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Case Report

Hypophosphataemia in a patient with Gitelman's syndrome

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Introduction

Gitelman's syndrome, also known as 'hypocalciuric variant' of Bartter's syndrome, is a primary renal tubular disorder characterized by chronic hypokalaemia, hypomagnesaemia, metabolic alkalosis, hypocalciuria with normocalcaemia, hyperreninaemic hyperaldosteronism, and normal renal function [1–3]. The clinical features allowing its differentiation from 'classical' Bartter's syndrome include low urine calcium excretion, absence of overt urine concentration defect and normal growth velocity [3,4]. The primary defect in this disorder may be in the distal convoluted tubules [3,5,6]. To the best of our knowledge profound hypophosphataemia has not previously been reported in patients with Gitelman's syndrome in the English literature. Herein, we describe a patient with the disease who developed hypophosphataemia with inappropriate phosphaturia, and we discuss the possible pathophysiological mechanisms involved.

Case report

A 27-year-old woman who had experienced a long-term history of muscle weakness and easy fatiguability was found to have hypokalaemia (serum potassium 3.05 mmol/l) on laboratory investigation, and was admitted to hospital. She denied diuretic or laxative abuse and licorice ingestion. Blood pressure was 110/70 mmHg, and physical examination was unremarkable. Results of laboratory investigations on admission are shown in Table 1. The outstanding features were hypokalaemia with inappropriate kaliuresis, hypomagnesaemia with inappropriate magnesiuria, hypochloraemia with high fractional chloride excretion, mild hypercalcaemia with hypocalciuria, hypophosphataemia with inappropriate phosphaturia, and moderate metabolic alkalosis. Plasma renin activity (PRA) was 13.2 ng/ml/h (normal value 0.9–3.3 ng/ml/h) and serum aldosterone level was 490 ng/l (normal value 40–160 ng/l), an inappropriately elevated value if we take into account the patient's hypokalaemia. Serum cortisol level was 0.45 μmol/l (normal value 0.22–0.68 μmol/l), serum parathormone level 18 pg/ml (normal value 10–55 pg/ml), serum calcitriol level 84 pmol/l (normal values 48–182 pmol/l), while serum erythropoietin was increased (42 μu/ml) (normal value 8.6–23.8 μu/ml).

Table 1. Laboratory investigation of the patient on admission

Parameters	
Haematocrit	0.46
Arterial pH	7.50
PCO_2 (kPa)	5.85
Serum bicarbonate (mmol/l)	33
Serum creatinine (μmol/l)	88.4
Serum sodium (mmol/l)	142
Serum chloride (mmol/l)	96
Serum potassium (mmol/l)	3.1
Serum magnesium (mmol/l)	0.54
Serum calcium (mmol/l)	2.7
Serum phosphate (mmol/l)	0.67
$FENa^+$ (%)[1]	0.52
Urine sodium (mmol/24 h)	135
$FECl^-$ (%)[1]	1.21
Urine chloride (mmol/24 h)	152
FEK^+ (%)[1]	19
TTKG[1]	18
Urine potassium (mmol/24 h)	90
$FEMg^{2+}$ (%)[1]	4.8
Urine magnesium (mmol/24 h)	6
$FECa^{2+}$ (%)[1]	0.2
Molar urinary calcium/creatinine[1]	0.02
Urine calcium (mmol/24 h)	3
$FEPO_4^{3-}$ (%)[1]	27.8
$TmPO_4^{3-}$/GFR (mmol/l)[1]	0.76
Urine phosphate (mmol/24 h)	17.8
Creatinine clearance (ml/min)	115

Standard formulae were used for the determination of fractional excretions of electrolytes. Transtubular potassium gradient (TTKG) was calculated from the equation: TTKG = (Urine potassium ÷ Uosm/Posm/serum potassium). Maximum tubular reabsorption rate for phosphate ($TmPO_4^{3-}$/GFR) was calculated by the Walton and Bijvoet nomogram [7].

[1]Two hours' fasting urine sample was used for determination.

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A water deprivation test produced an increase in urinary osmolality to 740 mosmol/kg with no increase in serum osmolality. A water load test was then performed. Following an overnight fast the patient was given 20 ml/kg tap water orally over 15 min and an equivalent amount of water was given to replace each voided specimen. A urinary osmolality of 84 mosmol/kg was achieved with serum osmolality depressed to 264 mosmol/kg. During hospitalization serum phosphorus ranged between 0.64 and 0.74 mmol/l, while $FEPO_4^{3-}$ ranged between 24 and 28% and $TmPO_4^{3-}$/GFR between 0.75 and 0.79 mmol/l. Potassium chloride solution was given orally in a dose of 60–80 mmol/day. Ten days later serum potassium level was 3.6 mmol/l and arterial pH was 7.46. However, hypophosphataemia and inappropriate phosphaturia persisted (serum phosphorus level was 0.68 mmol/l and $FEPO_4^{3-}$ was 28%). Treatment with magnesium aspartate (15 mmol/day) was initiated. After 2 weeks of treatment serum magnesium levels improved to 0.65 mmol/l, serum phosphorus levels rose to 0.97 mmol/l, while the fractional excretion of phosphorus decreased to 19% and the $TmPO_4^{3-}$/GFR increased to 0.93 mmol/l.

Discussion

Our patient fulfilled the criteria for the diagnosis of Gitelman's syndrome [1–4]. Moreover, she developed hypophosphataemia mainly due to inappropriate phosphaturia, evidenced by increased (>20%) $FEPO_4^{3-}$ and decreased (<0.87 mmol/l) $TmPO_4^{3-}$/GFR [7,8].

Several mechanisms could be responsible for the increased phosphate loss in the urine. However, the coexistent hypomagnesaemia should be considered as the principal cause, since experimental studies have demonstrated an ongoing phosphaturia accompanying progressive magnesium depletion [9,10]. In our case the amelioration of hypophosphataemia when hypomagnesaemia was corrected enforces the significance of hypomagnesaemia in the pathogenesis of decreased serum phosphorus levels.

Other possible mechanisms of the increased phosphate loss in the urine are:

(1) The coexistent metabolic alkalosis, which has been associated with an increased rate of phosphate excretion. It is not clear whether the inhibition of phosphate reabsorption in the proximal tubule and the distal nephron is due to competition between the bicarbonate anion and phosphate molecule in the tubular fluid, to a direct effect of the elevated serum bicarbonate, or to the elevated serum pH [11,12]. Moreover, in such cases a shift of phosphate into cells (although less than that experienced in respiratory alkalosis) contributes to the hypophosphataemia [11,12].

(2) The coexistent hypokalaemia. Hypophosphataemia associated with increased renal phosphate clearance has been reported in patients with hypokalaemia and potassium depletion [13]. Hypophosphataemia mainly attributed to hypokalaemia has also been reported in a child with Bartter's syndrome in the French literature [14]. However, this patient also exhibited hypercorticism, which can further aggravate or even cause phosphaturia with resultant hypophosphataemia. Although hypophosphataemia is often associated with hypokalaemia, mechanisms and pathophysiology remain unclear and could be related to a coexistent underlying cause. However, it has recently been reported that dietary potassium can influence the excretion of phosphate [15]. Increased potassium intake enhances the urinary excretion of phosphate, while potassium restriction has the opposite effect [15]. Yet, in our patient hypophosphataemia with inappropriate phosphaturia persisted despite the correction of both hypokalaemia and metabolic alkalosis after the administration of potassium chloride.

(3) The primary tubular lesion, which can be regarded as part of a more general tubular dysfunction held responsible for the manifestations of the disease, since there is evidence supporting the existence of a phosphate reabsorptive mechanism in the PTH-responsive, adenylcyclase-containing distal tubules [16].

(4) The prostaglandin-induced renal vasodilatation, which can also increase phosphate excretion. Renal vasodilatation with its consequent diminished filtration fraction lowers peritubular protein concentration and increases peritubular hydrostatic pressure, which may account for the phosphaturia [17]. Nevertheless, properties other than vasodilatation may be operative in vasodilator-induced phosphaturia. It should also be mentioned that the urinary excretion of prostaglandin E_2 is normal in Gitelman's syndrome [18].

We conclude that hypophosphataemia should be considered as an additional electrolyte abnormality observed in patients with Gitelman's syndrome.

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