PYREXIA OF UNKNOWN ORIGIN

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One week after receiving the measles, mumps, and rubella (MMR) immunisation, 14 month old Kate developed a non-pruritic "blotchy" erythematous macular rash. The rash was present over the proximal areas of her arms and legs and was most noticeable during the afternoon. Initially she remained otherwise well, but six days later developed coryzal symptoms and lethargy.

Kate's general practitioner (GP) was consulted. There was no significant past medical or family history. She was taking no regular medication and had no known allergies. On examination, apart from the rash and a pink throat, she appeared normal. He prescribed a course of amoxicillin.

The GP thought that a viral upper respiratory tract infection was the most likely diagnosis but nevertheless prescribed amoxicillin just in case the rash was caused by a bacterial infection. He also considered the possibility of a reaction to the MMR immunisation, but thought this was unlikely in view of the long history.

COMMENT

- About one week after the first dose of an MMR immunisation it is common to have symptoms of malaise, fever, and a rash, usually lasting 2–3 days. There is also an increased frequency of febrile convulsions at this time. These effects are likely to relate to the measles component and are less common after the second MMR immunisation.[1]

The next day Kate developed fever and diarrhoea (without blood or mucus). She also became unsettled and more lethargic. The intermittent fever and rash continued. Her mother and grandmother also developed diarrhoea. The GP was again consulted and a referral was made to the local hospital paediatric unit.

In view of the history of diarrhoea in family contacts, the GP considered the most likely diagnosis to be infectious gastroenteritis rather than a side effect of the amoxicillin. He was particularly concerned because Kate looked unwell.

On admission to hospital Kate's axillary temperature was 38.7°C and a maculopapular rash was noted (fig 1). The senior house officer assessed Kate and noted a pink throat but no other signs to indicate a focus of infection. Kate was well perfused with no signs of meningitis, but was crying inconsolably at times. There was no hepatosplenomegaly or lymphadenopathy. Examination was otherwise normal. Initial investigations were arranged (table 1).

The senior house officer was concerned about the unexplained fever, rash, neutrophilia, and raised C reactive protein (CRP) and so discussed Kate with the registrar on call. They agreed to start intravenous cefotaxime as broad spectrum cover for a possible invasive bacterial infection.

COMMENT

- In young children intravenous antibiotics should be started promptly if invasive bacterial disease (such as meningitis or septicaemia) is suspected to minimise the risk of serious complications. Without a clear diagnosis, the organisms that need to be covered include *Neisseria meningitides*, *Escherichia coli*, *Streptococcus pneumoniae*, and *Haemophilus influenza* type b. These are usually all sensitive to cefotaxime.

On the paediatric ward observations every four hours did not suggest any circulatory compromise and it was noted that Kate looked well when apyrexial. The following day the consultant paediatrician reviewed her on the ward round. At that time he found Kate to be apyrexial with no rash.

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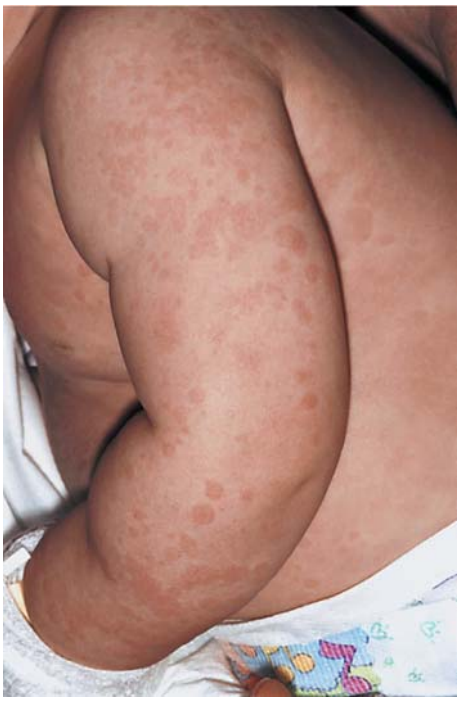

Figure 1 The maculopapular rash that affected the arms and legs but not the face. Reproduced with permission of the child's parents.

After reviewing the history, examination and investigation results a viral illness was thought to be the most likely diagnosis, but it was decided to continue the cefotaxime pending receipt of microbiology results due 48 hours after admission.

Later that day Kate had further "spikes" of temperature to over 38°C. These were associated with a pronounced rash over her inner thighs and arms, with sparing of her face. When pyrexial she looked unwell with anorexia and lethargy, and inconsolable crying. However, when apyrexial she looked brighter and the rash became faint.

On the morning ward round three days after admission Kate continued to have spikes of fever and appeared uncomfortable. The blood culture was negative and no pathogenic organisms had been grown from the stool specimen and throat swab. Further investigations were ordered: chest *x* ray (normal), lumbar puncture (normal cerebrospinal fluid (CSF) results), CRP (94 mg/l), white cell count (17 × 10^9/l; neutrophil count 12 × 10^9/l), stool for viral culture, repeat stool for microscopy and bacterial culture, blood for anti-streptolysin titre (ASOT), and serology for Epstein-Barr virus (EBV) and enterovirus. Cefotaxime was continued.

Table 1 Initial investigations

Haemoglobin	11.5 g/dl
Platelet count	545×10^9/l
White cell count	23.3×10^9/l
Neutrophil count	17.2×10^9/l
C reactive protein (CRP)	90 mg/l
Urea and electrolytes	Normal
Liver function tests	Normal
Erythrocyte sedimentation rate (ESR)	52 mm/hour
Urine microscopy and analysis	Normal
Throat swab for bacterial culture	Sent
Blood culture for bacteria	Sent
Stool microscopy and bacterial culture	Sent

The consultant paediatrician still considered a viral illness to be the most likely diagnosis, but in view of the prolonged pyrexia, rash, and history of irritability he wanted to exclude other infections. He knew that meningitis and pneumonia can be difficult to diagnose by clinical examination alone in a young child. At the same time he was reassured that some of the time Kate looked well and by the fact that the CRP and white cell count had not risen. He decided that continued observation was the best course of action.

Six days after admission no specific infection or other cause of the illness had yet been identified. Kate continued to have spikes of fever (fig 2) and diarrhoea. The opinion of a consultant in paediatric infectious diseases and immunology was requested.

This consultant reviewed the history including details of immunisations, travel, pets, parents' occupations, family, and any contact with infectious diseases. The irritability, diarrhoea (improving) and temperature chart were noted. On examination (while she was apyrexial and looking well) he noted the very faint generalised erythematous macular rash. There was no hepatosplenomegaly or lymphadenopathy and no heart murmur. Areas of mild skin peeling were noted on the right side of Kate's neck, right thumb and the tips of her left fingers.

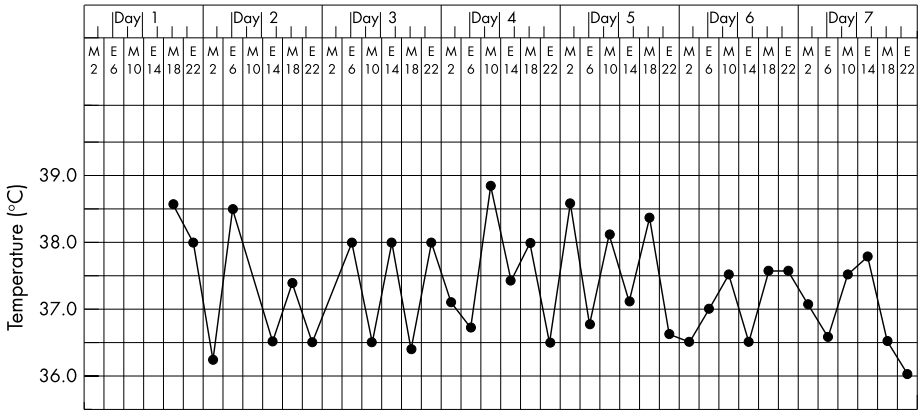

Figure 2 Temperature chart.

Table 2 Differential diagnoses considered and the investigations requested

Diagnosis	Relevant investigation
Incomplete Kawasaki disease	Echocardiogram Electrocardiogram Abdominal ultrasound
Systemic onset juvenile idiopathic arthritis	Serum ferritin concentration
Systemic lupus erythematosus	Autoantibody screen
Leukaemia	Blood film
Inflammatory bowel disease	White cell scan
Neuroblastoma	Abdominal ultrasound Urine catecholamines
Abscess, localised infection	White cell scan Abdominal ultrasound

The consultant reviewed the results and noted the raised erythrocyte sedimentation rate (ESR), mildly raised CRP, and thrombocytosis with no evidence as yet of any infectious organisms. He advised that the cefotaxime could be stopped since there was now little evidence of a bacterial infection.

He could not make a firm diagnosis, but drew up a list of possible causes and relevant investigations designed to distinguish between them (table 2). The clinical features were unchanged during the next 48 hours. These results were normal except for a serum ferritin concentration of 762 µg/l (normal < 40 µg/l).

The most likely diagnosis was thought to be either incomplete Kawasaki disease or systemic onset juvenile idiopathic arthritis (SOJIA). The pros and cons of each possibility were considered (table 3) and on balance it was thought that incomplete Kawasaki disease was the most likely.

COMMENT

- A raised serum ferritin concentration is a non-specific finding in several conditions (table 4). A concentration > 1000 µg/l is unusual and may indicate haemophagocytic syndromes, SOJIA, haemochromatosis, liver disorders, and malignancy. A normal serum ferritin concentration would make SOJIA very unlikely.

Oral aspirin (100 mg/kg/day in four doses) was started and Kate received immunosuppressive intravenous immunoglobulin (IVIG) at a dose of 2 g/kg eight days after admission. Counselling was given regarding the risks associated with IVIG and consent to treatment obtained. Blood was taken for storage before IVIG was administered in case future testing was necessary.

COMMENT

- IVIG is a blood derived product and, despite stringent testing of donors and the product, there remains a very small risk of transmitting blood borne viruses. The patient's family should also be aware of the theoretical risk of contracting blood borne infections that may, as yet, be unrecognised.
- For several months after the administration of IVIG serology testing of the patient will be altered by the treatment.

During the next five days spikes of temperature over 38.5°C continued, usually in the evenings.

The consultant knew this was unusual for Kawasaki disease and so reviewed the evidence in the literature to see if any particular treatment would be more appropriate. He found a retrospective study in which over 85% of children treated with IVIG within 10 days of onset of symptoms of Kawasaki disease remained pyrexial 48 hours after treatment started.[2] He found anecdotal reports of re-treatment with IVIG and pulses of steroid, but also read a recent review that stated that no comparative trials have been reported.[3] He decided to repeat the IVIG.

The IVIG (2 g/kg) was repeated 15 days after admission. The next day Kate was brighter and for the first time since admission she remained apyrexial for 12 hours. However, on day 17 the spikes of fever and rash returned.

The diagnosis of incomplete Kawasaki disease was still thought to be the most likely, but there was concern that occult malignancy may have been missed. A bone marrow aspirate was therefore arranged which was normal. In view of the poor response to the second dose of IVIG, it was decided to commence corticosteroids.

COMMENT

- A bone marrow aspirate should be considered in the investigation of pyrexia of unknown origin (PUO) even if the peripheral blood film is normal, especially before

Table 3 Evidence considered in the differential diagnosis

	Factors for this diagnosis	Factors against this diagnosis
Incomplete Kawasaki disease	Prolonged pyrexia Rash Peeling Irritability Thrombocytosis Raised inflammatory markers	No cervical lymphadenopathy No conjunctivitis No mouth involvement Peeling usually later
Systemic onset juvenile idiopathic arthritis	Pyrexia Irritability Rash Raised ferritin Thrombocytosis Raised inflammatory markers	No joint involvement detected No splenomegaly

corticosteroids are given as this treatment can mask leukaemia.

Kate received intravenous methylprednisolone (IVMP) infusions of 30 mg/kg/day for three days starting on day 19. Her fever and rash rapidly subsided, she became more comfortable, and her inflammatory markers fell. The aspirin dose was reduced to 5 mg/kg/day.

Unfortunately her symptoms flared again five days later causing great anxiety to her parents who could see no end to the problems. Further IVMP pulses over three consecutive days were given and produced symptomatic relief. However, after a further five days the pyrexia returned.

Options considered at this time were to give further IVMP pulses or to start oral corticosteroids. In view of difficulties with venous access and the lack of a sustained response, the latter option was taken.

Oral prednisolone was started (35 days after admission) at 2 mg/kg/once a day. On day 38 Kate refused to weight bear and her parents noted an intermittent swelling of her hands and feet. Examination revealed synovitis of the right wrist, both ankles and the first, second, and third proximal interphalangeal joints of the right hand. At this point she was referred to a paediatric rheumatologist.

The paediatric rheumatologist considered the following salient clinical features:

- The chronic nature (six weeks) of the systemic symptoms and the timing of onset of arthritis was not typical of Kawasaki disease, in which any arthritis usually occurs in the acute phase.
- The temperature pattern with a return to the baseline in between "spikes" of fever occurring on a daily basis (quotidian pattern) is typical of SOJIA.
- The rash was more pronounced when she was pyrexial and was more evident on her inner thighs and arms and spared her face. This pattern is more typical of SOJIA than Kawasaki disease.
- The raised serum ferritin concentration, neutrophil leucocytosis, absence of autoantibodies, and the lack of evidence suggesting an infection or malignancy were all consistent with a diagnosis of SOJIA.

A diagnosis of SOJIA was made and Kate was continued on the prednisolone and started on regular ibuprofen (40 mg/kg/day in divided doses). From day 40 she became more comfortable and less miserable, with an improvement in inflammatory markers including serum ferritin (fig 3).

Kate was referred to the paediatric rheumatology multidisciplinary team (physiotherapy, occupational therapy and a clinical nurse specialist), which provided a programme of physical therapy and support for her and her family. She was examined for uveitis by a paediatric ophthalmologist and this was normal. No IgG to varicella was detected in the serum saved since before the IVIG and therefore advice was given regarding the need for intravenous aciclovir should spots develop after chickenpox exposure.

An echocardiography (planned when the working diagnosis was Kawasaki disease) was performed eight weeks after initial admission and was normal (no coronary artery aneurysms). By this time she had developed mild Cushingoid features but no glycosuria or hypertension.

Kate remained on prednisolone (1 mg/kg on alternate days) and received regular ibuprofen. Oral methotrexate (steroid sparing agent) and folic acid were prescribed three months after the original admission. Chickenpox vaccination was considered but not given since the level of immunosuppression was likely to interfere with the response. Regular blood tests (full blood count, inflammatory markers and liver function tests) were arranged to monitor for efficacy and features of methotrexate toxicity.

SUBSEQUENT PROGRESS

The arthritis and systemic symptoms were well controlled on the prednisolone and methotrexate. Corticosteroids were gradually tapered and stopped over six months. Kate was unable to tolerate methotrexate by mouth because of nausea so this was changed to the subcutaneous route. This was well tolerated and improved the control of her disease, with the return of her inflammatory markers (including serum ferritin) to normal values. Liver function tests and neutrophil counts remained normal throughout.

Over the subsequent two years Kate had three flares of systemic symptoms which were controlled with IVMP pulses and tapering doses of oral steroids. Her joints have shown little evidence of active arthritis. She attends a playgroup where she joins in activities with her peers. Her parents understand that she has a rare form of JIA with a variable prognosis and requires long term follow up.

PYREXIA OF UNKNOWN ORIGIN (PUO)

There is controversy regarding diagnostic criteria for PUO.[4–6] Essentially this is a term for a prolonged (more than one week) pyrexial illness when the history, examination and all

Table 4 Common causes of a raised serum ferritin concentration

- Liver disease
- Infections
- Malignancy
- Active systemic onset juvenile idiopathic arthritis
- Systemic lupus erythematosis
- Kawasaki disease
- Haemophagocytic lymphocytosis
- Haemochromatosis

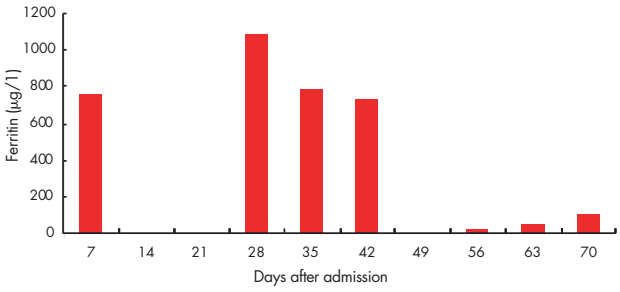

Figure 3 Serum ferritin concentrations.

Table 5 Suggested "standard investigations" to be performed before the situation is regarded as a PUO

- Full blood count
- Urea and electrolytes
- Liver function tests
- Inflammatory markers: CRP, ESR
- Blood cultures when pyrexial
- Anti-streptolysin titre
- Viral serology including Epstein-Barr virus
- Throat swab: culture for viruses and bacteria
- Chest *x* ray
- Urinalysis and urine microscopy and culture
- Stool for microscopy and culture for bacteria and viruses
- Three thick blood films if malaria is a possibility

CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

"standard investigations" (table 5) fail to indicate the diagnosis. The history needs to include details of immunisations, travel, pets, occupations of family members, family contact with infectious diseases and, if appropriate, sexual history. A list of the common and rare causes of PUO and their relevant clinical features and discriminatory investigations are shown in table 6.

KAWASAKI DISEASE

Kawasaki disease is an important cause of cardiovascular morbidity and mortality both in the acute phase (myocarditis or pericarditis) and long term (thrombosis of coronary artery aneurysms and atherosclerosis). Management with high dose aspirin and immunosuppressive IVIG reduces the incidence of cardiac complications if given within 10 days of the onset and probably if given later.[7] The diagnosis of Kawasaki disease is made when the described criteria[8] are met (table 7). The pyrexia is generally unremitting (that is, not returning to the baseline) and rarely lasts more than 15 days. Characteristic features usually occur from the third day of illness. Other features can include diarrhoea, sterile pyuria, arthritis, uveitis, aseptic meningitis, hepatitis, and hydrops of the gall bladder. Children are typically miserable. Acute phase reactants are raised as is the ESR, and typically there is a neutrophil leucocytosis and thrombocytosis. An

Table 6 Causes of pyrexia of unknown origin

Diagnosis	Suggestive features*	Useful investigations
Localised bacterial infections		
Abscess	Localising symptoms	Imaging, white cell scan
Endocarditis	New murmur, haematuria	Repeated blood cultures, echocardiogram
Mastoiditis	Localised tenderness	CT scan with contrast
Osteomyelitis	Localising symptoms	Bone scan, MRI
Septic arthritis	Localising symptoms	Joint ultrasound, joint aspiration
Sinusitis	Local pain	CT scan with contrast
Other infections		
Brucellosis	Hepatosplenomegaly, farming community	Prolonged culture of blood + urine, serology (*Brucella* spp)
Campylobacter	Diarrhoea	Stool microscopy and culture
Cat scratch disease	Lymphadenopathy, cat scratch	Lymph node biopsy, serology (Bartonella)
EBV	Lymphadenopathy	EBV IgM rise, EBV by PCR testing
Enterovirus	Rash	Stool viral culture, serology
Hepatitis	Jaundice, tenderness over liver	Serology
Leptospirosis	Farming, headache, myalgia, then jaundice	Serology (*Leptospira interrogans*)
Lyme disease	Rash, possibility of tick bite	Serology (*Borrelia burgdorferi*)
Malaria	Travel to endemic area	Blood film
Salmonella	Diarrhoea	Culture of stool, urine and blood
Shigella	Diarrhoea	Culture of stool
Tuberculosis	Contact history or residence in an endemic area	Tuberculin test, LDH
Yersinia	Diarrhoea	Culture stool and blood, serology
Post-infectious		
Acute rheumatic fever	Recent pharyngitis, Ducket Jones criteria	Throat swab, ASOT, Anti-DNAase B, ECG
Post-streptococcal reactive arthritis	Recent pharyngitis, arthritis	Throat swab, ASOT, Anti-DNAase B
Reiter syndrome	Urethritis, arthritis, and conjunctivitis	Culture of stool, HLA type (B27 predisposes)
Malignancy		
Hodgkin disease	Lymphadenopathy, weight loss, night sweats	Lymph node biopsy
Leukaemia	Splenomegaly, anaemia, thrombocytopenia	Blood film, bone marrow examination
Lymphoma	Lymphadenopathy	Lymph node biopsy, LDH
Neuroblastoma	Local mass, anaemia	Urine catecholamines, US of any mass
Wilms tumour	Abdominal pain and mass, haematuria	Abdominal/renal ultrasound
Connective tissue diseases		
Bechet's disease	Oral and genital ulcers, conjunctivitis	
Henoch-Schonlein purpura	Typical rash, haematuria, arthritis	
Juvenile dermatomyositis	Typical rash, muscle weakness	Creatinine kinase
Polyarteritis nodosa	Rash, joint involvement	Biopsy, renal angiography
Sarcoidosis	Arthritis, uveitis	ACE, biopsy of affected area if possible
Systemic lupus erythematosus	Typical rash, renal involvement	Anti ds DNA antibodies, renal biopsy
Systemic onset JIA	Arthritis, typical rash with fever, miserable	Ferritin
Wegener's granulomatosis	Respiratory tract involvement, renal failure	Biopsy, ANCA autoantibodies
Miscellaneous		
Drug induced fever	Suggestive drug history	Stop suspected drug
Factitious	Not present in hospital	Careful observation in different settings
Inflammatory bowel disease	Diarrhoea, weight loss	White cell scan
Kawasaki disease	Rash, peeling palms, cracked lips	Echocardiogram, US gall bladder
Periodic fever syndromes	Chronic episodic fever	Serial FBC, family history
Thyrotoxicosis	Weight loss, tremor, sweating, tachycardia	Thyroid function tests, thyroid autoantibodies

*"Suggestive features" may not be present
ACE, angiotensin converting enzyme; ANCA, antineutrophil cytoplasmic antibody; ASOT, anti-streptolysin titre; CT, computed tomography; EBV, Epstein-Barr virus; FBC, full blood count; LDH, lactate dehydrogenase; JIA, juvenile idiopathic arthritis; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; US, ultrasound.

Table 7 Diagnostic criteria for Kawasaki disease

The child must have a daily spiking high temperature for at least five days, with four out of the following five features:

- Bulbar conjunctival injection without exudates
- Changes in the oral mucosa including red cracked lips, red mouth and throat, and strawberry tongue
- Erythema and swelling of the hands and feet with subsequent peeling usually after three weeks
- Generalised erythematous rash especially on the trunk
- Cervical lymphadenopathy

echocardiogram in the acute phase can show evidence of myocarditis or pericarditis, which can cause heart failure or arrhythmias. Cardiac aneurysms take longer to develop and echocardiography should be performed at three weeks and repeated at 8–12 weeks after the onset of illness.

Over recent years it has been recognised that cardiac complications can also occur after illnesses that do not fulfil the prerequisite number of criteria. This is termed ''incomplete Kawasaki disease'' and it has been shown that immunosuppressive IVIG and high dose aspirin, given in the same regimen as for classical Kawasaki disease,[9] can reduce associated cardiovascular morbidity and mortality. Features most commonly occurring in incomplete Kawasaki disease (other than the classical criteria) are irritability, diarrhoea, sterile pyuria, and coryzal symptoms.[10]

JUVENILE IDIOPATHIC ARTHRITIS

Classification

Chronic arthritis in children is a heterogeneous group of diseases of mainly unknown aetiology. They are mainly clinically and genetically distinct from causes of chronic arthritis in adults. The latest classification uses the unifying term juvenile idiopathic arthritis (JIA) to describe arthritis of no known cause which persists for at least six weeks in a child under 16 years old.[11 12] This replaces the old terms ''juvenile chronic arthritis'' and ''juvenile rheumatoid arthritis''.

The classification lists the following seven subtypes:

- Oligoarticular onset JIA (persistent or extended)—Arthritis affecting up to four joints during the first six months of disease. If subsequently more than four joints are affected the term ''extended oligoarthritis'' is used, otherwise the term ''persistent oligoarthritis'' is used. This is the most common pattern (50% of all JIA) and usually involves large joints of the lower limbs, especially knees. These children have the best prognosis but are at high risk of asymptomatic uveitis and therefore must be screened regularly.
- Polyarthritis (rheumatoid factor negative)—Arthritis affecting five or more joints during the first six months. If IgM rheumatoid factor is not detected in blood then the child's disease falls in this group, which makes up 17% of all JIA. Severity is very variable.
- Polyarthritis (rheumatoid factor positive)—This subtype accounts for 7% of cases and is characterised by a symmetrical polyarthritis, nodules, and IgM rheumatoid factor being identified at least twice three months apart. Patients are typically adolescent girls and the prognosis is guarded as early joint damage often occurs.
- Systemic onset—SOJIA accounts for 11% of cases of JIA. It can occur at any age and often affects pre-school children but rarely in infancy. Similar incidence rates are seen in males and females.
- Enthesitis related arthritis—This term is used for arthritis and enthesitis (inflammation of tendon insertions). The group also includes arthritis or enthesitis with at least two of:
  - tenderness of the sacroiliac joint and/ or inflammatory spinal pain
  - HLA B27
  - family history in a first or second degree relative of HLA B27 related disease
  - anterior uveitis (usually symptomatic with redness, pain and blurred vision)
  - arthritis after 8 years of age in a boy (usually affecting large lower limb joints.

The distal large joints in the lower limbs are commonly affected with an asymmetrical presentation and there is a high risk of these patients developing ankylosing spondylitis in early adulthood.

- Psoriatic arthritis—Children with psoriasis and arthritis. This group also includes children with arthritis or psoriasis and at least two of:
  - dactylitis
  - pitting or onycholysis of nails
  - psoriasis in a first degree relative
- Other arthritis—This group is for children with idiopathic arthritis that does not fit the other groups.

Systemic onset juvenile idiopathic arthritis

The main features of SOJIA are summarised in table 8. Patients can be systemically very unwell and potentially life threatening complications may occur early in the disease course (for example, pericarditis, macrophage activation syndrome, sepsis). Prompt treatment with high dose corticosteroids can therefore be life saving. The decision to start immunosuppressive treatment has to be made after careful exclusion of other diagnoses, especially infection, Kawasaki disease, and malignancy, and is particularly difficult when definite evidence of arthritis is absent.

Systemic features may predate the arthritis by several weeks and occasionally longer. The arthritis typically involves the small joints of the hands and wrists, ankles, hips, knees, and cervical spine and about a third of children ultimately develop a severe polyarthritis. The physical signs of arthritis may be masked by corticosteroids given for acute systemic features (for example, carditis) and are often overlooked in the initial assessment. Musculoskeletal assessment does not have a high profile in undergraduate or postgraduate teaching and many paediatricians lack confidence in their ability to perform a competent musculoskeletal assessment.[13]

Table 8 Key features of systemic onset juvenile idiopathic arthritis (SOJIA)

- Prolonged pyrexia
- Intermittent characteristic rash
- Raised CRP, ESR, ferritin
- Leucocytosis (neutrophilia)
- Thrombocytosis
- Arthritis
- Hepatosplenomegaly
- Generalised lymphadenopathy
- Pericarditis

There are no pathognomic tests or agreed diagnostic criteria for SOJIA and so it remains a diagnosis based on the identification of recognised features and exclusion of other conditions. As in Kate's case, the initial differential diagnosis may be wide and there can be a delay of several weeks before the diagnosis is established. However, repeated careful examination of the temperature chart is helpful, especially in the early stages when arthritis is absent. The presence of a recurring evening spiking temperature, that returns to or falls below baseline in between spikes, is classical for SOJIA. Pyrexial episodes are also the most fruitful times for eliciting the rash, which is erythematous and maculopapular, often asymptomatic, and typically spares the face and extremities and can therefore be easily missed. The rash is typically on the inner thigh and arms, especially on areas of trauma or pressure (Koebner phenomenon). In the assessment of PUO, nursing staff and paediatricians must be encouraged to examine the undressed child when pyrexial. A photograph of the rash can be very useful as it may be transient.

Management of JIA

JIA is a not a benign disease and outcome is variable.[14] At least a third of patients have ongoing active disease into adulthood and many have sequelae of the disease or treatment—for example, joint damage requiring joint replacement, short stature from chronic disease compounded by steroid toxicity, localised growth problems (micrognathia or leg length inequality), visual loss from uveitis, and psychosocial morbidity with high unemployment. Optimal management requires early intervention by an experienced and coordinated multidisciplinary team. This should include input from a nurse specialist, physiotherapist, occupational therapist, paediatric rheumatologist, ophthalmologist, clinical psychologist, social worker, dentist, orthodontist, and orthopaedic surgeon. Transitional care for the adolescent and young adult needs to be well coordinated.

Corticosteroids are important agents, although there is increasing concern regarding their side effects including growth retardation, osteoporosis, and cataracts. Therefore exposure to systemic corticosteroids is minimised where possible by increasing use of intra-articular steroids and early use of DMARDs—disease modifying anti-rheumatic drugs (especially methotrexate). Calcium and vitamin D supplements are often given to children receiving corticosteroid treatment. Intra-articular corticosteroids (triamcinolone hexacetonide/acetonide) are usually given under sedation or general anaesthetic in young children or with entonox in older children. Joint injections with corticosteroid are a highly effective treatment, appear to be very safe, and increasingly multiple joints are injected at one session with ultrasound imaging used to deliver the drug more accurately to relatively inaccessible joints.

Intravenous methylprednisolone is used for severe polyarthritis or active SOJIA and is very useful as a disease remitting agent while starting methotrexate treatment which can take several months to be effective.

Methotrexate is the disease modifying drug of choice and there is evidence that early use helps to reduce joint damage and minimise the exposure to, and side effects of, corticosteroids. Long term studies show that methotrexate is beneficial and well tolerated in most children with side effects generally limited to occasional nausea, mild (reversible) elevations of serum liver enzymes, and mild bone marrow suppression. Doses up to and even beyond 1 mg/kg (30 mg/m^2) are used with very few reports of complications. The theoretical risk of malignancy and infertility has not so far been borne out in long term outcome studies. Folic acid supplementation is usually given and improves tolerability. Methotrexate is given once a week and increasingly by the subcutaneous route to improve bioavailability. Regular blood tests are needed to monitor for efficacy and side effects. Live vaccines should be avoided and in the non-immune patient intravenous aciclovir should be administered promptly at the first sign of chickenpox.

Patients who are refractory to high dose parenteral methotrexate are considered for novel immunosuppressive agents such as biologics (for example, soluble anti-TNF α receptor etanercept), autologous stem cell transplantation, or very high dose immunosuppression.

CLINICAL MESSAGE

- SOJIA should be considered as a cause of PUO
- Arthritis can be minimal or even absent initially (and for several weeks) in SOJIA
- Persistent pyrexia returning to baseline is suggestive of SOJIA
- A rash that is more pronounced when pyrexial is typical of SOJIA
- Involvement of a paediatric rheumatologist in the investigation of a PUO is recommended

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