Case Report

Pseudohypoparathyroidism presenting with seizures: a case report and literature review

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SUMMARY
Symptomatic hypocalcemia is frequently encountered in the Emergency Department, necessitating admission. It has a variety of underlying etiologies, with hypoparathyroidism and vitamin D deficiency being the most common. However, rarer etiologies such as pseudohypoparathyroidism, as was present in the current case, should not be overlooked. Reported here is a case of a young female patient presenting with generalized tonic clonic seizures. Electrocardiography revealed a prolonged QT interval which pointed towards a metabolic cause, and this was confirmed by laboratory results which indicated a low calcium level. A parathyroid pathology was obvious as the phosphate level was elevated. Pseudohypoparathyroidism, rather than hypoparathyroidism, was identified since the parathyroid hormone level was elevated. Other relevant differential diagnoses were excluded. The patient was treated with intravenous calcium initially and given regular oral calcium, calcitriol, and sevelamer.

Keywords
hypocalcemia, pseudohypoparathyroidism, seizures

1. Introduction
Symptomatic hypocalcemia is frequently encountered in the Emergency Department, necessitating admission. It has a variety of underlying etiologies, with vitamin D deficiency being the most common (1). Pseudohypoparathyroidism (PHP) is an uncommon cause of hypocalcemia attributed to parathyroid hormone (PTH) resistance, with a prevalence of 3.4 per 1 million according to one Japanese study (2) and 0.79 per 100,000 according to the Orphanet Report Series, November 2008 (3). PHP is diagnosed based on the exclusion of other differential diagnoses, and it can be confirmed by genetic analysis (3).

2. Case Report
A 34-year-old woman, with a medical history of three seizures in the past for which she did not seek medical treatment, presented with generalized body weakness and a subjective fever for two days prior. While being assessed in the Emergency Department, she developed generalized tonic clonic seizures that resolved spontaneously, followed by post-ictal confusion.

On examination, vital signs were within normal limits. A systemic physical exam was unremarkable, including a neurological and a musculoskeletal examination. Laboratory results (Table 1) revealed a very low corrected serum calcium level of 1.2 mmol/L [2.1-2.6 mmol/L] combined with a high serum phosphorus level of 1.86 mmol/L [0.87-1.45 mmol/L] in the absence of hypomagnesaemia (serum magnesium of 0.72 mmol/L [0.66-1.07 mmol/L]). These biochemical changes were combined with a high serum intact PTH of 108 pg/mL [15-65 pg/mL]. All of these findings are indicative of PHP. The low serum vitamin D level of 15 ng/mL [30-80 ng/mL] potentially added to the already low serum calcium level. Other pertinent laboratory abnormalities that suggested recent seizure activity were a high white blood cell count of 16.4 × 10³/µL [4-10 × 10³/µL] and elevated serum creatine kinase of 426 U/L [26-192 U/L].

Chest x-ray (CXR) revealed clear costophrenic angles and lung zones. The mediastinum and hila appeared normal. Cardiac size was within normal limits. Electrocardiography (ECG) (Figure 1) revealed a sinus rhythm with a prolonged QT interval (a corrected QT interval of 552), suggestive of hypocalcemia. A plain CT scan of the head (Figure 2) was unusual in that it revealed extensive bilateral symmetrical calcifications of basal ganglia, cerebellar dentate nuclei, and subcortical white matter. These calcium deposits substantiate the biochemical changes caused by PHP as mentioned above. Magnetic resonance imaging...
(MRI) of the head (Figure 3) confirmed the findings from the head CT scan as imaging revealed bilaterally symmetric calcifications involving the dentate nuclei, basal ganglia, and subcortical white matter regions with no abnormal soft tissue component, perifocal oedema, or mass effect. Electroencephalography (EEG) revealed bilateral frontal cerebral dysfunction but was otherwise unremarkable.

Course of treatment and outpatient follow-up:
The patient was given regular intravenous calcium gluconate, regular oral calcium carbonate, calcitriol, and sevelamer. She did not experience any further

Table 1. Laboratory results

| Laboratory results          | Patient values | Normal reference range |
|-----------------------------|----------------|------------------------|
| General hematology          |                |                        |
| White blood cell count (10^3/µL) | 16.4           | 4 - 10                 |
| Hemoglobin (g/dL)           | 11.6           | 12 - 15                |
| MCV (fl)                    | 75.8           | 83 - 101               |
| Platelet count (10^3/µL)    | 273            | 150 - 400              |
| General chemistry           |                |                        |
| Urea (mmol/L)               | 3.5            | 2.76 - 8.07            |
| Creatinine (µmol/L)         | 48             | 53 - 97                |
| Sodium (mmol/L)             | 137            | 135 - 145              |
| Potassium (mmol/L)          | 3.1            | 3.6 - 5.1              |
| Chloride (mmol/L)           | 92             | 96 - 110               |
| Magnesium (mmol/L)          | 0.72           | 0.66 - 1.07            |
| Glucose (mmol/L)            | 6.4            | 3.3 - 5.5              |
| C-reactive protein (mg/L)   | < 5            | 0 - 5                  |
| Bicarbonate (mmol/L)        | 17.5           | 24 - 30                |
| Albumin (g/L)               | 47             | 35 - 50                |
| Corrected calcium (mmol/L)  | 1.2 Low        | 2.1 - 2.6              |
| Phosphorus (mmol/L)         | 1.86 High      | 0.87 - 1.45            |
| Alkaline phosphatase (U/L)  | 76             | 45 - 129               |
| Creatine kinase (U/L)       | 426            | 26 - 192               |
| Myoglobin (ng/mL)           | 48             | 25 - 58                |
| Urine chemistry             |                |                        |
| 24-hour calcium (mmol/24 hours) | 2.2           | 2.5 - 7.5              |
| Endocrinology               |                |                        |
| Parathyroid hormone (pg/mL) | 108 High       | 15 - 65                |
| Vitamin D (ng/mL)           | 15 Low         | 30 - 80                |
| Thyroid stimulating hormone (mIU/L) | 2.51       | 0.27 - 4.20           |
| Thyroxine (pmol/L)          | 12.1           | 12 - 22                |

*Urine cAMP was not done after PTH administration, as it was not available.

Figure 1. ECG. This ECG strip is showing sinus rhythm with prolonged QT interval (QTc 552).
mutations, or methylation (loss of function) near the GNAS locus on chromosome 20q 13.3 (Table 2) (5,6).

The latter normally mediates the action of G protein-coupled receptors via the transcription of a signaling protein called Gs alpha (7). PHP 1b involves a normal phenotype, which differentiates it from the other PHP 1 subtypes (PHP 1a and 1c) that have clinical features of Albright hereditary osteodystrophy (AHO); however, laboratory results, namely hypocalcemia, hyperphosphatemia, high serum PHP, and low urine cyclic adenosine 3', 5'-monophosphate (cAMP) post PTH administration, are the same (Table 2). A high PTH level is usually apparent in childhood at the age of 2-3, and hypocalcemia is mostly symptomatic in adolescence before the age of 20 (7,8). Incidental PHP has also been reported in the literature based on the presence of asymptomatic hypocalcemia as part of a preoperative work-up (9). Later, genetic testing confirmed the diagnosis of PHP 1b. The inheritance of PHP 1b follows an autosomal dominant pattern, but sporadic cases of PHP 1b reported in the literature indicate that other exogenous and environmental factors may be in play (10-12). Based on the previous

3. Discussion

PTH plays a major role in keeping the body's calcium levels in check. When the serum calcium level is low, the parathyroid glands send signals to bone and the kidneys to raise serum calcium levels and maintain calcium homeostasis. These processes involve bone resorption, calcium absorption in the distal tubules, and vitamin D production via 1 alpha hydroxylase enzyme activation in the kidneys. Active vitamin D (1,25 dihydroxy vitamin D) will enhance intestinal absorption of calcium. When calcium levels are above normal, in contrast, the parathyroid glands are suppressed (4).

PHP, in simple terms, is hypoparathyroidism despite elevated PTH levels. This is due to the fact that the peripheral organs are unresponsive to the action of PTH. PHP is subdivided into different subtypes with different genetic mutations that include deletions, small

seizures during hospitalization. In a post-discharge visit 1 week later, the patient was asymptomatic, corrected calcium was 1.89 mmol/L, and PTH was still high at 106 pg/mL.
of renal receptors to the action of PTH. If this persists secondary hyperparathyroidism due to the resistance left untreated. This is attributable to the accompanying PHP can cause serious skeletal complications if beyond the basal ganglia, as were present in the current accumulation may play a major role in the formation There is some evidence that extracellular phosphate Such extensive calculations might be asymptomatic or have been likened to seizures or more severe neurological manifestations such as parkinsonism and impaired mental function (19). Other rarer causes of basal ganglia calculations include Down's syndrome, Fahr's syndrome, tuberous sclerosis, and Cockayne syndrome (22).

PHP can cause serious skeletal complications if left untreated. This is attributable to the accompanying secondary hyperparathyroidism due to the resistance of renal receptors to the action of PTH. If this persists long enough, it can reduce bone density, and mainly that of cancellous bones, via accelerated bone turnover (23). Elevated serum alkaline phosphatase (ALP) can be a marker of PHP-related bone disease that warrants a thorough skeletal survey (24).

The current patient presented with seizures, and this can be explained by the effects of PHP; namely hypocalcemia and widespread cortical and basal ganglia calculations as were mentioned earlier. In addition, vitamin D deficiency reduced the patient's calcium level even lower and might have contributed to clinically evident seizures. Normal serum ALP precluded the need for a detailed skeletal survey (Table 1). In conclusion, PHP is a rare cause of hypocalcemia that should be considered among differential diagnoses. The two aspects that distinguish the current case are the late presentation of the disease and the potentially preventable bone disease that may occur if the diagnosis of PHP is missed.

Table 2. Characteristics of PHP subtypes (5,6)

| Items                  | PHP 1a                                      | PHP 1b                                      | PHP 1c                                      | PHP II                                     | PPHP                                      |
|------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|--------------------------------------------|-------------------------------------------|
| Phenotype              | AHO + Hormonal resistance (PTH, TSH, Gn, GHRH) | Hormonal resistance (PTH +/− TSH)           | AHO + Hormonal resistance (PTH, TSH, Gn)   | No hormonal resistance                     | No hormonal resistance                     |
| Main molecular determinants | Maternal LoF in GNAS                       | Deletions in GNAS                           | No mutations                               | Few mutations reported                     | Paternal LoF in GNAS                       |
| Serum Ca               | Low                                         | Low                                         | Low                                         | Low                                        | Normal                                    |
| Serum P                | High                                        | High                                        | High                                        | High                                       | Normal                                    |
| Serum PTH              | High                                        | High                                        | High                                        | High                                       | Normal                                    |
| Urine cAMP post PTH    | Low                                         | Low                                         | Low                                         | Normal                                     | Normal                                    |

AHO, Albright hereditary osteodystrophy; Ca, calcium; cAMP, cyclic adenosine 3′, 5′-monophosphate; GHRH, growth hormone-releasing hormone; Gn, gonadotropin; LoF, loss of function; P, phosphorus; PHP, pseudohypoparathyroidism; PPHP, pseudo-pseudohypoparathyroidism; PTH, parathyroid hormone; TSH, thyroid stimulating hormone.

Table 3. Studies reporting late PHP 1b presentation

| Author, year (Ref.) | Age, gender | Patient characteristics | Clinical manifestations | Vitamin D level | Brain imaging |
|---------------------|-------------|-------------------------|-------------------------|-----------------|---------------|
| Iglesias et al., 2017 (8) | 65 year-old, female | Normal phenotype | Asymptomatic | Normal | Not done |
| Chong et al., 2013 (13) | 46 year-old, female | Normal phenotype | Symptomatic | Low | Not done |
| Chale-Matsau et al., 2018 (14) | 33 year-old, female | Normal phenotype | Symptomatic | Normal | Normal |
| Aggarwal et al., 2016 (15) | 23 year-old, female | Normal phenotype | Symptomatic | Normal | Normal |
| Van Rooijen et al., 2012 (16) | 18 year-old, female | Normal phenotype | Symptomatic | Low | Not done |
| Zeniya et al., 2014 (17) | 22 year-old, female | AHO phenotype | Symptomatic | Normal | Bilateral calcifications |
| Garg et al., 2011 (18) | 34 year-old, male | Normal phenotype | Symptomatic | Normal | Normal |

AHO, Albright hereditary osteodystrophy; PHP, pseudohypoparathyroidism.

Discussion of PHP

While there are numerous case reports addressing PHP 1b in the pediatric population, there are few PHP 1b cases involving a late presentation. Moreover, most of the published articles focus on the genetic mutations of the disease rather than the clinical aspects and disease implications. A review of the literature identified 7 relevant case reports that share some similarities as well as differences with the current case (Table 3) (8,13-18).

Hypoparathyroidism and PHP are the most common causes of basal ganglia calculations. Together, they account for more than two-thirds of cases (19). There is some evidence that extracellular phosphate accumulation may play a major role in the formation of these calculations (20). Widespread calculations beyond the basal ganglia, as were present in the current case, are uncommon in PHP (21). Such extensive calculations might be asymptomatic or have been likened to seizures or more severe neurological manifestations such as parkinsonism and impaired mental function (19). Other rarer causes of basal ganglia calculations include Down's syndrome, Fahr's syndrome, tuberous sclerosis, and Cockayne syndrome (22).

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