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Neurological manifestations of Behçet's disease in a Caribbean population: clinical and imaging findings

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Abstract Behçet's disease (BD) is a chronic relapsing multisystem disorder. While most frequently occurring around the Mediterranean and in Japan, isolated cases of BD have been reported in Africa south of the Sahara and in the Caribbean. The aim of this study was to describe our experience of BD in Guadeloupe (French West Indies) where the presence of the disease has not been reported previously. We analysed retrospectively the charts, and clinical and imaging features of patients native to Guadeloupe who were diagnosed with neurological manifestations of BD between 1989 and 1999. In our series of 13 cases, seven had neurological involvement. Neurological manifestations included meningoencephalitis or meningoencephalomyelitis in four cases, cerebral venous thrombosis in one case and peripheral neuropathy in two cases associated with myositis in one. Patients received treatment with colchicine (n=7), corticosteroids (n=6), immunosuppressive therapy (azathioprine and/or cyclophosphamide; n=4), acetylsalicylic acid (n=2) and oral anticoagulation for venous thrombosis (n=1). Long-term sequelae occurred only in patients with recurrent neurological disease. This study suggests that the frequency of BD in this Afro-Caribbean population is higher than this reported in Caucasian populations. Meningoencephalitis is associated with a poor prognosis while other patients achieved recovery.

Key words Behçet's disease · Caribbean · Neurological involvement

Introduction

Behçet's disease (BD) is an episodic disorder of unknown origin occurring mainly in young adults, originally described by the Turkish dermatologist Hulusi Behçet as characterised by the clinical triad of oral ulcers, genital ulcers and uveitis [5]. It is a systemic disease with variable manifestations involving the skin, eyes, joints, lungs, intestines, veins and nervous system. The frequency of nervous system involvement has varied from 5.3 % [25] to 25 % [4]. Neurological involvement is reported mainly during the active phase of the disease and is inaugural in 3 % of cases [1]. The disease is frequently encountered in Japan, the Middle East and many Mediterranean countries particularly Turkey [9, 22, 28, 33]. In these areas, it is a major cause of blindness, and has been linked to HLA-B5 or B51 antigens [8]. Although isolated cases have been reported in African and Afro-Caribbean individuals [13,14, 24, 26], the prevalence of BD in these people is unknown. In the present study we describe the clinical and radiological features of seven patients presenting neurological manifestations of BD in the French West Indian Island of Guadeloupe, where the presence of the disease has not been reported previously.

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Methods

All departments of medicine in Guadeloupe where patients with multisystem disorders, including BD could have been referred were asked to participate to the study and allow us to include the patients with suspected BD. Thirteen patients were referred to the Departments of Dermatology, Ophthalmology, or Neurology of the French West Indies University Hospital (Guadeloupe) over a 10-year period from 1989 among a total population of 420,000 mostly of African origin. All our patients were born and resident in Guadeloupe and were of Afro-Caribbean origin, except one who had a Japanese grandmother. The diagnosis was made according to the international classification of BD, in which recurrent oral ulceration was a prerequisite, with two more typical signs (genital ulcers, eye lesions, skin lesions, positive pathergy test) [15]. In the present study 11 patients had the complete syndrome criteria and were considered as definitive BD. Two patients (patients 5 and 12) who did not fulfil the international criteria were considered as probable BD [1].

In all cases, the standard biological study included blood examination, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), electrolytes, glucose, calcium, liver function and serum electrophoresis. The main differential diagnoses (tuberculosis, sarcoidosis and systemic lupus erythematous) were eliminated by chest radiography, microbacterial examinations, serum angiotensin-converting enzyme levels and antinuclear and anti-DNA antibodies. The HLA group was assessed in four cases. A pathergy skin test was performed in five cases. It was considered positive when a papule or pustule was obtained 48 hours after a single prick to the subcutaneous tissue with a 21G needle, through disinfected skin on the flexor aspect of the forearm. Among the 13 patients (Table 1), seven had neurological involvement and are reported individually in the present study.

Case reports

Clinical characteristics are summarised in Table 2.

Case 1

A 19-year-old woman was admitted in June 1997 with confusion, neck pain and fever. She also complained of temporal headache, fever, anorexia, asthenia and weight loss during the previous 6 months and described a 17-year history of recurrent buccal ulceration and a 3-year history of recurrent genital ulceration and arthralgia. Neurological examination revealed drowsiness, a meningeal syndrome, left hemiparesis and right IIIrd cranial nerve palsy. CT showed a contrast-enhanced capsular and thalamic nodular lesion. Cerebrospinal fluid (CSF) contained 200 cells/mm^3 with 36 % lymphocytes and 64 % polynuclear neutrophils, 212 mg/dL protein and normal glucose. Microbiological CSF studies were negative. She had a severe visual loss in the right eye. Fundus examination showed right retinal periphlebitis with perivenular infiltrates, papillary oedema with haemorrhage and macular oedema. The general examination showed oral and genital ulcers, facial folliculitis. The pathergy skin test was positive. Skin biopsy showed polymorphic superficial dermatitis and perivascular inflammation of the middle dermis containing neutrophil cells. The patient was negative for HLA B5. She was treated with 1 g IV pulse dose of methylprednisolone. A major improvement in her clini-

Table 1 Main clinical features of Behçet's disease in 13 patients

Patient	Sex	Ulcers		Pathergy test	Skin lesions	Neurological signs	Oph. signs	Articular signs	Vascular thrombosis	HLA B5 or B51	Follow up (years)
		B	G								
1	F	+	+	+	PF	ME	VUH	Yes		No	1
2	M	+	+	ND	V	ME		Yes		ND	11
3	M	+	+	ND	PF	ME				No	6
4	M	+	+	–	PF	ME				ND	9
5	M	–	–	+	PF	CVT, ME	V	Yes	CVT, LTP	No	4
6	M	+	+	–	EN	PN	V	Yes		ND	3
7	F	+	+	ND		PN, M	U	Yes		No	0.1
8	F	+	+	ND	PF					ND	5
9	M	+	+	+	EN, PF		U	Yes		No	5
10	F	+	+	ND	EN		U	Yes		No	5
11	F	+	+	ND	EN			Yes		ND	1
12	M	+	–	ND			U	Yes	LTP	ND	0.5
13	M	+	–	ND	PF		U	Yes	LTP, PE	ND	0.5

ND not determined, *B* buccal, *G* genital, *PF* pseudofolliculitis, *EN* erythema nodosum, *ME* meningoencephalitis, *CVT* cerebrovascular thrombosis, *M* myositis, *PN* polyneuropathy, *Oph* ophthalmological, *V* vasculitis, *U* uveitis, *H* hyalitis, *LTP* limb thrombophlebitis, *PE* pulmonary embolism

Table 2 Main neurological features and course of Behçet's disease

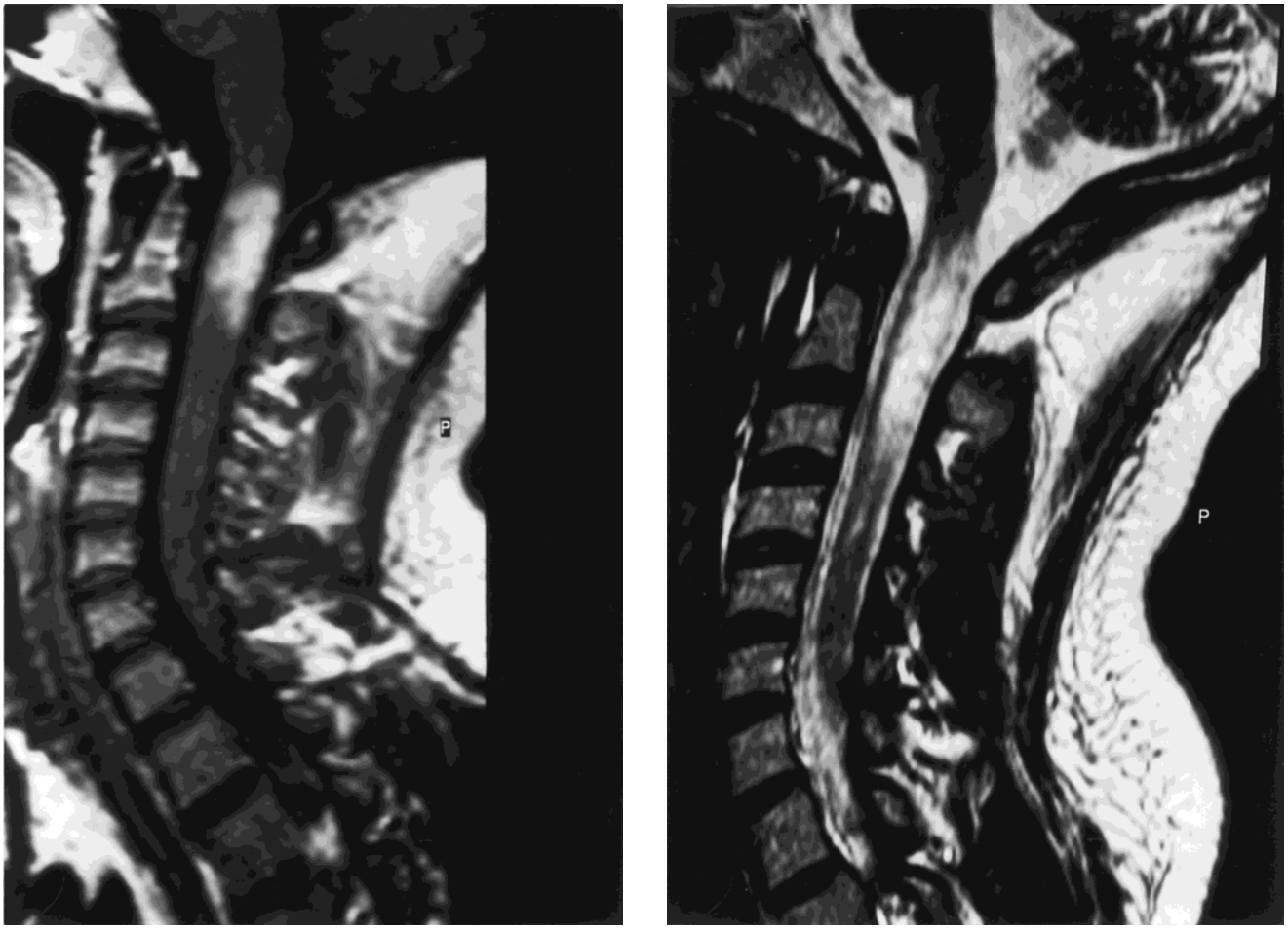
Patient	Sex/age at diagnosis (years)	Main neurological signs	MRI (T2-weighted sequences)	Diagnosis	Treatment	Residual signs
1	F/19	Meningitis, hemiparesis	a) 1 capsulo-thalamic nodular hypersignal b) 1 cervicospinal hyperintense area	ME	CST, CO, AZTH, CPH	Ataxia, Tetraparesis
2	M/33	a) Hemiparesis, VI, VII palsy, cerebellar syndrome b) Pseudobulbar palsy	a) 2 protuberential nodular hypersignals b) 1 hyperintense area of mesencephalon and diencephalon	ME	CST, CO, AZTH	Hemiparesis, Pseudobulbar palsy
3	M/25	a) Hemiparesis, nystagmus, III palsy b) Tetraparesis, dementia, pseudobulbar palsy	a) 2 capsulothalamic linear hypersignals b) 2 nodular hypersignals in pons c) 2 mesencephalic and subthalamic hyperintense areas	ME	CST, AZTH	Tetraparesis Pseudobulbar palsy Dementia
4	M/48	Monoparesis	1 thalamic hypersignal	ME	CST, CO, AZTH	none
5	M/30	Headache, confusion, hemiparesis, III, VI palsy	a) Hypersignals of internal capsule, thalamus, temporal, parietal, occipital lobes, mesencephalon b) SSS, LS thrombosis	CVT	CST, CO, AS, AC	Hemiparesis T2-MRI: 1 nodular subthalamic lesion
6	M/42	leg paresthesia	ND	PN	CST, CO, AS	None
7	F/54	leg paresthesia	ND	PN, Myositis	CO, CST	None

ND not determined, *ME* meningoencephalitis, *CVT* cerebrovascular thrombosis, *PN* polyneuropathy, *SSS* superior sagital sinus, *LS* lateral sinus, *CST* corticosteroids, *CO* colchicine, *AZTH* azathioprine, *CPH* cyclophosphamide, *AS* acetylsalicylic acid, *AC* anticoagulants

cal status was subsequently observed. She was discharged after 20 days and continued to receive an oral dose of 1 mg/kg/day corticotherapy and 1 mg/day colchicine. Corticosteroids were reduced over a period of 3 months to 20 mg/day. From October to December 1997 she complained of neck pain and developed progressive gait ataxia. Examination in December 1997 showed right hemiparesis, spasticity of all limbs, marked gait ataxia, anterior uveitis and hyalitis in the right eye. In February 1998, she had meningitis with hyperthermia and developed a subacute tetraplegia. Brain MRI showed a right capsular-thalamic nodular lesion which was not enhanced and corresponded to the sequelae of the previous inflammatory process. Spinal magnetic resonance imaging (MRI) revealed a large inflammatory area of the cervical spinal cord from the first to the fourth cervical vertebra (Fig. 1A, 1B). She received three IV infusions of cyclophosphamide (0.7 gr/m^2) each followed by 75 mg azathioprine, 1 mg/kg corticosteroids and 1 mg colchicine orally. Three months after starting immunosupressive therapy she contracted pulmonary tuberculosis, for which she received antibiotherapy. After a 3-year follow-up, her neurological status was unchanged with tetraparesis and marked gait ataxia, but she was still able to walk. Brain and spinal cord MRI showed an atrophy of the cervical spinal cord without abnormality of signal.

Case 2

A 33-year-old man was admitted in July 1989 with diplopia and fever. He reported arthralgia 3 months before admission. Neurological examination revealed left hemiparesis, right facial palsy, right VIth cranial nerve palsy, right dysmetria and dysdiadochokinesia. Cerebrospinal fluid (CSF) contained 40 cells/mm^3 with 50 % lymphocytes, 63 mg/dL protein and normal glucose. Microbiological studies of the CSF were negative. Brain T2-weighted MRI showed two right nodular hyperintensities in the pons. He received both 20 mg/day prednisone and antituberculosis treatment. His medical status partially improved. In February 1990 he presented with fever, slurred speech and swallowing impairment. Examination showed oral and genital ulcers, multidirectional bilateral nystagmus and right facial palsy. CSF contained 18 cells/mm^3 (60 % lymphocytes), 50 mg/dL protein and normal glucose. Brain CT showed a pontine contrast-enhancing lesion. Skin biopsy showed dermal perivascular and interstitial inflammation. Antituberculosis tetratherapy was withdrawn. Corticotherapy was maintained at 20 mg prednisone daily associated with 250 mg acetylsalicylic acid and 1 mg colchicine. In May 1991, after a 5-month interruption of therapy he developed alteration of consciousness and left hemiplegia. Treatment with 1 mg colchicine, 1 mg/kg prednisone and intravenous cyclophosphamide (0.7 g/m^2) was introduced with only partial improvement of neurological



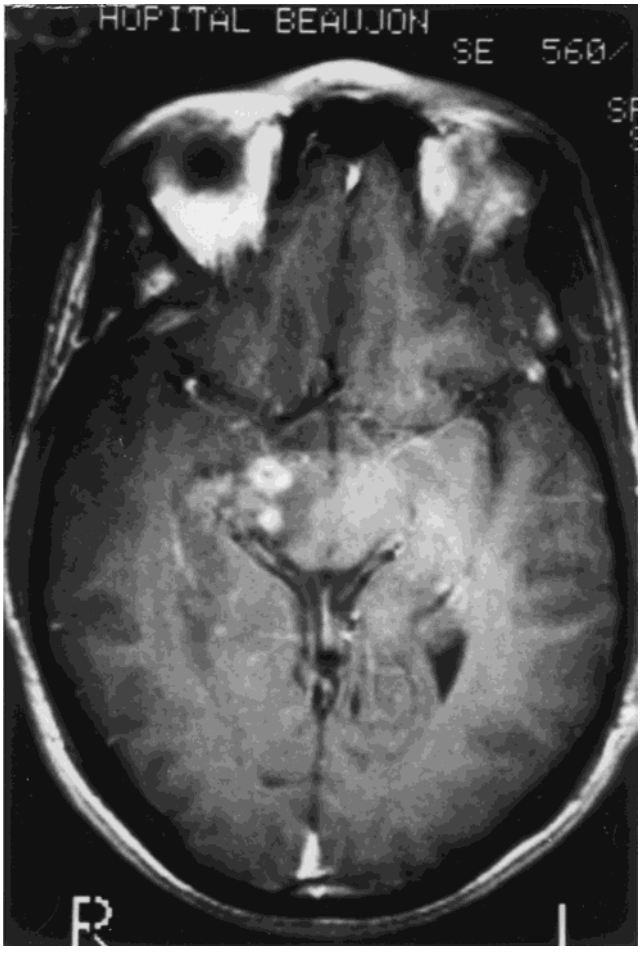
a) b)

Fig. 1 Neuroimaging of meningoencephalomyelitis (Patient 1). Spinal MRI shows a large hypointense lesion of the cervical spinal cord, enhanced by contrast in T1-weighted sequences (**A**) and hyperintense in T2-weighted sequences (**B**).

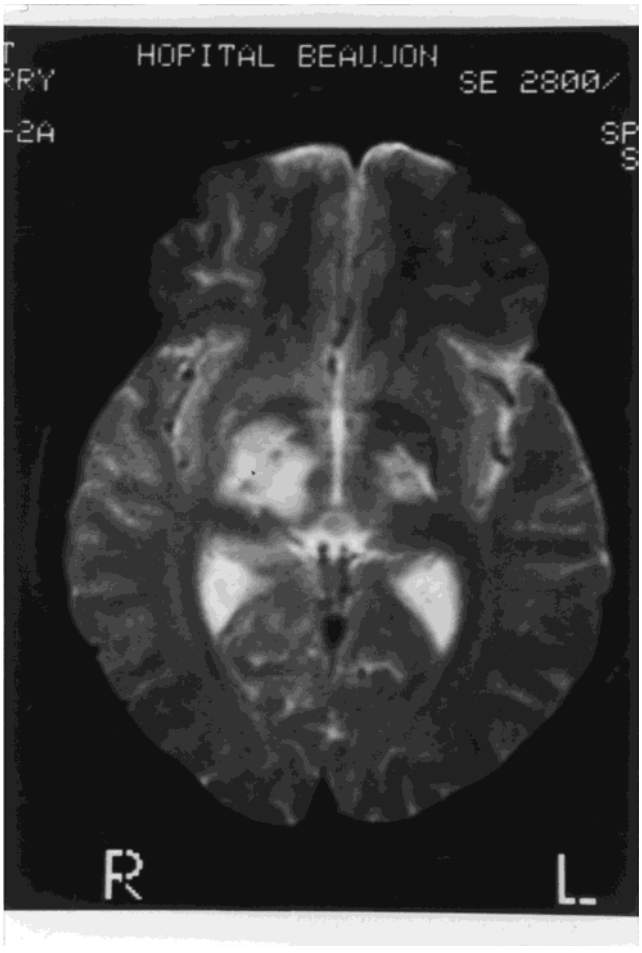
status. Intravenous cyclophosphamide was administered during the next 3 years: 0.7 g/m^2 every month for 2 years followed by 0.7 g/m^2 every 2 months for 1 year. After an 11-year follow-up, his neurological status was unchanged with left spastic hemiparesis and pseudobulbar palsy.

Case 3

A 25-year-old man suffered two episodes of subacute left hemiparesis, in March 1992 and September 1992. He described a 2-month history of asthenia, night sweating, abdominal pain, fever and a weight loss of 10 kg. Neurological examination in March 1992 showed left hemiparesis with hypaesthesia, multidirectional bilateral nystagmus, right IIIrd cranial nerve palsy. Brain MRI showed two right mesencephalic round lesions (Fig. 2A) and a linear hyperintense signal in the right internal capsule. CSF analysis was normal. Improvement occurred spontaneously within two months. Six months later, he presented with slurred speech, swallowing impairment, left hemiparesis, a cerebellar syndrome and oral ulcerations. Cranial MRI showed two large bilateral capsulo-thalamic areas of confluent hypersignals on T2-weighted MRI sequences (Fig. 2B) and bilateral subthalamo-mesencephalic lesions (Fig. 2C). CSF analysis showed 60 cells/mm^3 (80 % lymphocytes and 20 % polynuclear neutrophils). Microbiological studies of the CSF were negative. The patient was negative for HLA B5 group. His clinical status partially improved with daily IV pulses of 120 mg methylprednisolone followed by 10 to 15 mg oral prednisone daily. He was bedridden for 3 years. In 1996 corticosteroids were withdrawn for six months. During this period he experienced recurrent buccal and genital ulcers. He was given a monthly IV dose of cyclophosphamide (0.7 g/m^2) for 6 months followed by oral cyclophosphamide (50 mg/day). A mild



a)



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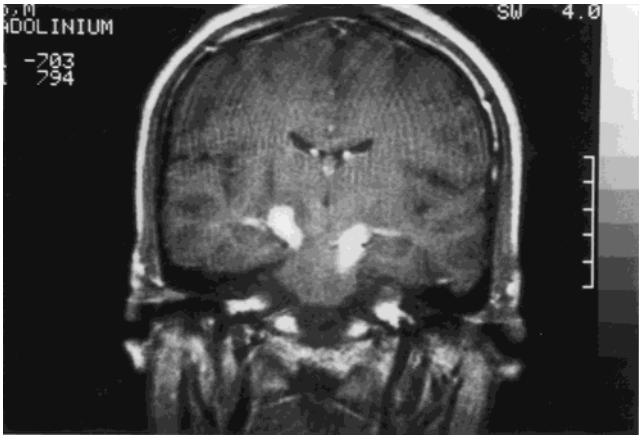

c)

Fig. 2 Magnetic resonance images of meningoencephalitis (Patient 3). Initial axial T1-weighted images after injection of gadolinium show 2 mesencephalic round hypointense lesions enhanced by contrast (**A**). After 6 months, axial T2 sections showing large capsulothalamic hyperintense areas (**B**); bilateral mesensephalic lesions extended to the subthalamic area, as visualized in and in T1-weighted coronal images after injection of gadolinium (**C**).

improvement in his clinical status was subsequently observed.

Case 4

A 48-year-old man of mixed African and Japanese origin was admitted in October 1989 for headache and fever at 40 °C. He had had hepatitis B in 1979 and also had 12-year history of recurrent oral and genital ulceration. Examination showed right arm weakness and genital ulceration. The CT findings were normal. Cerebrospinal fluid contained 1 leukocyte/mm^3 and 110 mg/dL protein. Cranial MRI showed a left thalamic nodular hyperintense lesions on T2-weighted sequences. Treatment with 30 mg prednisone was intro-

duced and progressively reduced to 10 mg in association with 1 mg colchicine and 100 mg azathioprine. His clinical status rapidly improved, while headache and arm weakness disappeared within 2 weeks. After 1 year, and until 2001, the patient had only moderate right pyramidal signs. He reported one more episode of oral ulcers and colchicine was raised to 2 mg daily.

Case 5

A 30-year-old man with a reduced platelet count since 1994 and a history of arthralgia presented an episode of right hemiparesis with aphasia and headache in August 1995. During the following weeks, he developed confusion, with right hemiparesis, slurred speech, left IIIrd and VIth cranial nerve palsy and swallowing impairment. Standard investigations revealed an increased ESR (66 mm), a CRP level of 107 mg/l and a raised leukocyte count of 12,600/mm^3. Brain CT and MRI showed a thrombosis of the longitudinal superior sinus and multiple infarcts in the left capsulothalamic, left temporal and right parietal regions and in the left mesencephalon. Cerebrospinal fluid contained 3 leukocytes/mm^3 and 50 mg/dL protein. The pathergy skin test was positive. The patient was HLA B5 negative. Methylprednisolone (100 mg) was initially administered and progressively reduced over a 6-week period combined with 250 mg acetylsalicylic acid. His medical status improved, but after 6 months he developed a left sural venous thrombosis, superficial thrombophlebitis in the left arm, recurrent episodes of right hemiparesis and retinal periphlebitis. Neurological investigations showed a new occipital hyperintense lesion on T2-weighted MRI resulting from a recurrent thrombosis of the longitudinal superior and right lateral sinus, confirmed by angiographic MRI and cerebral angiography. Treatment with acecoumarin was introduced, together with 80 mg prednisone and 1 mg colchicine. One year after disease onset his medical status had improved. The patient had moderate right arm weakness and was still able to work. Brain MRI showed a left nodular subthalamic hypointense lesion in T1, enhanced by contrast and hyperintense in T2-weighted sequences suggesting meningoencephalitis (Fig. 3).

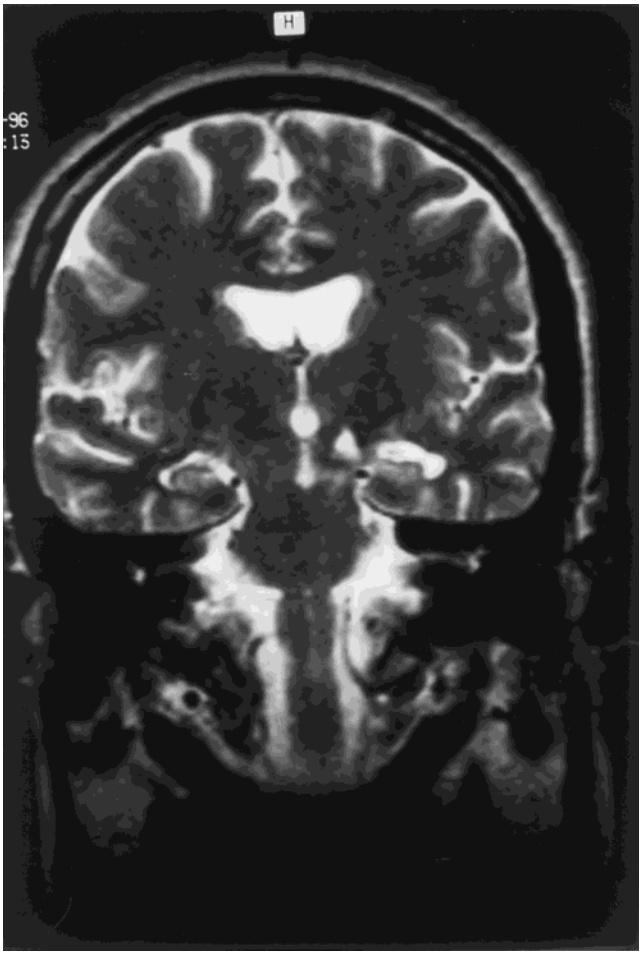

Fig. 3 T2-weighted coronal MRI (Patient 5). Left subthalamic hyperintense lesion

Case 6

A 42-year-old man with a 3-year history of recurrent oral ulcers was admitted in January 1995 with asthenia, bilateral leg paraesthesia, myalgia and arthralgia. Examination revealed oral ulcers, erythema nodosum, skin papulopustular lesions, areflexia and retinal periphlebitis. The pathergy skin test was negative. Nerve conduction studies demonstrated a moderate sensorimotor axonal neuropathy with a decreased amplitude of sensory and motor potentials. The patient did not take any medication or had no exposure to neurotoxic agent. He had no familial history of neuropathy. The principal causes of peripheral neuropathy such as diabetes, vitamin B deficiency, hypothyroidism, chronic renal failure, HIV or HTLVI infections had been excluded. Nerve biopsy was not performed. Treatment with 1 mg colchicine, 250 mg acetylsalycilic acid and 40 mg prednisone was introduced. The patient gradually improved and has been asymptomatic for the past 5 years.

Case 7

A 54-year-old woman with a 10-year history of recurrent oral and genital ulcers was admitted in July 1999 with asthenia, bilateral leg paraesthesia, arthralgia and oligoarthritis. She had a history of bilateral uveitis in 1989 and experienced during the last 10 years three episodes of myositis with myalgia, elevated creatine kinase and

myogenic recording on electromyography performed during the acute phase of one episode. The patient was negative for HLA B5 or B51 groups. Examination revealed oral ulcers, distal leg areflexia without distal sensory loss or weakness. Nerve conduction studies showed axonal sensory neuropathy with decreased amplitude of sensory potential and moderate slowing of sensory conduction. Velocity and amplitude of motor potentials were normal. Needle detection showed an increased temporal recruitment during voluntary contraction. The patient did not take any medication and had no exposure to neurotoxic agents. She had no familial history of neuropathy. The principal causes of peripheral neuropathy such as diabetes, vitamin B deficiency, hypothyroidism, chronic renal failure were excluded. HIV or HTLVI serology were negative. CSF analysis and biopsy were not performed. Treatment with 1 mg colchicine and 40 mg prednisone was introduced. The patient gradually improved but still had episodes of arthralgia until 2001.

Discussion

In the present study of 13 patients, 11 had the complete syndrome but two patients (patients 5 and 12) did not fulfil the international criteria. Patient 5 in the absence of oral ulcerations but with neurological and vascular involvement and three typical signs (eye lesions, skin lesions and positive pathergy test) was considered as belonging to the 3% of patients excluded by the international criteria [15]. In patient 12 the diagnosis of probable Behçet's syndrome was made on the basis of recurrent mouth ulceration, "typical" uveitis and recurrent venous thrombosis. The pathergy skin test had not been performed.

Clinically diagnosed BD in 13 patients out of a population of 420,000, suggests that the frequency of BD may be at least 3/100,000, which would be lower than in Turkey (population based rate of 80 to 300/100,000) [28] or Japan (hospital based rate of 10/100,000) [22] but higher than in the Yorkshire, United Kingdom (hospital based rate of 0.6/100,000) [11]. As with all hospital based retrospective studies, the incidence in the general population cannot be established and is probably underestimated by a selection of severe forms of the disease. However, the University Hospital being the unique institution for the diagnosis, treatment and follow up of patients requiring both internal medicine and neurological disorders, this number may be indicative of the incidence of the BD in the Guadeloupean population. The relatively high frequency of BD in Guadeloupe may be compared with that of other multisystem disorders, such as sarcoidosis (8/100,000) [6] or systemic lupus erythematous, which is the principal aetiological factor of nephropathy in young women in Guadeloupe (unpublished data). We observed a male predominance with a male/female *ratio* of 1.6:1, which was even more marked for patients with neurological complications (2.5:1). No association with HLA B5 was found in the present study. This result must be interpreted with caution, given the small number of patients and the unknown prevalence of HLA B5 or B51 in the Guadeloupean population. The frequency of neurological involvement in BD varies from 5.3 to 25% in the large patient series [4, 25] and 3.3% in a nationwide survey in Iran [9]. Out of 13 patients, seven had neurological forms which is much higher than expected and may reflect a selection of patients with neurological involvement or severe systemic symptoms more than a high level of neurological involvement in Afro-Caribbean cases. The estimation of the prevalence may require a more careful screening of BD in the Guadeloupean population.

Neurological involvement was the first symptom of the disease in two of our patients whereas it is reported to occur mainly during the active phase of the disease, and has been reported as a presenting symptom in only 3% of cases [1]. In both of our cases the definitive diagnosis was not made until the occurrence of ulceration. CNS involvement is considered to be the most severe manifestation of BD, with about 80% of such patients developing meningoencephalitis and/or myelitis and 4% to 17% with cerebral venous thrombosis (CVT), whereas involvement of peripheral nerves or muscle are rare complications of the disease [1, 16]. In the present study, the neurological manifestations were meningoencephalitis in four of the seven cases with neurological involvement, dural sinus thrombosis in one case and axonal neuropathy in two cases, associated in one case with myositis. The association of meningoencephalitis and myelitis found in one of our patients is reported to be common [1, 11]. Spinal lesions usually involve the dorsal [12, 17] or the cervical level [12, 16, 17]. The association of meningoencephalitis and CVT, however, is rare [25, 30] and was observed in one of our patients. Involvement of muscle, causing a polymyositis [3, 19] or peripheral neuropathy, with characteristics of a non-vasculitic axonal neuropathy [23, 31] is unusual and has not been seen in large series including 200 patients with neurological involvement [1, 16]. In our cases, the diagnosis of axonal sensory or sensory-motor distal polyneuropathy was based on electrophysiological recordings. They improved on corticotherapy.

Neuro-imaging features have been well characterised in BD [2, 14, 17, 26, 29]. Cerebral venous thrombosis in BD is not reported to have any specific features that would distinguish it from thrombosis of other origins [30]. The MRI findings in meningoencephalitis differ from other cerebral inflammatory diseases by the preferential location of lesions in the basal ganglia, brainstem or deep white matter region and the extensive

character of lesions [7, 26]. In our patients, brain MRI revealed 13 lesions, which mostly appeared as small nodular foci (7/13) enhanced by contrast (CT or T1-weighted MRI sequences) or as hyperimtense signals on T2-weighted sequences. Nodular lesions were located in the brainstem (4/7) or diencephalon (3/7). Other lesions involved large areas of the brainstem and/or the diencephalon (4/13) or appeared as linear high signals in the internal capsule (2/13). The latter are thought to be a specific finding of neuro-Behçet's disease [26].

Treatment for BD is not standardised but usually consists of colchicine, corticosteroids and immunosuppressive drugs [10, 21, 32]. Considering the lack of controlled therapeutic trials in Behçet's disease, evidence for a therapeutic response is only empirical and not proven. Our clinical experience after a long-lasting follow-up period (2 to 10 years) was that immunosuppressive drugs, especially sequential pulses of cyclophosphamide, could be effective in controlling severe forms of BD. However, they might need to be used early in the course of meningoencephalitis to prevent severe neurological sequelae.

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