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Report of Dialysis-Induced Hypophosphatemia Leading to Reversible Encephalopathy Prevented by Adding Phosphorus to the Dialysate

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Phosphorus · Dialysate · Encephalopathy · Hypophosphatemia · Hemodialysis

Abstract
Patients with advanced chronic kidney disease have an inability to excrete phosphorus normally leading to high serum concentrations of phosphorus. The hyperphosphatemia is even more pronounced in dialysis patients who often require large doses of phosphorus binders to combat the problem. Hemodialysis is able to remove fair amount of the extra phosphorus; however, the removal is often hampered by the fact that the phosphorus is removed only from the extracellular compartment and phosphorus is mainly intracellular. The end result being a high serum phosphorus concentration at the beginning of dialysis, a sharp decline in the value by the end of dialysis and significant rebound of serum phosphorus concentration a few hours after stopping dialysis as phosphorus moves out of the cells. Here, we describe 2 hemodialysis patients with normal predialysis serum phosphorus concentration and preexisting conditions that made them at risk for developing encephalopathy who developed recurrent obtundation toward the end of the dialysis treatments. After confirming critical postdialysis hypophosphatemia, phosphorus was added to the dialysate baths and the episodes of encephalopathy associated with dialysis ceased.

Introduction

Since phosphorus is mainly intracellular, and we only dialyze the extracellular space and the fact that the intracellular phosphorus concentration will take time to equilibrate with intravascular phosphorus concentration, the phosphorus concentration rises rapidly right after dialysis treatment (rebound), and then remains fairly stable until the next dialysis treatment. Rebound of serum phosphorus is noted after a standard dialysis treatment. For example, 2 h after dialysis, serum phosphorus concentration can rebound by an average of 31% in one study of 12 patients [1, 2]. However with hemodiafiltration, the rebound averaged 69% in the same 12 patients [2].

The clinical manifestations of hypophosphatemia are largely dependent on the degree and the rate of phosphorus depletion with the phosphorus concentration usually being below 1 mg/dL (0.32 mmol/L) in symptomatic patients [3]. The symptoms and signs are because of intracellular phosphate depletion (fall in intracellular adenosine triphosphate level and red blood cell 2,3-diphosphoglycerate levels) [3].

The low phosphorus levels affect various systems including cardiopulmonary (impaired myocardial contractility, higher incidence of ventricular arrhythmias in the setting of acute myocardial infarction, impaired diaphragmatic contractility), skeletal, and smooth muscle (proximal myopathy, dysphagia, ileus, rhabdomyolysis), hematologic

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system (hemolysis, decreased phagocytosis and granulocyte chemotaxis, defective clot retraction, and thrombocytopenia seen with severe hypophosphatemia), and central nervous system. Neurologic symptoms can vary from mild irritability and paresthesias to more severe symptoms such as delirium, generalized seizures, and coma. Severe hypophosphatemia can lead to metabolic encephalopathy, with central and extra pontine myelinolysis having been also reported [3]. Whether an acute drop in the serum phosphorus concentration such as occurs with hemodialysis can predispose patients to symptoms with even higher serum phosphorus concentrations is not known.

The report of these 2 cases was approved by our Investigational Review Board (approval #19-27187). Informed consent was waived as both patients had already passed away at the time of writing of the case reports and the study being retrospective chart review only.

Case 1

A 63-year-old African American woman first presented to our hospital in January 1999. At that time she already had a well-established diagnosis of diabetes (hemoglobin A1C of over 13), diabetic retinopathy, diabetic neuropathy, hypertension, hepatitis C, obstructive sleep apnea, and history of intravenous heroin and crack use. In late 2000, she developed mild renal insufficiency that progressed over the years culminating with the need for dialysis in February 2007.

Her dialysis sessions were for the most part uneventful until January 12, 2015, when she experienced confusion after dialysis with no loss of consciousness having walked into the dialysis unit with normal mental function. She developed hypotension to systolic blood pressure of 70s at the end of dialysis, but by the time she presented to the emergency department, she remained confused despite blood pressure of 110/45. At the time of this event, she was on clonazepam, nifedipine, benazepril, labetalol, sevelamer, oxybutynin, fluticasone/salmeterol inhaler, hydrocodone/acetaminophen, diphenoxylate as needed for diarrhea, renal vitamins, and pregabalin. None of the above medications were new in the 6 months prior to the event. Laboratory testing sent from the emergency room 75 min after the end of dialysis revealed the following values: Na 146 mEq/L, K 3.6 mEq/L, Cl 110 mEq/L, CO_2 30 mEq/L, Mg 2.0 mg/dL, phosphorus 1.9 mg/dL, Ca 9.0 mg/dL, BUN 18 mg/dL, and Cr 3.36 mg/dL. Computed tomography (CT) with angiogram of the brain showed only chronic small vessel ischemic changes with no signs of acute stroke. The confusion resolved a few hours after admission and was eventually attributed to hemodynamic changes during dialysis.

On June 10, 2015, she again developed confusion with systolic blood pressure dropping to 90s at the end of hemodialysis. At the time of presentation to hemodialysis, she was not confused and was at her baseline function. She was given 2 L crystalloids with no improvement. Laboratory evaluation sent from emergency department, 50 min after the end of dialysis revealed the following values: Na 143 mEq/L, K 3.5 mEq/L, Cl 108 mEq/L, CO_2 28 meq/L, phosphorus 1.6 mg/dL, Mg 2.2 mg/dL, Ca 9.1 mg/dL, BUN 29 mg/dL, and creatinine 3.49 mg/dL. Repeated CT of the brain showed no significant changes from prior study. The mental status changes persisted for 10–12 h and eventually she was back at her baseline mental function and was able to be discharged from the hospital on June 12. Again the onset of confusion with having been on dialysis was attributed to hemodynamic factors during dialysis, although there was never a documented blood pressure of <90 mm Hg systolic.

On August 12, 2015, similar episode occurred toward the end of dialysis during which she was found severely altered and unarousable despite stable vitals with heart rate in the 90s, systolic blood pressure around 140 mm Hg, and oxygen saturation of 100%. She spontaneously woke up after 4 h. CT of the brain showed no significant new changes. Laboratory evaluation sent from the hospital 3 h after the end of dialysis revealed the following: Na 139 mEq/L, K 3.1 mEq/L, Cl 103 mEq/L, CO_2 28 mEq/L, Mg 2.1 mg/dL, phosphorus 0.9 mg/dL, Ca 8.8 mg/dL, BUN 16 mg/dL, and creatinine 3.54 mg/dL. Hypophosphatemia was corrected with sodium phosphate intravenously and sevelamer was stopped. With all of these episodes, her blood sugar had been >60 mg/dL, but with this episode, she was even given a bolus of D50 without response. Also blood cultures performed on the second and third admissions showed no growth. A further episode of confusion after dialysis occurred on August 17, 2015 which again resolved spontaneously few hours after dialysis despite having stopped the sevelamer. Vitals were stable during this episode. After this episode, we suspected that part of her altered mental status changes during dialysis may be attributable to low phosphorus concentration at the end of dialysis although the predialysis phosphorus levels were normal.

From January 2015 until August of that year, her monthly predialysis serum phosphorus concentrations ranged from 3.5 to 6.1 mg/dL with a mean of 4.5 and a median of 4.4. During this entire period, she was taking sevelamer 2,400 mg 3 times per day with meals. With all these episodes, the serum phosphorus concentrations checked around 1–3 h after stopping dialysis were low. She was being dialyzed for 3 h with an F180 dialyzer at a blood flow of 450 mL/min and a dialysate flow of 800 mL/min with a dialysate comprised of 1 part acid bath, 1.72 parts base, and 42.28 parts product water (45×). Her dialysate bath consisted of potassium concentration of 2 mEq/L, calcium of 2.5 mEq/L, and bicarbonate of 28 mEq/L. Starting September 2, 2015, we started adding sodium phosphate 30 mLs to the acid bath of 2-compartment dialysate delivery system. We used 15 mL sodium phosphates inj, USP (Hospira, Inc., Lake Forest, IL, USA) containing 45 mM (3 mM/mL) of phosphorus, which also contains 60 mEq sodium (4 mEq/mL) bottles in order to add the phosphate salt (used 2 bottles with each dialysis treatment). This product contains monobasic sodium phosphate, monohydrate, 276 mg, dibasic sodium phosphate, anhydrous, 142 mg in each mL of the salt. Thus with each dialysis we added, 90 mmol of elemental phosphorus to 3.43 L of acid bath, which dilutes to 26.24 mmol/L. After being diluted again 45 times to make the final dialysate, the concentration will become 0.58 mmol/L. Converting from mmol/L to mg/dL will result in a final dialysate phosphorus concentration of 1.8 mg/dL.

On September 9, 2015, with adding the phosphorus to dialysate and taking no binders, her predialysis phosphorus concentration was 8.8 mg/dL. At this time she was restarted on 800 mg sevelamer with each meal. From September 2015 until her death in July 2016, the predialysis phosphorus ranged from 5.2 to 8.6 mg/dL.

Table 1. Pre- and postdialysis serum phosphorus concentration for the first patient

Date	Pre dialysis serum phosphorus value, mg/dL	Serum phosphorus value 90 min into dialysis, mg/dL	Serum phosphorus at the end of 3 h dialysis, mg/dL	Was phosphorus added to the dialysate?
August 14, 2015	4.3	1.9	1.4	No
August 19, 2015	4.3	2.9	2.7	No
August 24, 2015	6.8	ND	2.0	No
August 26, 2015	6.5	ND	2.0	No
September 21, 2015	9.8	ND	3.9	Yes
September 23, 2015	9.1	ND	3.1	Yes
April 13, 2016	6.3	ND	3.2	Yes

After starting to add the phosphorus to the dialysate, she was admitted to the hospital once in September 2015 for fatigue and swelling of the leg and once in April 2016 for chest pain and dyspnea on exertion. On July 18, 2016, she presented to hospital with syncopal episode with no immediate obvious cause. On July 19, she is found in her room not breathing with a pulse of 10. Attempts at resuscitation are unsuccessful. Table 1 shows the serum phosphorus concentration at the start of the dialysis treatment, 90 min into the treatment and at the end of the dialysis treatment for this patient on the specified dates. Notice some of the values were with adding phosphorus to the dialysate and some were without adding phosphorus. The patient did not develop symptoms during any of these treatments.

To summarize, this patient developed 4 episodes of altered mental status right after dialysis from January to August 2015, all associated with a low postdialysis serum phosphorus concentration. After adding minimal amounts of phosphorus salt to the dialysate and decreasing the phosphorus binders, there were no further episodes of confusion right after dialysis treatments from September 2015 until July 2016.

Case 2

Sixty-eight-year-old woman was seen in October 2007 in the renal clinic for advanced progressive chronic kidney disease and nephrotic range proteinuria (creatinine was 5.95 mg/dL). Lab data available from a different hospital showed a creatinine of 3.7 mg/dL and HbA1c of 5.8% in July 2007. At that time she already had a diagnosis of type 2 diabetes mellitus for the past 4 years, proliferative diabetic retinopathy, hypertension for the past 2 years, cirrhosis of the liver, and hyperlipidemia. Hemodialysis thrice weekly is started in November 2007. From that point until 2015, she is further diagnosed with tuberculous lymphadenitis treated with 4 drug therapy for 1 year in 2012 and subdural hematoma requiring right-sided craniotomy in 2013 with residual left greater than right side weakness.

Her dialysis sessions were uneventful until October 19, 2015, when she presented to dialysis in her usual state but subsequently was acutely unresponsive after hemodialysis. During this episode, her heart rate was 70, systolic blood pressure was 130, and blood glucose was 96 mg/dL. Medication at this time was amlodipine, docusate, glipizide, pravastatin, senna, sevelamer 2,400 mg 3 times per day, hydrocodone-acetaminophen, multivitamins, aspirin, clonidine, famotidine, hydralazine, lisinopril, minoxidil, and insulin. Neurologic examination showed right eye deviation, flaccidity on left side, and some spontaneous right upper extremity movements which likely were mild worsening of her previous baseline neurological findings. CT showed a 6 mm subdural hematoma with no mass effect and unchanged from previous CT in 2013. Neurosurgery was consulted and recommended stopping aspirin for 7 days and starting levetiracetam for 7 days as it was thought that the event could possibly represent a seizure. She received intravenous levetiracetam and phenytoin in the emergency department. Labs 1 h after dialysis revealed Na 142 mEq/L, K 3.3 mEq/L, Cl 97 mEq/L, CO_2 31 mEq/L, phosphorus 2.3 mg/dL, magnesium 2.4 mg/dL, potassium 3.3 mEq/L, and chloride 97 mEq/L. Patient improved in the hospital and subsequently discharged home 2 days later.

On December 2, 2015, she developed similar episode of confusion after the dialysis (normal mentation at the beginning of dialysis) and was taken to the emergency department. Vitals were stable during the episode. Laboratory testing immediately postdialysis revealed a serum phosphorus concentration of 1.2 mg/dL, Na 137 mEq/L, K 4.0 mEq/L Cl 95 mEq/L, CO_2 32 mEq/L. CT of the brain showed old subdural hematoma. She was given a load of levetiracetam as the possible cause of confusion was thought to be seizure although not confirmed by EEG.

She had 2 further admissions on middle of January and on February 3, 2016. Each time again she presented to dialysis normal but developed confusion by the end of dialysis. Her post-dialysis serum phosphorus concentration during the episode in February was found to be 1.6 mg/dL, Na 138 mEq/L, K 3.6 mEq/L, Cl 97 mEq/L, CO_2 31 mEq/L 40 min after dialysis was stopped. The serum phosphorus is not available with the January admission as she was admitted to an outside hospital. After the February admission, it is thought that hepatic encephalopathy is clearly playing a role in her episodes of confusion and patient is started on lactulose.

The predialysis serum phosphorus concentrations on monthly laboratory done in the outpatient dialysis unit ranged between 3.3 and 6.2 mg/dL from October 2015 until April 2016. Up until this time, she was being dialyzed for three and a half hours with an F160 dialyzer at a blood flow of 350 mL/min and a dialysate flow of 500 mL/min with a dialysate comprised of 1 part acid bath, 1.72 parts base, and 42.28 parts product water (45×). Her dialysate bath consisted of potassium concentration of 3 mEq/L and calcium of

Table 2. Pre- and postdialysis serum phosphorus concentration for the second patient

Date	Predialysis serum phosphorus value, mg/dL	Postdialysis serum phosphorus value, mg/dL	Was phosphorus added to the dialysate?
December 2, 2015	6.2	1.1	No
February 19, 2016	4.0	1.8	No
March 16, 2016	8.6	3.3	No
September 9, 2016	5.9	1.5	No
October 28, 2016	6.5	2.3	Yes

2.5 mEq/L. Starting April 1 it was decided to add phosphorus to her dialysate to mitigate the possible contribution of postdialysis hypophosphatemia as a contributing factor to her recurrent postdialysis mental status changes. We started adding sodium phosphate 30 mL to the acid bath of 2-compartment dialysate delivery system. We used 15 mL sodium phosphates inj, USP (Hospira, Inc., Lake Forest, IL, USA) containing 45 mM (3 mM/mL) of phosphorus, which also contains 60 mEq sodium (4 mEq/mL) bottles in order to add the phosphate salt (used 2 bottles with each dialysis treatment). This product contains monobasic sodium phosphate, monohydrate, 276 mg, dibasic sodium phosphate, anhydrous, 142 mg in each mL of the salt. Thus with each dialysis, we added 90 mmoL of elemental phosphorus to 3.43 L of acid bath, which dilutes to 26.24 mmol/L. After being diluted again 45 times to make the final dialysate, the concentration will become 0.58 mmol/L. Converting from mmol/L to mg/dL will result in a final dialysate phosphorus concentration of 1.8 mg/dL.

Table 2 shows the serum phosphorus concentration at the start of the dialysis treatment and at the end of the dialysis treatment for this patient on the specified dates. Notice some of the values were with adding phosphorus to the dialysate and some were without adding phosphorus. The patient did not develop symptoms during any of these treatments.

After starting to add phosphate to her dialysate starting April 1, she did not have any further episodes of confusion until January 2017, whereas she had 6 episodes from October 2015 until March 2016, 4 of them occurring towards the end of the dialysis treatment. In June 2016, she had a percutaneous liver biopsy in order to find the cause of her cirrhosis, which was unknown despite extensive laboratory testing.

Thus, it seems that with the addition of phosphorus to the dialysate the episodes of postdialysis confusion resolved for the most part (April 2016 until June 2017), although patient continued to have episodes of hepatic encephalopathy unrelated to dialysis. By comparison, she had 4 episodes of dialysis associated confusion from October 2015 until April 2016. During the entire time after February 2016, patient was receiving frequent doses of lactulose and at times even rifampin.

Discussion

Most described consequences of hypophosphatemia include red cell dysfunction, rhabdomyolysis, and generalized muscle weakness. Uncommonly more central neurological dysfunction has been reported as a consequence of hypophosphatemia. The first report of hypophosphatemia (found by us in the literature) causing or contributing to encephalopathy was actually on a series of 12 dialysis patients in 1981 who developed dialysis encephalopathy likely due to aluminum overload [4]. The report found that hypophosphatemia was a risk factor for the development of encephalopathy.

Subsequently, there have been a few case reports of alcoholics with possible Wernicke's encephalopathy worsened by hypophosphatemia from 1980s to 1990s [5, 6]. Radiological changes in the brain (basal ganglia, thalamus, and occipital lobes) from hypophosphatemia have also been described in a 38-year-old woman with severe hypophosphatemia, which were reversible with improvements in serum phosphorus concentration [7]. In 2003, Jansen et al. [8] described a 69-year-old woman who developed severe weakness and encephalopathy due to hypophosphatemia.

Although the common cause of central pontine myelinosis is rapid correction of severe hyponatremia, hypophosphatemia has rarely been described to cause central pontine myelinolysis also [9, 10]. The mechanism being severe hypophosphatemia disrupts the Na^+/k^+ ATPase pump leading to apoptosis and central pontine myelinolysis. A total of 3 patients have been described in the 2 articles with 2 of the patients recovering mental function and the third not surviving.

Another report describes a 49-year-old diabetic woman with diabetic ketoacidosis who developed severe encephalopathy with a serum phosphorus concentration of <0.6 mg/dL [11]. The patient improved after correction of phosphorus depletion. The authors suggested that encephalopathy from hypophosphatemia is due to direct impairment of cerebral electrophysiological activity rather than cardiac flow alterations.

There is also one case report of hypophosphatemia leading to neurologic dysfunction in a marathon runner and the symptoms of aphasia, muscle weakness, and par-

esthesias resolved after normalization of serum phosphorus [12]. The serum phosphorus concentration on this 37-year-old male marathon runner was 0.9 mg/dL prior to repletion.

Hypophosphatemia leading to encephalopathy has typically occurred in chronic alcoholics, poor nutritional status patients, and critically ill patients undergoing refeeding [13]. Several electrolyte disturbances such as hypophosphatemia, hypomagnesemia, hypokalemia, and fluid imbalance are noted in refeeding syndrome due to shift of fluid and electrolytes in a malnourished patient after the introduction of nutrition therapy.

Other than the already described study with increased risk of dialysis encephalopathy in patients with hypophosphatemia, only one other patient on dialysis who developed encephalopathy as result of hypophosphatemia has been reported in the literature after extensive search [14]. A 61-year-old woman with end-stage kidney disease on continuous ambulatory peritoneal dialysis for 1 year (was on hemodialysis for 10 years prior to this) developed generalized muscle weakness and confusion with a serum phosphorus level of 0.8 mg/dL, and there is improvement in the neurologic state after restoration of phosphorus to 2.2 mg/dL.

Here 2 patients are described with risk factor for developing encephalopathy who mainly developed recurrent acute mental status changes toward the end of dialysis. Both patients were found to be profoundly hypophosphatemic with these episodes right after dialysis. A few hours after stopping dialysis, hypophosphatemia resolved and mental function improved. The patients were on phosphate binders with normal serum phosphorus concentrations prior to starting dialysis on monthly laboratory testing. After the patients were found to be hypophosphatemic, the phosphorus binders were stopped, and phosphorus was added to the dialysate. With these interventions, there were no more episodes of altered mental status postdialysis. Table 3 summarizes all of the serum phosphorus concentrations available for both patients during each of the encephalopathy episodes.

We believe that our 2 patients developed encephalopathy because of phosphorus shifts during dialysis. Both patients had consistently normal serum phosphorus concentration prior to dialysis; however, at the end of dialysis, they both were developing profound hypophosphatemia and subsequently several hours postdialysis the serum phosphorus would autocorrect as the intracellular phosphorus would move out of the cells. Holding phosphorus binders in these patients led to high predialysis serum phosphorus concentration and did not necessarily prevent the occurrence of hypophosphatemia after dialysis. Adding phosphorus to the dialysate allowed prevention of severe hypophosphatemia with dialysis and allowance of phosphorus binders to correct the hyperphosphatemia prior to dialysis.

Table 3. The first serum phosphorus concentration available after the encephalopathy episode

Patient No.	Date	Serum phosphorus, mg/dL	Time since the end of dialysis, min
1	January 2015	1.9	75
1	June 2015	1.6	50
1	August 2015	0.9	180
2	October 2015	2.3	60
2	December 2015	1.2	0
2	February 2016	1.6	40

Both of these patients had risk factors for developing encephalopathy. The first patient likely had some degree of COPD with CO_2 retention, and the second patient clearly suffered from recurrent episodes of hepatic encephalopathy. However, the repeated occurrence of encephalopathy postdialysis pointed to a role for postdialysis-induced hypophosphatemia as the exacerbating factor. In both patients, these episodes of dialysis-induced encephalopathy were completely prevented by adding phosphorus to the dialysate. We recommend nephrologist to consider postdialysis hypophosphatemia as a contributing factor for patient who become encephalopathic on dialysis. The optimal treatment in these patients would be to add phosphorus to the dialysate with continued therapy with phosphorus binders if indicated.

Even though the literature reports a serum phosphorus concentration of <1 mg/dL as the serum phosphorus concentration that will lead to symptoms, we believe in our patients hypophosphatemia did contribute to encephalopathy despite not always having a documented serum phosphorus concentration of <1 mg/dL for 3 reasons. First, the measurement was not taken right after dialysis had ended, thus some rebound had already occurred. One can imagine that the serum phosphorus concentration at the onset of the encephalopathy may have been significantly lower than the value available. Second, both of these patients had other reasons for having encephalopathy, which may have lowered their threshold for developing confusion to a higher serum phosphorus concentration. Finally with dialysis, the serum phosphorus concentration

is lowered more rapidly than happens physiologically, and this may lead to symptoms at a higher serum phosphorus concentration than otherwise.

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None.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional research committee at which the studies were conducted (Investigational Review Board approval 19-27187) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Divya Koganti helped draft the manuscript and obtained all patient data. Dr. Ramin Sam conceptualized and designed the writing of the case reports and reviewed and corrected the manuscript.

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