

CASE REPORT

Hyperthermia in the course of tetany in a child with Dent's disease – case report

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ABSTRACT

Tetany is a condition in which serum electrolyte disturbances lead to increased neuronal excitability. We describe a case of life-threatening tetany in a 2.5-year-old boy with Dent's disease linked with the CLCN5 gene. Dent's disease is a renal tubular disorder characterized by a proximal tubule defect resulting in low-weight proteinuria, hypercalciuria, phosphaturia, impaired urinary acidification, nephrolithiasis/nephrocalcinosis and progressive renal failure. In the presented patient, multiple electrolyte derangements in the form of hyponatremia, hypochloremia, hypokalemia, hypocalcemia, and hypomagnesemia, determined by Dent's disease, led to the development of diffuse muscle spasm and rhabdomyolysis, which ended with acute hyperthermia and seizures. Although, due to acuity of symptoms sepsis was suspected, the child showed dramatic improvement after the aggressive electrolyte repletion. We emphasize the need for considering tetany in patients with unstable vital signs, muscle cramping and medical conditions underlying electrolyte disorders.

KEY WORDS:

rhabdomyolysis, hyperthermia, tetany, Dent's disease.

INTRODUCTION

The care of patients with medical conditions contributing to electrolyte disturbances may present unusual challenges to clinicians in the form of sudden metabolic disorders. Tetany is a condition of hyperexcitability of the nervous system due to multiple metabolic abnormalities [1, 2]. Its presentation may range from asymptomatic patients to life-threatening episodes [1, 2]. Tetany in various presentations has been reported in the literature, but its occurrence in Dent's disease has not been widely described [3–5].

CASE REPORT

MEDICAL HISTORY

This 2.5-year-old boy was born at 39 weeks' gestation with a birth weight of 3420 g, Apgar score of 10 points

with features of facial dysmorphism, with a history of transient respiratory distress, grade 2 intraventricular hemorrhage, urinary tract infection and a posterior urethral valve. Throughout his first year of life, psychomotor impairment and failure to thrive were observed. At the age of 12 months, the patient was admitted to the nephrology department with hyponatremia, hypophosphatemia, high serum alkaline phosphatase level, low serum 25-hydroxyvitamin D level, normal parathormone, compensated metabolic acidosis, normal renal function (eGFR 111 ml/min/1.73 m²), proteinuria, hypercalciuria, hyperphosphaturia, hyperuricosuria, rickets and the presence of fine kidney stone formations. The diagnostic approach was directed towards renal proximal tubule dysfunction [1, 2]. Due to genetic screening, using array comparative genomic hybridization, deletion in chromosome Xp11.23-p11.22 including the CLCN5 gene responsible for Dent's disease 1, as well as USP27X and SHROOM4 genes implicated in developmental disorders, was found

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[3, 4]. Oral supplementation of salt, sodium bicarbonate, vitamin D and a mixture of phosphates was implemented. One year later, the 2-year-old boy presented with hyponatremia, hypophosphatemia, hypocalcemia, hypokalemia, hypomagnesemia, normal kidney function (eGFR 137 ml/min/1.73 m²), proteinuria and glycosuria. Complementary treatment based on calcium, potassium and magnesium supplementation was introduced.

CLINICAL PRESENTATION

One hot, summer day, at the age of 2.5 years, the patient presented with an abrupt onset of muscle cramping, with redness and swelling of forearms and calves. On admission, the child was afebrile, normotensive with undisturbed respiratory function, normal oxygen saturation on room air, mildly elevated heart rate (110 beats per minute), tearful and thirsty. The boy's height was 70 cm (below the 3rd percentile), his weight was 6.5 kg (below the 3rd percentile), and the skin was found to be dry and red. The boy's feet were plantarflexed, forearms and calves were tough, hands and ankles were swollen. Blood tests revealed hyponatremia (131 mmol/l), hypochloremia (87.8 mmol/l), hypokalemia (3.18 mmol/l), hypocalcemia (total Ca 1.54 mmol/l, Ca²⁺ 0.68 mmol/l), hypomagnesemia (0.45 mmol/l), hyperphosphatemia (1.79 mmol/l), venous blood gas showed pH of 7.35, pCO₂ of 44 mm Hg, HCO₃ of 24.1 mmol/l, BE -1.5 mmol/l, C-reactive protein (CRP) was negative (0.43 mg/l), glucose was within the normal range (94.7 mg/dl), uric acid was low (122 μmol/l), eGFR was 88 ml/min/1.73 m², creatine kinase (CK) concentration (229 IU/l) was mildly elevated (Table 1). In urine, a trace of protein was present. Difficulty in gaining venous access determined the fact that

the initial treatment comprising paracetamol, fluids, electrolytes, along with milk infant formula was administered orally. Within the next two hours successful cannulation was performed but the patient's condition deteriorated. Severe muscle twitching followed by diffuse muscle spasm and opisthotonos posturing, temperature rising to 40.5°C, despite receiving antipyretics, tachycardia up to 200 beats per minute, blood pressure 120/93 mm Hg, and respiratory rate 35 breaths per minute were reported. Electrocardiography (ECG) and pulse oximetry monitoring were initiated. ECG showed supraventricular tachycardia. Finally, generalized tonic-clonic seizures accompanied by a decrease in oxygen saturation on room air were observed. Laboratory findings at that critical point revealed a slight increase in serum concentrations of sodium (132 mmol/l), chloride (89.4 mmol/l), calcium (1.66 mmol/l) and magnesium (0.46 mmol/l), but more than previously pronounced hypokalemia (2.69 mmol/l) and lower serum ionized calcium level (0.64 mmol/l). Venous blood gas showed pH of 7.57, pCO₂ of 22.3 mm Hg, HCO₃ of 20 mmol/l, BE 0.3 mmol/l. CRP was invariably negative (0.18 mg/l), serum CK (778 IU/l) increased significantly. Tonic-clonic seizures terminated with rectal diazepam. Body surface cooling was applied with damp towels and ice packs. Oxygen flow by face mask was given and oxygen saturation reached 93%. Due to the severe presentation, our patient was empirically treated for sepsis with intravenous antibiotics and fluids. Intensive electrolyte repletion was initiated. The swift reversal of tetany and stabilization of clinical conditions were achieved due to the use of calcium, magnesium and potassium-containing solutions. The patient showed dramatic improvement in symptoms after the infusion and his vital signs returned to normal values. Six hours later, the patient's laboratory

TABLE 1. Laboratory values of the patient during the first day of the hospital course

Variable	10:00 p.m.	00:30 a.m.	06:00 a.m.	Reference range
Sodium [mmol/l]	131	132	146	136–145
Chloride [mmol/l]	87.8	89.4	108.7	98–107
Potassium [mmol/l]	3.18	2.69	2.67	3.5–5.1
Calcium [mmol/l]	1.54	1.66	1.89	2.2–2.7
Ionized calcium [mmol/l]	0.68	0.64	0.83	1.1–1.35
Magnesium [mmol/l]	0.45	0.46	0.84	0.7–0.95
Phosphorus [mmol/l]	1.79	1.16	0.97	0.81–1.45
pH	7.357	7.574	7.398	7.35–7.46
pCO ₂ [mm Hg]	44	22.3	31.7	35–45
HCO ₃ [mmol/l]	24.1	20.2	19.1	21–27
BE [mmol/l]	-1.5	0.3	-4.5	-2.5–2.5
C-reactive protein [mg/l]	0.43	0.18	2.2	0–5
Creatine kinase [IU/l]	229	778	9618	60–80
Creatinine [μmol/l]	29	–	35	21–36

tests were notable for the following: sodium 146 mmol/l, chloride 108.7 mmol/l, potassium 2.67 mmol/l, calcium 1.89 mmol/l, ionized calcium 0.83 mmol/l, magnesium 0.84 mmol/l, venous blood gas showed pH of 7.39, pCO₂ of 31.7 mm Hg, HCO₃ of 19.1 mmol/l, BE -4.5 mmol/l, CRP 2.2 mg/l. However, his serum CK increased, peaking at 9618 IU/l (Table 1). The following morning the child's clinical exam normalized and antibiotics were ceased, although the correction of electrolyte imbalance was continued.

DISCUSSION

In this life-threatening emergency that occurred in our patient, Dent's disease determined multiple electrolyte abnormalities leading to the development of severe tetany. It was a hot day and the child could have been dehydrated, which enhanced electrolytic disturbances typical for Dent's disease [6–10].

Dent's disease is a renal tubular disorder characterized by a proximal tubule defect resulting in low-weight proteinuria, hypercalciuria, nephrolithiasis/nephrocalcinosis and progressive renal failure [6–10]. Phenotypic heterogeneity of Dent's disease describes diverse symptoms including phosphaturia, glycosuria, uricosuria, kaliuresis, impaired urinary acidification, and hypophosphatemic rickets [8–10]. This disease is linked to mutations in either the CLCN5 (Dent's disease 1) or OCLR1 (Dent's disease 2) gene located on chromosome Xp11.22 and Xq25 respectively, or with no mutations in either gene (Dent's disease 3) [9, 10]. The CLCN5 gene encodes a voltage-gated chloride antiporter localized in subapical endosomes of the proximal tubule and other parts of the nephron, impairment of which in Dent's disease 1 disturbs reabsorption of filtered proteins (β 2-microglobulin, transferrin, vitamin D, and retinol-binding protein), but also implicates other transport functions of the proximal tubule, which leads to renal glucose, calcium, phosphate, potassium, and magnesium wasting and polyuria [6, 7, 9, 10]. Under conditions of extremely fragile homeostasis, in patients with Dent's disease, any additional stress such as heat exhaustion may cause a severe electrolyte imbalance [11].

Tetany is a condition in which an abnormal serum electrolyte concentration such as hypocalcemia, hypomagnesemia, hypokalemia or alkalosis leads to increased neuronal excitability [1, 2]. Mild symptoms may include muscle cramps and paresthesia of hands and feet. In severe cases the patient may present with generalized muscle spasms, seizures, and myocardial dysfunction [1, 2]. Hypocalcemia is the best known cause of tetany; it can also cause cardiac disturbances and seizures [2]. Respiratory alkalosis and hypokalemia may also contribute to tetany. Alkalosis promotes the binding of calcium to albumin and can reduce the fraction of ionized calcium in the blood [12]. Hypokalemia can independently cause nerve irritability [13]. Hypomagnesemia may re-

duce the threshold for hypocalcemia to cause tetany [2]. Low magnesium levels increase renal potassium wasting, which may potentiate hypokalemia [14]. Most case reports of tetany in the literature include some combination of the above metabolic derangements [3–5].

Dent's disease comprises a whole spectrum of disturbances that can cause tetany [7, 10]. In our patient, in a condition of hypocalcemia and hypomagnesemia muscle cramps occurred. It is also possible that, due to hypokalemia, the boy developed nontraumatic nonexertional rhabdomyolysis prior to the presence of tetany [15–17]. The release of intracellular phosphorus from myocytes could have contributed to the acute hypocalcemia by binding serum calcium, which ended with tetany [16, 17]. High phosphorus concentration and mildly elevated CK on admission supported this theory. Persistent muscle rigidity generated pain and swelling. The child was hyperventilating due to soreness and anxiety. Hyperventilation caused alkalosis and a decrease in the ionized fraction of serum calcium, which finally evoked a generalized tetanic spasm [1, 12]. Tetanic spasm precipitated exertional rhabdomyolysis, a potentially fatal syndrome in which uncontrolled skeletal muscle hypermetabolism generated hyperthermia and muscle breakdown [15–17]. Finally, acute hyperthermia evoked febrile seizures. Due to the severity of the child's presentation and combination of clinical symptoms, the differential diagnosis included sepsis, meningitis, malignant hyperthermia, and serotonin syndrome. Although sepsis and/or meningitis were considered due to the child's fever, tachycardia, tachypnoea, opisthotonos posturing, and seizures, CRP was invariably negative and, on admission, there was no evidence of infection. The patient's hyperthermia could have raised the suspicion for malignant hyperthermia or serotonin syndrome, but the boy had no exposure to neuroleptic or serotonergic medications [18, 19].

CONCLUSIONS

The patient's alarming clinical presentation was a consequence of multiple electrolyte aberrations leading to life-threatening tetany combined with rhabdomyolysis. This case emphasizes the need to consider tetany as a diagnosis in a patient with unstable vital signs and diffuse muscle cramps, especially in those with pre-existing medical conditions contributing to electrolyte disturbances.

DISCLOSURE

The authors declare no conflict of interest.

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