Hypocalcemia – a Diagnostic Challenge

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Abstract
Objective – The authors aimed to describe a case of a rare etiology of hypocalcemia in a child, and highlight the importance of clinical suspicion for prompt diagnosis of calcium disturbances.

Case Report – The 5-year-old male child did not have any symptoms up to 4 days prior to presentation, but fever and a rash, followed by acute onset of seizures prompted presentation to the pediatric emergency department. Clinical records revealed that he had been found to have left hand lesions, global developmental delay, and height below the 3th percentile in a previous assessment. The combination of severe hypocalcemia, hyperphosphatemia, increased PTH levels, and identification of a mutation on a GNAS genetic test, confirmed the diagnosis of type Ia pseudohypoparathyroidism (PHP Ia).

Conclusion – In this case report, the combination of clinical and biochemical findings led to the diagnosis. Hence, it is important to consider the many possible etiologies of seizures and hypocalcemia, taking into account the clues provided by clinical history and physical examination.

Key Words: Hypocalcemia • Seizures • Pseudohypoparathyroidism • Genetic Diseases.

Introduction

Calcium is essential to cell function and is regulated by several mechanisms, namely the parathyroid hormone (PTH), vitamin D and calcium-sensing receptors. Under normal circumstances, calcium levels remain within the narrow range of 2.1–2.6 mmol/L (ionized calcium 1.2–1.3 mmol/L) (1, 2). Epidemiological data regarding pediatric hypocalcemia are limited. Among infants and children, hypocalcemia is often found in admissions to intensive care units, usually related to acute illness and stress. However, there are other causes that must be taken into consideration, and in consequence the diagnosis must follow a systematic approach. Chronic causes of hypocalcemia may be divided into two main groups: disorders involving PTH, and those related to vitamin D (1, 2).

Clinical manifestations depend on age, the underlying cause, and the duration of disease progression. Symptoms may be intermittent and usually appear when ionized calcium levels fall below 0.63mmol/l (2.5 mg/dl). A tetanic crisis (carpopedal spasm, laryngospasm and focal/generalized seizures) and a wide spectrum of neuromuscular symptoms (localized tremors, hyperreflexia, paresthesia, cramps and muscle contractures) are most common (2). Any patient with symptomatic hypocalcemia should receive intravenous calcium. Seizures do not usually respond to anticonvulsant medication, but resolve when calcium levels normalize. When possible, the primary cause should be treated (3).

In this article, the authors aim to report a case of a rare etiology of hypocalcemia in a child, and highlight the importance of clinical suspicion for diagnosis of calcium imbalances.
Case Report

This case report describes a 5-year-old male child. He was delivered at 37 weeks of gestation by normal vaginal delivery, with appropriate weight and length for gestational age. Laboratory tests and antenatal scans were unremarkable. The newborn physical examination and neonatal screening tests (metabolic and endocrine disorders, hearing loss and critical congenital heart disease screening tests) were normal. Supplementation with cholecalciferol was administered during the first year of life.

The child was asymptomatic until 4 days prior to presentation, but fever and rash, followed by acute onset of seizures prompted presentation to the pediatric emergency department. This episode was characterized by hypertonia, ocular retroversion and generalized tremor, lasting approximately 10 seconds.

Clinical records revealed he had had follow-up appointments at the Orthopedics Outpatient Clinic due to the presence of left hand lesions (Fig. 1). Previous computerized tomography revealed calcinosis of the soft tissues, including the skin, of non-specific etiology, but his bones and joints were spared. He also had regular follow-up in speech and occupational therapy for global developmental delay. His weight was stable between the 15th and 50th percentile. His height fell below the 3rd percentile in a previous assessment (according to the World Health Organization curve). On physical examination, he was alert. He had a macular exanthema on his trunk and cervical region. The remaining examination was unremarkable.

Laboratory test results showed significant to severe hypocalcemia (total calcium 1.35 mmol/L and ionized calcium 0.49 mmol/L; normal range (NR): total calcium 2.1–2.6 mmol/L, ionized calcium 1.2–1.3 mmol/L) and hyperphosphatemia (phosphorus 2.45 mmol/L; NR 1.4–2.1 mmol/L). Blood count, C-reactive protein and sodium, potassium and magnesium levels were normal. An electrocardiogram showed a sinus rhythm and normal QT interval (0.435 seconds adjusted to age and gender). 25-hydroxyvitamin D levels were low (5.9 ng/mL; NR 20–40 ng/mL) and PTH markedly increased (648.7 pg/mL; NR 15–65 pg/mL). The patient was admitted for further care and etiological investigation.

The combination of severe hypocalcemia, hyperphosphatemia and increased PTH levels raised the suspicion of pseudohypoparathyroidism associated with vitamin D deficiency. Eye examination detected the presence of subcapsular cataracts. Chest and upper and lower limb X-rays were performed, showing no evidence of rachitic costal rosary or enlargement of bone epiphyses, that are associated with rickets. Cranial magnetic resonance imaging showed no calcifications. Blood tests assessing endocrine function of insulin growth factor type 1 (IGF-1) and thyroid-stimulating hormone (TSH) were also performed. IGF-1 was normal and thyroid function showed a normal free thyroxine level (FT4; 0.74 ng/dL; NR 0.65–2.65 ng/dL) with a slight increase in TSH (7.93 uUI/mL; NR 0.7–5.4 uUI/mL) and for that reason surveillance was maintained. A GNAS genetic test identified a heterozygosity mutation, which, combined with the biochemical and phenotypic alterations, confirmed the diagnosis of type Ia pseudohypoparathyroidism.

![Subcutaneous calcifications on the left hand.](Fig. 1)
The parents’ genetic test was negative for this mutation.

After correction of calcium levels (with intravenous calcium gluconate bolus) and supplementation with 25-hydroxyvitamin D, there were no more convulsive episodes. He was discharged after 19 days of hospitalization with long-term oral treatment for PHP, including calcium (calcium carbonate, 50 mg/kg/day), calcitriol (0.06 μg/kg/day) and cholecalciferol (1330 UI/day). During the 2 years of follow-up, hypocalcemia did not recur, and doses of oral therapy were progressively reduced. Thyroid function normalized in subsequent assessments, and IGF-1 remained normal. School performance improved. His height profile improved, and is currently on the 15th percentile, and his weight progressively increased, reaching obesity (body mass index z-score of 2.07).

Discussion

Pseudohypoparathyroidism (PHP) is a rare cause of hypocalcemia, with a prevalence of 3.4 per 1 million in a Japanese study, and 0.79 per 100,000 according to the Orphanet Report Series in November 2008. This is based on a diagnosis of exclusion and can be confirmed by genetic testing (4). PHP includes an heterogeneous group of diseases characterized by resistance of target organs to PTH, resulting in hypocalcemia, hyperphosphatemia and increased PTH without vitamin D deficiency, however, both can coexist. It can be classified into 4 types (Ia, Ib, Ic, II) according to phenotypic findings, biochemical alterations and genetic mechanisms (5, 6).

The main PHP subtypes (Ia and Ib) are due to inactivating mutations in the GNAS gene that encodes the alpha subunit of the Gs protein. Patients with PHP Ia have obesity, multiple hormone resistance, and Albright’s hereditary osteodystrophy (AHO), a congenital syndrome with one or more of the following clinical features: short stature, brachydactyly, subcutaneous ossifications, facial changes and developmental delay. On the other hand, patients with PHP Ib generally do not have AHO. In PHP Ic, patients clinically mimic PHP Ia, but no Gs protein defect is found (7). Diagnosis is often made when the patient develops symptoms due to hypocalcemia, usually during periods of rapid growth, which may or may not be associated with vitamin D deficiency (8).

In this case, the presence of fever and exanthema preceding seizures pointed to an infectious cause. The extensive etiological study initially carried out, namely the assessment of electrolyte imbalance, allowed us promptly to establish initial differential diagnoses. Therefore, it is essential to rule out all other possible causes of seizures, even when the etiology seems obvious. PTH and phosphorus levels, associated with subcutaneous calcifications and delayed psychomotor development, are essential for the diagnosis.

PHP Ia can also present with hormonal resistance, such as THS and IGF-1, justified by the expression of GNAS in the thyroid, gonads and pituitary, which implies monitoring the levels of these hormones.

Regarding thyroid function, patients may have increased TSH levels, with normal or slightly reduced thyroid hormones, or congenital hypothyroidism, since an increased TSH level may be present at birth and be detected in neonatal screening. In this case, elevated TSH and normal FT4 levels were detected initially. IGF-1 levels were normal, but in the lower limit of the normal range (70 ng/mL, NR 49-231ng/mL). Finally, resistance to PTH usually develops during childhood (8).

A GNAS genetic study identified a heterozigous pathogenic mutation with a c.2277 del variant. The parents’ genetic test did not identify any mutation, so it was assumed that this was a new mutation, as has already been described (7). Treatment of PTH resistance is similar to other forms of hypoparathyroidism, and consists of oral supplements of calcium and active vitamin D (e.g., calcitriol). There is no specific treatment for the various features of AHO, and it requires multidisciplinary follow-up. Additional endocrine disorders, such as hypothyroidism, hypogonadism and growth hormone deficiency, should be investigated and treated.

In this case report we show how the combination of clinical and biochemical findings led to the
diagnosis of AHO. Hence, it is important to consider the many possible etiologies of seizures and hypocalcemia, taking into account the clues provided by anamnensis and physical examination.

Conflicts of Interest Statement
The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.
Informed consent was obtained from the parents of the patient for publication of the case report.

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