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TITLE OF CASE

Hypophosphataemia: An important cause of collapse

AUTHORS OF CASE ***Please indicate corresponding author by *(after the author's name)***

David M Williams[1,2*], Natasha Shrikrishnapalsuriyar[1], David E Price[1], Jeffrey W Stephens[1,2]

1. Department of Diabetes & Endocrinology, Morriston Hospital, Swansea, SA6 8NL UK
2. Diabetes Research Unit, College of Medicine, Swansea University, Swansea SA2 8PP, UK

SUMMARY ***Up to 150 words summarising the case presentation and outcome***

We present a case of a 44 year-old male civil servant who presented to the Emergency Department following an episode of collapse. He was usually fit and well and whilst at work he had developed a headache with pins and needles over his face and subsequently collapsed. On arrival to ED, he had a GCS of 4/15. There was no history of note apart from being prescribed citalopram for depression. Laboratory investigations revealed severe hypophosphataemia (phosphate 0.19mmol/L) and no other electrolyte abnormality. He was commenced on intravenous phosphate and his GCS improved to 15 within four hours. Further investigations revealed no cause for his severe hypophosphataemia and repeat bloods in clinic follow-up showed a normal phosphate level.

BACKGROUND

Collapse is one of the commonest presenting complaints during the acute medical take, and is typically a consequence of cardiac or neurological disturbance. Despite the common nature of this complaint, it is often challenging to diagnose the cause of collapse in some patients.

Electrolyte disorders can affect cardiac and neurological function, resulting in collapse. Electrolyte disorders known to cause collapse include hypocalcaemia (1), hypercalcaemia (2), hypokalaemia (3), hyperkalaemia (4), hyponatraemia (5) and hypernatraemia (6). However, hypophosphataemia is not commonly associated with collapse; although previous reports associate hypophosphataemia with acute confusion (7), visual hallucinations (8) and Wernicke's encephalopathy (9). Hypophosphataemia has also been associated with seizures

(10) and coma (11), though importantly these cases were also associated with re-feeding and alcohol abuse, respectively.

In this case report, we describe a patient who presented with collapse caused by severe hypophosphataemia with no other significant co-morbidity.

CASE PRESENTATION ***Presenting features, medical/social/family history***

A 44-year-old gentleman who worked for the DVLA presented to the Emergency Department (ED) with a collapse. He was normally fit and well and was prescribed citalopram for depression. He did not smoke or drink alcohol and took no illicit drugs. He had developed a headache associated with pins and needles over his face and left arm whilst at work, and subsequently collapsed. When the paramedics arrived, he had a GCS of 15, blood pressure 144/78, capillary blood glucose 11.8mmol/L and was afebrile.

On arrival to the ED his GCS had dropped to 4/15. Other than his reduced GCS, the physical examination was unremarkable and there were no signs of neck rigidity or rash.

INVESTIGATIONS ***If relevant***

His admission ECG showed normal sinus rhythm. The full blood count and electrolytes were normal. His bone profile demonstrated a calcium level of 2.51mmol/L (normal range 2.20-2.60mmol/L) and a magnesium level of 0.77mmol/L (normal range 0.70-1.00mmol/L). The only biochemical abnormality found was a low serum phosphate of 0.19mmol/L (normal range 0.80-1.50nmol/L). During the admission, five days following replacement of his serum phosphate, his urinary phosphate level was noted to be normal. A CT head taken on admission was also unremarkable.

Further investigations including serum parathyroid hormone, vitamin D, immunoglobulins, anti-TTG antibodies. Echocardiogram showed no evidence of LV dysfunction or valvular disturbance. Figure 1 demonstrates his serum phosphate level from hospital admission to clinic follow-up.

DIFFERENTIAL DIAGNOSIS ***If relevant***

The differential diagnosis included:

- Possible seizure with a prodromal episode of pins and needles over the body.
- Possible encephalitis, given his sudden history of collapse and reduced GCS.
- Cardiac syncope should also be considered, though this young adult and ECG demonstrating normal sinus rhythm and a normal QTc.

TREATMENT ***If relevant***

He was commenced on a 500ml intravenous infusion of phosphate polyfusor over 12 hours. By the next day his phosphate had increased from 0.19mmol/L to 1.13mmol/L. Whilst having this infusion, his GCS improved to 15 within 4 hours and he remained alert throughout the remainder of the admission. During his admission to hospital, he underwent further testing including Holter monitoring which showed sinus rhythm and an echocardiogram demonstrating good ventricular function with an ejection fraction of 55%. His biochemical markers were within normal limits, and his serum phosphate was measured daily. By day four of his hospital admission, he was started on oral Phosphate Sandoz as his phosphate decreased to 0.75mmol/L and had returned to normal three days afterwards. The cause of his hypophosphataemia remains unknown.

OUTCOME AND FOLLOW-UP

After 8 days of admission, he was discharged from hospital with a serum phosphate of 1.22mmol/L. He was followed up in the Endocrine clinic 4 weeks later with repeat blood tests which were within normal limits. His phosphate level since the admission has been within normal limits with no subsequent re-admission. The cause of his hypophosphataemia remains unknown. There was no evidence of re-feeding syndrome or alcoholism and his

further biochemical investigations remained normal.

DISCUSSION ***including very brief review of similar published cases (how many similar cases have been published?)***

Hypophosphataemia is a relatively common electrolyte disturbance in certain sub-groups, prevalent in up to 3.1% of hospital inpatients, up to 33.9% of patients admitted to intensive care units, up to 30.4% with chronic alcoholism and up to 80% of septic patients (12). Mild (0.65-0.79mmol/L) and moderate (0.32-0.64mmol/L) hypophosphataemia may present with non-specific symptoms such as generalised muscle weakness, myalgia and fatigue. Patients with severe hypophosphataemia (<0.32mmol/L) may present with serious sequelae such as confusion, hallucinations and seizures. As a result of its non-specific symptoms, this electrolyte disturbance is often not considered and the patient's symptoms subsequently misdiagnosed (13).

The treatment of hypophosphataemia can be achieved with oral, intravenous or intradialytic therapy. The treatment approach is determined by the serum phosphate level and the patient's symptoms. Generally, oral replacement would best be given to those with mild to moderate symptoms and levels of hypophosphataemia, whilst patients with severely low phosphate and/or symptoms, or who are unable to take phosphate orally would receive intravenous replacement. It is important to closely monitor the patient, as intravenous phosphate administration can provoke ECG changes, seizures, life-threatening hypocalcaemia and hyperkalaemia (13).

There are many causes of hypophosphataemia, including malnutrition (refeeding syndrome, anorexia nervosa, malabsorption, alcohol abuse), endocrine (hyperparathyroidism), renal (X-linked hypophosphatemia, hereditary hypophosphatemic rickets, Fanconi syndrome), respiratory alkalosis (sepsis, salicylate poisoning, anxiety) and medications (cisplatin, tetracyclines, aminoglycosides, antiretrovirals) (13). Rarely, hypophosphataemia is caused by oncogenic osteomalacia, in which elevated serum fibroblast growth factor 23 (FGF 23) levels induce hypophosphataemia by binding proximal tubule cells, thereby reducing renal phosphate reabsorption (14). Typically, this results from tumours of the bone or soft tissue which secrete FGF 23, causing elevated serum FGF 23 levels and subsequent hypophosphataemia by renal wasting (15). Typically, this disease presents insidiously with progressive weakness, bone and muscle pain and fractures (16). This was not tested for in this patient, which is beyond the scope of routine investigation of hypophosphataemia in this setting. However, it should be considered in patients who present with such biochemical findings and a history of non-specific symptoms such as weakness, generalised pain or recurrent fractures, and investigated by testing serum FGF 23 levels.

As shown in previously published cases of patients presenting with acute and severe hypophosphataemia, it is often difficult to establish the cause of hypophosphataemia in patients and the cause often remains unknown (7).

This case highlights the need for a comprehensive history, examination and biochemistry in the assessment of patients who present to ED with collapse, as such electrolyte disorders are easily reversible. Subsequent work-up to determine the cause of hypophosphataemia should also occur to prevent recurrence and to permit treatment of the underlying disorder.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points***

- Hypophosphataemia causes collapse, and should be excluded at clinical presentation.
- Intravenous phosphate should be used to treat patients with severe hypophosphataemia and reduced consciousness.
- It is important to consider the underlying cause of hypophosphataemia to prevent recurrence.

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Figure captions

Figure 1 demonstrates the patient's serum phosphate level from admission to clinic follow-up

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Graph showing the course of phosphate level over the hospital admission