Adult-onset Still’s disease: still a diagnosis of exclusion.
A nested case-control study in patients with fever of unknown origin

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Abstract

Objective
Several sets of criteria have been proposed to classify adult-onset Still’s disease (AOSD), those of Yamaguchi being the most commonly used. The Yamaguchi criteria demand the exclusion of other conditions. A clinical scale, recently proposed by Crispin et al., but not yet validated, would allow a positive diagnosis of AOSD in a majority of patients, without the need of thorough diagnostic procedures.

Methods
From a database of 447 patients with classical fever of unknown origin (FUO), collected over a 10-year period (2000-2009) at a general internal medicine department of a university hospital, 22 patients with AOSD according to the Yamaguchi criteria were extracted and compared with 44 controls, matched to index year. Clinical and laboratory parameters were recorded. Sensitivity, specificity and accuracy of the Yamaguchi criteria and of the clinical score were assessed.

Results
Lower age, joint symptoms, rash, throat ache, neutrophilic leukocytosis, and elevated erythrocyte sedimentation rate were the principal characteristics supporting a diagnosis of AOSD in patients with FUO. Sensitivity, specificity, and accuracy of the Yamaguchi criteria were 95% or more. The clinical scale, while being specific (98%), lacked sensitivity (55%) and had lower accuracy (83%).

Conclusion
In patients with FUO, the Yamaguchi criteria are a time honored and reliable guide to a diagnosis of AOSD. The clinical scale may serve to rule in, rather than to rule out, AOSD. In many patients, Still’s disease is still a diagnosis of exclusion.

Key words
adult-onset Still’s disease, fever of unknown origin, diagnosis.
Introduction

Fever of unknown origin (FUO) remains a diagnostic challenge. Even nowadays, the cause is not found in a substantial portion of patients (1, 2). Especially patients with episodic fevers are challenging, with up to half ending up without diagnosis in spite of a thorough search and a dedicated follow-up in experienced and equipped centres (2, 3).

Adult-onset Still’s disease (AOSD) is a classical though infrequent cause of non-hereditary and often episodic fever in younger adults. In spite of a temptation to use this label indiscriminately in a young patient with relapsing fevers, this diagnosis should only put forward if certain criteria are fulfilled. Diagnostic rigor may even acquire more pertinence as the ongoing elucidation of the pathogenesis of this auto-inflammatory syndrome raises the hope of more specific therapies (e.g. anti-interleukin-1 antagonism) (4).

The manifestations of AOSD are protean, no pathognomonic symptoms or signs exist, and the course and prognosis are variable. The diagnosis is a clinical one. Several overlapping sets of criteria for AOSD have been published (5-10). Yamaguchi’s classification criteria set is the most commonly used and best validated (5, 11-12). Most sets include exclusionary criteria (5-8). In 2005, Crispin et al. have constructed a clinical scale as a tool to positively diagnose AOSD in patients with FUO (13). However, the value of the clinical scale has not been validated in an independent patient cohort.

In the present work, we aim to articulate how patients with AOSD, diagnosed strictly using the established criteria of Yamaguchi et al. (5), stand out against other patients presenting with longstanding and perplexing fevers. Additionally, the test characteristics of the clinical scale (13) were assessed.

Methods

Between January 1, 2000, and December 31, 2009, 577 adult patients with a prolonged unexplained febrile illness presented to the general internal medicine department of the University Hospital in Leuven, Belgium. Four hundred forty-seven patients fulfilled the criteria of classical community-acquired fever of unknown origin according to the contemporary definition of de Kleijn et al. (Table IA) (14), and had sufficient data at presentation and sufficient follow-up (at least 6 months for patients without diagnosis) (Fig. 1). All patients with a possible diagnosis of AOSD were extracted. The patients fulfilling the Yamaguchi criteria (Table IB) (5) were regarded as cases. For each case, two controls were randomly extracted from the database. Cases and controls were matched only to index year.

For cases and controls, demographic and clinical characteristics were extracted from the files, including age, sex, maximal body temperature, and final diagnosis. Episodic fever (as opposed to continuous fever) was defined as at least 2 episodes of fever, with fever-free intervals of at least 2 weeks and apparent remission of the underlying illness (3). The presence of arthralgia, arthritis, sore throat, rash, lymphadenopathy, hepatomegaly, splenomegaly, pleuritis, and pericarditis were noted. Laboratory parameters at presentation were recorded, including peripheral blood counts, liver enzymes, ferritin, erythrocyte sedimentation rate, and C-reactive protein. For each patient, the Yamaguchi criteria were assessed and the clinical scale (according to Crispin et al., Table IC) was calculated (5, 13).

Treatment and outcome, including survival, were recorded.

Categorical and continuous variables are expressed as number (percentage) and as median (interquartile range), respectively. We used the Pearson chi-square to compare categorical variables and the Mann-Whitney test to compare continuous variables. Test characteristics, calculated for the Yamaguchi criteria and the clinical scale included sensitivity, specificity, and accuracy. The Spearman rank correlation coefficient was determined to study the dependence between the number of Yamaguchi criteria and the clinical scale. Statistical analyses were performed using SPSS 19.0 software. All statistical testing was performed using unpaired 2-tailed tests, with significance set at $p<0.05$. The study protocol was approved by the ethics committee of the University Hospi-
tals, Leuven. As the study was descriptive and did not demand deviation from standard clinical care, the need for informed consent was waived.

Results
In 25 of the 447 adult patients with classical FUO, a clinical diagnosis of AOSD was suspected. Twenty-two met at least 5 Yamaguchi criteria, including at least 2 major ones, and were considered AOSD cases (5). The 3 other patients (presenting with FUO and pericarditis, meningitis, and weight loss, respectively) did not have sufficient Yamaguchi criteria and were excluded from further analysis. Forty-four controls with FUO were randomly selected, matched to the cases according to index year (Fig. 1). The final diagnosis in the controls were: infectious diseases in 11 (ana-
plasmosis, bartonellosis, Q-fever, and pyelonephritis in 2 each; tuberculosis, pneumonia and endocarditis in 1 each), multisystem noninfectious inflammatory diseases in 9 (granulomatosis with polyangiitis, and giant cell arteritis, in 2 each; Sjögren’s syndrome, Behçet’s disease, polyarteritis nodosa, sarcoidosis, and systemic lupus erythematosus in 1 each), malignancies and related disorders in 6 (lymphoma in 3; bronchial adenocarcinoma, transitional cell carcinoma, and myelodysplastic syndrome, in 1 each), miscellaneous disorders in 8 (inflammatory pseudotumor, factitious fever, drug fever, de Quervain thyroiditis, chondrocalcinosis, immunoglobulin G2 (IgG2) deficiency (with failure to respond to pneumococcal polysaccharide vaccine), familial Mediterranean fever, and Schnitzler’s syndrome in 1 each), and uncertain in 10.

Clinical characteristics and selected laboratory parameters are compared in Tables IIA and IIB, respectively. Cases were younger, and presented with arthralgia and arthritis, rash, sore throat, lymphadenopathy, and hepatomegaly more frequently. Maximal height and periodicity of the fever did not differ between cases and controls. Serositis was not more frequent in cases than in controls. Cases were more anemic at presentation and had higher leukocyte, neutrophil, and platelet counts, serum ferritin levels and erythrocyte sedimentation rates. CRP and transaminase levels were comparable between groups. By definition, the sensitivity of the Yamaguchi criteria was 100%. Five controls met 5 Yamaguchi criteria each. A final diagnosis was established in 3 (IgG2 deficiency with recurrent streptococcal angina, drug fever, Schnitzler’s syndrome, respectively), and remained uncertain in 2: a 24-year-old female with spontaneous resolution of a 2 month’s fever shortly after admission, and a 65-year-old female with neutrophilic alveolitis of unknown cause. Considering the last 2 patients as false-positives yielded a specificity of the Yamaguchi criteria of 95%, and an accuracy of 97%. The clinical scale

### Table I. Criteria.

<table>
<thead>
<tr>
<th>A. Definition of classical fever of unknown origin (adapted from 14)</th>
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<tbody>
<tr>
<td>1. Illness of more than 3 weeks duration.</td>
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<tr>
<td>2. Temperature of at least 38.3°C (101°F) or lower temperature with signs of inflammation on several (three or more) occasions;</td>
</tr>
<tr>
<td>3. No diagnosis or reasonable (eventually confirmed) diagnostic hypothesis after performing a standard initial diagnostic investigation protocol.&quot;</td>
</tr>
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<td>4. Exclusion of immunocompromised patients.</td>
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*Standardised thorough history and physical examination, routine blood tests (erythrocyte sedimentation rate or C-reactive protein, haemoglobin, leukocyte and differential count, creatinine, sodium, potassium, protein electrophoresis), enzymes (alkaline phosphatase, aminotransferase, lactate dehydrogenase, creatine phosphokinase), urinalysis, anti-nuclear and antineutrophil cytoplasmic antibodies, cultures of blood and urine, x-ray of the chest, abdominal ultrasonography, examinations indicated by clues obtained by the aforementioned tests.

#### IB. Yamaguchi criteria for classification of adult-onset Still’s disease (5).

**Major criteria**
1. Fever of 39°C or higher, lasting 1 week or longer
2. Arthralgia lasting 2 weeks or longer
3. Typical rash: macular or maculopapular nonpruritic salmon-pink eruption usually appearing during fever
4. Leukocytosis (≥10 x 10⁹/l) including ≥80% neutrophils

**Minor criteria**
1. Sore throat
2. Lymphadenopathy and/or splenomegaly
3. Abnormal liver tests, particularly elevations in aspartate and alanine aminotransferase and lactate dehydrogenase concentrations
4. Negative rheumatoid factor and negative antinuclear factor

**Exclusions**
1. Infections
2. Malignancies
3. Other rheumatic diseases

Classification of adult Still’s disease requires 5 or more criteria including 2 or more major criteria. Any disease listed under “Exclusions” should be excluded.

#### IC. Clinical scale for the diagnosis of adult-onset Still’s disease in the setting of fever of unknown origin (13).

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Points</th>
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<tbody>
<tr>
<td>Arthritis</td>
<td>10</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7</td>
</tr>
<tr>
<td>Still’s rash</td>
<td>5</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>5</td>
</tr>
<tr>
<td>Neutrophilia*</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
</tr>
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If a patient with fever of unknown origin has ≥30 points, the diagnosis of adult-onset Still’s disease can be established. *total neutrophil count >9.5 x 10⁹/l
was 30 or more in 12 of the 22 cases and in 1 of the 44 controls (the false positive being the patient with IgG2 deficiency and recurrent streptococcal pharyngitis). Thus, the clinical scale had a sensitivity of 55%, a specificity of 98%, and an accuracy of 83%. The number of Yamaguchi criteria and the clinical scale correlated significantly (Spearman’s rho: .82, p <0.0005).

Half of the cases received corticosteroid therapy. All cases recovered eventually. In contrast, 5 controls succumbed to their illness (lymphoma in 2, and bronchial carcinoma, tuberculosis, and giant cell arteritis in one each) (p=0.069).

**Discussion**

In this single-centre nested 1:2 case-control study in patients with FUO, we describe our experience with AOSD patients, encompassing a decade. AOSD is a relatively rare condition. Over 600 patients have been described in literature (15). Major academic centres are estimated to see 1 to 3 new cases of AOSD per year (16). This estimate compares well with the 22 cases described in the present study, conducted between 2000 and 2009. In a study of FUO patients encountered in the preceding decade (1990-1999), we diagnosed AOSD in 18 patients (2).

Although the clinical presentation of AOSD can be quite heterogeneous, 4 so-called cardinal features stand out: high peaking fevers, articular and cutaneous involvement and elevated leukocyte counts (15). Each of these characteristics were present in over 75% of our cases, as was sore throat.

Fever height and periodicity failed to discriminate between AOSD cases and controls. Half of our cases presented with a single febrile episode. Although the majority of patients with AOSD reported joint pains, frank arthritis was noted in less than half, a figure lower than that found in most other series, typically originating from rheumatology centres (15). Organomegaly and serositis were inconsistent features and serositis was not more prevalent in cases than in controls. By definition, the lower age limit for the diagnosis of AOSD is 16 years. No upper age limit exists and current diagnostic criteria sets do not consider age (5-10, 13). However, the average AOSD case in our study was almost half that of the typical patient with FUO. Hence, especially in older patients with FUO, a diagnosis of AOSD requires careful exclusion of alternative conditions.

AOSD has no pathognomonic features and its diagnosis remains a clinical one. Several criteria sets have been proposed, with most containing exclusion criteria (5-8). The Japanese criteria published by Yamaguchi et al. have been the most popular and influential and were used in the present study to define the cases (5). We refrained to use own clinical judgment as the basis for diagnosis and the description of yet a new set of criteria, because this approach, without independent validation, may induce circular reasoning. The sensitivity of the Yamaguchi criteria was thus 100%, while the specificity was 95%. This high specificity is partially tributary to the exclusionary criterion, which is an intrinsic part of the Yamaguchi criteria. Indeed, in 3 of the 5 controls meeting the Yamaguchi criteria an alternate diagnosis was established. Yamaguchi et al., in their original paper, noted 96% sensitivity and 92% specificity (5). Mason et al. compared the sensitivities of 6 sets of criteria and found the Yamaguchi criteria to be the most sensitive (94%) (11). In their study, no control group was available to calculate specificities. A Chinese study, published in 2011, found the Yamaguchi criteria more sensitive (79%) and accurate (87%) than 3 sets of criteria published in the 1980’s (12). Crispin et al. analysed 26 patients
with AOSD and 135 patients with FUO due to other conditions and found the Yamaguchi criteria to be 83% sensitive and 91% specific (13). They constructed a clinical scale, with sensitivity and specificity in the original report of 77% and 98% respectively. Our case-control study, which is the first to reexamine the Yamaguchi criteria for adult-onset Still’s disease, confirmed a high specificity in the original report of 77% and a specificity of 83% (15). Thus, the clinical scale seems to be established in the presence a proper constellation of symptoms, signs and laboratory parameters, and after careful exclusion of alternate conditions.

References


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