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Magnetic resonance imaging in an HTLV-I antibody positive patient with tropical spastic paraparesis

Sir: Recently interest has been shown in the magnetic resonance imaging of patients with HTLV-I antibody positive tropical spastic paraparesis (TSP).¹⁻³ The MRI changes in TSP may only be mild and with the sensitivity of MRI in detecting lesions these may be fortuitous rather than disease associated.¹ We describe below the case of a young West Indian woman with a spastic paraparesis in whom there were extensive white matter lesions on MRI with an oligoclonal pattern to the CSF electrophoresis and circulating HTLV-I antibodies.

A 36 year old woman who had lived all her life in Grenada, presented with a 3 year history of dragging the left leg progressing to stiffness in both legs and unsteadiness when walking. In 1979, she had pulmonary tuberculosis, treated medically. There was no suggestion of a vasculopathy and she was a non-smoker. General physical examination was normal, except for a spastic paraparesis with bilateral extensor plantar responses. There was reduced vibration sense below the costal margins and position sense was impaired in the feet.

Routine blood tests were normal, as was full myelography. The CSF contained 2 white cells, 0.4 g/l protein and 3.2 mmol/l of glucose. Oligoclonal bands were present in the CSF but not in the serum. Serum angiotensin converting enzyme was 35 (16-53 mmol/minute/ml). Visual evoked potentials were normal. The CT brain scan revealed low attenuation lesions in the white matter, particularly in the periventricular region. MRI (fig.) showed multiple areas of abnormally increased signal in the white matter of both hemispheres and brain stem.

Fig MRI scan showing multiple areas of high signal

The clinical and laboratory findings in our patient would have suggested a diagnosis of multiple sclerosis except that she had lived her life in the West Indies where the disease is rare.⁴ The finding of HTLV-I antibodies in the blood is consistent with a clinical diagnosis of tropical spastic paraparesis.⁵ The clinical similarity of the two diseases has been dealt with elsewhere but the pathology is quite different with an inflammatory meningeal process with mononuclear cell infiltration predominating in TSP.¹ The extent of the white matter changes on MRI of our patient is unlikely to be fortuitous, age related or due to ischaemic or granulomatous pathology. It may well be that the degree of white matter involvement depends on the stage of the illness and the suggestion⁶ that the lesions in TSP are more sparse than in multiple sclerosis is not supported by this case.

As the pathological changes are so different in the two conditions, it is disappointing that the MRI findings are similar. This case, like others, demonstrates the need for full investigation of patients with spinal cord symptomatology and negative myelography. We are grateful to Dr A Dalglish and Dr K Cruickshank for performing the HTLV-I antibody screen on our patient.

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Parkinsonism as first manifestation of lymphomatoid granulomatosis

Sir: Lymphomatoid granulomatosis (LG) was first described in 1972 by Liebow *et al.* as an angiocentric and angiodestructive lymphoproliferative and proliferative disorder of the lungs. LG has a distinctive organ distribution most frequently involving lung, skin, renal interstitium and central nervous system (CNS). Although initially described as a vasculitis, it is now considered that LG is a lymphoproliferative lesion composed predominantly by T-lymphocytes.² Two-thirds of the patients die with a median survival of 14 months despite therapy, and a definable lymphoma is found to have developed in 12% of the patients. The time interval between initial diagnosis and lymphoma range from weeks to several years.³

CNS dysfunction has been reported in 20% and peripheral neuropathies in 15% of patients.⁴ However, extrapyramidal involvement has been rarely described. We report a case of a woman with pulmonary LG and extrapyramidal manifestations.

In December 1986, a 67 year old woman was admitted to hospital because of cough, fever, weight loss and inability to walk. In 1984 she had developed a mood disorder and she was treated with tricyclic compounds without any improvement. In April 1985, the

patient complained of unsteady gait. Neurological examination revealed a festinating gait and cogwheel rigidity more evident on the right side. A brain CT scan was normal. Then, her walking disability increased progressively, despite treatment with biperiden. On admission, the temperature was 37.8°C. On physical examination, there was no lymphadenopathy, but the spleen was enlarged. The patient was confused and showed a discrete rest tremor in both hands, cogwheel rigidity and inability to walk. Chest radiographs revealed multiple bilateral pulmonary nodules. Abdominal ultrasonography showed homogeneous enlargement of the spleen. ESR was 55 mm in the first hour. The following tests were normal or negative: complete blood count, electrolytes, glucose, liver and kidney tests, serum protein electrophoresis and immunoglobulin levels, antinuclear antibodies and rheumatoid factor levels, total complement, bone marrow biopsy, blood and urine cultures, sputum cytology and sputum Ziehl stain, serum titres for brucella, salmonella, cytomegalovirus, Epstein-Barr virus and toxoplasma, ECG and brain CT scan, CSF was colourless with three lymphocytes, glucose 100 mg/dl, total protein 32 mg/dl and no atypical cells. Cranial MRI showed periventricular hyperintensity. Bronchoscopic and gastroscopic examination were both negative. Fine-needle aspiration cytology of one of the pulmonary nodules was negative. A biopsy was taken at thoracotomy.

Microscopical examination of the surgical specimen showed several fairly well-demarcated masses containing foci of necrosis and haemorrhage and a dense polymorphous cellular infiltrate. The infiltrate was composed of varying numbers of lymphocytes plasma cells, large and atypical mononuclear cells and histiocytes. In some areas the infiltrate was present around the blood vessels and invaded the full thickness of their walls. Immunohistochemical studies on formalin-fixed, paraffin embedded tissues indicate that the majority of the infiltrate was composed of lymphoid cells with features of T-cells (Positivity for leucocyte common antigen and UHCL-1, weak positivity for MT-1, and almost complete negativity for MB-2, Ig G, Ig M, Ig A, λ , and κ) (UHCL-1 and MT-1 are pan-T antigens and MB-2 is pan-B antigen). A diagnosis of lymphomatoid granulomatosis (angiocentric lymphomas) was made.

Treatment with prednisone and cyclophosphamide was started and the patient was discharged one month later. The patient showed complete remission of neurological symptoms and neurological exam-

ination was then normal. She has completed three courses of CHOP and the disease remains inactive ten months later.

The issue of whether LG is a reactive, vasculitic process or a neoplasm has been a major point of controversy, LG was originally described as a lesion in the gray zone between a vasculitis and a lymphoproliferative process. Many cases of LG have been found to be T-cell proliferations⁵ and many authors regard these cases as T-cell lymphomas.² Recently, one of the co-authors of Liebow's original paper has stated that virtually all the lesions that would formerly have been called LG are primary lymphoproliferative disorders and that most are malignant lymphomas.⁶ At present, LG and polymorphic reticulosis (PR) (so-called midline malignant reticulosis or non-healing midline granuloma), its upper airway's equivalent,⁷ are considered malignant T-cell lymphomas. The term angiocentric immunoproliferative lesion⁸ (angiocentric lymphoma⁹) has been proposed recently for a spectrum of disorders including LG and PR. Angiocentric lymphoma has distinctive anatomical, architectural and cytological features, as well as a natural history different from other non-Hodgkin's lymphomas.

The CNS is involved in 20% of cases and the peripheral nervous system in 15% of patients. The spectrum of neurological manifestations is large and many patients show multifocal disease.⁴ The lesion may appear exclusively confined to the CNS.^{10,11} Post-mortem studies have demonstrated ischaemic lesions and vascular infiltration by abnormal lymphoid cells.¹² The disease may remain indolent or progress, and long term remissions may be achieved by the early use of corticosteroids and cyclophosphamide. Extrapyramidal manifestations have been rarely described. Patton and Lynch¹³ reported a patient with LG and cogwheel rigidity, weakness and dysmetria. Lopez Gaston¹⁴ reported a patient with laryngeal LG and Parkinsonism, diplopia and brainstem alterations. Postmortem studies have shown subclinical morphological changes in the basal ganglia of two further cases.^{15,16} In the present case we want to emphasise that there was no clinical recovery after anticholinergic drug and levodopa treatment (Sivemot 25/250 mg tid). However, a rapid improvement occurred after the beginning of corticotherapy. On the other hand, neuroimaging failed to demonstrate a CNS lesion. The only one finding was a nonspecific hyperintensity symmetrically surrounding the lateral ventricles. That finding has also been reported in cases of CNS involvement in systemic vasculitis.¹⁷ The mechanisms of

the Parkinsonism in this case are not clear. It may be due to reduced blood flow in the basal regions of the brain, secondary to lymphoid infiltration.

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Neuroleptic malignant syndrome in a patient with Wilson's disease

Sir: The neuroleptic malignant syndrome (NMS) is a rare but potentially lethal complication of treatment with neuroleptic drugs. It is manifested by Parkinsonian symptoms accompanied by fever and signs of autonomic instability. Most of the reports of NMS concern patients with schizophrenia or major affective disorders.^{1,2} We here describe a case of NMS in a patient suffering from Wilson's disease who was taking neuroleptics. To our knowledge this is the first such report.

The patient is an 18 year old man who was well until August 1984. Pregnancy and birth were normal and no serious illness during childhood was reported. He has an older sister who is healthy. His parents are also healthy and not consanguineous. In September 1984 he showed evidence of mental disturbance. He became agitated and began to experience delusions (mainly of a persecutory and homosexual content) and visual and auditory hallucinations. He slept poorly and had anorexia and weight loss. In April 1985, 4 mg haloperidol, 90 mg thioridazine and 6 mg biperiden daily were started. His mental state improved but he developed marked Parkinsonian features and medication was discontinued 10 days later. Until August 1985, the patient was drug free but the Parkinsonian signs, mainly a left hand rest tremor, persisted. During this drug free period he again became agitated, deluded and hallucinated. He was then given

300 mg chlorpromazine, 25 mg loxapine, 4 mg trifluoperazine and 150 mg orphenadrine daily. A few days later his mental state was improved, but the Parkinsonian signs worsened. These drugs were therefore stopped. In November 1985, the patient was receiving only 20 mg diazepam and 150 mg orphenadrine daily. Just before admission to Eginition Hospital (8 January 1985) there was an exacerbation of his psychiatric symptoms. 30 mg haloperidol, 300 mg chlorpromazine and 15 mg trihexyphenidyl daily were restarted. On admission he was sweating profusely, dysarthric with marked sialorrhoea, rigidity, choreiform movements, opisthotonic posturing and fever (39.3°C). He required help to be fed, while his conscious level fluctuated. The respiratory rate was 29/min and the pulse 130/min. Blood pressure was 145/80 mm Hg. From time to time he developed oculogyric crises accompanied by retrocollis and elevation in blood pressure (to 180/120 mm Hg) of about 10 min duration. The following day all neuroleptic drugs were discontinued. On 15 January he received only 15 mg diazepam and 80 mg propranolol daily. On neurological examination he was cooperative. He showed fixity of facial expression. His fundi and pupils were normal. Tongue movements were very limited. Both arms were very rigid. Power was normal but discrete finger movements were very poorly performed. The tendon reflexes were sluggish, abdominal reflexes symmetrical, and both plantar responses flexor. There was no detectable sensory deficit and general examination was normal. A detailed investigation of the blood, liver, and thyroid function was performed. Other investigation included: antinuclear, anti-DNA and antiviral antibodies, C-reactive protein, α antistreptolysin-O, ECG, EEG, muscle biopsy, motor and sensory conduction velocity. Wright, Widal, Weil-Felix, Paul-Bunnell, VDRL, ELISA test were also performed and urine, blood and CSF cultured. All these tests and laboratory data were normal except an elevation of serum CK (340 U/l, normal up to 76) and aldolase (9.8 U/l, normal up to 7.6). Computed tomography of the brain showed moderate ventricular enlargement without changes in the region of the basal ganglia. The serum caeruloplasmin level was severely reduced at 0.06 g/l (normal 0.2-0.4) and the serum copper level was also reduced at 5.7 μ mol/l (normal 11.0-22.0). Urinary copper excretion over 24 h was abnormal at 4.4 and 5.1 μ mol/l (normal 0-1.0). Liver biopsy showed evidence of cirrhosis with deposition of copper and copper associated protein. Kayser-Fleisher rings were readily

detectable with a slit lamp. The diagnosis of Wilson's disease was therefore clearly confirmed during the next 20 days his condition deteriorated. Tone was greatly increased in all muscle groups and his temperature rose to 39.5°C. Finally he became mute, withdrawn and unresponsive. Because of his elevated serum CK, high fever, extrapyramidal signs and autonomic dysfunction the diagnosis of NMS was made. Bromocriptine up to 40 mg/day, dantrolene 200 mg/day and amantadine 200 mg/day were given. Shortly afterwards the patient's condition, including conscious level, muscular rigidity and fever improved considerably. On 5 March, the temperature was normal and remained so afterwards. He was able to feed himself and he could also stand up and walk with support. In contrast his mental condition deteriorated. On 12 March ECT was started and gradually the drug doses were reduced. By 5 April, after 12 ECT treatments he was receiving no drugs except for 80 mg/day propranolol. He was able to speak and communicate. The elevated serum enzymes (CK and aldolase) fell to normal. His psychotic condition was improved with the exception of his impulsive behaviour. Because of the primary diagnosis (Wilson's disease) at this stage (June 1986) treatment with penicillamine 500 mg/day was initiated. One week later this treatment was discontinued because of leucopenia and thrombocytopenia. In September 1986 treatment with trientine dihydrochloride 1200 mg/day was started. The results of 24 hour copper excretion estimation indicated a reduction to the normal limits. One year later (February 1987) the patient is psychiatrically and neurologically well apart from slight rigidity (mainly of the left hand) and dysarthria. During all this last period (6 months) he received 1200 mg trientine dihydrochloride, 30 mg diazepam and 12 mg benzexol daily and there was no need to give any neuroleptic drug.

The patient fulfilled all the primary criteria for NMS given by Levenson³ (fever, rigidity, increased CK) and five of his six secondary criteria (only leucocytosis exempted). In addition the patient met all the three criteria for the definite diagnosis of NMS given by Pope *et al.*⁴ (hyperthermia, severe extrapyramidal effects, autonomic dysfunction). To our knowledge no case of NMS in a patient with Wilson's disease has hitherto been reported though NMS cases in patients with organic brain syndromes, mainly with basal ganglia pathology, such as Huntington's chorea or Parkinson's disease, have been described.^{5,6} Caroff⁷ has suggested that organic brain diseases might be