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Case report

Central pontine myelinolysis without hyponatraemia

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Central pontine myelinolysis is an acquired demyelinating disorder of uncertain origin that predominantly affects the centre of the basilar portion of the pons. Several theories have been proposed to account for this condition, prominent among them being abnormalities in serum sodium concentration. We report on a patient who had central pontine myelinolysis with extrapontine lesions and Wernicke's encephalopathy but who maintained a normal or high serum sodium concentration throughout his hospital admission.

CASE REPORT. A 52-year-old man was admitted to hospital following two tonic-clonic seizures. There was a long history of excessive alcohol consumption of more than 100 units per week. One week prior to admission he had stopped drinking alcohol because he had become increasingly confused. He was on no regular medication. There was no history of trauma or epilepsy. On examination he was apyrexic, anicteric and not clinically dehydrated. He scored 11 on the Glasgow Coma scale.[1] There were no abnormal neurological signs in the cranial nerves. Tone in the limbs was flaccid with hyporeflexia and flexor plantar responses. Sensation was intact. He became agitated and was commenced on multiple vitamin supplements and 40 mg chlordiazepoxide on a decreasing regimen. Initial investigations showed serum sodium 139 mmol/l, potassium 2·9 mmol/l, glucose 6·7 mmol/l and urea 6·9 mmol/l. Liver function tests were normal apart from serum gamma-glutamyl transferase 236 U/l (usual range 7 – 46).

Despite an adequate oral fluid intake he became more confused. He was disorientated in place and time and was unable to recognise his relatives. There was no asterixis or hepatic fetor. Serum ammonia was 57 μmol/l (13 – 52). Electroencephalography showed a mild generalised abnormality of a non-specific nature. CT scan of the brain revealed no evidence of intracranial haemorrhage or central pontine myelinolysis. Magnetic resonance imaging was not performed.

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He remained confused and on the seventh hospital day developed a right basal pneumonia. Despite intravenous antibiotics he continued to deteriorate and died seven days later from cardiac arrest.

Throughout the 14 days his serum sodium concentration was measured daily or every second day and gradually rose from 139 mmol/l to 153 mmol/l. Liver enzymes remained approximately constant.

At necropsy the liver (1420 g) showed micronodular cirrhosis with fatty change and Mallory's hyaline deposits in the hepatocytes. Coronal slicing of the brain (1414 g) revealed no macroscopic haemorrhagic necrosis or atrophy of the mamillary bodies. Histologically the mamillary bodies and periventricular gray matter showed characteristic changes of Wernicke's encephalopathy with capillary prominence, ring haemorrhages, astrocytic gliosis and foamy macrophages. In the cerebellum there was atrophy of the anterior superior vermis with widespread Purkinje cell loss, proliferation of Bergman astrocytes, mild granular cell loss and isomorphic gliosis in the molecular layer. The pons on horizontal sectioning showed a roughly triangular area of granular softening disposed symmetrically in the centre of the basis pontis (Fig 1). Sections from this area showed clearly defined incomplete demyelination, mainly involving the transverse pontocerebellar fibres: there was a total loss of oligodendrocytes with both focal macrophage and reactive astrocyte infiltration. The tegmentum was not involved. Foci of myelinolysis were also seen throughout the subcortical white matter in the frontal, temporal and parietal areas and in the internal capsule. Electron microscopy of the edges of these subcortical lesions revealed many myelin sheaths undergoing vesicular-tubular myelinolysis (Fig 2) and acute necrosis of some accompanying oligodendroglia.

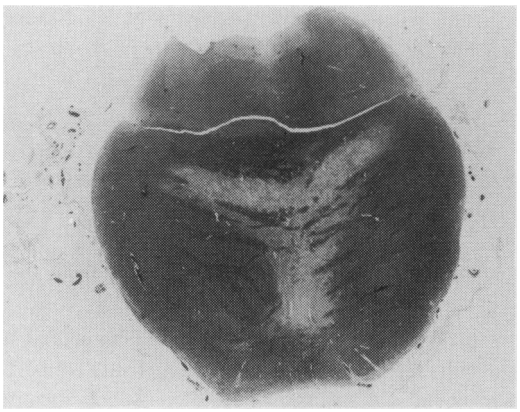

Fig 1 (above). Transverse section of midpons showing central area of demyelination.

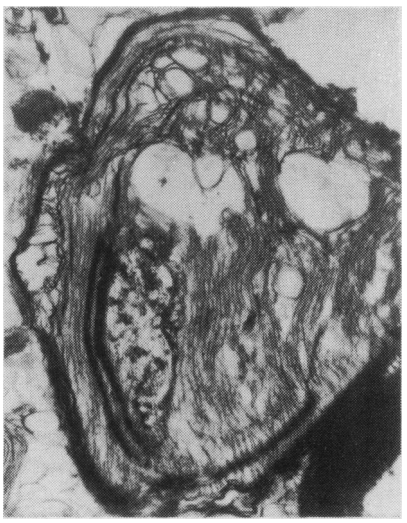

Fig 2 (right). Electron micrograph (X 20,500) showing vesicular-tubular myelin breakdown in a subcortical white matter lesion.

DISCUSSION

This patient presented with clinical features of central pontine myelinolysis, namely, an acute confusional state, seizures, flaccid quadriparesis and a history

of chronic alcohol use. Wernicke's encephalopathy does not completely explain his mental confusion as the confusion progressed despite rapidly administered intravenous thiamine. Also seizures and flaccid quadriparesis are not features of Wernicke's encephalopathy.[2] The clinical spectrum of central pontine myelinolysis includes coma, the "locked-in" syndrome, seizures, facial weakness, pseudobulbar palsy, quadriparesis and behavioural changes without focal signs.[3, 4, 5] The rapid neurological deterioration in this case is typical of central myelinolysis. In other cases reported most of the demyelinating lesions have evolved in two to four weeks.[4]

There is no diagnostic test for central pontine myelinolysis. The CT scan may be normal as in this case, or may show a non-enhancing hypodense lesion in the ventral pons.[6] Magnetic resonance imaging is more sensitive than CT in visualising the pontine lesion but may also be normal early in the course of the disease.[7] Few cases of central pontine myelinolysis are diagnosed in life probably because the clinical manifestations are obscured by other neurological abnormalities, or are absent if the lesion is small.[3, 5]

The initial reports of central pontine myelinolysis coincided with the first widespread use of intravenous therapy to treat electrolyte abnormalities.[8] In particular central pontine myelinolysis has been reported as developing when a low serum sodium concentration is increased at a rate greater than 12 mmol/l/day.[9] However, other authors argue that rapid correction of hyponatraemia in itself is not dangerous, provided that hypernatraemia does not develop during the first 48 hours of therapy.[10] Hyponatraemia alone has been blamed for producing the condition.[11] In animals pontine and extra-pontine myelinolysis can be induced more easily by rapid correction of chronic than of acute hyponatraemia.[12] The rapid correction of chronic hyponatraemia results in dehydration whereas rapid correction of acute hyponatraemia reduces to normal the levels of water in the brain. This rapid change in the levels of water in the brain is thought to be an essential component in the pathogenesis of central pontine myelinolysis.

Alteration in serum sodium concentration cannot be excluded as an aetiological factor in our patient, as it may have occurred prior to his hospital admission. However, many recently reported series of central pontine myelinolysis have included cases with normal serum sodium. McKee and colleagues found the characteristic pontine and extra-pontine lesions in ten patients who died from severe burns,[5] and hyponatraemia was not present in any of these patients.

Central pontine myelinolysis is invariably associated with some other serious, often life-threatening disease. The condition was initially described in 1959 in alcoholic and malnourished individuals with liver disease.[4] In more than half the cases it appeared in the late stages of chronic alcoholism, often co-existing with Wernicke's encephalopathy. Other frequently noted associations are patients with hepatic cirrhosis, Wilson's disease,[13] chronic renal failure, severe burns,[5] lymphoma, carcinoma, leukaemia,[14] acute haemorrhagic pancreatitis and as a complication of renal[15] or liver[16] transplantation. These disorders may result in abnormalities of astrocyte metabolism with a reduced ability to generate new intracellular anions in response to osmotic change.[17] Demyelination may then develop when a rapid change in serum osmolality results in osmotic endothelial injury and opening of the blood-brain barrier. This would allow entry of myelinotoxic factors from the bloodstream and also generate vasogenic cerebral oedema,

a known precipitant of demyelination. The rapid change in serum osmolality may be due to anions other than sodium, or to uraemia or hyperglycaemia. Individual variation in the reaction of central nervous tissue to similar degrees of osmotic stress may determine susceptibility. At present this is speculative but until these mechanisms are elucidated it will not be possible to predict who might develop central pontine myelinolysis.

It is important to consider the possibility of central pontine myelinolysis in any severely ill patient who develops an unexplained behavioural disorder with or without neurological signs. There is no specific treatment but major fluctuations in serum osmolality should be avoided as clinical and radiological recovery from central pontine myelinolysis is possible.[7, 18]

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