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 [1].

Keywords: Systemic onset JIA; Juvenile idiopathic Arthritis; Salmon colored rash; Polyarthritis; Autoimmune; Remitting fever

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), 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 febrile course 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 [2-9].

Table 1: Most common clinical features of systemic onset JIA [2].

| Clinical Feature | Description |
|-----------------|-------------|
| Arthritis | 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: |
| | - Erythematous rash |
| | - Generalized lymphadenopathy |
| | - Enlargement of liver or spleen |
| | - Serositis |
| Exclusions: | - Pustules or a history of pustulis 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, sacroilitis 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 |

H/A: human leukocyte antigen; IgM, immunoglobulin M.

Case Report

Yusuf Eken*
Utrecht University, Netherlands

*Corresponding author: Yusuf Eken, Utrecht University, Beneluxlaan 753 1363BJ almere Holland, Netherlands, Tel: 0031647958978; Email: yusuf.eken@gmail.com
Received: July 16, 2016 | Published: December 06, 2016

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 [1].

Keywords: Systemic onset JIA; Juvenile idiopathic Arthritis; Salmon colored rash; Polyarthritis; Autoimmune; Remitting fever

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), 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 febrile course 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 [2-9].

Table 2: Criteria for Still’s disease [5-7].

| Diagnosis | Criteria |
|-----------|----------|
| Fever | 35°C |
| Cervical lymph nodes | Enlarged |
| Spleen | Enlarged |
| Liver | Enlarged |

Case Report

Case 1:
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 nodule not enlarged. The lungs were clear to auscultation. There was no evidence of hepato-splenomegaly. 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 leucocytes (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, Leptospriose. EBV, Mycoplasma, Parvovirus B 19, Adenovirus, Coxsackie, Measles, CMV, Borrelia burgdorferi, Serologic test for a bacterial infection with streptococ bacteria showed elevation in antibody titer. (Table 3) Microbiological cultures remained negative. Fecal, blood,
Fever of Unknown Origin with Polyarthritis

throat, urine cultures showed no recent infection. Fecal culture on Salmonella en 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.

Table 3: Laboratory investigations.

| Test      | Admission | Week 1 | Week 2 | Week3 |
|-----------|-----------|--------|--------|-------|
| 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: Antistreptolysine O titer, AST (aggl) 437, Anti DNase B titer (aggl) 180Day 35: AST 479 IE/ml, Anti DNase B 167 IE/ml

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 [10]. 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 [2-9]. The clinical features are similar to Adult onset Still’s disease. [3,4,8,9] 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. [2-8] 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.

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 monocular disease course and eventually recover almost completely, after a variable period. A small proportion of children have a polyyclic 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 [11].

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 [12,13]. 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 [14-17]. The role of especially IL-1 in the pathogenesis of s-JIA and predictors of response to IL-1 inhibition has been studied [16,18-21].

Abnormal expression of three of the most important pro-inflammatory cytokines-interleukin-6 (IL-6), IL-1, and tumor necrosis factor-a (TNF-alpha) is characteristic of systemic JIA. De Benedetti and Martini [33] 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 [22-24].
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 [25-29]. The abnormalities in regulation of IL-6 are also probably responsible for the limitation of growth, thrombocytosis, and microcytic anemia seen in this disease [27,28].

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 [30-34]. 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 [35-38]. 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 [39]. Autonomus stem cell transplantation for systemic onset JIA can be a future remedy. There have been studies in the past [40-49].

Final Diagnosis:
Systemic onset juvenile idiopathic arthritis.

References
1. Still GF (1897) On a form of chronic joint disease in children. Med Chir Trans 80: 47-59.
2. Petty RE, Southwood TR, Manners P, Baum J, Glass DN et al. (2001) International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edinburgh, 2001. J Rheumatol 31 (2): 390-392.
3. Evesen KJ, Noscent HC (2006) Epidemiology and outcome of adult onset Still’s disease in Northern Norway. Scand J Rheumatol 35 (1): 48-51.
4. Riera E, Olve A, Narvaez J, Holgado S, Santo P, et al. (2011) Adult onset Still’s disease: review of 41 cases. Clin Exp Rheumatol 29 (2): 331-336.
5. Cush JJ, Medsger TA Jr, Christy WC, Herbert DC, Cooperstein LA (1987) Adult-onset Still’s disease: clinical course and outcome. Arthritis Rheum 30(2): 186-194.
6. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, et al. (1992) Preliminary criteria for classification of adult Still’s disease. J Rheumatol 19(3): 424-430.
7. Fautrel B, Zing E, Golmand JL, Le Moel G, Bissery A, et al. (2002) Proposal for a new set of classification criteria for adult-onset Still disease. Medicine (Baltimore) 81(3): 194-200.
8. Baevanov G, Trizas T, Pappas G, Akritidis N (2012) A series of 22 patients with adult onset Still’s disease presenting with fever of unknown origin. A difficult diagnosis Clin Rheumatol 31 (1): 49-53.
9. Franchini S, Dagna L, Salvo F, Aiello P, Baldissera E, et al. (2010) Adult onset Still’s disease: clinical presentation in a large cohort of Italian patients. Clin Exp Rheumatol 28: 41-48.
10. Behrens EM, Beukelman T, Gallo L, Spangler J, Rosenkranz M, et al. (2008) Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOAR). J Rheumatol 35(2): 343-348.
11. Spiegel LR, Schneider R, Lang BA (2000) Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: a multicenter cohort study, Arthritis Rheum 43 (11): 2402-2409.
12. Modesto C, Woo P, García-Consuegra J, Merino R, García-Graneno M, et al. (2001) Systemic onset juvenile chronic arthritis, polyarticular pattern and hip involvement as markers for a bad prognosis. Clin Exp Rheumatol 19(2): 211-217.
13. Sandborg C, Holmes TH, Lee T, Biederman K, Bloch DA, et al. (2006) Candidate early predictors for progression to joint damage in systemic juvenile idiopathic arthritis. J Rheumatol 33 (11): 2322-2329.
14. De Benedetti F, Ravelli A, Martini A (1997) Cytokines in juvenile rheumatoid arthritis. Curr Opin Rheumatol 9(5): 428-433.
15. Pignatti P, Vivarelli M Meazza, Rizzolo MG, Martini A, et al. (2001) Abnormal regulation of interleukin in systemic juvenile idiopathic arthritis. J Rheumatol 28(7): 1670-1676.
16. De Benedetti F, Pignani P, Massa M, Sartriana P, Ravelli A, et al. (1995) Circulating levels of interleukin 1 beta and of interleukin 1 receptor antagonist in systemic juvenile chronic arthritis. Clin Exp Rheumatol 13(6): 779-784.
17. Keul R, Heinrich PC, Muller-Newen G, Muller K, Woo P (1998) A possible role for soluble IL-6 receptor in the pathogenesis of systemic onset juvenile chronic arthritis Cytokine 10(9): 729-734.
18. Hashkes PJ, Uziel Y, Laxer RM (2010) The safety profile of biologic therapies for juvenile idiopathic arthritis. Nat Rev Rheumatol 6(10): 561-571.
19. Quartier P, Allantaz F, cinaz R, Pillet P, Messean C, et al. (2011) a multi centre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic onset juvenile idiopathic arthritis (anajistrial). Ann rheum dis 70: 747-754.
20. Gattorno M, Piccini A, Lasià D, Tassi S, Bricca G, et al. (2008) The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 58(5): 1505-1515.
21. Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE, et al. (2011) Anakinra as first line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum 63(2): 545-555.
22. Lepore L, Pennesi M, Saletta S (1994) Study of IL-2, IL-6, TNF alpha, IFN garruna and beta in the serum and synovial fluid of patients with juvenile idiopathic arthritis. Clin Exp Rheumatol 12: 561-565.
23. Rooney M, David j, Symons j, Di Giovine F, Varshini H, et al. (1995) Inflammatory cytokine responses in juvenile chronic arthritis. Br j Rheumatol 34(5): 454-460.
24. Prieur AM, Kaufmann MT, Griselli C, Dayer JM (1987) Specific interleukin-1 inhibitor in serum and urine of children with systemic juvenile chronic arthritis. Lancet 282(1): 1240-1242.
25. Mangge H, Kenzian H, Gallieti S, Neuwirth G, Liebmann P, et al. (1995) Serum cytokines in juvenile rheumatoid arthritis: correlation with conventional inflammation parameters and clinical subtypes. Arthritis Rheum 38(2): 211-220.
26. De Benedetti F, Alouzi T, Moretta A, Lazzaro D, Costa P, et al. (1997) Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I: a model for stunted growth in children with chronic inflammation. Clin Invest 99(4): 643-650.

27. Fishman D, Faulks G, Jeffery R, Mohamed-Ali V, Yudkin JS, et al. (1998) The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. Clin Invest 102(7): 1369-1376.

28. De Benedetti F, Massa M, Pignani P, Albani S, Novick D, et al. (1994) Serum soluble interleukin 6 (IL-6) receptor and IL-6/soluble IL-6 receptor complex in systemic juvenile rheumatoid arthritis. J Clin Invest 93(5): 2114-2119.

29. Pignatti P, Ciapponi L, Galle P, Hansen MB, Massa M, et al. (2003) High circulating levels of biologically inactive IL-6/SIL-6 receptor complexes in systemic juvenile idiopathic arthritis: evidence for serum factors interfering with the binding to gp130. Clin Exp Immunol 131(2): 355-363.

30. Pascual V, Albantaz F, Arce E, Punaro M, Banchereau J (2005) Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med 201(9): 1479-1486.

31. Lequerre T, Quartier P, Rosellini D, Aloufi F, De Bandt M, et al. (2008) Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis 67(3): 302-308.

32. Puechal X, De Bandt M, Berthelot JM (2011) Tocilizumab in refractory juvenile idiopathic arthritis: a preliminary experience in France. Ann Rheum Dis 70(5): 1505-1515.

33. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y et al. (2008) Macrophage activation syndrome complicating systemic juvenile idiopathic arthritis, J. Pediatr. 153(6): 1285-1292.

34. Sawhney S, Woo P, Murray K (2001) Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child 85: 421-426.

35. Immonen K1, Savolainen H, Kautiainen H, Hakala M, et al. (2008) Long-term outcome of amyloidosis associated with juvenile idiopathic arthritis. J Rheumatol. 35 (5): 907-912.

36. De Benedetti F, Martini A (1998) Is systemic juvenile rheumatoid arthritis an interleukin-6 mediated disease? J Rheumatol 25(2): 203-207.

37. Wulffraat NM, Brinkman 0, Ferster A, Opperman J, Ten Cate R (2003) Long-term follow-up of autologous stem cell transplantation for refractory juvenile idiopathic arthritis. Bone Marrow Transplantation 342: 561-564.

38. Quartier P, Prieur AM, Fischer A (1999) Haemopoietic stem-cell transplantation for juvenile chronic arthritis. Lancet 353: 1885-1886.

39. Ogilvie BM, Fife BS, Thompson SD, et al. (2003) The -174G allele of the interleukin-6 gene confers susceptibility to systemic arthritis in children: a multicenter study using simplex and multiple juvenile idiopathic arthritis families. Arthritis Rheum 48: 3202-3206.

40. De Benedetti F, Meazza C, Vivarelli M (2003) Functional and prognostic relevance of the -173 polymorphism of the macrophage migration inhibitory factor gene in systemic onset juvenile idiopathic arthritis. Arthritis Rheum 48: 1398-1407.

41. Barnes MG, Grom AA, Thompson SD, Griffin TA, Pavlidis P, et al. (2009) Subtype-specific peripheral blood gene expression profiles in recent-onset juvenile idiopathic arthritis. Arthritis Rheum 60 (7): 2102-2112.

42. De Jager W, Hoppenreijs EP, Wulffraat NM, Wedderburn LR, Kuis W, et al. (2007) Blood and synovial fluid cytokine signatures in patients with juvenile idiopathic arthritis: a cross-sectional study. Ann Rheum Dis 66 (5): 589-598.

43. Frosch M, Ahlmann M, Vogt T, Wittkowski H, Wulffraat N, et al. (2009) The myeloid-related proteins 8 and 14 complex, a novel ligand of toll-like receptor 4, and interleukin-1beta form a positive feedback mechanism in systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 60(3): 883-891.

44. Gattorno M, Piccini A, Lasiglie D, et al. (2008) The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 58(5): 1505-1515.

45. Ravelli A, Magni-Manzoni S, Pistorio A, Besana C, Foti T et al. (2005) Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis, J. Pediatr. 146(5): 598-604.

46. Devetaki P, Massa M, Robbioni P, Ravelli A, Burgio GR, et al. (1991) Correlation of serum interleukin-6 levels with joint involvement and thrombocytosis in systemic juvenile rheumatoid arthritis. Arthritis Rheum 34(9): 1158-1163.