Case Report

Severe Central Nervous System Involvement in Juvenile Dermatomyositis

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ABSTRACT. We present 3 patients with juvenile dermatomyositis (JDM) and severe central nervous system (CNS) complications. All patients had at least 4 positive criteria of Bohan and Peter, which confirmed a definite diagnosis of JDM. They were all male, and had a relatively high creatinine kinase value at admission (1532-4260 U/l). Besides, progressive proximal muscle weakness and rash, one patient presented with rapid irreversible decline of vision. Ophthalmologic examination showed active vasculitis of the retina. After 2 weeks of treatment with immunosuppressive drugs and being in improved, relatively stable clinical condition, all 3 patients developed generalized tonic-clonic convulsions. Other causes of the neurological symptoms could be excluded. In all 3 patients, the course of JDM was fatal. The clinical symptoms and further investigations in our patients show CNS involvement in JDM. Although rarely reported, CNS vasculopathy can be a serious and life-threatening complication of JDM. (J Rheumatology 2003;30:2059–63)

Key Indexing Terms:
JUVENILE DERMATOMYOSITIS CENTRAL NERVOUS SYSTEM VASCULITIS

Juvenile dermatomyositis (JDM) is an inflammatory myopathy of unknown origin in which the immune system targets the microvasculature of the skeletal muscles and the skin, leading to proximal muscle weakness and a typical rash, particularly affecting face and hands[1]. The vasculitis often involves not only the muscles and skin, but can also involve the gastrointestinal tract, lungs, subcutaneous tissue, eyes, and even the heart[1]. Severe vasculopathy is shown to be a negative prognostic factor[2]. Esophageal involvement has also occurred in more severe disease[1]. A high initial creatinine kinase (CK) level (more than 10 times the normal value) has been correlated with an unfavorable outcome[3].

In contrast to other autoimmune diseases in childhood with systemic vasculitis, such as systemic lupus erythematosus (SLE), reports on central nervous system (CNS) involvement are extremely rare in JDM[1]. One case of biopsy proven CNS vasculitis in JDM (together with involvement of the myocardium) has been reported in a 6-year-old girl with an acute, rapidly progressive, and fatal course, 3 days following admission[4]. She was treated with oral prednisone (1.4 mg/kg/day). Postmortem examination revealed endothelial necrosis in the cerebrocortical capillaries. Five other cases have been reported, suggestive of CNS dysfunction in JDM[5-8]. A child with agammaglobulinemia had recurrent generalized grand mal convulsions appearing shortly after the first signs of JDM[5]. He was given oral prednisolone but progressed into a coma. Autopsy showed sparse infiltrates in the walls of the small blood vessels. A poorly documented case report showed perivascular infiltration of cerebral vessels at autopsy of a young child with JDM and sudden seizures[6]. Hussain reported a girl presenting with JDM and chorioretinitis[7]. Being put on oral prednisolone 2 mg/kg/day, she developed generalized cerebral convulsions. She recovered without any additional immunosuppressive treatment. Recently, 2 other children were reported by Ramanan[8]. One child, receiving oral prednisolone at the presentation of JDM, was given oral methotrexate (MTX) and intravenous (IV) methylprednisolone pulse because of poor disease control. She suddenly suffered multiple seizure periods, was treated with IV gamma globulin (IVIG) and IV cyclophosphamide and is doing well. The other patient with JDM was started on oral prednisolone but relapsed a few months later and started with IV methylprednisolone pulse, followed by oral prednisolone and cyclosporine. The child developed a sudden and prolonged generalized seizure and cyclophosphamide was given, followed by a plasma exchange. The patient died of a cardiac arrest. Postmortem examination was refused.

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We present 3 patients with JDM with severe CNS complications.

CASE REPORTS

Case 1. An 11 year old boy presented with a 2-month history of malaise, fatigue, and a progressive proximal muscle weakness. Two weeks before admission he developed skin lesions on the face, the chest, and both arms. At presentation, there was an erythematous and edematous rash on the face and arms. Edema of the lips and eyelids was seen, together with periorbital erythema. The oral mucosa showed swelling and ulceration. The extensor surfaces of the elbows, knees, and metacarpophalangeal joints showed marked redness (Gottron's sign). He was tachypnoeic. Moreover, he suffered from a rapid irreversible decline of vision. The clinical suspicion of JDM was confirmed by elevated muscle enzymes: CK 4260 U/l, aldolase 29 U/l, and serum transaminases SGOT 720 U/l, SGPT 420 U/l. Immunological investigations revealed that he was negative for antinuclear antibody (ANA) and rheumatoid factor. Muscle histopathology revealed necrotic and regenerating muscle fibers, with deposits positive for IgG, IgM, C1q, C3d, and IgA. The electromyogram (EMG) showed fibrillation, polyphasic, small motor-unit potentials, and repetitive discharges, conclusive for the diagnosis of JDM. Ophthalmologic investigation showed active retinal vasculitis with exudates and edema *in fundo* (Figure 1). Moderate restrictive pulmonary abnormalities were present. No gastrointestinal involvement was noted. Treatment with high dose IV glucocorticoids (2 mg/kg/day) was started. After one week, MTX was added to the treatment, because of aggravation of the retinal involvement. He developed moderate hypertension (diastolic blood pressure 95-100 mmHg), which was successfully treated with oral hydralazine and propranolol. Despite a clearly improved clinical condition 2 weeks after admission, he developed tonic-clonic convulsions. There was no fever. Serum levels of electrolytes, calcium, magnesium, and glucose were normal. Serum sodium was low (130 mmol/l) but stable for several days. Coagulation results were normal. C-reactive protein (CRP) was negative (3 mg/l). Lumbar puncture showed a normal protein concentration (34 mg/dl), a normal glucose and 3 white blood cells/mm^3 in the cerebrospinal fluid (CSF). A culture of the CSF was negative. Cultures of the blood, stool, sputum, and urine were also negative for microbial pathogens (bacterial, fungal, and viral). Serologic tests revealed no recent infection with toxoplasmosis, cytomegalovirus, Epstein-Barr virus, coxsackie virus, and adenovirus. Cerebral computed tomographic (CT) scan showed no signs of bleeding or infarction, but prominent frontal blood vessels were seen after IV contrast. Radioactive nuclear scan showed asymmetrical perfusion in both hemispheres. Anti-epileptic drugs (phenytoin) were started successfully. The steroids were gradually tapered because of elevation of diastolic blood pressure (100 mmHg). However, the retinal vasculitis persisted. Also, other neurologic symptoms developed after one week, including motor aphasia and bulbar paresis. At that time, there were no other signs of decreasing muscular function. Electroencephalogram (EEG) showed asymmetrical irritative abnormalities of the temporal and occipital regions. The elevated CK levels dropped after another (regular) dose of MTX and the motor aphasia resolved. Nine weeks after admission he developed an interstitial pneumonia, possibly related to aspiration and leading to respiratory insufficiency. He was started on broad spectrum antibiotics, but no infectious agent was isolated. His muscle strength was inadequate to maintain spontaneous breathing. Therefore, cyclophosphamide was started at a dose of 200 mg/m^2 during 5 consecutive days. Despite optimal ventilatory support conditions, there were increasing abnormalities on his chest radiographs, although bronchial lavage did not reveal any infectious agent. He died 19 weeks after presentation (12 weeks after admission) because of irreversible lung damage. Postmortem brain examination showed destruction of small vessels in the thalamus with extravasation of blood.

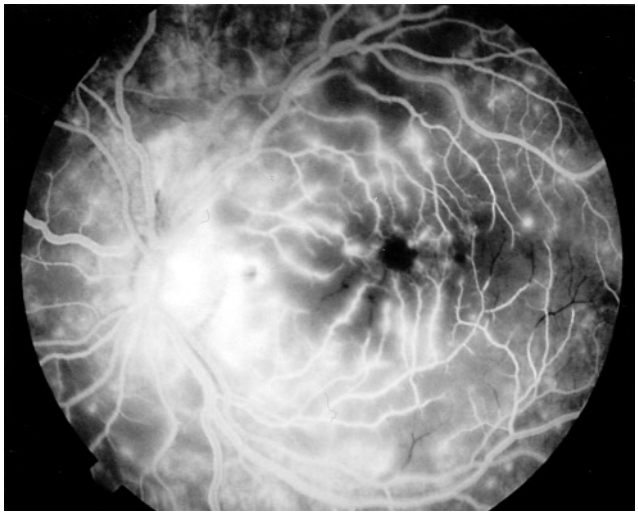

Figure 1. The late phase of the fluorescein angiogram of the right fundus shows staining of the ischemic vessels around the macula with staining of the optic disc. The late phase of the left eye shows a comparable picture.

Case 2. An 11-year-old boy was diagnosed as JDM after a one-month history of progressive proximal muscle weakness and a typical erythematous rash on the malar surfaces and upper eyelids. He also suffered from reddish papules on the extensor areas of the hands, elbows, and knees. The serum CK level was elevated (3923 U/l). He was negative for ANA. Muscle biopsy was performed, showing disseminated necrotic muscle fibers with perivascular infiltrates. IgM, IgA, C1q, and C3c were present in the vessels. Lung function showed moderate restrictive abnormalities. Moreover, a decreased esophageal motility was shown by radiographic contrast studies. He was successfully treated with glucocorticoids at a dose of 2 mg/kg/day for 2 weeks, followed by a daily dose of 1 mg/kg. Two weeks later, he developed tonic-clonic convulsions. He had a normal body temperature. There was no hypertension (diastolic blood pressure maximum 90 mmHg). Serum levels of electrolytes (sodium 136 mmol/l), calcium, magnesium, and glucose were normal. Coagulation results were normal. CRP was 10 mg/l. Lumbar puncture showed an elevated protein concentration (60 mg/dl), a normal glucose and 1 white blood cell/mm^3 in the CSF. A culture of the CSF was negative. Cultures of the blood, stool, sputum, and urine were also negative for bacterial, fungal, and viral pathogens. Serologic tests revealed no recent infection with cytomegalovirus, Epstein-Barr virus, herpes simplex virus, *Mycoplasma pneumoniae*, *Chlamydia*, varicella zoster virus, and adenovirus. Despite adequate anti-epileptic drug treatment with phenytoin, the convulsions persisted and he developed respiratory insufficiency. CT scan showed small areas of hypodensity in the right occipital region as well as in the paraventricular regions. High dose glucocorticoids (1 mg/kg/day) were continued and IVIG was added to the therapy. Within 48 h progressive neurological damage was seen and after weaning of mechanical ventilation, he appeared to be in a deep coma. High dose IV cyclophosphamide was started on suspicion of CNS vasculitis. Cerebral magnetic resonance imaging (MRI) scan showed multiple infarctions in the occipital and thalamic regions and a generalized edema (Figure 2). EEG showed continuous multifocal epileptic activity. Because of irreversible brain damage all treatment was stopped, and he died 19 weeks after presentation. Postmortem brain examination showed multiple ischemic infarctions probably present for several weeks, with loss of normal structure of the brain tissue. In the cortical regions, there was evidence of severe emboli, possibly due to vasculitis.

Case 3. A 4-year-old boy was diagnosed with JDM after a one-month history of persisting low grade fever, malaise, and progressive muscle weakness. Gradually he developed a raised erythematous rash over the malar area and a violaceous discoloration over his upper eyelids. Examination of the oral cavity showed aphthous lesions. Erythematous papular lesions on the elbows, knees, and hands were consistent with Gottron's sign. Nail bed telangiectasia and skin ulcerations were present. There was a marked difficulty swallowing. Muscle biopsy showed perifas-

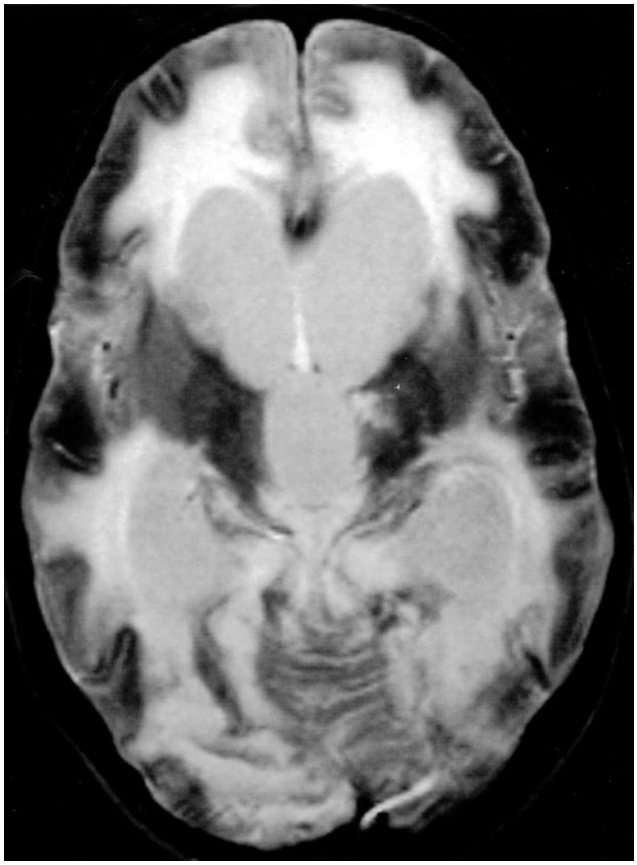

Figure 2. T2-weighted cerebral magnetic resonance imaging shows multiple infarctions in the occipital and thalamic regions and a generalized edema.

cicular atrophy. On EMG, fasciculations at rest and high-frequency discharges were seen. Serum CK was elevated (1532 U/l). An ANA screen was negative. He was started on glucocorticoids at a dose of 2 mg/kg/day, tapered to a dose of 1 mg/kg/day after 2 weeks. He was transferred to our unit because of insufficient clinical response and oral cyclosporine was successfully added 8 weeks after onset of disease, with normalization of CK values. He developed a severe pneumonia 7 weeks after admission and antibiotics were started. Two weeks later, while in stable clinical condition, he had a sudden generalized seizure. At that time, there were no oxygenation problems and there was no fever. Serum levels of electrolytes (sodium 138 mmol/l), calcium, magnesium, and glucose were normal. Coagulation results were normal. CRP was not elevated (2 mg/l). Lumbar puncture showed a normal protein concentration (18 mg/dl), a normal glucose, and no white blood cells in the CSF. A bacterial and viral culture of the CSF was negative. Bacterial, fungal, and viral cultures of the blood, stool, sputum, urine, and skin were also negative. Serologic tests revealed no recent infection with toxoplasmosis, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella zoster virus, *Mycoplasma pneumoniae*, and influenza virus. EEG showed delta waves in the right parieto-occipital region, which could be due to vasculitis. Anti-epileptic drugs were given successfully, but there was subsequent development of respiratory failure and the need for artificial ventilation. Pulmonary symptoms became even more prominent. There was improvement of muscle strength and eventually disappearance of all neurologic symptoms. Because of the rapid and unexplained deterioration of his pulmonary condition, no other diagnostic tests (CT, MRI, angiography) could be performed. Cyclosporine was discontinued because of the effects on immunosuppression. IVIG therapy was given instead for 4 days. Despite extensive treatment, the boy died of respiratory complications, 12 weeks after admission. Brain autopsy was not allowed.

DISCUSSION

JDM is characterized by persistent and progressive proximal muscle weakness in combination with a typical rash. One of the hallmarks of JDM is the occurrence of a diffuse vasculitis which especially affects the skin and the skeletal muscle[1]. The oral and gastrointestinal mucosa can also be involved leading to ulceration and necrosis. Diffuse vasculitis is clearly associated with more severe disease[2]. In active disease, transient retinal exudates and "cotton wool" spots following retinal vessel inflammation have been described, leading to a usually temporary loss of vision[1]. Descriptions of nervous system involvement in JDM have dealt mainly with peripheral nerve abnormalities. Although depression and wide mood swings can be observed, CNS involvement is rarely reported in JDM[1], whereas involvement of the CNS frequently occurs in other autoimmune diseases with systemic vasculitis in childhood, such as SLE and scleroderma[9].

Our 3 patients presented with at least 4 criteria of Bohan and Peter, which confirms a definite diagnosis of JDM[10]. All 3 patients were boys and all had a high serum CK at the onset of the disease. This high value could be associated with an unfavorable outcome[3]. Two of the 3 patients, patients 2 and 3, had esophageal involvement that also proved to be a negative prognostic factor[1]. All 3 patients developed new CNS symptoms, after being treated for more than two weeks with immunosuppressives and while they were in a relatively stable clinical condition.

The symptoms of the first 2 patients would very well fit a diagnosis of CNS vasculopathy. In patient 1, cerebral CT scan showed prominent frontal blood vessels after IV contrast and radioactive nuclear scan showed asymmetrical perfusion in both hemispheres. In patient 2, multiple infarctions and generalized edema were seen on cerebral MRI scan.

CNS vasculitis in connective tissue disorders shows cerebral capillaries exhibiting fibrinoid necrosis of intraluminal fibrin thrombi. Because this is not the hallmark of a true vasculitis, the term vasculopathy is more appropriate. Post mortem it was not possible to confirm this diagnosis morphologically in both patients. This might be due to the long interval between the onset of symptoms and immunosuppressive treatment given during this interval. In patient 2, brain examination showed multiple infarctions and severe emboli, possibly due to vasculitis.

In patient 3, the respiratory symptoms were most prominent, but did not explain the obvious CNS involvement since there was no hypoxic period at the time of his pneumonia. An EEG showed abnormalities that could be due to vasculitis. Therefore, in this patient also, the CNS symptoms are suggestive of direct CNS involvement in the course of the JDM.

Vasculitis/vasculopathy involving the CNS is difficult to diagnose[9]. Although biopsy of the brain is the gold standard of diagnosis[9,12], postmortem histology was not conclusive in 2 of our patients. Presumptive diagnosis of CNS vasculitis frequently is made on the basis of an angiogram[9]; however the severity of clinical symptoms of our patients restricted the performance of this invasive diagnostic test. One study showed that the sensitivity of non-invasive tests for angiogram positive vasculitis is excellent (> 90%) when both lumbar puncture and a non-invasive imaging study (CT or MRI) are performed[11]. In patient 2, the elevated protein levels in the CSF together with abnormalities on both CT and MRI, confirm a probable diagnosis of CNS vasculopathy. At the time of presentation of these 3 cases, no other imaging techniques were yet available, but even the resolution of magnetic resonance angiography, single-photon emission computed tomography (SPECT), and positron emission tomography (PET) currently remain insufficient to detect fine vascular abnormalities[12].

Obviously, the differential diagnosis for the neurological symptoms of our patients was broad. However, repeated cultures could not identify any infectious agents, and coagulation disorders could also be excluded. At the time of convulsions, there was no period of hypoxia and all patients were in a relatively stable clinical condition. There was no marked hypertension in any of the children. This drug-induced complication could have been the consequence of the use of corticosteroids. Furthermore, electrolyte abnormalities, another side-effect of this treatment, were absent at the time of convulsions. An alternative explanation for the neurologic deterioration in patient 1 could be MTX-induced leukoencephalopathy[13]. However, this generally occurs as a complication of much higher doses of MTX (doses > 500 mg/m^2 IV) used in the treatment of malignancies and is particularly common after intrathecal administration and concomitant radiation. Besides, the radiographic findings on CT scan were not compatible with this diagnosis, normally showing diffuse periventricular white matter hypodensities and subcortical hypodense foci. In patient 3, cyclosporine-induced toxicity could have been the cause of his neurological problems. A reversible posterior leukoencephalopathy syndrome is described in patients receiving cyclosporine, together with other immunosuppressive drugs[14]. However, patient 3 never showed toxic levels of cyclosporine.

All 3 patient were treated one to 2 months after the onset of their disease. The initial therapy was high-dose oral prednisolone (2 mg/kg), tapered in patient 2 and 3, before referral to our unit. Their overall well-being and muscle strength improved, so there was no direct reason to augment the dose. In patient 1, MTX was added to the therapy because of aggravation of the retinal vasculitis. In patient 3, cyclosporine was given because of deterioration several weeks after onset of disease. The sudden generalized seizures were totally unexpected. When reviewing the recent literature, the data suggest that in the case of refractory disease, IV pulse methylprednisolone should be combined with MTX[15]. IVIG has been reported to have benefit in combination with the ongoing treatment in resistant disease[15]. It is clear that we should be more aware of the presence of the negative prognostic factors as in these 3 patients. Our patients had evidence of vasculitis (nailfold telangiectasia, oral, and skin ulcerations), 2 of them had esophageal involvement, and patient 1 had retinal vasculitis. All 3 also had high initial CK values, which has proven to be a negative prognostic factor. The history of these 3 patients shows that despite better possibilities for treatment, JDM remains a serious disease with a considerable longterm morbidity. Thirty years ago, the prognosis of JDM was extremely poor with mortality rates of more than 30%[1]. The introduction of corticosteroid therapy and other immunosuppressive medication has led to a dramatic decrease of morbidity and mortality in patients with JDM. With better treatment of the myositis, symptoms other than muscle weakness may become more prominent.

In these cases, the clinical picture and further investigations strongly suggest a CNS involvement of their autoimmune disease. Diagnostic tools to show the CNS vasculopathy are often too invasive. With our current experience, we suggest initiating more aggressive therapy both in children with severe disease and in children in relatively stable condition who have negative prognostic factors, to prevent serious complications of JDM. Unfortunately, no other indicators of future neurological involvement in the course of the disease seem to be apparent. In severe disease, a combination of IV methylprednisolone and MTX should be started with the addition of IVIG in deteriorating cases[15]. There are limited reports of other immunosuppressive agents such as cyclophosphamide, cyclosporine, and azathioprine[15]. Promising new monoclonal agents such as tumor necrosis factor-α inhibitors or anti-CD20 antibodies are now being tested in the treatment in JDM. IVIG should be added to the regular treatment when dealing with severe life-threatening complications, with an effect as quick as 2 to 3 days after infusion. The addition of IV methylprednisolone and MTX seems to maintain the improvement after some weeks.

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