Paediatric rheumatology more than just arthritis

Awareness of the symptoms and signs of paediatric rheumatological conditions is important for the primary care physician to allow an early diagnosis and prompt therapy of affected children.

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Childhood arthritis affects an estimated one in 1000 children below the age of 16 years. Paediatric rheumatologists not only treat children with arthritis but are also pivotal to the care of children with other less prevalent but often life-threatening diseases. These conditions include juvenile dermatomyositis, juvenile systemic lupus erythematosus (SLE), periodic fever syndromes and a number of vasculitides. Some of these conditions mirror adult disease patterns quite closely, whereas others have a very different disease course and management approach. Early diagnosis and appropriate specialist treatment is critical to the outcome of children with these conditions. Thus primary care physicians who are often the first point of presentation for symptomatic children need to be aware of these diseases in childhood and have a working understanding of their symptoms and physical findings to facilitate early diagnosis and effective shared care in the longer term.

This article briefly outlines the characteristics of a number of important paediatric rheumatological conditions other than juvenile idiopathic arthritis, which will be covered in a forthcoming article in *Medicine Today*.

Juvenile dermatomyositis

Juvenile dermatomyositis is the most common chronic inflammatory myopathy of childhood. It has an incidence of three per million children per year. The disease is characterised by the following:

- proximal muscle weakness
- violaceous rash over the eyelids (Figure 1) and extensor surfaces of the elbows, fingers and knees (Figure 2), which may sometimes be mistaken for psoriasis
- presence of Gottron's papules (Figure 2)
- nail fold capillary abnormalities (Figure 3)
- raised levels of muscle enzymes (creatine kinase, aspartate aminotransferase, lactate dehydrogenase and aldolase)
- changes in MRI consistent with myositis in proximal muscles (Figure 4).

Electromyography and muscle biopsy are occasionally required for diagnosis in some cases.

IN SUMMARY

- **An awareness of the signs and symptoms of the rarer rheumatological conditions of childhood is important.**
- **Early diagnosis and specific therapy have been shown to improve outcomes of children with these conditions.**
- **Symptoms are often nonspecific, especially in patients with systemic lupus erythematosus, and diagnosis depends on careful history taking and examination.**
- **Kawasaki disease should be considered in children with fever persisting for more than five days or in those displaying the typical clinical characteristics.**
- **Patients with symptoms or signs suggestive of these rheumatological conditions should be referred for assessment by a paediatric rheumatologist or paediatrician.**

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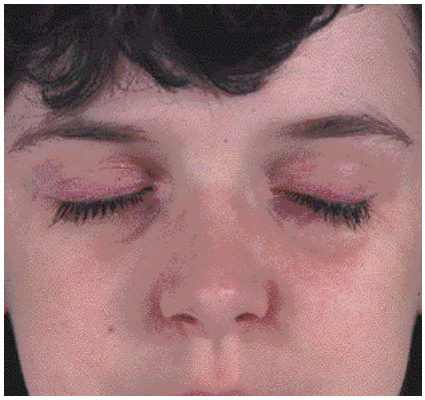

Figure 1. Typical violaceous rash of juvenile dermatomyositis involving the eyelids and periocular areas.

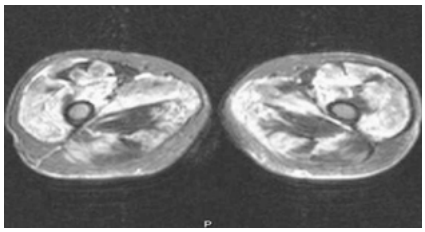

Figure 4. MRI scan of the proximal thighs of a patient with juvenile dermatomyositis showing patchy areas of bright signal through the muscles indicating the presence of extensive myositis.

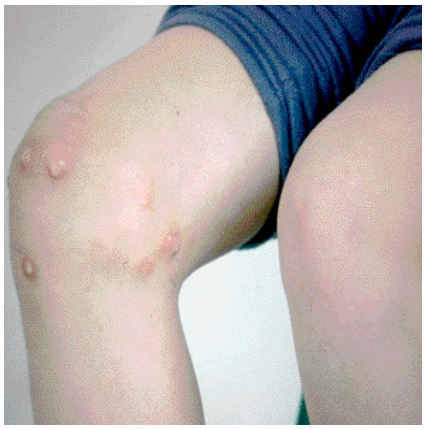

Figure 5. Areas of nodular subcutaneous calcinosis over the knee with some overlying skin erythema, skin breakdown and areas of calcium extrusion as a complication of juvenile dermatomyositis.

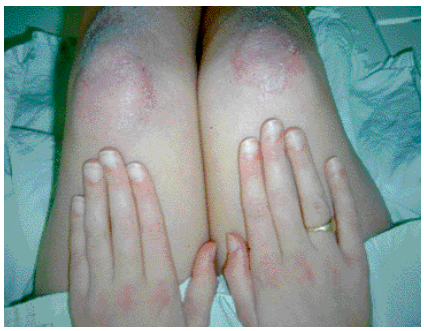

Figure 2. Involvement of the skin overlying the extensor surfaces of the knees and small joints of the hands with the rash of juvenile dermatomyositis. Also visible are small shiny areas of skin overlying the interphalangeal joints, which are atrophic and called Gottron's papules.

Clinically, the rash is often the first clue to the diagnosis and may resemble eczema or psoriasis. Muscle weakness tends to be more slowly progressive and is frequently well compensated for by children who adapt or stop engaging in difficult activities such as sports. Proximal muscle weakness may be apparent on history taking if there is difficulty in activities such as climbing stairs, getting out of bed or standing from the sitting position.

Complications of juvenile dermatomyositis include respiratory compromise due to muscle weakness, pulmonary vasculitis, swallowing difficulties due to bulbar muscle involvement, gastrointestinal vasculitis, bowel perforation, and, in the longer term, subcutaneous tissue calcification (Figure 5). Unlike the case in adults, dermatomyositis in children is not associated with malignancy.

Early diagnosis is critical in preventing complications. Treatment is with high-dose corticosteroids and immunosuppressive agents.

Juvenile SLE

Juvenile SLE, similar to its adult counterpart, is a multisystem autoimmune disease with a female predominance. The incidence in childhood is around one to

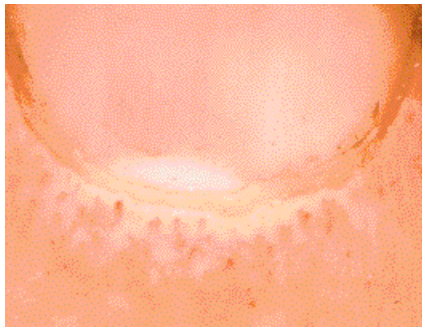

Figure 3. Nail fold capillary changes of juvenile dermatomyositis showing prominent dilated blood vessels with areas of tortuosity and capillary drop out.

three in 10,000 per year, with the median age at diagnosis of approximately 12 years and the median time to diagnosis around four months from the onset of symptoms. Juvenile SLE has a distinct ethnic distribution with a higher prevalence in those of African, Asian and Indian subcontinent backgrounds. The classification criteria for juvenile SLE are shown in the Table and reflect the truly multisystem nature of the disease.

Patients with juvenile SLE frequently present with constitutional symptoms of fever, fatigue and weight loss. They are often diagnosed with nonspecific viral infections or a postviral syndrome to explain the prolonged duration of symptoms. The finding of the classic malar or 'butterfly' rash often prompts the clinician to consider juvenile SLE as a diagnosis (Figure 6). However, when this rash is present the patient will often manifest other symptoms or signs that confirm the diagnosis of juvenile SLE. These include arthritis that is painful and often polyarticular, painless palatal ulceration (Figure 7), and cutaneous vasculitis especially evident on the fingers and toes (Figure 8). These signs are often present early in the disease course.

Some patients will present with more dramatic symptoms, including severe haemolytic anaemia, immune thrombocytopenic purpura, severe

neuropsychological presentations such as psychosis, stroke, transverse myelitis or acute renal failure. Patients, especially adolescent girls, with any of the above presentations should have juvenile SLE included in their differential diagnosis.

Laboratory investigation is an important part of diagnosis and ongoing management. Antinuclear antibodies (ANA) are almost always present in high titre and anti-double stranded DNA antibodies (anti-dsDNA) are highly specific for the diagnosis. Other haematological abnormalities such as lymphopenia and thrombocytopenia are common and patients will often have depressed complement levels (C3 and C4) and positive antiphospholipid antibodies.

Ten-year survival rates for juvenile SLE are approximately 86%, with mortality related to severe renal and neuropsychiatric disease. Deaths are a result of ongoing disease activity, infection related to generalised immune dysfunction or a complication of immunosuppressive therapy. In the longer term, patients with juvenile SLE are at significantly increased risk of cardiovascular disease and this is a major source of mortality and morbidity. Therefore, other cardiovascular risk factors such as elevated serum lipids and cigarette smoking need to be avoided.

There have been significant improvements in the long-term outcomes for children with juvenile SLE with the advent of specialised care and advanced treatment modalities; however, early referral and treatment remains critical.

Treatment involves the use of high-dose corticosteroids initially and in most cases this is combined with a second immunosuppressive agent such as azathioprine or mycophenolate. Care must be taken in patients treated with long-term corticosteroids to ensure adequate dietary calcium and vitamin D intake to avoid the complication of steroid-induced osteopenia; many patients will require supplementation.

Hydroxychloroquine is also used frequently in the management of articular or cutaneous manifestations and has been shown to favourably improve serum lipids levels. Very careful ongoing follow up to monitor disease activity and complications of therapy is essential in these children.

Neonatal lupus erythematosus

Neonatal lupus erythematosus is a very rare condition caused by transplacental transfer of maternal anti-Ro (SSA) and anti-La (SSB) autoantibodies. It may occur in mothers with known autoimmune disease but is more common in asymptomatic mothers. Disease occurs in less than 1% of fetuses of mothers with positive autoantibodies.

The most serious complication of neonatal lupus erythematosus is damage to the neonatal developing cardiac conduction system and fetal heart block, which may cause permanent heart block. Heart block is usually identified during routine antenatal care. It can be treated with antenatal maternal corticosteroids but with quite poor success meaning that damage to the neonatal conduction system is often permanent requiring pacemaker insertion soon after delivery.

Other manifestations of neonatal lupus erythematosus include a characteristic rash that appears between 2 and 6 months of age (Figure 9), transaminitis and thrombocytopenia. In the longer term, communicating hydrocephalus occurs in

Table. Classification criteria for juvenile SLE*[1]

Criteria	Manifestation	Frequency (%)
Malar rash	'Butterfly' facial rash	30–80
Discoid rash	Erythematous patches	5–10
Photosensitivity	Rash as a result of sun exposure	35–50
Oral ulcers	Usually palatal and painless	10–30
Arthritis	Nonerosive	60–90
Serositis	Pleuritis	25–75
	Pericarditis	15–25
Renal	Active sediment or proteinuria	50–80
Neurologic	Seizures, psychosis	5–30
Haematologic	Haemolytic anaemia	30–40
	Leucopenia (<4.0 x 10^9/L)	50–75
	Lymphopenia (<1.5 x 10^9/L)	50–75
	Thrombocytopenia (100 x 10^9/L)	50–75
Immunologic	Anti-dsDNA antibodies	60–70
	Anti-Sm antibodies	40–50
	False positive venereal disease research laboratory test	–
	Positive lupus erythematosus cell preparation	–
Antinuclear antibody		100

* The classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person is said to have SLE if any four of the 11 criteria are present, serially or simultaneously during any interval of observation. This list of criteria is not exhaustive of SLE manifestations and experienced physicians may make a diagnosis if fewer than four criteria are present.

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PHOTO COURTESY OF DR SEAN O'NEILL, SYDNEY

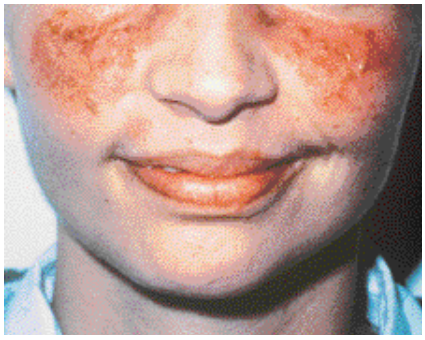

Figure 6. The malar rash of SLE involving the cheeks, bridge of the nose and forehead, resulting in the 'butterfly' appearance.

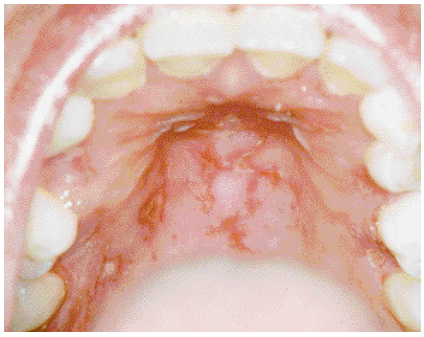

Figure 7. Vasculitis palatal ulceration of SLE with areas of erosion, haemorrhage and granulation that is very different from common aphthous ulceration.

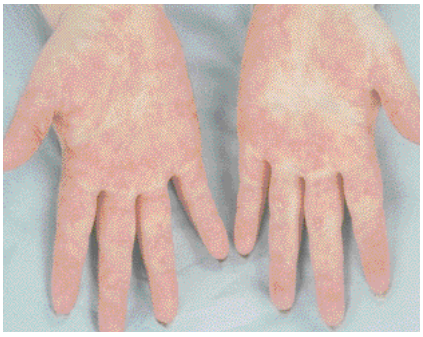

Figure 8. Vasculitic rash involving the hands of a patient with SLE. Small areas of ulceration can be seen. The soles of the feet can also be affected.

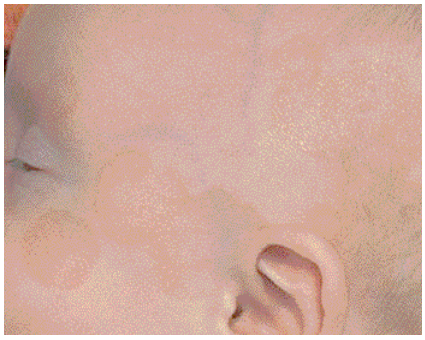

Figure 9. Typical annular rash of neonatal lupus. This is sometimes mistaken for tinea capitus.

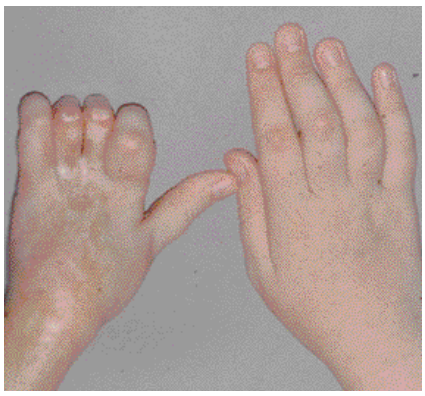

Figure 10. Severely affected upper limb showing typical shiny smooth skin texture and band-like lesion seen with linear morphea. This patient has a poorly functioning hand with flexion contracture of the fingers but relative sparing of the thumb.

a proportion of patients with neonatal lupus erythematosus. Cutaneous, hepatic and haematological manifestations resolve as the maternal antibodies are cleared from the infant's circulation.

Juvenile scleroderma

Systemic scleroderma is extremely rare in childhood and shows similar patterns to the adult version of the disease. Localised forms of scleroderma (often called morphea) are more common with an incidence of one per 100,000 children per year. Localised scleroderma may present as either plaques or linear lesions of thickened, fibrosing skin (Figure 10).

Although juvenile scleroderma is predominantly a cutaneous condition, the underlying tissues, including fascia, muscle, joints and bone, may be involved. When the face and scalp are affected there may be involvement of the underlying brain or orbit. Impaired tissue growth in underlying affected areas may cause significant deformity, particularly when the face is involved (Figure 11). Thus corticosteroids and immunosuppressive agents are sometimes used in an attempt to slow or halt the progress of localised scleroderma, even in the absence of strong level evidence.

Other connective tissue diseases

Mixed connective tissue disease, sarcoidosis, antiphospholipid syndrome and Sjögren's syndrome are extremely rare in paediatric populations.

Raynaud's phenomenon

Raynaud's phenomenon is a vasospastic condition affecting small vessels, particularly those of the fingers, toes, nose and ears. It is characterised by a classic triphasic colour change (white, blue then red), of which two out of three colour changes are required for diagnosis. Raynaud's phenomenon may be primary or secondary. If it is seen as part of the symptomatology of another inflammatory condition, including juvenile SLE, juvenile dermatomyositis, mixed connective tissue disease or systemic sclerosis, it is considered to be secondary.

Primary Raynaud's syndrome in childhood is a benign condition that is triggered by the cold or rapid temperature changes. Patients should be advised to dress appropriately in cold weather to maintain a stable core temperature. Features such as a positive ANA, nail fold capillary changes similar to those seen in juvenile dermatomyositis (Figure 3), frequent long-lasting episodes or digital ulceration all suggest that the Raynaud's phenomenon is secondary to an underlying connective tissue disease that requires further investigation. Vasodilators are indicated in patients with severe Raynaud's phenomenon.

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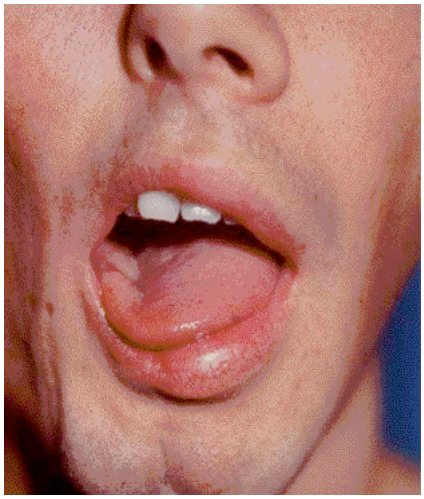

Figure 11. Severe growth deformity of the nose, mouth, tongue and jaw resulting from linear morphea involving the right side of the face.

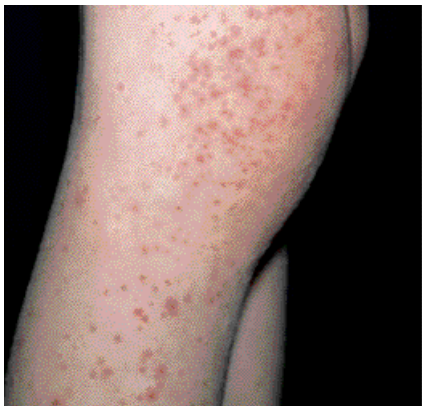

Figure 12. Henoch-Schönlein purpura rash.

Clinical criteria for diagnosis of classic Kawasaki disease

To diagnose Kawasaki disease, patients should have fever persisting for five or more days* and the presence of at least four of the following principal clinical features:†

- changes in extremities of the following:
  - acute; erythema of the palms and/or soles, oedema of the hands and/or feet
  - subacute; periungal peeling of fingers or toes in weeks two and three
- polymorphous exanthema
- bilateral bulbar conjunctival injection without exudate
- changes to the lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse erythema of oral and pharyngeal mucosae
- cervical lymphadenopathy (>1.5 cm diameter), usually unilateral.

Other diseases with similar findings should be excluded first.

* In the presence of four or more clinical features the diagnosis of Kawasaki disease can be made by experienced physicians on the fourth day of fever.

† In patients with five days of fever and less than four principal features, Kawasaki disease can be diagnosed in the presence of coronary artery abnormalities on an echocardiogram or angiogram.

Vasculitis

Vasculitis occurs when there is inflammation of blood vessels and it is classified according to the size of the vessel affected. A number of vasculitides occur in childhood, some of which are more common than others. Two of the most common ones, Henoch-Schönlein purpura and Kawasaki disease, are described below.

Other vasculitides including Wegner's granulomatosis, polyarteritis nodosa, Takayasu's arteritis, Churg-Strauss vasculitis and Behcet's disease all occur in paediatric populations but with far lower frequencies than the conditions discussed below. These conditions should be considered in the differential diagnoses of children with unexplained fever, weight loss, constitutional symptoms, rashes and arthritis.

Henoch-Schönlein purpura

Henoch-Schönlein purpura is the most common paediatric vasculitis affecting children aged 5 to 15 years. It affects small vessels and may have an infectious trigger in some cases. It presents with the triad of palpable purpura over the lower limbs in almost 100% of cases (Figure 12), colicky abdominal pain (45% of cases) and arthritis/arthralgia (70% of cases). Half of all patients with Henoch-Schönlein purpura will have microscopic haematuria at presentation and some will develop nephritic or nephrotic syndrome. Just over 5% of patients with abnormal urinalysis at presentation will develop long-term renal impairment, and almost 20% of those with nephritic or nephrotic syndrome will develop long-term renal impairment. Overall, less than 1% will develop end-stage renal failure.

Other manifestations include melaena, intussusception, pancreatitis, intestinal perforation and painful scalp or scrotal swelling. Most cases are self-resolving with patients requiring only supportive therapy with anti-inflammatory medications for joint pains. Severe abdominal pain may warrant corticosteroid therapy, whereas patients with renal impairment or nephritic or nephrotic syndromes require consideration for renal biopsy. Blood pressure and urine analysis should be monitored during follow up. Patients with persistently normal urinalysis for six months do not require long-term follow up, but all other patients should be monitored continuously.

Kawasaki disease

Kawasaki disease is a vasculitis affecting medium-sized blood vessels and is of unknown aetiology. It affects boys more often than girls and has an incidence of 5 to 10 per 100,000 children. About 80 to 90% of cases occur in children below the age of 5 years and children of oriental background have a 10 times higher risk than other children. Kawasaki disease has now replaced rheumatic fever as the most common cause of acquired heart disease in the developed world.

Kawasaki disease is characterised primarily by persistently high fevers. There is no specific diagnostic test and the diagnosis relies on the classification criteria shown in the box on this page. The classic clinical findings for this condition are outlined below.

- Peripheral changes of erythema and swelling in the acute febrile phase (Figure 13). This is followed by epidermal peeling in the subacute phase (Figure 14).
- Polymorphous exanthema that is nonspecific but never vesicular in form (Figure 15).
- Bilateral conjunctival injection that is nonexudative and classically displays perilimbal sparing (Figure 16).
- Mucosal membrane changes including lip erythema and cracking, strawberry tongue, diffuse erythema of the oral and pharyngeal mucosae (Figure 17).
- Cervical lymphadenopathy (Figure 18).

Patients with Kawasaki disease will usually have elevated inflammatory markers, leucocytosis and mild anaemia in the acute phase and may also have sterile pyuria, which can result in a mistaken diagnosis of an urinary tract infection. In the convalescent phase (seven or more days after the onset of fever) platelet counts may rise precipitously.

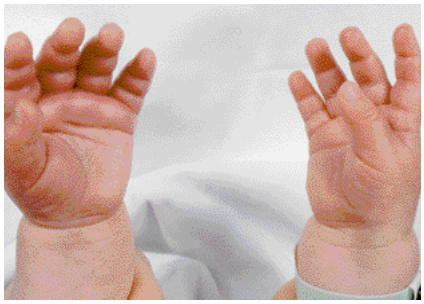

Figure 13. Infant with swelling and erythema of the hands as part of the acute manifestations of Kawasaki disease.

The acute illness of Kawasaki disease is a self-limited condition; however, if left untreated it has a predilection for involving the coronary arteries and may cause segmental inflammation of these vessels.

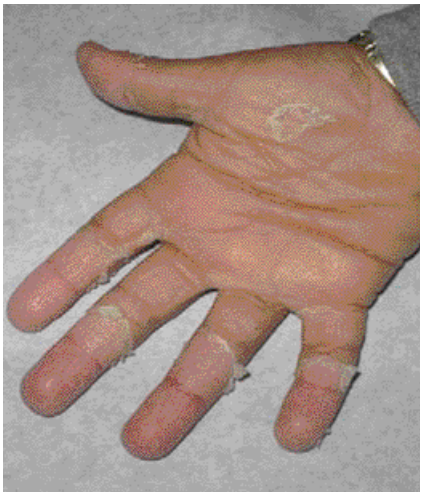

Figure 14. Desquamation of the palms of the hand as are often seen in the subacute phase of Kawasaki disease. The peeling is characteristically periungal and sheet like as seen in this example. Less dramatic examples of peeling are more frequent.

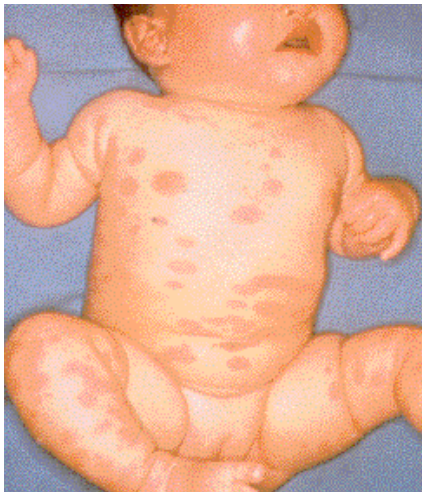

Figure 15. A polymorphous skin rash seen in Kawasaki disease. As the description suggests the rash may come in many forms but is never vesicular in nature.

Mortality is one in 1000 patients even when they are treated appropriately. This is due to myocarditis or arrhythmia in the acute phase. The coronary arteries will be affected and may become aneurysmal or stenosed in 20% of patients who are untreated, placing them at risk of thrombosis, myocardial ischaemia and infarction.

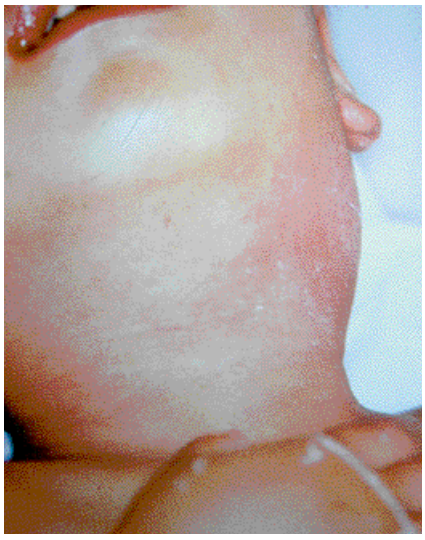

Figure 18. An example of cervical adenitis that was mistaken for bacterial infection but was part of the symptomatology of Kawasaki disease.

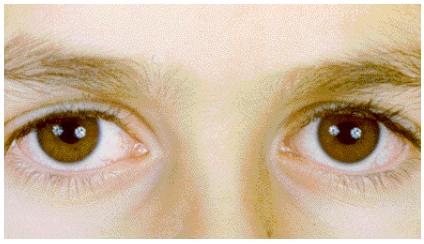

Figure 16. Bilateral conjunctivitis as seen in Kawasaki disease. This patient shows typical perilimbal sparing with a rim of unaffected sclera adjacent to the iris. The conjunctivitis of Kawasaki disease has no exudate.

Treatment of Kawasaki disease involves infusion of intravenous immunoglobulin immediately when the diagnosis is made. This intervention is known to reduce the risk of coronary involvement to less than 5%. Patients are also given antiplatelet doses of aspirin to counter the increased risk of coronary artery thrombosis due to alterations in endothelial function of affected vessels. Patients require an echocardiographic assessment by a paediatric cardiologist and ongoing follow up. Patients with large coronary aneurysms require anticoagulation.

Primary care physicians play an important role in the diagnosis of Kawasaki disease, and must maintain a high index of suspicion, attend to careful history taking and perform a specific examination looking for the clinical features. This disease should be considered in all children with prolonged fever for more than five days even in the presence of fewer than four of the established clinical criteria.

Summary

The field of paediatric rheumatology deals with a number of uncommon but important conditions in addition to arthritis in children. Many of these conditions have quite specific symptoms and signs that sometimes mirror those seen in adults with the same version of the disease; however, this is not always the case. Other conditions such as Henoch-Schönlein purpura and Kawasaki disease are largely limited to children. Awareness of the symptoms and signs of these diseases is important for the primary care physician to allow early diagnosis and prompt therapy of affected children. Patients with signs or symptoms to suggest a diagnosis of one of these conditions should be referred for assessment by a paediatrician or paediatric rheumatologist. MT

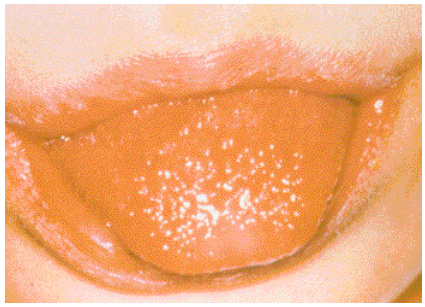

Figure 17. Child with typical oral changes of Kawasaki disease including erythematous lips and strawberry tongue.

Reference

1. Benseler SM, Silverman ED. Systemic lupus erythematosus. Pediatr Clin N Am 2005; 52: 443-467.

COMPETING INTERESTS: None.