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A rare case of hemodialysis-related portosystemic encephalopathy and review of the literature.

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A rare case of hemodialysis-related portosystemic encephalopathy and review of the literature.

Abstract

Hemodialysis-related portosystemic encephalopathy (HRPSE) is a clinical phenomenon where portosystemic encephalopathy (PSE) develops without liver dysfunction, usually caused by changes in the portosystemic blood flow related to hemodialysis. We describe the case of a 22-year old patient with a transjugular intrahepatic portosystemic shunt (TIPS) who developed HRPSE several months after initiation of hemodialysis.

Symptoms resolved after therapy with laxatives and neomycin and relocation of the hemodialysis catheter from the superior caval vein to the femoral vein.

Key words: portosystemic encephalopathy, hemodialysis, TIPS, shunt

Case

We present a 22-year old man who suddenly developed somnolence and confusion at the end of the first half of a hemodialysis session. He was born with congenital liver fibrosis with autosomal recessive polycystic kidney disease (ARPKD) and required renal replacement therapy since the age of 1. He received a first kidney transplant at the age of 4, which failed by the age of 7 due to BK polyomavirus nephropathy. He received a second kidney transplant at the age of 8, which again failed at the age of 20 because of humoral rejection. He has since been treated with dialysis. He started on peritoneal dialysis (PD) but due to PD catheter dysfunction he switched to hemodialysis one and a half years later. Since then, he received thrice-weekly hemodialysis via a tunnelled central venous catheter in the right jugular vein. The patient also suffered from congenital liver fibrosis with portal hypertension. A transjugular intrahepatic portosystemic shunt (TIPS) was placed at the age of 7 because of portal hypertension with refractory ascites and hypersplenism with anemia and leukopenia. At the age of 8 a splenectomy had to be performed for deep thrombocytopenia due to persistent splenomegaly with hypersplenism. In his fourth month of hemodialysis, the diagnosis of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) was made by the ophthalmologist after an episode of vision disturbances, for which a tapered course of high dose corticosteroids was started. His current medication comprised tacrolimus and corticosteroids, a proton pump inhibitor, calcium antagonist, diuretic, phosphate binder and vitamin D supplementation. When six months in hemodialysis, the patient became progressively somnolent and disorientated at the end of the first half of one of his hemodialysis sessions. This was the first time he experienced such overt encephalopathic symptoms, although he had been complaining of severe fatigue after every session ever since he started hemodialysis six months ago, and had mentioned that he had been feeling somewhat sleepy and confused for a few hours after the last dialysis session two days earlier. The last few days there were also some gastro-intestinal complaints including constipation and ructus. On the initial examination, hemodynamic parameters were stable without fever. Physical assessment revealed impaired consciousness and speech, disorientation, a flapping tremor of both upper limbs, global hyperreflexia and a bilateral sustained ankle clonus. Clinical examination of the heart, lungs and abdomen was normal. Differential diagnosis at that moment was hepatic encephalopathy, uremic encephalopathy, APMPPE-related cerebral vasculitis, infection/sepsis, dialysis disequilibrium syndrome and posterior reversible encephalopathy syndrome (PRES). A blood analysis performed after hemodialysis (table 1) revealed leukocytosis (15×10^6 ; normal 4.3-10) with a normal erythrocyte sedimentation rate (ESR) (10 mm/u; normal 0-10) and CRP (<2.9 mg/L; normal

<3.0). Creatinine was 2.17 mg/dL with mild hypokalemia (3.2 mmol/L; normal 3.5-5.1). Post-dialysis urea was 49 mg/dL, with mean pre-dialysis urea values of 140 mg/dL. Notably, there was a high serum ammonia level of 105 μ mol/L (normal $\leq$ 19) with normal liver function tests (ASAT 22 U/L, ALAT 45 U/L, AF 147 U/L, bilirubin 0.63 mg/dL, INR 1.06). There were no recent ammonia levels to compare. Urgent magnetic resonance imaging (MRI) of the brain, done to exclude cerebral vasculitis because of the association with APMPE, showed multiple white matter lesions in both hemispheres (Figure 1), also seen on a previous MRI, but no signs of cerebral vasculitis. Electroencephalogram was suggestive for metabolic encephalopathy. Abdominal ultrasonography (including elastography) showed fibrosis and a patent TIPS, no ascites. According to these findings, the presumed diagnosis at that moment was hemodialysis-related portosystemic encephalopathy (HRPSE). The hypothesis of pre-existing low-grade portosystemic encephalopathy (PSE), due to increased shunting over the TIPS during hemodialysis, was put forward, with current constipation and/or the high dose corticosteroids as enhancing factors.

Treatment with lactulose syrup and lactulose enemas was started with prompt improvement of the encephalopathic state and decrease in serum ammonia. Afterwards, fluctuating symptoms remained despite optimal laxation with lactulose syrup and enemas. Four days later, a new hemodialysis session was initiated at a very low blood flow rate. However, after 30 minutes encephalopathic symptoms reoccurred and the hemodialysis session was immediately stopped. Neomycin needed to be associated to the medical treatment. We hypothesized that the tip of this catheter located in the superior vena cava created a negative pressure (suction) at the level of the hepatic veins, which might have increased the shunting of ammonia-rich blood over the TIPS. Therefore, we also decided to change the hemodialysis access and a new catheter was placed in the right femoral vein. The next hemodialysis session performed via the femoral catheter went uneventfully as went all subsequent sessions. Neomycin was stopped after seven days and the lactulose treatment could be tapered down. Four weeks later the patient underwent a living donor kidney transplant and dialysis could be discontinued. Up to now, six months after transplantation, he never experienced symptoms of PSE again. A time course of the aforementioned clinical and biochemical evolution as well as the associated treatment is displayed in Figure 2. (*Table 1, figure 1 and 2 near here*)

Discussion

PSE is a progressive, but potentially reversible disorder, which can present as a wide spectrum of neuropsychiatric abnormalities and motor disturbances that ranges from mild alteration to coma and death. The mainstay for pathogenesis and treatment is elevated ammonia in serum and in the central nervous system. From the gut, ammonia normally enters the portal circulation and is converted to urea by the liver, which is subsequently renally excreted₍₁₎. The main cause of evolution of PSE is hepatic cirrhosis, although hyperammonemia may occur in patients with a portosystemic shunt (PSS) in the absence of intrinsic liver disease with liver decompensation, as seen in our case. Hemodialysis-induced hemodynamic changes can increase the pressure gradient between the inferior caval vein (ICV) and portal vein (PV) over a PSS (2). During hemodialysis, the inner pressure of the IVC decreases after fluid removal, with subsequent increased flow of portal ammonia-rich blood into the systemic circulation through the PSS, leading to hemodialysis-related portosystemic encephalopathy (HRPSE).

Our case is the first report of a TIPS-associated HRPSE. The presence of a TIPS is a known risk factor for PSE. The pathogenesis is due to a combination of increased bioavailability of gut-derived toxins and hypoperfusion of the hepatic microcirculation. As mentioned before, hemodialysis can create hemodynamic changes with an increase of the ICV-PV pressure gradient. As ammonia-rich portal venous blood flows into the systemic circulation, substances such as ammonia may cause central nervous system toxicity. Figure 3 shows the close proximity of the jugular hemodialysis catheter with its tip in the superior caval vein and a TIPS. In view of this anatomic relation, we assumed that by altering the access of hemodialysis from the jugular to the femoral vein, these hemodynamic changes would be decrease. In combination with optimal laxation and antibiotics, our patient's symptoms indeed resolved. After his living donor kidney transplant a couple of weeks later, hemodialysis could be stopped and the patient remained asymptomatic. (*figure 3 near here*)

HRPSE is a rare entity with a scarce number of case reports found in the literature. We found eight cases of dialysis-related portosystemic encephalopathy with full text in English. (Table 2) (2-8). (*Table 2 near here*) Male/female ratio was equal with an average patient age of 64,8 (range 32-79 years). All of the cases were related to abnormal intra-abdominal shunt vessels discovered during the work-up of encephalopathy in dialysis patients. These shunt vessels may be congenital or develop spontaneously or following abdominal injury or surgery. Most of the congenital shunts concern the left gastric vein or splenic vein and the left renal vein. Duration of

intermittent hemodialysis until occurrence of symptoms varied from one month to 15 years. Treatment for HRPSE typically involves either conservative therapy (dietary protein restriction, lactulose, antibiotics) or blocking of the shunt flow by interventional embolization or shunt ligation.

Oi et al. (2) described two cases of PSE in hemodialysis patients with shunt vessels who presented with opposite changes in serum ammonia concentration. The authors suspected the presence of congenital shunts, because subtle encephalopathy already developed prior to the initiation of hemodialysis. The hypothesis is that the pre-existing shunts grew due to progression of chronic kidney disease and the subsequent fluid overload. In the first case ammonia concentration decreased and symptoms improved after hemodialysis. The authors assume that dialysis removed ammonia from the blood at a greater rate than that being added by the increased shunt blood flow.

The second patient began to show more overt abnormal behavior after hemodialysis one year after its initiation. His ammonia level and symptoms continued deteriorating during hemodialysis despite conservative therapy. It was only after balloon-occluded retrograde transvenous obliteration (B-RTO) that the ammonia level decreased and his symptoms disappeared. By this, it should be noted that hemodialysis does not always deteriorate PSE and that treatment can vary depending on the patient's pathophysiological condition and an individualised approach is necessary.

One case of a Spanish patient who developed PSE after peritoneal dialysis was also reported (5). He developed hepatic encephalopathy 15 months after starting continuous ambulatory peritoneal dialysis therapy. During work-up, a shunt between the left gastric and azygos veins was found. Despite transfer to hemodialysis treatment, episodes of encephalopathy remained. Only after surgical ligation of the gastric vein, symptoms disappeared. The authors speculated that increased intra-abdominal pressure and vasodilation caused by peritoneal dialysis solutions in a patient with a spontaneous PSS resulted in ammonia-rich blood flow from the portal vein to the superior vena cava with resultant encephalopathy. The other five cases (3, 4, 6, 7, 8) all concern patients with occurrence of encephalopathy during hemodialysis. Two of them received definitive surgical ligation of the shunt and the other three received B-RTO, all with successful outcome.

In conclusion, intermittent hemodialysis is a risk factor for increased flow of ammonia-rich blood from the portal into the systemic circulation through large intra-abdominal shunts. In patients who suddenly have a decrease of consciousness or change in behaviour during or after

hemodialysis, PSE should be ruled out, including screening for these shunts. Optimal treatment contains definitive closure of the shunt. Previous case reports describe particularly congenital shunts, while our case is the first concerning a TIPS. Total closure of TIPS should be avoided due to possible complications of portal hypertension. Other measures to reduce flow from the portal to the systemic circulation should be considered in these cases, for example by changing the location of the hemodialysis catheter.

Table 1. Blood analysis during first days of hospitalisation.

	Day 0 Before dialysis and symptoms	Day 0 Just after stopping dialysis, during symptoms	Day 1 No dialysis	Day 4 Just after stopping dialysis, during symptoms	Reference values
Sedimentation	10	10			0 - 10 mm/u
Hemoglobine	/	11.0	10.6	10.2	13 - 17 g/dL
Leukocytes	/	15.0	23.4	22.9	4.3 – 10 .10 ^{E9} /L
Creatinine	4.44	2.17	4.47	6.95	0.63 – 1.10 mg/dL
eGFR CKD-EPI	18	42	17	10	ml/min./1.73m ²
Ureum	139	49	91	141	13 – 43 mg/dL
Sodium	139	137	138	144	136 – 145 mmol/L
Potassium	3.8	3.2	3.6	3.7	3.5 – 5.1 mmol/L
Chloride	104	100	103	106	101 – 109 mmol/L
Bicarbonate	/	26	28	24	21 -32 mmol/L
Calcium	2.47	2.31	2.18	2.21	2.19 – 2.55 mmol/L
CRP	<2.9	<2.9	<2.9	<2.9	<3.0 mg/L
Albumin	/	36	31	32	35 – 52 g/L
Glucose	/	110	78	65	74 – 100 mg/dL
LDH	/	332	249	280	84 – 246 U/L
CK	/	74	48	71	46 – 171 U/L
ASAT	21	22	21	19	<35 U/L
ALAT	41	45	41	41	<45 U/L
AF	138	147	121	129	53 – 128 U/L
Gamma-GT	233	245	214	199	<55 U/L
Total bilirubin	/	0.63	0.43	0.41	0.30 – 1.2 mg/dL
Ammonia	/	105	62	93	≤ 19 µmol/L
Tacrolimus	/	3.8	3.5	3.6	µg/L

Table 2. Cases of portosystemic encephalopathy with a relation to dialysis.

Age	Sex	Symptoms	Cause of CKD	Dialysis and duration	Shunt	Treatment	Nationality	Year	Reference
57	M	DOC	DN	HD 1 mo.	SMV – LGV- LRV	Surgical ligation	Japan	1995	3
68	M	DOC	FSGS	HD 1 mo.	LGV - LRV	Surgical ligation	Japan	2004	4
75	M	DOC	IgAN	PD 15 mo.	LGV – AV - SVC	Surgical ligation	Spain	2007	5
79	F	Discrepant conversation	DN	HD 15 yr.	SV - LRV	B-RTO	Japan	2013	6
32	F	DOC	CIN	HD 1 yr.	Intrahepatic vein	B-RTO	Taiwan	2013	7
75	F	DOC/ Parkinsonism	DN	HD 5 yr.	SV - LRV	B-RTO	Japan	2015	8
78	F	DOC	BNS	Before HD	LGV- LRV	Conservative	Japan	2015	2
55	M	DOC	DN, Unilateral renal hypoplasia	HD 1 yr.	SV – LRV	B-RTO	Japan	2015	2
22	M	DOC/flapping tremor	ARPKD	HD 7 mo.	TIPS	Relocation dialysis catheter	Belgium	2018	Our case

DOC: disturbance of consciousness, DN: diabetic nephropathy, FSGS: focal segmental glomerulosclerosis, IgAN: IgA nephropathy, CIN: chronic interstitial nephritis, BNS: benign nephrosclerosis, ARPKD: autosomal recessive polycystic kidney disease, SMV: superior mesenteric vein, LGV: left gastric vein, LRV: left renal vein, AV: azygos vein, SVC: superior vena cava, SV: splenic vein, B-RTO: Balloon-occluded Retrograde Transvenous Obliteration

Figure 1. Axial FLAIR brain MRI shows multiple hyperintense white matter lesions with central hypointensity in both cerebral hemispheres, already apparent on previous MRI images from more than fifteen years ago. These are most likely non-specific sequelae of either inflammatory, infectious, vascular or metabolic origin.

Figure 2. Time course of the patient's clinical features, serum ammonium level and treatment.

Figure 3. Close anatomical proximity of the jugular venous catheter with its tip in the superior caval vein and the TIPS (red arrow).

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