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# Relevance of application of the Yamaguchi criteria for patients with suspected juvenile idiopathic arthritis in the absence of arthritis symptoms

## *Znaczenie stosowania kryteriów Yamaguchi u osób z podejrzeniem młodzieńczego idiopatycznego zapalenia stawów w przypadku braku objawów zapalenia stawów*

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Key words: systemic-onset juvenile idiopathic arthritis, adult-onset Still's-disease, ILAR criteria, Yamaguchi criteria.

Słowa kluczowe: młodzieńcze idiopatyczne zapalenie stawów o początku układowym, choroba Stilla u dorosłych, kryteria ILAR, kryteria Yamaguchi.

**Summary**

**Aim of the study:** Systemic juvenile idiopathic arthritis (sJIA) is characterized by systemic inflammation beside arthritis. Many children may have delayed onset of arthritis. We aimed in our study to determine whether the Yamaguchi criteria (for adult onset Still's disease) can be applied in diagnosis of sJIA, especially in absence of arthritis.
**Material and methods:** The cross-sectional study included 30 patients diagnosed with sJIA, those patients diagnosed by the treating paediatrician with 'definite' sJIA (fulfilling the International League of Associations for Rheumatology [ILAR] classification criteria) or 'suspected' sJIA (not fulfilling the ILAR criteria). The fulfilment of the variables in both the ILAR criteria and the Yamaguchi criteria was recorded for each patient at the time of first presentation.
**Results:** We included 16 boys and 14 girls. Ten patients were diagnosed with suspected sJIA due to the presence of typical systemic features but failed to fulfil the ILAR criteria, especially absence of arthritis in 9 of them. Yamaguchi criteria were fulfilled in a higher number of patients (23/30, 76.7%) as compared to those who fulfilled the ILAR criteria (20/30, 66.7%). All 10 patients with suspected sJIA fulfilled the Yamaguchi criteria, and 11 patients (36.7%) had delayed onset of arthritis. Overall, the 30 patients (100%) in the present study fulfilled either ILAR criteria or Yamaguchi criteria.
**Conclusions:** There is a subgroup of patients with sJIA in whom arthritis is absent or delayed. The use of the Yamaguchi criteria in this subgroup of patients may be useful for early diagnosis and treatment of sJIA. Thus, further studies are needed to integrate supplementary criteria that increase the strength of both the Yamaguchi and the ILAR criteria.

**Streszczenie**

**Cel pracy:** Młodzieńcze idiopatyczne zapalenie stawów (MIZS) o początku układowym charakteryzuje to, że zapaleniu stawów towarzyszy ogólnoustrojowy stan zapalny. Początek zapalenia stawów u dzieci często występuje z opóźnieniem. Celem badania było ustalenie, czy możliwe jest stosowanie kryteriów Yamaguchi (używanych w chorobie Stilla u dorosłych) do rozpoznawania MIZS o początku układowym, zwłaszcza przy braku objawów zapalenia stawów.
**Materiał i metody:** Badanie przekrojowe obejmowało 30 pacjentów z MIZS o początku układowym, których pediatra zakwalifikował jako „zdecydowany" przypadek MIZS (spełnione kryteria klasyfikacji ILAR) lub „podejrzenie" MIZS (niespełnione kryteria klasyfikacji ILAR). Dla każdego pacjenta odnotowano wszystkie kryteria ILAR i kryteria Yamaguchi spełnione w chwili pierwszego zgłoszenia.
**Wyniki:** Do badania zakwalifikowano 16 chłopców i 14 dziewczynek. U 10 pacjentów podejrzewano MIZS o początku układowym z uwagi na obecność typowych cech układowych przy jednoczesnym braku spełnienia kryteriów ILAR, a zwłaszcza braku objawów zapalenia stawów u 9 z tych chorych. W badaniu więcej pacjentów spełniało kryteria Yamaguchi (23/30; 76,7%) niż kryteria ILAR (20/30; 66,7%). Kryteria Yamaguchi spełniało 10 pacjentów z podejrzeniem MIZS o początku układowym, a u 11 osób (36,7%) zapalenie stawów wystąpiło z opóźnieniem. Ogółem 30 pacjentów uczestniczących w badaniu (100%) spełniało albo kryteria ILAR, albo kryteria Yamaguchi.
**Wnioski:** Istnieje podgrupa pacjentów z MIZS o początku układowym, u których objawy zapalenia stawów nie są obecne bądź występują z opóźnieniem. Wykorzystanie kryteriów Yamaguchi w tej

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grupie pacjentów może być przydatne w rozpoznawaniu i leczeniu choroby. Niezbędne są dalsze badania nad stosowaniem kryteriów dodatkowych zwiększających znaczenie zarówno kryteriów Yamaguchi, jak i kryteriów ILAR.

## Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood and describes a group of clinically heterogeneous arthritides which begin before the age of 16 years and persist for at least 6 weeks [1]. At onset, systemic JIA, which represent nearly 10% of all cases of JIA, is distinguished from other forms by prominence of extra-articular features such as spiking fever, typical fleeting pink macular rash, generalized lymphadenopathy, hepatosplenomegaly, and occasionally polyserositis [2]. The pathogenic mechanisms underlying the heterogeneity of systemic JIA are not well understood [3]. The aetiology of JIA is still unknown, and the genetic component is complex [4].

In comparison between sJIA and other JIA groups, one important difference is that arthritis may be a non-prominent and/or a delayed-onset manifestation. Arthritis has been reported to be a manifestation delayed up to 10 years in a subset of sJIA patients [5].

International League of Associations for Rheumatology (ILAR) criteria require the presence of arthritis to define a patient as having sJIA [6]. Strict adherence to the ILAR criteria may lead to delay in the diagnosis of sJIA, resulting in early morbidity and mortality in sJIA patients [5].

Recently researchers have reported that sJIA patients before the onset of arthritis (suspected sJIA) appear clinically and immunologically similar to patients fulfilling the ILAR criteria (definite sJIA) [7].

Most studies comparing Still's disease (sJIA) in children and adult onset Still's disease (AOSD) have not found a significant difference in the clinical manifestation at the time of presentation [8–12].

Various criteria are available for the diagnosis of AOSD, and none of these criteria depend heavily on the presence of arthritis. The Yamaguchi criteria are the most sensitive (96%) and specific (92%) for the diagnosis of AOSD [13, 14].

The aim of the present study was to determine the possible application of the Yamaguchi criteria in the diagnosis of children presenting with typical systemic manifestation of sJIA including serositis but still not having developed arthritis (named as 'suspected' sJIA), for early diagnosis and treatment of sJIA patients.

## Material and methods

The study was conducted between March 2011 and March 2013 in the Rheumatology Clinic of the Cairo University Specialized Pediatric Hospital. The study was conducted retrospectively using hospital records and was approved by the Cairo University Clinical Research Ethics Committe. It included 30 patients, only patients diagnosed by the treating paediatrician as having 'definite' sJIA (fulfilling the ILAR classification criteria) or 'suspected' sJIA (not fulfilling the ILAR criteria) were included. All patients were diagnosed with sJIA (definite or suspected) in the last 3 years (Table I).The study group compromised 16 males (53.3%) and 14 females (46.7%). Mean age of patients was 9.03 ±4.02 years; mean age at diagnosis was 6.52 ±3.20 years and mean duration of symptoms at time of presentation was 106.33 ±76.36 days. Mean duration of

**Table I.** Variables of the ILAR and Yamaguchi criteria

| ILAR criteria (acc. to [6]) | Yamaguchi criteria (acc. to [4]) |
|---|---|
| Arthritis in one or more joints associated or preceded by daily fever of at least 2 weeks duration, that is documented to be quotidian for at least 3 days, and accompanied by one or more of the following:<br>1. Evanescent (non-fixed) erythematous rash<br>2. Generalized lymphadenopathy<br>3. Serositis<br>4. Hepatomegaly and/or splenomegaly | Major criteria:<br>1. Fever of ≥ 39°C lasting ≥ 1 week<br>2. Arthralgia lasting ≥ 2 weeks<br>3. Typical rash*<br>4. Leukocytosis (≥ 10,000/cmm) including 80% or more granulocytes<br><br>Minor criteria:<br>1. Lymphadenopathy and/or splenomegaly<br>2. Sore throat<br>3. Liver dysfunction<br>4. Negative rheumatoid factors (RF) and negative antinuclear antibody (ANA) test |
| | • Diagnosis is made when there are 5 or more criteria which include at least 2 major criteria |

**Typical rash = non-pruritic macular or maculopapular salmon coloured rash (usually over the trunk or extremities while febrile)*

**Table II.** Clinical and laboratory data of patients in the study ($n$ = 30)

| Variables | Frequency | Percentage |
|---|---|---|
| Component of ILAR and Yamaguchi criteria: | | |
| Fever ≥ 2 weeks | 30 | 100 |
| Rash | 27 | 90 |
| Component of ILAR criteria: | | |
| Arthritis | 21 | 70 |
| Generalized lymphadenopathy | 8 | 26.7 |
| Serositis | 6 | 20 |
| Hepatomegaly and/or splenomegaly | 11 | 36.7 |
| Component of Yamaguchi criteria: | | |
| Arthralgia | 25 | 83.3 |
| Splenomegaly | 5 | 16.7 |
| Lymphadenopathy | 3 | 10 |
| Sore throat | 16 | 53.3 |
| Leukocytosis* | 24 | 80 |
| Liver dysfunction | 3 | 10 |
| Negative ANA | 27 | 90 |
| Negative RF | 30 | 100 |

**Leukocytosis (WBC ≥ 10,000/cmm)*

the delay between onset of systemic manifestation and onset of arthritis was 29.10 ±72.18 days. Clinical and laboratory data of patients are summarized in Table II.

All included patients had been investigated to rule out malignancies and infections as causes of fever of unknown origin (FUO).

The fulfilment of the variables in both the ILAR criteria and the Yamaguchi criteria was recorded for each patient at the time of first presentation to our hospital (refer to Table I for the criteria) [8, 15].

We considered the following symptoms present whether patients had it at presentation at our hospital or at any time during the course of the disease in the past history: characteristic fever, arthralgia, serositis, and sore throat. However, clinical signs (typical rash, splenomegaly, hepatomegaly and lymphadenopathy) and laboratory criteria (leucocytosis, liver dysfunction and negative ANA, RF) were considered present if they had been observed and reported at the time of presentation at our hospital.

Patients were considered to have arthritis only if the arthralgia was associated with either significant swelling or any 2 of the following findings: increased warmth over the joint, pain with limitation of range of motion, deformity, which had been documented by the physician at the time of presentation. The duration between onset of fever and onset of arthritis was recorded from the patients' files and by asking the parent.

The study protocol was approved by the Institutional Ethical Committee and written consent was obtained from the parents of all participating subjects before the study.

### Statistical methods

Data analysis was performed through Statistical Package for Social Sciences (SPSS) version 15. Data are expressed as mean, median, standard deviation (SD) and percentage. Comparison was performed through the $\chi^2$ test for qualitative variables. Comparison between 2 quantitative variables was performed through the $t$-test, while one-way ANOVA was used for comparison between more than 2 quantitative variables. Pearson's correlation was also used. $P$-values less than 0.05 were considered significant.

## Results

All the 30 patients had fever (ILAR and Yamaguchi criteria). The second most commonly fulfilled component was rash (90%) (ILAR and Yamaguchi criteria), then arthralgia ≥ 2 weeks (Yamaguchi criteria) was seen in 25 patients (83.3%) and only 21 patients (70%) had arthritis (ILAR criteria) at presentation.

In our study, 23 patients (76.7%) fulfilled Yamaguchi criteria and 20 patients (66.7%) fulfilled ILAR criteria. Ten patients who failed to fulfil the ILAR criteria fulfilled the Yamaguchi criteria, and among 20 patients who fulfilled the ILAR criteria 7 patients did not fulfil the Yamaguchi criteria (Table III).

Comparison between patients who fulfilled the ILAR criteria (definite sJIA) and those who did not fulfil the ILAR criteria (suspected sJIA) is shown in Table IV.

The mean age at the time of the study and at diagnosis of children with definite sJIA was significantly higher than in those with 'suspected' sJIA ($p$ = 0.02, 0.04, respectively). The mean erythrocyte sedimentation rate (ESR) was significantly higher in patients with 'suspected' sJIA than those with definite sJIA ($p$ = 0.04).

In 10 patients who failed to fulfil the ILAR criteria, 9 of them had no arthritis. So our 30 patients were grouped according to the presence or absence of arthritis. The comparison between the 2 groups is shown in Table V.

Mean age of patients was significantly higher and mean duration of fever was significantly prolonged in patients with arthritis ($p$ = 0.04 and 0.01, respectively). Rash was significantly more frequent in patients with arthritis ($p$ = 0.02) and lymphadenopathy was significantly more frequent in patients without arthritis ($p$ =

**Table III.** Patients who fulfilled the ILAR criteria and Yamaguchi criteria

| | ILAR criteria fulfilled | ILAR criteria not fulfilled | Total |
|---|---|---|---|
| Yamaguchi criteria fulfilled | *n* = 13 | *n* = 10 | *n* = 23 |
| Yamaguchi criteria not fulfilled | *n* = 7 | *n* = 0 | *n* = 7 |
| Total | *n* = 20 | *n* = 10 | *n* = 30 |

**Table IV.** Comparison between patients with definite sJIA and those with suspected sJIA

| Characteristics | Definite sJIA (*n* = 20) | Suspected sJIA (*n* = 10) | *p*-value |
|---|---|---|---|
| Age (mean ± SD) | 10.25 ±3.88 | 6.60 ±3.24 | **0.02** |
| Male/female ratio | 0.5 | 1.5 | 0.5 |
| Mean age at diagnosis of disease (years) | 7.30 ±3.25 | 4.95 ±2.59 | **0.04** |
| Mean duration of symptoms at time of presentation (days) | 99 ±56 | 121 ±108.67 | 0.5 |
| Average number of affected joints | 3.45 ±1.47 | 4 ±1.25 | 0.3 |
| Number of patients with arthralgia | 16 (80%) | 9 (90%) | 0.4 |
| Number of patients with rash | 20 (100%) | 7 (70%) | **0.03** |
| Number of patients with sore throat | 10 (50%) | 6 (60%) | 0.5 |
| Number of patients with generalised lymphadenopathy | 2 (10%) | 1 (10%) | 0.7 |
| Number of patients with lymphadenopathy | 3 (15%) | 5 (50%) | 0.06 |
| Number of patients with hepatomegaly | 4 (20%) | 2 (20%) | 0.7 |
| Number of patients with splenomegaly | 3 (15%) | 2 (20%) | 0.6 |
| Number of patients with serositis | 5 (25%) | 1 (10%) | 0.3 |
| Mean ESR (mm/h) | 91.8 ±30 | 110.9 ±19.34 | **0.04** |
| Mean haemoglobin (gm/dl) | 9.83 ±1.85 | 8.8 ±1.84 | 0.2 |
| Mean WBC (× $10^3$/$mm^3$) | 12.94 ±5.66 | 16.9 ±4.15 | 0.06 |
| Mean platelet count (× $10^3$/$mm^3$) | 521.15 ±182.02 | 542.6 ±186.61 | 0.8 |
| Mean ALT (U/l) | 42.7 ±54.09 | 28.5 ±15.01 | 0. 4 |
| Mean AST (U/l) | 46.8 ±93.44 | 29 ±11.6 | 0.5 |

= 0.03). Mean ESR and mean WBC were significantly higher in patients without arthritis ($p$ = 0.04 and 0.05, respectively). During follow-up (until the end of our study) 2 patients with 'suspected' JIA developed arthritis. In those 2 patients, the delay between first presentation and development of arthritis was 6 months in 1 child and 4 months in the other.

All the 20 patients who fulfilled the ILAR criteria had arthritis at presentation. However, with proper history taking from parents of patients, 11 of these patients had a history of delay between onset of systemic features and onset of their arthritis. The mean duration of the delay was 43.65 ±85.35 days and the median was 16.5 days.

## Discussion

The strict diagnosis of sJIA (previously labelled as Still's disease) by fulfilment of all ILAR criteria leads to the presence of children who clearly have this disease, but cannot be classified as having sJIA due to the absence of arthritis [4]. Extensive research on the pathogenesis of sJIA has been done since the publication of the ILAR criteria in 2004.

Certain cytokines and biomarkers which are characteristically increased in sJIA have been discovered by many researchers, for example, interleukin-18 (IL-18) [15, 16], macrophage migration inhibitory factor (MIF) [17, 18], myeloid related proteins 8 and 14 (MRP 8/14) [19, 20], soluble IL-receptor [21], S100A12 [22] and others. The utility of these biomarkers in diagnosis of patients with sJIA has been studied [15, 18, 20, 22, 23], and it was revealed that these biomarkers are helpful not only for diagnosing sJIA but also for distinguishing children with sJIA from patients with other subtypes of JIA, other inflammatory diseases and infection [4]. Also, Vastert et al. [7] showed that the clinical characteristics,

**Table V.** Comparison between patients with arthritis and those without arthritis

| Characteristics | Patients with arthritis ($n$ = 21) | Patients without arthritis ($n$ = 9) | $p$-value |
|---|---|---|---|
| Age (mean ± SD) | 9.95 ±4.02 | 6.89 ±3.30 | **0.04** |
| Male/female ratio | 1.1 | 1.25 | 0.6 |
| Mean age at diagnosis of disease (years) | 7.10 ±3.30 | 5.17 ±2.65 | 0.1 |
| Mean duration of symptoms at time of presentation (days) | 104.29 ±59.71 | 111.11 ±110.39 | 0.8 |
| Mean duration of fever at time of presentation (days) | 88.57 ±53.22 | 42.33 ±22.67 | **0.01** |
| Number of patients with arthralgia | 16 (76.2%) | 9 (100%) | 0.1 |
| Number of patients with rash | 21 (100%) | 6 (66.7%) | **0.02** |
| Number of patients with sore throat | 11 (52.4%) | 5 (55.6%) | 0.6 |
| Number of patients with generalised lymphadenopathy | 2 (9.5%) | 1 (11.1%) | 0.7 |
| Number of patients with lymphadenopathy | 3 (14.3%) | 5 (55.6%) | **0.03** |
| Number of patients with hepatomegaly | 4 (19%) | 2 (22.2%) | 0.6 |
| Number of patients with splenomegaly | 3 (14.3%) | 2 (22.2%) | 0.5 |
| Number of patients with serositis | 5 (23.8%) | 1 (11.1%) | 0.4 |
| Mean ESR (mm/h) | 92.19 ±29.30 | 112.11 ±20.11 | **0.04** |
| Mean haemoglobin (gm/dl) | 9.61 ±2.07 | 9.18 ±1.45 | 0.6 |
| Mean WBC ($\times 10^3/mm^3$) | 13.09 ±5.55 | 17 ±4.39 | **0.05** |
| Mean platelet count ($\times 10^3/mm^3$) | 526.81 ±179.3 | 531.78 ±194.57 | 0.9 |
| Mean ALT (U/l) | 41.43 ±53.04 | 29.89 ±15.22 | 0.5 |
| Mean AST (U/l) | 45.52 ±91.26 | 30 ±11.83 | 0.6 |

the mean value of many of the above biomarkers and the response to the therapy in 'suspected' sJIA patients without arthritis were similar to those in sJIA patients fulfilling the ILAR criteria. Nevertheless, these biomarkers are not routinely available and are expensive.

On the other hand, many studies have involved the comparison between children with sJIA and adults with AOSD, and most of these studies revealed a lack of any significant difference between both groups as regard systemic features [8–12], the articular manifestation or sequelae [8, 10–12]. However, Pay et al. [24] reported a few significant differences between paediatric and adult patients as regards clinical and laboratory features. Likewise, Lin et al. [9] reported differences between sJIA children and AOSD adults in articular outcomes.

In spite of these few differences, the presence of a large number of similarities allows the authors to consider that AOSD and sJIA may be the same disease and children may react differently [8–12, 24]. So considering these similarities, sJIA patients were expected to fulfil the diagnostic criteria of AOSD, and we applied this expectation in our study and used the Yamaguchi criteria (a relatively simple tool with clinical and basic laboratory features). We found that 76.7% of our patients fulfilled the Yamaguchi criteria and only 66.7% fulfilled the ILAR criteria for sJIA, as in the studies by Kumar et al. [4] and Behrens et al. [25], who reported that ILAR criteria were fulfilled in 58% and 31% of the sJIA patients respectively. In our study, the failure of ILAR criteria was mainly due to the absence of arthritis. Also we found that 13 (65%) patients with definite sJIA ($n$ = 20) fulfilled the Yamaguchi criteria – not as surprising as the report by Luthi et al. [10], who found that all 9 of their sJIA patients fulfilled the Yamaguchi criteria.

Pay et al. [24] found that all sJIA patients in their study fulfilled the ILAR criteria, 5/25 (20%) sJIA patients did not have arthritis at initial presentation, and we found in our study that 11/20 (55%) sJIA patients did not have arthritis at initial presentation.

The definition of sJIA by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) for initiating treatment in patients was different from the ILAR criteria for sJIA in the absence of arthritis and was based on fever and systemic features such as characteristic rash,

adenopathy and serositis. Provided that malignancy and infection have been excluded, the opinion of CARRA was that the ILAR criteria might lead to exclusion of patients who need to be treated as having sJIA [26].

In our study, the Yamaguchi criteria seem to be more helpful in patients with the absence of arthritis (9/9; 100%) as compared to patients with arthritis (14/20; 70%). These results are similar to the finding by Kumar et al. [4], who reported the Yamaguchi criteria in the absence of arthritis in 12/13 patients (92.3%) as compared to patients with arthritis (11/18; 61.1%).

Characteristic evanescent rash is considered as one of the features in sJIA [5, 26]. We observed the rash in 27 patients (90%), similar to the value in Europe and North America reported by Behrens et al. [25] and Modesto et al. [27], who found the presence of rash in about 80% of patients. However, Kumar et al. [4], Seth et al. [28] and Singh et al. [29] reported the prevalence of rash as between 27% and 58% in Indian sJIA patients. The lower incidence of rash in the studies in India may be explained by darker skin colour that makes the rash difficult to see. This difficulty may be considered as a further limitation of the ILAR criteria in patients with darker skin colours.

In our study, when both (ILAR and Yamaguchi) criteria were used either alone or in combination, all our patients ($n$ = 30) could be diagnosed with sJIA, similarly to the observations reported by Kumar et al. [4].

## Limitation

Possibly in our study it would be useful to take long-term follow-up data, as it is possible that suspected sJIA may evolve into another rheumatological disorder disease. Additionally, sore throat as part of the Yamaguchi criteria can be reduced specifically in children.

## Conclusions

Arthritis as an essential criterion for the diagnosis of sJIA may be absent or delayed in the subgroup of sJIA. Some changes in the ILAR criteria for sJIA to make them more inclusive are suggested. Application of the Yamaguchi criteria (arthritis as an essential criteria is not considered) might allow the criteria to be more clinically useful. These changes may allow early diagnosis and treatment of children with sJIA and prevent some of the morbidity associated with delayed diagnosis of sJIA.

*The authors declare no conflict of interest.*

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