Increased Beta₂-microglobulin in CSF of multiple sclerosis

Sir: Increased cerebrospinal fluid (CSF) levels of beta₂-microglobulin (B₂m) have been found in a number of primary central nervous system (CNS) diseases¹ as well as in neurological complications of systemic malignancies,^{2,3} cerebrovascular lesions⁴ and CNS infection.⁵ However, there are discrepancies in the values obtained by several authors for B₂m in CSF of multiple sclerosis patients.^{1,2,5} This may be due to the fact that these studies were performed in small series of patients without taking into account whether they were in relapse or not. We felt, therefore, that the study of CSF B₂m in relation to clinical activity in multiple sclerosis would be of interest.

We studied 30 patients with clinically definite multiple sclerosis.⁶ They were divided into two groups: Group A comprised 14 patients in a stable phase of the disease. Group B included 16 patients who were studied during an acute exacerbation of multiple sclerosis, their sera and CSF having been withdrawn within 3 weeks from the onset of the attack. Control CSF and serum data were obtained from 16 age-matched patients who did not show signs of organic neurological disease and their CSF study was unremarkable. Serum and CSF B₂m was measured by means of an ELISA developed in our laboratory.⁷ No significant difference in serum B₂m was found between the two multiple sclerosis groups and controls, being 1.77 ± 0.19 mg/l for group A, 1.86 ± 0.18 mg/l for group B and 1.80 ± 0.12 mg/l for controls (mean $\pm$ standard error of the mean).

CSF biochemical parameters studied are shown in the table. CSF IgG, IgG index,⁸ daily IgG synthesis⁹ and B₂m were found to be significantly higher in multiple sclerosis patients in relapse. The ratio CSF/serum

albumin was, however, within normal limits,⁸ thus showing a normal blood-brain barrier function.

The origin of increased CSF B₂m in multiple sclerosis patients remains unclear. Higher B₂m values in CSF compared with serum would indicate an intrathecal production and was found in every patient of group B. Whether B₂m comes from tissue destruction or from T-cell activation¹⁰ is at present unknown. Nevertheless, it seems likely that CSF B₂m may be an index of multiple sclerosis activity.

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References

- 1 Starman JJP, Vos J, Van der Helm HJ. The B₂-microglobulin content of the cerebrospinal fluid in neurological disease. *J Neurol Sci* 1977;33:45-9.
- 2 Mavlight GM, Stuckey SE, Cabanillas FF, et al. Diagnosis of leukemia or lymphoma in the central nervous system by beta-2-microglobulin determination. *N Engl J Med* 1980;303:718-22.
- 3 Koch TR, Lichtenfeld KM, Wiernik PH. Detection of central nervous system metastasis with cerebrospinal fluid beta-2-microglobulin. *Cancer* 1983;52:101-4.
- 4 Terent A, Hällgren R, Venge P, Bergström K. Lactoferrin, lysozyme and B₂-microglobulin in cerebrospinal fluid. Elevated levels in patients with acute cerebrovascular lesions as indices of inflammation. *Stroke* 1981;12:40-6.
- 5 Hällgren R, Terent A, Venge P. Lactoferrin, lysozyme and B₂-microglobulin levels in cerebrospinal fluid. *Inflammation* 1982;6:291-303.
- 6 Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;13:227-31.
- 7 Ferreira A, Revilla Y, Bootello A, Gonzalez Porque P. Use of the ELISA to detect and quantify histocompatibility antigens and their subunits. *J Immunol Meth* 1983;65:373-81.
- 8 Tibbling G, Link H, Ohman S. Principles of albumin and IgG analyses in neurological disorders. I Establishment of reference values. *Scand J Clin Lab Invest* 1977;37:385-90.
- 9 Tourtellotte WW, Potvin AR, Fleming JO, Murthy KN, Levy J, Potvin JH. Multiple sclerosis: measurement and validation of central nervous system IgG synthesis rate. *Neurology* 1980;30:240-4.
- 10 Kin K, Kasahara T, Itoh Y, Sakurabayashi I, Kaway T, Morita M. B₂-microglobulin production by highly purified human T and B lymphocytes in cell culture stimulated with various mitogens. *Immunology* 1979;36:47-54.

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Late onset adrenomyeloneuropathy

Sir: Adrenomyeloneuropathy is a disorder of lipid metabolism which results in the accumulation of long chain fatty acids. The accumulation and associated dysfunction is most marked in those cells which depend highly on lipid metabolism: adrenal cortex, gonads, cerebral cortex and myelin sheaths of peripheral nerves. The condition is thus characterised by the association of Addison's disease and hypogonadism, with progressive peripheral and central neurological disease, and is usually familial. Inheritance is X-linked, and expression is usually confined to males, but several variants have been described.³ The best recognised form of this condition is that which occurs in children (adrenoleukodystrophy, Addison-Schilder's disease),⁴ with rapidly progressive neurological damage resulting in death within the first 15 years of life. However, a family history is not invariable, and the condition may present later.¹ In their review of 303 cases, Moser *et al*⁵ described only five patients who first developed neurological symptoms after age 21 years, and none with both Addison's disease and neurological signs who presented after 37 years of age.

In 1975 a 53 year old milkman was admitted to hospital with clinical and biochemical

Table CSF findings in multiple sclerosis patients and controls*

	Controls (n = 16)	Group A (n = 14)	Group B (n = 16)
CSF albumin (mg/dl)	19.93 $\pm$ 1.29	18.92 $\pm$ 2.19	23.18 $\pm$ 1.96
CSF/S albumin ratio	4.42 $\pm$ 0.26	4.38 $\pm$ 0.43	4.68 $\pm$ 0.55
CSF IgG (mg/dl)	2.72 $\pm$ 0.40	4.00 $\pm$ 0.57†	5.50 $\pm$ 0.62‡§
IgG index	0.45 $\pm$ 0.04	0.90 $\pm$ 0.11‡	1.15 $\pm$ 0.10‡
Daily IgG synthesis (mg/day)	3.05 $\pm$ 2.5	5.4 $\pm$ 2.15†	15.46 $\pm$ 3.38‡§
B ₂ m (mg/l)	1.49 $\pm$ 0.19	1.51 $\pm$ 0.22	3.21 $\pm$ 0.30‡

A: patients in a stable phase. B: patients in relapse.

*Values reported as mean $\pm$ SEM.

†Significantly different from control p < 0.05 (Student t-test).

‡Significantly different from control p < 0.01.

§Significantly different from Group A of patients p < 0.05.

||Significantly different from Group A of patients p < 0.01.

features of Addisonian crisis. He was successfully resuscitated and commenced on corticosteroid replacement therapy. The diagnosis was confirmed by a short Synacthen test. Despite pleural thickening seen on the chest radiograph there was no evidence that his disease was tuberculous; adrenal antibodies were negative. He complained coincidentally of a 5 year history of progressive difficulty in walking and was noted to have signs of spastic paraparesis. Skull radiograph, isotope brain scan, CSF examination, B12 and serological tests for syphilis were normal and no definite diagnosis was made. He remained comparatively well on replacement therapy and was able to continue his job, working 7 days a week, for a further 6 years. In 1981 he was forced to retire through immobility. Always abrupt in his manner, he became increasingly cantankerous and given to swearing. In December 1983 his dementia became overt with worsening quadriplegia, cerebellar signs, confusion, faecal and urinary incontinence. There was no clinical evidence of peripheral sensory neuropathy; ankle reflexes were brisk and associated with clonus. The diagnosis of adrenomyeloneuropathy was suspected. EEG showed bilateral slow wave activity with no specific features. Peripheral nerve conduction studies suggested axonal neuropathy as previously reported by others.⁶ Accumulation of long-chain fatty acids (C26) was determined in skin fibroblast culture; the C26:C22 ratio was 0.90 (normal 0.55–0.90). Serum testosterone was low (4.1 nmol/l), while LH and FSH were borderline high (11.3 U/l and 8.6 U/l, respectively). He was not investigated further and died in July 1984 following admission to hospital for terminal nursing care. Post-mortem appearances of brain, adrenal cortices and gonads were characteristic with widespread cerebral demyelination with perivascular cellular infiltrates and foamy vacuolation of adrenal cortical and Leydig cells.⁴

Schaumburg and colleagues¹ have drawn attention to late onset adrenomyeloneuropathy as a variant of the better-recognised childhood form. In their report of five cases and review of four others, there were eight males and one female, and age of onset ranged from 9 to 44 years. In one adult there were no affected family members, and in two others family history was unknown. Detailed family history had not been sought at first in our patient, but subsequent enquiry revealed that his maternal grandfather may have been paralysed, although not demented, when he died 50 years earlier, age 80. The patient's mother was said to

have taken to her bed at the age of 57 years and remained there for the last 18 years of her life. However she was not thought to be demented or paralysed, and it is not clear if her confinement was for medical or social reasons. There were no other relatives with either demyelination of adrenocortical failure. He had no children.

The possibility of adrenomyeloneuropathy should be borne in mind in clinical practice. Indeed it may be more common than is generally recognised and may account for some cases of adrenocortical failure even in the absence of neurological signs. Although typically a disease of early life, occasional cases present very late.

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References

- 1 Schaumburg HH, Powers JM, Raine CS, *et al.* Adrenomyeloneuropathy: a probable variant of adrenoleukodystrophy. *Neurology* 1977;27:1114–9.
- 2 Moser HW, Moser AB, Kawamura N, *et al.* Adrenoleukodystrophy: studies of the phenotype, genetics and biochemistry. *J Child Neurol* 1980;147:217–24.
- 3 O'Neill BP, Moser HW, Saxena KM. Familial X-linked Addison's disease as an expression of adrenoleukodystrophy (ALD): elevated C26 fatty acid in cultured skin fibroblasts. *Neurology* 1982;32:543–7.
- 4 Schaumburg HH, Powers JM, Raine CS, Suzuki K, Richardson EP. Adrenoleukodystrophy: a clinical and pathological study of 17 cases. *Arch Neurol* 1975;32:577–91.
- 5 Moser HW, Moser AE, Singh I, O'Neill BP. Adrenoleukodystrophy: survey of 303 cases: biochemistry, diagnosis and therapy. *Ann Neurol* 1984;16:628–41.
- 6 Mamoli B, Graf M, Toifi K. EEG, pattern-evoked potentials and nerve conduction velocity in a family with adrenoleukodystrophy. *Electroencephalogr Clin Neurophysiol* 1979;47:411–9.

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Improved phonation during fever in brainstem dysarthrophonia

Sir: Dysphonia and dysarthria are common sequelae of brainstem pathology as it is in this part of the brain that the direct neural control of phonation, articulation, breathing and their complex coordinated execution during speech takes place. Thermoregulatory disturbances are also not infrequent after brainstem damage. Recently we treated a patient who after sustaining a severe brainstem insult, exhibited a combination of dysphonia, dysarthria and relapsing fever most probably of central origin. There was a remarkable improvement in the patient's phonatory ability during fever. This phenomenon is new in our clinical experience and we could not find such a case reported in the literature.

A 21 year old male sustained a head injury in a road accident rendering him immediately unconscious. Brain and cervical spine CT failed to reveal fractures; however, brain oedema and intracranial air bubbles were noted. About 2 weeks later he contracted pseudomonas meningitis which responded to antibiotic therapy. He became afebrile and his CSF remained normal thereafter. Neurological examination 2 months after injury revealed spastic tetraplegia, anisocoria, hypoaesthesia on the right side of the face with reduced corneal reflex, right sixth and peripheral seventh cranial nerve palsies, bilateral attenuation of the gag reflex and deviation of the tongue to the right. Repeated CT revealed widening of the ambient cisterns, interpeduncular and quadrigeminal cisterns.

Fig CT scan showing widening of the quadrigeminal cistern.