



# Severe Hypocalcemia and Extreme Elevation of Serum Creatinkinase in a 16-Year Old Boy with Pseudohypoparathyroidism Type Ib

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## ABSTRACT

Calcium is essential for proper muscular function and metabolism. Myopathy with high creatinkinase activity can be a rare manifestation of hypocalcemia of various origin, such as vitamin D deficiency, hypoparathyroidism, pseudohypoparathyroidism (PHP). 16-year old previously healthy boy was admitted to intensive care unit with convulsions lasting for three minutes and a transient loss of consciousness. Laboratory results revealed severe hypocalcemia (total S-Ca < 1.0 mmol/L; normal 2.2–2.6 mmol/L), hyperphosphatemia (S-P 2.8 mmol/L; normal 0.6–1.6 mmol/L). Serum creatinkinase (S-CK) activity was 32  $\mu$ kat/L (normal 0.57–2.45  $\mu$ kat/L). Other basic biochemical parameters including creatinine, troponin, alkaline phosphatase were within normal values. Calcemia was gradually corrected within two weeks by intravenously and orally administered calcium and by cholecalciferol. S-CK reached a maximum of 222  $\mu$ kat/L on day 4 and dropped to 7.2  $\mu$ kat/L on day 14. Boy had no myalgias, neither clinical signs of myopathy. Echocardiography was normal with normal myocardial contractility, without any signs of calcification. The serum level of parathyroid hormone (S-PTH) was high (12 pmol/L; normal 0.7–5.5 pmol/L), fully compatible with the diagnosis of PHP. Molecular analysis revealed pseudohypoparathyroidism type Ib (PHP1b). In conclusion, manifest tetany and even mild myopathy with very high S-CK can occur in hypocalcemic patients and usually resolves after normalization of hypocalcemia.

## KEYWORDS

calcium; hypocalcemia; pseudohypoparathyroidism; creatinkinase; myopathy

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## INTRODUCTION

Calcium is essential for proper muscular function, muscle contraction and metabolism. Myopathy with high creatinase activity (S-CK) can be a rare manifestation of hypocalcemia of various origin, such as vitamin D deficiency, hypoparathyroidism, pseudohypoparathyroidism (1–14).

## CASE REPORT

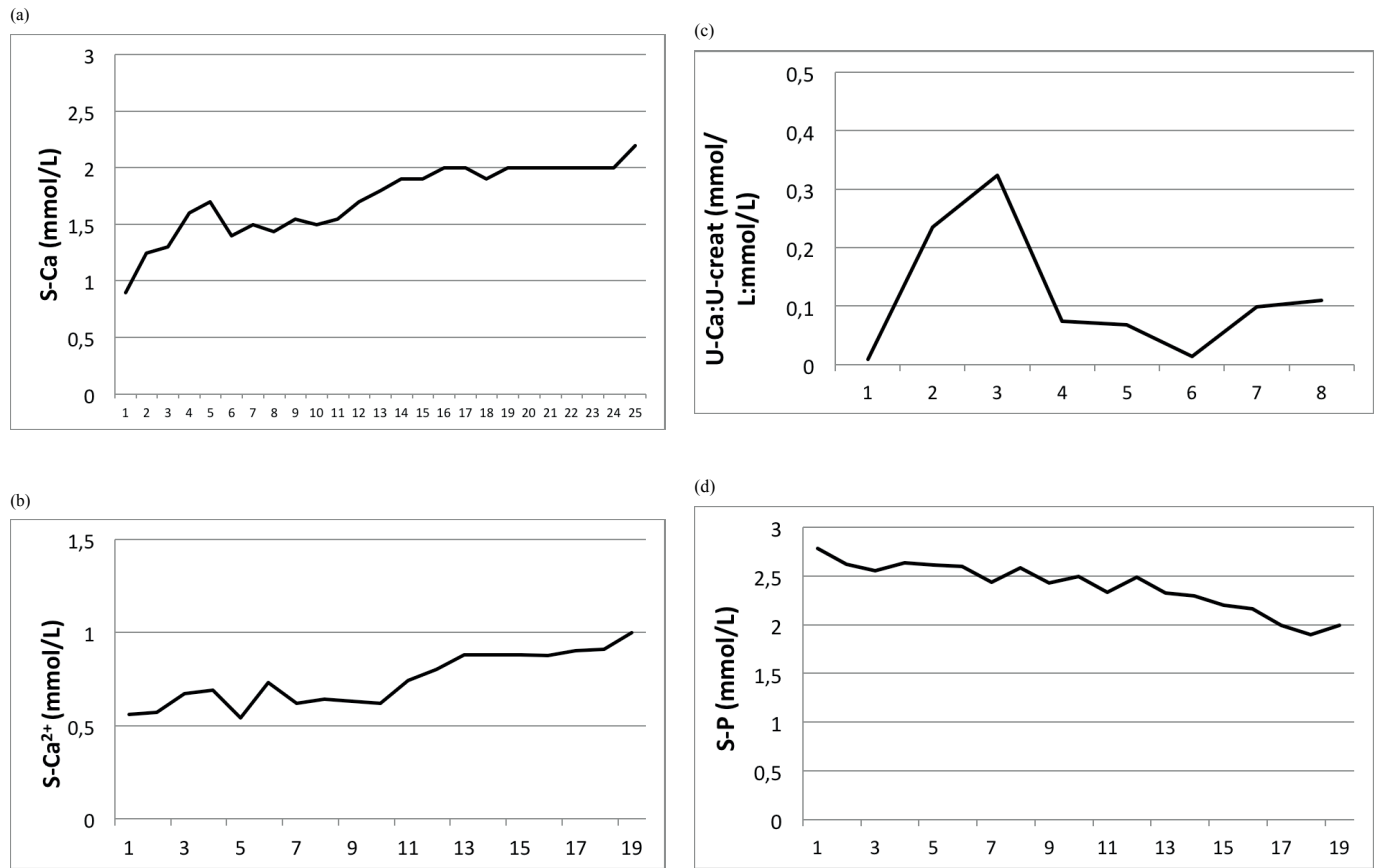
A 16-year old previously healthy boy with uneventful personal history and normal anthropometric data (height 172 cm i.e. 25–50 percentile), weight 64 kg i.e. 50–75 percentile) was admitted to intensive care unit due to convulsions lasting for three minutes and a concomitant loss of consciousness. Upon admission, he was already vigile; Glasgow coma scale (GCS) was 12 points, with positive Chvostek's sign. Laboratory results revealed severe hypocalcemia (total S-Ca < 1.0 mmol/L; normal 2.2–2.6 mmol/L; ionised serum calcium, S-Ca<sup>2+</sup> 0.56 mmol/L; normal 1.12–1.23 mmol/L) (Figure 1a,b), hyperphosphatemia (S-P 2.8 mmol/L; normal 0.6–1.6 mmol/L), mild hypomagnesemia (S-Mg 0.64 mmol/L; normal 0.7–1.0 mmol/L). Total serum creatinase (S-CK) activity was 32  $\mu$ kat/L (normal 0.57–2.45  $\mu$ kat/L). Capillary blood pH was normal (pH 7.388 and 7.424, respectively). Other basic biochemical parameters (serum sodium, potassium, chloride, creatinine, urea nitrogen, troponin and glucose levels, serum activity of aspartate-aminotransferase, alanin-aminotransferase, alkaline phosphatase - S-ALP) were within normal reference ranges. Urinary calcium/creatinine ratio (U-Ca/U-creat) was initially low (0.01 mmol/L:mmol/L; normal 0.1–0.5) (Figure 1c). Urinary dipstick test, including hemoglobin and myoglobin was negative. He immediately received intravenous (i.v.) infusion of 5% dextrose with 10% calcium gluconate and magnesium sulphate. His total calcemia improved within five hours to 1.25 mmol/L (Figure 1a), and S-Mg to 0.88 mmol/L, but S-CK further increased to 38  $\mu$ kat/L (Figure 2). The following day he received oral calcium (3000 mg/day) and oral cholecalciferol (20,000 IU/day) together with i.v. calcium gluconate. There was a gradual improvement in S-Ca, reaching 1.9 mmol/L on day 14 (Figure 1a). There was a slow gradual decrease in S-P (Figure 1d). However, initially high S-CK was further on rise and began to drop on day 6 (Figure 2). The patient had no myalgias, neither clinical signs of myopathy. There was initially prolonged QTc interval of 0.47 seconds on electrocardiogram, without any signs of myocardial damage, this was normalised on day 14 (QTc 0.42 seconds). Echocardiography was normal with normal myocardial contractility, without any signs of calcification. Abdominal ultrasonography revealed nephrocalcinosis without any signs of urolithiasis. Basal ganglia calcifications were apparent on the magnetic resonance imaging (MRI) of the brain. Patient had no cataract on ophthalmological exam. Lumbar spine bone mineral density (L1-L4 BMD) was within age-related reference range (1.188 g/cm<sup>2</sup>; 0.4 SD Z-score). As mentioned before, the serum levels of creatinine and ALP were normal (66  $\mu$ mol/L and 2.2  $\mu$ kat/L, respectively). The wrist X-ray was normal, without any signs

of osteomalacia. The serum level of parathyroid hormone (S-PTH) was high (10.3 and 12 pmol/L, respectively; normal 0.7–5.5 pmol/L). These findings ruled out vitamin D deficiency, chronic renal failure and hypoparathyroidism and were fully compatible with the diagnosis of pseudohypoparathyroidism (PHP). The boy was discharged on day 14 and remained thereafter on calcium (2000 mg/day) and vitamin D supplementation (cholecalciferol 20,000 IU/day, calcitriol 0.25  $\mu$ g/day). Currently, he is 21 years old, on calcium and vitamin D (cholecalciferol and calcitriol) supplementation with S-Ca 2.2–2.3 mmol/L, no further convulsions occurred. His parents had normal levels of S-Ca, P, ALP, PTH. His brother, who is five years his senior, had asymptomatic hypocalcemia (total S-Ca 1.4 mmol/L) and high S-PTH (14 pmol/L), also confirming the diagnosis of PHP. Therefore, he was also started on calcium and vitamin D supplementation.

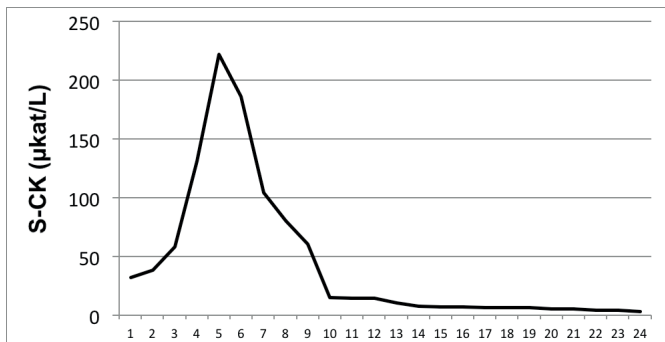
Mutational analysis of GNAS gene by Multiple-Ligation Probe amplification revealed deletion of exons STX 16-5 and STX 16-6 together with methylation loss of alternative promotor GNAS1A in both brothers, thus arriving at the diagnosis of pseudohypoparathyroidism type Ib (PHPIb). Mutation of GNAS gene was not detected, confirming diagnosis of PHP Ib.

## DISCUSSION

Pseudohypoparathyroidism is a receptor disorder, an end-organ resistance to biological actions of PTH, resulting in hypocalcemia and hyperphosphatemia (15–17). Pseudohypoparathyroidism is caused by genetic defects of GNAS gene, encoding the alpha-subunit of the stimulatory G protein (G $\alpha$ ), a signaling protein essential for the actions of PTH. Pseudohypoparathyroidism is further classified into two main types PHP-I and PHP-II. In PHP-I, both nephrogenous cAMP generation and phosphate excretion following exogenous PTH administration are low compared to those observed in normal subjects. Two principal subtypes of PHP-I have been defined: PHP-Ia and PHP-Ib. Patients with PHP-Ia have, besides PTH-resistance, Albright's hereditary osteodystrophy (AHO), a combination of physical features, such as obesity, short stature, soft tissue calcifications, brachydactyly and mental retardation, together with additional hormonal abnormalities, including hypothyroidism and hypogonadism caused by end organ resistance to thyroid-stimulating hormone (TSH) and gonadotropins (15). Pseudohypoparathyroidism Ib is caused by epigenetic changes at one or multiple differentially methylated regions within GNAS and is therefore characterized by end organ resistance to biological effects of PTH, mostly without dysmorphic features. However, resistance to other hormones and variable features of AHO can also occur (15–17). In PHP-II, nephrogenous cAMP generation is normal, but the urinary excretion of phosphate is impaired. The treatment is currently the same for patients with either PHP-Ia,b or PHP-II and includes calcium supplementation and administration of vitamin D (15). In 2016 the EuroPHP network developed a new classification to include all disorders with impairments in PTH and/or PTHrP signalling pathway, and these have been grouped



**Fig. 1** (a) Total calcemia (S-Ca; mmol/L) on a daily basis (reference values 2.2–2.6 mmol/L); (b) Ionised serum calcium levels (S-Ca<sup>2+</sup>; mmol/L) on a daily basis (reference values 1.12–1.23 mmol/L); (c) Urinary calcium/creatinine ratio levels (U-Ca: U-creatinine; mmol/L: mmol/L) on a daily basis (reference values 0.1–0.5 mmol/L); (d) Serum phosphate levels (S-P; mmol/L) on a daily basis (reference values 0.6–1.6 mmol/L).



**Fig. 2** S-creatininase (S-CK, µkat/L) on a daily basis (reference values 0.57–2.45 µkat/L).

under the term “inactivating PTH/PTHrP signalling disorder (iPPSD)” (16, 17).

Several observations reported S-CK elevation in children and adults with hypocalcemia mostly due to hypoparathyroidism (5–10) or PHP (11–14). The mechanism has not yet been elucidated and high S-CK values are believed to be probably the result of rhabdomyolysis or repeated muscle contractions in tetanic seizures (2–5). In another study, microscopic evaluation of bioptic samples revealed muscle cells vacuolar degeneration, focal hyaline degeneration and multiple focal muscle fiber hyaline degeneration with sarcolemma cells hyperplasia in patients with hypoparathyroidism and chronic hypocalcemia (8).

Hypocalcemia may even lead to cardiac arrhythmias (18) and heart failure (19–22). Furthermore, cardiomyopathy with cardiac failure has been reported in patients with hypocalcemia (19, 20).

Our patient presented with severe hypocalcemia due to PHP-1b, manifest tetany, transiently elevated S-CK with normal cardiac function and without severe myopathy. We did not assess the vitamin D status of this patient at the time of admission, however, normal S-ALP, high S-P together with normal wrist X-ray clearly ruled out vitamin D deficiency.

## CONCLUSION

Manifest tetany and even mild myopathy with very high S-CK can occur in hypocalcemic patients and usually resolves after normalization of hypocalcemia.

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