Uremic encephalopathy in patients undergoing assisted peritoneal dialysis: a case series and literature review

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Abstract

We sometimes hesitate to switch renal replacement therapy from peritoneal dialysis (PD) particularly in elderly patients due to their physical tolerance levels and lifestyles. Here, we describe the cases of three patients treated with PD alone despite an anuric status who subsequently developed uremic encephalopathy, which was successfully treated with hemodialysis (HD). The first patient was a 75-year-old woman who developed uremic encephalopathy with an anuric status and inadequate PD after 7 months of treatment. HD immediately improved her condition; encephalopathy did not recur with combined therapy of PD and HD. The second patient was a 69-year-old woman who developed anuria and was treated with combined therapy. Her arteriovenous fistula was obstructed; therefore, she was treated with PD alone. Total weekly Kt/V was sufficiently high at 1.95; however, she developed uremic encephalopathy the following month, which was successfully treated with HD. The third patient was an 84-year-old woman who developed anuria, but was treated with PD alone with adequate total weekly Kt/V of 2.2. PD could not be performed for 2 days because of myocardial infarction intervention; subsequently, she developed uremic encephalopathy, which was successfully treated with HD. These cases are the first of their kinds, wherein patients undergoing PD, developed uremic encephalopathy without any obvious triggers, including drugs, and illustrate the necessity of initiating combined therapy for such patients considering the risk of developing severe uremia leading to uremic encephalopathy, in spite of it being less preferable for elderly patients due to their physical conditions and lifestyles.

Keywords Encephalopathy · Peritoneal dialysis · Uremia · Anuria · Elderly · Hemodialysis

Introduction

We should consider switching renal replacement therapy (RRT) from peritoneal dialysis (PD) alone to hemodialysis (HD) or combined therapy of PD and HD in cases with severe decline in residual renal function (RRF) [1, 2]. However, this switch is sometimes avoided, particularly for elderly patients undergoing PD because of the belief that continuing assisted PD is more suitable than switching to HD or combined therapy with respect to their physical tolerance levels and lifestyles. Herein, we describe the first three

cases of patients treated with PD alone despite their anuric status who subsequently developed uremic encephalopathy, which was successfully treated with HD.

Case reports

Case 1

A 75-year-old woman was treated with assisted PD for end-stage renal disease (ESRD) from diabetes mellitus (continuous ambulatory PD 2 L twice per day, with the use of 1.5% glucose dialysate 2 L and 2.5% glucose dialysate 2 L). Her RRF declined and total weekly Kt/V decreased to 1.31 with a high-average peritoneal transport rate with dialysate/plasma creatinine concentration ratio (D/P_{Creat}) of 0.80 and the ratio of dialysate glucose concentrations (D/D_0) of 0.30, but the patient and her family refused an increase in PD dose or RRT switch because they were unwilling to change their lifestyles. After 7 months, the patient suffered from syncope and consciousness disorder with a Glasgow Coma

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Scale (GCS) of eye (E), 4; verbal (V), 2; and motor (M), 4 accompanied by limb tremor. She neither had fever nor high blood pressure, which made the diagnosis of reversible posterior leukoencephalopathy syndrome (RPLS) or posterior reversible encephalopathy syndrome (PRES) least likely (Table 1). There was no identifiable infection; therefore, antibiotics were not administered before admission and we could deny a drug-induced encephalopathy. Laboratory data revealed an elevated serum beta 2-microglobulin (β 2MG) level of 30.9 mg/L and malnutrition inflammation and atherosclerosis syndrome (MIA syndrome), but no other abnormal findings, including hypoglycemia and electrolyte imbalance (Table 1). Her serum glucose level was slightly increased (224 mg/dL); however, this did not cause hyperosmolar hyperglycemic syndrome (HHS). We did not strongly suspect Wernicke's encephalopathy (WE) because she did not display conditions triggering WE such as chronic alcoholism, prolonged intravenous feeding without proper supplementation, or prolonged fasting or starvation. Additionally, except for encephalopathy, the other signs included in the classic triad of WE (oculomotor dysfunction and gait ataxia) were not present in the patient. Magnetic resonance imaging (MRI) and examination of cerebrospinal fluid did not reveal any significant abnormalities. Electroencephalogram (EEG) findings included prominence of slow waves, such as θ waves (4–5 Hz) and δ waves (2 Hz), which reflected uremic encephalopathy (Fig. 1a). We treated her with HD thrice weekly, which immediately improved the consciousness disorder. EEG findings dramatically improved with the disappearance of slow waves, and α waves (8–9 Hz) were mostly documented (Fig. 1b). Recovery of the patients' status without thiamine administration definitely proved the absence of WE. After discharge, combined therapy was initiated, which led to improvement of MIA syndrome with an increase in body weight (Table 1), and uremic encephalopathy did not recur throughout the follow-up period.

Case 2

A 69-year-old woman was treated with assisted PD for ESRD because of microscopic polyangiitis, which was well controlled with prednisolone. Combined therapy was initiated 7 months later because she developed anuria. After 2 years, her arteriovenous fistula was obstructed; therefore, she was treated with PD alone (automated PD 8 L per day, with the use of 1.5% glucose dialysate 4 L and 2.5% glucose dialysate 4 L). Total weekly Kt/V was well maintained at 1.95 and peritoneal transport rate was low average with D/P_{Creat} of 0.51 and D/D_0 of 0.46; however, tetanic convulsions and disturbances in consciousness with a GCS of E4V1M4 occurred the following month. She was afebrile with normal blood pressure (Table 1). There was no sign of infection; therefore, antibiotics were not administered

before admission and during hospitalization, which proved the absence of drug-induced encephalopathy. We detected an elevated β 2MG level of 50.2 mg/L and MIA syndrome (Table 1). High levels of white blood cell and serum C-reactive protein were considered as secondary reactions to a maintenance dose of prednisolone (3 mg) for polyangiitis and MIA syndrome, respectively. Serum glucose level was within the standard range, ruling out the possibility of coma from hypoglycemia and HHS. MRI and cerebrospinal fluid examination revealed no abnormalities. EEG findings revealed high-voltage and slow waves in the convulsions (Fig. 1c), which disappeared when diazepam was administered whereas α waves (9–10 Hz) and spike-slow-waves appeared (Fig. 1d). We treated the patient's encephalopathy with HD thrice weekly, which immediately improved the consciousness dysfunction. The EEG findings were almost normal with a background of regular α waves (8–9 Hz) (Fig. 1e). WE was ruled out because of the absence of conditions triggering it, the other signs included in the classic triad of WE (except for encephalopathy), and because her condition improved without thiamine administration. A new arteriovenous fistula was formed and combined therapy was re-initiated; her condition remained good with intensive care provided by her son, a visiting physician, visiting nurses, and home caregivers. Increased serum albumin and improved C-reactive protein levels after 6 months indicated improvement in the MIA syndrome; however, her body weight continued to decrease due to chronic nontuberculous mycobacterial pulmonary infections.

Case 3

An 84-year-old woman was initiated on assisted PD for ESRD due to unknown disease; however, RRF rapidly declined and she developed anuria within 6 months. She and her family refused to switch to HD or combined therapy because of perceived difficulty attending a clinic for HD, even once a week. Therefore, we continued PD treatment alone, with adequate total weekly Kt/V of 2.2 (automated PD 8.8 L per day, with the use of 1.5% glucose dialysate only). Peritoneal transport rate was categorized into low average with D/P_{Creat} of 0.63 and D/D_0 of 0.39. After 6 months, she was hospitalized for acute myocardial infarction. We could not perform PD or HD for 2 days because of catheter interventions, but considered skipping of dialysis tolerable because it is common in patients undergoing HD. However, she developed consciousness dysfunction with a GCS of E1V1M4, limb tremor, and myoclonus. β 2MG was slightly elevated at 29.3 mg/L (Table 1), but MRI and cerebrospinal fluid findings were normal. EEG findings exhibited diffuse slow waves (Fig. 1f). Intravenous cefazolin (1 g) was administered once to prevent an infection at the site of catheter intervention; however, the antibiotic was unlikely

Table 1 Laboratory data on the day of onset, 6 months before, and 6 months after. For case 3, there was no data for 6 months after onset because of the patient's death

Time	Case 1			Case 2			Case 3		
	6 months before	Day of onset	6 months after	6 months before	Day of onset	6 months after	6 months before	Day of onset	After HD
Body temperature (°C)		36.5			36.4			36.0	
Blood pressure (mmHg)	97/54	128/70	132/67	144/94	132/82	149/99	140/85	85/46	97/53
White blood cell count (cells/ μ L)	5400	9300	8200	15,500	15,000	13,600	8900	22,900	19,400
Hemoglobin (g/dL)	9.7	11.4	11.4	11.2	11.2	12.2	10.8	7.1	9.8
pH		7.41			7.44			7.47	
Bicarbonate (mEq/L)		34.1			22.8			23.6	
Total protein (g/dL)	5.8	5.6	5.2	6.7	5.6	6.0	6.4	4.4	4.6
Albumin (g/dL)	3.1	2.3	2.1	3.0	2.1	2.5	2.4	1.7	1.8
Blood urea nitrogen (mg/dL)	42	38.7	Before HD: 18, after HD: 8	Before HD: 42, after HD: 9	47	Before HD: 40, after HD 8	29	55	16
Creatinine (mg/dL)	5.01	5.69	Before HD: 6.24, after HD: 3.08	Before HD: 8.70, after HD 2.10	9.59	Before HD: 7.32, after HD: 1.98	5.0	6.25	2.06
Sodium (mEq/L)	138	138	139	140	141	137	140	132	141
Potassium (mEq/L)	4.4	3.5	3.2	3.2	4.2	3.9	3.1	3.7	3.6
Calcium (mg/dL)	9.8	10.4	9.1	9.8	9.1	9.8	10.5	9.5	9.8
Phosphorus (mg/dL)	4.1	3.4	3.3	5.1	10.0	8.4	4.9	4.3	1.9
Parathyroid hormone (pg/mL)	27.0	8.0	56	226.0	308.1	544.6	202.0	218.0	
C-reactive protein (mg/dL)	0.18	0.48	0.18	1.87	4.74	1.46	1.02	5.55	7.29
β 2 microglobulin (mg/L)	26.4	30.9	Before HD: 34.9, after HD: 12.5	Before HD: 48.6, after HD: NA	50.2	Before HD: 44.9, after HD: 8.6	17.9	29.3	15.5
Glucose (mg/dL)		224			123			101	
Ammonia (μ g/dL)		22	26		13	12			
BNP (pg/mL)	99.1	159.9	47.0	291.8	567.2	246.4	144.0	977.3	
Body weight (kg)	55.0	53.5	56.5	38.5	35.0	34.1	53.3	52.3	50.9

HD hemodialysis, BNP brain natriuretic peptide

Fig. 1 **a** Diffuse θ waves (4–5 Hz) and δ waves (2 Hz) were detected in the electroencephalogram when the patient in case 1 developed consciousness disorder accompanied by limb tremor. **b** After several hemodialysis sessions, electroencephalogram findings dramatically improved with the disappearance of θ and δ waves and appearance of α waves (8–9 Hz). **c** Diffuse high-voltage and slow waves were detected in the electroencephalogram when the patient in case 2 experienced convulsion. **d** When diazepam was administered to the

patient in case 2, the slow waves disappeared and α waves (9–10 Hz) appeared. Some abnormal slow and spike waves were mixed. **e** After a few HD sessions, electroencephalogram findings almost became normal with the background of regular α waves (8–9 Hz). **f** Diffuse θ waves (4–5 Hz) and δ waves (2 Hz) were detected in the electroencephalogram when the patient in case 3 developed consciousness disorder accompanied by limb tremor and myoclonus

to be the cause of encephalopathy. Her normal serum glucose level made the diagnosis of hypoglycemia and HHS least likely (Table 1). We treated her with HD on successive days, and she became awake and alert immediately. WE was ruled out because of the absence of conditions triggering it, the other signs included in the classic triad of WE (except for encephalopathy), and because her condition improved without thiamine administration. However, she developed idiopathic pancreatitis and died 3 weeks after the improvement of encephalopathy. We could not perform EEG again because of her deteriorating condition.

Discussion

Encephalopathy is frequently encountered in patients with ESRD undergoing HD and PD. We reviewed cases of encephalopathy in adult patients undergoing PD in the past 20 years (Table 2). Kt/V was available only in one study with 2.1 [16]; therefore, we selected serum creatinine value as the marker of uremic solute retention. The differential diagnosis of encephalopathy in dialysis patients can be challenging and primarily includes uremic encephalopathy, dialysis disequilibrium syndrome, dialysis dementia, cerebrovascular accident, central nervous system infection, and intoxication [3]. As shown in Table 2, WE and RPLS or PRES may possibly be the cause of encephalopathy in patients undergoing PD. In contrast, our cases were novel encephalopathy cases that were believed to be simply caused by uremic solute retention during PD without any causal drugs nor presence of WE or RPLS/PRES and were successfully treated in only a few sessions of HD.

Uremic encephalopathy is an acquired toxic syndrome characterized by delirium in patients with untreated or inadequately treated ESRD; however, toxins causing uremia have not been definitively identified. Brain amino acid metabolism may be impaired in such cases, which leads to an imbalance between excitatory and inhibitory neurotransmitters and the accumulation of false neurotransmitters categorized as “middle molecules” [4]. RRF and HD play significant roles in removing middle molecules, particularly in patients undergoing PD and combined therapy, respectively, because PD is less effective at removing middle molecules than RRF or HD [5]. Therefore, the risk of developing uremic encephalopathy appears to be elevated while treating patients with anuria only with PD. In our cases, uremic encephalopathy developed despite PD within half a year after RRF dissipation. Notably, uremic encephalopathy occurred regardless of well-maintained total weekly Kt/V , which suggested hidden inadequacy of PD treatment despite total weekly Kt/V being satisfactory. Furthermore, our patients developed uremic encephalopathy, whereas most anuric patients treated with PD alone do not develop uremic encephalopathy. We believe

that the state of MIA syndrome, which seemed to have developed in all of our cases, accompanied by decreased serum albumin levels as well as body weight, and increased serum C-reactive protein levels could have contributed to the development of uremic encephalopathy.

Inflammatory mediators and oxidative stress, in addition to uremic solutes, are thought to contribute to the pathogenesis of central nervous system (CNS) disorders in chronic kidney disease (CKD) patients [6–8]. Furthermore, a recent study demonstrated the involvement of inflammatory pathways and oxidative stress in cerebral tissues and disruption of the blood–brain barrier in the development of CNS dysfunction in CKD rats [9]. Other experimental data suggest that the inflammatory state should exacerbate inflammation and oxidative stress in the CNS induced by indoxyl sulfate, which is a well-known uremic nephron–vascular toxin [10]. Although clinical evidence is insufficient, these data from fundamental studies support the hypothesis that patients with MIA syndrome are susceptible to developing uremic encephalopathy as a CNS manifestation. Additionally, the body weight in all cases decreased from 6 months before the treatment was started in combination with increased serum brain natriuretic peptide levels in all our cases, suggesting that relative volume excess is associated with decreased lean body weight. Therefore, we could not deny that we overestimated Kt/V by underestimating fluid volume (V) in the patients. In general, the most common EEG finding in uremic encephalopathy is prominent slow waves. Intermittent frontal rhythmic θ activity and paroxysmal, bilateral, high-voltage δ waves are also frequent, whereas triphasic waves may appear in the frontal regions [11]. In general, uremic encephalopathy reverses with dialysis within a few sessions of HD [12], and similarly in our cases, consciousness returned immediately after a few HD sessions.

Assisted PD is a feasible option for elderly patients because, in Japan, they generally prefer to live in a familiar area with their family until the end of life. Technical survival and quality of life are reported to be well maintained in elderly patients undergoing PD [13]. Moreover, the rates of infection and mortality in patients undergoing PD assisted by visiting nurses and an intensive care system are comparable to those in self-sustaining patients undergoing PD [14]. However, some patients hesitate to switch from PD alone to combined therapy partly, because PD does not require the patients to visit a clinic and also because there are very few community-based medical care facilities that provide combined therapy of both PD and HD in Japan. In our cases, severe uremia developed as a result of hesitating to initiate HD because the patients and their families preferred to avoid a change in their lifestyle. Nonetheless, only one session of HD per week combined with PD may alleviate the burden of visiting nurses and their family to support patients. We should make efforts to provide community-based social care

Table 2 Summary of clinical, electroencephalographic, and imaging features of patients undergoing peritoneal dialysis with encephalopathy in our series and reported cases

Refs.	Age (y)/sex	Cr (mg/dL)	PD vintage	Diagnosis	Clinical features	EEG	CT/MRI	Treatment	Outcome
[15]	69/F	14.2	2 y	Drug-induced (CFPM)	Confusion	Generalized continuous sharp waves	No focal lesion	Stop CFPM, AED	Resolved
	58/F	15.0	4 y	Drug-induced (INH, RFP)	Confusion	Frequent sharp and slow waves over frontal area	No focal lesion	AED	Resolved
	40/F	11.9	7 y	Drug-induced (CFPM)	Stupor	Generalized sharp and spike wave discharges at 3–4 Hz	Normal	AED	Improved
	46/F	12.5	7 y	Drug-induced (CAZ, CPFX)	Confusion	Slow background activity, continuous polymorphic theta and delta waves, frequent bilateral frontal sharp waves	Normal	AED	Improved
[16]	35/F	NA	14 m	WE	Disorientation	NA	No focal lesion	Thiamine	Died
[17]	59/M	14.1	NA	Drug-induced (CFPM)	Confusion	Nonspecific increase in 4–8 Hz activity, no sharps or spikes	NA	NA	Resolved
	62/F	10.2	NA	Drug-induced (CAZ)	No verbal response	Epileptic discharges and increased theta activity, triphasic waves	NA	NA	Improved
	60/F	9.5	NA	Drug-induced (CFPM)	Disorientation	High-amplitude, 2–3 Hz delta waves with frequent triphasic waves	NA	NA	Resolved
[18]	47/M	NA	1 y	Drug-induced (PIPC/TAZ)	Confusion and abnormal behavior	Unremarkable	Unremarkable	Stop PIPC/TAZ	Resolved
[19]	57/F	NA	5 y	Drug-induced (PIPC/TAZ)	Generalized tonic-clonic seizure	NA	Normal	Stop PIPC/TAZ, HD	Resolved
[20]	61/F	6.2	1 y	Hypophosphatemia	Muscle weakness and confusion	NA	Unremarkable	Potassium phosphate and milk	Resolved
[21]	24/M	13.0	6 m	RPLS/PRES	Unconsciousness and generalized seizure	Unremarkable	Abnormally increased signal intensity involving bilateral occipital lobes	BP management, volume control, HD	Resolved
[22]	80/F	5.6	NA	Drug-induced (CFPM)	Confusion	Periodic short-interval diffuse discharge with shifting predominance, along with diffuse background slow waves with 4–6 Hz	Profound leukoaraiosis	Stop CFPM	Improved

Table 2 (continued)

Refs.	Age (y)/sex	Cr (mg/dL)	PD vintage	Diagnosis	Clinical features	EEG	CT/MRI	Treatment	Outcome
[23]	24/F	13.6	3 y	RPLS/PRES	Generalized seizures and unconsciousness	NA	Abnormalities in the posterior regions of the cerebral hemisphere, consistent with white-matter vasogenic edema	BP management, volume control	Resolved
[24]	35/F	13.6	3 y	Drug-induced (baclofen)	Mental deterioration	Normal	No gross abnormality	Stop baclofen, HD	Resolved
[25]	37/F	NA	4 y	Drug-induced (CTRX)	Agitation, paranoia, and visual hallucinations	5–6 Hz theta and 2–4 Hz delta slowing diffusely but most prominent in the right posterior temporal, parietal, and occipital head regions	No focal lesion	Stop CTRX	Resolved
[26]	23/M	17.3	NA	RPLS/PRES	Confusion and generalized seizure	NA	Increased signal predominantly involving the posterior and paramedian parietal and occipital lobes with relative symmetry	AED, BP management, volume control	Resolved
[27]	53/M	NA	NA	Drug-induced (INH)	Lack of finger–nose coordination, DDK, intentional tremor, wide based gait and impaired tandem walking	NA	Hyperintensities in bilateral dentate nuclei of cerebellar hemispheres	Stop INH	Resolved
[28]	38/F	NA	16 y	WE	Altered consciousness, lagophthalmos, and seizures	NA	Bilateral symmetrical hyperintensity in both mammillary bodies, the medial thalamus, the dorsal portion of midbrain, and the medulla	Thiamine	Improved
[29]	51/M	NA	5 y	WE	Psychophysical agitation, with compromised coordination of movements, ataxic gait, and alterations in speech	NA	Hyperintensities of back-medial thalamic and periaqueductal membranes compatible with Wernicke's encephalopathy	Thiamine, HD	Resolved

Table 2 (continued)

Refs.	Age (y)/sex	Cr (mg/dL)	PD vintage	Diagnosis	Clinical features	EEG	CT/MRI	Treatment	Outcome
Current study	75/F	5.69	7 m	Uremic encephalopathy	Syncope and unconsciousness	Prominence of slow waves, such as theta waves (4–5 Hz) and delta waves (2 Hz)	Unremarkable	HD	Resolved
	69/F	9.59	2 y	Uremic encephalopathy	Tetanic convulsions and unconsciousness	High-voltage and slow waves	Unremarkable	AED, HD	Resolved
	84/F	6.25	1 y	Uremic encephalopathy	Unconsciousness, limb tremor, and myoclonus	Diffuse slow waves, such as theta waves (4–5 Hz) and delta waves (2 Hz)	Unremarkable	HD	Resolved

Ref reference, *Cr* creatinine, *PD* peritoneal dialysis, *EEG* electroencephalogram, *MRI* magnetic resonance imaging, *CT* computed tomography, *y* year, *m* month, *M* male, *F* female, *NA* not available, *AED* antiepileptic drugs, *CFFM* cefepime, *INH* isoniazid, *RFP* rifampicin, *CZ* ceftazidime, *CPFX* ciprofloxacin, *PIP/CTAZ* piperacillin/tazobactam, *BZD* benzodiazepine, *BP* blood pressure, *DDK* dysidiachokinesia, *HD* hemodialysis, *RPLS* reversible posterior leukoencephalopathy syndrome, *PRES* posterior reversible encephalopathy syndrome, *CFTX* ceftriaxone, *WE* Wernicke's encephalopathy

services that support elderly patients and their families with any RRT.

In conclusion, the cases reported here illustrate the necessity to initiate combined therapy in patients with anuria undergoing PD, considering the risk of developing severe uremia leading to uremic encephalopathy. At the same time, the development of community-based systems that support the home environment of elderly patients with any RRT is necessary.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Human and animal rights All procedures performed in this case report were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This case series was granted exemption from review by the ethics committee of the Japanese Red Cross Medical Center.

Informed consent Informed consent was obtained from all individual participants included in the study.

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