

CASE REPORT

Systemic Juvenile Idiopathic Arthritis in two children; case report on clinical course, challenges in diagnosis and the role of FDG-PET/CT-scan

S. Sahba¹ | A. Huurnink² | J. M. Van den Berg³ | B. Tuitert¹ | S. J. Vastert⁴ | G. W. Ten Tusscher^{1,5} 

¹Department of Paediatrics, Dijklander Hospital Hoorn, Hoorn, The Netherlands

²Department of Nuclear Medicine, Dijklander Hospital Hoorn, Hoorn, The Netherlands

³Department of Pediatric Immunology, Rheumatology and Infectious Diseases, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

⁴Department of Paediatric Rheumatology and Immunology, Wilhelmina Children's Hospital Utrecht, Utrecht University, Utrecht, The Netherlands

⁵Department of General Practice, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Correspondence

G. W. Ten Tusscher, Dijklander Hospital Hoorn, Maelsonstraat 3, 1642 NP Hoorn, Netherlands.
Email: g.tentusscher@westfriesgasthuis.nl

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Abstract

Systemic juvenile idiopathic arthritis (sJIA, also called Still's disease) is a rare childhood auto-inflammatory disease with significant morbidity. This case report illustrates the clinical course and highlights diagnostic challenges. FDG-PET/CT imaging may be beneficial in the diagnostic process for some cases, in order to achieve rapid diagnosis and early treatment.

KEYWORDS

diagnostics, immunology, nuclear imaging

1 | INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA, also known as Still's disease) is a rare auto-inflammatory disease presenting in children under 16 years of age and accounts for 10% of all types of juvenile idiopathic arthritis. It is the most severe subtype with significant morbidity and even mortality.¹ The reported prevalence of sJIA varies between 7–150 per 100,000, and incidence numbers vary between 1 and 22 per 100,000 per year.² This case report illustrates diagnostic challenges in young children, discusses considerations with respect to laboratory testing and physical examination of joints, and highlights a possible role of FDG-PET/CT in diagnosing cases where classical features are not (yet) present.

2 | CASE PRESENTATION

2.1 | Case 1—History and examination

A 5-year-old girl was referred to our clinic with fever for six days, non-productive cough and general malaise despite amoxicillin treatment for two days. Past medical history was uneventful. She complained of diffuse pain in the lower extremities. Physical examination showed slight wheezing at auscultation and no other abnormalities. Laboratory blood tests and a lung X-ray revealed elevated infectious parameters and a possible consolidation (Table 1). The most probable diagnosis was thought to be a bacterial pneumonia or viral infection. Serological

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TABLE 1 Overview of relevant laboratory results prior to and during admission of case 1

CASE 1	Day 0 (second presentation, day of admission)		Day 2	Day 5	Day 8	Day 12	Day 15 ^a	Units
	Day-2 (first presentation)	Day 0 (second presentation)						
Days of admission	326 (H)	437 (H)	232 (H)	177 (H)	122 (H)	150 (H)	32 (H)	mg/L
C-reactive protein (CRP)	—	111 (H)	—	—	—	129 (H)	22 (N)	mm/h
Erythrocyte sedimentation rate (ESR)	—	—	—	—	—	—	—	—
Hemoglobin	—	—	—	—	7.0 (N)	6.0 (N)	—	mmol/L
Leukocytes	16.4 (H)	17.3 (H)	12.1 (N)	13.0 (N)	15.2 (N)	19.9	—	×10 ⁹ /L
Neutrophils	14.0 (H)	14.0 (H)	8.8 (N)	—	12.7 (L)	—	—	×10 ⁹ /L
Thrombocytes	338 (N)	412 (N)	—	—	485 (N)	540 (N)	—	×10 ⁹ /L
Ferritin	—	—	3501 (H)	1891 (H)	—	1247 (H)	356 (H)	ug/L
Interleukin 18 (IL-18)	—	—	—	—	—	>20000 (H)	—	pg/mL
								reference value <200 pg/mL

^aTwo days after start of treatment with Anakinra (IL-1 antagonist) 2 mg/kg.

testing for mycoplasma was performed and the girl was discharged with azithromycin. Two days later the fever and pain had persisted and inflammatory markers had increased (Table 1). Mycoplasma serology was negative and physical examination showed no abnormalities. She was admitted for treatment with intravenous (IV) antibiotics due to fever of unknown origin. During admission, physical examinations did not reveal any signs of arthritis, skin rash or other clues. From the third day of admission, she developed fever spikes with simultaneous pain and general malaise with a normal clinical state in between.

Laboratory tests revealed an elevated ferritin level (Table 1). Criteria for both hemophagocytic lymphohistiocytosis (HLH) and sJIA were not met. Extensive screening for various infectious diseases was negative. A more extensive categorical workup of infectious, oncologic, auto-immune and immunodeficiency disorders was considered. In consultation with a tertiary centre, it was opted to perform an FDG PET-CT scan, which showed marked elevated metabolic activity diffusely in the spleen, the red bone marrow, and some inguinal lymph nodes (Figure 1A–D). This pattern of metabolic activity, without signs of primary malignancy, focus of infection or synovitis/arthritis of the joints, was suggestive of sJIA without arthritis.

2.1.1 | Treatment and follow-up

Neuroblastoma was fully excluded with urine testing. Cytokine levels in the blood showed an extremely elevated level of IL-18, suggesting sJIA.^{3–8} In a tertiary health centre, the girl was started on daily administration of anakinra 2mg/kg. A marked decrease in fever spikes, pain and inflammatory markers was seen within 3 days (Table 1). She received daily injections of anakinra for the following 3 months. Her clinical state continued to improve, and successful tapering was achieved after 3 months with persisting clinical inactive disease.

2.2 | Case 2—History and examination

A 6-year-old boy was presented because of fever spikes despite amoxicillin treatment and mild pain in the shoulders. Prior to presentation at our clinic, there had been a sore throat and a maculo-papular exanthema. Besides mild pain in both shoulders, there were no other localizing symptoms. Past medical history was uneventful. Physical examination revealed no abnormalities. Laboratory tests revealed signs of inflammation (Table 2). The most probable diagnosis was a viral infection, so watchful waiting with serological testing for viral pathogens was decided.

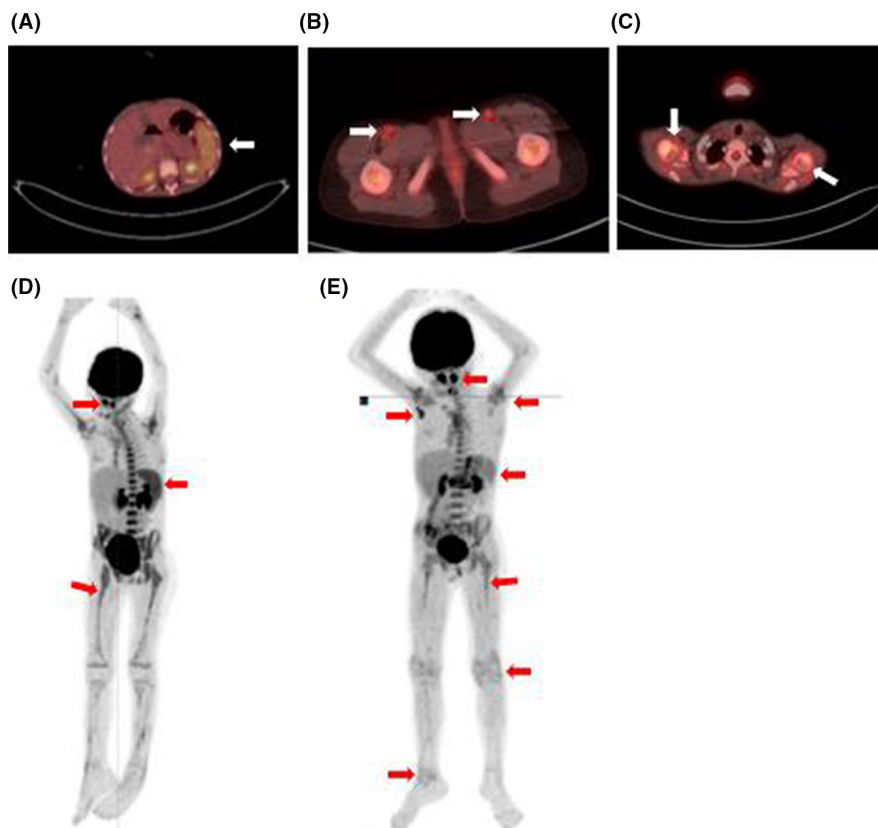


FIGURE 1 (A) Axial view case 1. Diffuse uptake in spleen (arrow) is shown. (B) Axial view case 1. Diffuse uptake in bilateral inguinal lymph nodes (left arrow) is observed. (C) Axial view case 2. Diffuse uptake in synovium of both shoulders (arrows) is shown. (D) Maximum intensity projection (MIP) in coronal direction of case 1. Diffuse uptake in tonsils (arrow 1, counted from above), spleen (arrow 2), and red bone marrow (arrow 3) is shown. (E) Maximum intensity projection (MIP) in coronal direction case 2. Diffuse uptake in tonsils (arrow 1, counted from above), synovium bilateral shoulders (arrow 2), unilateral right axillary lymph node (arrow 3), spleen (arrow 4), red bone marrow (arrow 5), and mild increase in synovium both knees (arrow 6) and synovium right ankle (arrow 7) is shown

At revision, six days later, we learned that the daily fever spikes had persisted and viral serology was negative. Inflammatory parameters had increased (Table 2). He was admitted for additional examinations due to fever of unknown origin.

During admission the boy reported pain in his knee during fever spikes, but no signs of arthritis were observed during repeated examinations. SJIA was considered, but the diagnostic criteria were not met. Extensive screening for infectious disease was negative. Workup of oncologic, auto-immune and immunodeficiency causes was considered, but after consultation of a tertiary centre, we first performed an FDG-PET/CT scan. Both shoulders, knees and the right ankle joint showed mildly elevated uptake, suggesting synovitis. The images also revealed higher uptake in bilateral axillary lymph nodes and unilateral inguinal lymph nodes (Figure 1C–E), and moderately diffuse uptake in the red bone marrow and slightly diffuse in the spleen. These findings, in the absence of signs for a focal active infection or malignancy, were suggestive of sJIA with polyarthritis.

2.2.1 | Treatment and follow-up

In a tertiary healthcare centre, physical examination performed by paediatric rheumatologists revealed a mild arthritis in multiple joints (right wrist, right hip and knee, left ankle and both shoulders). Neuroblastoma was excluded using urine testing. IL-18 levels in the blood were extremely elevated, suggesting sJIA. Daily injections of anakinra 2 mg/kg were started. His fever spikes and pain disappeared, and the inflammatory markers decreased markedly (Table 2). He received daily injections of anakinra for 3 months with an excellent result within 2 months of treatment. After 3 months of treatment, tapering will be attempted.

3 | DISCUSSION

These cases provide examples of how clinical suspicion of sJIA may arise in the diagnostic process and the challenges in diagnosing sJIA when arthritis is not present or clinically overt.

TABLE 2 Overview of relevant laboratory results prior to and during admission of case 2

CASE 2	Day 0 (second presentation, day of admission)					
	Day-6 (first presentation for fever spikes)	Day 0 (second presentation, day of admission)	Day 8	Day 10	Day 13 ^a	Units
CRP	60 (H)	75 (H)	64 (H)	54 (H)	8.1 (N)	mg/L
ESR	—	—	—	113 (H)	—	mm/h
Hemoglobin	5.7 (L)	5.1 (L)	5.8 (L)	5.0 (L)	5.4 (L)	mmol/L
Leukocytes	16.5 (H)	13.9 (N)	14.3 (N)	13.9 (N)	5.0 (L)	$\times 10^9/L$
Neutrophils	12.5 (H)	10.6 (H)	11.4 (H)	—	—	$\times 10^9/L$
Thrombocytes	458 (N)	538 (N)	689 (H)	—	627 (H)	$\times 10^9/L$
Ferritin	—	605 (H)	—	1451 (H)	493 (H)	ug/L
IL-18	—	—	—	14865 (H)	—	pg/mL reference value <200 pg/mL

^aTwo days after start of treatment with Anakinra (IL-1 antagonist) 2 mg/kg.

3.1 | SJIA clinical characteristics and pathophysiology

SJIA is characterized by severe systemic inflammation and characteristics include daily fever spikes combined with i.e. general malaise, serositis, arthralgia and/or arthritis (in up to 15% of cases).^{11,12} Typically, complaints of pain and illness/malaise are only present during fever spikes. Two phenotypes of disease manifestations exist, a systemic inflammatory phenotype (type I, often early in the disease course) and an articular chronic phenotype (type II).¹³⁻¹⁵ Research suggests that symptoms may be the result of an excessive production of pro-inflammatory cytokines due to overactivation of innate immune mechanisms.^{13,16} Interleukin-1 (IL-1), its family member cytokines (i.e. IL-18) and cytokines that it induces (IL-6) are important players within the innate immunity and play a major role in the pathophysiology of sJIA.^{13,16,17} In adults, a similar disease is referred to as adult onset Still's disease (AOSD), suggesting that sJIA and AOSD represent the same disease with different ages of onset.¹² A potentially life-threatening complication of sJIA is macrophage activation syndrome (MAS, a specific form of HLH), where overwhelming activation of macrophages and lymphocytes leads to excessive inflammation and tissue destruction, causing, i.e. hemorrhages, kidney damage and even multiple organ failure.^{15,18-20} Extremely high levels of ferritin are associated with occurrence of MAS, which requires immediate action.²¹⁻²⁴

3.2 | Diagnostic methods

Presence of arthritis for a definite diagnosis of sJIA is currently under debate. Recently, a new set of classification criteria for sJIA has been proposed (modified Yamaguchi criteria), excluding arthritis from the mandatory symptoms (Table 3).¹² There are several distinct laboratory

TABLE 3 Definition of sJIA based on modified Yamaguchi criteria (2018 Martini et al)

Quotidian fever (rising to $\geq 39^\circ\text{C}$ once a day and returns to $\leq 37^\circ\text{C}$ between fever peaks) for at least **3 consecutive days** and reoccurring over a duration of **at least 2 weeks**, accompanied by **two major criteria OR 1 major criterion and 2 minor criteria**:

Major criteria:

- (1) evanescent (nonfixed) erythematous rash;
- (2) arthritis.

Minor criteria:

- (1) generalized lymph node enlargement and/or hepatomegaly and/or splenomegaly; (2) serositis;
- (3) arthralgia lasting 2 weeks or longer (in the absence of arthritis);
- (4) leukocytosis ($\geq 15,000/\text{mm}^3$) with neutrophilia.

features in patients with sJIA. Hyperferritinemia combined with elevated levels of both C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are found in most patients.¹¹ Elevations of cytokines IL-6, and specifically IL-18, are also seen.^{13,26} Based on recent research, elevated levels of IL-18 appear to be a strong indicator of active sJIA.¹³ Other possible laboratory features include anemia, leukocytosis (sometimes with prominent leukemoid reactions with white blood cell counts >50,000), thrombocytosis and hypoalbuminemia.^{1,25}

3.3 | Possible diagnostic challenges when sJIA is suspected

The diagnosis of sJIA proved to be difficult in both of our cases despite using the current classification criteria. We identified factors which may have hampered the diagnostic process. Firstly, physical examination of the joints to identify signs of arthritis has proven to be difficult in children with sJIA, who are often sick and in bed. In case two, subtle signs of clinical arthritis were only noticed by the paediatric rheumatologist after transferral to a tertiary centre, despite previously repeated examination by capable general paediatricians. There is an important lesson in this with regard to examination of joints in children. Localizing symptoms regarding joints (i.e. pain, resisting mobilisation or burdening of joints) in young children (<8 years old) should be examined thoroughly by including ultrasound sonography of the affected joints or consultation of an academic hospital or clinical expert, i.e. paediatric rheumatologist for a specialized examination.

A second challenge in diagnosing sJIA may be absence of arthritis in a child with fever of unknown focus. The differential diagnosis of fever of unknown focus may be categorized into infectious diseases, non-infectious inflammatory diseases, malignancies and miscellaneous causes.^{25,27-30,31,32} In cases where, despite thorough examination of the joints, no signs of arthritis are found, we see an important role for FDG-PET/CT scans. FDG-PET/CT scans combine high spatial resolution with detection of increased intracellular glucose metabolism, making it a highly sensitive modality for detecting potential pathology in all possible categories of diagnoses mentioned. Several studies evaluating FDG-uptake patterns in patients with sJIA and AOSD showed that sJIA/OASD results in increased FDG-uptake in the red bone marrow and the spleen, generally combined with FDG-uptake in slightly enlarged (<1.5 cm) lymph nodes at various sites.^{3,28,33-37,38} This pattern with high accumulation in the bone marrow and spleen, without other sites of FDG accumulation, is a generally uncommon finding, and should direct the diagnostic work up

to sJIA or AOSD. On the other hand, mild to moderately increased accumulation of FDG in the bone marrow, and to a lesser extent in the spleen, is a common non-specific finding in patients with fever. This is probably the result of non-specific proliferation of immune cells through an interleukin-dependent upregulation of glucose transporters. This may also explain the more pronounced FDG-uptake in bone marrow and spleen in patients with sJIA and OASD, since excessive secretion of various interleukins seems to be an important aspect of the disease. However, Kanetaka et al. showed that children with sJIA who had apparent FDG-uptake at the joints (due to synovitis) had less FDG-uptake in the bone marrow and spleen.³⁷ In case one, the FDG-PET/CT scan enabled us to rule out an abscess or malignant tumour while the pattern of high FDG-uptake in bone marrow, spleen and some lymph nodes pointed towards sJIA. In case two, the FDG-PET/CT scan revealed synovitis of multiple joints, which was not recognized earlier, pointing towards sJIA and polyarthritis. So, FDG-PET/CT scan images may not be appropriate to diagnose sJIA, but may be helpful in the diagnostic process towards sJIA by substantially narrowing the possible sources of fever, and providing patterns of inflammation that can fit in the diagnosis of sJIA.

The third challenge in the diagnostic process of sJIA may be the role of ferritin levels. In AOSD, it is known that hyperferritinemia is present in >80% of cases.³⁹ Research in children with sJIA indicates that a majority (60%–70%) of children also develop hyperferritinemia.^{40,41} Importantly, hyperferritinemia is not specific for sJIA and may also be found in several other autoimmune, infectious or malignant diseases.⁴² However, a retrospective study of children with hyperferritinemia found that sJIA was the cause in 48% of 87 cases, suggesting it to be an important clue for sJIA.^{42,43} In our cases, ferritin levels were elevated in both cases. Case two showed a mild elevation at first and increased later in the disease course, consistent with the course of sJIA. We conclude that ferritin levels and their course should be monitored closely since they form an important clue for sJIA in children with fever spikes of unknown origin with or without arthritis.

3.4 | Prognosis and treatment of sJIA

If left untreated, half of the sJIA patients develop severe persistent disease which may lead to severe articular damage. Early and adequate treatment with the IL-1 receptor antagonist anakinra is beneficial for the prognosis.^{9,10} Previously, first-line treatment of sJIA consisted of NSAIDs and long-term systemic high-dose glucocorticoids but was undesirable due to its well-known side effects.^{13,44}

Recently, a biological disease modifying anti-rheumatic drug (DMARD) in the form of a specific IL-1 antagonist anakinra was approved for first-line treatment in sJIA patients and is known to achieve meaningful response in >50% of sJIA patients within 3 months of treatment, if started in an early phase of the disease.^{1,11,45} Treatment of sJIA with DMARDs results in a good prognosis.

4 | CONCLUSION

sJIA is a rare acquired auto-inflammatory disease in children with significant morbidity and sometimes even mortality. Early diagnosis is imperative but may be challenging in young children. We recommend that sJIA be considered in any child with unexplained fever spikes and arthralgia or malaise in the absence of an evident infectious focus. Therefore, in these cases, ferritin levels should be monitored since they form an important clue for sJIA. Furthermore, determining arthritis in young children has proven to be difficult and may require thorough examination using (ultra-sound)imaging or joint examination by a clinical expert. Lastly, we argue that FDG-PET/CT imaging may be helpful specifically for those children presenting without overt clinical arthritis to rule out differential diagnoses and identify sources of inflammation to further guide diagnosis. In all of these considerations, it may prove valuable to consult an expert early.

AUTHOR'S CONTRIBUTION

SS, resident paediatrician treated the patients. She wrote the largest portion of the manuscript; AH, nuclear physician provided the images and their interpretation. He contributed tot the discussion portion of the manuscript; JMvdB, paediatric rheumatologist was consultant for the patients. He played an active role in the generation and editing of the manuscript; BT, treating paediatrician was responsible for initial diagnostiscs. She played a role in the description of the cases. SJV, paediatric rheumatologist was consultant for the patients. He played a role in editing the manuscript; GWtT, treating paediatrician, participated in, and supervised the generation and editing of the manuscript.

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CONFLICTS OF INTEREST

None.

DATA AVAILABILITY STATEMENT

All relevant data are available and can be found in Tables S1 and S2.

CONSENT

Written informed consent was obtained from the parents/guardians to publish this report in accordance with the journal's patient consent policy.

ETHICAL APPROVAL

Not relevant.

ORCID

G. W. Ten Tusscher  <https://orcid.org/0000-0001-6448-5631>

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