Letters

Plasma citrate in motor neuron disease

Sir: The aetiology of motor neuron disease is still unknown. The role of heavy metals such as lead, mercury and manganese as possible aetiological agents has been discussed, but their significance has not been widely accepted.\(^1\)\(^2\) Aluminium has also been incriminated because of its known neurotoxicity\(^3\) and because high concentrations have been found in the central nervous system of patients suffering from motor neuron disease.\(^3\) As aluminium does not readily cross the intestinal mucosa or the blood-brain barrier without a chelating agent, it is interesting to note that citrate, which is a strong chelating agent, has been reported to be significantly raised in eight motor neuron disease patients.\(^4\)

We studied the plasma citrate levels in an extended series of patients suffering from motor neuron disease, and their matched controls.

The diagnosis of motor neuron disease was made according to the usual criteria and agreed upon by at least two neurologists. Nineteen patients with motor neuron disease and 27 controls were studied (table). For each patient one or two controls matched for sex, age, degree of muscular wasting, disability and inactivity were selected. They were also carefully matched for type of involvement (central, peripheral or bulbar). If the motor neuron disease patient had both significant central and peripheral symptoms, he was given two controls.

The 13 controls with central lesions had the following diagnosis: cerebral infarction, multiple sclerosis and myelopathy of unknown aetiology. The 14 controls with peripheral symptoms were diagnosed as: mononeuropathy, polyneuropathy, brachial plexus lesion, Guillain-Barré syndrome, sequelae after poliomyelitis and dystrophia myotonica. Four patients with bulbar paresis as the main symptom were listed among the motor neuron disease patients with peripheral symptoms and their controls had the following diagnosis: dysphagia due to hemilossomy, fibrosis oesophagi and Wallenberg syndrome.

The mean age was the same in all groups, 63–64 years (table). No patient or control had a metabolic disorder such as diabetes mellitus. Blood tests were taken in the morning (about 9 am). Citrate was determined by a method using citrate lyase (Boehringer, Mannheim) essentially according to the technique described by Toftegaard Nielsen.\(^5\) The analysis was made blindly and the results were statistically evaluated by Wilcoxon's test.

The results are given in the table. The mean plasma citrate level in 19 motor neuron disease patients was 0.127 (SD = 0.025) mmol/l and 0.116 (SD = 0.035) mmol/l in a control group of 27 patients. When the patients are split into groups with mainly peripheral and mainly central symptoms, the plasma citrate levels were 0.130 (SD = 0.025) mmol/l in both motor neuron disease groups, 0.118 (SD = 0.033) mmol/l in the peripheral, and 0.114 (SD = 0.038) mmol/l in the central control group. In all groups the differences are small and statistically not significant.

Several authors have reported that glucose metabolism is abnormal in motor neuron disease.\(^6\)\(^7\) Saffer et al.\(^8\) studied the metabolism in eight patients suffering from motor neuron disease and controls matched for degree of muscle wasting, physical inactivity and age. They concluded that the synthesis or release of insulin was impaired owing to pancreatic islet cell damage in motor neuron disease. Moreover, they found that blood pyruvate and lactate levels were normal, whereas blood citrate was nearly doubled compared to controls. This is interesting bearing in mind that citrate is a strong chelating agent, which might promote the transfer of neurotoxic metals across the blood-brain barrier into the central nervous system.

In the present study blood citrate levels were estimated in 19 patients with motor neuron disease and 27 controls carefully matched according to the criteria of Saffer et al.,\(^9\) and in addition for sex and type of lesion (peripheral, central or bulbar). This study does not verify the findings of Saffer et al. The blood citrate levels are slightly elevated in motor neuron disease patients compared to controls, but the difference is not statistically significant.

STEINAR T VILMING, Department of Neurology, The Regional Hospital, Örebro, Sweden (author's present address: The Central Hospital of Akershus, University of Oslo, 1474 Nordbyhagen, Norway)

References


Table Patients with motor neurone disease and their matched controls: Number (n), age and blood citrate

<table>
<thead>
<tr>
<th>Central lesions</th>
<th>Peripheral lesions</th>
<th>Total</th>
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<tbody>
<tr>
<td>n</td>
<td>Age (years)</td>
<td>Citrate (mmol/l)</td>
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<tr>
<td>Motor neurone disease</td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>13</td>
<td>63</td>
</tr>
<tr>
<td>Range</td>
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Opsonolus in hyperosmolar nonketotic coma

Sir: Opsonolus is the term used to describe rapid, irregular and chaotic eye movements that occur in all directions. This phenomenon has been associated with encephalitis, neuroblastoma, remote carcinomas, demyelinating disease, intoxications, thalamic haemorrhage, hemispheric glioblastoma, Friedreich ataxia and hydrocephalus.1 We describe a patient in hyperosmolar nonketotic coma with opsonolus. We believe that this is the first report of opsonolus in metabolic disorders.

A 64-year-old woman was admitted for evaluation of right upper abdominal pain and fever. On admission, neurological examination was normal. Vital signs were normal except for body temperature 38-4°C. The fever of unknown cause persisted after admission. A CT scan of the liver revealed multiple space occupying lesions. The patient was treated with antibiotics and steroid hormone. Four weeks after admission she became obtunded. Her skin was dry. The next day she was semicomatose. She showed appropriate withdrawal of the limbs to painful stimuli but was unresponsive to verbal commands. The pupils were of normal size and responded briskly to light. A striking finding was the presence of opsonolus. Continuous, rapid and chaotic ocular saccades were noted with irregular myoclonic jerks in the face and four limbs. The eye movements were conjugate and mainly in the horizontal plane but with rotary and vertical components. Ice water caloric stimuli transiently produced conjugated deviation of both eyes toward the irradiated ear and opsonolus stopped during the deviation. The eye movements persisted unchanged with lids open and closed. Deep tendon reflexes were hypoactive in the four limbs. Plantar responses were flexor. Laboratory values at the time of semicoma included: serum osmolality, 410 mosmol/kg; blood glucose, 827 mg/dl; serum sodium, 172 mmol/l; serum potassium, 4.1 mmol/l; serum calcium, 11.3 mg/dl; serum chloride, 115 mmol/l; BUN, 66 mg/dl; creatinine, 1.2 mg/dl; arterial blood pH, 7.49; PaO₂, 49 mm Hg; PaCO₂, 45 mm Hg; SGOT, 194 IU (normal, 12 to 34 IU); SGPT, 228 IU (normal, 5 to 29 IU); alkaline phosphatase, 190 U (normal, 3 to 13 U); and serum ammonia, normal. Urine showed glycosuria without ketones. An EEG demonstrated diffuse slowing in the delta and theta range.

Treatment with insulin and intravenous fluid replacement was instituted. The patient soon became responsive to verbal stimuli. Opsonolus and myoclonus disappeared within 24 hours of the therapy, which brought the serum osmolality level to 362 mosmol/kg; blood glucose value to 340 mg/dl and serum sodium level to 164 mg/dl. Four days after initiation of the therapy, her mental state was almost normal and the osmolality was controlled between 310 and 340 mosmol/kg. The blood sugar was between 100 and 200 mg/dl and serum electrolytes were normal. However, renal and liver function deteriorated acutely. Seven days after initiation of the therapy, the patient became comatose and died. Postmortem examination was performed. She was found to have an adenocarcinoma in the tail of the pancreas with multiple metastasis to the liver. The microscopic and macroscopic examination failed to reveal any structural lesion in the brain.

Our case with carcinoma of pancreas developed opsonolus and unresponsiveness when the patient had nonketotic hyperglycaemic hyperosmolality. The eye movements and alteration in consciousness resolved with correction of the hyperosmolar state. No structural lesion could be demonstrated in the brain at necropsy. Although opsonolus may occur with remote effects of carcinomas,2 its appearance is not transient as in our case. This indicates that the opsonolus was due to the hyperosmolar nonketotic coma.

This appears to be the first report of a patient with opsonolus in metabolic disorders. However, Keane et al2 reported opsonolus in a case with a unilateral glioblastoma who had greatly elevated serum glucose and urea nitrogen values. The authors also described transient opsonolus in two cases with thalamic haemorrhage complicated by metabolic disorders. One patient had azotaemia and hyponatraemia. Another showed hyperglycaemia. These three cases suggest the possibility that the metabolic disorders might cause or play a part in opsonolus.

The anatomic basis of opsonolus has not yet been determined. The frequent association of opsonolus with ataxia and occasional necropsy findings in the cerebellum support the suggestion that opsonolus is a sign of cerebellar involvement.2 Evidence from a limited number of cases suggests, however, the involvement of brainstem in at least some cases of opsonolus.2 Our case revealed no pathologic changes in the brain, including cerebellum and brainstem.

Many mechanisms may be responsible for opsonolus.2 A metabolic basis seems most likely in our case. Histochemical studies of brain have been performed rarely with opsonolus and hyperosmolar coma.3 Ross and Zeman4 carried out histochemical study in a patient with opsonolus and bronchogenic carcinoma. The authors described definitely decreased succinate dehydrogenase activity in the dentate nucleus. They suggested a possible relation between the opsonolus and the biochemical change in the dentate nucleus. Ziegels5 reported that plasma hyperosmolarity diminished the same enzyme activity in the ependymal epithelium of the rat but did not investigate the activity in the dentate nucleus. Although no conclusion can be drawn from these two reports, we speculate that hyperosmolality may induce some biochemical alteration in the dentate nucleus which causes opsonolus.

References
4 Keane JR. Transient opsonolus with thalamic

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