

# Fever of unknown origin with polyarthritis

## Abstract

We describe a 14 years old male child presented with since 5 days of fever, polyarthritis and Salmon colored rash. For almost a century, this disorder is first recognized by George Frederic Still.<sup>1</sup>

**Keywords:** systemic onset JIA, juvenile idiopathic arthritis, salmon colored rash, polyarthritis, autoimmune, remitting fever

Volume 5 Issue 7 - 2016

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**Received:** July 16, 2016 | **Published:** December 06, 2016

## Introduction

This disease has been defined as systemic arthritis by the International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA), 2 systemic-onset juvenile rheumatoid arthritis (JRA) by the American College of Rheumatology classification, or systemic-onset juvenile chronic arthritis by the European League against Rheumatism classification. Diagnosis of systemic arthritis by the ILAR criteria requires the presence of arthritis and a documented quotidian fever of at least 2 weeks' duration, plus one of the following: typical rash, generalized lymphadenopathy, enlargement of liver or spleen, or serositis. Criteria and exclusions are shown in Table 1&2.<sup>2-9</sup>

## Case I

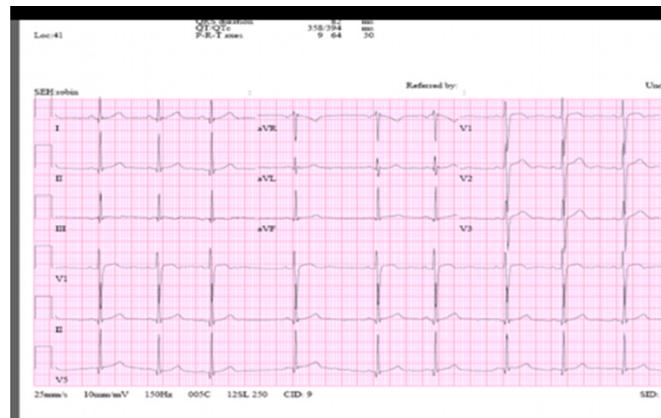
He complained of since 5 days pain in throat, skin rash and fever up to 39°C with since 3 days pain and swelling in the wrist and ankles. Physical Examination showed a child with normal vital signs. He was alert, good oriented in time/space and person. He had diffuse spread over his whole body salmon colored erythematous rash since 5 days (disappeared during admission after 6 days). ENT examination revealed red throat, Lymph nodes not enlarged. The lungs were clear to auscultation. There was no evidence of hepatosplenomegaly. Left knee painful at extension, not warmer than right knee, no swelling and painful wrists with limited movement.

Laboratory tests (Table 3) showed striking elevation in indicators of inflammation. CRP reached a maximum value of 259 (in first week of admission), BSE 77. White cell count is elevated (Leukocytes total number) and with a predominance of polymorphonuclear leukocytes (neutrophils). Thrombocytes at admission 359, increased to near 600. Liver- and kidney function normal. LDH increased from 677 to 1018. ANA negative, ANCA negative. Reuma factors negative. Serologic tests for infection were negative for: Brucella, Bartonella, Leptospirose. EBV, Mycoplasma, Parvovirus B 19. Adenovirus, Coxsackie, Measles, CMV, Borrelia burgdorferi, Serologic test for a bacterial infection with streptococcal bacteria showed elevation in antibody titer. (Table 3) Microbiological cultures remained negative. Fecal, blood, throat, urine cultures showed no recent infection. Fecal culture on *Salmonella* and *Shigella*, *Campylobacter*, *Yersinia* species was negative. Mantoux test for tuberculosis infection was negative.

Radiological examination revealed no signs of malignancy. Roentgen image of thorax showed heart normal size, lungs normal, lymph nodes. Echo abdomen showed normal liver, kidney, spleen.

Skeletscintigrafie showed increased uptake at left foot and left wrist; meaning poly-arthritis / poly-synovitis. Roentgen image of

left knee showed osteochondritis dissecans ECG: normal, no sign of pericarditis (no low voltage, no ST-segment elevation, no T-wave inversion) see Figure 1.



**Figure 1** ECG no sign of pericarditis (no low voltage, no ST-segment elevation, no T-wave inversion).

## General discussion

This case study described a 14 years old child with persistent fever since two weeks, rash, and polyarthritis. The onset of the disease with features of recurrent fever and polyarthritis is nonspecific and may suggest bacterial or viral infection, malignancy, or another inflammatory disease. The most common clinical features in 136 children with systemic-onset JRA were fever (98%), arthritis (88%) and rash (81%). Only 39% had lymphadenopathy, 10% had pericarditis, and fewer had hepatosplenomegaly.<sup>10</sup> Patient in our case had the required criteria for the diagnosis of systemic arthritis by the ILAR criteria. (Fever of at least 2 weeks' duration, plus typical rash). Criteria and exclusions are shown in Table 1&2.<sup>2-9</sup> The clinical features are similar to Adult onset Still's disease.<sup>3,4,8,9</sup> When we compare our case of systemic onset JIA with Adult onset Still's disease criteria, than we come to conclusion that the required criteria for Diagnosis of Still disease is similar. Child described in our case has 5 major criteria (fever >39 longer than 1 week, arthritis, salmon colored rash, leucocytosis > 10.000, with >80% neutrophils) and one minor criteria (negative Rheumatoid Factor and ANA) according to Yamaguchi. Our case had 3 major criteria and one minor criteria according to Fautrel. See for ILAR criteria Table 1, for criteria of Yamaguchi and Fautrel Table 2.<sup>2-8</sup> The possibility of a childhood vasculitis or malignancy is excluded by radiological investigations and other clinical investigations. This exclusion criteria are also named in ILAR criteria and criteria for Still's disease.

**Table 1** Most common clinical features of systemic onset JIA<sup>2</sup>

Systemic juvenile idiopathic arthritis: International League of Associations for Rheumatology (ILAR) diagnostic criteria	
Arthritis in any number of joints together with a fever of at least 2 weeks' duration that is documented to be daily (quotidian) for at least 3 days and is accompanied by one or more of the following:	
• Evanscent rash	
• Generalized lymphadenopathy	
• Enlargement of liver or spleen	
• Serositis	
Exclusions:	
• Psoriasis or a history of psoriasis in the patient or a first-degree relative	
• Arthritis in an HLA B27-positive male beginning after the sixth birthday	
• Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis—or a history of one of these disorders in a first-degree relative	
• The presence of IgM RF on at least two occasions at least 3 mo apart	

HLA, human leukocyte antigen; IgM, immunoglobulin M.

**Table 2** Criteria for Still's disease<sup>5-7</sup>

	Cush et al (1987) <sup>5</sup>	Yamaguchi et al (1992) <sup>6</sup>	Fautrel et al (2002) <sup>7</sup>
Design	Single center, retrospective	Multicenter, retrospective	Single center, retrospective
Data analysis	Descriptive	Discriminatory statistical analysis	Logistic regression analysis
Cohort size	21	90	72
Disease duration	11.8 years	3.8 years	2.9 years
Case definition	Fever $\geq$ 39°C and arthralgia/arthritis with any 2 of leukocytosis, JRA, rash, serositis/RES involvement	Clinical diagnosis upheld after case review by expert committee	Patients undergoing further treatment and clinical diagnosis upheld after prolonged observation and case review by one expert
Excluded from analysis	RF > 1:80 ANA > 1:100	Non-definite cases after review (n = 56)	Non-definite cases after review
Comparator group			
Criteria set	Fever $\geq$ 39°C and arthralgia/arthritis with any 2 of leukocytosis, JRA, rash, serositis/RES involvement	267 definite non-AJOD cases Major: Fever $\geq$ 39°C for > 1 week, arthralgia $>$ 2 weeks, maculopapular non-pruritic salmon-pink rash, leukocytosis $\geq$ 10,000/mm <sup>3</sup> with $\geq$ 80% neutrophils Minor: Rash, serositis, lymphadenopathy, and/or splenomegaly, abnormal aminotransferases, negative rheumatoid factor or ANA assay	130 definite non-AJOD cases Major: Spiking fever $\geq$ 39°C, transient erythema, pharyngitis, neutrophils $>$ 80%, glycosylated hemoglobin $>$ 20% Minor: Typical rash, leukocytosis $\geq$ 10,000/mm <sup>3</sup>
Required	As above	At least 5 criteria, including 2 major	Four major criteria or 3 major and 2 minor criteria
Exclusion needed	None	Infections, malignancies, vasculitides	None
Sensitivity for set	Not analyzed	96%	81%
Specificity for set	Not analyzed	92%	98%

JRA, juvenile rheumatoid arthritis; RES, reticuloendothelial system; RF, rheumatoid factor; ANA, antinuclear antibody.

This case shows that not the presence of the clinical evident features in the onset but the evolution of the disease eventually made the diagnosis of systemic onset juvenile idiopathic arthritis. About 40% of the children with systemic JIA follow a monocylic disease course and eventually recover almost completely, after a variable period. A small proportion of children have a polycyclic course characterized by recurrent episodes of active disease interrupted by periods of remission without medications. Studies have shown that more than one-half of the children with systemic JIA have a persistent disease course which has resulted in progressive involvement of more and more joints and moderate to severe functional disability.<sup>11</sup>

The most important early predictors of destructive arthritis are polyarthritis, thrombocytosis, persistent fever, or the need for systemic corticosteroids in the first 6 months after disease onset.<sup>12,13</sup> Treatment consisted in this case of NSAIDs. Patient received high dose Naproxen. Because of side effect is NSAID switched to Indometacine retard 75 mg. With NSAID is used both to aid in control of the systemic inflammatory features (e.g., fever) and to modulate joint pain and inflammation. Because systemic features seldom respond satisfactorily to NSAIDs alone, if the diagnosis is firmly established, the early use of glucocorticoids is indicated. Intravenous methylprednisolone (30 mg/kg/day to a maximum of 1 g/day on 1 to 3 consecutive days) is effective in controlling systemic and articular features of the disease, but the effect is often short-lived. Therefore, oral prednisone (1 to 2 mg/kg/day to a maximum of 60 mg/day in one or more doses) is often necessary. Disease-modifying antirheumatic drugs have been traditionally used in patients with s-JIA, with the goal of sparing glucocorticoids, but their efficacy is usually limited.

Although most of the evidence is provided by uncontrolled studies, biologic agents that inhibit the three pivotal inflammatory cytokines (TNF, IL-1 and IL-6) have already changed the approach to the treatment of s-JIA.<sup>14-17</sup> The role of especially IL-1 in the pathogenesis of s-JIA and predictors of response to IL-1 inhibition has been studied.<sup>16,18-21</sup>

**Table 3** Laboratory investigations

Test	Admission	Week 1	Week 2	Week 3
Leucocytes	17.5	29.2	21	17.2
Neutrophils	15.1	25.4	18.6	13.2
CRP	164	259	217	45
BSE (mm/h)		77	63	45
LD			677	1018
Thrombocytes	359	521	441	

Note: Day 1: Antistreptolysin O titer AST (aggl) 437, Anti-DNAse B titer (aggl) 180  
Day 35: AST 479 IE/ml, Anti-DNAse B 167 IE/ml

Abnormal expression of three of the most important pro-inflammatory cytokines-interleukin-6 (IL-6), IL-1, and tumor necrosis factor-a (TNF-a)-is characteristic of systemic JIA. De Benedetti and Martini<sup>13</sup> suggested that systemic JIA is an IL-6-mediated disease. Evidence to support that hypothesis is strong. IL-6 is markedly elevated in the blood and synovial fluid.<sup>22-24</sup> The IL-6 level increases just before each fever spike and correlates with the systemic activity of the disease, arthritis, and increase in acute phase reactants.<sup>25-29</sup> The abnormalities in regulation of IL-6 are also probably responsible for the limitation of growth, thrombocytosis, and microcytic anemia seen in this disease.<sup>27,28</sup>

There is accumulating evidence that inhibition of IL-1 or IL-6 is highly efficacious in a significant number of patients with persistent s-JIA, with improvements seen in both systemic symptoms and arthritis.<sup>30-34</sup> The long-term benefits of these approaches still need to be determined. One of the complications of systemic onset juvenile arthritis is macrophage activation syndrome (MAS). MAS bears close resemblance to secondary hemophagocytic lymphohistiocytosis (HLH) and is associated with serious morbidity and sometimes death.<sup>35-38</sup> Other complication of systemic onset JIA is secondary amyloidosis. The outcome of JIA-associated amyloidosis in the Finnish series was also poor, with a mortality rate of 42% and renal insufficiency or renal transplantation required in 25% of survivors, after a mean follow-up of 15 years.<sup>39</sup> Autonomous stem cell transplantation for systemic onset JIA can be a future remedy. There have been studies in the past.<sup>40-49</sup>

## Final diagnosis

Systemic onset juvenile idiopathic arthritis.

## Acknowledgements

None.

## Conflicts of interest

The authors declare no conflict of interest.

## Funding

None.

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