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 syndromes 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16 patients who were studied during an acute exacerbation of multiple sclerosis, their sera and CSF having been withdrawn within 3 weeks from the onset of the attack.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.7 The ratio of serum 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 ± 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.

JC ALVAREZ-CERMEÑO
LM VILLAR
G ROY
A FERREIRA
A BOTELLO
A GIMENO
P GONZALEZ-PORQUÉ
Departments of Neurology and Immunology
Hospital Ramón Y Cajal,
Carretera de Colmenar Km 9100
Madrid 28034, Spain

References

Table
CSF findings in multiple sclerosis patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 16)</th>
<th>Group A (n = 14)</th>
<th>Group B (n = 16)</th>
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<tbody>
<tr>
<td>CSF albumin (mg/dl)</td>
<td>19.93 ± 1.29</td>
<td>18.92 ± 2.19</td>
<td>23.18 ± 1.96</td>
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<tr>
<td>CSF IgG ratio</td>
<td>4.42 ± 0.26</td>
<td>4.38 ± 0.43</td>
<td>4.68 ± 0.55</td>
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<td>B2m (mg/dl)</td>
<td>2.72 ± 0.40</td>
<td>4.00 ± 0.57</td>
<td>5.50 ± 0.62</td>
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<td>IgG index</td>
<td>0.45 ± 0.04</td>
<td>0.90 ± 0.11</td>
<td>1.15 ± 0.10</td>
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<tr>
<td>Daily IgG synthesis (mg/day)</td>
<td>3.05 ± 2.5</td>
<td>5.4 ± 2.15</td>
<td>15.46 ± 3.84</td>
</tr>
<tr>
<td>B2m (mg/l)</td>
<td>1.49 ± 0.19</td>
<td>1.51 ± 0.22</td>
<td>3.21 ± 0.30</td>
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</table>

A: patients in a stable phase. B: patients in relapse.
*Values reported as mean ± SEM.
†Significantly different from control p < 0.05 (Student’s 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.

Late onset adrenomyeloneuropathy

Sir: Adrenomyeloneuropathy is a disorder of lipid metabolism which results in accumulation of long chain fatty acids.1 The accumulation and associated metabolic function is most marked in those cells which depend highly on lipid metabolism: adrenals, 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.2 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: Adison-Schiller’s disease),1 which rapidly progressive neurological damage occurring in the first 15 years of life. However, even a family history is not invariably, and the condition may present later.4 In their review of 303 cases, Moser et al5 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...
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. 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 colleagues5 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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WJ Jeffcoate
D McGregor
GR Hopkinson†
City Hospital, Hucknall Road,
Nottingham NG5 1PB, UK.

*Present address: Royal Infirmary, Bristol BS2 8HW, UK.
†General practitioner, Gedling, Nottingham.

References

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Improved phonation during fever in brainstem dysarthrophonia

Sirs: 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 the injury revealed spastic tetraplegia, anisocoria, hypoesthesia on the right side of the face with reduced corneal reflex, right sixth and peripheral seventh cranial nerve palsies with bilateral attenuation of the gag reflex and deviation of the tongue to the right side. Repeated CT revealed widening of the ambient, interpeduncular and quadrigeminal cisterns.

Fig CT scan showing widening of the quadrigeminal cistern.