Paraneoplastic necrotising myelopathy in a case of AIDS with lymphoma

Paraneoplastic necrotising myelopathy is a rare and still obscure neurological complication of malignancy.[1] Spinal cord affection is common in patients with HIV infection,[2] but necrosis of the spinal cord in AIDS is rare and usually caused by opportunistic infections.[2] Our patient had AIDS and immunoblastic lymphoma with a necrotising myelopathy, not due to an infectious or vascular cause.

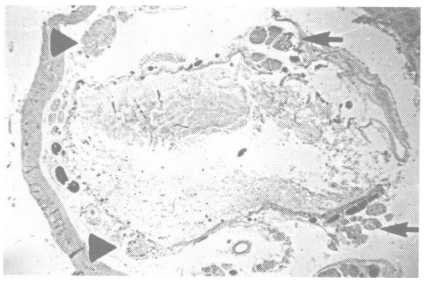
A 29 year old male homosexual patient had been known to be HIV positive since 1987. In 1990 he developed AIDS and *Pneumocystis carinii* pneumonia. Azidothymidine had to be discontinued due to anaemia. In December 1991 he started complaining of a slowly ascending numbness, which began in both feet and reached the T10 level in April 1992. At the same time he developed a weakness in his legs, dull pain on the right, and reduced pain and temperature sensation in the left leg, as well as left maxillar and mandibular herpes zoster. Lumbar puncture showed 43 cells/μl, mostly lymphocytes, plasma cells, and several eosinophilic granulocytes, and protein (5·9 g/l). The serum/CSF protein ratio indicated a severe disturbance of the blood-brain barrier. T2 weighted spinal MRI showed thickening and enhanced water content of the thoracic cord, maximum at the T12 level. A spinal infiltration of a lymphoma was suspected, but examinations of bone marrow, repeated lumbar punctures, or radiographs of the lungs did not show evidence for a lymphoma at that time. Repeated serological tests for neurotropic viruses, toxoplasmosis, syphilis, borreliosis, cryptoccocosis, listeriosis, and candidosis were negative in serum and CSF. The neurological deficits were rapidly progressive and treatment with acyclovir and corticosteroids had no effect. Further MRI a month later no longer showed the intramedullar lesion. The patient was discharged six weeks after admission with a flaccid paraplegia, an incomplete loss of sensibility below T8, and complete incontinence.

At the end of September 1992 he was readmitted with a lymphoma of the lung and cerebral involvement. The paraplegia had become spastic and the level of sensibility loss was now at T6. He was still completely incontinent and had decubitus ulceration. The lymphoma was not treated and the patient died two months later of respiratory failure due to pulmonary problems.

Postmortem examination showed an immunoblastic lymphoma of both lungs, bronchopneumonia of the left lung, and pleural effusions on both sides. There was cerebral involvement of the lymphoma in both hemispheres but no opportunistic infections of the brain and no signs of increased intracranial pressure.

The thoracic meninges stuck to the cord, which was very soft in the thoracic region. On cross sections the softening was confined to the thoracic cord. On both ends of the softened part of the cord there was a roughly 1cm long region of pencil-like softening. There was no macroscopic evidence for angioma, vascular obstruction, or tumour infiltration. Histologically, the thoracic cord displayed the aspect of complete coagulation necrosis with few macrophages. No vascular disease, tumour, or viral, bacterial, fungal, or parasitic infection were found in the spinal cord. No fibrin thrombi were seen despite a study of numerous sections. Only a few mononuclear inflammatory infiltrates were present. The dorsal roots were generally well preserved, whereas the anterior roots showed a substantial loss of myelinated nerve fibres (figure). In the cervical cord, the fasciculus gracilis exhibited a complete loss of myelinated nerve fibres, whereas the fasciculus cuneatus was not affected. The lumbar and sacral cord was well preserved. Immunohistochemistry for herpes simplex 1 and 2 viruses and cytomegalovirus as well as in situ hybridisation for herpes simplex, JC, and varicella zoster viruses were negative. No viruses were found on electron microscopy.

Tumour infiltration, a vascular cause, especially Foix-Alajouanine's syndrome, and an infectious aetiology can be ruled out on serological, histological, and electron microscopical grounds. In particular a herpes simplex infection would have had affected the dorsal roots.[3] The histological features were identical with paraneoplastic necrotising myelopathy, first described by Nonne[4] (quoted in Foliss and Netky[5]). Although the lymphoma was not discovered at the first admission, it is likely to have existed at that time. To our knowledge paraneoplastic necrotising myelopathy has not been described in AIDS before.



Complete coagulation necrosis of the thoracic cord. The arrows mark the well preserved dorsal roots that rules out necrotising myelopathy caused by herpes simplex type 2. Arrowheads mark the ventral roots, which are less stained due to a severe loss of myelinated nerve fibres. There is no evidence for angioma, vascular obstruction, or tumour infiltration. Few mononuclear inflammatory cells are present. The histological features are identical with the paraneoplastic necrotising myelopathy first described by Nonne.[4] (Goldner stain, magnification × 4·5).

L M DRACH
Neurologisches Institut (Edinger-Institut)
W ENZENSBERGER
Klinik für Neurologie
T FABIAN
G HERRMANN
Zentrum der Pathologie Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt/M, Germany

Correspondence to: Dr Lutz M Drach, Neurologisches Institut (Edinger-Institut), Deutschordenstrasse 46, D-60528 Frankfurt/Main, Germany.

1 Henson RA, Urich M. *The neurological manifestations of systemic malignant disease:* Oxford. Blackwell, 1982:433.
2 Artigas J, Grosse G, Niedobitek F. Neuropathology of AIDS. In: Artigas J, Grosse G, Niedobitek F, eds. *The central nervous system in AIDS.* New York: Springer, 1993:79–200.
3 Iwamasa T, Utsumi Y, Sakuda H, Yohitake H, Kakazu T, Kubota R, Nakagawa M. Two cases of necrotizing myelopathy associated with malignancy caused by *Herpes simplex* virus type 2. *Acta Neuropathol* 1989;**78**: 252–7.
4 Nonne M. Ueber acute Querlähmungen bei maligner Neubildung der Wirbelsäule. Ein Fall von acuter transversaler Degeneration des Dorsalmarks bei allgemeiner Knochen-Carcinose. *Berl Klin Wschr* 1903;**40**:728–32
5 Foliss AGH, Netky MG. Progressive necrotic myelopathy In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology.* Vol 9. Amsterdam: North-Holland, 1970:452–68.

Total tau protein immunoreactivity in lumbar cerebrospinal fluid of patients with Alzheimer's disease

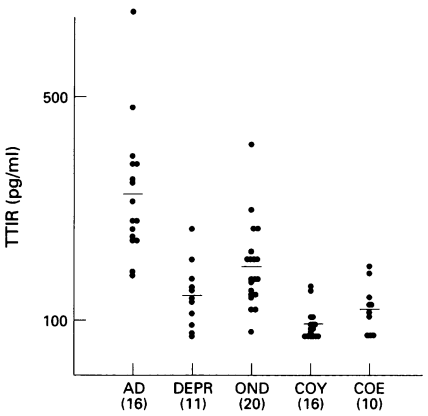
Alzheimer's disease is the most frequent cause of dementia in elderly people. The definite diagnosis can only be established by (semi) quantitative histopathological examination of neuritic plaques and neurofibrillary tangles. Neurofibrillary tangles are composed of bundles of paired helical filaments, the main component of which is the microtubule associated tau protein in a pathologically hyperphosphorylated form. Because valid biological markers for the in vivo diagnosis of Alzheimer's disease are still lacking, the recent development of assays allowing the detection of tau protein in CSF is of much interest.[1–3] The diagnostic value of these assays needs further validation.

We have measured total tau protein immunoreactivity in a series of 73 lumbar CSF specimens with a modified version of a specific sandwich enzyme linked immunoabsorbent assay (ELISA; Innogenetics, Belgium).[2] Informed consent was obtained before lumbar puncture. The patients were subdivided into five groups:

(1) 16 patients (10 women, six men, mean age 73·2 (SEM) 3·6 years) with probable Alzheimer's disease according to the NINCDS-ADRDA criteria; in addition, a mini mental state examination (MMSE)[4] was performed; (2) 11 elderly patients (eight women, three men, mean age 68·3 (SEM 4·2) years) with major depression (DEPR) according to ICD-10 and DSM-III R; (3) 20 patients (11 men,nine women, mean age 58·7 (SEM 3·4) years) with other neurological disorders without cognitive impairment; (4 and 5) 16 young subjects (12 women, four men, mean age 37·8 SEM 2·5) years) and 10 elderly subjects (five women, five men, mean age 62·3 (SEM 3·9) years) without CNS disease, in whom lumbar puncture was performed for exclusion purposes.

There was a highly significant ($P < 0·005$) increase in concentrations of tau protein in the Alzheimer's disease group compared with the elderly depressive patients, patients with other neurological disorders, and young and elderly controls (figure). The elderly depressive patients had a non-significant increase compared with elderly controls; the difference compared with young controls was significant ($P < 0·01$). Elderly and young controls were not different. Patients with other neurological disorders had significantly higher values ($P < 0·005$) than both young and elderly controls. There was a significant negative correlation of MMSE score with total tau protein concentrations when all patients with Alzheimer's disease were included ($r = -0·6106$, $P < 0·01$). However, the correlation was non-significant ($r = -0·2830$, $P > 0·05$) when only patients with MMSE greater than 10/30 points were tested.

There exists, hitherto, no study of total tau protein immunoreactivity in CSF of neuropsychiatric disorders which includes all of the patient groups investigated in the pre-



Concentrations of total tau protein immunoreactivity (TTIR) in lumbar CSF of patients with Alzheimer's disease (AD), elderly depressed patients (DEPR), patients with other neurological diseases (OND), young controls (COY), and elderly controls (COE). Mean values are indicated by horizontal bars.

sent study. Our investigation showed a highly significant increase of CSF total tau protein in patients with probable Alzheimer's disease compared with elderly depressive patients, patients with other neurological disorders, and young and elderly controls. It seems plausible that these increases are the result of enhanced release of tau protein from damaged neurons into the extracellular space and, as a consequence, into CSF. Recent results suggested an arbitrary cut off value of 200 pg/ml, at which only a small percentage of healthy controls are positive.[2] Based on our data, we would propose a 10% higher cut off value, of about 225 pg/ml, to better distinguish the elderly depressive patients as well as young and elderly controls. The observed difference between patients with Alzheimer's disease and elderly depressive patients confirms a recent study and is of particular interest.[1] Depressive periods can be accompanied by a severe impairment of attention, receptivity, and concentration which may mimick a dementing process. Thus early neurochemical identification of a depressive syndrome is of great importance for appropriate therapeutic strategies. The reason for more tau protein in depressed patients than in young controls is unknown. On the other hand, the non-significant difference between young and elderly controls leads to the assumption that increased tau protein is not merely a marker of aging itself.

There are contradictory reports regarding the correlation between MMSE and total tau protein immunoreactivity in the CSF of patients with Alzheimer's disease.[1-3] From our data there was a significant correlation only when including the whole range of scores, which became non-significant when excluding the patients with severe dementia. These results corroborate neuropathological findings which showed a significant correlation between the number of neurofibrillary tangles and MMSE only when including severely demented patients.[5] In conclusion, total tau protein concentration in CSF is an important candidate for discriminating patients with Alzheimer's disease from elderly depressed patients as well as from young and elderly controls without mental illness. Further studies on other neurodegenerative diseases are in progress. Moreover, different combinations of tau protein antibodies to detect exclusively normal or hyperphosphorylated tau protein may help to further evaluate the diagnostic value of tau determinations in CSF.

NORBERT RÖSLER
ILDIKO WICHART
KURT A JELLINGER
Ludwig Boltzmann Institute of Clinical Neurobiology, Lainz Hospital, Vienna, Austria

Correspondence to: Dr Norbert Rösler, Psychiatrische Universitätsklinik, Hauptstrasse 5, D-79104 Freiburg, Germany.

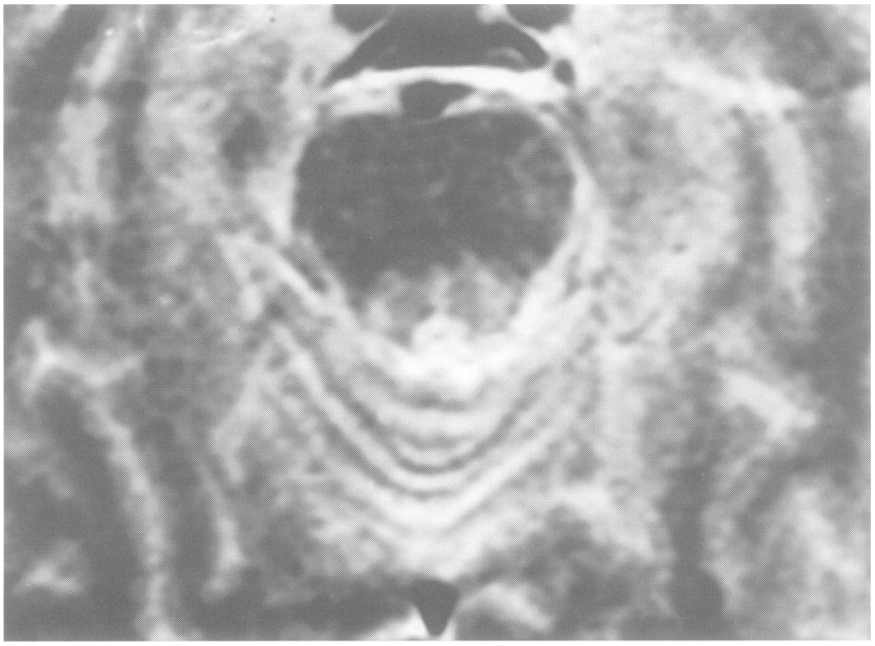
1 Hock C, Golombowski S, Naser W, Müller-Spahn F. Increased levels of tau-protein in cerebrospinal fluid of patients with Alzheimer's disease—correlation with degree of cognitive impairment. *Ann Neurol* 1995; 37:414–5.
2 Van de Voorde A, Vanmechelen E, Vandermeeren M, Dessaint F, Beckman W, Cras P. Detection of tau in cerebrospinal fluid. In: Iqbal K, Mortimer JA, Winblad B, Wisniewski HM, eds. *Research advances in Alzheimer's disease and related disorders*. New York: John Wiley, 1995:189–95.
3 Vigo-Pelfrey C, Seubert P, Barbour R, Blomquist C, *et al*. Elevation of microtubule-associated tau in the cerebrospinal fluid of patients with Alzheimer's disease. *Neurology* 1995;45:788–93.
4 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
5 Jellinger K, Bancher C, Fischer P, Lassmann H. Quantitative histopathologic validation of senile dementia of the Alzheimer type. *Eur J Gerontol* 1992;3:146–56.

Bilateral infarction of the rostral pontine tegmentum as a cause of isolated bilateral supranuclear sixth nerve palsy related to hypertension

The difficulty in locating in vivo the paramedian pontine reticular formation (PPRF), which is the immediate premotor centre for saccade generation, has been a major obstacle to a better clinical understanding of many neuro-ophthalmological syndromes.[1 2] Lateral rectus weakness from a pontine lesion is usually associated with other neurological signs.[3] We report a hypertensive man with an isolated gaze disorder consisting of a severe bilateral abduction palsy and a subclinical bilateral gaze palsy—that is, bilateral conjugate slowness of saccades—with no other identifiable aetiology, who had a bilateral pontine infarction involving the rostral PPRF, seen on MRI.

A 64 year old man with a history of mild hypertension and hyperlipidaemia was referred for evaluation of painless horizontal diplopia of sudden onset. There was no history of head trauma, diabetes mellitus, or any other systemic disorder. Blood pressure was 150/100 mm Hg. Neurological examination was normal except for a complex type of gaze defect—namely, mild bilateral conjugate slowness of saccades with an additional severe right lateral rectus weakness and pronounced esotropia of the left eye on straight gaze. No nystagmus or internuclear ophthalmoplegia was seen and the rest of the extraocular movements were full. "Doll's head" manoeuvre (vestibular ocular reflex) in the direction of the palsy was intact. Pupil sizes and light reflexes were normal in both eyes. Sensation in the first division of the trigeminal nerve was intact. Facial and masseter muscles were of normal strength and there were no signs of long tract involvement. Results of routine laboratory tests, including CSF analysis, were unremarkable. Brain MRI (0·5 T) showed only minor bilateral hyperintensities at the upper pontine tegmentum, without definite relevance. One week later he suddenly complained of dizziness and a more intense diplopia on horizontal gaze. His neurological examination showed a newly developed complete paralysis of abduction of the left eye. A second MRI disclosed bilateral hyperintensities at the rostral pontine tegmentum compatible with infarction (figure). The oculomotor dysfunction resolved two months later with only a persistent mild bilateral slowness of saccades and no lateral rectus weakness.

Our patient's brain MRI showed a bilateral infarction with involvement of the rostral pontine tegmentum containing the PPRF, the structure responsible for the gen-



Axial T2 weighted MRI obtained with a 0·5 Tesla unit shows bilateral hyperintensities at the rostral pontine tegmentum compatible with infarction.