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Central nervous system disease in patients with macrophagic myofasciitis

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Summary

Macrophagic myofasciitis (MMF), a condition newly recognized in France, is manifested by diffuse myalgias and characterized by highly specific myopathological alterations which have recently been shown to represent an unusually persistent local reaction to intramuscular injections of aluminium-containing vaccines. Among 92 MMF patients recognized so far, eight of them, which included the seven patients reported here, had a symptomatic demyelinating CNS disorder. CNS manifestations included hemisensory or sensorimotor symptoms (four out of seven), bilateral pyramidal signs (six out of seven), cerebellar signs (four out of seven), visual loss (two out of seven), cognitive and behavioural disorders (one out of seven) and bladder dysfunction (one out of seven). Brain T_2-weighted MRI showed single (two out of seven) or multiple (four out of seven) supratentorial white matter hyperintense signals and corpus callosum atrophy (one out of seven). Evoked potentials were abnormal in four out of six patients and CSF in four out of seven. According to Poser's criteria for multiple sclerosis, the diagnosis was clinically definite (five out of seven) or clinically probable multiple sclerosis (two out of seven). Six out of seven patients had diffuse myalgias. Deltoid muscle biopsy showed stereotypical accumulations of PAS (periodic acid–Schiff)-positive macrophages, sparse CD8+ T cells and minimal myofibre damage. Aluminium-containing vaccines had been administered 3–78 months (median = 33 months) before muscle biopsy (hepatitis B virus: four out of seven, tetanus toxoid: one out of seven, both hepatitis B virus and tetanus toxoid: two out of seven). The association between MMF and multiple sclerosis-like disorders may give new insights into the controversial issues surrounding vaccinations and demyelinating CNS disorders. Deltoid muscle biopsy searching for myopathological alterations of MMF should be performed in multiple sclerosis patients with diffuse myalgias.

Keywords: inflammatory myopathy, myofasciitis, macrophage, multiple sclerosis, vaccine

Abbreviations: CK = creatine kinase; HBV = hepatitis B virus; MMF = macrophagic myofasciitis; PAS = periodic acid–Schiff

Introduction

Macrophagic myofasciitis (MMF) is a new type of inflammatory myopathy of recent emergence in France (Gherardi *et al.*, 1998) and other western countries (Cabello *et al.*, 1999; Navarro *et al.*, 1999). It is characterized by stereotypical accumulations of tightly packed, non-epithelioid macrophages, in epi-, peri- and endomysium (Gherardi *et al.*, 1998). MMF is distinct from previously described idiopathic inflammatory myopathies, granulomatous myopathies and fasciitis–panniculitis syndromes (Carpenter *et al.*, 1992; Naschitz *et al.*, 1996). It was initially believed to represent an infectious disease on the grounds of histopathological similarities with Whipple's disease (Misbah *et al.*, 1997) and occasional response to antibiotic therapy, but it was recently recognized as an unusual reaction to intramuscular injection of aluminium-containing vaccines (Gherardi *et al.*, 1999; WHO Vaccine Safety Advisory Committee, 1999). Ninety-two cases of MMF have been documented from January 1993 to May 2000 by an expert group of myopathologists at the Association Française contre les Myopathies. The main presenting manifestation of MMF was diffuse muscle pain. Fourteen patients (15%) also had evidence of CNS involvement (Authier *et al.*, 1999; Granel *et al.*, 1999), including eight with a symptomatic demyelinating CNS disorder, four with asymptomatic abnormal hypersignals in the white matter at MRI and two with a cerebrovascular disease. In the present report we describe seven of the eight patients with biopsy-proven MMF and symptomatic demyelinating CNS involvement.

Patients and methods

All seven patients were adults (age range = 27–53 years; five females, three males). They were evaluated in neurological centres and underwent complete physical examination and the following laboratory tests: serum creatine kinase (CK) determination (six out of seven), EMG (five out of seven), deltoid muscle biopsy (seven out of seven), CSF examination (seven out of seven), sensory, auditory and visual evoked potentials (six out of seven), brain MRI (seven out of seven), duodenal biopsy (five out of seven) and other biological tests including serum protein immunoelectrophoresis, CH50, C3 and C4 levels, rheumatoid factor, antinuclear and anticardiolipin antibodies, cryoglobulinaemia, TPHA (treponema pallidum haemagglutination assay), VDRL (venereal disease research laboratory test), serology for hepatitis B and C viruses, HIV (human immunodeficiency virus) and serum angiotensin converting enzyme-level determination.

Clinical histories

Patient 1

A 53-year-old caucasian woman presented with fatigue and diffuse myalgias at rest and on exertion, that were followed by dizziness and unsteadiness within a few months. One year later, she experienced visual loss and left hand paraesthesias and clumsiness. Physical examination showed right sensory hypoaesthesia, left hand clumsiness and bilateral Babinski's sign. CSF was normal. Brain fluid-attenuated inversion recovery and T_2-weighted MRI disclosed multiple supratentorial periventricular and pericallosal white matter hypersignals with corpus callosum atrophy. Visual and sensory evoked potentials were delayed and abnormal, suggesting CNS involvement. Initial diagnosis was multiple sclerosis. CK levels, EMG and thigh muscle MRI were normal. Deltoid muscle biopsy was performed because of myalgias.

Patient 2

A 51-year-old caucasian woman presented with a remitting–relapsing left sensory hemisyndrome from age 39 years. From age 41 years, she also complained of fatigue and diffuse myalgias. Physical examination was normal. CSF, sensory, visual and auditory evoked potentials were normal. Brain T_2-weighted MRI disclosed a single supratentorial white matter hyperintense signal. Initial neurological diagnosis was multiple sclerosis. CK levels, EMG and thigh muscle MRI were normal. Deltoid muscle biopsy was performed because of myalgias.

Patient 3

A 49-year-old caucasian woman presented with a 15-year-history of CNS involvement, manifesting as transient paraesthesias and clumsiness in hands at age 34 years, transient vertigo at age 38 years and progressive spastic paraplegia from age 46 years. At age 47 years she developed fatigue, diffuse myalgias and arthralgias. CSF showed moderately increased protein level (0.53 g/l). Brain T_2-weighted MRI disclosed multiple supratentorial white matter hyperintense signals. Visual and sensory evoked potentials were delayed and abnormal, suggesting multifocal CNS involvement. Auditory evoked potentials were normal. Initial diagnosis was multiple sclerosis. Deltoid muscle biopsy was performed to investigate myalgias.

Patient 4

A 32-year-old caucasian man presented with a 1-month history of acute mania with delusions and agitation. During hospitalization, behavioural disorders improved under neuroleptic treatment, but the patient developed depression, bradypsychia, athymormia and bulimia. Neurological examination showed pyramidal signs in lower limbs and cerebellar dyskinesia of left upper limb. No muscle symptoms were noted. Routine blood tests were normal. Brain T_2-weighted MRI showed bilateral frontal and temporal high

intensity lesions. CSF examination showed 29 cells/ml (70% lymphocytes) and increased protein level (1.3 g/l) with oligoclonal bands. Whipple's disease was first suspected but duodenal biopsy was normal, PCR (polymerase chain reaction)-based detection of *Tropheryma whippelii* was negative and treatment by trimethoprim-sulfamethoxazole was inefficient. Deltoid muscle biopsy was performed to assess a mitochondrial disease.

Patient 5

A 32-year-old caucasian man presented with a 10-year history of progressive left hemiplegia and myalgias. In childhood, he had experienced several attacks of transient hemiparesia of unknown origin, without apparent sequelae, considered as hemiplegic migraine. At age 22 years, he sprained his left ankle and physical examination disclosed pyramidal signs in the left lower limb. At age 27 years, he developed mild pyramidal signs in left upper limb and myalgias. At age 32 years, his condition markedly worsened and physical examination showed left spastic hemiparesia with dysmetria and bilateral Babinski's sign. CSF examination showed increased protein level (0.92 g/l) with oligoclonal bands. Brain T_2-weighted MRI disclosed multiple supratentorial white matter hyperintense signals. Sensory, visual and auditory evoked potentials were delayed and abnormal. Initial diagnosis was multiple sclerosis. Deltoid muscle biopsy was performed to assess mitochondrial disease.

Patient 6

A 26-year-old caucasian woman presented with diffuse myalgias and fatigue a few months after vaccination against hepatitis B virus (HBV). Two years later, she experienced a bilateral visual loss, diagnosed as bilateral optic neuritis, with complete recovery after intravenous methylprednisolone. Seven years after the onset, she complained about recurrence of myalgias and recent urgency of micturition. Physical examination was normal. CSF, visual, auditory and sensory evoked potentials and brain T_2-weighted MRI were normal. A urodynamic study was suggestive of a central neurological bladder disorder. Initial diagnosis was multiple sclerosis. CK and EMG were normal. Deltoid muscle biopsy was performed because of myalgias.

Patient 7

A 48-year-old caucasian man presented with a 4-year history of progressive paraparesis and diffuse myalgias. Physical examination showed spastic paraparesis and cerebellar syndrome. CSF examination showed 6 cells/ml and increased protein level (0.59 g/l). Brain T_2-weighted MRI disclosed one supratentorial white matter hypersignal. Visual and auditory evoked potentials were normal. Initial diagnosis was probable multiple sclerosis. CK levels and EMG were normal. Deltoid muscle biopsy was performed because of myalgias.

Results

Clinical data and relevant laboratory tests are summarized in Table 1 and in Fig. 1. Six patients had diffuse myalgias as the prominent muscle symptom. Presence or absence of myalgia could not be established in Patient 4 because of cognitive impairment. Proximal weakness, serum CK elevation and myopathic EMG were not observed. Routine blood tests were normal or not contributory. All patients had stereotypical MMF at muscle biopsy (Figs 2 and 3). Myopathological alterations included (i) focal infiltration of epimysium, perimysium and perifascicular endomysium by sheets of large cells of the monocyte/macrophage lineage (CD68+, CD1a–, S100–), with a finely granular periodic acid–Schiff (PAS) positive content, appearing as small osmiophilic spiculated structures on electron microscopy (Fig. 2); (ii) lack of necrosis, epithelioid or giant cells and mitotic figures (Fig. 2); (iii) presence of lymphocytic infiltrates, mainly CD3+/CD8+, intermingled with macrophages or surrounding microvessels; and (iv) inconspicuous muscle fibre damage (Fig. 2). Microorganisms could not be detected by appropriate staining (Ziehl-Neelsen, auramine, Gram) and electron microscopy. As assessed by their individual vaccination booklet and the information provided in the general practitioner's files, all seven patients had received aluminium-containing vaccines (HBV vaccine: four out of seven, tetanus toxoid vaccine: one out of seven, both HBV and tetanus toxoid: two out of seven) 3–78 months before muscle biopsy (median = 33 months).

In the six patients with muscle symptoms, evidence of CNS involvement preceded (three out of six), followed (two out of six), or was contemporary with (one out of six) muscle involvement. All patients had neurological manifestations, including hemisensory or sensorimotor symptoms (four out of seven), bilateral pyramidal signs (six out of seven), cerebellar signs (four out of seven), visual loss (two out of seven), cognitive and behavioural disorders (one out of seven) and bladder dysfunction (one out of seven). The routine clinical diagnosis was multiple sclerosis in six patients and Whipple's disease in one (Patient 4). In Patient 4, the diagnosis of Whipple's disease was finally ruled out on the grounds of normal duodenal biopsy, negative PCR-based detection of *Tropheryma whippelii* and inefficacy of antibiotic treatment and the final diagnosis was possible multiple sclerosis. Using Poser's criteria for multiple sclerosis (Poser *et al.*, 1983), five patients had 'clinically definite multiple sclerosis' (Patients 1–3, 5 and 6) and two had 'clinically probable multiple sclerosis' (Patients 4 and 7). None of the patients fulfilled neurological or extra-neurological criteria for CNS Whipple's disease (Louis *et al.*, 1996). The temporal relationship between aluminium-containing vaccine administration and both CNS and muscle symptoms is presented in Fig. 1. In all patients with muscle symptoms, aluminium-vaccine injection preceded myalgias. Evidence of aluminium-vaccine injection before onset of CNS involvement was established in all patients but one (Patient 2) in

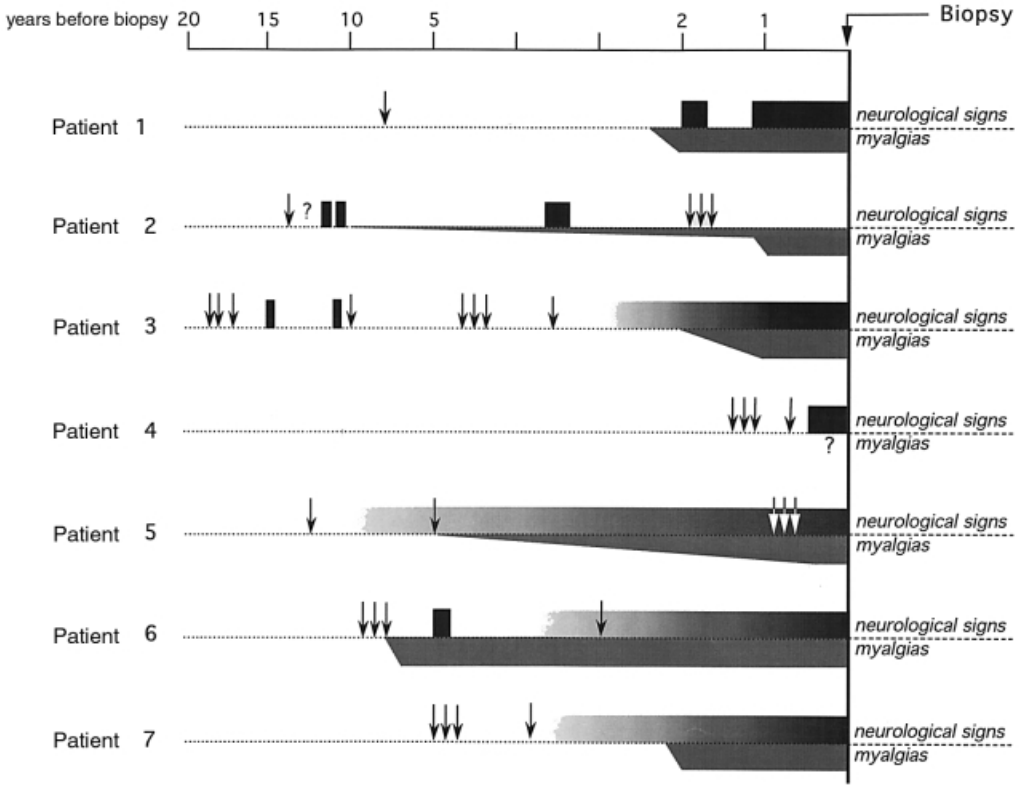

Fig. 1 Bidimensional diagrammatic representation of the temporal relationship between aluminium-containing vaccine administration and both CNS and muscle symptoms in each patient. Arrows = aluminium-containing vaccine (tetanus toxoid or HBV) injection; black areas = neurological symptoms (shading-off: chronic involvement with progressive worsening); grey areas = myalgias. In the case of Patient 2, vaccine administration was performed before the first neurological manifestations because of travels between tropical areas, but the type of vaccines could not be determined.

whom vaccination of unknown type had been administered before the onset of the first CNS manifestations. Cytological CSF examination showed mild lymphocytosis in one patient (Patient 4) and was normal in others (six out of seven). The CSF protein level was found to be increased in four out of seven patients, with oligoclonal bands in two. Sensory evoked potentials were abnormal in four out of six patients, visual evoked potentials in three out of six and auditory evoked potentials in one out of six. T_2-weighted brain MRI (Fig. 3) showed single (two out of seven) or multiple (four out of seven) supratentorial white matter hyperintense signals and corpus callosum atrophy (one out of seven). It was normal in Patient 6. Six patients underwent a duodenal biopsy that yielded neither PAS-positive macrophages in the lamina propria (six out of six) nor PCR-based detection of *Tropheryma whippelii* (four out of four). Clinical evolution of CNS involvement was remittent–progressive (three out of seven), progressive (three out of seven), or remittent (one out of seven). In Patient 1, both CNS and muscle symptoms improved under a combination of oral prednisone (1/2 mg/kg/day) and antibiotics (azithromycin 2 g/day + ciprofloxacin 1 g/day). Patients 2 and 6 recovered from their myalgias within 4 weeks after oral prednisone (1/2 mg/kg/day) administration. Patient 2 was free of neurological symptoms at time of treatment. Patient 6 did not improve in terms of the neurological urinary symptoms under steroids. In Patients 3, 5 and 7 intravenous methylprednisolone and oral methotrexate (Patient 3 only) were ineffective on both myalgias and neurological symptoms. In Patient 4, antibiotic treatment (trimethoprim-sulfamethoxazole) was ineffective on CNS involvement.

Discussion

All seven reported patients had MMF and a CNS disease meeting Poser's criteria for definite (five out of seven) or probable (two out of seven) multiple sclerosis.

Muscle involvement in our patients was similar to that reported in other patients with MMF (Gherardi *et al.*, 1998). Patients with MMF detected by French myopathology centres from 1993 to 1997 had diffuse myalgias (86%) and arthralgias (64%), marked asthenia (43%) and, less often, muscle weakness (36%) and fever (29%) (Gherardi *et al.*, 1998). Abnormal laboratory findings such as elevated CK levels, increased erythrocyte sedimentation rate, or myopathic EMG were infrequently detected (Gherardi *et al.*, 1998). Muscle biopsy showed dense accumulations of large macrophages, with a finely granular basophilic and PAS-positive cytoplasm, in epi-, peri- or endomysium. No giant cells were observed. Electron microscopy showed small intracytoplasmic

Table 1 *Clinical data and laboratory tests*

	Patient 1	Patient 2	Patient 3
Age (years)*/sex	53/F	51/F	49/F
Age (years) of detection of			
muscle involvement	50	41	49
CNS involvement	51	39	34
General symptoms	Fatigue	Fatigue	Fatigue
Muscular symptoms and signs	Diffuse myalgias, muscle tenderness	Diffuse myalgias, muscle tenderness	Diffuse myalgias, muscle tenderness
Serum CK level	N	N	n.d.
EMG	N	N	n.d.
Muscle biopsy	Macrophagic myofasciitis	Macrophagic myofasciitis	Macrophagic myofasciitis
Neurological symptoms and signs	Dizziness, right sensory hemisyndrome, left hand clumsiness and paraesthesias, bilateral Babinski sign	Relapsing left sensorimotor deficit	Transient hands clumsiness and paraesthesias, vertigo, spastic paraplegia
CSF	N	N	Protein 0.56 g/l with 26% γ-globulins (polyclonal), 3 cells/mm^3
Evoked potentials	Abnormal VEP and SEP	N	Abnormal VEP and SEP
T_2-weighted brain MRI	Multiple HS in supratentorial periventricular and pericallosal white matter, thin corpus callosus	One HS in supratentorial periventricular white matter	Multiple HS in supratentorial periventricular white matter
Initially proposed neurological diagnosis	Secondary progressive MS	Relapsing–remitting MS	Secondary progressive MS
Evidence for i.m. aluminium-containing vaccine injection (number of injections)	Tetanus ($n = 1$)	HBV ($n = 3$)	Tetanus + HBV ($n = 8$)
Vaccination prior to CNS involvement (delay)	Yes (66 months)	?	Yes (anti-tetanus: 2 yrs before first attack; anti-HBV: 4th injection 12 months before paraplegia)
Outcome	i.v. MP: ineffective antibiotics[†]: improvement of fatigue and paraesthesias oral steroids[‡]: complete improvement of myalgias	i.v. MP: ineffective antibiotics[†]: ineffective	i.v. MP: ineffective methotrexate: ineffective oral steroids[‡]: complete improvement of myalgias and fatigue

Table 1 *Continued*

	Patient 4	Patient 5	Patient 6	Patient 7
Age (years)*/sex	30/M	32/M	27/F	48/M
Age (years) of detection of:				
muscle involvement	–	27	19	46
CNS involvement	30	22	21	44
General symptoms	None	None	Fatigue	None
Muscular symptoms and signs	None	Diffuse myalgias	Diffuse myalgias	Diffuse myalgias
Serum CK level	N	N	N	N
EMG	n.d.	N	N	N
Muscle biopsy	Macrophagic myofasciitis	Macrophagic myofasciitis	Macrophagic myofasciitis	Macrophagic myofasciitis
Neurological symptoms and signs	Cognitive and behavioural disorders, pyramidal syndrome in lower limbs, left upper limb dyskinesia	Spastic left hemiparesia, bilateral Babinski sign	Visual acuity loss, urgency of micturition	Spastic paraparesis, cerebellar syndrome
CSF	Protein 1.3 g/l with oligoclonal bands, 29 cells/mm^3 (70% lymphocytes)	Protein 0.92 g/l with oligoclonal bands, 5 cells/mm^3	N	Protein 0.59 g/l, 6 cells/mm^3
Evoked potentials	n.d.	Abnormal VEP, AEP and SEP	N	Abnormal SEP
T_2-weighted brain MRI	Multiple HS in supratentorial frontal and temporal white matter	Multiple HS in supratentorial white matter	N	One HS in supratentorial white matter
Initially proposed neurological diagnosis	Suspected Whipple's disease	Secondary progressive MS	Secondary progressive MS	Clinically probable MS
Evidence for i.m. injection of aluminium-containing vaccine (number of injections)	HBV (n = ?)	Tetanus + HBV (n = 5)	HBV (n = 4)	HBV (n = 4)
Vaccination prior to CNS involvement (delay)	Yes (2 months)	Yes (anti-tetanus injection <12 months before onset of chronic left hemiparesia; next anti-tetanus injection <10 months before involvement of left upper limb; 3rd anti-HBV injection 8 months before worsening of hemiparesia)	Yes (anti-HBV: 3rd injection 2 years before first attack)	Yes (6 months)
Outcome	Trimethoprim-sulphamethoxazole: ineffective	i.v. MP: ineffective	Steroids[‡]: improvement of myalgias	i.v. MP: ineffective

CK = creatine kinase; CSF = cerebrospinal fluid; VEP = visual evoked potentials; AEP = auditory evoked potentials; SEP = sensory evoked potentials; EMG = electromyogram; HS = hyperintense signal; MP = methylprednisolone; WM = white matter; MS = multiple sclerosis; n.a. = not available; n.d. = not done; N = normal; i.v. = intravenous; i.m. = intramuscular. *At time of muscle biopsy; [†]azithromycin 2 g/d p.o. + ciprofloxacin 1 g/d p.o.; [‡]prednisone 1/2 mg/kg/d (duration of treatment not less than 2 months).

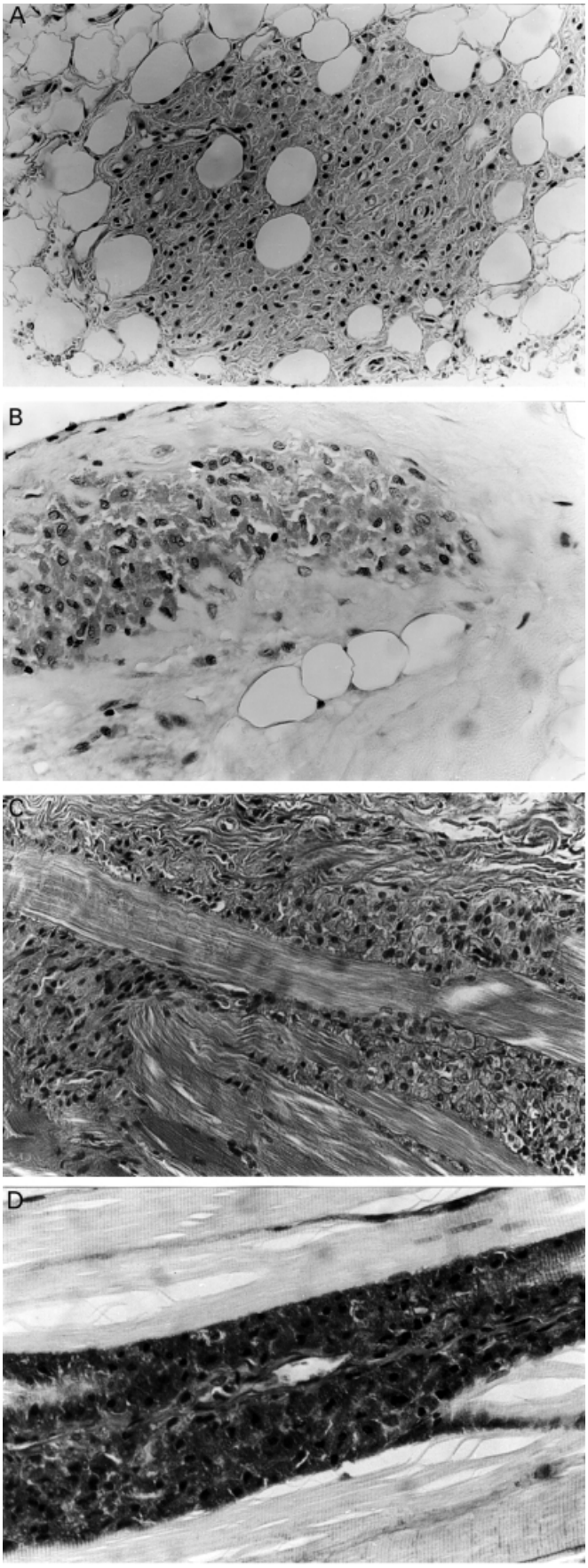

Fig. 2 Deltoid muscle biopsy, light microscopy: Patients 3 (**C** and **D**), 4 (**B**) and 5 (**A**). Focal infiltrates of large cohesive macrophages in muscle fascia (**B**) and in perimuscular fat tissue (**A**) (paraffin section, haematoxylin eosin stain). Sheets of densely packed large macrophages infiltrating endomysium (**C**) (paraffin section, haematoxylin eosin stain). Finely granular PAS-positive cytoplasmic content of macrophages (**D**) (paraffin section, PAS). Magnification: **A** and **C**: ×100; **B** and **D**: ×200.

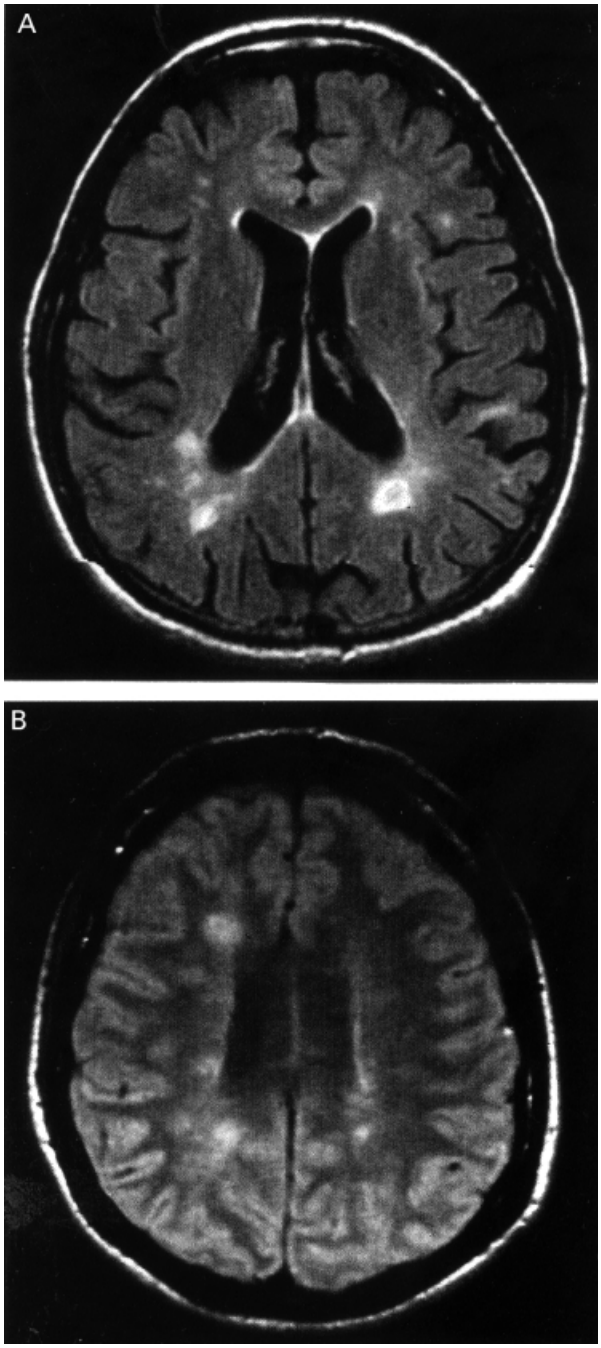

Fig. 3 Brain MRI: Patients 1 (**A**) and 4 (**B**). Fluid-attenuated inversion recovery (**A**) and T_2-weighted (**B**) MRI images showing multiple lesions in supratentorial periventricular white matter.

osmiophilic structures in macrophages and no micro-organisms. These inclusions did not react with calcium stain. CD8+ T-cell infiltrates were observed either intermingled with macrophages or in the form of small perivascular cuffs. Myonecrosis, atrophy and myopathic changes were virtually absent. PAS-positive macrophages could not be detected anywhere other than in muscle and fascia. Appropriate investigations failed to detect viral or bacterial infection. Most patients responded well to oral steroids, whether combined or not with antibiotic therapy. In brief, MMF appeared distinct from previously described inflammatory myopathies, including idiopathic inflammatory myopathies, sarcoid-like myopathies, Shulman's disease (eosinophilic fasciitis), eosinophilia–myalgia syndrome and other fasciitis–panniculitis syndromes (Carpenter *et al.*, 1992; Banker, 1994; Naschitz *et al.*, 1996). The rapid emergence of MMF suggested an environmental aetiology (Gherardi *et al.*, 1998). In a preliminary study using various analytical techniques, the cytoplasmic inclusions of macrophages were shown to contain high amounts of aluminium whereas serum aluminium levels were normal, suggesting focal aluminium accumulation into the muscle rather than systemic intoxication (Gherardi *et al.*, 1999). Aluminium is used as an adjuvant of vaccines against HBV, hepatitis A virus and tetanus toxoid and is usually administered intramuscularly into the deltoid muscle in adults. All MMF patients have been shown to have circulating antibodies to HBV, hepatitis A virus or tetanus toxoid, positive anti-HBV testing being due to previous vaccination, as assessed by the isolated positivity of anti-HBV antibodies, in 88% of patients (Gherardi *et al.*, 1999). In-depth re-evaluation of patient histories revealed documentation of intramuscular injections of aluminium-containing vaccines months to years prior to biopsy, as demonstrated in the present series where administration of HBV vaccine, tetanus toxoid vaccine or both HBV and tetanus toxoid vaccines has been performed 3–78 months (median = 33 months) before muscle biopsy yielding MMF lesions. A recent workshop of the WHO Vaccine Safety Advisory Committee, aimed at reviewing the scientific evidence about MMF, recognized that it is 'a distinctive histopathological entity that may be caused by intramuscular injection of aluminium-containing vaccines' (WHO Vaccine Safety Advisory Committee, 1999). In this session, it has been shown that intramuscular injections of such vaccines in experimental animal models induce comparable but transient lesions at the site of injection, suggesting that MMF may occur in 'a predisposed subset of individuals with impaired ability to clear aluminium from the deltoid muscle' (WHO Vaccine Safety Advisory Committee, 1999). Whether or not this could reflect a macrophagic dysfunction of genetic or acquired origin has not yet been defined. To our knowledge, only a very few patients with MMF have been identified outside France (USA, two; UK, one; Portugal, one and Spain, two) (Cabello *et al.*, 1999; Navarro *et al.*, 1999). Why MMF is detected at a much higher rate in France than in other countries remains speculative, but a local pharmaceutical cause linked to manufacturing practices of the implicated vaccines seems unlikely (WHO Vaccine Safety Advisory Committee, 1999).

Our patients had a CNS involvement sharing similarities with multiple sclerosis. There was no direct evidence of demyelinating disorder, however, although both clinical symptoms and MRI findings were in keeping with such a condition. Admittedly, neuropathological examination could be the only way to determine the exact nature of CNS lesions. Multiple sclerosis is not known to cause myalgias (Layzer, 1994). In contrast, numerous conditions can produce multifocal CNS syndrome with a relapsing and remitting course in young adults (Paty *et al.*, 1991). None of our patients had clinical, histological or serological evidence of vasculitis or connective tissue disease. The diagnosis of Whipple's disease was initially considered because of detection of PAS-positive macrophages at muscle biopsy (Swash *et al.*, 1977; Louis *et al.*, 1996; Misbah *et al.*, 1997), but neither neurological symptoms suggestive of Whipple's disease (oculomasticatory or oculofacial–skeletal myorythmia, supranuclear vertical gaze palsy, dementia, or hypothalamic manifestations) (Romanul *et al.*, 1977; Adams *et al.*, 1987; Wroe *et al.*, 1991; Louis *et al.*, 1996), nor evidence of systemic Whipple's disease (lymphadenopathies, digestive symptoms, evidence of bacilliform structures, macrophage infiltration or positive PCR-based detection of *Tropheryma whippelii* in digestive mucosa) was observed. Sarcoidosis is another condition that may involve muscle and CNS (Matthews, 1992). Our patients showed no evidence of systemic sarcoidosis and their neurological symptoms did not suggest neurosarcoidosis that preferentially involves the base of the brain and posterior fossa (Gray *et al.*, 1997). MRI in neurosarcoidosis may show multiple periventricular enhancing areas mimicking multiple sclerosis (Matthews, 1992), but it also typically shows localized space-occupying lesions, meningeal involvement and hydrocephalus, all abnormalities not observed in our patients (Matthews, 1992; Sharma, 1997). Above all, myopathological features of MMF are clearly distinctive from those of sarcoidosis.

Conceivably, the condition of our patients could have resulted from (i) a chance association between MMF and multiple sclerosis; (ii) a unique pathological process affecting both skeletal muscle and CNS, mimicking but distinct from multiple sclerosis; (iii) a multiple sclerosis-associated risk to develop MMF, or the opposite; and (iv) a predisposing factor common to MMF and multiple sclerosis, favouring co-expression of diffuse myalgias and multiple sclerosis in some individuals. Further studies are needed to substantiate or invalidate these hypotheses.

There is controversy regarding the possible association between HBV-vaccination and multiple sclerosis (Tourbah *et al.*, 1999; Zipp *et al.*, 1999). Our patients had muscle symptoms starting 15 days to 48 months after vaccination and CNS symptoms starting or worsening 3–66 months after vaccination. Only Patient 4, who developed a progressive demyelinating disorder 3 months after HBV vaccination,

would be considered as post-vaccinal acute disseminated encephalomyelitis using recommanded criteria (Griffin, 1990; Tourbah *et al.*, 1999). In fact, the post-vaccinal period during which symptoms of neurological disease might be considered to be associated with the effects of vaccination is arbitrary, ranging from 10 weeks to 6 months according to different studies (Tourbah *et al.*, 1999). In addition, most demyelinating CNS diseases observed shortly after vaccination resemble classic multiple sclerosis rather than monophasic acute disseminated encephalomyelitis (Tourbah *et al.*, 1999). As stated above, a chance association between multiple sclerosis and MMF is possible. However, the high proportion of multiple sclerosis (8.7%) in patients with MMF, which is regarded as a very rare adverse reaction to vaccines, is quite impressive. The prevalence of subclinical white matter abnormalities, detected by brain MRI, has not been yet evaluated in MMF patients. We believe that our findings should be taken into account in the debate on the association between HBV vaccination and multiple sclerosis in two respects. First, since both HBV vaccines and tetanus toxoid vaccines were implicated in our patients, aluminium adjuvants, instead of vaccine antigens themselves, could be regarded as potentially deleterious, as previously suggested (McMahon *et al.*, 1992). Aluminium-containing vaccines induce the development of earlier, higher and longer-lasting immunity compared with soluble vaccines. Aluminium adjuvants act by depot formation at the site of injection, but also induce immune activation that includes IL-1 (interleukin-1) production by monocytes, eosinophilia, complement activation, and increased specific and non-specific IgG1 and IgE antibody responses (Gupta *et al.*, 1995). Secondly, persistent MMF lesions may be associated with an immunological process underlying particular susceptibility of some individuals to develop multiple sclerosis. Interestingly, MMF was occasionally associated with the recent onset of an autoimmune disease, including systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis, in our initial series (Gherardi *et al.*, 1998), suggesting that MMF patients could be at risk of developing autoimmune disorders other than multiple sclerosis. In animal experiments, lympho-plasmacytic infiltrates were observed in the vicinity of macrophages when the complete vaccine was used, defining the so-called immunogenic granuloma that was not formed when the adjuvant was used alone and that increased when polyantigens were added to the vaccine containing aluminium-adjuvanted vaccine (Balouet *et al.*, 1977). It is therefore possible that persistent local antigen presentation assessed by the lymphocytic component of MMF lesions is involved in the emergence of autoimmune disorders.

Nearly 100% of the 60 million French population have been immunized against tetanus toxoid and, among adults (age >15 years), 26 million (31%) have been immunized against HBV (Ministère de l'emploi et de la solidarité). By comparison, 92 patients with MMF, including eight with a multiple sclerosis-like disorder, is a very small number. HBV infection is a major public health problem, infection affecting ~300 million people worldwide and is a major cause of chronic liver disease and hepatocellular carcinoma, killing an estimated 1 million people each year (Zipp *et al.*, 1999). According to the recommendations of the WHO vaccine safety advisory committee, there is no basis at present for recommending a change in HBV vaccination practices (WHO Vaccine Safety Advisory Committee, 1999).

We conclude that (i) MMF is an emerging condition characterized by stereotypical myopathological alterations attributed to aluminium-containing vaccines, which manifests by diffuse myalgias; (ii) multiple sclerosis-like CNS disease may be observed in patients with MMF; and (iii) deltoid muscle biopsy searching of the myopathological alterations of MMF should be performed in multiple sclerosis patients with myalgias.

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