Juvenile dermatomyositis: a review[1]

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Juvenile dermatomyositis (JDMS) is an uncommon disease; even large referral centres see only two or three new cases a year (Sullivan *et al.* 1977, Dubowitz 1976). Although dermatomyositis was first described in 1887 independently by Wagner and by Hepp, and approximately 300 cases of JDMS have been described since then, it is only in the last twenty years that the differences between the adult and juvenile forms have been appreciated (Banker & Victor 1966).

Unlike many other muscle diseases of childhood, JDMS is responsive to treatment and, if diagnosed early and treated vigorously, the great majority of affected children can be expected to make a good recovery (Schaller 1973, Rose 1974, Goel 1976).

Clinical features

The mean age of onset of JDMS is about 7 years, ranging from the first year of life upwards (Wedgewood *et al.* 1953), and girls are affected twice as frequently as boys (Roberts & Brunsting 1954).

JDMS is a chronic inflammatory disease affecting muscle and skin but also often involving the gastrointestinal tract (Banker & Victor 1966). Cardiac muscle, joint, renal and cerebral involvement can also occur, but much less frequently, and are not usually a major cause of morbidity (Bitnum *et al.* 1964).

Muscle disease

The disease usually has an insidious onset and it may be several months before the parents realize that their child is getting weaker. An acute onset of weakness is much less frequent (Bitnum *et al.* 1964, Sullivan *et al.* 1972). The proximal muscle groups are classically more affected than the distal groups, exhibiting progressive weakness and often tenderness in a symmetrical distribution. Parents notice that their child has difficulty in walking upstairs or bending over to tie up his shoe-laces or pick things off the ground. As the muscle weakness progresses bulbar signs appear, with the child developing a nasal type of speech and progressive difficulty in swallowing food; this, in association with a weakened ability to cough, leads to aspiration. If left untreated, the disease will either spontaneously arrest or will progress until the child is completely bedridden, with death supervening due to hypoventilation and aspiration (Wedgewood *et al.* 1953, Everett 1957, Hill & Wood 1970).

Skin rashes

The skin rash has a characteristic distribution. There is a facial rash which is a violaceous periorbital rash that spreads onto the nasal bridge and malar areas. Associated periorbital oedema can be very marked. Frequently a scaly erythematous rash occurs on the hands, especially over the knuckles, and there is often an associated erythema over the elbows, knees, medial malleoli and shawl area. In time the rash fades, leaving postinflammatory areas of hyperpigmentation and scarring (Christianson *et al.* 1956, Banker & Victor 1966). The rash waxes and wanes in intensity, often due to photosensitivity (Roberts & Brunsting 1954, Everett 1957) and therefore exacerbations of the rash can occur without any other evidence of disease recrudescence. Severe skin ulceration, which may be related to the vasculitis (see below), can also occur.

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Calcinosis

A particular characteristic of JDMS is calcinosis. It occurs in two forms: a subcutaneous form similar to that seen in adult scleroderma, with a predilection for elbows, knees and fingers; and the 'classical' form of calcinosis that involves intermuscle fascial planes. The subcutaneous form is more frequently recognized the longer the patient is followed and is not related to disease severity. Extrusion through the skin or secondary abscess formation are complications. The intermuscle fascial plane variety is a major cause of disability and does seem to be correlated with disease activity (Sewell *et al.* 1978). Calcinosis occurs in about 40% of patients and is functionally severe in about 15% (Malleson & Schaller, unpublished).

Diagnosis

Strict criteria for the definition of dermatomyositis have been set out by Bohan & Peter (1975). For a definite diagnosis, three or four of the following criteria (plus rash) are required: (1) symmetrical limb girdle weakness; (2) muscle biopsy evidence of myositis and muscle necrosis; (3) elevation of muscle enzymes (Pearson 1966, Rose & Walton 1966); (4) electromyographic changes of myositis (Richardson 1956).

EMG and muscle biopsies may not be essential if there is typical muscle weakness with raised muscle enzymes and rash, and if other diseases such as systemic lupus erythematosus and mixed connective tissue disease have been excluded by the appropriate serological tests. Several muscle enzymes, such as aspartate-amino transferase (AST), aldolase and creatine phosphokinase (CPK), should be measured as any one enzyme may be normal when the others are abnormal, particularly early in the disease (Bitnum *et al.* 1964, Sullivan *et al.* 1972, Malleson & Schaller, unpublished). However, if there is any doubt about the diagnosis, a muscle biopsy is neccessary. A muscle that is clinically affected but not severely atrophied should be selected. The specimen should be examined by both light and electron microscopy.

Pathology

The main pathological feature of juvenile dermatomyositis is a vasculitis affecting small arteries and veins of muscle, skin, subcutaneous tissue and gastrointestinal tract (Banker & Victor 1966). The earliest changes in the muscle are seen on electron microscopy to be endothelial cell damage with swelling, cell necrosis and regeneration (Banker 1975). These changes may be seen on light microscopy as prominence of the endothelium, with later intimal hyperplasia. As the endothelial cell changes develop, the more obvious light microscopy findings of an inflammatory cell infiltrate surrounding and infiltrating the blood vessels of the perimysium and extending into the endomysium can be seen; the cells are initially polymorphonuclear leukocytes, but later lymphocytes, histiocytes and plasma cells. Following this, fibrin thrombus formation and occlusion of the blood vessel lumen occur (Boylan & Sokoloff 1960). The resulting ischaemia causes a zonal type of muscle fibre infarction scattered throughout the muscle in the area supplied by the affected arterioles. The single fibre necrosis and regenerative changes seen in adult type dermatomyositis do not seem to occur to any great extent in JDMS. The vasculitis described in muscle occurs also in other tissues and is the pathological basis for the gastrointestinal perforations that are a major cause of morbidity and mortality in the disease (Wedgewood *et al.* 1953). The precipitating factor for these pathological changes is unknown.

Immunology

Whitaker & Engel (1972) showed granular deposits of immunoglobulin and C3 in the intima of blood vessels from muscle biopsies of children with dermatomyositis. The degree of deposition seemed to correlate with disease activity and they postulated that these deposits represented immune complexes, the exact nature of the antigen and antibody involved remaining unclear. Antinuclear antibody and rheumatoid factor occasionally occur but are usually transient findings (Pachman & Cooke 1980). Antibody to polymyositis antigen PM-I, a nuclear antigen distinct from ribonucleoprotein, deoxyribonucleic acid and Sm antigen,

found in some patients with polymyositis (Wolfe *et al.* 1977), has been found in 4 of 18 (20%) children with JDMS by Pachman & Cooke (1980). They suggested that PM-I antibody may identify a subset of patients, but offered no evidence that the children with PM-I antibody had a clinical course any different from those without the antibody. Antimyosin antibodies have been found in adult patients with polymyositis or dermatomyositis, but they also occurred as commonly in muscular dystrophies and neurogenic muscle disease (Caspary *et al.* 1964) and therefore probably represent secondary phenomena. Antimyoglobulin antibodies in polymyositis were also described in a brief communication (Nishiai & Harms 1972), but this is almost the only evidence to suggest that direct anti-muscle humoral immunity is important in polymyositis.

Evidence for the role of cell-mediated immunity in polymyositis is much stronger. Dawkins (1965) showed that a myositis histopathologically similar to adult polymyositis could be produced *in vivo* in animals by injection of heterologous muscle mixed with Freund's adjuvant. Currie *et al.* (1971) found that lymphocytes from patients with active polymyosits produced cytotoxic effects on muscle cell cultures, but that lymphocytes from patients with other muscle diseases did not. More recently, Dawkins & Mastaglia (1973) showed that lymphocytes from patients with active disease layered directly onto ^{51}Cr-labelled monolayers of chick embryo muscle, induced damage within eighteen hours as measured by ^{51}Cr release. Interestingly, lymphocytes from patients on high-dose prednisolone or azathioprine showed little toxicity compared with those from patients on low-dose steroids, perhaps indicating the importance of using high-dose steroids to adequately treat polymyositis. If chick embryo fibroblasts were used instead of muscle, cytotoxicity could not definitely be shown, suggesting, though not proving, that the antigen was specifically a component of muscle. Johnson *et al.* (1972) showed that lymphocytes from polymyositis sufferers incubated with autologous muscle produced a lymphotoxin with cytotoxic effects on human fetal muscle monolayers. This lymphotoxin could not be produced from control subjects nor from lymphocytes of patients incubated without autologous muscle, suggesting that the cytotoxicity is truly specific for muscle.

Whether muscle from patients with polymyositis contains a specific autoantigen or is 'contaminated' with an immunogenic infectious agent such as a virus, or contains an antigen that cross-reacts with an infectious agent to which the patient has been sensitized, remains unclear. The presence of sensitized lymphocytes and their role in disease activity, however, does seem proven. It is uncertain what relevance this work on adult polymyositis has to JDMS.

Speculations concerning viral infections

The possibility that viral infections are important in the aetiology of dermatomyositis, either by direct invasion or by indirectly sensitizing lymphocytes, is intriguing; the evidence, however, is confusing. Chou (1967) described intranuclear and intracytoplasmic filamentous tubular structures in muscle from a patient with chronic polymyositis, which he thought were similar to myxovirus particles. Tubular aggregates are found prominently in the endothelium of intramuscular blood vessels in dermatomyositis and other 'collagen' diseases, and it has been suggested that these represent virions (Györkey *et al.* 1972); but such aggregates also occur in controlled non-viral situations and probably represent membranous specializations in the endoplasmic reticulum during unusual cellular activity (Banker 1975).

Intranuclear particles in endothelial and muscle cells of biopsies from 5 children with JDMS have been found (Banker 1975). These particles could represent virions of the Papova group. However, attempts to identify viruses by isolation immunofluorescence or tissue culture in these children and other patients with polymyositis or dermatomysitis, have been persistently negative. Tang *et al.* (1975) isolated a coxsackie virus from the muscle of an eleven-year-old girl with a chronic muscle disease, but she had had the disease from infancy and it was almost certainly not JDMS. Finally, a dermatomyositis-like illness has occurred as a complication of persistent systemic echo virus infection in patients with congenital hypogammaglobulinaemia

(Gotoff *et al.* 1972, Zieglar & Penny 1975, Bardalas *et al.* 1977), but although viruses could be isolated from several organs, they were not clearly shown in the muscle of the patients described.

Histocompatibility locus antigens

Pachman & Cooke (1980) demonstrated a relationship between JDMS and HLA-B8, with 72% of Caucasians with JDMS having this antigen compared to 21% of Caucasian controls. The relative risk for JDMS in patients with HLA-B8 was 11.5%, a risk equal to or greater than that of other HLA-B8 associated diseases. Further studies with particular reference to D locus typing are being performed (Malleson, Schaller & Hanson, unpublished).

Management

Untreated JDMS has an extremely bad prognosis. Before steroids were used with any frequency, approximately one-third of patients died, one-third were severely crippled and only one-third were functionally normal (Wedgewood *et al.* 1953, Bitnum *et al.* 1964). In recent series, where all patients received steroids, the prognosis has dramatically improved: there is a mortality of 10% or less and only 10% of patients are severely crippled (Sullivan *et al.* 1977, Pachman & Cooke 1980, Malleson & Schaller, unpublished). Although antibiotics and physiotherapy have contributed to this remarkable improvement, there is no doubt that steroids are the mainstay of therapy (Rose 1974).

It seems that in the majority of patients, JDMS becomes quiescent after about two years (Wedgewood *et al.* 1953); the aim of treatment is to minimize damage during this period. It is usual to start steroids in high doses (prednisolone 2 mg/kg/day) in divided doses initially and, after about three weeks, being guided both by clinical progress and particularly changes in muscle enzyme levels, to taper slowly down to a daily maintenance dose (5–10 mg/day) for approximately two years. Dubowitz (1976), however, does not accept the need for high steroid dosages.

Exacerbations of the disease occur in about 50% of cases during the first two years (Malleson & Schaller, unpublished). They can often be predicted and successfully minimized by measuring muscle enzymes as soon as the patient complains of increased fatigue or other nonspecific symptoms, and by rapidly increasing the steroids for a short period if the enzymes show a rise from their previous levels (Sullivan *et al.* 1972). Recurrences of the disease two years after diagnosis are uncommon and perhaps occur more frequently in patients who have received steroids in smaller doses or for a short period of time.

There is the occasional patient in whom the disease runs a malignant course despite the early use of high-dose steroids. In these cases, immunosuppressive therapy may be justified. Jacobs (1977) has successfully used intravenous methotrexate or azathioprine in 5 children enabling steroids to be stopped or reduced to non-toxic levels, and several other authors have described the value of intravenous methotrexate or azathioprine in adult dermatomyositis or polymyositis and these series have contained the occasional child (Malaviya *et al.* 1968, Sokoloff *et al.* 1971, Metzger *et al.* 1974). Although immunosuppressive therapy is probably of value, the published results do not enable a comparison to be made with steroid therapy.

More recently plasmapheresis has been proposed as a therapeutic modality in unremitting cases (Dau & Bennington 1981). However, this must remain an experimental and speculative procedure for the immediate future.

Muscle weakness and secondary contractures are an inevitable part of JDMS. The importance of vigorous physiotherapy both at hospital and at home in minimizing permanent contractures cannot be over-emphasized (Schaller 1973).

Many drugs have been used in the management of calcinosis, including aluminium hydroxide, diphosphonates and probenecid, but none have been in controlled trials and the occurrence of spontaneous resolution suggests that 'circumspection is required in assessment of the benefits which have been claimed for specific therapies' (Sewell *et al.* 1978).

Conclusion

Juvenile dermatomyositis appears to be a different disease from adult dermatomyositis. It is not associated with an increased frequency of malignancy, it is complicated by calcinosis, and histologically it seems to be due to a systemic vasculitis. Before the introduction of steroids its prognosis was poor, but with their use it is now a disease in which a good outcome can usually be expected.

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References

Banker B Q (1975) *Journal of Neuropathology and Experimental Neurology* **34,** 46–75
Banker B Q & Victor M (1966) *Medicine* **45,** 261–289
Bardalas J A, Winkelstein J A, Seto D S Y, Tsai T & Rogol A D (1977) *Journal of Pediatrics* **90,** 396–399
Bitnum S, Daeschner C W, Travis L B, Dodge W F & Hopps H C (1964) *Journal of Pediatrics* **64,** 101–130
Bohan A & Peter J B (1975) *New England Journal of Medicine* **292,** 344–347, 403–407
Boylan R C & Sokoloff L (1960) *Arthritis and Rheumatism* **3,** 379–386
Caspary E A, Gubbay S S & Stern G M (1964) *Lancet* ii, 941
Chou S M (1967) *Science* **158,** 1453–1455
Christianson H B, Brunsting L A & Perry H O (1956) *American Medical Association Archives of Dermatology* **74,** 581–589
Currie S, Saunders M, Knowles M & Brown A E (1971) *Quarterly Journal of Medicine* **40,** 63–84
Dau P C & Bennington J L (1981) *Journal of Pediatrics* **98,** 237–239
Dawkins R L (1965) *Journal of Pathology and Bacteriology* **90,** 619–624
Dawkins R L & Mastaglia F L (1973) *New England Journal of Medicine* **288,** 434–438
Dubowitz V (1976) *Archives of Disease in Childhood* **51,** 494–500
Everett M A (1957) *Archives of Internal Medicine* **100,** 70–76
Goel K M (1976) *Archives of Disease in Childhood* **51,** 501–506
Gotoff S, Smith R D & Sugar O (1972) *American Journal of Diseases in Children* **123,** 53–56
Györkey F, Sinkovics J G, Min K W & Györkey P (1972) *American Journal of Medicine* **53,** 248–258
Hepp P (1887) *Berliner Klinische Wöchenschrift* **24,** 389–391
Hill R H & Wood W S (1970) *Canadian Medical Association Journal* **103,** 1152–1156
Jacobs J C (1977) *Arthritis and Rheumatism* **20,** Suppl No. 2; pp 338–341
Johnson R L, Fink C W & Ziff M (1972) *Journal of Clinical Investigation* **51,** 2435–2449
Malaviya H N, Many A & Schwartz R S (1968) *Lancet* ii, 485–488
Metzger A, Bohan A & Goldberg L S (1974) *Annals of Internal Medicine* **81,** 182–189
Nishiai M N & Harms M (1972) *Lancet* ii, 1205
Pachman L M & Cooke N (1980) *Journal of Pediatrics* **96,** 226–234
Pearson C M (1966) *Annual Review of Medicine* **17,** 63–82
Richardson A T (1956) *Proceedings of the Royal Society of Medicine* **49,** 111–114
Roberts H M & Brunsting L A (1954) *Postgraduate Medicine* **16,** 396–404
Rose A L & Walton J N (1966) *Brain* **89,** 747–768
Rose A L (1974) *American Journal of Diseases in Children* **127,** 518–522
Schaller J G (1973) *Journal of Pediatrics* **83,** 699–702
Sewell J R, Liyanage B & Ansell B M (1978) *Skeletal Radiology* **3,** 137–143
Sokoloff M, Goldberg L S & Pearson C M (1971) *Lancet* i, 14–16
Sullivan D B, Cassidy J T, Petty R E & Burt A (1972) *Journal of Pediatrics* **80,** 555–563
Sullivan D B, Cassidy J T & Petty R E (1977) *Arthritis and Rheumatism* **20,** Suppl. No. 2; pp 327–331
Tang T T, Sedmak G V, Siegsmund K A & McCreadie S R (1975) *New England Journal of Medicine* **292,** 608–611
Wagner E (1887) *Deutsche Archiv für Klinische Medizinische* **40,** 241–266
Wedgewood R J, Cook C D & Cohen J (1953) *Pediatrics* **12,** 447–466
Whitaker J N & Engel W K (1972) *New England Journal of Medicine* **286,** 333–338
Wolfe J F, Adelstein E & Sharp G C (1977) *Journal of Clinical Investigation* **59,** 176–178
Zieglar J B & Penny R (1975) *Clinical Immunology and Immunopathology* **3,** 347–352