Hong Kong College of Physicians
Case report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

Name of candidate (print and sign)
Hospital and Unit: Specialty:
Name of supervisor (print and sign):
Date(s) and place (hospital) of patient encounter: August 2018
Date of report submission: September 2021

Case report

Title: An Elderly Woman with Generalized Numbness

Case history:

Mrs. Ng was an 81-year-old woman with a past medical history of liver cirrhosis associated with chronic hepatitis B infection without portal hypertension, chronic low back pain, osteopenia, and depression under care by private doctors. She was a non-smoker and a non-drinker. Her medications include calcium carbonate chewable tablet, tenofovir disoproxil fumarate (TDF), alprazolam, zopiclone, and mianserin.

She attended the Accident and Emergency Department (AED) for generalized numbness described as the feeling of "pins and needles" with an onset of around two weeks ago. The numbness involved her arms and legs at onset with no apparent precipitating factors or events. The symptoms did not show worsening or progression throughout the week. She denied any facial drooping, speech problems, limb weakness, nor gait disturbance. She denied any shortness of breath, dizziness, nor palpitation. She recalled no recent injury with chronic neck and back pain as usual. Her neck and back pain, and stiff hands were chronic. There was no sphincter disturbance. She denied any recent gastroenteritis nor recent vaccination.

Mrs. Ng was afebrile with stable vitals. Neurological examination showed a Glasgow Coma Scale of 15/15. Cranial nerve and cerebellar examinations were unremarkable. Muscle tone was not flaccid with full limb power at both proximal and distal muscles. There was no hypo- or areflexia on deep tendon reflexes and there was an absent of myelopathic hand signs. There was an intact sensation to pain and proprioception, and there was no sensory level. She had no neck mass/swelling, and she was clinically euthyroid. There was no skin rash, nor inflammatory arthropathy. A post-void bladder scan showed no retention of urine.
A non-contrast computed tomography of the brain was performed and showed age-related cerebral atrophy with small-vessel changes. A panel of blood tests was taken from AED (including complete blood count, electrolytes, liver and renal function tests). The complete blood count showed a normal mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC). Her electrolytes were abnormal with hypokalemia, (3.2mmol/L), hypocalcemia (2.02mmol/L corrected to

serum albumin of 32g/L), and hypophosphatemia (0.34mmol/L), despite a normal renal function (Creatinine 86 micromol/L).

A nerve conduction test showed no evidence of demyelination nor axonal degeneration. Workup along with a normal neurological exam suggested that her numbness was unlikely to be a neurologic cause. The fasting blood test showed no evidence of diabetes mellitus and her thyroid function was normal. Vitamin B12 and folate were not deficient. Enzyme immunoassay for treponemal antibodies was negative. The serum potassium and phosphate were persistently low despite repeated oral replacement. Hence, it was postulated the culprit of her numbness was likely due to her deranged electrolytes.

Urine and plasma phosphate and creatinine levels were measured before replacement – plasma phosphate 0.48mM, urine phosphate 10.7mM, plasma creatinine 144 micromol/L, and urine creatinine 4.09mM. The fractional excretion of phosphate (FE_{PO4}) was 80% - a level above 5% suggests a renal loss of phosphate. The total vitamin D level was sufficient (76nm/L, normal 50-220nm/L) and the parathyroid hormone level was normal (5.1 pmol/L, normal 1.6-6.9pmol/L). Venous blood gas showed metabolic acidosis with a bicarbonate level of 14.8mM, and the anion gap was 12 (normal 8-16). Urine pH was 5.1 and the urine anion gap, which was calculated from urine cations (sodium and potassium) minus anions (chloride), was negative. In the absence of diarrhea, a normal anion gap metabolic acidosis with negative urine anion gap was highly indicative of type 2 (proximal) renal tubular acidosis. In addition, further urine testing showed glucosuria and high urinary protein level. A combination of proximal renal tubule acidosis, hypokalemia, urinary phosphate loss, and glucosuria suggest Fanconi syndrome, a generalized proximal (type 2) renal tubular dysfunction.

Fanconi syndrome in an elderly lady was unlikely related to a familial disorder such as Wilson's Disease. Mrs. Ng also denied any risk of heavy metal exposure nor any evidence of hemolysis to suggest paroxysmal nocturnal hemoglobinuria. A negative serum protein electrophoresis without a reversed albumin to globulin concentration made M-protein disorder (amyloidosis, and multiple myeloma) unlikely. There were also no signs and symptoms suggestive of Sjogren's syndrome and the anti-extractable nuclear antigen was unremarkable. Her medication history was further clarified with her private doctor. The patient was previously taking lamivudine for her chronic hepatitis B infection. She experienced a viral breakthrough secondary to tyrosine-methionine-aspartate-aspartate (YMDD) motif mutation. Lamivudine was then switched to adefovir dipivoxil. However, adefovir dipivoxil was changed to tenofovir disoproxil fumarate (TDF) two months ago. The temporal relationship suggested Fanconi syndrome secondary to TDF. After consulting gastrointestinal team and nephrology team, the tenofovir disoproxil fumarate was changed to tenofovir alafenamide with close monitoring electrolytes and acidosis while waiting for renal tubule recovery. Mrs. Ng's numbness resolved with the correction of electrolytes. Electrolytes normalized and the replacement was gradually tapered off.

Discussion and literature review

Hypophosphatemia is defined as a serum phosphate level is below 0.88mmol/L according to the laboratory reference range in Queen Elizabeth Hospital. Note that different laboratories and different countries/regions may have a slightly different cutoff. [1] Symptoms of hypophosphatemia usually occur when serum phosphate is below 0.64mmol/L, and they can be broad and non-specific, involving the cardiopulmonary system, nervous system, and musculoskeletal systems. Symptoms include shortness of breath, decreased exercise tolerance, proximal myopathy, irritability, paresthesia, and delirium. Serious or even life-threatening complications such as rhabdomyolysis, respiratory failure, ileus, ventricular arrhythmia, seizure, and encephalopathy can occur with severe hypophosphatemia (below 0.32mmol/L). [1]

Causes of hypophosphatemia can be broadly categorized into three mechanisms – decreased intestinal absorption, increased urinary excretion/loss, and internal redistribution. [2] A combination of different mechanisms is also common. Factors contributing to decreased intestinal absorption can chronic diarrhea, prolonged antacid or phosphate binder use, vitamin D deficiency or resistance, and severe malnutrition, chronic alcoholism or a strict dietary phosphorus restriction. Increased urinary loss or excretion is most commonly seen in patients with primary hyperparathyroidism, vitamin D deficiency or resistance, renal tubular defects (including Fanconi syndrome), and drug-related (such as diuretics, glucocorticoids, and mineralocorticoid). Internal redistribution involves the redistribution of phosphate from an extracellular to an intracellular compartment, and it is the most common cause of hypophosphatemia. [1,2] The frequent causes of this redistribution include acute respiratory alkalosis secondary to hyperventilation (due to pain, sepsis, anxiety, and in patient on mechanical ventilation), recovery from malnutrition (including the refeeding syndrome), drug-related (such as insulin, glucagon, steroid, and beta-agonists), and rapid cell proliferation/uptake (hungry bone syndrome, leukemia, and use of colony-stimulating factors). [1,2]

Evaluation for hypophosphatemia includes and, often is evident from a detailed history. Calculation of the fractional excretion of phosphate (FE_{PO4}) is especially useful in delineating renal loss of phosphate from other causes (decreased intestinal absorption and internal redistribution). The formula to calculate FE_{PO4} is (urinary phosphate x plasma creatinine x 100) divided by Plasma phosphate x urinary creatinine. A FE_{PO4} greater than or equal to 5% suggests a renal loss. In this case, Mrs. Ng has a FE_{PO4} of 80%. Subsequent workup should include measuring the parathyroid hormone level, vitamin D level, serum calcium/ionized calcium level, blood gas for any metabolic acidosis, and urinalysis for any glucosuria and aminoaciduria, if available. [1,2] Treatment of hypophosphatemia involves the treatment of underlying cause and serum phosphate level will normalize with the treatment of underlying cause; hence, phosphate replacement is not always necessary. However, replacement of phosphate is recommended for those with serum phosphate below 0.32mmol/L regardless of symptoms, and for those with

a level below 0.64mmol/L with symptoms. [2,3]

Renal tubular acidosis (RTA) is a disorder characterized by the impairment in the homeostasis of acid-base balance by the renal tubules. RTA is most commonly suggested in a clinical setting of a normal anion gap metabolic acidosis with the absence of diarrhea. There are different types of RTA, which are distinguished by the site of defect in the renal tubules and the mechanism of the defect. Proximal (or Type 2) renal tubular acidosis is caused by the impaired ability to reabsorb bicarbonate in the proximal renal tubules. [4] The diagnosis of type 2 RTA is further supported by the finding of a urine pH below 5.3 and a negative urine anion gap which provide indirect evidence of the presence of acidification in the distal renal tubule and the presence of renal ammonium excretion, respectively. Both findings suggest the presence of normal anion gap metabolic acidosis is due to a defect in the proximal renal tubules. [4]

Proximal RTA can occur as an isolated defect in bicarbonate reabsorption in proximal renal tubules but can also, and more commonly, as part of a generalized renal tubule dysfunction known as Fanconi syndrome. [4,5] Fanconi syndrome is characterized by a generalized dysfunction in the proximal renal tubule in the absorption of bicarbonate, electrolytes, glucose, and amino acids/protein, resulting in phosphaturia, glucosuria, aminoaciduria/proteinuria, and proximal RTA. The causes of Fanconi syndrome can be genetic/inherited and acquired. Inherited causes include mitochondrial disorder, Wilson's disease, glycogen storage diseases, etc. Acquired causes include M-protein related (amyloidosis, multiple myeloma), heavy metal exposure (lead, mercury, and copper), vitamin D deficiency, Sjogren's syndrome, and drug-related, such as nucleotide reverse transcriptase inhibitor (tenofovir disoproxil fumarate), platinum-based alkylating agents (cisplatin), aminoglycosides, and carbonic anhydrase inhibitor (acetazolamide). [4,5]

Tenofovir is a nucleotide reverse transcriptase inhibitor which acts as an acyclic analog of adenosine monophosphate (AMP) without an hydroxyl group at 3' carbon; thereby, terminating DNA transcription. It is administered as a prodrug in the form of tenofovir disoproxil fumarate (TDF), where it is delivered intracellularly to convert to tenofovir and phosphorylated to tenofovir diphosphate, the active drug form. However, in the plasma, some of the TDF will be converted to tenofovir before reaching into the cells. When filtered into the renal tubules, tenofovir can cause renal toxicity in 2-8% via direct tubular cytotoxicity or depletion of epithelial cell mitochondrial DNA. [6] Renal toxicity related to TDF includes acute kidney injury and Fanconi syndrome. TDF associated renal toxicity can be managed by drug discontinuation with normalization of renal function. However, up to 2% of the cases of TDF induced Fanconi syndrome may result in dialysis and chronic kidney failure [6,7]. Tenofovir alafenamide (TAF) was approved by the U.S Food and Drug Administration in 2016. Compared with TDF, TAF has much greater plasma stability and more efficient intracellular delivery; hence, the dose of TAF can be given at approximately one-tenth ($1/10^{th}$) of TDF with 91% less plasma tenofovir detected. [7,8] A pooled analysis involving approximately 9300 patients on TDF and TAF showed much

improved renal safety of TAF compared with TDF with no cases of proximal renal tubulopathy and much less drug discontinuation related to the renal adverse event for those on TAF. [8]

Tables and figures

References:

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No of words in Case History and Discussion (excluding references): 1,751 words

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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