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POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME AFTER EXCESIVE AMINO-ACID PARENTERAL NUTRITION-CASE REPORT

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a reversiblesubacute neurologic state that despite other causes, such as immunosuppression, chemotherapy, sepsis, preeclampsia, renal failure, transplantation, autoimmune disorders, can occur as a result of a toxic effect of some drugs or medications. Uncontrolled hypertension results in loss of cerebral autoregulation, vasogenic edema and neurologic signs and symptoms such as severe headaches, visual disturbances, seizures, confusion, somnolence and sometimes loss of consciousness.

The condition is usually self-limiting, but reversibility depends on the early recognition and fast removal of the toxic agent, as a trigger of the disorder. Here, we present a case of a 53 year old patient who presented himself at our clinic in a septic state of abdominal origin. He underwent an abdominal surgery, afterwards he received a combination of strong antibiotics according to microbiologal findings, supportive therapy and parenteral nutrition as his state demanded. Septic state, antibiotic therapy and high rates of amino acid infusion for parenteral nutrition resulted in neurologic disturbance during the treatment.

CT scan and MRI of the brain stated the diagnosis of PRES. Late recognition and uncontrolled prolonged aggressive parenteral amino acid infusion were the most probable reasons for fast deterioration, consecutive brain damage and the patient's death.

Keywords: Posterior reversible encephalopathy syndrome, hypertension, neurologic deficit, vasogenic edema, high-rate parenteral nutrition

Introduction

Posterior reversible encephalopathy syndrome (PRES) also known as Posterior reversible leukoencephalopathy syndrome, brain hyper-perfusion encephalopathy or brain capillary leak syndrome is a rare neurologic disorder which develops as a result of acute hypertension and the inability of the brain circulation at the posterior fossa to regulate the blood flow.

Loss of autoregulation, together with hyper-perfusion and damaged integrity of the blood brain barrier (BBB) results in occurrence of vasogenic edema [1, 2, 5, 6, 7].

If there is a prompt recognition of the state, according to the patient's signs and symptoms, and the trigger is isolated and removed, there may not be a resultant ischemia and permanent brain damage [6].

If the state is unrecognized, it may result in severe brain damage and even the patient's death. PRES was first described in 1996 as a distinct entity by the American neurologist Judy Hinchey at al., although in the previous years many radiologists described almost identical CT and MRI findings [2, 5]. One of the possible pathophysiological mechanisms is disordered cerebral vascularization along with impaired cerebral autoregulation that causes increase in cerebral blood flow and cerebral hyper-perfusion [2, 5, 7].

Concomitant endothelial dysfunction and disruption of BBB causes cerebral hypo-perfusion and consecutive vasogenic edema to develop.

An additional mechanism is immunological activation. Cytokines, Lactate dehydrogenase (LDH) and vascular endothelial growth factor (VEGF) also cause dysregulation in vascular permeability [2].

Although reversible, if not recognized and treated promptly, the condition may lead to death.

Case Report

A 53-year old patient presented himself at the hospital with severe abdominal pain and distension in a septic state with a several day anamnesis of vomiting, breathing difficulty and febrile state.

He immediately underwent a CT scan imaging which showed pleural effusion and atelectasis and aero-liquid levels and cystic formation in gastro-lienal space without visible demarcation.

Two months ago he underwent abdominal surgery for hepatic echynococcosis and had a biopsy of a neck lymph node of unknown origin. Biochemistry showed high levels of all infectious markers, so he was sent to the operating room immediately.

Operative findings showed abdominal abscess and bowel damage and intestinal resection and anasthomosis were made. Post-operatively he received dual antibiotic therapy, analgesic and supportive therapy. Because of liquidothorax and persistent hypoproteinemia, a thoracic drain was placed.

The patient had slow and poor recovery and during his hospital treatment he underwent three consecutive abdominal surgeries because of dehiscence and placement of feeding stoma.

During his treatment, he received parenteral nutrition, but he had continuous low protein levels, thereby the infusion rate of aminoacid solution were very high, but on the contrary, infusion rates of glucose and fatty solutions were inadequate, according to the ESPEN protocols.[8].

According to microbiology results, he was put on Linezolid. On the third day of Linezolid introduction in his therapy, he complained of severe headaches, blurred vision, confusion and seizures. He had hypertension unresponsive to therapy, which developed before Linezolid introduction, while the patient was on total parenteral nutrition, prepared mainly with amino acids. Assuming that blurred vision is a side effect of Linezolid treatment, it was discontinued, but aminoacid infusion rate remained constantly high.

Results of CT scan and MRI of the brain referred to the diagnosis of PRES. Because of the worsened condition of the patient and the newly developed cardiac and respiratory insufficiency, mechanical ventilation and inotropic therapy were necessary.

The septic state remained present and all antibiotic modalities were used, which led to the conclusion that the patient had mycotic infection, so caspofungin was introduced in the therapy.

With already persistent hepato-renal failure, in a few days of ICU treatment, the patient died. During the treatment, it was never taken into account that the probable triggers of hypertension and neurologic deficit were a result of high aminoacid infusion rate, which caused PRES.

Table 1. Changes in complete blood count and infectious markers, *RBC*-red blood cells, *HGB*-hemoglobin, *HCT*-hematocrit, *WBC*-white blood cells, *PLT*-platelets, *CRP*-C-reactive protein

	RBC (10^12/)	*HGB (g/L)*	*HCT (rv)*	*WBC (10^9/L)*	*PLT (10^9/l)*	*CRP (mg/L)*
11.01	3.82	105	0.339	7.6	479	243.7
12.01	3.75	107	0.325	18.0	545	265.4
13.01	2.90	80	0.254	13.0	458	287.4
14.01	2.54	74	0.223	15.3	506	282.9
16.01	3.03	85	0.271	16.0	486	273.7
20.01	2.54	72	0.230	14.0	488	214.4
22.01	3.15	92	0.269	11.1	434	163.4
24.01	2.87	79	0.248	9.8	353	98.9
25.01	2.84	78	0.249	14.8	434	182
26.01	2.79	77	0.241	9.7	425	241.5
28.01	3.41	100	0.296	8.3	455	107.3
31.01	3.37	98	0.286	13.5	260	101.7
01.02	2.80	76	0.245	9.4	223	190.9
04.02	3.14	86	0.269	6.2	223	135.4
06.02	2.39	69	0.204	7.9	220	171.2
08.02	2.33	68	0.204	7.0	147	284.5
10.02	3.29	93	0.285	5.3	219	150.8
16.02	3.00	89	0.257	7.0	353	233.8
19.02	3.19	89	0.276	7.9	500	100.5
22.02	3.14	89	0.267	5.7	369	290.6
24.02	3.13	93	0.271	4.6	274	318.9
25.02	2.77	82	0.241	4.4	145	257.8
26.02	2.48	68	0.220	6.3	186	250.9

As shown in the table which represents the consequent laboratory results on daily basis, there are high levels of infectious markers since the admission in the hospital, which rose in the beginning of the treatment, even though he was on triple antibiotic regimen.

After the first operation he was put on Piparacilin/Tazobactam, Vancomycin and Metronidazole. The first results from the abdominal abscess showed presence of Corinebacterium, sensitive to Linezolid, which was introduced in the therapy along with antimycotic Fluconazole, because of the presence of Candida albicans.

During the treatment, there was a slight drop in the infectious biomarkers, but never to the normal range values. It was obvious, according to the lab results and clinical presentation, that the patient suffered from sepsis, but still compensated. Glucose levels and degradation products were in normal range, as was the complete blood count, and there was a slight hypoproteinemia and electrolyte disbalance.

The protein deficiency was compensated with albumin 20% and amino acid solutions as total parenteral nutrition. Continuous drop of the protein levels caused development of ascites, bilateral pleural effusion and peripheral edema, and was the reason for raising the levels of amino acid infusion rate, which at some point exceeded the normal range values. Despite the intensive treatment, the overall condition of the patient did not improve.

Table 2. Changes in electrolyte values, degradation products and bilirubin as markers of renal and liver function, *Na*-sodium, *K*-potassium, *Cl*-chlorides, *Crea*-creatinine, *Total/Ind/Dirbil*-total/indirect/direct bilirubin

	Na^+ (mmol /L)	*K^+ (mmol/L)*	*Cl^- (U/L)*	*Creat. (umol/L)*	*Urea (mmol/L)*	*Total bil. (umol/L)*	*Indir. bil (umol/L)*	*Dir. bil (umol/L)*
11.01	132	3.2	104	50	2.5	6.1	1.8	4.3
12.01	139	4.5	110	75	3.6	10.6	2.8	7.8
13.01	140	3.8	112	207	7.7	9.4	1.4	8.0
14.01	143	3.7	112	282	11.5	9.8	2.8	7.0
15.01	141	4.1	111	302	12.9	11.0	2.1	8.9
18.01	147	3.3	115	273	17.7	14.4	3.0	14.4
20.01	153	3.1	120	249	15.9	9.6	2.6	7.0
24.01	145	3.4	112	193	7.8	9.0	2.7	6.3
26.01	146	3.5	115	192	6.8	8.1	3.1	5.0
29.01	140	4.0	105	173	7.7	6.9	2.7	4.2
30.01	138	3.7	103	169	9.6	10.0	3.6	6.4
31.01	140	3.7	106	151	11.7	11.7	4.4	7.3
02.02	143	3.3	109	111	9.9	9.9	2.8	7.1
05.02	136	3.9	106	93	8.9	11.4	2.6	8.8
07.02	135	4.2	101	107	8.4	17.8	13.0	4.8
09.02	138	4.1	106	107	10.2	7.9	3.2	4.7
11.02	142	4.2	107	104	6.8	8.1	3.1	5.0
13.02	141	4.2	106	90	6.7	5.2	1.2	4.0
17.02	138	4.1	106	71	4.1	5.4	1.5	3.9
19.02	135	4.0	100	63	3.3	6.6	2.4	4.2
21.02	125	5.2	91	73	4.3	6.8	4.4	2.4
22.02	127	4.1	92	67	4.0	6.4	1.2	5.2
24.02	129	3.8	96	71	4.4	11.1	2.4	8.7
25.02	135	3.5	103	63	4.0	12.9	5.9	7.0
26.02	132	2.8	102	61	3.8	10.1	1.4	8.7

On the third post-operative day, the patient went back to the OR, because of the abdominal adhesions and at the same time two thoracic drains were placed. Biochemistry of the pleural effusion showed presence of Acinetobacter, as well as hemoculture. Colomycin was the next antibiotic used in the treatment of this infection.

During his hospital stay he underwent two more abdominal interventions, and ileostomy was instilled, because the overall condition did not improve at any time of the treatment. The continuous mycotic infection was treated with Caspofungin.

Table 3. Changes in hepatic enzymes as markers of Hepatic insufficiency, *GGT*-gamma-glutamyltransferase, *LDH*-lactate dehydrogenase, *ALT*-alanine aminotransferase, *AST*-aspartate aminotransferase, *AP*-alkaline phosphatase, *Alb*-albumin, *Glob*-globulin, *Tot. pro.*-totalprotein.

	GGT (U/L)	*LDH (U/L)*	*ALT (U/L)*	*AST (U/L)*	*AP (U/L)*	*Alb. (g/L)*	*Glob. (g/L)*	*Total prot. (g/L)*
11.01	144	100	20	13	120	24	26	50
12.01	101	128	17	13	97	21	22	43
13.01	85	171	15	17	86	20	23	43
14.01	104	201	11	16	90	23	24	47
15.01	87	202	10	17	77	22	24	46
18.01	180	216	10	17	79	25	26	51
20.01	205	202	9	16	72	24	25	49
24.01	185	194	7	13	90	24	26	50
26.01	141	261	11	11	96	26	26	52
29.01	184	200	<6	8	121	26	26	52
30.01	254	295	<6	13	142	28	28	56
31.01	301	317	6	14	149	26	24	50
02.02	366	218	8	14	170	28	25	53
05.02	398	270	31	40	159	29	26	55
07.02	664	369	90	108	353	29	33	62
09.02	558	258	38	35	266	28	26	54
11.02	485	227	17	17	240	30	26	56
13.02	361	179	8	12	166	29	26	55
17.02	276	196	9	13	157	31	24	55
19.02	278	150	8	11	147	34	26	60
21.02	417	310	14	30	242	33	26	59
22.02	449	162	22	24	273	33	27	60
24.02	639	191	35	46	355	34	29	63
25.02	774	454	150	292	478	26	26	52
26.02	709	173	117	97	406	29	25	54

During the treatment the patient complained of intensive headache, nausea, vomiting and blurred vision to the level of blindness.

Refractory hypertension and epileptic seizures developed. In the first place, Linezolid was removed, assuming it was the cause of blindness, but the state remained the same.

Magnetic resonance imaging was performed and there were signs of PRES.

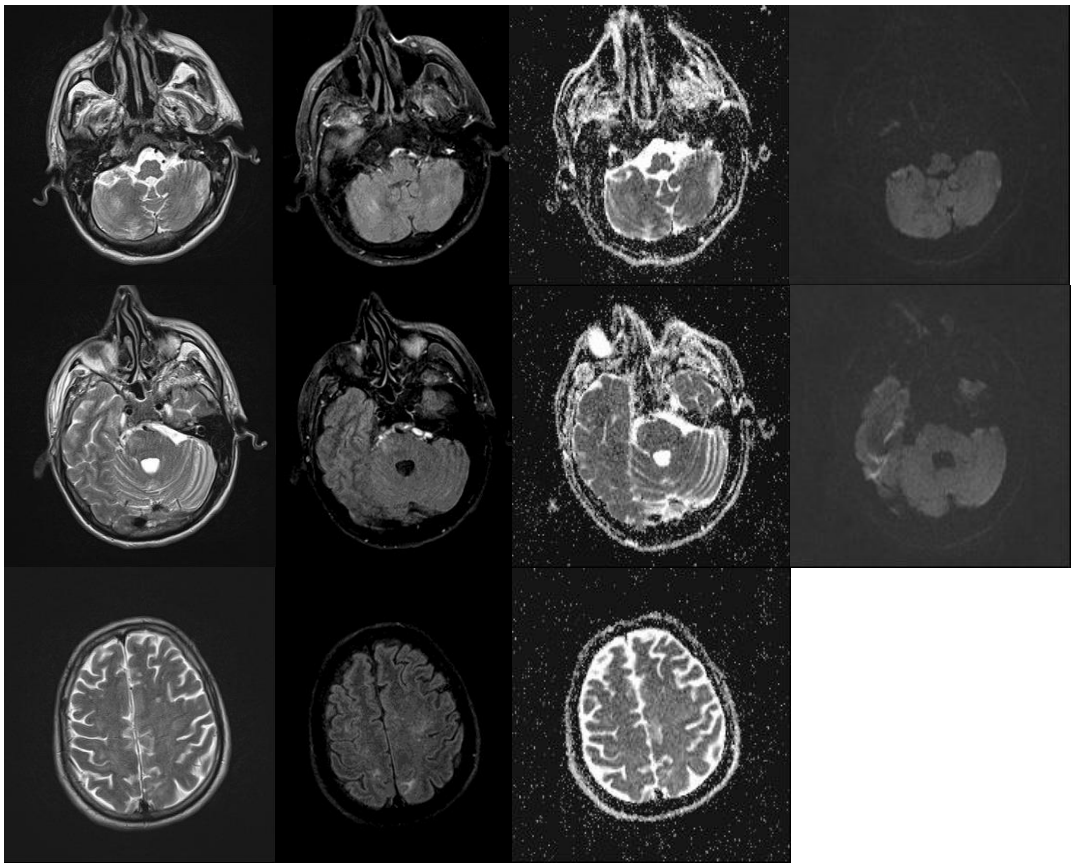

Figure 1. Brain MRI-hypersignal lesions on T2 and FLAIR without diffusion restriction, hyperintensity on ADC map dominantly in posterior circulation, cerebellum, pons and parietooccipital regions billateral subcortical with vasogenic edema in few of them. PRES in subacute phase.

Because of the multiple organ failure state and symptoms of PRES, the patient was intubated, put on mechanical ventilation and the high dose amino acid solution was discontinued. But all the measures were taken late and unfortunately the patient died after 43 days of treatment.

The occurrence of PRES could only be explained as a result of a high rate amino acid infusion.

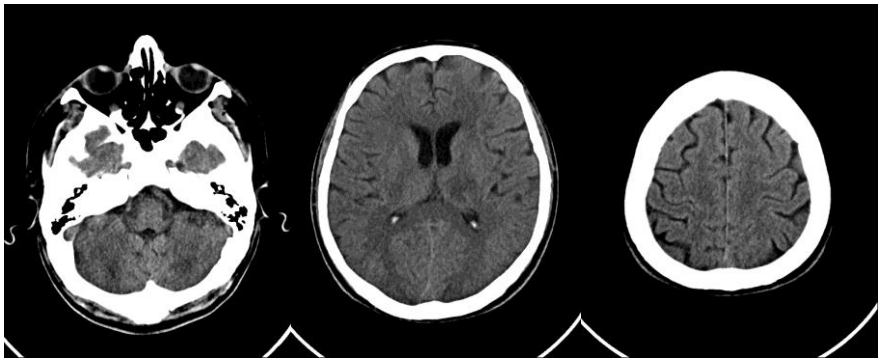

Figure 2. KTM-existence of vasogenic edema with ischemic zones

Discussion

Posterior reversible encephalopathy syndrome is a neurotoxic state that if unrecognized and untreated, can cause irreversible brain damage and be complicated to the level of unconsciousness and death. Two theories are explaining the origin of the condition, hypoperfusion and cytotoxic, according to the trigger factor [5, 7]. It is usually self-limiting condition that when promptly recognized can be resolved in a few weeks [2, 6].

The symptoms develop in a matter of hours and can be triggered by newly developed hypertension, immunosupressants, eclampsia, transplantation, cytostatic therapy, sepsis and certain drugs and treatment modalities [1, 2, 5, 7].

It can develop secondary to derangements of cerebral autoregulation which leads to brain hypoperfusion, and results in endothelial damage and consequent vasogenic edema formation [1, 5, 7].

Fugate at al. suggested the following criteria for the diagnosis of PRES: neurological symptoms of acute onset, neuroimaging abnormalities of (focal) vasogenic edema and the reversibility of clinical and/or radiological findings [5, 6].

MRI is the golden imaging method for diagnosing PRES. Tatsuka at al. developed the MRI algorithm for diagnosis of PRES [2,7]. In a recent study by Karia at al. MR imaging severity correlated with clinical outcomes in 135 patients [5].

Gao and Pirker at al. separately observed decreased serum albumin in up to 85% of patients with PRES of miscellaneous etiology [5].

The normal range of amino acid intake with parenteral nutrition, according to ESPEN, is 0,8-1,2 mg/kg/day (in critically ill can rise up to 1,5g/kg/day) and should be combined with glucose, fatty acids, micronutrients and electrolytes [8, 9].

In two studies, the optimal whole body protein sparing effects were achieved when amino acids were infused at mean rates of 1,3g/kg/day and 1,5g/kg/day in trauma and sepsis, respectively.

No further advantages were observed when more amino acids were provided in these groups in both studies, adequate energy was given parenteraly as fat and glucose [8]. In critical illness and sepsis, the metabolic disturbances usually cause hyperglycemia, and raise the necessity for insulin therapy along with the parenteral nutrition [9].

The risk of overfeeding syndrome complications is identical with the risk of underfeeding.

Conclusion

In our case, the excessive infusion of amino acid solutions for total parenteral nutrition, to correct the low total protein and albumin levels was the trigger of symptoms of PRES.

Administration of excessive amino acid solutions, especially to patients with renal or hepatic insufficiency, or patients in septic state may result in amino acid imbalance, hyperamonemia, prerenal azotemia, stupor and coma.

The doses of amino acids for administration in these patients should be calculated according to their nutritional status and needs. Should adverse reactions to the infusion develop, the administration should be discontinued and the patients` state reevaluated.

In our case, the infused levels of amino acids were almost doubled and not adequately combined with other nutrients.

This step along with the clinical condition of the patient and his catabolic state, led to development of PRES and multi organ failure. Unrecognized trigger of PRES was the main reason for neurologic deterioration and unfortunate resultant death.

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