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## **Central nervous system complications in two cases of juvenile onset dermatomyositis**

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### **Abstract**

Central nervous system (CNS) complications are rarely reported in either juvenile or adult onset inflammatory myositides, such as dermatomyositis and polymyositis. We report two children, aged 4 and 10 yr respectively, with a diagnosis of juvenile dermatomyositis, both of whom subsequently developed clinical features of severe CNS involvement, possibly consistent with cerebral vasculopathy. One child died from apparent brainstem involvement; the other developed seizures, pseudoseizures and clinical depression which responded to aggressive immunosuppression. Although the vasculopathy or vasculitis underlying this disorder is known to have a systemic distribution, CNS involvement has rarely been reported and may be under-recognized.

**KEY WORDS:** Dermatomyositis, Cerebral vasculopathy, Seizure, Central nervous system.

Juvenile dermatomyositis (JDM) is a rare disorder, with an incidence of 1.9/1 000 000 children aged <16 yr [1]. Though JDM may be thought of as a homogeneous condition [2], it is in fact rather heterogeneous, not only in markers of disease activity, as has been alluded to previously [3], but also in the clinical profile. This is evidenced by the highly variable presentation, course and degree of systemic or internal organ involvement. Pulmonary, cardiovascular and gastrointestinal complications are well described in recent reviews [4, 5], but neurological dysfunction is reported infrequently, usually as isolated case reports [6–9].

A review of the literature identified only three case reports of central nervous system (CNS) involvement in JDM. We believe that the two further cases described here underline the systemic or 'vasculopathic' nature of this disorder.

### **Case 1**

A 10-yr-old Afro-Caribbean girl presented to our unit with a 3-month history of generalized weakness, difficulty walking, and painful arm movements. She

rapidly developed painful swelling of both knees, and subsequently a classic dermatomyositis rash over the eyelids and Gottron's papules on the extensor surfaces of the hands and knees. Her muscle enzymes were elevated and a clinical diagnosis of juvenile onset dermatomyositis with associated polyarthritis was made. This was supported by characteristic changes on magnetic resonance imaging (MRI) of her thigh muscles. Of note, these features were preceded by a 2-yr history of mild colour changes in her hands, which were felt to be consistent with possible Raynaud's phenomenon. Immunological investigations revealed that she was positive for Hep-2 anti-nuclear antibody at 1:5120 with a speckled pattern; she was negative for antibodies to extractable nuclear antigen (ENA) but positive for anti-ribonucleoprotein (RNP) with a low titre, and negative for anti-double-stranded DNA. She had no definitive features of mixed connective tissue disease (MCTD) at this stage. The only significant medical history was of episodic asthma, which was treated with bronchodilators as required and was not suggestive of interstitial lung disease.

Her dermatomyositis was initially treated with oral prednisolone at a dose of 2 mg/kg with rapid improvement. Three months later, however, because of worsening disease control, new-onset polyarthritis and difficulty in weaning her from steroids, she was commenced on oral methotrexate at 15 mg/m<sup>2</sup> for

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its disease-modifying and steroid-sparing effects. Subsequently, because of persistent inflammatory arthritis she had both knee joints aspirated and injected with corticosteroid.

Readmission to hospital was required 5 months after initial presentation because of poor overall disease control with increased joint pain and impaired mobility. She was treated with pulses of high-dose intravenous (i.v.) methylprednisolone over several weeks. Subsequent to this she developed moderate persistent hypertension (blood pressure 130–150/90–100), requiring treatment with oral nifedipine, with good effect. Four days later she suffered an episode of altered consciousness, repetitive jerking movements of the limbs and rolling of the eyes, lasting 2 min, which was thought to be consistent with a seizure episode.

General examination, including neurological reflexes and fundal examination, was normal after a brief postictal period. All biochemical investigations were normal, including blood sugar level immediately after the seizure, which was  $>8.6$  mmol/l. Urea, electrolytes, calcium and magnesium were normal, as was her oxygen saturation. She was treated with broad-spectrum antibiotics, because of a subsequent low-grade fever noted in the following 12 h, to cover a possible infectious cause for her clinical state. However, multiple blood cultures and a subsequent lumbar puncture were negative. A CT scan of the brain performed at this stage was reported as normal.

Over the subsequent 2 weeks she had multiple episodes of similar abnormal limb movements and altered consciousness, each lasting a few minutes, followed by unresponsiveness for up to 15 min. An electroencephalogram (EEG) and MRI with angiography (MRA) of her brain were performed and were unremarkable. A diagnosis of possible cerebral vasculopathy associated with dermatomyositis was made, and the patient was treated with three pulses of i.v. immunoglobulin while she continued on high-dose oral steroids. In view of the continued daily seizure-like episodes, increasing polyarthritis, persistent weakness and inability to be weaned from corticosteroids, i.v. cyclophosphamide was administered ( $750$  mg/m<sup>2</sup>) immediately and was given monthly thereafter. Methotrexate was stopped and gradual general improvement was noted. Continued episodes of altered consciousness were seen once or twice per week, but were preceded by definite anxiety-related symptoms and hyperventilation. These subsequent events were thought to be pseudo-seizures. Her disease course was associated with marked emotional lability and some depressive ideation. She was managed with psychological counselling, rebreathing techniques for hyperventilation, and gradual steroid reduction, and there was significant reduction and eventual cessation of the episodes. No further true seizures were noted after the first 2 weeks. She continued to do well and was given a total of six monthly pulses of i.v. cyclophosphamide.

At the 26-month follow-up she is in drug-induced disease remission on a combination of low-dose steroids

and azathioprine. Functionally, she is doing well and back in full-time schooling.

## Case 2

A 4-yr-old Italian girl was diagnosed with juvenile dermatomyositis in her country of origin when, at the age of 2½ yr, she presented at her local hospital with painful joints, a typical dermatomyositis rash over the extensor surfaces, including a heliotrope rash over the eyelids, and proximal muscle weakness. A (blind) muscle biopsy was performed and was said to be unremarkable. Creatine kinase (CK) was not elevated, though she had raised aldolase levels. She was also noted to have hepatosplenomegaly and elevated liver enzymes, which were presumed to reflect abnormal liver function at this stage [alanine aminotransferase (ALT) 186 IU/l (normal range 10–25), aspartate aminotransferase (AST) 167 IU/l (normal range 15–45) and  $\gamma$ -glutamyl transferase (GGT) 112 IU/l (normal range 10–22)]. She was commenced on prednisolone 2 mg/kg/day orally. Initially improvement was seen and her prednisolone was gradually decreased to 0.3 mg/kg/day. She relapsed 9 months after initial presentation, when her liver function tests became more abnormal with ALT 514 IU/l, AST 362 IU/l and GGT 544 IU/l. Liver biopsy at that time was thought to be suggestive of sclerosing cholangitis. She was weaned rapidly from steroids, and was referred to a hepatology service in London, UK. Extensive investigations in that unit included abdominal ultrasound, liver biopsy and repeat liver function tests. The ultrasound and liver biopsy revealed a mild non-specific hepatitis thought to be consistent with a possible vasculopathic manifestation of dermatomyositis. No evidence of sclerosing cholangitis was seen. There was no evidence of hepatitis B or C, or Epstein–Barr virus. A skin biopsy showed features typical of dermatomyositis.

At this stage she was transferred to our paediatric rheumatology unit, where she was noted to have a typical but severe dermatomyositis rash, widely distributed over the extensor surfaces, including the elbows, knees, metacarpophalangeal MCP and proximal interphalangeal PIP joints, with a classical heliotrope rash over the eyelids. Evidence of severe vasculopathy was seen, including pitted scarring and oedema of the face and extremities and fresh vasculitic lesions on her fingers and toes (Fig. 1). Her hands showed multiple, large, partially healing ulcerations over the elbows, knees and metacarpophalangeal joints of different ages (Fig. 2). She had dysphonia, with a nasal quality to her voice, indicating palatopharyngeal weakness, proximal muscle weakness of her hip and shoulder girdle, trunk and anterior neck flexor muscles. A mild polyarthritis was seen and she was able to walk less than 20 m, with a markedly abnormal gait consistent with proximal myopathy. Investigations revealed lactate dehydrogenase (LDH) elevated at 1388 U/l (normal range 470–900), with the CK normal at less than 20 U/l (normal



FIG. 1. The dorsum of both hands of a 4-yr-old girl (case 2), showing evidence of a typical distribution of the dermatomyositis rash over the extensor surfaces of the small joints of the hands. Oedema of the hands is present and there is evidence of small scattered healing ulcers with scarring. A diffuse livedo reticularis pattern of the hands is also suggested.

range 15–130). MRI of her proximal thigh muscles confirmed muscle involvement with some oedema consistent with inflammation. A diagnosis of chronic ulcerative or vasculopathic dermatomyositis was made and she was commenced on i.v. methylprednisolone pulses 30 mg/kg/day for three consecutive days, followed by a combination of oral prednisolone and cyclosporin 2 mg/kg. Subsequently she developed a persistent but modest increase in blood pressure to 135/80, but this was well controlled with oral nifedipine.

During the second week of hospitalisation she improved significantly, with a reduction in her rash and improved muscle strength. Ten days after treatment commenced however, she had a sudden prolonged and generalized seizure with evidence of a small haematemesis either during or just before this, followed by a depressed conscious state. Following resuscitation, she was urgently transferred to the paediatric intensive care unit (PICU), where she was intubated and ventilated. On admission to the PICU her blood pressure was noted immediately after seizure to be 170/110, although it had been normal several hours previously. It remained moderately elevated subsequently. An echocardiogram and electrocardiogram were normal. Liver function tests

became markedly elevated. A CT scan of the brain was unremarkable. A lumbar puncture was performed, and was normal. Over the next 2 days she was weaned from ventilation and extubated, but abnormal neurological signs were noted, including right ptosis and hypertonia of the right upper and lower limbs. Subsequently, on day 4, a left flaccid hemiplegia with flexor spasm of the right arm was noted. She required reintubation because of poor respiratory effort. Her blood pressure continued to be elevated (140/108) and she was started on a labetalol infusion with some success. An EEG was suggestive of cerebral vasculopathy. A subsequent MRI showed lacunar changes in the basal ganglia and thalamus, also consistent with both recent and previous vasculopathy (Fig. 3). Intracranial appearances were otherwise normal and there was no evidence of intracranial haemorrhage, mass lesion or hypoxic encephalopathy. A bolus of cyclophosphamide was given i.v. on day 6, to treat the presumed uncontrolled vasculopathy. Daily plasma exchange was started on day 7 because of continued deterioration, and two exchanges were performed. Despite this she continued to deteriorate, with abnormal limb and eye movements, absence of spontaneous respiratory effort and extremely labile blood pressure. She subsequently had a cardiac arrest



FIG. 2. The left elbow of the patient shown in Fig. 1 (case 2), showing multiple, large, partially healed chronic ulcers on the dorsum of the left elbow, with surrounding erythema.

and resuscitation was unsuccessful. Permission for a post-mortem was refused.

## Discussion

Neurological involvement in JDM has been reported with either peripheral or central manifestations. The former has been reported as neuropathy presenting during the course of JDM, though the existence of true neuromyositis remains controversial [6, 10]. Interestingly, both reported patients had ulcerative dermatomyositis, presented with altered sensation in the lower limbs and responded well to the addition of oral methotrexate, which was given when there was no discernible improvement with prednisolone. The precise mechanism of this rare complication is poorly understood, but biopsy evidence suggested that ischaemia secondary to endoneural injury was the likely cause [6].

Complications in juvenile onset dermatomyositis, as highlighted in this paper, could occur for a number of reasons. These include vasculopathy as part of dermatomyositis; true cerebral vasculitis of small- to medium-sized vessels (particularly in overlap syndromes); hypoxic ischaemic encephalopathy secondary

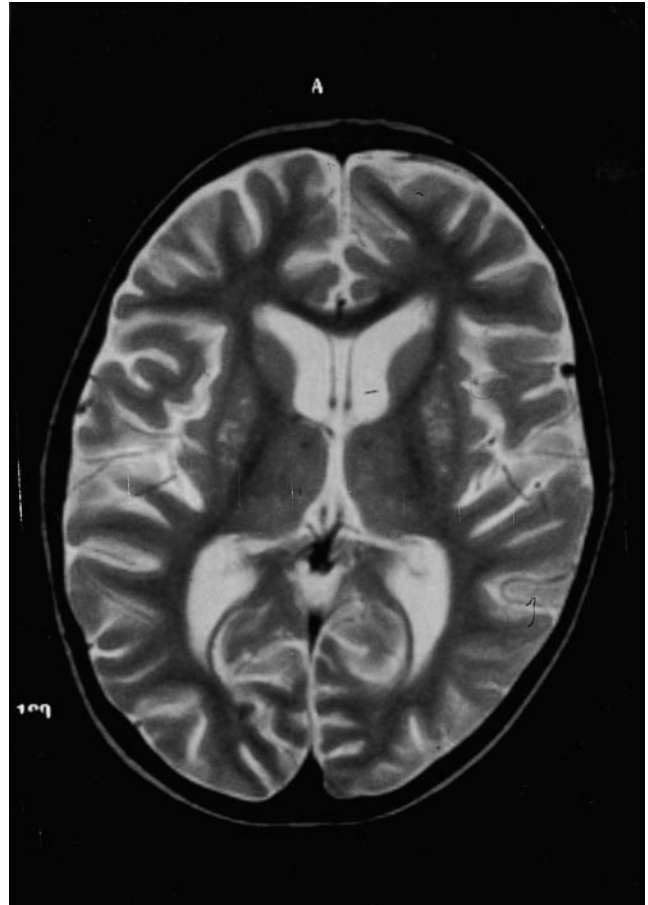


FIG. 3. MRI of the brain of the patient shown in Figs 1 and 2 (case 2), 2 days after a prolonged seizure and severe CNS deterioration. Scattered high signal is evident in both the thalamus and the basal ganglia, indicative of probable old and new vasculopathy.

to cerebral hypoperfusion (with poor myocardial function in some patients); hypertensive encephalopathy; and possibly as a consequence of drug treatment.

The use of corticosteroids has been implicated either because of associated hypertension or electrolyte abnormalities, or intracerebral fluid shifts. In case 2, severe hypertension was noted at the time of, but not before, her initial seizures, and though her blood pressure was still elevated while she was in the PICU it was not severely so, apart from the lability as a preterminal event.

Cyclosporin-associated encephalopathy is also a recognized cause of seizures. This drug is highly lipid-soluble and crosses the blood-brain barrier. The reported toxicity has occurred in patients with both therapeutic and toxic blood levels, and may be increased by high-dose steroids [7-9, 11-14]. Toxic levels of cyclosporin were not detected in our patient, however.

The patients described here perhaps represent two ends of the clinical spectrum of CNS involvement in JDM. The first patient, with possible cerebral vasculopathy and no other serious organ involvement or poor

prognostic signs, responded well to increased immunosuppression; the second patient, with chronic cutaneous ulcerations and a severe disease course with rapidly progressive neurological signs, remained unresponsive to therapy and died. In addition, these patients illustrate that CNS involvement may occur either in apparent isolation in patients with JDM who otherwise have a good prognosis, or as a component of multi-system involvement, especially with chronic cutaneous ulcerations [7, 15].

In case 1 it was difficult to differentiate true seizures from what were thought to be pseudoseizures secondary to hyperventilation. Although we could not prove cerebral vasculopathy, particularly in a macroscopic sense, her overall disease severity, the lack of ability to be weaned from steroids and possible complications from the steroid treatment necessitated the use of aggressive immunosuppressive therapy. The high-risk nature of cerebral angiography and the low diagnostic detection rate of MRA prevented definite delineation of abnormal cerebral vasculature.

It is important to emphasize that the vascular pathology in JDM is not a true vasculitis in that there is no invasion of the vessel wall with inflammatory cells. The implication is that the vessel wall itself is not the target of immune attack in this manner. Furthermore, the vascular pathology in dermatomyositis is often limited to small arterioles and capillaries and is very unlikely to be demonstrated without biopsy, and its distribution would not be expected to follow that of primary vasculitis of small to medium vessels, as might be seen in overlap syndromes [16].

It could be argued that the presence of anti-RNP antibodies together with myositis and arthritis suggests a possible diagnosis of MCTD in case 1. CNS involvement in children with MCTD has been reported [17], including the occurrence of seizures. Patients with MCTD usually have high titres of anti-RNP and ENA, more extensive organ involvement (gut, renal, pulmonary) and a more extensive polyarthritis, particularly including the hands, all of which were absent in our case. She appeared to have true JDM with some overlap features (polyarthritis), as has been reported frequently in JDM [18].

The pseudoseizures which occurred later, associated with emotional lability and depressive symptoms in this patient, probably constituted an organic brain syndrome effect, possibly secondary to high-dose steroids. In a previous case report the aetiopathogenesis of organic psychosis in JDM was linked to cerebral hypoxic damage secondary to 'vasculitic' manifestations [19].

Although CNS (brainstem) vasculopathy was thought to be the most likely cause for the neurological manifestations in case 2, as evidenced by the changes in the EEG and MRI, no histopathological evidence was available to confirm this, as the child's parents declined a post-mortem. Cerebral angiography was also not performed due to the severity of the patient's clinical state. The onset of CNS manifestation was precipitous and unexpected. The MRI and EEG supported but were

not definitive for cerebral vasculopathy. Although hypertensive encephalopathy cannot be ruled out, the MRI would support an argument against this, and the preceding elevation of blood pressure was only moderate.

It is clear that CNS complications, though rare, do occur in JDM. This underlines the potentially serious multi-organ involvement in this autoimmune inflammatory disorder, especially in treatment-resistant cases. We believe that early initiation of immunosuppressive therapy, with medication such as cyclophosphamide, is essential whenever there is evidence of major organ involvement or severe skin ulceration (a marker of severity and risk of vascular organ damage). Though the second case was treated relatively early in the disease course, intensive immunosuppression was delayed.

A review of the literature and our current experience suggests the following key features of CNS involvement in JDM. First, patients commonly present with motor seizures. Secondly, it is critical to exclude electrolyte abnormalities, infections, cerebral oedema, drug toxicity and myocardial function abnormalities (which may cause cerebral hypoperfusion). Unequivocal demonstration of cerebral vasculopathy is challenging, but MRI/MRA may give valuable information if large vessels are involved. It is possible that MR spectroscopy may have given clearer evidence of the type and extent of CNS involvement in our patients, but was unavailable in our institution at the time of treatment of these patients. Finally, aggressive immunosuppression and multi-organ support are critical to the outcome of this rare but potentially fatal systemic complication of JDM [6–8].

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