-1.09, 5.5+/-0.87, p= 0.1). However, polyarthritis at the diagnosis, relapses at 6 months and chronic pattern with systemic form were significantly associated to erosive arthritis respectively (p= 0.006, p= 0.02, p= 0.02) (Table 3).

Table 3: Prognostic factors of erosive arthritis.

Characteristics	Group with erosive arthritis n=19	Group without erosive arthritis n=61	p
Mean Age	31.57+/-14.39	34.44+/-12.63	p = 0.4
Polycyclic course	3/19 (15.8)	12/61 (19.6)	p=0.7
Chronic course with Systemic Form	13/19 (68.4)	24/61 (39.3)	p=0.02
Arthritis	17/19 (89.4)	37/61 (60.6)	p=0.01
Polyarthritis	15/17 (88.2)	17/37 (45.9)	p=0.006
DAS28**	5.9+/-1.09	5.5+/-0.87	p=0.1
HAQ*	1.73+/- 0.87	1.73+/- 0.79	p=0.9
Ferritin ≥ 5 N	14 (73.7)	45 (73.8)	p=0.7
GF[a] ≤ 10%	5/10 (50)	19/37 (51.3)	p=0.7
Prednisone mg/day at 12 months	30.88+/-25.69	12.61+/- 11.05	p=0.1
Relapses at 6 months	11 (57.9)	17 (27.8)	p=0.02
Note: *HAQ: Health Assessment Questionnaire **DAS28: Disease Activity Score a GF: glycosylated Ferritin.			

Discussion

This study investigated the prognostic factors in Adult Onset Still's Disease. Several clinical studies searched strong biomarkers for the diagnosis and prognosis of AOSD [11, 12, 13]. High serum ferritin greater than 5-fold upper than normal value was more frequent and specific for AOSD compared to controls [2].

The laboratory findings of AOSD reported in the main literature series were high CRP, high ferritin with low glycosylated ferritin, polynucleosis, elevated liver enzymes and negative autoimmunity tests [1, 2, 4, 6, 7, 9, 14]. Ferritin was considered as a pro inflammatory protein, which leads to high production of Interleukine 1, Interleukin 6, Nuclear Factor-Kb and cytokine storm [15]. However, few series reported the importance of GF as a useful biomarker for the diagnosis of AOSD [2, 4, 9]. GF ≤ 20% had a good specificity (87.1%) for the diagnosis of AOSD and it is a major criterion in Fautrel classification [2, 4].

The low level of glycosylated ferritin in inflammatory conditions is due to the deficiency in glycosylation process of the ferritin that cannot follow high ferritin production [3]. Moreover, a previous study reported that glycosylated ferritin remained low despite the disease course [16].

In our experience, the dosage of GF at the diagnosis is useful for its diagnostic and prognostic value. Glycosylated ferritin with a cut off value ≤ 25% was more frequent than the cut off value ≤ 20% and may be considered for the diagnosis of AOSD. Lower Glycosylated Ferritin rate (GF ≤ 10 %) is a predictive factor of poor outcomes in AOSD.

The systemic score of Pouchot was recently validated by an Italian team who reported that a cutoff point ≥ 7 was associated to the occurrence of life-threatening complications [1, 17]. This severity score was already modified by Rau, who included arthritis and high serum ferritin [18]. Some studies reported the importance of ferritin as prognostic factors [9]. High ferritin and persistent polyarthritis were associated to the chronic course of the disease and the progress in the erosion score [6]. However, few studies focused on the prognostic value of GF. Lower GF was associated to the occurrence of RHL in AOSD, without determination of a cutoff point in this study [19].

Furthermore, GF was associated to early diagnosis of AOSD, which can reduce the diagnostic delay [9]. Nevertheless, GF is not available in all centers and can be low in other diseases such as hemophagocytic lympho-histiocytosis regardless of the cause, Gaucher's disease or tuberculosis [3]. Recent studies reported an increase of the incidence of AOSD, likely due to a better known of the clinical picture, which needs identification of prognostic factors [20].

Key messages

Lower Glycosylated Ferritin (GF ≤ 10 %) is predictive of life-threatening complications particularly hemophagocytic syndrome and high relapses rate with corticosteroid dependence.

Persistent high fever, abdominal pain, liver abnormalities, anemia and high disease activity are predictive of chronic course.

Polyarthritis, high relapses rate during follow up and chronic course with systemic form are predictive of erosive arthritis.

Disclosure

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Conflict of interest

The authors have declared no conflicts of interest concerning this work.

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