A young man with a fatal encephalopathy

There are three striking features of this case. The first is the rapidly progressive pace of the illness, resulting in death within five weeks of onset. The second is the CSF lymphocytosis. The third is the multifocal nature of the lesions on the MR imaging

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CASE PRESENTATION

History

In early 1999, a right-handed manufacturing engineer in his thirties presented to his general practitioner (GP) with a week-long history of diminished sensation and paraesthesiae affecting his left arm and leg. Two months prior to presentation he had contracted a 'flu-like illness that had left him with persistent fatigue. At presentation, his GP noticed weakness of his left hand and made a presumptive diagnosis of multiple sclerosis. He prescribed a five-day course of oral prednisolone 40 mg daily, which the patient took for only one day, making a transient improvement. The next day he had difficulty making decisions at work and was stopped by the police for speeding in a residential area. Two weeks after the onset of his neurological symptoms, he was admitted to a local hospital with confusion and then transferred to the Neurology department in Edinburgh the following day.

Two years beforehand, in 1997, he had been diagnosed with right-sided sciatica with magnetic resonance (MR) imaging evidence of an L5/S1 posterolateral disc prolapse, compressing the right S1 nerve root. This had settled with conservative management. Four years previously, in 1995, he developed idiopathic urticaria, at which time an alkaline phosphatase of 195 u/L was recorded. He had had unprotected sexual intercourse with an HIV-positive ex-girlfriend six years earlier in 1993, but on three occa-

sions in the six months after this relationship his HIV antibody tests were negative. He had lived abroad in France and Morocco, although he had not contracted any known infections there. His wife said that he was allergic to ecstasy.

Examination

When transferred to the Neurology department he was uncooperative and made incomprehensible sounds. There was no evidence of meningeal irritation. His eyes opened spontaneously and fundoscopy was normal. Cranial nerve examination was unremarkable. He had a spastic catch in both arms and clonus at both ankles. He moved all four limbs spontaneously and localized pain in each. The jaw jerk and all deep tendon reflexes were brisk with bilateral upgoing plantar responses. General examination only revealed a tattoo on his right knee and seborrhoeic dermatitis of his face.

Investigations

Blood tests

The following investigations were normal: urea and electrolytes, glucose, liver function, calcium, magnesium, phosphate, haemoglobin, platelets, coagulation screen [including prothrombin time, activated partial thromboplastin time (APTT) ratio, and fibrinogen concentration], C-reactive protein (CRP), immunoglobulins (and protein electrophoresis), antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), extractable nuclear antigens (ENA), Rose Waaler test, auto-antibody screen (including antiparietal, antismooth muscle, antimitochondrial and antiglomerular basement membrane antibodies), complement studies (C3 and C4), syphilis serology (VDRL), blood culture, urine culture, *Borrelia burgdorferi* and herpes simplex virus (HSV) serology, long-term blood cultures for *Mycobacterium tuberculosis*, and blood cryptococcal antigen (CRAG). His CD4 count was $651/\text{mm}^3$ (reference range 500–1500) with a CD4/CD8 ratio of 2.4 (normal).

The following investigations were abnormal: the ESR was 20 mm in the first hour, the patient had a peripheral white cell count of $16.3 \times 10^9/\text{L}$ (neutrophils $13.4 \times 10^9/\text{L}$), and he developed a persistent lymphopaenia of $1.0 \times 10^9/\text{L}$ (reference range 1.5–4.0). An HIV antibody test was not performed.

Cerebrospinal fluid

At the referring hospital, a lumbar puncture

had been performed. The opening pressure was 20 cm of cerebrospinal fluid (CSF). The CSF was slightly cloudy, with mild xanthochromia, a protein of 0.61 g/L (reference range 0.14–0.45 g/L), 660 erythrocytes/ mm^3 , 84 white cells/ mm^3 (100% lymphocytes), normal glucose ratio and Gram stain, negative CSF CRAG, Ziehl-Nielsen stain and HSV PCR. Bacterial and mycobacterial culture of the CSF yielded no growth. CSF cytology revealed a mild chronic inflammatory cell infiltrate.

Imaging

A chest X-ray was normal. Computed tomography (CT) of the brain, also performed at the referring hospital on the day of admission, had shown an area of low density, 1 cm in diameter, in the right frontal lobe, with no evidence of contrast enhancement (Fig. 1). Two days after admission to the Neurology department, pre- and post contrast T_1 and dual echo MR imaging of the brain demonstrated multiple, white matter abnormalities in periventricular and subcortical locations, the thalamus and midbrain, ranging from a few millimetres to 1.5 cm in size, with some evidence of contrast enhancement (Fig. 2).

Neurophysiology

An electroencephalogram (EEG) revealed marked generalized irregular slow wave activity associated with multifocal repetitive sharp wave complexes, mainly in the frontal and left temporal regions (Fig. 3).

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Figure 1 Enhanced computed tomography of the brain on the day of admission to the referring hospital, showing an area of low density, 1 cm in diameter, in the right frontal lobe, with no evidence of contrast enhancement.

Figure 2 (a,b) Dual echo axial magnetic resonance (MR) imaging of the brain showing multiple, white matter abnormalities in periventricular and subcortical locations. (c) Post-contrast T1-weighted coronal MR imaging of the brain showing ring-enhancement of a white matter lesion adjacent to the trigone of the left lateral ventricle, but no enhancement of the meninges.

Clinical course

He was treated with intravenous aciclovir, ceftriaxone, sulphadiazine, pyrimethamine, folinic acid and methylprednisolone without improvement. Soon after admission he developed type I respiratory failure and was transferred to the intensive care unit for intubation and ventilation. He became anaemic (Hb 10.9 g/dL, MCV 89.7 fl) and his neutrophil leucocytosis persisted. A further examination of the CSF five days after admission revealed the opening pressure to be 25 cm of CSF with a protein of 0.87 g/L and 20 white cells/mm³ (100% lymphocytes). His clinical condition gradually deteriorated over the following fortnight. A further CT of the brain revealed diffuse low density of the periventricular white matter and the brainstem, blood in the posterior pons and midbrain, sulcal effacement, and compression of the ventricles and basal cisterns (Fig. 4). He died the next day, three weeks after hospital admission. An autopsy was performed.

DISCUSSION

Professor Neil Scolding

There are three striking features of this case. The first is the rapidly progressive pace of the illness, resulting in death within five weeks of onset. The second is the CSF lymphocytosis. The third is the multifocal nature of the lesions on the MR imaging. The course of this illness makes an underlying inflammatory or infective immunological disease the most likely explanation. All the clinical and radiological findings plainly point to central nervous system disease. The differential

Figure 3 Electroencephalogram showing marked generalized irregular slow wave activity associated with multifocal repetitive sharp wave complexes, mainly in the frontal and left temporal regions.

Figure 4 Unenhanced computed tomography of the brain the day before death, showing (a) diffuse low density of the periventricular white matter and the brainstem, sulcal effacement, compression of the ventricles and basal cisterns, and (b) blood in the posterior pons and midbrain (arrow).

Table 1 Differential diagnosis of this patient's inflammatory encephalopathy

Primary central nervous system inflammatory disorders
Multiple sclerosis and variants
Acute disseminated encephalomyelitis and variants
Systemic inflammatory/immunological diseases
Systemic lupus erythematosus and other connective tissue diseases
Primary antiphospholipid syndrome
Organ-specific auto-immune disease (e.g. Hashimoto's thyroiditis)
Sarcoidosis
Behçet's disease
Rheumatoid disease
Cerebral vasculitis
Primary angiitis of the central nervous system
Primary systemic vasculitides
Wegener's granulomatosis
Microscopic polyangiitis
Polyarteritis nodosa
Giant cell arteritis
Churg–Strauss syndrome
Secondary vasculitis
Drugs (e.g. sulphonamides)
Infections (e.g. hepatitis B/C, fungal infections)
Connective tissue diseases (e.g. systemic lupus erythematosus, Sjögren's disease)
Malignancy (myeloproliferative)
Sarcoidosis
Cryoglobulinaemia
Neoplasia
Infectious disorders
HIV-related (toxoplasmosis, <i>Mycobacterium tuberculosis</i> , cytomegalovirus, cryptococcus, progressive multifocal leucoencephalopathy)
Herpes simplex virus, and other viruses
Whipple's disease
Non-inflammatory disorders
atrial myxoma
infective endocarditis
thrombotic thrombocytopenic purpura
cholesterol embolization syndrome
intracranial venous thrombosis
Susac's syndrome
mitochondrial disease (e.g. Leigh's disease)
Malignancy
paraneoplasia
lymphoma
multifocal glioma

diagnosis of a subacute multifocal inflammatory encephalopathy is very wide (Table 1), but this is a not uncommon clinical problem, and a rational process of elimination is possible.

Salient clinical features

The onset and aggressive pace of this patient's ill-

ness help narrow the differential diagnosis, but many other features of the history could represent either important clues or be wholly irrelevant to the neurological problem. The preceding 'flu-like illness suggests postinfectious problems. A history of HIV exposure six years beforehand is hard to dismiss outright (despite there being negative HIV tests over the following six months), and his travel history also helps to concentrate attention on infectious disorders. The suggestion of parenteral drug misuse indicates a mode of acquisition of opportunistic infections. Idiopathic urticaria with some liver function disturbance can occur with almost any illness, including HIV seroconversion, and it can also occur at the onset of malignancy, particularly lymphoma. Furthermore his allergy to ecstasy potentially implicates the whole gamut of other recreational drugs and toxins, which can directly induce a number of neurological complications. His sciatica, however, is certainly irrelevant, because disc prolapse had been demonstrated on MR imaging.

There are no neurological signs that help in the differential diagnosis – some evidence of cerebral irritation, impaired conscious level, but no meningism or suggestion of focal deficits.

In the investigation of this inflammatory encephalopathy, there were several potentially significant omissions: lupus anticoagulant, anti-cardiolipin, thyroid and antigliadin antibodies. The 100% lymphocytosis in the spinal fluid is not terribly specific, especially as it is not clear whether the patient had had antibiotics beforehand. The EEG is not particularly helpful; it is consistent with a multifocal inflammatory, rather than a diffuse metabolic, encephalopathy.

Differential diagnosis – unlikely candidates

Many of the listed causes of an acute inflammatory encephalopathy can be quickly dismissed (Table 1). The lack of growth of *Mycobacterium tuberculosis* from the CSF, and negative HSV CSF PCR militate against those diagnoses. Whipple's disease, although common in clinicopathological conferences, is not in keeping with the clinical presentation. The absence of a cardiac murmur is against infective endocarditis and atrial myxoma. The imaging is not really consistent with intracranial venous thrombosis and neither is the clinical picture. The non-inflammatory conditions that in other circumstances can mimic vasculitis, such as the cholesterol embolization syndrome and mitochondrial disease, can be dismissed. There is nothing in the story positively to

suggest sarcoidosis. I have seen multifocal glioma presenting with relapsing remitting episodes responsive to steroids, but there are too many discrete lesions in this case to be consistent with the diagnosis. Paraneoplastic disease does not really fit with the presentation either.

The anti-phospholipid antibody syndrome can cause an acute ischaemic encephalopathy with (usually) a subacute presentation including confusion, quadriparesis, extensor plantar responses, elevated protein and occasionally an elevated cell count in the CSF. ANA is not an effective screening test, and the omission of antiphospholipid and anticardiolipin antibodies makes the disorder a possibility. However, the negative ANCA, the normal ESR, APTT, platelet count and the other negative auto-antibody tests do help to eliminate a number of the conventional systemic vasculitides and the nonvasculitic systemic disorders. There is nothing positively to support primary angitis of the CNS.

The original HIV exposure, his lifestyle, seborrhoeic dermatitis, the presence of a low total lymphocyte count and a CD4 count toward the bottom end of the range might suggest HIV. However, 90% of seroconversions occur within three months of exposure (this patient was exposed and was tested repeatedly over a six-month course), and it is becoming extremely rare for seroconversion to occur more than six months after exposure. Moreover, this patient's illness does not really resemble either the neoplasms or opportunistic infections that occur in the context of the acquired immunodeficiency syndrome (AIDS). Cytomegalovirus (CMV) generally presents with a diffuse encephalitis or ventriculo-encephalitis, accompanied by retinitis. Negative serology and the absence of a response to appropriate treatment militate against toxoplasmosis. It is extremely unusual to have cryptococcal disease without positive serology. The MR imaging is not compatible with progressive multifocal leucoencephalopathy (PML). But most of all, the peripheral CD4 lymphocyte subset count > 500 rules out the neurological complications of HIV, as the great majority of them occur only when the CD4 count is below 100 (Jung & Paauw 1998). It is unclear why the total lymphocyte count was low, but the CD4 count was sufficiently high to help rule out complications of HIV due to immunosuppression.

Differential diagnosis – probable candidates

This only leaves three probable candidates for

the diagnosis: vasculitis (caused by drugs, infections, or conceivably secondary to a lymphoma), diffuse or multifocal lymphoma, or acute disseminated encephalomyelitis (ADEM).

The brain imaging helps narrow down the differential diagnosis. The multifocal white matter lesions on the MR imaging (Fig. 2a,b), tending to cluster around the ventricles, with their longitudinal axes perpendicular to the ventricles are very typical of multiple sclerosis, while a single enhancing lesion with symmetrically distributed lesions of the same age (Fig. 2c) suggests ADEM (Kesselring et al. 1990), but of course these findings are not absolutely specific. The premorbid CT scan (Fig. 4a,b) shows that the patient is clearly coning – probably causing small dural haemorrhages from end arteries as the brain stem drags the circle of Willis down with it – but it is the cerebral hemispheres that I think are the most informative. As well as showing very marked oedema and loss of cortical sulci, there are substantial abnormalities in the white matter, which has become extremely pale. This suggests to me that the multifocal process has spread to become a much more diffuse, myelinoclastic process.

These imaging appearances help to exclude the lymphomatous disorders. Although these can cause multifocal disease, and a (paraneoplastic) vasculitic illness, with MR imaging very much like Fig. 2(a–c), they would be unlikely to cause diffuse myelinoclasia.

Of the three diagnostic categories, the absence of a vasculitic rash makes small vessel vasculitis unlikely as the two almost always occur together, but infectious or drug-induced vasculitides are possibilities. Fungal vasculitis can become a diffuse parenchymal infection, similar to the diffuse white matter disorder apparent on the final CT (Fig. 4a). The most common predisposing factor to fungal vasculitis is type II diabetes, but even though this patient was not substantially immunosuppressed, the high dose intravenous methylprednisolone might have encouraged a fungus to behave in this aggressive manner. Heroin, and particularly cocaine, can cause a number of different neurological complications, such as strokes attributable to vasospasm, and multifocal lesions with an underlying pathology that rarely includes vasculitis. Moreover, cocaine and heroin can also cause a very diffuse myelinoclasia, particularly if they are inhaled, usually presenting with a posterior fossa syndrome. Drug-induced or fungal vasculitis therefore remains possible.

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Both MS (the so-called diffuse cerebral sclerosis of Schilder, Schilder 1912) and ADEM can spread in this way from a multifocal process to a diffuse one with extremely large and even confluent white matter lesions. The absence of any response at all to intravenous methylprednisolone and the very rapid progressive fatal course are very unusual in MS. The initial 'flu-like illness renders ADEM much more likely than MS and its variants as a final diagnosis. Although I believe drug-induced (cocaine) or fungal vasculitis remain possibilities, the clinical course and imaging features to my mind make ADEM the more likely diagnosis.

QUESTIONS

Peter Harvey (retired Consultant Neurologist, London, UK): One thing that struck me was that oligoclonal bands were not mentioned.

Neil Scolding: Yes, oligoclonal bands would have been helpful. It was also surprising that an HIV antibody test was not performed.

Adam Zeman: The Infectious Diseases team advised us to rely on the CD4 count, and we reached the same final diagnosis as Neil on the basis of that information. Given that the patient's CD4 count was over 500, and that the neurological complications of AIDS are extremely unusual above a CD4 count of 200, we did not perform an HIV antibody test.

PATHOLOGY

Professor Jeanne Bell

The autopsy was performed 22 h after death. The

general findings were those of a pale young man with a tracheostomy. The lungs were heavy, oedematous and contained a purulent exudate indicative of bronchitis. The cardiovascular system and gastrointestinal tract were normal, although he had a large soft spleen and reactive lymph nodes. There was purulent urine in the bladder and ureters.

On macroscopic examination of the central nervous system, the scalp and skull were normal, but the dura mater was extremely tense, enclosing a soft, swollen brain weighing 1850 g. Samples of the brain were removed for virology investigation. Although there was no midline shift, the brainstem was expanded, and the uncus and the tonsils were grooved and herniated, but not necrotic. After removing the dura, the leptomeninges appeared slightly cloudy at the base but not really enough to indicate meningitis and the cranial nerves and circle of Willis looked normal. His pituitary gland was soft. Sections of the fixed brain showed features consistent with raised intracranial pressure: the brain was very swollen and there was effacement of the grey/white matter junction. Occasional small petechial haemorrhages were present in the periventricular region of the thalamus (Fig. 5). The central white matter was disintegrating with a very 'shaggy' ventricular lining (Fig. 5). Larger haemorrhages were present in the midbrain and pons, which also appeared focally necrotic.

On microscopic examination, the brain took up stains rather poorly with widespread pallor of the central white matter, reflecting multiple demyelinated lesions (Fig. 6). In the white matter – and to a lesser extent in the grey matter – there was macrophage infiltration, and a degree of astrogliosis (Fig. 7), but only very occasional perivascular lymphocytic cuffing (Fig. 8) and sparse leptomeningeal lymphocytic infiltrates (Fig. 9). Similar changes were also found in the corticospinal tracts of the spinal cord. Haemorrhages, centred on necrotic vessels, were confirmed in the brainstem (Fig. 10). As would be expected from a swollen, herniated brain, there was hypoxic neuronal damage in the cornu ammonis, entorhinal cortex and Purkinje cells of the cerebellum. Many white matter axons in the brainstem stained positive for beta-amyloid precursor protein (Fig. 11), which is a good marker for neuronal damage, and in some areas ischaemia had proceeded to incipient infarction. Focal infarction of the pituitary was confirmed, as expected with this degree of brain swelling and damage. Outside the central nervous system, the enlarged spleen showed

Figure 5 Coronal slice of cerebral hemispheres showing disintegration of swollen brain tissue, petechial haemorrhages in the wall of the third ventricle (arrow), and irregular ventricular lining (dashed arrow).

Figure 6 Perivascular demyelination of cerebral white matter. Luxol fast blue $\times 100$.

Figure 7 Damaged white and grey matter with macrophage infiltration and slight astrocytosis. Haematoxylin and eosin $\times 200$.

Figure 8 Focal perivascular lymphocytic cuffing in the grey matter (arrow). Haematoxylin and eosin $\times 100$.

Figure 9 Sparse leptomeningeal lymphocytic infiltrate (arrow). Haematoxylin and eosin $\times 100$.

Figure 10 Haemorrhagic focus in the pons centred on a necrotic vessel (arrow). Haematoxylin and eosin $\times 100$.

Figure 11 Hypoxic damage within the pons, showing axonal swellings and varicosities (many staining positively for beta amyloid precursor protein) $\times 100$.

phagocytosis of sequestered erythrocytes, explaining the anaemia during the patient's illness.

The differential diagnosis for these appearances includes ADEM, acute haemorrhagic leucoencephalomyelitis (Hurst's disease, Hurst 1941), acute multiple sclerosis (Marburg's disease, Marburg 1906), viral encephalitis, and PML. This patient's pattern of spreading demyelination – not always centred on blood vessels – does not quite fit ADEM, which is characterized by lesions of the same age (comprising perivascular demyelination with a mononuclear infiltrate) maximal in the pons and spinal cord, with occasional petechial haemorrhages. Nor does the infrequency of petechial haemorrhages and their predominant distribution in the brainstem fit acute haemorrhagic leucoencephalomyelitis, which is characterized by multiple petechial haemorrhages surrounding necrotic vessels, especially in the cerebrum. Although viral encephalomyelitis cannot be excluded by the absence of inclusion bodies in this case, the fact that no virus was grown from the autopsy brain tissue, and the pattern of blood vessel necrosis and haemorrhages, do militate against this diagnosis. There was no evidence of HIV-related pathology, nor of PML using the JC probe.

This case is somewhat on the dividing line between ADEM and acute multiple sclerosis (Table 2) (van Bogaert 1950). However, the swollen disintegrating brain with pervasive, synchronous demyelination, sparse astrocytes and fibrinous exudates in the blood vessels is inconsistent with the focal, clearly demarcated, demyelinating lesions of acute multiple sclerosis, which is why the final pathological diagnosis is ADEM.

Questions

Neil Scolding: I attributed the haemorrhages that were apparent on the CT scan in the brainstem towards the end of the illness to traction on the brainstem because of the herniation. But you are saying they are part of the pathological process in ADEM?

Jeanne Bell: I am quite sure they are in this case because of the necrotic vessels and fibrin, indicating ongoing necrosis in the brainstem. The changes are not purely agonal. In this respect the case was tilting towards the pathology of acute haemorrhagic leucoencephalitis in the brainstem, but as you know ADEM can show haemorrhagic lesions.

Charles Warlow: Professor Compston, do you want to say anything about this case and whether you would have used intravenous immunoglobulin?

Alastair Compston (Professor of Neurology, Cambridge, UK): I think that this has been very instructive, and Professor Scolding has taken us very logically to arrive at the correct diagnosis. The clinical course is perhaps more like Hurst's disease and less like ADEM. Hurst's disease tends to result in death, whereas people with ADEM tend to deteriorate over a month or so and then survive. I would have given intravenous immunoglobulin or Campath-1H (Moreau T et al. 1994), but I think it is unlikely that either of them would have made a significant difference.

CONCLUSION

Professor Neil Scolding's clinical diagnosis:
Acute disseminated encephalomyelitis
Professor Jeanne Bell's pathological diagnosis:
Acute disseminated encephalomyelitis

COMMENT

ADEM is at the more severe end of the spectrum of acute, inflammatory demyelinating diseases of the central nervous system. It has also been called postinfectious and postvaccination encephalomyelitis because it is sometimes preceded by infections, which may or may not be identified (most notably measles, but there are many other reported associations) or vaccinations (particularly smallpox and rabies vaccine containing neural tissue, but also diphtheria, tetanus, pertussis and others). However, whether or not some of

Table 2 Neuropathological findings in acute disseminated encephalomyelitis (ADEM) and acute multiple sclerosis (Marburg's disease)

ADEM	Acute multiple sclerosis
Swollen brain, lesions not visible macroscopically	Lesions visible macroscopically
Perivascular demyelination visible microscopically throughout the nervous system	One or many demarcated, demyelinating lesions
Lesions all the same age	Lesions of different ages
Astrocytes inconspicuous	Astrocytes very conspicuous
Fibrinous exudate and possibly haemorrhage around blood vessels	Blood vessel changes absent
Macrophages conspicuous	Macrophages conspicuous
Lymphocytic infiltrate	Lymphocytic infiltrate

these associations are causal is disputed (Gale et al 1994; Murphy & Austin 1985). Other post/para-infectious inflammatory, demyelinating disorders have also been associated with ADEM, including neuropathy, radiculopathy and the Guillain-Barré syndrome (Stüve & Zamvil 1999). It is likely that T-cell mediated reactions – probably against myelin basic protein – in parallel with B-cell responses are responsible for generating the inflammatory damage in ADEM (Scolding 1999).

The clinical course of ADEM has made it a popular subject for clinicopathological conferences (Case records of the Massachusetts General Hospital 1995; Orrell 1996). It tends to be an aggressive, monophasic illness predominantly of childhood, which hardly ever recurs, of intermediate severity between MS and acute haemorrhagic leucoencephalomyelitis, although clinically distinguishing ADEM from these disorders during life can be difficult (Schwarz et al. 2001). Whilst ADEM tends to progress over hours to a peak in days, spontaneous recovery – which is often incomplete – usually occurs over weeks to months. Mostly the disease seems to be self-limiting, but the case fatality may be as high as 20% and up to one third may be left with a permanent neurological deficit. The diagnosis of ADEM is most frequently established on the basis of characteristic findings on MR imaging of the brain (multifocal asymmetric white matter lesions in periventricular and subcortical locations, that commonly enhance synchronously with contrast medium) (Kesselring et al. 1990; Singh et al. 1999).

Many treatments for ADEM have been reported, but none have been tested in a randomised controlled design. High dose intravenous methylprednisolone is the mainstay of treatment (Straub et al. 1997), but intravenous immunoglobulin (Pradhan et al. 1999), plasmapheresis (Kanter et al. 1995), interferon beta, cyclophosphamide, and even hypothermia (Takata et al. 1999) are sometimes used, especially when there is no initial response to corticosteroids.

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