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ORIGINAL ARTICLE

Identifying Risk Factors for Central Pontine and Extrapontine Myelinolysis After Liver Transplantation: A Case–Control Study

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Abstract
Background Central pontine and extrapontine myelinolysis (CPEPM) is a rare but potentially fatal complication after orthotopic liver transplantation (OLT). The aim of this study was to identify risk factors for development of CPEPM after OLT and to assess patient outcome.
Methods We reviewed the clinical data of 1,378 patients who underwent OLT between 1987 and 2009 in Geneva, Switzerland and Edmonton, Canada. Nineteen patients (1.4 %) developed CPEPM. We compared their characteristics with control patients, matched by age, gender, date of OLT, and MELD score.
Results The 19 patients with CPEPM (7F, mean age 52.1 ± 2 years) had a mean MELD score of 26 ± 2.2. Before OLT, patients who develop CPEPM presented more frequently low (<130 mmol/l; $p < 0.04$) and very low (<125 mmol/l; $p < 0.009$) sodium than controls. In patients developing CPEPM, the number of platelet units and fresh frozen plasma transfused during surgery was higher ($p = 0.05$ and 0.047), hemorrhagic complications were more frequent after OLT ($p = 0.049$), and variations of sodium before and after OLT were higher ($p = 0.023$). The association of >2 of these conditions were strongly associated with CPEPM ($p = 0.00015$). Mortality at 1 year of patients developing CPEPM was higher (63 vs. 13 %, $p < 0.0001$).
Conclusions High MELD score patients undergoing OLT, receiving massive perfusions of Na-rich products, experiencing surgery-related hemorrhagic complication and important fluctuations of Na are at risk of developing CPEPM. Therefore careful monitoring of natremia in the perioperative period and use of water-free perfusion in case of massive blood-products transfusion are critical points of this patient management.

Keywords Orthotopic liver transplantation · MELD · Neurological complications · Central pontine and extrapontine myelinolysis · Hyponatremia · Hemorrhagic complications · Mortality

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Introduction

First described by Adams et al. [1] in 1959 central pontine myelinolysis (CPM) is a symmetrically demyelinating

lesion of the pons often associated with demyelination of other areas of the central nervous system (extrapontine myelinolysis, EPM; [2]). Occasionally reversible [3] or asymptomatic [3, 4] this disease is often associated with severe neurological symptoms frequently progressing to death or permanent neurological damage. Diagnosis is made through correlation of clinical findings with neuroimaging, mainly magnetic resonance imaging (MRI). Radiologic findings may appear days to weeks after the onset of symptoms and are not always correlated neither to symptoms severity nor to clinical evolution [5, 6]. The exact etiology of CPM remains unclear, but it is supposed that any rapid and important osmotic shifts could induce injury to the endothelial cells resulting in their tight junctions break and the release of myelinotoxic factors that can mediate oligodendroglial injury and dissolution of the myelin sheaths.

The incidence of CPM after orthotopic liver transplant (OLT) varies from 0.29 to 11.4 % in observational studies [6–12] to 28.6 % in autopsy series [13–18]. Liver transplant patients represent the third largest group of CPM (17.4 %), after chronic alcoholic patients (39.4 %) and patients who undergo quick correction of hyponatremia ($>$0.5 mmol/l/h; 21.5 %; [19]), with about 165 documented cases published from 1986 to 2009 [4–12, 14, 20–32]. The majority of these publications are case reports and retrospective clinical observational studies without control group.

Hyponatremia or its rapid correction is a recognized cause of CPM but, after OLT, some specific risk factors are suspected such as pre-OLT encephalopathy, previous alcoholism, severe malnutrition and ionic disorders associated with end-stage cirrhosis and the use of diuretics. Perioperative volume of blood products infused [10, 11] and, after OLT, the use of calcineurin inhibitors, CNIs [33, 34] may be a risk factor to develop neurological complications [24, 27, 30].

The aim of this study was to identify risk factors for development of clinically relevant central pontine and EPM (CPEPM) after OLT and to assess patient outcome.

Methods

Patient Selection

We retrospectively reviewed the clinical data of 1,378 patients who underwent OLT between July 1987 and December 2009 in the Geneva, Switzerland ($n = 523$) and Edmonton, Canada ($n = 855$) liver transplant programs.

The study was approved by the Ethics Committee of both centers.

CPEPM diagnosis was made on neurological symptoms correlated with brain MRI. Neurological symptoms suggestive of CPEPM were progressive lethargy, flaccid quadriparesis, decreased reflexes, dysarthria, dysphagia, aphasia, ophthalmoplegia, akinesia, pyramidal syndrome, choreoathetosis, catatonia, or ataxia. In association with these symptoms, CPEPM was diagnosed by MRIs showing hyperintense signals on T2-weighted and FLAIR imaging in the central pons, thalamus, basal ganglia, cerebellum and subcortex, without enhancement or mass effect [22, 35]. Increased signals on diffusion-weighted imaging in the same regions were also considered [36]. Patients with other neurological findings such as stroke or absence of typical MRI imaging were excluded.

Nineteen patients were diagnosed as having CPEPM. For each of these patients, we selected two control patients without CPEPM, matched by age $\pm$ 10 years, gender, date of OLT $\pm$ 18 months, MELD score [37] calculated as (0.957 ln(creatinine) + 0.378 ln(bilirubin) + 1.120 ln(international normalized ratio of prothrombin) + 0.643) $\times$ 10(36) $\pm$ 5 points, emergency status, and compared their clinical and biochemical parameters before, during, and after OLT.

Risk Factors for CPEPM After OLT

To determine risk factors for CPEPM after OLT, we compared the CPEPM group ($n = 19$) with the control group ($n = 38$) for the following clinical and biochemical parameters.

Pre-operative Clinical Parameters on the Day of OLT

Gender, body mass index (BMI), indication for OLT, CHILD score at OLT, encephalopathy at OLT graded from 1 to 3, and ascites at OLT graded from 1 to 3.

Pre-operative Biochemical Parameters (Just Before OLT)

Creatinine, INR, bilirubin, albumin, Hb, platelets, white blood cells (WBCs), glucose, Na, K, Mg, ASAT, ALAT, GGT, and alkaline phosphatase.

Donor's Data

Age, gender, and BMI.

Per-operative Clinical Parameters

Warm and cold ischemia time, number of red blood cells (RBCs), platelet units and fresh frozen plasma (FFP) transfused during surgery, episodes of hypotension defined as

mean arterial pressure <60 mmHg, and episodes of hypertension defined as mean arterial pressure >100 mmHg.

Post-operative Clinical Parameters

Delay between OLT and clinical CPEPM onset, cerebral MRI description in case of CPEPM, CPEPM evolution, cause of death and its delay after CPEPM and OLT, day of extubation, immunosuppression (use of steroids and doses, blood levels of tacrolimus, cyclosporine, rapamune, everolimus), immunosuppression switch after diagnosis of CPEPM, hemorrhage after OLT requiring transfusion or surgery, post-OLT metabolic acidosis (pH < 7.39 and normal p_{CO_2}), post-OLT hypoxemia (arterial p_{O_2} < 8 kPa on ABG while in ICU), post-OLT hypercapnia (arterial p_{CO_2} > 6 kPa on ABG while in ICU), and occurrence of rejection, treatment of rejection and its delay before CPEPM.

Post-operative Biochemical Parameters

Highest value between OLT and clinical CPEPM or highest value during the 15 days following OLT for the controls: Na, K, osmolality, AST, ALT, WBC, creatinine and CNI and m-TOR inhibitors trough levels.

Lowest value between OLT and clinical CPEPM or lowest value during the 15 days following OLT for the controls: Hb, platelets, albumin, glucose, Na, and Mg.

Statistical Analysis

Numerical data are expressed as percentage (%), mean with standard deviation (SD) or median with range, as appropriate. Quantitative variables were compared using Student *t* test or Mann–Whitney test as needed. Pearson χ^2 or Fisher exact test was used for qualitative parameters. Survival rates were evaluated using Kaplan–Meier curves and log-rank test. Values of $p < 0.05$ were considered statistically significant. Data analysis was performed using the SPSS statistical software version 20.0 (IBM SPSS Statistics).

Results

Out of 1,378 patients who underwent OLT from 1987 to 2009, 19 (1.4 %) developed clinical CPEPM. There were 7 women and 12 men, with a mean age of 52.1 ± 2 years, a mean MELD score of 26 ± 2.2, and a median MELD score of 24 (11–40), a median CHILD score of 13 (10–14). Indications for OLT were: alcoholic cirrhosis in 9 patients (47 %), HCV cirrhosis in 4 (21 %), primary biliary cirrhosis (PBC) in 2 (10.5 %), fulminant hepatitis in 1 (5 %), and other causes of cirrhosis in 3 (1 HBV cirrhosis, 1 idiopathic cirrhosis and 1 AIAD; 16.5 %). Two of these patients had a hepatocellular carcinoma, HCC (Table 1).

Pre-operative Clinical and Biochemical Parameters

Patients and controls were similar in terms of pre-operative clinical and biochemical parameters. INR values tended to be higher in patients who developed CPEPM after OLT ($p = 0.059$). Patients who developed CPEPM presented more frequently low (<130 mmol/l; 47.4 vs. 21 %, $p < 0.04$) and very low (<125 mmol/l; 26.3 vs. 0 %, $p < 0.009$) plasma sodium than controls (Table 2).

Donors Parameters

Donors parameters such as BMI (25.3 ± 1.2 vs. 24.6 ± 0.8 kg/m^2) and age (48 ± 5.5 vs. 45.1 ± 3 years) were similar.

Per-operative Clinical Parameters

Per-operative clinical parameters showed that warm and cold ischemia time, episodes of hypertension (mean arterial pressure >100 mmHg), and episodes of hypotension (mean arterial pressure <60 mmHg) did not differ between the two groups. The number of platelet units and FFP transfused during surgery was significantly higher in patients who developed CPEPM (8.3 ± 6 vs. 4 ± 0.8, $p = 0.05$, and 19.5 ± 5 vs. 10.6 ± 1.4, $p = 0.047$). The number of RBCs units was higher in patients with CPEPM but did not reach statistical significance (Table 3).

Table 1 Cases and controls characteristics

	Cases	Controls	*p*
Geneva (*n*)	7	14	
Edmonton (*n*)	12	24	
Total (*n*)	19	38	
Gender F/M	7/12 (37 %)	13/25 (34 %)	0.844
Age at CPM mean (years)	52.1 ± 2	52.6 ± 1.2	0.827
MELD mean ± SD	26 ± 2.2	25.6 ± 1.3	0.872
Median (range)	24 (11–40)	24.5 (11–41)	
CHILD median (range)	13 (10–14)	12 (8–15)	
OLT indications	9 (47 %)	14 (37 %)	0.856
OH	4 (21 %)	9 (24 %)	
HCV	2 (10.5 %)	6 (16 %)	
PBC	1 (5 %)	2 (5 %)	
Fulminant hepatitis	3 (16.5 %)	7 (18 %)	
Others	2	4	
HCC			

Table 2 Pre-operative clinical and biochemical parameters

Mean ± SD	Cases	Controls	*p*
INR	2.86 ± 0.6	1.91 ± 0.14	0.059
Creatinine (mmol/l)	132 ± 16	135 ± 12.5	0.829
Bilirubin (mmol/l)	264.3 ± 61.6	276.2 ± 44	0.710
Albumin (g/l)	28.2 ± 1.5	31.1 ± 1.2	0.140
Hemoglobin (g/l)	95.4 ± 4.4	96.3 ± 3.7	0.493
Platelets (U/ml)	55.8 ± 5	66.8 ± 4	0.223
Glucose (mmol/l)	8.9 ± 2.4	6.3 ± 0.3	0.933
Sodium (mmol/l)	133 ± 2.2	134.8 ± 0.9	0.623
Na <130 mmol/l, *n* (%)	9 (47.4)	8 (21)	0.04
Na <125 mmol/l, *n* (%)	5 (26.3)	0	0.009
Potassium (mmol/l)	4.17 ± 0.1	4.4 ± 0.13	0.154
Magnesium (mmol/l)	0.71 ± 0.06	0.8 ± 0.07	0.360
AST (IU/l)	94.7 ± 28	113 ± 44	0.393
ALT (IU/l)	159 ± 37	162 ± 52	0.332
Ascites 1/2/3[a]	1/9/9	6/11/21	0.284
Encephalopathy[b] 0/1–2/3–4	1/9/9	6/16/16	0.521
BMI (kg/m^2)	25.3 ± 1.2	24.6 ± 0.8	0.733

[a] According to CHILD score

[b] According to New Haven score

Table 3 Perioperative parameters

Mean ± SD	Cases	Controls	*p*
Hypotension (TAM <60 mmHg) (%)	53	37	0.336
Hypertension (TAM >100 mmHg) (%)	12.5	30.5	0.145
Cold ischemia time (min)	488.6 ± 45	483.8 ± 24	0.463
Warm ischemia time (min)	57.4 ± 4	56 ± 2	0.802
Red blood cells (units)	14 ± 4	8 ± 1.2	0.08
Fresh frozen plasma (units)	19 ± 5	10.6 ± 1.4	0.047
Thrombapheresis (units)	8.3 ± 6	4 ± 0.8	0.05

Post-operative Clinical Parameters

Six of the 19 patients with CPEPM remained intubated 2–30 days after the first neurocognitive impairment. Cyclosporine was used in 12 patients (63 %) who developed CPEPM and in 42 % of controls (ns). Tacrolimus was used in 37 % of patients who developed CPEPM and in 53 % of controls (ns). Steroids were used in 79 % of patients of both groups. Hemorrhagic complications requiring transfusion or surgery occurred in 32 % (6/19) of patients who developed CPEPM and in 10.5 % (4/38) of controls ($p = 0.049$). Metabolic acidosis (pH <7.39 and normal p_{CO_2}), hypoxemia (arterial p_{O_2} <8 kPa on ABG while in ICU), and hypercapnia (arterial p_{CO_2} >6 kPa on ABG while in ICU) did not differ between the two groups after OLT (Table 4). Episodes of rejection did not play any role in the etiology of CPEPM as the majority of them occurred usually after the apparition of neurological symptoms.

Post-operative Biochemical Parameters

The percentage of patients with high CNI trough levels (cyclosporinemia >300 µg/l and tacrolimus trough levels >15 µg/l) was similar in both groups (58 vs. 50 %: ns). The variations of Na before and in the first days after OLT were higher in patients with CPEPM than in controls (15.9 ± 1.9 vs. 11.1 ± 0.9 mmol/l, $p = 0.023$). Patients with CPEPM tended to undergo quicker correction (≥0.5 mmol/l/h) of hyponatremia during the first 24 h after OLT (7/19: 36.8 % vs. 6/38: 15.8 %, $p = 0.07$). The peak values of osmolarity, potassium, AST, ALT, creatinine, and WBC after OLT were similar in both groups. The lowest value of Hb, platelets, albumin, glucose, Na, Mg between OLT and clinical CPEPM or lowest value during the 15 days following OLT for the controls was similar in both groups (Table 4).

Post-operative Clinical and Radiological Parameters

The neurological manifestations of CPEPM occurred in 9.53 ± 6.56 days after OLT, the earliest 3 days after and the latest 25 days after OLT. Brain imaging was performed within a median of 6 days (1–33) after the first symptoms. MRI features of patients with suspected CPEPM are detailed in Table 5. Majority of patients show pontine and extrapontine lesions on T2/FLAIR. Eleven patients (58 %) were switched to m-TOR inhibitors after CPEPM, CNI levels were reduced for the other eight patients. Mortality at 1 year of patients developing CPEPM was significantly increased (63 vs. 13 %, $p < 0.0001$; Fig. 1).

Risk Factors of Developing CPEPM

Severe and very severe hyponatremia, transfusion of ≥4 platelet units (median of platelet units transfused in patients with CPEPM), of ≥12 FFP (median of FFP transfused in patients with CPEPM), hemorrhagic complications and increasing of Na ≥12 mmol (median of Na variation after OLT in patients with CPEPM) in the post-operative course were identified as risk factors for developing CPEPM. Only 8 % (3/38) of the controls presented >2 of these risks compared with 50.65 % (10/19) of patients with CPEPM. The association of ≥3 of these risk factors was strongly associated with CPEPM occurrence ($p = 0.00015$).

Table 4 Post-operative parameters

	Cases	Controls	*p*
Immunosuppression			0.245
Tacrolimus, *n* (%)	7 (37)	20 (53)	
Cyclosporine, *n* (%)	12 (63)	16 (42)	
Sirolimus, *n*		1	
No immunosuppression, *n*		1	
Hemorrhagic complications, *n* (%)	6 (32)	4 (10.5)	0.049
Acidosis (pH < 7.39 and normal p_{CO_2}), *n* (%)	7 (36)	15 (39.5)	0.905
Hypoxemia (arterial p_{O_2} <8 kPa), *n* (%)	7 (36)	8 (21.6)	0.302
Hypercapnia (arterial p_{CO_2} >6 kPa), *n* (%)	6 (31)	8 (21.6)	0.524
Na changes >0.5 mmol/h in the first 24 h after OLT, *n* (%)	7 (36.8)	6 (15.8)	0.07
Na changes before–after OLT[a] (mmol/l), mean ± SD	15.9 ± 1.9	11.1 ± 0.9	0.023
Peak ALAT value after OLT (mmol/l), mean ± SD	848.5 ± 164.4	1,061.2 ± 175.4	0.617
Peak ASAT value after OLT (UI/l), mean ± SD	1,157.7 ± 191.6	1,469 ± 200.6	0.488
Peak osmolarity value after OLT, mean ± SD	314.2 ± 7	308 ± 4	0.357
CNI trough levels: FK >15 or CyA >300 μmol/l (%)	58	50	0.851

[a] Highest value between OLT and clinical CPEPM or highest value during the 15 days following OLT for the controls

Discussion

Our study, the largest published till date, using homogenous control population including patients with similar age, gender, MELD score, and date of transplantation, shows that CPEPM after OLT results of an addition of risk factors leading to important shifts in plasma sodium concentration in the first days after surgery. Our data confirm that severe hyponatremia at the moment of transplantation and important peri-operative serum Na variation are risk factors of developing CPEPM and reveal the role played by the number of FFP units and thrombapheresis transfused during surgery and by post-operative hemorrhagic complications requiring transfusion or surgery. The addition of more than two of these conditions was strongly associated with CPEPM occurrence. Pre-operative INR values tend to be higher in patients who develop CPEPM and may have increased the risk of surgery-related hemorrhagic complications and massive transfusion. This confirms the conclusion of Lee et al. [11] that the use of massive transfusion and volume replacement during surgery may favor the occurrence of CPM. Thrombapheresis, FFP and RBC units are rich in sodium and cause rapid serum sodium shift.

In the present report, patients with CPEPM had significantly greater and tended to have quicker (≥0.5 mmol/l/h in the first 24 h) sodium fluctuation after OLT. We failed to demonstrate that quick Na correction occurred only in the first 24 h after OLT probably because more than one-third of the patients who developed CPEPM underwent re-operation and/or transfusions after transplantation causing Na fluctuation later in the post-transplantation course.

There was a significantly larger percentage of patients with severe (<130 mmol/l) and very severe (<125 mmol/l) hyponatremia in the group with CPEPM as compared with the patients without CPEPM despite the fact that the mean pre-operative plasma sodium concentrations were similar in case and control groups. CPEPM may occur in patients with relatively normal serum sodium: in presence of an osmotic challenge, neuroglia activate energy-dependant cell surface pumps (e.g., Na–K ATPase) to rapidly counteract the electrolyte derangement. In patients with liver failure or in case of malnutrition, it is postulated that glia cells may inherently lack a plentiful supply of glucose or glycogen, hence relatively minor osmotic derangements might lead to a rapid depletion of cellular energy supply and cell death [38, 39]. A lack of adequate concentrations of organic osmolytes predisposes the brain to osmotic injury [40].

Hyponatremia is a common complication of advanced cirrhosis mainly related to impairment in the renal capacity to eliminate solute-free water causing a reduction in serum sodium concentration and hypo-osmolality. This dilutional hyponatremia reflects hemodynamical dysfunction associated with severe portal hypertension [41]. In addition, the use of diuretics in patients with hypervolemic hyponatremia is another cause of hyponatremia in this population of patients with advanced cirrhosis. According to the increased risk of developing CPEPM in case of severe hyponatremia before OLT, diuretics should be used with caution in patients with plasma sodium ≤130 mmol/l. Albumin perfusion rich in sodium and known to inhibit antidiuretic hormone should be encouraged before OLT and more effective treatment of dilutional hyponatremia such as vaptan should be studied in patients on waiting list. Peri-operative management of patients undergoing liver transplantation should include careful monitoring of sodium plasma concentration and preference of water-free perfusion in case of massive transfusion of blood products.

Table 5 MRI features of patients with suspected CPEPM

Patients	Time of symptoms after OLT (days)	Type of symptoms	Time of MRI after OLT (days)	MRI features			Pontine-brain stem lesions	Extrapontine-brain stem lesions	Outcomes
				T1	T2/FLAIR	DWI			
1	8	Complete aphasia Flaccid tetraparesia	14, 17	−	+	−	No	Yes	Speaking improvement *Death at 4 months* recurrent disease
2	23	Altered consciousness	51	−	++	−	Yes	Yes	*Death at 2 months* multisystem failure
3	5	Dysarthria, dysphagia	8, 18						Able to speak 1 week later, by 4 months able to be up with walker and discharged from hospital *Death at 8 years* sepsis
4	6	Locked in syndrome	7	−	+++	−	Yes	Yes	Understand verbal communication, quadriplegia *Death at 4 months* sepsis, multisystem failure
5	3	Seizure	16	−	++	−	Yes	No	*Alive*
6	7	Coma, seizure	7, 18	+	+++	−	Yes	Yes	No significant clinical improvement *Death at 4 months* treatment withdrawal
7	6	Respiratory failure, coma	20	−	++	−	Yes	Yes	Clinical improvement, extubation, remained confused *Death at 2 months* cardiovascular
8	5	Confusion	34	−	+++	−	Yes	No	No significant clinical improvement *Death at 3 months* subarachnoid hemorrhage
9	6	Seizure, coma	12	−	+	+	Yes	Yes	Waked up at 5 weeks, walked at 7 weeks, discharged from hospital at 5 month *Alive*
10	16	Dysarthria	19	−	+	−	Yes	No	*Alive*
11	12	Altered consciousness	18	−	+++	+	Yes	Yes	Tracheotomy, persistent seizure despite treatment, open eyes *Death at 9 months* malignancy
12	17	Hand and arm tremor	17	−	++	+	Yes	Yes	*Death at 7 months* pulmonary disease
13	4	Aphasia, tetraparesia	9, 23	−	++	+	Yes	Yes	No significant clinical improvement *Death at day 46* respiratory arrest on obstruction of the canula
14	5	Seizure, flaccid tetraparesia	10	−	++	++	Yes	No	Coma *Death at day 16*
15	7	Seizure	11, 20	−	+++	−	Yes	No	Persistent dysarthria, psycho-motor slowering *Death at month 4* chronic rejection
16	9	Coma, left extrapyramidal syndrome, right pyramidal syndrome	15, 53	−	+++	+	Yes	Yes	Persistent dysarthria, psycho-motor slowering, dependent for everyday life *Death at month 11* HCV recurrence

Table 5 continued

Patients	Time of symptoms after OLT (days)	Type of symptoms	Time of MRI after OLT (days)	MRI features			Pontine-brain stem lesions	Extrapontine-brain stem lesions	Outcomes
				T1	T2/FLAIR	DWI			
17	3	Coma	36	−	++	+	Yes	Yes	Clinical improvement with residual confusion
									Discharge from hospital after 4 months
									Persistent cerebellar syndrome
									Alive and independent
18	4	Seizure, altered consciousness	25	−	+++	+	Yes	No	Discharge from hospital after 11 months, lived in a medical home
									Persistent spastic tetraparesia, cerebellar ataxia, severe dysarthria
									Death at 8 years lung carcinoma
19	11	Aphasia, apraxia, extrapyramidal syndrome	32	−	+++	−	No	Yes	Discharge from hospital after 3 months
									Persistent dysarthria
									Death at 7 years colic carcinoma

Majority of patients show pontine and extrapontine lesions on T2/FLAIR

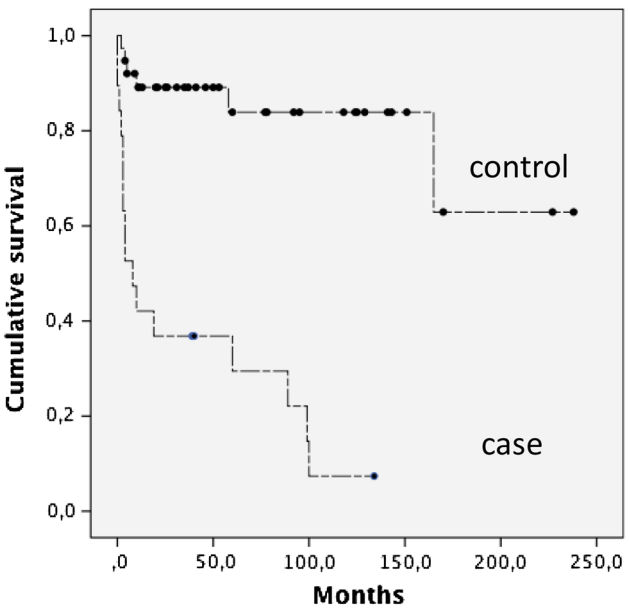

Fig. 1 Survival in the two groups, log-rank $p < 0.001$

In the pre-operative clinical data we did not find any difference in terms of encephalopathy, ascites, and BMI. Indications for OLT were similar in both groups and, despite the fact that CPM has often been associated with alcohol consumption, this study shows that neurological complications could occur equally in patients with end-stage liver diseases of any etiology.

Most of the patients with CPEPM had high MELD score (mean 26 ± 2.2, median 24, range 11–37) and were representative of the general population waiting for OLT; the decreased liver function was not by itself a risk factor to develop CPEPM as the controls had similar MELD score. Recently, Lee et al. [11] published the first and unique case–control study with cases of CPM and age-, gender-, and date of operation-matched controls. They suggested that the MELD–Na score, as indicator of severe end-stage cirrhosis, predicts the occurrence of CPM. As their patients were not matched for the MELD score, they concluded that patients with more severe liver dysfunction had higher risk to develop CPM. But, as shown in our study, the MELD score is not a strong predictor of CPEPM occurrence. Still the presence of more severe patients on the waiting list will potentially increase the incidence of CPEPM after liver transplantation.

We did not observe any association among CPEPM, the type of immunosuppression, and high CNI trough levels. Still, some reports incriminate CNI in the occurrence of CPEPM [42]. We cannot exclude that cyclosporine or tacrolimus played a role in our patients neurological deterioration. Nevertheless none of our patients with suspected CPEPM showed the classical but controversial lesions described in CNI toxicity, such as the posterior reversible encephalopathy syndrome or diffuse microangiopathy.

CPEPM was associated with a significantly higher mortality rate. Despite the fact that CPEPM was not the direct cause of every death, it probably increases the risk of pulmonary infections, sepsis, and multisystem failure. In addition, severe neurological symptoms probably changed the general way to take care of specific pathology such as HCV recurrence.

Our study is the largest one published till date reporting patients who developed CPEPM after OLT and the second to be controlled. However, this work has several limitations. It is a retrospective analysis covering 22 years of our liver transplantation program and therefore lacking interesting data such as osmolality before and after OLT, fluctuation of serum sodium during surgery, total fluid infusion, etc.

Our patients were selected on a retrospective mode based on the development of suggestive neurological symptoms, confirmed by a typical image of demyelinisation on MRI. Controls had no MRI imaging and we cannot exclude subclinical CPEPM. Findings from autopsy series suggest that asymptomatic or mildly symptomatic CPEPM may be significantly more common than suspected in OLT patients. Therefore only a prospective study with pre- and post-transplant MRI and neurological follow-up will be able to determine the real incidence of CPEPM after OLT and the actual risk factors for this rare but potentially fatal complication. However, CPEPM is such a rare event after OLT that a prospective analysis would be difficult to obtain.

Conclusion

Our study shows that in high MELD score patients undergoing OLT, severe hyponatremia, massive perfusions of Na-rich products, post-operative hemorrhagic complications and important fluctuations of serum sodium are risk factors of developing CPEPM. The addition of more than two of these conditions is strongly predictive of CPEPM. This rare but potentially severe complication, albeit more frequent in case of severe hyponatremia, may concern patients with normal or near normal serum sodium concentration in presence of other risk factors. We can postulate that the incidence of CPEPM will increase in the future. Indeed, patients with higher MELD scores and consequently increased risk of surgery-related hemorrhagic complication, massive transfusion, or sodium shifts are now selected for OLT. Therefore, diuretic drugs should be used with caution before OLT in patient with hyponatremia, effective drugs against dilutional hyponatremia such as vaptan should be studied in this specific situation, careful monitoring of natremia in the perioperative period, and use of water-free perfusion in case of massive blood-products transfusion are critical points of this patient management.

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Conflict of interest Isabelle Morard, Yvan Gasche, Mark Kneteman, Christian Toso, Ariane Mentha, Glenda Meeberg, Gilles Mentha, Norman Kneteman, and Emiliano Giostra declare that they have no conflict of interest.

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