Fever of unknown origin in childhood: difficulties in diagnosis

Katherine Martin, E Graham Davies, John S Axford

Case report
A twelve year old white boy presented to another hospital with a two month history of intermittent fever with night sweats, general malaise, arthralgia and myalgia. He had marked cervical lymphadenopathy. Latex agglutination for toxoplasma antibodies was positive at a dilution of 1/128. A diagnosis of acquired toxoplasmosis was made and sulphadiazine 1 g four times a day, trimethoprim 300 mg twice a day and folic acid 15 mg alternative days, were started. Over the next week he developed a generalised urticarial rash, peripheral oedema and profuse bloody diarrhoea and was referred to our unit.

On examination he was delirious with a persistent fever of up to 42°C and he was bleeding from his nose and mouth. He was generally oedematous with marked ascites and bilateral pleural effusions. His skin was erythematous with a petechial rash and after a few days began to desquamate. His liver was palpable 5 cm below the costal margin. Full blood count and film revealed a normochromic normocytic anaemia (haemoglobin 6.8 g/dl), neutrophilia with left shift (white cell count 41.6 x 10^9/l with 93% polymorphonuclear cells) and thrombocytopenia (platelet count 66 x 10^9/l). The circulating lymphocyte count was normal (1.2 x 10^9/l). Coagulation studies revealed evidence of disseminated intravascular coagulation (prothrombin time 16 s (control 11-15 s), kaolin partial thromboplastin time 68 s (control 34-48 s), thrombin time 18 s (control 11-15 s), plasma fibrinogen 1.2 g/l (normal 2.0-4.0 g/l), fibrinogen degradation products 64 to 128 mg/l (normal < 8 mg/l)). Erythrocyte sedimentation rate (ESR) was 30 mm/hour, C-reactive protein (CRP) 208 mg/l. Liver function tests were abnormal: alanine transaminase 91 IU/L (normal range 1-40), gamma glutamyl transferase 134 IU/L (normal range 0-60), bilirubin 18 micromol/L (0-17), alkaline phosphatase 217 IU/L (30-100) and albumin 18 g/l (35-45). Renal impairment was apparent with a raised serum creatinine (224 micromol/L (60-110)). Chest radiograph showed right middle lobe consolidation. Abdominal ultrasound scan (USS) confirmed hepatosplenomegaly and ascites. Echocardiogram showed a small pericardial effusion.

A diagnosis of Stevens-Johnson syndrome with acute renal failure and disseminated intravascular coagulation (DIC) was made. Supportive therapy, broad spectrum antibiotics and discontinuation of sulphonamides resulted in marked improvement. Cultures of blood, cerebrospinal fluid, urine and stool grew no pathogenic organisms. Repeat toxoplasma serology showed a positive dye test (125 units) and positive latex agglutination at a dilution of 1/128, but negative IgM by enzyme linked immunosorbent assay and immunosorbent agglutination assay, indicating probable past infection. Serology for Epstein-Barr virus, cytomegalovirus, viral hepatitis, mycoplasma, brucella, leptospira and legionella was negative. Mantoux at a dilution of 1/1000 was anergic. Anti-streptolysin 'O' titre was less than 200 IU/ml, anti-deoxyribonucleic acid B titre was less than 100 U/ml. Anti-nuclear antibody was negative. Plasma immunoglobulin levels and immunoglobulin G subclass levels were within the normal range and complement studies were normal.

Two weeks after admission the patient was much improved but had persistent intermittent fevers and marked hepatomegaly. Liver function tests returned to normal. Repeat abdominal USS showed a diffusely abnormal liver texture. Liver biopsy showed minimal focal fatty change with no signs of vasculitis. Bone marrow trephine showed hypercellularity and reactive changes only. Both were sterile on culture.

The patient continued to experience daily fevers (fig 1) and a fine evanescent rose coloured maculopapular rash which exhibited Koebner's phenomenon (fig 2) was noted for the first time at the peak of the fever. He developed swelling and stiffness of the proximal interphalangeal joints of the hands and effusions in the left knee and right ankle joints. A diagnosis of systemic onset juvenile chronic arthritis (S-JCA) was made and the
patient was treated with diclofenac sodium 50 mg three times a day. Slit lamp examination of the eyes was normal. Two weeks later there was no improvement in systemic symptoms although the arthritis had largely resolved. The haemoglobin had fallen to 6.4 g/dl necessitating transfusion. As the patient remained systemically unwell and in view of the rapidly falling haemoglobin, prednisolone 40 mg/day was added with resultant slow improvement. After resolution of disease activity steroids were weaned and the patient currently remains well and off all medication.

Discussion
Differential diagnosis of fever of unknown origin in childhood
This case illustrates well some of the pitfalls in the diagnosis of S-JCA. The child’s initial presentation was with fever of unknown origin (FUO) which has been defined as “the presence of fever for eight or more days in a child in whom a careful and thorough history and physical examination and preliminary laboratory data fail to reveal the probable cause of fever”. The differential diagnosis of FUO is wide and includes infectious diseases (systemic and localised), autoimmune rheumatic diseases, and neoplasia (table 1). The commonest cause in childhood is infectious disease (22–55%)\(^3\) (see table 2).

Table 1 Causes of FUO

<table>
<thead>
<tr>
<th>Infections</th>
<th>Post-infectious inflammatory disease, for example, rheumatic fever</th>
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<tbody>
<tr>
<td>Non infectious inflammatory diseases</td>
<td>S-JCA</td>
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<tr>
<td>For example</td>
<td>systemic lupus erythematosus</td>
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<td>polyarthritis nodosa</td>
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<td>Kawasaki’s disease</td>
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<td>inflammatory bowel disease</td>
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<td>sarcoidosis</td>
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<td>familial mediterranean fever</td>
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<td>Malignancies</td>
<td>leukaemia</td>
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<td>For example</td>
<td>lymphoma</td>
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<td>neuroblastoma</td>
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<td>Wilms’ tumour</td>
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<td>Miscellaneous</td>
<td>febrile fever</td>
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<td>drug fever</td>
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<td></td>
<td>diabetes insipidus</td>
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<td>hypothalamic dysfunction</td>
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<td>ectodermal dysplasia</td>
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<td>familial dysautonomia</td>
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Table 2 Infections presenting as FUO

| Systemic, for example                          | Infectious mononucleosis*                                        |
|                                                | cytomegalovirus*                                                 |
|                                                | hepatitis A, B*                                                 |
|                                                | human immunodeficiency virus*                                    |
|                                                | tuberculosis*                                                    |
|                                                | salmonellosis*                                                   |
|                                                | brucellosis*                                                     |
|                                                | legionellosis                                                    |
|                                                | cat scratch fever                                                |
| Bacterial, for example                         |                                                                  |
| Rickettsial disease (for example, Q fever)     |                                                                  |
| Chlamydial diseases (for example, psittacosis)  |                                                                  |
| Spirochaete infections (for example, Lyme disease*, leptospirosis) | |
| Parasitic infections (for example, malaria, toxoplasmosis) | |
| Fungal infections (for example, histoplasmosis) | |

Localised
Urinary tract infection
Osteomyelitis*
Sinusitis
Endocarditis
Occult abscesses (for example, hepatic, pelvic)

*may also cause arthritis
Fever of unknown origin in childhood: difficulties in diagnosis

Retrospective analyses of admissions in the United States of America with FUO show that a diagnosis of ‘juvenile rheumatoid arthritis’ was made in three to thirteen per cent of cases.\textsuperscript{2-5} Other autoimmune rheumatic diseases (systemic lupus erythematosus, Henoch-Schönlein purpura, polyarteritis nodosa, undefined vasculitis) account for up to a further 5% of cases. Autoimmune rheumatic diseases were commoner in the older age group (JCA was diagnosed in seven of 48 cases of FUO aged six years or older).\textsuperscript{2}

An infectious aetiology was initially considered in the above case. Marked cervical lymphadenopathy together with a positive latex agglutination test for toxoplasma misled the referring clinicians into a diagnosis of acquired toxoplasmosis. Latex agglutination for toxoplasma measures IgG and detectable titres of IgG usually persist for life after acute infection. Serological diagnosis of acute toxoplasmosis requires either the detection of IgM or a rise in IgG titre.

Systemic onset juvenile chronic arthritis. Diagnostic criteria and epidemiology

Diagnostic criteria for systemic onset juvenile chronic arthritis have recently been suggested.\textsuperscript{6} The criteria for the diagnosis of ‘definite’ S-JCA are arthritis, characteristic rash and intermittent fever lasting for more than two weeks. A ‘probable’ diagnosis of S-JCA can be made if there is typical rash and fever, organomegaly and/or lymphadenopathy and/or serositis in the absence of arthritis.

Juvenile chronic arthritis (JCA) has an annual incidence of approximately one in five to ten thousand children.\textsuperscript{7-9} Four to thirty per cent of these present with systemic onset disease.\textsuperscript{7-15} S-JCA may occur at any age throughout childhood. The reported sex incidence varies showing an excess of males in some series\textsuperscript{8-9, 11-14} and an excess of females in others.\textsuperscript{15-17}

The diagnosis of S-JCA was delayed in this case because the clinical picture was obscured by the development of a persistent high fever, desquamating erythematous rash, mucositis, encephalopathy, renal failure and DIC. This was attributed to an acute hypersensitivity reaction to sulphasazine. Intolerance to sulphonamides appears to occur with increased frequency in patients with S-JCA. Sustained high fever and rash were reported in three of four patients with S-JCA treated with sulphasalazine.\textsuperscript{18} In one case there were associated liver function abnormalities. Two children out of five with S-JCA were withdrawn from a second study of sulphasalazine\textsuperscript{19} because of severe side effects (fever, rash and leucopaenia in one and nausea, vomiting, headache and abnormal liver function tests in the other). DIC has also been described in S-JCA both as a direct manifestation of disease activity in association with renal and hepatic damage,\textsuperscript{20-21} in association with presumed infection\textsuperscript{22} and in association with non-steroidal anti-inflammatory drug and intramuscular gold therapy.\textsuperscript{21}

As the acute hypersensitivity reaction resolved the clinical picture returned to that at presentation with intermittent spiking fevers, although marked hepatomegaly persisted. In addition to the high spiking quotidian fever (fig 1), the appearance of the characteristic rash (fig 2) and arthritis led to the diagnosis of JCA. Our patient demonstrates the need for thorough and repeated examination which other authors have stressed.\textsuperscript{4, 13}

Clinical features of systemic onset juvenile chronic arthritis

(A) TYPICAL FEATURES

Daily or twice daily temperature elevations to 39°C or above with rapid return to baseline are characteristic of S-JCA and often accompanied by sweating, chills, myalgia and arthralgia. Typically the fever spike occurs in the evening. However, intermittent fevers are also seen in pyogenic infections, tuberculosis and lymphoma\textsuperscript{1} and several authors\textsuperscript{5} have found that the pattern of fever was not useful in differentiating the cause of FUO.

A rash occurs in up to 94% of children with S-JCA\textsuperscript{9, 13-14} but may not be present or characteristic on initial evaluation. Typically it is erythematous, fine and macular. It is evanescent, usually appearing at the height of the fever and it is therefore essential to re-examine the child when febrile. The commonest sites are the trunk and limbs\textsuperscript{23} but the face and neck are affected in more than 50% of cases and the rash may also occur on the palms and soles. Occasionally, the rash may be confined to the axillae and might therefore be missed unless specifically searched for. The rash is rarely pruritic, but Koebner’s phenomenon is common at sites of friction from clothing and may sometimes be demonstrated by rubbing the skin.

Children with S-JCA may develop oligo- or poly-arthritis. The commonest sites of arthritis in S-JCA are the wrists, knees, ankles, elbows, hips, metacarlo-phalangeal joints and proximal inter-phalangeal joints.\textsuperscript{12} Involvement of the temporo-mandibular joints also occurs frequently and involvement of the cervical spine is present at onset of disease in about a quarter of patients.\textsuperscript{12} Although arthralgia and myalgia are frequent but non-specific symptoms at the onset of S-JCA, arthritis may be transient or absent at presentation. In Schaller and Wedgwood’s series\textsuperscript{15} 29 of 32 patients with S-JCA had overt arthritis during the first month of disease but Calabro describes 18 of 40 children with systemic onset disease in whom arthritis was initially absent.\textsuperscript{9} These children were originally diagnosed as having FUO, the diagnosis of S-JCA being made after the development of arthritis four months to nine years (mean 2·2 years, median 8·5 months) after the onset of fever.

(B) OTHER FEATURES

Reticuloendothelial hyperplasia, most frequently lymphadenopathy, occurs in approximately 80–90% of children with active
S-JCA, but is also common in other causes of FUO. Lymphadenopathy may occasionally be so prominent as to suggest a lymphoma. Hepatomegaly (occurring in one third of cases) is less common than splenomegaly (found in approximately 75% of cases), although massive hepatomegaly has been reported.

Serositis is common in S-JCA. Pericardial effusions are detectable in more than 80% of patients during active disease although symptomatic pericarditis is much less frequent. Constrictive pericarditis and cardiac tamponade are extremely rare. Pleural effusions are less common than pericardial effusions and usually small. Subclinical myocarditis is reported to occur in up to 10% of children with S-JCA although clinically significant myocardial involvement is rare. Myocarditis may present with chest pain or heart failure but tachycardia out of proportion to the degree of pyrexia or anaemia may be the only clinical sign. Differentiation from viral myocarditis may be difficult. Both pericarditis and myocarditis have been reported as the presenting manifestations of S-JCA.

Differentiation of S-JCA from acute rheumatic fever may cause problems especially in the presence of S-JCA associated carditis. Although functional cardiac murmurs are common, valvular disease is extremely rare in JCA. Rheumatic fever is rare in children under the age of five years and the fever pattern in rheumatic fever is typically more sustained and lower grade than that of S-JCA. Associated arthritis is typically migratory, asymetric and painful. There may be evidence of a previous group A β-haemolytic streptococcal infection, although the ASOT may be moderately and chronically elevated in approximately one third of children with JCA.

Abdominal pain is occasionally a prominent feature of S-JCA and may increase the difficulty in distinguishing S-JCA from inflammatory bowel disease (which may also cause FUO and arthritis). Abdominal pain or distension may occasionally be so severe as to suggest an acute abdomen. Pneumonitis has rarely been reported in S-JCA, but is usually mild and transient. Cerebral manifestations (marked irritability, drowsiness, seizures and meningismus) have been reported in 25% of one series of children with S-JCA, but these are rare in other series except in relation to complicating factors such as metabolic derangements or salicylate toxicity. Iridocyclitis should be sought in all patients with JCA but is uncommon in systemic onset disease.

**Laboratory investigations**

Laboratory investigations are frequently unhelpful in the diagnosis of S-JCA. Autoimmune serology is characteristically negative. Severe anaemia (commonly hypochromic and microcytic) and thrombocytosis are usual in S-JCA but non-specific. Neutrophilia is often pronounced but may also be a false pointer to bacterial infection. Leucopaenia and thrombocytopenia are rare and should lead to the consideration of alternative diagnoses such as malignancies or systemic lupus erythematosus. Transaminases are common and hypoalbuminaemia may be marked. The erythrocyte sedimentation rate is and C-reactive protein are often considerably raised and hypergammaglobulinaemia is common. Serum ferritin levels are characteristically extremely high during active phases of S-JCA. Fassbender et al reported a decreased proportion of concanavalin A reactive alpha,-acid glycoprotein (AGP) variants in patients with S-JCA compared with healthy controls and patients with acute bacterial infections. Children with S-JCA have an increased prevalence of agalactosyl oligosaccharides associated with immunoglobulin G compared with healthy controls. The prevalence of agalactosyl-IgG is not increased, however, in patients with infectious diseases. The investigation of glycosylation of immune molecules may prove useful in discriminating between acute infection and active JCA.

Malignancy is the cause of 2-13% of cases of FUO in children in the USA, is sometimes associated with arthralgia or arthritis and has been misdiagnosed as S-JCA. The pattern of fever is usually remittent (that is, the temperature fluctuates but does not return to normal), in contrast to JCA and bone or joint pain may be more pronounced than in S-JCA. Careful examination of full blood count and film for any abnormalities is therefore essential. Severe anaemia, leucopaenia, thrombocytopenia or abnormal white blood cell appearance on the blood film are indications for bone marrow examination. In addition to its role of diagnosis of haematological malignancies, bone marrow examination may rarely be of use in the diagnosis of infection. A predominance of plasma cells has been reported in the bone marrow of patients with JCA but also occurs in patients with FUO. Bone marrow examination may not always be diagnostic of a leukaemia at presentation and may need to be repeated.

**Radiographic features**

Careful examination of radiographs may reveal lesions characteristic of leukaemia (osteopaenia, lytic lesions, metaphyseal rarefaction and periosteal lesions). Chest radiographs may reveal asymptomatic pleuritis or an increased cardiac shadow indicating possible pericarditis or myocarditis. Scanning procedures such as abdominal and pelvic USS, abdominal computed tomography, radioisotope bone scanning, indium and gallium scanning may be helpful to exclude alternative diagnoses but rarely lead to an unsuspected diagnosis in cases of FUO. Rheumatoid arthritis has been reported to be a cause of false positive indium-labelled polymorphonuclear leucocyte scans.

**Summary**

We have described a child with systemic onset juvenile chronic arthritis who presented...
initially with fever of unknown origin. Treatment of a presumed infection led to a severe allergic response with Stevens-Johnson syndrome and cardiac failure and DIC. This reaction obscured the features of the underlying disease and delayed the diagnosis.

Key points
- Systemic onset juvenile chronic arthritis often presents with fever of unknown origin.
- Arthritis may be absent at presentation.
- Thorough and repeated examination for the typical rash and careful temperature charting may aid diagnosis.
- A wide variety of alternative diagnoses may need to be considered in the absence of typical features.

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