Diagnostic Value of Ferritin and Glycosylated Ferritin in Adult Onset Still's Disease

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ABSTRACT. ***Objective.*** To determine the usefulness of serum ferritin and glycosylated ferritin (GF) levels in diagnosing adult onset Still's disease (AOSD).

Methods. We performed a retrospective multicenter study of 205 patients who had ferritin and GF assays in one hospital laboratory. Records of all patients were reviewed, and a standardized questionnaire used to extract all data available at the time of the assay. The clinicians' final diagnosis was also recorded. Patients were classified as having "certain AOSD" (based on Yamaguchi's criteria) or a control disease. The concordance of ferritin and GF levels with final diagnosis was evaluated.

Results. In total 49 AOSD and 120 control patients were eligible. The mean ferritin value was significantly higher in the AOSD group (4752 ± 9599 µg/l) than in the control group (1571 ± 3807 µg/l), $p = 0.029$. GF was significantly lower in AOSD patients (15.9 ± 11.9%) than in the control group (31.5 ± 18.7%), $p < 0.001$. The combination of a GF level of ≤ 20% with ferritin above the upper limit of normal yielded a sensitivity of 70.5% and specificity of 83.2%. The combination of a GF level ≤ 20% with ferritin 5 times normal produced a sensitivity of 43.2% and specificity of 92.9%. This latter combination allowed an AOSD diagnosis to be ruled out for 6 of the 8 control patients who met Yamaguchi's positive criteria.

Conclusion. Ferritin and GF levels are powerful diagnostic markers of AOSD. They may be helpful in clinical practice for excluding differential diagnoses. (J Rheumatol 2001;28:322–9)

Key Indexing Terms:
ADULT ONSET STILL'S DISEASE ARTHRITIS FERRITIN
GLYCOSYLATED FERRITIN DIAGNOSIS

In 1971, Bywaters described the first cases of adult onset Still's disease (AOSD)[1], a clinical entity considered the adult counterpart — that is, in patients older than 17 years at onset — of the systemic juvenile arthritis described by Still a century ago[2]. Its principal clinical characteristics are a high (39 to 40°C), spiky and often evening fever, a maculopapular rash usually concomitant with the fever, and peripheral joint involvement. Other features consistent with the clinical presentation of AOSD include pharyngitis, lymphadenopathy or splenomegaly, myalgia, pericarditis, or pleuritis. Laboratory findings include elevated leukocyte and polymorphonuclear neutrophil (PMN) counts, liver dysfunction, and negative tests for antinuclear antibodies and rheumatoid factor (RF)[1,3-10]. Although its frequency is difficult to estimate, a recent Japanese study calculated its prevalence at 0.73 and 1.47 per 100,000 and its incidence rate at 0.22 and 0.34 per 100,000 for men and women, respectively[11].

Despite this precise description, AOSD is often difficult to diagnose. Incomplete or atypical forms may mimic other diseases — infectious (Epstein-Barr virus, EBV, or endocarditis), neoplastic (especially lymphoma), or rheumatic (polyarteritis nodosa or dermatomyositis/polymyositis), for example. This point is critical, because some treatments for AOSD, such as steroids or immunosuppresive agents, can worsen the course of these differential diagnoses, especially the infectious diseases. Several sets of classification criteria have been published and can be helpful for diagnosis[4,5,12-15]. Yamaguchi's criteria are the most sensitive and specific[15,16], but like all classification criteria they are not intended for diagnostic purposes.

Since the late 1980s, several authors have suggested that an increased serum ferritin level may indicate AOSD[17-22]. Mechanisms leading to the hyperferritinemia during AOSD are not perfectly understood. These ferritin levels are generally higher than those observed during inflammatory

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Submitted February 14, 2000 revision accepted August 8, 2000.

response or liver cytolysis. The best cutoff point is still under debate; although a serum ferritin level > 5 times the upper limit of normal (5N), i.e., 1000 µg/l, is considered by several authors as suggestive of AOSD[17,19,20,23], another author requires higher values (> 4000 µg/l)[18]. A more recent report (in abstract form) found that the 5N cutoff point had a sensitivity of 74.8% and a specificity of 83.2%[23].

Others contest that serum ferritin has any diagnostic value. Lee, *et al* examined the 1826 ferritin assays > 1000 µg/l performed in their laboratory over one year[24]; these high levels were associated with a wide variety of disorders, including liver diseases (especially hemochromatosis and Gaucher's disease) and kidney diseases, cancers, and various infections, notably acquired immune deficiency syndrome. Because AOSD has so low a prevalence, the positive predictive value of a high ferritin level remains low[24,25].

Several isoforms of ferritin have been described, one of which is glycosylated ferritin (GF)[26]. Although serum ferritin levels rise during several inflammatory conditions and liver diseases, the percentage of GF is often low and does not seem to respond to the same stimuli. Van Reeth, *et al*, in a preliminary study, reported that the percentage of GF in AOSD is low and differs dramatically from levels for other systemic diseases[27]. Other authors have made similar observations[28].

We investigated the diagnostic value of both ferritin and GF levels in a large series of patients. The ferritin and GF values in patients with AOSD were compared with those in patients with infectious, neoplastic, and other systemic diseases; their sensitivity and specificity were calculated; and their clinical relevance was compared with other diagnostic features of AOSD.

MATERIALS AND METHODS

Patients. We retrospectively reviewed the cases of 205 patients whose ferritin and GF levels were assayed at the biochemistry laboratory of Bichat Hospital (GLM) between January 1993 and June 1998. These assays had been performed either because a diagnosis of AOSD had been suggested or an increased ferritin level was noted. Patients' records were reviewed and their data collected onto a standardized questionnaire about all the signs known at the time of the assay and considered relevant to diagnosis. These included all characteristic features of AOSD: fever > 39°C, arthralgias or arthritis, typical rash, pharyngitis, lymphadenopathy and splenomegaly, myalgia, pleuritis and pericarditis, episodes during childhood, leukocyte and PMN counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST), antinuclear antibodies, and RF. The final diagnosis by the referring clinicians at the most recent visit was also recorded. This questionnaire was designed to determine if patients satisfied classification criteria of different systemic diseases: for AOSD[15], Behçet's disease[29], polymyositis (PM) and dermatopolymyositis (DM)[30], rheumatoid arthritis (RA)[31], systemic lupus erythematosus (SLE)[32,33], Sjögren's syndrome[34], and spondyloarthropathy (SpA; both the ESSG[35] and Amor[36] criteria). Three investigators (BF, BSM, PT) reviewed records and completed the questionnaires for patients from hospitals within the Paris metropolitan area. For patients from other areas of France, the referring physicians were contacted by mail and asked to collect the data. Patients were considered as having active disease if disease related clinical or biological signs were present at the time of ferritin assays.

Patients were classified into 2 principal groups, an AOSD group and a control group. The AOSD group comprised patients who were eventually diagnosed by their referring physician with AOSD and who met Yamaguchi's criteria, including exclusion of the differential diagnoses. None of these patients satisfied other disease criteria sets. Patients for whom an AOSD diagnosis was definitely excluded were assigned to the control group, which contained 5 subgroups: other systemic diseases, liver diseases, fever of unknown origin, infections, and neoplasia. Because no gold standard is available for AOSD, all patients with AOSD who did not meet Yamaguchi's criteria or for whom a diagnostic doubt persisted at their last visit were excluded from the analysis, as were all control patients for whom an AOSD diagnosis was not completely ruled out.

Serum ferritin and glycosylated ferritin assays. Serum ferritin concentration was determined by a Stratus® fluorimetric enzyme immunoassay (Dade-Behring, Paris-La Défense, France). Normal laboratory values, determined from 50 healthy donors, were 100 ± 35 µg/l (10–200) for women, and 153 ± 42 µg/l (20–300) for men. GF was determined by Worwood's technique, with minor modifications[27,37]. This method separates glycosylated from nonglycosylated ferritin on the basis of concanavalin-A (Con-A) affinity[38]. Briefly, a serum sample was incubated with Con-A sepharose 4B (Pharmacia Biotech Europe, Saclay, France) on a roller mixer for 2 h at room temperature. The sample was then centrifuged at 3000 rpm for 15 min, and unbound ferritin, i.e., nonglycosylated ferritin, was recovered in the supernatant. Total ferritin was measured by an identical procedure except that the sepharose 4B with which the serum sample was incubated did not include Con-A. The GF fraction was obtained by subtracting Con-A unbound ferritin from total ferritin and was expressed as a percentage of total ferritin. This method was available only for serum with total ferritin > 45 µg/l. Normal GF values ranged from 50 to 80%[26] (and data not shown). A preliminary study by Van Reeth, *et al* defined a cutoff point (≤ 20%) for GF in most patients with AOSD[27].

Statistical analysis. All calculations were performed with SAS software (SAS Institute, Cary, NC, USA). The ferritin and GF levels were expressed as mean ± standard deviation (SD). Statistical analysis included a Student's t test to compare the means of the AOSD and control groups, and one-way analysis of variance (using the General Linear Models Procedure of SAS software) to compare the means of the AOSD group and the control subgroups. Chi-square test assessed the significance of the difference in the frequencies of hyperferritinemia and decreased GF among the various groups. The diagnostic value of both assays was evaluated by calculating their sensitivity and specificity. The low prevalence of AOSD makes it pointless to calculate positive and negative predictive values. Correlations between ferritin and GF and clinical features or laboratory findings from the questionnaire were measured by analysis of variance for qualitative items and by Pearson correlation coefficient for quantitative variables. These analyses used the squares of ferritin and GF to obtain a normal distribution of the values.

RESULTS

Of the 205 patients whose records we reviewed, 112 were women and 94 men; 36 patients were excluded because AOSD could not be definitely excluded or diagnosed. Of the remaining 169, 49 patients were diagnosed with AOSD — 28 women and 21 men. Their mean age was 36.8 ± 14.0 years at disease onset and 38.9 ± 13.5 years at the time of the ferritin assays. Of the 120 control patients (59 women and 61 men, mean age 49.3 ± 16.6 yrs at ferritin assay), 62 had systemic diseases: unclassified polyarthritis (n = 10), polyarteritis nodosa and other vasculitis (n = 8), RA (n = 7), SLE (n = 7), sarcoidosis (n = 5), giant cell arteritis or

polymyalgia rheumatica (n = 5), SpA (n = 4), relapsing polychondritis (n = 3), familial Mediterranean fever (n = 2), polymyositis (n = 2), scleroderma (n = 1), or other inflammatory conditions (n = 8). Twenty-two patients had a specific liver disease, notably Gaucher's disease (n = 11) or hemochromatosis (n = 6). Five patients had fever of unknown origin. Twenty-one had infectious diseases: bacterial (n = 10: pyogenic bacteria or mycobacteria), viral (n = 10: human immunodeficiency virus, hepatitis A virus, hepatitis B virus, EBV, parvovirus B19), or parasitic (n = 1: toxoplasm); all patients with viral hepatitis had predominantly systemic manifestations. Ten patients had neoplasia: non-Hodgkin's lymphoma (n = 4), acute leukemia (n = 2), lung cancer (n = 2), Hodgkin's disease (n = 1), and prostate cancer (n = 1). A hemophagocytic syndrome was observed in 2 patients: one associated with AOSD, and one with a viral infection. Table 1 summarizes the principal clinical and laboratory abnormalities for the AOSD and control groups. The cardinal symptoms of AOSD — fever, arthralgias, rash, and increased leukocyte and PMN counts — were significantly more frequent in patients with AOSD than in controls. Of the 169 eligible patients, 120 (71%) had active disease at blood sampling (39/49 and 81/120 for AOSD and control patients, respectively); 54 were being treated with oral prednisone and 18 with nonsteroidal antiinflammatory drugs (NSAID).

The mean serum ferritin value (Figure 1) was 4753 ± 9599 µg/l (range 14–49,267) in patients with AOSD and 1571 ± 3807 µg/l (range 7–35,565) in control subjects (p = 0.029). The difference in this value between patients with AOSD and controls with other systemic diseases was also significant (p < 0.05); the mean serum ferritin value for the latter was 994 ± 2167 µg/l (range 7–12,515). No statistically significant difference in serum ferritin levels was observed between patients with AOSD and the other control subgroups.

Serum GF levels could be determined for only the 157 patients with serum ferritin ≥ 45 µg/l: 12 (5 AOSD, 7 controls) patients had levels below that. The mean level of glycosylated ferritin (Figure 2) was 15.9 ± 11.9% (range 3–55) for AOSD patients, compared with 31.5 ± 18.7% (range 5–80) for controls (p = 0.0001). The difference was also significant when patients with AOSD were compared with 4 of the 5 subgroups: other systemic diseases 27.2 ± 17.1% (range 5–69), liver diseases 43.4 ± 20.7% (range 11–80), fever of unknown origin 37.4 ± 12.8% (range 22–57), and infection 30.4 ± 19.2 (range 5–63) (p < 0.05). Although the mean GF level in patients with neoplasia (28.3 ± 15.3%, range 5–58) was markedly higher than that for AOSD patients, the difference was not statistically significant.

We evaluated the number of AOSD and control patients in 3 different groups of ferritin values: normal, above the upper limit of normal but less than 5N, and higher than 5N. We did the same for GF values: normal, slightly decreased (50 to 20% of normal), and dramatically decreased (≤ 20%). Table 2 gives the results. AOSD and control patients differed significantly for ferritin (p = 0.013) and GF (p = 0.001).

In all, 110 patients, 33 with AOSD (67.3%) and 77 (64.2%) disease controls, had elevated serum ferritin levels (p = 0.7). By contrast, ferritin values > 5N were observed in 20 of 49 patients with AOSD (40.8%) compared with 24 of 120 control patients (20%) (p = 0.005). Among the latter,

Table 1. Clinical and laboratory features of AOSD and control patients.

	AOSD, n = 49	Controls, n = 120					
		Total	Subgroups				
			I	LD	SD	F	N
	n (%)	n (%)	n	n	n	n	n
Fever > 39°C	43 (87.7)	42 (35.0)	9	2	22	2	7
Arthralgias	46 (93.8)	46 (38.3)	2	4	35	3	2
Rash	38 (77.5)	23 (19.2)	5	0	15	1	2
Pharyngitis	27 (55.1)	4 (3.3)	0	1	2	0	1
Myalgias	21 (42.8)	21 (17.5)	6	1	12	1	1
Lymphadenopathy/splenomegaly	21 (42.8)	32 (26.7)	3	7	14	0	8
Elevated ESR > 50 mm/h	38 (77.5)	53 (44.2)	15	0	31	1	6
Elevated CRP	42 (85.7)	71 (59.2)	16	2	43	3	7
Leukocytosis > 10,000/mm^3	44 (89.8)	41 (34.2)	10	5	21	2	3
PMN > 80%	35 (71.4)	16 (13.3)	7	0	5	1	3
Elevated AST, ALT, LDH	34 (69.4)	47 (39.2)	12	4	19	3	9
Positive ANA	2 (4.0)	20 (16.7)	3	0	12	2	3
Positive RF	0 (0.0)	11 (9.2)	1	0	9	0	1

Subgroups: I: infection (n = 21), LD: liver disease (n = 22), SD: systemic disease (n = 62), F: fever of unknown origin (n = 5), N: neoplasia (n = 10). ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, PMN: polymorphonuclear neutrophil, LDH: lactate dehydrogenase, ANA: antinuclear antibodies, RF: rheumatoid factor.

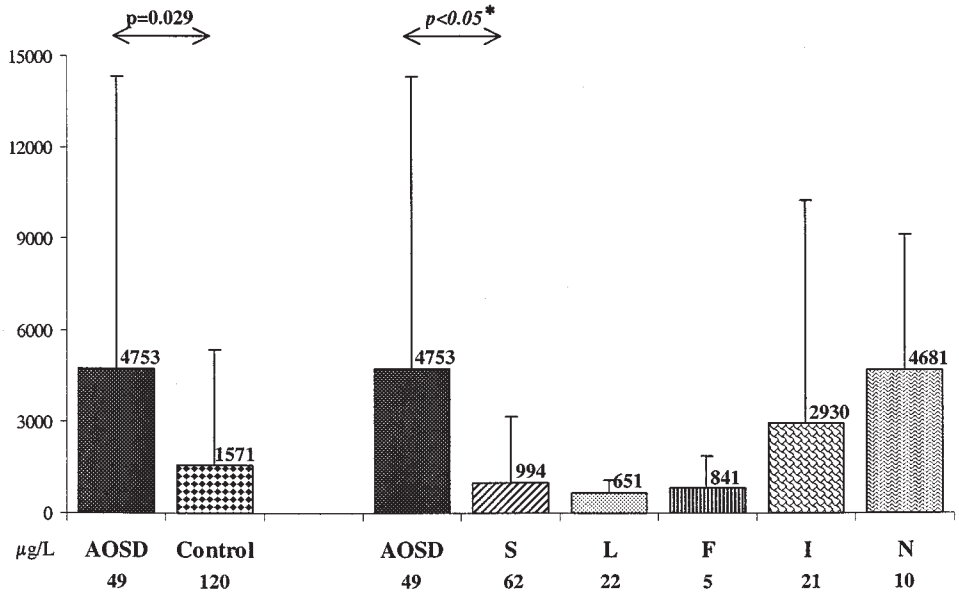

Figure 1. Serum ferritin levels in AOSD and control patients. Exact values are indicated at the top and the number of patients in each group at the bottom of each histogram. p values by Student's t test or *one-way ANOVA. AOSD: adult onset Still's disease, S: other systemic diseases, L: liver diseases, F: fever of unknown origin, I: infections, N: neoplasias.

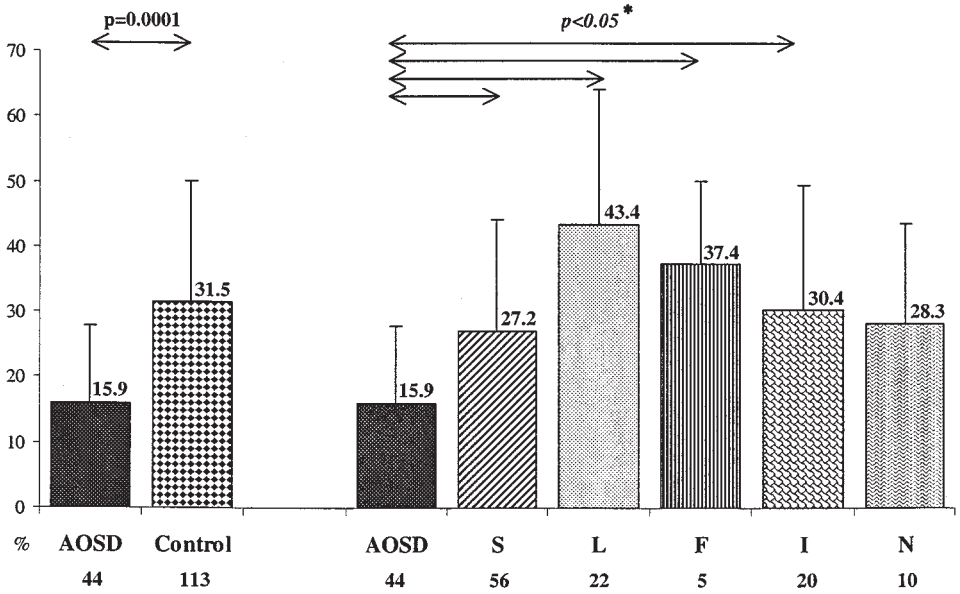

Figure 2. Percentages of glycosylated ferritin in AOSD and control patients. Exact values are indicated at the top and the number of patients in each group at the bottom of each histogram. p values by Student's t test or *one-way ANOVA. AOSD: adult onset Still's disease, S: other systemic diseases, L: liver diseases, F: fever of unknown origin, I: infections, N: neoplasias.

ferritin levels > 5N were rarest among patients with liver (9.1%) or other systemic diseases (14.5%); they were much more frequent in neoplasia (70%).

Glycosylated ferritin was < 20% for 35 of 44 patients with AOSD (79.5%); 4 had values ≤ 5%, 15 between 6 and 10%, and 16 between 11 and 20%. Only 38 of 113 control patients (33.6%) had a value of ≤ 20% (p = 0.001). Eight patients with AOSD had slightly decreased levels of GF (20–50%), but their presentation did not differ from that of the AOSD patients with more severely depleted GF. Only one AOSD patient had a normal GF value, and her assay took place 5 years after her last AOSD flare. Of the control

Table 2A. Frequency of normal and elevated ferritin levels. Percentages for control subgroups are only given for information, because 4 subgroups (infection, liver disease, fever, neoplasia) were small.

	Ferritin		
	Normal n (%)	> N and ≤ 5N n (%)	> 5N n (%)
AOSD*, n = 49	16 (32.7)	13 (26.5)	20 (40.8)**
Controls*, n = 120	43 (35.8)	53 (44.2)	24 (20)**
Infection, n = 21	6 (28.6)	10 (47.6)	5 (23.8)
Liver disease, n = 22	2 (9.1)	18 (81.8)	2 (9.1)
Other systemic disease, n = 62	31 (50.0)	22 (35.5)	9 (14.5)
Fever unknown origin, n = 5	3 (60.0)	1 (20.0)	1 (20.0)
Neoplasia, n = 10	1 (10.0)	2 (20.0)	7 (70.0)

*Global analysis between AOSD and controls, p = 0.013 (chi-square). **Statistical difference between AOSD and control comparing (> 5N) versus (N and < 5N), p = 0.005 (chi-square).

Table 2B. Frequency of normal and low (either slightly or dramatically) glycosylated ferritin. 5 AOSD patients and 7 controls had serum ferritin < 45 µg/l, therefore glycosylated ferritin evaluation was not available. Percentages for control subgroups are only given for information, because 4 subgroups (infection, liver disease, fever, neoplasia) were small.

	Glycosylated Ferritin		
	Normal, n (%)	21–50%, n (%)	≤ 20%, n (%)
AOSD*, n = 44	1 (2.3)	8 (18.2)	35 (79.5)**
Controls*, n = 113	22 (19.5)	53 (46.9)	38 (33.6)**
Infection, n = 20	4 (20.0)	8 (40.0)	8 (40.0)
Liver disease, n = 22	10 (45.5)	7 (31.8)	5 (22.7)
Systemic disease, n = 56	6 (10.7)	28 (50.0)	22 (39.3)
Fever unknown origin, n = 5	1 (20.0)	4 (80.0)	0 (0.0)
Neoplasia, n = 10	1 (10.0)	6 (60.0)	3 (30.0)

*Global analysis between AOSD and controls, p = 0.005 (chi-square). **Statistical difference between AOSD and control comparing (≤ 20%) versus (> 20%), p = 0.001 (chi-square).

patients whose GF was 20% or below, 22 had systemic diseases, 5 liver diseases, 8 infections, and 3 neoplasia. Three of these 38 patients satisfied Yamaguchi's criteria: a woman with Hodgkin's disease had fever, lymphadenopathy, a leukocyte count > 10^4/mm^3, more than 80% of which were PMN, an increased LDH level, and serum ferritin of 12,785 µg/l; the second patient had peripheral B27+ SpA, with oligoarthritis, "sausage" toe, fever, rash, increased AST and ALT levels, and ferritin within normal range (100 µg/l); the third had HIV infection and was finally diagnosed with disseminated tuberculosis, with fever, oligoarthritis, lymphadenopathy, elevated AST, ALT and LDH, and a ferritin level of 32,565 µg/l. Two patients had hemophagocytic syndromes, and both had GF levels > 20%: 24% for a patient with AOSD, and 48% for a patient with a viral infection.

Table 3 summarizes the diagnostic utility of various combinations and cutoff points of these 2 assays. Serum ferritin above N, considered alone, had medium sensitivity (67.3%) and poor specificity (35.8%) (a); the 5N cutoff point had high specificity (80%) but low sensitivity (40.8%) (b). The percentage of GF was useful considered alone, with a sensitivity of 79.5% and a specificity of 66.4%. The combination of both ferritin and GF was also interesting:

Table 3. Diagnostic value of serum ferritin and glycosylated ferritin. Sensitivity and specificity have been calculated for different cutoff points and combinations. The study population included 49 AOSD and 120 controls for a and b, 44 AOSD and 11 controls for c, d, and e. Positive and negative predictive values are not available since AOSD prevalence is extremely low.

	Sensitivity, %	Specificity, %
(a) Ferritin > N	67.3	35.8
(b) Ferritin > 5N	40.8	80.0
(c) Glycosylated ferritin ≤ 20%	79.5	66.4
(d) Ferritin > N and glycosylated ferritin ≤ 20%	70.5	83.2
(e) Ferritin > 5N and glycosylated ferritin ≤ 20%	43.2	92.9

when the N cutoff point was used for ferritin (d), specificity was 83% and sensitivity was also good at 70.5%. In combination with the higher (5N) ferritin cutoff point, specificity reached 93%, but sensitivity dropped to 43.2%. Despite this poor sensitivity, however, this combination may be very helpful in clinical practice for ruling out differential diagnoses.

Using one-way ANOVA, we investigated the possible correlation of either ferritin or GF values with the principal nonquantitative clinical and laboratory indicators. Serum ferritin levels were associated with fever, arthromyalgias, pharyngitis, lymphadenopathy, pleuropericarditis, and liver cytolysis (increased AST, ALT, LDH) (data not shown). GF, however, was not associated with any of these signs. Possible correlations with quantitative laboratory findings were assessed by Pearson correlation coefficient. This could be determined only for the patients with AOSD and other systemic diseases, because neither ferritin nor GF was normally distributed in the other groups. This test indicated that ferritin, but not GF, was correlated with ESR, CRP, leukocytes, and PMN (data not shown).

DISCUSSION

A GF level ≤ 20% appears to be a better diagnostic marker of AOSD than an elevated level of serum ferritin, and the combination of both abnormalities is even better. In our data, serum ferritin was not as useful as indicated in other reports[20,23]. The specificity of a ferritin value above the upper normal limit (35.8%) is too unspecific to be helpful in clinical practice. Ferritin > 5N is more valuable, but its sensitivity was lower in our series (40.8%) than reported by Ohta, *et al* (69%)[20] or Ushiyama, *et al* (74%)[23]. A possible explanation is that our series included AOSD patients with inactive disease — 10 of 49 (20.4%). Several of the departments involved in the study were tertiary medical centers, and some patients were already under treatment with NSAID or steroids, which partially controlled the disease. Ferritin is known to be one of the proteins overexpressed during the inflammatory process[39], and one report has showed its link with AOSD activity[40]. Our correlation analysis confirmed this point: ferritin was statistically associated with the principal symptoms of AOSD. These data emphasize the limited diagnostic value of serum ferritin for AOSD patients with inactive disease.

The specificity that we observed for ferritin (> 5N) is quite close to some published data (80% versus 83.2% for Ushiyama *et al*[23]), but is not entirely consistent with other series[18,24]. In daily practice, an extremely high ferritin level (> 5N) is more likely to be due to diseases other than AOSD, which has a very low prevalence. The limitations of relying on ferritin levels are underlined by the great range of ferritin levels within the different subgroups. Its high SD lowers its diagnostic value, assessed alone, for any given patient. The only statistical and clinically relevant difference in ferritin values was for AOSD patients compared with those in the other systemic diseases subgroup. The small size of the subgroups might partly account for the lack of significance of the differences with the other subgroups, especially liver diseases and fever of unknown origin. However, this explanation does not apply to the infection and neoplasia subgroups, which had mean ferritin values very close to that for AOSD, and SD were large. Serum ferritin levels thus cannot differentiate patients with AOSD from those with the diseases requiring exclusion by Yamaguchi's diagnostic criteria. Because these include infectious and neoplastic diseases, the treatments for which differ substantially from that of AOSD, this differential diagnosis is a serious problem for clinical practice.

As our preliminary data suggested[27], GF appears more promising for AOSD diagnosis[27]. The mean level of GF was significantly lower among patients with AOSD than controls. This difference was also observed for 4 of the 5 subgroups — other systemic diseases, infections, liver diseases, and fever of unknown origin. Moreover, the mean GF level among the neoplasia subgroup was markedly higher than among patients with AOSD, although the difference was not statistically significant. A likely explanation for this statistical result, however, is the small size of the neoplasia group, especially since its mean level and SD were nearly identical to those in the systemic disease subgroup, for which the difference was significant. This important point requires confirmation in larger patient samples, so that the discriminant diagnostic power of GF can be assessed more exactly.

Seventy-three patients in our series had GF ≤ 20%; half of these patients (n = 35) had AOSD: thus in this group, but not in the abnormal ferritin group, AOSD patients were overrepresented. This finding is indirect evidence that GF is valuable for AOSD diagnosis. Its sensitivity (79.5%) and specificity (66.4%) are close to those found here and in the literature[15] for the principal laboratory signs of AOSD, that is, leukocytes > 10,000/mm^3 and PMN > 80%. In the Japanese study, sensitivity and specificity were respectively 89% and 58% for leukocytes > 10,000/mm^3, 83% and 66% for PMN > 80%, and 78% and 78% for a combination of both. GF ≤ 20% should, as these 2 laboratory findings are, be considered a cardinal feature of AOSD, as should the association of GF ≤ 20% with elevated ferritin, either above the upper normal value or 5 times greater than this value. Despite its low sensitivity, the latter combination is highly specific and may thus be especially helpful for the differential diagnosis of AOSD.

Alone, with no other manifestations, neither high ferritin levels nor low GF levels are sufficient to diagnose AOSD. They must, however, be considered as important tools for AOSD diagnosis. Their precise place among signs, symptoms, and findings that suggest AOSD must be determined in further studies. In our series, 8 control patients had a clin-

ical presentation compatible with AOSD and met Yamaguchi's classification criteria. Four of them had elevated ferritin value (> 5N), 3 had GF < 20%, but only 2 had the combination of elevated ferritin with GF lower than 20%. One of these 2 patients had non-Hodgkin's lymphoma and the second had HIV linked disseminated tuberculosis. The diagnoses of the 6 other patients were splenic lymphoma, acute myeloblastic leukemia type 2, HLA-B27+ SpA (in 2 cases), giant cell arteritis, and hepatitis of unknown origin (presumed to be viral).

Our study excluded from analysis 36 patients with uncertain diagnosis. These are the patients who pose real clinical problems, for whom GF and/or ferritin might help therapeutic decision making. Considered together with Yamaguchi's criteria, these assays might make it easier to rule out the possible differential diagnoses — Yamaguchi's exclusions, which constitute the main drawback to his criteria set. Additional studies are needed to understand the exact mechanisms leading to excess ferritin production, glycosylated or not, in a various range of disorders.

ACKNOWLEDGMENT

The authors thank Fabienne Lucas-Vasseur for computer assistance and data management, Dr. Anne Bissery for statistical analysis, and Dr. Ann E. Clarke for her thoughtful comments about the manuscript. They also thank the French clinicians who provided patient records: Pr. M. Thomas (Bondy); Pr. P. Galanaud (Clamart); Pr. J.L. Bussière, Dr. J. Schmidt (Clermont-Ferrand); Pr. P. Vinceneux (Colombes); Dr. E. Kaloustian, Dr. P. Veyssier (Compiègne); Dr. J. Crouzet, Dr. J. Denis, Dr. M. Duterque (Corbeil); Dr. V. Botcazou (Draguignan); Dr. C. Michel, Dr. B. Schubert (Mulhouse); Dr. I. Aimone-Gastin, Pr. M.A. Bigard, Pr. P. Canton, Dr. L. Chone, Pr. M. Duc, Dr. P. Kaminsky, Dr. H. Schuhmacher (Brabois Hospital, Nancy); Dr. Y. Le Cocguic (American Hospital, Neuilly); Pr. M.C. Aumont, Dr. N. Belmatoug, Pr. C. Carbon, Pr. J.P. Coulaud, Pr. J. Hakim, Dr. H. Mouas, Dr. E. Palazzo, Pr. J.L. Vildé (Bichat Hospital, Paris); Dr. L. Weiss (Broussais Hospital, Paris); Pr. A. Kahan (Cochin Hospital, Paris); Pr. R. Zittoun (Hotel-Dieu, Paris); Dr. M. Gayraud (Montsouris Institute, Paris); Dr. H. Zylberberg (Necker Hospital, Paris); Pr. J.P. Vernant, Pr. B. Wechsler (Pitié-Salpêtrière Hospital, Paris); Pr. C. Mayaud (Tenon Hospital, Paris); Dr. F. Daniel, Pr. G. Herreman (Saint-Joseph Hospital, Paris); Dr. C. Halimi (Senlis).

REFERENCES

1. Bywaters EGL. Still's disease in the adult. Ann Rheum Dis 1971;30:121-33.
2. Still GF. On a form of chronic joint disease in children. Med-Chir Trans 1897;80:47-9.
3. Wouters JMGW, van de Putte LBA. Adult-onset Still's disease: clinical and laboratory features, treatment and progress of 45 cases. Q J Med 1986;61:1055-65.
4. Cush JJ, Medsger TA, Christy WC, et al. Adult-onset Still's disease. Clinical course and outcome. Arthritis Rheum 1987;30:186-94.
5. Reginato AJ, Schumacher HR, Baker DG, et al. Adult onset Still's disease: experience in 23 patients and literature review with emphasis on organ failure. Semin Arthritis Rheum 1987;17:39-57.
6. Ohta A, Yamaguchi M, Kaneoka H, et al. Adult Still's disease: review of 228 cases from literature. J Rheumatol 1987;14:1139-46.
7. van de Putte LBA, Wouters JMGW. Adult onset Still's disease. Bailleres Clin Rheumatol 1991;5:263-75.
8. Pouchot J, Sampalis JS, Beaudet F, et al. Adult Still's disease: manifestations, disease course and outcome in 62 patients. Medicine (Baltimore) 1991;70:118-36.
9. Masson C, Le Loët X, Lioté F, et al. Adult Still's disease. I. Manifestations and complications in 65 cases in France. Rev Rhum [Engl Ed] 1995;62:748-57.
10. Masson C, Le Loët X, Lioté F, et al. Adult Still's disease. II. Management, outcome and prognostic factors. Rev Rhum [Engl Ed] 1995;62:758-65.
11. Wakai K, Ohta A, Tamakoshi A, et al. Estimated prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological survey in Japan. J Epidemiol 1997;7:221-5.
12. Goldman JA, Beard MR, Casey HL. Acute febrile juvenile rheumatoid arthritis in adults: cause of polyarthritis and fever. South Med J 1980;73:555-63.
13. Calabro JJ, Londino AV. Adult onset Still's disease. J Rheumatol 1986;13:827-8.
14. Kahn MF, Appelboom T. Syndrome de Sharp. In: Kahn MF, Peltier AP, Meyer O, Piette JC, editors. Les maladies systémiques. 3rd ed. Paris: Flammarion; 1991:545-56.
15. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19:424-30.
16. Masson C, Le Loet X, Lioté F, et al. Comparative study of 6 types of criteria in adult Still's disease. J Rheumatol 1996;23:495-7.
17. Ota T, Higashi S, Suzuki H, Eto S. Increased serum ferritin levels in adult Still's disease [letter]. Lancet 1987;1:562-3.
18. Gonzalez-Hernandez T, Martin-Mola E, Fernandez-Zamorano A, et al. Serum ferritin can be useful for diagnosis in adult onset Still's disease. J Rheumatol 1989;16:412-3.
19. Ota T, Higashi S, Masuda M, et al. Serum ferritin as a useful test for diagnosis of adult Still's disease. Jpn J Rheumatol 1990; 2:119-25.
20. Ohta A, Yamaguchi M, Tsunematsu T, et al. Adult Still's disease: a multicenter survey of Japanese patients. J Rheumatol 1990;17:1058-63.
21. Akritidis N, Giannakakis I, Giouglis T. Very high serum ferritin levels in adult onset Still's disease. Br J Rheumatol 1996;36:608-9.
22. Schiller D, Mittermayer H. Hyperferritinemia as a marker of Still's disease. Clin Infect Dis 1998;26:534-5.
23. Ushiyama O, Ohta A, Suzuki N, et al. Diagnostic characteristics of serum ferritin level in adult Still's disease [abstract]. Arthritis Rheum 1997;40 Suppl:S264.
24. Lee MH, Means RT. Extremely elevated serum ferritin levels in a university hospital: Associated diseases and clinical significance. Am J Med 1995;98:566-71.
25. Morgan MAM, Hoffbrand AV, Laulicht M, et al. Serum ferritin concentration in Gaucher's disease [letter]. BMJ 1983;286:1864.
26. Craigg S, Wagstaff M, Worwood M. Detection of a glycosylated subunit in human ferritin. Biochem J 1981;199:565-71.
27. Van Reeth C, Le Moel G, Lasne Y, et al. Serum ferritin and isoferritins are tools for diagnosis of active adult onset Still's disease. J Rheumatol 1994;21:890-5.
28. Higashi S, Ota T, Eto S. Biochemical analysis of ferritin subunits in sera from adult Still's disease patients. Rheumatol Int 1995; 15:45-50.
29. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990;335:1078-80.
30. Tanimoto K, Nakano K, Kano S, et al. Classification criteria for polymyositis and dermatomyositis. J Rheumatol 1995;22:668-74.
31. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
32. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
33. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus

erythematosus [letter]. Arthritis Rheum 1997;40:1725.
34. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340-7.
35. Dougados M, van der Linden S, Juhlin R, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropahy. Arthritis Rheum 1991; 34:1218-27.
36. Amor B, Dougados M, Mijiyawa M. Critères de classification des spondylarthropathies. Rev Rhum Mal Osteoartic 1990;57:85-9.
37. Worwood M, Cragg SJ, Wagstaff M, Jacobs A. Binding of human serum ferritin to concanavalin A. Clin Sci 1979;56:83-7.
38. Debray H, Decout D, Strecker G, et al. Specificity of twelve lectins towards oligosaccharides and glycopeptides related to N-glycosylproteins. Eur J Biochem 1981;117:41-55.
39. Konijn AM, Hershko C. Ferritin synthesis in inflammation. Br J Haematol 1977;37:7-15.
40. Schwarz-Eywill M, Heilig B, Bauer H, et al. Evaluation of serum ferritin as a marker for adult Still's disease activity. Ann Rheum Dis 1992;51:683-5.