Validation of the Fautrel Classification Criteria for Adult-Onset Still's Disease

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Original research

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Abstract (256 words)

Objectives: To validate the Fautrel classification criteria for adult-onset Still's disease (AOSD) and to compare the discriminative performance to that of the Yamaguchi criteria.

Methods: We retrospectively reviewed the medical charts of 426 patients who had serum ferritin level and percentage glycosylated ferritin assayed at the biochemistry laboratory of Bichat Hospital. Medical data were extracted by use of a standardized form. All clinical, biological, and imaging features were collected, as well, evidence favoring an alternative diagnosis, specifically symptoms suggestive of other immune-mediated inflammatory diseases (IMID) or active infections. Patients were classified as AOSD patients or controls according to a predefined procedure, including consultation with a multidisciplinary expert group. Algorithms corresponding to the Fautrel and Yamaguchi classification criteria were applied for each patient.

Results: 54 AOSD and 278 control patients were included. For the Fautrel criteria, the sensitivity was 87.0%, specificity 97.8%, and positive and negative predictive value 88.7% and 97.5%. For the standard Yamaguchi set– without strict application of exclusion criteria– the sensitivity was 96.3%, specificity 98.9%, and positive and negative predictive value 94.5% and 99.3%. If we applied a stricter definition of exclusion criteria, the sensitivity of the Yamaguchi set decreased to 31.5%. As wall, 37 AOSD diagnoses were missed.

Conclusion: This study validates the Fautrel classification criteria with a cohort independent of that used for the original publication. This criteria set demonstrates good sensitivity and specificity, overcomes exclusion criteria and includes glycosylated ferritin level. It also confirms the high discriminative power of the Yamaguchi criteria, albeit substantially affected by how exclusion criteria are interpreted.

Keywords: adult onset Still’s disease; classification; diagnosis; ferritin; infection

Introduction

First described in 1971 by Bywaters (1), adult-onset Still's disease (AOSD) is considered a multigenic auto-inflammatory disorder (2,3). Its incidence has been estimated at 0.16 per 100,000 in France (4), and 0.22 and 0.34 per 100,000 for men and women in Japan. Its prevalence was calculated at 0.73 and 1.74 for men and women in Japan (5). Its main clinical features are a high spiking fever, maculopapular rash usually concomitant with the fever, polyarthralgia, sore throat, lymphadenopathy, and hepatosplenomegaly. Other features reported are myalgia, serositis, weight loss, abdominal pain, and more anecdotally, neurological manifestations, renal impairment and ophthalmologic involvement. Its biological abnormalities include leukocytosis, elevated polymorphonuclear neutrophil counts, elevated erythrocyte sedimentation rate and C-reactive protein level, and abnormal liver function results (1,2,6–11). For the last 20 years, the diagnostic value of serum ferritin and percentage of glycosylated ferritin has been suggested. Indeed, the synthesis of ferritin is increased under inflammatory conditions (12,13). Its level is increased in AOSD and is correlated with disease activity (14–16). A marked decrease in glycosylated ferritin level was reported to be highly suggestive of AOSD (15). In 2001, Fautrel et al. demonstrated a specificity of 92.9% for AOSD diagnosis with the combination of glycosylated ferritin percentage $\leq$ 20% and serum ferritin level greater than 5-fold the normal- value (15). Decreased glycosylated ferritin percentage persists several weeks or even months after AOSD flares and is less associated with variations in disease activity (17). Other authors have demonstrated an association of glycosylated ferritin level with more rapid diagnosis (18). However, low glycosylated ferritin fraction is not completely specific of AOSD and has also been reported in hemophagocytic lympho-histiocytosis (HLH) (19).

Because of the clinical heterogeneity and low prevalence of AOSD, its diagnosis is difficult. It often remains an exclusion diagnosis. Several differential diagnoses, namely infectious, neoplastic, autoimmune and systemic diseases, should be ruled out. Several clinical cases of misdiagnosis and inadequate therapeutic prescriptions have been reported (20–29). Misdiagnosis could have important adverse consequences, because AOSD treatments, such as corticosteroids or immunosuppressive agents, can worsen the course of these differential diagnoses, especially infectious or neoplastic diseases.

Several classification criteria have been published. Although they were not intended for AOSD diagnosis but rather to identify homogeneous groups of patients in clinical research, they can be helpful for clinicians at the time of diagnosis (7,30–37) (Supplemental table 1). All were developed with retrospective data. Most of these classifications included exclusion criteria (7,30–32,37) and were developed without any control group (7,9,30,31,37). One study analyzed the sensitivity of several sets of criteria with a observational cohort of AOSD patients and showed the Yamaguchi criteria with the highest sensitivity (36). Another study demonstrated the highest sensitivity (96.2%) and good specificity (92.1%) for the Yamaguchi criteria (32).

In 2002, Fautrel et al. (33) proposed a new classification criteria set for AOSD, including the previously-mentioned biological parameters but with the advantage of not including exclusion criteria. The selected variables were classified into minor (maculopapular rash, leukocytes $\geq$ 10,000/mm^3) and major criteria (spiking fever $\geq$ 39°C, arthralgia, transient erythema, pharyngitis, polymorphonuclear neutrophil percentage $\geq$ 80%, glycosylated ferritin percentage $\leq$ 20%). AOSD was diagnosed with the presence of 4 major criteria or 3 major and 2 minor criteria. The sensitivity was 80.6% and specificity 98.5%, the latter being higher than that obtained with other sets (33). This classification set includes the value of glycosylated ferritin indicating the pathognomony of this disease.

This study objective was to validate the Fautrel classification criteria with a different cohort and to compare its discriminative performance to that of the Yamaguchi criteria.

Patients and Methods

Study design

A retrospective, monocentric, observational, case control study was conducted.

Study population

We included all adult patients under management at the Pitié-Salpêtrière University Hospital in Paris who had ferritin and glycosylated ferritin assay testing at the biochemistry laboratory of Bichat Hospital from January 2000 to April 2013.

We excluded patients who were less than 18 years old, had incomplete medical charts, and were included in the previous study.

Collected data

Data were extracted from medical charts by one investigator (DL) who used a standardized form. The index date was the date of the glycosylated ferritin assay. All clinical, biological, and imaging features available at the time of or before the index date were collected as discrete variables (present or absent for clinical parameters, normal or abnormal for biological parameters according to predefined thresholds). Information suggestive of an alternative diagnosis was carefully searched, especially that corresponding to other immune-mediated inflammatory diseases [IMIDs, i.e., corresponding to criteria contained in other IMID classification sets, such as for Behcet's disease (38,39), giant cell arteritis (40), inflammatory myopathies (41), systemic lupus erythematosus (42), Sjogren's syndrome (43), familial Mediterranean fever (44), rheumatoid arthritis (45), spondyloarthritis (46,47), and HLH (48)]. In addition, diagnostic investigations to exclude an active infection or a neoplastic disease were noted. The diagnosis by the referring physician at the last follow-up was also noted (case report form in Supplemental table 2 and criteria for other IMIDs in Supplemental table 3).

Diagnostic certification of cases and controls

Patients were classified as AOSD patients or controls, based on clinical and laboratory information extracted from medical charts at the time of ferritin dosage or later. Inclusion in the AOSD group required: 1) a diagnosis of AOSD retained by the referring physician at last follow-up, 2) a diagnosis of AOSD retained by the investigator (DL), and 3) meeting none of the classification criteria sets for IMID described previously. Controls included patients

without the AOSD definition and those with HLH, neoplasia, other IMIDs, hepatic diseases, infections, or other conditions. For patients with a discrepancy between the final diagnosis and classification criteria and/or featuring several classification criteria, group adjudication was performed by a multidisciplinary expert group (BF, GG, JP, LA, SGL) after revision of the case. During the multidisciplinary adjudication, patient data were presented in terms of a report summarizing disease history, clinical, laboratory and imaging findings and satisfaction of IMID classification criteria sets, except for the Yamaguchi and Fautrel classification sets which were not presented. In case of residual uncertainty despite the expert adjudication, cases were excluded.

Satisfying of AOSD classification criteria

Algorithms corresponding to the Fautrel and Yamaguchi classification criteria were applied to each patient. The classification criteria items that were missing in the medical chart – missing data – were considered absent.

Exclusion criteria were managed in two ways. The first was Yamaguchi classification in which these criteria were defined as absent according to the referring physician (indicated in the chart) and present if the final diagnosis was an infection, neoplasia or IMID. This method is designated hereafter as the “standard Yamaguchi classification”. Second, exclusion criteria were defined as absence of exclusion criteria according to the referring physician and performance of diagnostic investigations including at least blood cultures, Epstein-Barr virus serology or PCR, and dosage of rheumatoid factor and anti-nuclear antibodies. The choice of these complementary exams was based on the Yamaguchi et al. study (32). This method is designated hereafter as the “strict Yamaguchi classification”.

In addition, three composite classifications were applied to each patient. The first corresponded to the standard Yamaguchi classification, with the addition of ferritin level as a major criterion (considered present with ferritin level higher than normal), and is called "Yamaguchi +F>N" hereafter. The second corresponded to the standard Yamaguchi classification with the addition of glycosylated ferritin percentage (considered present with glycosylated ferritin fraction $\leq$ 20%), and was called "Yamaguchi +FG $\leq$ 20%". The three corresponded to the standard Yamaguchi classification with the addition of ferritin level 5 fold upper limit of the normal (considered present with ferritin level >5N), and was called "Yamaguchi +FG>5N".

Statistical analysis

Quantitative data are described with mean ± SD and categorical data as number (percentage). The two groups were compared by Student *t* tests for quantitative variables and chi-square test or exact Fisher test for categorical variables. For each diagnostic method, sensitivity, specificity, positive and negative predictive values were estimated with their 95% confidence intervals by the bootstrap procedure with 1000 replicates. Sensitivity and specificity of the two classification criteria sets were compared by McNemar test. All computations involved use of SAS v9.3 (SAS Institute, Cary, NC, USA). $P<0.05$ was considered statistically significant.

Results

Population characteristics

During the study period, 1093 ferritin and glycosylated ferritin assays were performed by the biochemistry laboratory of Bichat Hospital. These assays involved 761 patients, of whom 426 had available and complete medical records. Overall, 81 of these cases were assessed by the multidisciplinary expert group. Finally, we identified 54 patients with AOSD and 278 were controls. We excluded 94 patients: 68 because they were younger than 18 years old or data from the medical record were incomplete and 26 because AOSD could not be definitely excluded or diagnosed (Figure 1).

The distribution of diseases for controls are in Table 1. The category "other" included especially drug eruption, urticaria, cristal arthropathies, and psychosomatic disorders.

Clinical and biological characteristics

Table 2 shows the main clinical and laboratory characteristics of AOSD patients and controls. The mean age of AOSD patients was 38.9$\pm$15.6 years and 37.0% were male. AOSD patients were younger than controls. The cardinal symptoms of AOSD– fever, arthralgia, rash, leukocytosis and elevated polymorphonuclear neutrophils– were more frequent in AOSD patients than controls. Serum ferritin level > normal values (N) was higher for AOSD patients than controls (41/54 [75.9%] vs 155/278 [55.8%]), corresponding to a specificity of 44.2%. Ferritin level >5-fold higher than N was higher for AOSD patients than controls (28/54 [51.9%] vs 44/278 [15.8%]), corresponding to a specificity of 84.2%. Moreover, glycosylated ferritin fraction $\leq$ 20% was more frequent for AOSD patients than controls (34/54 [63.0%] vs 36/278 [13.0%], corresponding to a specificity of 87.1%. The combination of ferritin level >5N and glycosylated ferritin fraction $\leq$ 20% was more frequent for AOSD patients than controls (14/54 [25.9%] vs 32/278 [11.5%], corresponding to an interesting specificity of 88.5% but a low sensitivity of 25.9%. AOSD patients and controls showed significant differences in the frequency of most variables except for gender, pericarditis, renal failure and anti-neutrophil cytoplasmic antibodies (ANCA).

Additional tests performed to rule out active infection

Table 3 summarizes the tests performed to exclude an active infection. The mean number of tests was 7.5±6.0 (median 6.0) for patients with AOSD. Blood cultures were more frequent for AOSD patients than controls (26/54 [48.2%] vs 89/278 [32.0%]). Epstein-Barr virus serology or PCR was more frequent for AOSD patients than controls (26/54 [48.2%] vs 82/278 [29.5%]). Bacteriological analysis of body fluids (including cerebrospinal fluid, broncho-alveolar fluid, pericardial fluid, joint fluid, and sampling from abscesses) was more frequent for controls than AOSD patients (51/278 [18.4%] vs 3/54 [5.6%]). Six of the 54 AOSD patients (11.1%) had additional tests during further disease flares.

Discriminative performance of Fautrel criteria

The Fautrel criteria had sensitivity 87.0%, specificity 97.8%, and positive and negative predictive value 88.7% and 97.5%. Six patients were falsely classified as AOSD by this set, and seven AOSD diagnoses were missed. The false-positive cases were finally diagnosed as Castleman disease, endocarditis, pneumonitis, anti-NMDA (N-methyl-D-aspartate) receptor encephalitis, connective and granulomatosis (n=1 each). Among the seven missed AOSD patients, two had a monocyclic systemic form, three a polycyclic systemic form, and two a chronic articular forms. Two of these seven patients were discussed during the multidisciplinary consultation.

These false-negative cases were classified as AOSD by the standard Yamaguchi set, which had sensitivity 96.3%, specificity 98.9%, and positive and negative predictive value 94.5% and 99.3%. Using the standard Yamaguchi criteria set, three controls were falsely classified as AOSD, and two AOSD diagnoses were missed. The three controls falsely classified as AOSD had an inflammatory myopathy, anti-NMDA receptor encephalitis and an unclassified inflammatory disease. The two AOSD missed cases had a polycyclic systemic form and were correctly classified with the Fautrel set. One of these cases was assessed during the multidisciplinary consultation. If we applied a stricter definition of exclusion criteria, the sensitivity of the Yamaguchi set decreased to 31.5% ($p < 0.0001$). In addition, 37 AOSD diagnoses were missed, although one alone was falsely classified as AOSD.

The composite set, "Yamaguchi+F > N", had sensitivity 100.0%, specificity 97.1%, and positive and negative predictive value 87.1% and 100.0%. With this set, the number of false-negative cases was reduced to 0. However, this combination wrongly classified eight controls

as AOSD: five had a diagnosis of IgA nephropathy, pelvic fibrosis, sarcoidosis, unclassified autoimmune disease, unclassified autoinflammatory syndrome and the remaining three were previously misclassified with the standard Yamaguchi set.

The composite set, "Yamaguchi + F > 5N", displayed sensitivity 96.3%, specificity 98.6%, and positive and negative predictive value 92.9% and 99.3%. With this set, the number of false-negative cases was reduced to 0, and the number of false-positive cases was reduced to 4. The The latter included one patient with unclassified connectivite and three controls previously misclassified with the standard Yamaguchi set.

The composite set, "Yamaguchi+FG $\leq$ 20%", had sensitivity 98.2%, specificity 98.6%, and positive and negative predictive value 93.0% and 99.6%. There was one false-negative case and four false-positive cases. The latter included one patient with chronic urticaria and three controls previously misclassified with the standard Yamaguchi set. The misclassified patients are described in Table 5.

These different sets showed excellent performance. However, the differences did not reach statistical significance, which did not allow us to compare these sets.

Discussion

This study validates the Fautrel classification criteria for AOSD with a different cohort than the original one. This criteria set shows good sensitivity and specificity, overcomes exclusion criteria and includes glycosylated ferritin fraction level. It also confirms the high discriminative power of the Yamaguchi criteria, which are highly affected by how exclusion criteria are interpreted. In addition, the two classification criteria sets featured no significantly significant differences.

The study design for validating classification criteria for AOSD is challenging. The first limitation of our study is its retrospective design. Although a prospective design is desirable to avoid any missing data, the low incidence of the disease, estimated at 0.16 per 100,000 in France (4), and the absence of a national cohort limit the feasibility of this design. Likewise, none of the other criteria sets were developed prospectively, which confirms this difficulty (7,9,30–32,34,37). To minimize the bias in data recording, we ensured that patient records were comprehensive, and we used a standardized data collection form. However, the quality of medical charts was not consistent and several cases were excluded because of incomplete data. The second limitation concerns the selection of controls. The purpose of classification criteria is to separate AOSD patients and those with a disorder mimicking AOSD (49). Only the studies of Yamaguchi et al. (32), Fautrel et al. (33), Crispin et al. (34), Vanderschueren et al. (35) and our present study defined a control group. We selected the patients which both ferritin and glycosylated ferritin assay results. To our knowledge, combination of these 2 assays is prescribed only for patients with suspected AOSD or HLH (19). These data allowed us to identify cases and controls in the same population. Moreover, the identification of cases and controls was independent of serum ferritin and glycosylated ferritin levels to avoid any selection bias. Crispin et al. (34) defined controls as patients with fever of unknown origin as defined by Petersdorf and Beeson, and separately defined AOSD patients. The patient selection in the study by Vanderschueren et al. (35) was based on fever of unknown origin. The size of the control group was also questionable. Because of our selection process, we did not calculate the number of needed controls, and five controls were included for one AOSD case. In comparison, three controls were included in the Yamaguchi et al. study (32), five in the Crispin et al. study (34), and two in the Fautrel et al. and Vanderschueren et al. studies (33,35).

The classification procedure for AOSD patients was not based on Yamaguchi criteria set, unlike the Vanderschueren et al. validation study. However, physicians in charge of patients were fully aware of these classification criteria which might have influenced their final diagnosis. To limit this bias, we defined a procedure based on physician judgment at different steps to ascertain diagnosis and properly classify patients. The Yamaguchi et al. study was the only other one to use experts' judgment. This identification procedure of cases and controls is not perfect, but represents the most neutral approach to compare classification criteria sets.

Integrating the Yamaguchi exclusion criteria in data collection was complex. Indeed, these criteria include infections, malignancies, and rheumatic diseases. In current practice, what corresponds to these terms is unclear. Rheumatic diseases include rheumatoid arthritis and spondyloarthritis or IMID in a broader sense. We cannot determine whether additional investigations can reasonably eliminate all the confounding disorders. Previously cited studies (33–35) do not describe how these criteria were handled. In our study, exclusion criteria were first considered absent if the referring physician considered them as eliminated and present if the final diagnosis was infection, neoplasia or IMID, and second, considered absent if the referring physician had performed enough diagnostic investigations to rule them out, defined as at least blood culture, Epstein-Barr virus serology or PCR, dosage of rheumatoid factor and anti-nuclear antibodies. The choice of these additional tests was based on the Yamaguchi et al. study (32).

In our study, the control group included patients with the main confounding disorders with AOSD. However, the spectrum of diagnoses slightly differed from that in other studies (32–35). Our control group included some with liver diseases and no fever of unknown origin. Also, this is the only study including patients with HLH. Because of the similarity of clinical and biological signs of these two disorders, distinguishing them in common practice is difficult. The Fautrel classification criteria set demonstrated its ability to correctly classify these two distinct disorders.

The cardinal manifestations of AOSD– fever, arthralgia, rash, leukocytosis and increased polymorphonuclear neutrophils– were present in more than 70% patients with AOSD. The frequency of these manifestations in our study population was similar to that reported for other series (8,10,18,32,33,50). Myalgia was observed in 35.2% of patients with AOSD. This symptom was found in comparable proportions in most studies (18,32,50), except in the Pouchot et al. study (10), in which 84% of patients had myalgia. Moreover, the present study

confirms the diagnostic value of serum ferritin level > 5N and glycosylated ferritin level <20% (15,16,33).

We noted a great heterogeneity in both the number and type of the additional diagnostic tests performed. Some patients underwent no laboratory exams, whereas others had more than 20 tests. The lack of precise definition of the Yamaguchi exclusion criteria, in the form of a comprehensive list of diagnoses to exclude or exams to perform, explains this disparity. This situation attests to the complexity of Yamaguchi criteria used in clinical research.

The present study validates the Fautrel criteria for AOSD in a different cohort than the initial one, with sensitivity 87.0%, specificity 97.8% and accuracy 96.1%. This classification criteria set displayed higher sensitivity than the other sets except Yamaguchi's (36). Moreover, all evaluated sets achieved excellent performance. The differences among criteria did not reach statistical significance. A likely explanation for this result was the small size of the AOSD group. Finally, this study confirms the excellent performance of the Yamaguchi and Fautrel classification criteria in clinical research. The lower sensitivity of the Fautrel classification is offset by the absence of exclusion criteria. Moreover, this classification includes glycosylated ferritin level confirmed as specific in our study. In addition, the discriminative power of the Yamaguchi criteria is highly affected by how exclusion criteria are interpreted. In fact, by applying stricter exclusion criteria, the sensitivity significantly decreased to 31.5%. Although not perfect, the Fautrel classification seems more manageable than the Yamaguchi criteria in clinical research. Further validation studies should be carried out on other populations in other countries in order to confirm these data. A better understanding of the pathophysiology of AOSD could be the key to a more reliable diagnostic approach.

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Figure 1: Flow of patients in the study

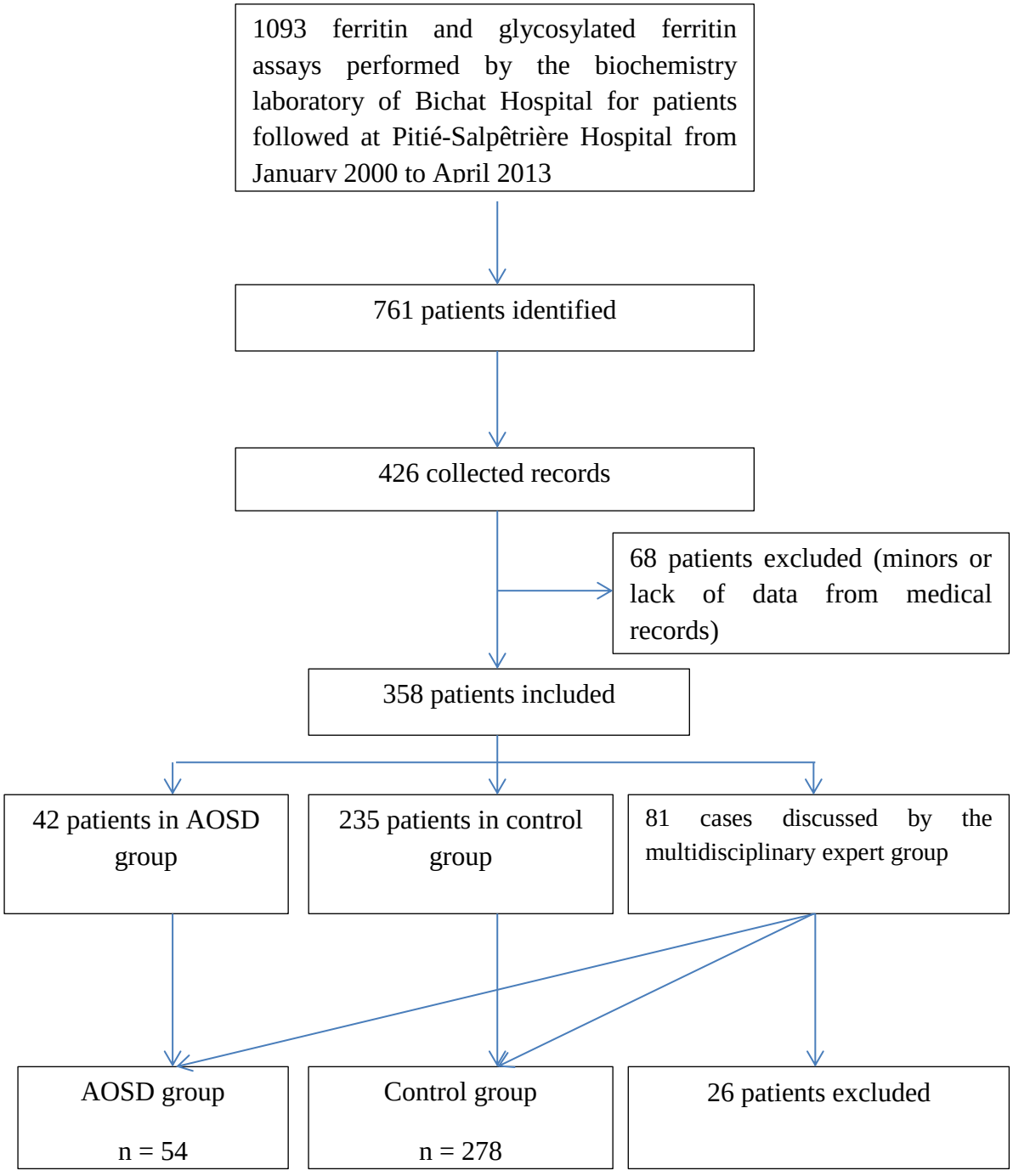

Table 1 : Control group diagnoses

	Specific Diagnosis
IMID (n=118)	6 rheumatoid arthritis 15 spondyloarthropathies 12 systemic lupus erythematosus 8 myositis 15 vasculitis (including 4 associated with ANCA) 8 giant cell arteritis or polymyalgia rheumatic 6 sarcoidosis 11 autoinflammatory syndromes (including 4 familial Mediterranean fever) 2 relapsing polychondritis 35 miscellaneous systemic disorders
Infectious diseases (n=51)	33 bacterial infections (including 9 tuberculosis) 17 viral infections 1 malarial episode to *Plasmodium ovale*
Neoplasia (n=21)	4 Hodgkin's lymphoma 9 other hematological malignancies 8 solid cancers (affecting pharynx, lung, colon, uterus)
HLH (n=15)	7 HLH secondary to infection 5 HLH secondary to neoplasia 2 HLH secondary to systemic diseases 1 HLH secondary to drug hypersensitivity
Liver diseases (n=5)	2 hemochromatosis 1 autoimmune hepatitis 2 NASH
Other (n=68)	

Abbreviations: IMID = immune-mediated inflammatory diseases; ANCA = anti-neutrophil cytoplasmic antibodies; HLH = hemophagocytic lympho-histiocytosis; NASH = non alcoholic steato-hepatitis

Table 2: Main clinical and laboratory characteristics of patients with adult-onset Still's disease (AOSD) and controls

	AOSD (n=54)	**Controls (n=278)**	**p value**
Age, mean±SD (yr)	38.9±15.6	44.5±17.3	0.03¤
Follow-up after diagnosis (yr)	4.0±3.7	ns	
Male, n (%)	20 (37.0)	116 (41.7)	0.52§
Spiking fever ≥39°C	48 (88.9)	100 (36.0)	**<0.0001§**
Arthralgia	54 (100)	116 (41.7)	**<0.0001§**
Arthritis	25 (46.3)	39 (14.0)	**<0.0001§**
Myalgia	19 (35.2)	43 (15.5)	**<0.001§**
Maculopapular rash	38 (70.4)	15 (5.4)	**<0.0001§**
Transient erythema	10 (18.5)	10 (3.6)	**<0.001$**
Pharyngitis	36 (66.7)	11 (4.0)	**<0.0001§**
Lymphadenopathy or splenomegaly	33 (61.1)	80 (28.8)	**<0.0001§**
Pericarditis	8 (14.8)	22 (7.9)	0.12$
Leukocytes count ≥10,000/mm^3	46 (85.2)	91 (32.7)	**<0.0001§**
PMN count ≥80%	43 (79.6)	55 (19.8)	**<0.0001§**
Renal failure (creatinine ≥ 110µmol/L)	1 (1.9)	22 (7.9)	0.15$
Elevated liver enzymes or LDH	38 (70.4)	120 (43.2)	**<0.001§**
Negative ANA	40 (74.1)	117 (42.1)	**<0.0001§**
Negative RF	40 (74.1)	116 (41.7)	**<0.0001§**
Serum ferritin>N*	41 (75.9)	155 (55.8)	**<0.01§**
Serum ferritin >5N*	28 (51.9)	44 (15.8)	**<0.0001§**
Glycosylated ferritin≤20%	34 (63.0)	36 (13.0)	**<0.0001§**
Serum F >5N* and GF≤20%	14 (25.9)	32 (11.5)	**<0.01$**
ANCA	0 (0.0)	9 (3.2)	0.36$

Data are n (%) unless indicated.

Abbreviations: AOSD = adult-onset Still's disease; ns = not specified; PMN = polymorphonuclear neutrophil; LDH = lactate dehydrogenase; ANA = anti-nuclear antibodies; RF = rheumatoid factor; F = ferritin; GF = glycosylated ferritin; ANCA = anti-neutrophil cytoplasmic antibodies.

*Normal serum ferritin levels were 200 µg/L for women, 300 µg/L for men. ">N" = serum ferritin level higher than the upper normal value, ">5N" = serum ferritin level greater than 5-fold the upper normal value.

¤Student test, §chi-square test, $Fisher exact test

Table 3: Additional diagnostic tests performed to exclude infectious differential diagnosis in AOSD patients and controls

	AOSD (n=54)	Controls (n=278)	p value
No. of complementary exams ± SD, mean±SD	7.5±6.0	6.5±5.2	0.20
Range	0-25	0-23	
Exams performed			
Blood cultures	26 (48.2)	89 (32.0)	**0.02**[§]
Bacterial urinalysis	20 (37.0)	69 (24.8)	0.06[§]
Stool cultures	5 (9.3)	15 (5.4)	0.34[$]
Bacteriological analysis of other body fluids	3 (5.6)	51 (18.4)	**0.01**[§]
Tuberculosis research	13 (24.1)	76 (22.9)	0.62[§]
Syphilis serology	9 (16.7)	58 (20.9)	0.48[§]
Borrelia burgdorferi serology	11 (20.4)	65 (23.4)	0.63[§]
Other bacterial serology or PCR	29 (53.7)	123 (44.0)	0.20[§]
HIV serology	32 (59.3)	154 (55.4)	0.60[§]
Hepatitis B serology	34 (63.0)	162 (58.3)	0.52[§]
Hepatitis C serology	35 (64.8)	165 (59.4)	0.45[§]
Cytomegalovirus serology or PCR	27 (50.0)	97 (34.9)	**0.04**[§]
Epstein-Barr virus serology or PCR	26 (48.2)	82 (29.5)	**<0.01**[§]
Parvovirus B19 serology or PCR	13 (24.1)	58 (20.9)	0.60[§]
Other viral serology or PCR	17 (31.5)	80 (28.9)	0.69[§]
Malaria research	3 (5.6)	25 (9.0)	0.59[$]
Toxoplasmosis serology	7 (13.0)	37 (13.3)	0.95[§]
Other parasitic serology	8 (14.8)	34 (12.2)	0.60[§]
Mycological research	0 (0.0)	12 (4.3)	0.23§

Data are n (%) unless indicated.

Abbreviations: AOSD = adult-onset Still's disease; BK = bacillus of Koch; HIV = human immunodeficiency virus

[§]chi-square test, [$] Fisher exact test

Table 4: Evaluation of AOSD classification criteria

Criteria sets	AOSD (n=54)	Control (n=278)	Sensitivity (%) 95% CI	Specificity (%) 95% CI	PPV (%) 95% CI	NPV (%) 95% CI	Accuracy (%) 95% CI
Fautrel	47	6	87.0 [77.1-95.7] °	97.8 [96.0-99.3] °	88.7 [73.3-96.2]	97.5 [95.5-99.3]	96.1 [94.0-98.0]
Yamaguchi							
Standard	52	3	96.3 [90.6-100.0]	98.9 [97.5-99.8]	94.5 [87.2-100.0]	99.3 [98.2-100.0]	98.5 [97.0-99.7]
Strict	17	1	31.5 [19.1-43.6] ****/°°°°	99.6 [98.9-100.0] */°	94.4 [81.3-100.0]	88.2 [84.8-91.5]	88.6 [85.2-91.9]
Composite set							
Yamaguchi + F > N	54	8	100.0 [100.0-100.0] **/°	97.1 [95.1-98.9] */°	87.1 [78.3-94.6]	100.0[100.0-100.0]	97.6 [96.1-99.1]
Yamaguchi + F > 5N	54	4	96.3 [89.7-100.0] */NA	98.6 [97.1-99.6] */°	92.9 [85.5-98.3]	99.3 [97.9-100.0]	98.2 [96.7-99.4]
Yamaguchi + FG ≤ 20%	53	4	98.1 [93.8-100.0] */°	98.6 [97.1-99.7] */°	93.0 [86.0-98.3]	99.6 [98.9-100.0]	98.5 [97.0-99.7]

Abbreviations: PPV = positive predictive value; NPV = negative predictive value; F > N = means serum ferritin level higher than the upper normal value; FG = glycosylated ferritin; NA = not applicable
Comparing the Fautrel set and this set according to the Mc Nemar test: *p ≥0.05, **p <0.05, ***p <0.01, ****p <0.001
Comparing the standard Yamaguchi set and this set according to the Mc Nemar test: °p ≥0.05, °°p <0.05, °°°p <0.01, °°°°p <0.001
CI95 were assessed by bootstrap procedure with 1000 replicates

Table 5: Description of misclassified patients by the different studied classifications

Criteria sets	False positive	False negative
Fautrel	Castleman's disease Endocarditis Pneumonitis Anti-NMDA receptor encephalitis Unclassified connectivite Unclassified granulomatosis	2 monocyclic systemic forms 3 polycyclic systemic forms 2 chronic articular forms
Standard Yamaguchi	Inflammatory myopathy Anti-NMDA receptor encephalitis Unclassified inflammatory diseases	2 polycyclic systemic forms
Strict Yamaguchi	Anti-NMDA receptor encephalitis	37 patients
Yamaguchi+F > N	IgA nephropathy Pelvic fibrosis Sarcoidosis Unclassified autoimmune disease Unclassified autoinflammatory syndrome Inflammatory myopathy Anti-NMDA receptor encephalitis Unclassified inflammatory diseases	None
Yamaguchi+F > 5N	Anti-NMDA receptor encephalitis Unclassified inflammatory diseases Unclassified connectivite Inflammatory myopathy	None
Yamaguchi+FG $\leq$ 20%	Chronic urticaria Inflammatory myopathy Anti-NMDA receptor encephalitis Unclassified inflammatory diseases	1 patient

Abbreviations: NMDA = N-Methyl-D-Aspartate; F >N = means serum ferritin level higher than the upper normal value; FG = glycosylated ferritin

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Supplemental table 1: Classification criteria sets for diagnosis of adult-onset Still's disease (AOSD)

Manifestation	**Goldman (1980) (30)**	**Calabro (1986) (31)**	**Cush (1987) (9)**	**Reginato (1987) (7)**	**Kahn (1991) (37)**	**Yamaguchi (1992) (32)**	**Fautrel (2001) (33)**	**Crispin (2005) (34)**
Fever	XX	XX	XX	XX	XX	XX	XX	
Arthritis/arthralgia	XX	XX	XX	XX	XX	XX	XX	10
Sore throat/pharyngitis				X	X	X	XX	7
Myalgia		XX			X			
Lymphadenopathy	X	X	X	X		X		
Splenomegaly	X	X	X	X		X		5
Hepatomegaly		X	X					
Serositis (pleuritic or pericarditis)	X	X	X	X	X			
Maculopapular rash		X	X	XX	XX	XX	X	5
Transient erythema	X						XX	
Organ involvement				X				
Similar episode in childhood					XX			
Leukocytosis	XX	X	X	XX	XX	XX	X	18
PMN>80%							XX	
Negative RF	XX	XX	XX			X		
Negative ANA		XX	XX		XX	X		
Liver dysfunction				X		X		
Glycosylated ferritin ≤20%							XX	
Exclusion criteria	XX	XX		Yes, def1	Yes	Yes, def2		
Positive diagnosis	5 major +>1 minor	4 major +>2 minor	4 major +>2 minor	4 major Or fever +arthritis +1 major +>1 minor And no exclusion criteria	>4 major +no exclusion criteria Or 3 major +>3 minor +no exclusion criteria	>5 criteria including >2 major +no exclusion criteria	4 major or 3 major +2 minor	>30 points
Sensitivity/specificity						**96.2%/92.1%**	**80.6%/98.5%**	**76.9%/98%** **After validation 55%/98%**

XX = major criteria ; X = minor criteria; def1 = negative blood cultures, negative synovial fluid, and negative serology for known bacterial, parasitic, fungal, and viral infections, negative for rheumatoid fever (RF), absence of monoclonal gammapathy; def2 = absence of infections, malignancies or rheumatic disease; PMN = polymorphonuclear neutrophil; ANA = anti-nuclear antibodies

Supplemental table 2: The Case Report Form

Patient				Sex	F/M	Age	
Rheumatology	Start of arthritis				Temperature	≤37	0
						37< <39°	0
	Arthralgia		0			39≤ <41°	0
					Duration of febrile illness		
	Arthritis	0	0				
		0< <3	0		Morning stiffness	absent	0
		≥3	0			<15'	0
						15'≤ <60'	0
		Symmetric	0			60'≤ <3h	0
		Destructive	0			≥3h	0
					Night waking		0
	Reaching hand		0				
					Muscular weakness		0
	Myalgia	spontaneous	0				
		To the pressure	0		Weight loss >4kg		0
		To the effort	0				
	Inflammatory back pain		0		Entesopathy	absent	0
	Rocking buttock pain		0			0< ≤7	0
	Heel pain		0			≥8	0
	Family history of spondyloarthropathy		0				

Dermatology	Transient erythema	0	Psoriasis	0
	Vespertilio	0	Erythema « érysipéloïde »	0
	Raynaud	0	Palmoplantar pustulosis	0
	Photosensitivity	0	Papulo-pustule	0
	Discoid lupus	0	Folliculitis/Pseudofolliculitis	0
	Sclerodactyly	0	Recurrent mouth ulcers	0
	Sausage fingers	0	Allergy at the injection	0
	Gottron sign	0	Nodules	0
	Lilac edema of the eyelids	0	Erythema nodosum	0
	Erythema face extension members	0	Livedo reticularis	0
	Macular rash	0	Digital ulcers	0

Nephrology	Proteinuria	0≤ <0,5 g/j	0	Creatinine	<110 µmol/L	0
		0,5≤ <1 g/j	0		110≤ <135	0
		1≤ <2 g/j	0		≥135 µmol/L	0
		≥2 g/j	0			
	Hematuria		0	Blood urea nitrogen	≤7 mmol/L	0
	Leukocyturia		0			
	Cylindruria		0		>7 mmol/L	0

Cardiology	Pericarditis	0	Phlebitis	0
	Endocarditis	0	Miscarriages>3	0
	HTA (diastolic >9)	0	Arterial thrombosis	0

				Vein thrombosis		0
				Aneurism		0
Pneumonology	Asthma		0	Interstitial syndrome		0
	Respiratory failure		0	Pleurisy		0
Neurology	Headache		0	Mono / polyneuropathy		0
	Epilepsy		0	Psychosis		0
	Anomaly temporal pulse		0			
Gynecology / Urology						
	Salpingitis		0	Epididymitis		0
	Cervicitis		0	Orchitis		0
	Genital ulcer		0	Urethritis		0
	Recurrent ulcers		0	Testicular sensitivity		0
Stomatology	Angina		0	*Date*		
	Pharyngitis		0			
	Subjective dry mouth		0	Chondrite		0
	Objectively dry mouth		0	Maxillary sinusitis		0
	BSGA		0	Mouth ulceration		0
Ophtalmology	Uveitis		0	Subjective dry sd		0
	Scleritis		0	Objective dry sd		0
	Keratitis		0			
	Conjunctivitis		0	Retinal vasculitis		0
Gastroenterology	Diarrhea	acute	0	*Date*		
		chronic	0	Peritonitis		0
	Inflammatory enteropathy		0	Hepatomegaly		0
Hepatology	Jaundice		0	Hepatocellular insufficiency		0
	ASAT		0	gamma GT		0
	ALAT		0	Alkaline phosphatase		0
Hematology	Lymph nodes		0	Splenomgaly		0
	Leukocytes	<4000 /mm3	0	Hemolytic anemia		0
		4≤ <10000	0	Thrombocytopenia < 100000 /mm3		0
		≥10000 /mm3	0	Neutropenia		0
	Neutrophils	≥ 80 %	0	VS 1st time	> 20 mm	0
	Lymphocytes	< 1500 /mm3	0		> 50 mm	0
	Eosinophils	≥ 10 %	0	CRP	increased	0
	Triglycerides	increased	0	Hypofibrinogenemia		0
Biological	LDH		0	CPK	increased	0
	Bilirubin	increased	0			
Immunology	Antinuclear Factors		0	Latex		0
	Ac anti-dsDNA		0	Waaler Rose		0
	Ac anti-Sm		0	Ac anti-CCP		0
	Ac anti-SSA		0	Ac anti-cardiolipin		0
	Ac anti-SSB		0	Ac anti-beta2GP1		0
	Ac anti-RNP		0	Ac lupus anticoagulant		0

	Ac anti-JO1		0	False syphilis serology		0
	ANCA		0	*Other*		0

Infectious	Blood cultures		0	CMV serology	primary infection	0
	EBV serology	primary infection	0		old immunity	0
		old immunity	0		negative	0
		negative	0	VZV serology	primary infection	0
	VIH serology	positive	0		old immunity	0
		negative	0		negative	0
	VHC serology	primary infection	0	PVB19 serology	primary infection	0
		old immunity	0		old immunity	0
		negative	0		negative	0
	VHB serology	primary infection	0	Toxoplasmosis serology	primary infection	0
		infection	0		old immunity	0
		old immunity	0		negative	0
		vaccination	0	*Other*		0
	VHA serology	primary infection	0			
		old immunity	0			
		negative	0			

HLA	B27	0	DR3
			DR4

Articular fluid	Element number	Crystals
	Cell type	Germ

Radio	Joint erosions	0
	Sacroiliitis	0

EMG	Myogenic syndrome	0
	Neurogenic syndrome	0

Histology	Muscular biopsy	myositis	0	PRB ou BSGA	amylose AA	0
	Vascular biopsy	vasculitis	0			
	BSGA	infiltrate	0			
	TAB	infiltrate	0			

Treatment	NSAID	response +	0
	Corticosteroids	response +	0
	Colchicine	response +	0
	Other		

Diagnosis set out initially

Finally sucessfull diagnosis   Decline from the onset of symptoms

Evolution if several sample

Date

Fever
Rash
Polyarthralgia
Polyarthritis
Myalgia
Pharyngitis
Lymph nodes
Splenomegaly
Cardiac involvement
Pulmonar involvement

VS
CRP
Leukocytes
PMN
Erythrocytes
Platelets
ASAT
ALAT
Alkaline phosphatase
Gamma GT
CPK
LDH
Creatinine

Ferritin
Glycosylated ferritin
Thrust

Partial remission
Complete remission

Radiographic erosions

Infectious episodes

Ongoing treatment

Supplemental table 3 : Criteria

BEHCET DISEASE

Recurrent oral aphthosis	0	**Dg if total ≥ 3**
Recurrent genital aphthosis	0	
Uveitis	0	
Retinal vasculitis	0	
Erythema nodosum	0	
Pseudo-folliculitis	0	
Papulo-pustule	0	
Pathergy positive test	0	
Arterial thrombosis	0	
Vein thrombosis	0	
Aneurism	0	

DERMATOPOLYMYOSITIS / POLYMYOSITIS

Symmetrical proximal muscle weakness	0	**Dg pure DPM if total ≥ 4 (including rash)** **Dg pure DPM if total ≥ 3 (including rash)**
Elevated CPK	0	
EMG triad	0	
Potential polyphasiq power unit Fibrillations, points +, increased integration activity Complex repetitive discharges high frequency		
Abnormal muscular biopsy	0	**Dg pure PM if total ≥ 4** **Dg probable PM if total ≥3**
Degeneration, regeneration, necrosis, Phagocytosis, interstitial mononuclear infiltrate		
Typical rash of DPM	0	

LUPUS ERYTHEMATOSUS

Vespertilio	0		
Eruption of discoid lupus	0		
Photosensitivity	0		
Ulcérations buccales ou nasopharyngées	0		
No erosive polyarthritis	0		**Dg if total ≥ 4**
Pleurisy or pericarditis	0		
Proteinuria > 0,5 g/j	0		
Hematuria without low reason	0		
Leukocyturia without low reason	0		
Convulsions	0	0	
Psychosis	0		
Hemolytic anemia	0	0	
Leukopenia <4000	0		
Lymphopenia <1500	0		
Thrombocytopenia<10000	0	0	

	Antinuclear factors		0
	Ac anti-DNA	0	0
	Ac anti-Sm	0	
	Ac anti-cardiolipin	0	
	Ac anti lupus coagulant	0	
	False syphilis serology	0	

GOUGEROT SJÖGREN

	Subjective dry eye sd		0
	Subjective dry mouth sd		0
	Objective dry eye sd		0
	Objective dry mouth sd		0
	BSGA +		0
	Ac anti-SSA	0	0
	Ac anti-SSB	0	

Dg if total ≥4 (including n°5 or n°6)
Dg if total ≥3 goals

PERIODIC DISEASE

	Fever		0
	Arthritis	0	0
	Pleurisy	0	
	Pericarditis	0	
	Peritonitis	0	
	Amylose AA	0	
	Colchicine +	0	
	Relapsing fever	0	
	Erythema érysipélatoïde	0	
	Family history with a relative degree 1	0	

Final dg si total >4
Probable dg si total ≥3

HORTON

	Early symptoms after 50 years		0
	Headaches		0
	Abnormality of the temporal pulse		0
	Increased VS		0
	TAB +		0

Dg if total ≥3

RHEUMATOID ARTHRITIS

	≥1 arthritis		0
	≥1 radiological erosion		0
1	achievement of 2-10 large joints	0	0
2	1-3 small joints	0	
3	4-10 small joints	0	
5	>10 joints (including 1small)	0	
2	RF or anti-CCp <3N	0	
3	RF or anti-CCp >3N	0	

Dg if total =1

1	duration> 6 weeks	0
1	CRP or VS +	0

AXIAL SPONDYLOARTHRITIS

	Inflammatory back pain	0 0
	arthritis	0
	enthesitis	0
	uveitis	0
	dactylitis	0
	psoriasis	0
	MICI	0
	NSAID +	0
	Familial history of SA	0
	HLA B27	0
	sacro-illiitis MRI	0

Dg if total = 1

PERIPHERAL SPONDYLARTHOPATHY

	arthritis	0 0 0
	enthesitis	0
	dactylitis	0
	uveitis	0 0
	psoriasis	0
	MICI	0
	infection	0
	HLA- B27	0
	sacro-iliitis MRI	0
	Inflammatory back pain	0
	Familial history of SPA	0

Dg if total =1

HEMOPHAGOCYTIC LYMPHO-HISTIOCYTOSIS

	Fever	0
	Splenomegaly	0
	Cytopenia affecting at least 2 lines	
	Hb < 9 g/dL	0 0 0
	Platelets < 100000 mm3	0
	Neutrophils < 1000 mm3	0
	Triglycerides > 3 mmol/l	0 0
	Fibrinogen < 1,5 g/L	0
	Hemophagocytosis	0
	No neoplasia	0
	Ferritin > 500 ug/L	0
	Soluble receptor IL2 ≥24000 UI/L	0

Dg if total ≥5