Behçet syndrome presenting as cerebrovascular disease

Sirs: Initially described as a triad of recurrent oral aphthous stomatitis, genital ulceration and uveitis, Behçet disease is now known to be a systemic illness that in 10% to 25% of patients involves the nervous system.\(^1\)\(^-\)\(^2\) The neurological symptoms usually begin six months to several years after the mucocutaneous manifestations, and often occur concomitantly with exacerbations of the mucocutaneous lesions.\(^3\)\(^-\)\(^4\) In rare patients, however, the neurological manifestations may precede other signs of Behçet disease.\(^5\)-\(^6\)

Meningoencephalitis, often affecting the brain stem, is the most common neurological involvement. It is characterised by fever, headache, stiff neck, and focal neurological deficits such as hemiparesis, quadriaparesis, cerebellar deficits, cranial nerve palsies, and aphasia. Other neurological manifestations include seizures, encephalopathy, pseudotumour cerebri, myelitis and peripheral neuropathy.\(^1\)\(^-\)\(^3\) \(^7\)\(^-\)\(^8\) Occlusion of cerebral arteries is either considered not to be a feature of this disease\(^2\) or to occur only in rare instances.\(^9\)\(^-\)\(^10\) We report a patient with Behçet disease who presented with cerebral transient ischaemic attacks that antedated mucocutaneous manifestations of the disease by several years.

A 43-year-old white man was first examined in November 1971 when, in the course of one week, he suffered three transient periods of inability to talk and weakness and parasthesias of the right upper extremity that lasted approximately three hours. In the prior two years he had experienced migratory arthralgia of large joints as well as occasional myalgia. There was no history of hypertension or cardiovascular disease, and no risk factors for vascular disease. Blood pressure was 100/60 mm Hg, pulse 80 and regular, temperature 37.1°C. He ran an intermittent and low grade fever, and had left axillary and bilateral inguinal lymphadenopathy. Neurological examination was normal. Complete blood counts, erythrocyte sedimentation rate, serum electrolytes, glucose, urea nitrogen, creatinine, calcium, phosphorous, bilirubin, cholesterol, triglycerides, uric acid, lactic dehydrogenase, aldolase, transaminases, creatine kinase, coagulation time, prothrombine time, partial thromboplastin time, fibrinogen, and protein electrophoresis were normal. Venereal disease research laboratory (VDRL), fluorescent treponemal antibody absorption test (FTA-ABS), latex rheumatoid factor (RF) and fluorescent antinuclear antibody test (ANA) were negative. Urinalysis was normal. Creatine and creatinine in serum and urine were also normal. Lumbar puncture showed an opening pressure of 150 mm H₂O. The cerebrospinal fluid (CSF) contained no red cells, 20 leukocytes/mm³ (90% lymphocytes, 3% monocytes, 7% polymorphonuclear leukocytes) and normal glucose level. Total protein was 65 mg/dl (upper limit of normal: 45 mg/dl), and protein electrophoresis showed prealbumin 3.4 mg/dl (5.2%), albumin 23.2 mg/dl (35.7%), alpha-1 globulin 2.0 mg/dl (3.1%), alpha-2 globulin 3.3 mg/dl (5.1%), beta globulin 5.3 mg/dl (8.2%) and gamma globulin 27.8 mg/dl (42.7%) (upper limit of normal: 13%). VDRL and FTA-ABS in the CSF were negative. Blood, urine and CSF cultures were negative. The EEG showed focal theta activity over the left parietotemporal regions that was accentuated by hyperventilation. CT scan was not available at the time. Pneumoencephalogram, muscle and lymph node biopsy specimens were normal. Left carotid angiography demonstrated minor irregularities of the internal carotid artery and, with the first injection of contrast, a very high grade stenosis of the left middle cerebral artery approximately 1.5 cm from its origin. With a second contrast injection, a total occlusion of the previously stenotic area was observed. The patient immediately developed non-fluent aphasia and a right hemiparesis. Examination showed decreased verbal output with inability to repeat and write but relatively spared auditory and written comprehension, mild right lower face weakness, tongue deviation towards the right, marked weakness of the right upper extremity involving more severely the distal than proximal muscles, mild right leg weakness and slight right-sided hypeflexia. Recovery began ten minutes after the onset of symptoms and was almost complete in three hours. Mild weakness of the right deltoid, triceps, supinators and

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finger and wrist extensor muscles, however, persisted. He was treated with corticosteroids and anticoagulants. He had no further episodes of transient neurological dysfunction.

In July 1972 he began having severe generalised non-throbbing headaches as well as occasional numbness and paresthesias in the feet and right leg. Neurological examination showed mild residual weakness of the right upper extremity and mild bilateral papillodema. Symptoms resolved promptly after increasing the corticosteroid dose. In February, 1973 he noticed a decreased vision in the left eye that developed over two to three days. Visual acuity was 20/20 OD, 20/200 OS. Funduscopic examination showed blurred disc margins in the left eye and bilateral venous congestion. The vision in the left eye quickly improved and returned to normal in five days. In March, 1974 he suffered a left C7 sensory-motor radiculopathy that improved with conservative therapy. In April, 1974 he had a laparotomy for acute appendicitis that was followed by a stormy postoperative course with prolonged dynamic ileus. In September, 1974 he complained of fatigue, myalgia involving particularly the lower extremities, gait clum siness, urinary urgency, and numbness around the waist and in both legs. Examination demonstrated a slight spastic gait and bilaterally upgoing toes. He remained stable for the ensuing two years.

In January, 1977 he noticed increased numbness in both feet and difficulty walking. Examination showed decreased position sense and vibratory sensation in both feet, unsteady gait and bilateral upgoing toes. Head CT was normal. A repeat muscle biopsy was normal. Skin biopsy showed nonspecific lymphocytic infiltration. In May, 1977 he noticed increasing weakness of right upper and lower extremities. Examination showed a moderate right hemiparesis with slight hyperreflexia, and a pulsatile nodule in the right axillary region. Angiography demonstrated an aneurysm of the right axillary artery and occlusion of the left internal carotid artery at the carotid bifurcation. The right carotid system was normal and there was cross-filling to the left hemisphere.

On June 26, 1977, upon waking in the morning, he noticed almost total blindness of the left eye. Visual acuity was light perception and funduscopic examination showed narrow arterioles and a white opaque retina, suggestive of ischaemic retinopathy. The right eye was normal. Visual acuity in the left eye improved slightly to finger counting over the ensuing weeks but showed no further improvement. In April, 1978 he developed a left sixth nerve paresis that recovered in four weeks. Funduscopic examination at that time showed left optic atrophy. He continued complaining of myalgia, particularly in the lower extremities, and clumsiness of gait. Examination in August, 1978 demonstrated a mild right hemiparesis, diffuse hyperreflexia with bilateral upgoing toes, decreased sensation for all modalities in both feet, and a mildly spastic gait. In February, 1979 he complained that his gait had worsened as had the numbness in both legs. He also noticed painful ulcers in his mouth. Examination showed oral aphthous ulcers, increased hyperreflexia and spasticity, increased sensory deficit in the lower extremities, and a positive Romberg sign. Slit lamp examination demonstrated uveitis of the left eye with hypopyon and cellular infiltration of the vitreous. All symptoms followed a remittent-progressive course with periods of exacerbation followed by periods of incomplete remission. Head CT in March, 1985 showed moderate cortical atrophy and mild ventricular enlargement. He has not developed genital ulcers.

Blood studies during the course of the disease, including erythrocyte sedimentation rate, protein electrophoresis, immunoelectrophoresis, and complement C3 and C4 concentrations were repeatedly normal. CSF exams were done at frequent intervals that did not exceed 10 months. Glucose was normal. Leukocytes ranged from 11 to 45/mm³ (78-100% lymphocytes), and total protein from 52 to 80 mg/dl, the gamma globulin fraction ranging from 33% to 64% of the total protein. No oligoclonal bands were present. CSF immunoelectrophoresis on January, 1985 showed an IgG concentration of 29.5 mg/dl (upper limit of normal: 10 mg/dl), and IgA and IgM of less than 6.7 mg/dl. The de novo CNS IgG synthesis was 120 mg/day (normal: less than 10 mg/day). No clear correlation existed between CSF changes and clinical exacerbations of the disease.

The clinical features of this patient are those of Behçet disease. He is unique, however, in that transient ischaemic attacks were the initial neurological manifestation and antedated the classic mucocutaneous and ocular symptoms by several years. Subsequently he developed oral ulcers and uveitis with hypopyon which allowed the diagnosis of Behçet disease. He also displayed atypical CNS manifestations of the disease such as arthralgia, vascular lesions, gastrointestinal symptoms, retinal and optic nerve involvement, and neurological manifestations of meningoencephalomyelitis. Indeed, multiple nervous system sites were involved at varying times which resulted in the characteristic fluctuating course of neuro-Behçet syndrome.

Vascular lesions in Behçet disease occur much more frequently in the venous system than in the arterial system. Reports on arterial lesions are indeed rare and sporadic except from Japan. The two types of arterial lesions recognised in Behçet disease, occlusion and aneurysm, were present in our patient, the former in the cerebral vessels and the latter in the axillary artery. Stenotic or occlusive disease may involve large vessels such as the subclavian, femoral and popliteal arteries, but involvement of the cerebral vessels is exceptional. Alema, in a thorough review of the literature, concluded that “carotid thrombosis has never been reported in patients with Behçet’s disease, nor has post mortem examination revealed any change in brain vessels attributable to arteritis or thrombophlebitis.” Occlusion of large cerebral vessels, however, although uncommon, has been reported, both clinically and pathologically. Shimizu et al observed common carotid artery occlusion in two of 81 cases of vascular–Behçet investigated from a pool of 1731 patients with Behçet syndrome, and Urayama et al reported cerebral artery occlusion in two of 31 cases with vascular Behçet syndrome that were found among 868 patients with Behçet syndrome. The aggregate results of these two Japanese series indicate a prevalence of stenotic cerebrovascular disease in Behçet syndrome of 4/2599, or 0.155%. Neurological symptoms, however, were not reported to have antedated the mucocutaneous and ocular symptoms in these patients, as they did in the patient reported here. The lack of risk factors for vascular disease in our patient, combined with the presence of arthralgia, lymphadenopathy and CSF changes at the time the ischaemic symptoms occurred leave little doubt that the cerebrovascular occlusive pathology was a manifestation of Behçet disease. The main pathological change is a lymphocytic infiltration advancing from the adventitia toward the intima through the elastic laminae which can lead to thrombus formation. A mild CSF pleocytosis with preponderance of lymphocytes, a moderate increase in total protein and elevation of gamma globulin content are commonly seen in neuro-Behçet disease. Our patient showed a remarkable increase in the CSF concentration of gamma globulin and IgG and in the rate of de novo CNS IgG syn-
thesis, but had normal CSF albumin and normal plasma proteins. Similar changes often occur in multiple sclerosis and other chronic and subacute inflammatory diseases of the nervous system but are usually of lesser degree than those observed in our patient. Elevations of CSF gamma globulin to levels higher than 30% of the total protein are very unusual in neurological disorders other than subacute sclerosing panencephalitis and chronic rubella panencephalitis. Oligoclonal bands, however, often seen in chronic inflammatory disorders of the nervous system, were not observed in our patient.

This patient emphasises the protean clinical manifestations of Behçet disease and suggests that this diagnosis should be entertained in young patients with cerebrovascular disease and evidence of a chronic noninfectious inflammatory CNS process.

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Lhermitte's "sign" due to thoracic cord compression

Sir: Lhermitte's "sign", really a symptom, is a sensation of an electric shock radiating down the body and into the limbs on flexion of the neck. Lhermitte described the condition in 1924 and believed it was pathognomonic of multiple sclerosis. Marie et al had described a similar symptom in a patient who had injured the cervical spine. The symptom occurs in 25-33% of patients with multiple sclerosis but has been reported in many other conditions including cervical spondylosis, tuberculosis of the cervical spine, arachnoiditis, radiation myelitis, tumours of the cervical cord, Behçet's disease and subacute combined degeneration of the cord. Clinical opinion is that "this phenomenon denotes a lesion of the cervical cord and occurs most frequently but not exclusively in patients with demyelinating disease". Most patients in whom it has been reported, however, have no compressive or structural disease that is easily localised to the cervical cord. Although the arms are spared in the majority of patients, the possibility that pathology in the thoracic cord might give rise to this clinical phenomenon has not been considered.

A 23-year-old woman presented to her general practitioner describing a tingling sensation, which began in her feet and ascended both legs over 3-4 weeks, being associated with numbness in both legs. At the same time she described the feeling of an "electric shock" radiating down her back and into both legs on flexion of her neck. Because of the presence of Lhermitte's "sign" it was assumed that she had suffered an episode of demyelination and no further investigation was undertaken. Apart from a brief episode of improvement her condition became progressively worse and she was referred for a neurological opinion 6 months later. In addition to the sensory disturbance, she now also described a two month history of weakness of the legs, which impaired her running. She was admitted for investigation by which time she had developed urinary urgency and occasional incontinence. The major complaint was, however, Lhermitte's phenomenon, which radiated to the legs but not to the arms. For this reason she suspected clinical diagnosis was one of demyelinating disease.

On examination she was a fit young woman. Neurological examination revealed a mild spastic paraparesis with a sensory level to superficial sensation at the level of D7. The reflexes were symmetrically brisk and the plantars were extensor. Routine haematological and biochemical investigations were normal. A myelogram showed a complete block at D5 caused by extradural compression. The texture of the adjacent vertebral body appeared abnormal. A D5 laminectomy was performed and a hard, well calcified tumour was removed. The histology was that of a cavernous haemangioma. Post-operatively the Lhermitte's "sign" resolved, bladder function returned to normal and there was no weakness in her legs.

Although Lhermitte's "sign" is most commonly seen in multiple sclerosis it should not be regarded as pathognomonic. It does occur with other pathology affecting the cervical cord. This case demonstrates that symptoms, without radiation to the upper limbs, can be caused by pathology in the thoracic cord. In this case the pathology was extrinsic, but it is possible that similar symptoms might arise from intrinsic demyelinating lesions in the thoracic cord. In