

Central pontine myelinolysis in liver transplantation

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Abstract

Five cases of central pontine myelinolysis (CPM) were detected by neuropathological examination in a series of 50 patients coming to necropsy after liver transplantation. One patient also had extrapontine myelinolysis. In no case was the diagnosis made during life. Only two patients showed rapid rises in serum sodium concentrations. The incidence of hyponatraemia, before and after transplantation, and rapid rises in serum sodium in patients with CPM was significantly greater than in the 45 patients showing no neuropathological evidence of CPM.

It is concluded that there is a high incidence of CPM after liver transplantation, that clinical diagnosis is difficult, and that there is no simple direct correlation between rapid serum sodium changes and the development of this condition. Avoidance of major electrolyte fluctuations at the time of liver transplantation is recommended but it must be emphasised that CPM may occur without any rapid rise in serum sodium concentration.

Central pontine myelinolysis (CPM) is characterised by symmetrical loss of myelin in the pontine basalis, with relative preservation, at least in the early stages, of axons and neuronal cell bodies. The clinical effects range from minor neurological impairment to a fully developed "locked in" syndrome.¹ Since the condition was first described over 30 years ago² many case reports, clinical series, and reviews have appeared, and extrapontine variants are now recognised.³⁻¹⁰ Vulnerable patients included the severely ill, alcoholics, those with liver disease and those sustaining large swings in serum electrolyte concentrations.¹¹ Liver transplant recipients fall into some or all of these categories and, therefore, a high incidence of CPM might be expected.

The precise aetiology of CPM is uncertain, but the overly rapid correction of hyponatraemia may be an important factor.¹²⁻²⁰ The importance of changes in serum sodium concentration has been challenged,^{21 22} however, and there is continuing controversy.²³⁻²⁹ Patients undergoing liver transplantation in our centre have serum electrolyte concentrations closely monitored throughout their clinical course and are, therefore, a suitable

group in which to study the role of serum sodium in the pathogenesis of CPM.

Methods

Up to the end of 1989, 279 patients had received 326 orthotopic liver transplants at the Queen Elizabeth Hospital, Birmingham. One hundred and seventeen (41.9%) had died at the time of this study and of these 71 (60.7%) came to necropsy at our centre. Cerebral tissue was collected from 52 patients, including 47 entire brains. As the pons was not sampled in two cases only 50 cases were included in the study. This group comprised 34 females and 16 males and represented 42.7% of all deaths following liver transplantation. The mean age was 37.9 years; 41 were adults (range 21-63 years) and nine were children. These patients had received 64 transplants, including 13 retransplants and one patient who was transplanted three times.

Gross external findings were determined at necropsy and the brains then fixed whole by suspension in 10% formalin for three to six weeks before slicing. In the 47 cases collected prospectively the brain stem and cerebellum were detached and the cerebrum sliced coronally at one cm intervals. Any grossly obvious lesions were sampled for histological examination. Routinely, blocks were also taken from frontal, temporal, parietal and occipital lobes, hippocampus, basal ganglia, thalamus, cerebellum and medulla. The pons was carefully examined for evidence of CPM and blocks taken at mid-pontine level. In cases where the clinical history suggested pontine disease or where there was evidence of CPM in the first block, additional blocks were taken to include rostral and caudal pons. In three cases only single random blocks of pons were available for study.

The tissue was processed to paraffin wax using a standard technique and sections were cut and stained with haematoxylin and eosin and luxol fast blue. In cases where initial sections were suspect for CPM, immunohistochemical stains for glial fibrillary acidic protein (GFAP) and neurofilament protein were prepared using an indirect immunoperoxidase technique,³⁰ and further blocks of tissue were stained with oil red O to detect neutral fat.

All clinical records were carefully scrutinised and particular note was made of neurological features and serum sodium changes in both the periods before and after transplantation.

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Table 1 Patient details

Case number	Age	Sex	Indication for transplantation	Post-transplant survival (days)	Antemortem diagnosis of CPM
OL102	16	F	Chronic active hepatitis	54	No
OL103	47	M	Alcoholic cirrhosis	51	No
OL119	54	M	Primary sclerosing cholangitis	18	No
OL211	45	M	Haemochromatosis	87	No
OL278/279	8	F	Fulminant non-A, non-B hepatitis	2	No

Results

Five brains (10%) showed histological evidence of CPM and the basic clinical data for these patients are summarised in table 1. Three were female (including two children) and two were male; mean age was 34 years (range 8–54). In one case (OL211) the condition was suspected on gross examination of the pons. One patient (OL278/279) underwent early retransplantation for primary non-function; the remainder were single transplants. Mean survival after transplantation was 42 days (range two to 87).

NEUROLOGICAL FINDINGS

Case OL102 (female, aged 16) was drowsy preoperatively, but there was no electroencephalographic evidence of encephalopathy. The drowsiness persisted after transplantation, with generalised weakness and an episode of grand mal fitting on the 38th postoperative day. Case OL103 (male, aged 47) was in grade 1–2 hepatic encephalopathy before transplantation and developed grand mal seizures three days postoperatively. He remained weak and encephalopathic until death.

Case OL119 (male, aged 54) was not encephalopathic before transplantation but developed pronounced spasticity in all limbs,

worse on the right side, by the fifth postoperative day. He developed grand mal fits around the same time, with deviation of the head and eyes to the left. An electroencephalogram showed continuous epileptic activity, mainly on the right side. From day 11, he had repeated episodes of respiratory arrest, recovering spontaneously each time after a temporary period of artificial ventilation. Neurological examination suggested a pseudobulbar palsy. He deteriorated and died on day 18.

Case OL211 (male, aged 45) was in grade 2–3 encephalopathy before transplantation and postoperatively never regained full consciousness. He sustained grand mal fits on the third postoperative day with right conjugate eye deviation. Facial dystonia and dyskinesia developed and he became generally rigid with increased upper limb tone, flaccid paraparesis of the lower limbs, and drowsiness.

Case OL278/279 (female, aged 8) was transplanted in grade 4+ coma but died 13 hours after the second transplantation without regaining consciousness. No focal neurological abnormalities were noted at any stage.

Death in the first four cases was attributed to sepsis and multi-organ failure and in the last case, to cerebral oedema and coning. CPM was

Figure 1 Case OL102, showing a sharply demarcated area of demyelination in the basal pons. Descending cortical fibres are relatively spared (LFB stain).

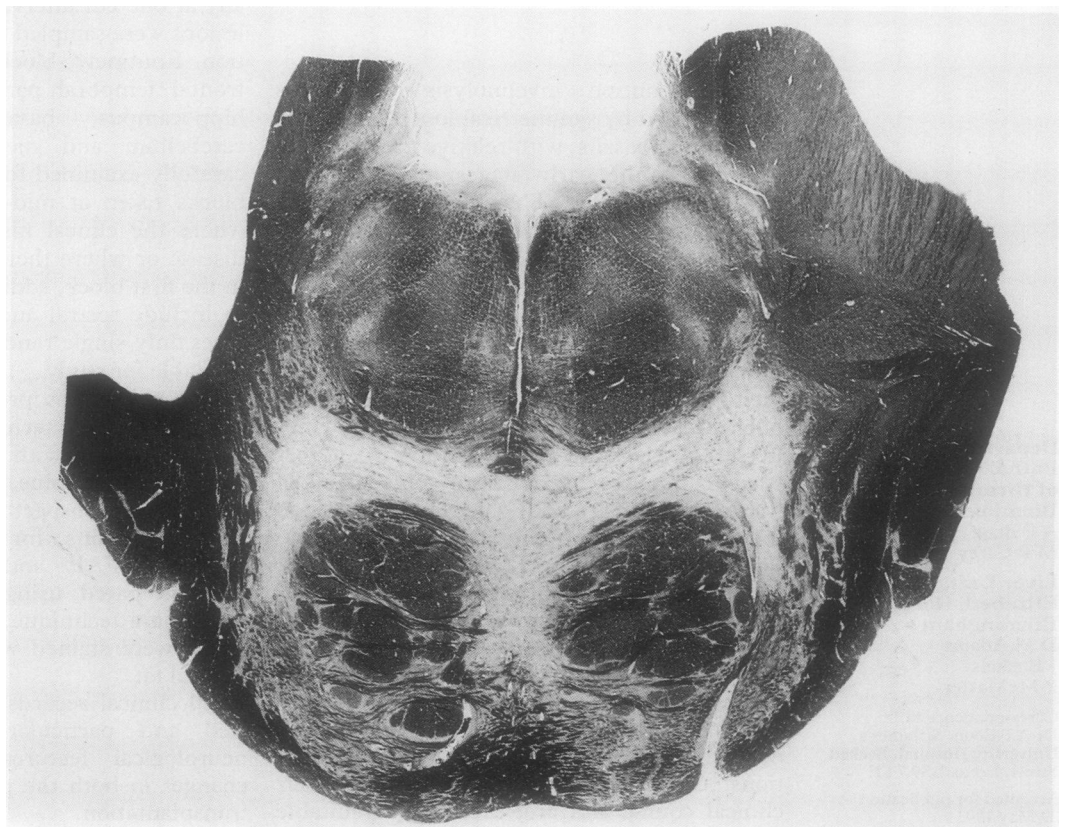
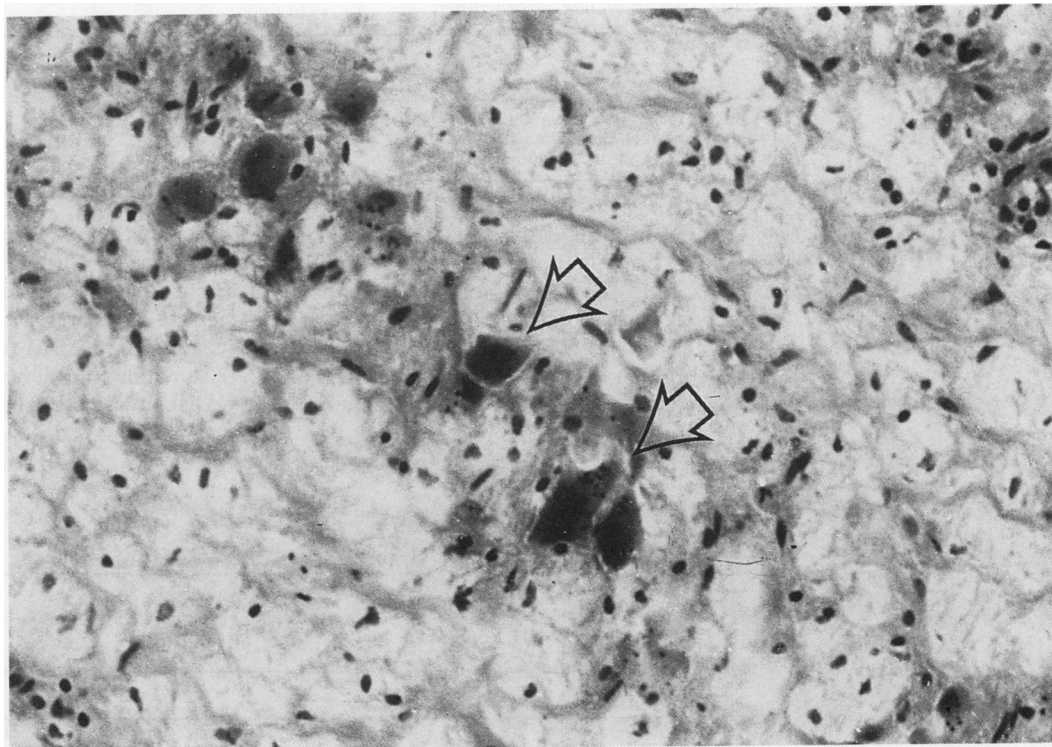


Figure 2 Case OL211, showing the accumulation of foamy macrophages in an area of demyelination. Neuronal cell bodies are identifiable (arrows).



not diagnosed clinically in any of these patients, but in retrospect, was probably a major contributing factor in the death of cases OL102, OL119, and OL211.

HISTOLOGICAL FINDINGS

In three cases (OL102, OL211, and OL278/279) histological features were typical of CPM. There were symmetrical demyelinating lesions in the basal pons with a "bats wing" configuration in coronal section and relative sparing of longitudinal fasciculi (fig 1). Areas of demyelination were sharply demarcated from normal tissues. Foamy macrophages, fairly scanty in

case OL278/279, were scattered throughout the lesions and both neuronal cell bodies and axons were relatively well preserved (fig 2). A variable degree of fibrillary astrocytosis was evident on immunostaining for GFAP (fig 3). In case OL211 similar changes were present in the lateral geniculate nuclei, indicating extrapontine myelinolysis. Other findings were: severe generalised cerebral oedema in case OL278/279, severe hypoxic-type neuronal damage in cases OL102 and OL278/279, and widespread Alzheimer type II astrocytosis, indicating hepatic encephalopathy, in cases OL211 and OL278/279.

Figure 3 Case OL103, showing fibrillary astrocytosis (GFAP stain).

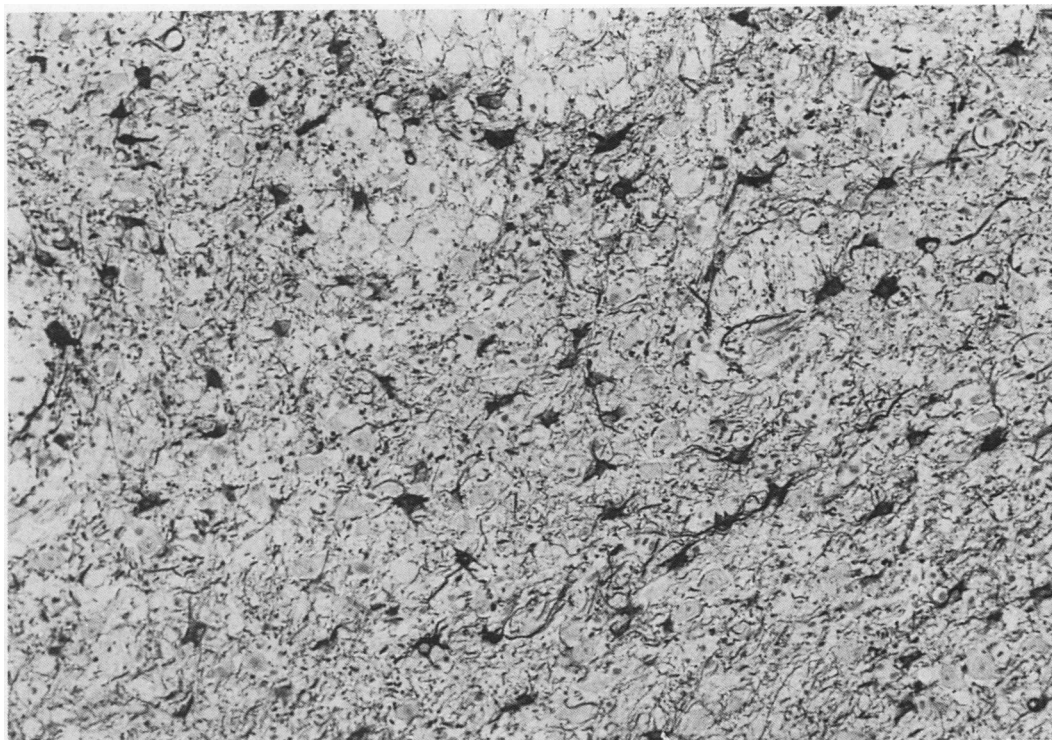


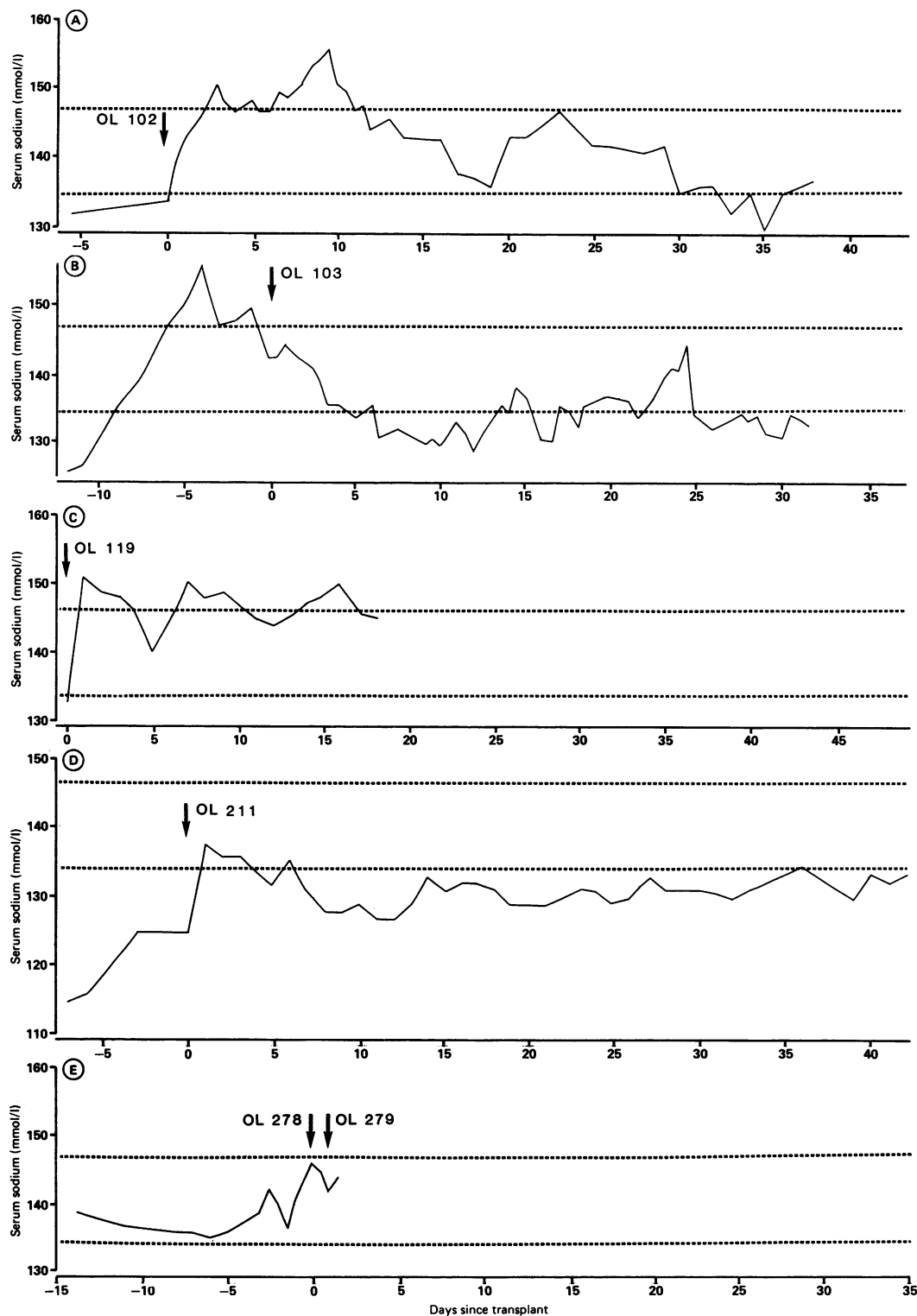
Table 2 Serum sodium abnormalities

	CPM on histology (n = 5)	No evidence of CPM (n = 45)	Total (n = 50)
Serum [Na ⁺] shift of > 12 mmol/l/day	2	16	18
Pre-transplant [Na ⁺] < 133 mmol/l	4	19	23
Post-transplant [Na ⁺] > 147 mmol/l	3	12	15

The findings in cases OL103 and OL119 were less obviously due to CPM in initial sections. Both showed bilateral, approximately symmetrical areas of demyelination in the basal pons. These were situated less centrally, however, than in the first three cases and showed a greater degree of axonal degeneration

with “balloon” formation, less conspicuous foamy cells, and more prominent fibrillary astrocytosis. Features were, however, sufficiently similar to the spectrum of changes recognised in CPM to make the diagnosis with reasonable confidence. Other findings in case OL103 included a single, small, recent but well

Figure 4A–E Serum sodium values (mmol/l) against time (days) in each case of histologically confirmed CPM. Time of transplantation (↓) and normal reference intervals (133–147 mmol/l)



Pathogenesis of central pontine myelinolysis

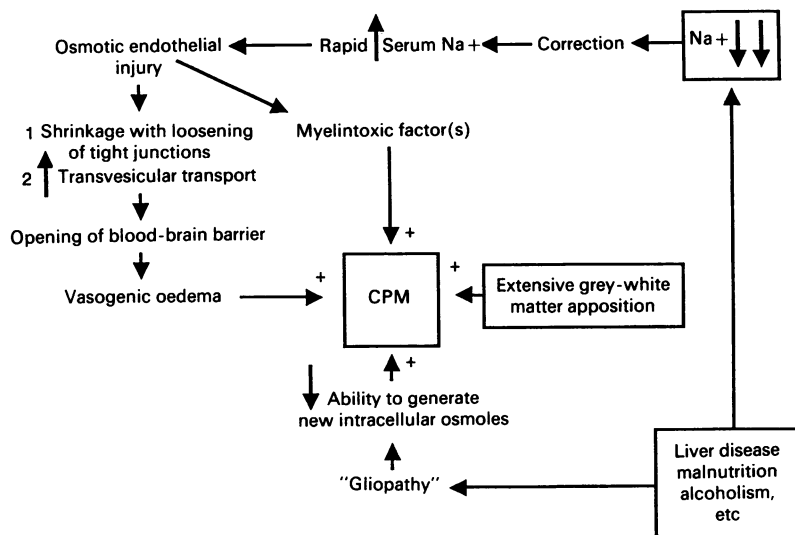


Figure 5 Hypothetical pathogenesis of CPM.

circumscribed focus of sterile haemorrhage in the subcortical white matter of the right parietal lobe; the aetiology was uncertain. In case OL119 bilateral areas of hypoxic-type laminar necrosis of the parietal cortex were present in typical arterial "watershed" zones.

BIOCHEMICAL FINDINGS

Serum sodium values for each of the five patients with CPM were plotted (figs 4A–E). "Steep" rises (> 12 mmol/l/day)¹⁰ were encountered only in cases OL119 and OL211 and neither became hypernatraemic. Slower, but more sustained rises to mildly hypernatraemic concentrations, were noted in cases OL102 and OL103. Rises in cases OL102, OL119, and OL211 coincided with transplantation, while in case OL103 this preceded operation by several days. In case OL278/279 serum sodium values remained within normal reference intervals.

Examination of serum sodium values in the 45 patients without histological evidence of CPM showed 16 who sustained at least one increase of > 12 mmol/l/day (in 15 this coincided with transplantation), 19 with preoperative hyponatraemia, and 12 who became hypernatraemic for at least one post-operative day (table 2). There were no significant differences between this group and the patients with CPM with respect to the incidence of any of these factors taken individually. Collectively, however, the incidence of these serum sodium abnormalities was significantly higher in the group with CPM (χ^2 test = 8.949 with 3 degrees of freedom; $p < 0.05$).

Discussion

CPM was first described in 1959 by Adams *et al*² and has subsequently been reviewed on many occasions. The incidence in unselected necropsy series varies from 0.16%³¹ to 5.8%.⁵ About 10% of patients with chronic liver disease may have histological evidence of

CPM,¹⁷ although lesions are often small. We have shown a similar incidence in liver transplant recipients, including those transplanted for chronic and acute liver disease, confirming that this group has a high risk of developing CPM. These findings are comparable with those of the only other major study of CPM in liver transplantation.³² Interestingly, two out of our five cases were children, as were three out of 11 cases described by Estol *et al*.³² CPM in children is rare outside the context of liver transplantation.

Few cases of CPM are diagnosed in life, although the routine use of computed tomography scanning and magnetic resonance imaging has increased diagnostic accuracy.^{1,33,34} The classic features of "locked-in" syndrome—quadriplegia and pseudobulbar palsy, are often absent if the lesion is small, or may be obscured by other neurological abnormalities. This seems particularly so in liver transplant recipients³² where the effects of hypoxia,³⁵ sepsis,³⁶ drug toxicity,^{37,38} metabolic derangement^{39,40} and hepatic encephalopathy⁴¹ may predominate. All our patients had a complicated course with multi-organ failure and polychemotherapy. None was diagnosed before necropsy, reflecting not only the difficulty in interpreting complex neurological signs but also the relative underuse of advanced imaging techniques in this country, compared with America.^{18,32,42} It is, therefore, important to consider the possibility of CPM in *any* patient with neurological problems, or even behavioural disorders,⁴² after liver transplantation.

We have found CPM in 10% of our necropsy series; the condition was an important contributor to death in three cases. In the absence of other complications the other two probably would have survived, though with unpredictable neurological deficits. As Pfister *et al*¹ showed that clinical recovery from CPM was possible, minor degrees of CPM may remain undiagnosed in transplant survivors. Currently, there are few studies of neuropsychiatric function in long term liver transplant survivors⁴³ and the contribution of occult CPM to overall morbidity is unknown. The collection of accurate data would require the routine application of more sophisticated imaging techniques than are presently available.³²

Once established, CPM causes irreversible structural cerebral damage. Prevention of this common complication of liver transplantation is therefore crucial. It is often implied that CPM is a simple and direct consequence of a "rapid" rise in serum sodium concentration, with demyelination occurring as a result of osmotic "stress". A "safe" upper limit of 12 mmol/l/day is cited.¹⁰ The results of this study do not support this contention. Indeed, in one of our cases (OL278/279) recorded serum sodium values remained within normal reference intervals during the entire clinical course and in two others rises in serum sodium were within conventional "safe" limits. Conversely, 16 patients with no evidence of CPM showed rises greater than 12 mmol/l/day. There was a similar lack of correlation with

respect to incidences of hypo- and hypernatraemia before and after transplantation. The clinical and experimental evidence in favour of some relation to a combination of these factors is, however, persuasive.^{12-20 44-46}

It seems likely that individual variation in the reaction of central nervous tissue to similar degrees of osmotic stress must be very important to the development of CPM. As patients with liver disease are particularly susceptible, liver failure may lead to disruption of astrocyte metabolism with resulting abnormalities of blood-brain barrier function and a decreased ability to generate new intracellular osmoles in response to osmotic changes. Norenberg⁴⁷ has suggested that the aetiological factors may interact through the pathogenic mechanisms illustrated in fig 5. At present this is speculative, but until these mechanisms are elucidated, and vulnerable patients identified preoperatively, it will not be possible to predict who might develop CPM.

Meanwhile, major fluctuations in serum sodium concentration in the perioperative period should be avoided. Even moderate, but sustained, rises should be identified at an early stage. CPM must be looked for in patients who, for whatever reason, do sustain such fluctuations and should not be dismissed in those with consistently "normal" sodium concentrations.

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