Case Report

Severe hypocalcemia due to hypoparathyroidism associated with HIV: A case report

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ARTICLE INFO

Keywords:
HIV
Human immunodeficiency virus
Hypocalcemia
Hypoparathyroidism
Vitamin D

ABSTRACT

Calcemia is not routinely determined among people living with human immunodeficiency virus (HIV). In people living with HIV, the most frequent electrolyte disturbance is hyponatremia and since symptoms of hypocalcemia often are unspecific, calcium is typically measured with some delay. Hypocalcemia in people living with HIV is mainly due to indirect causes such as vitamin D deficiency, renal failure, or drug related. However, in rare cases direct viral involvement of the parathyroid glands has been reported. We present a case of a 67-year-old male living with HIV who presented at an emergency department with symptomatic severe hypocalcemia, without any previous history of neck surgery, radiation therapy or large infections in the head and neck area. At the time of admission serum concentrations were for ionized calcium 0.98 mmol/L (ref. 1.18–1.32 mmol/L) and PTH 1.3 mmol/L (ref. 2.0–8.5 pmol/L). Vitamin D status was sufficient with 25OHD at 73 nmol/L to 112 nmol/L (ref. 60–160 nmol/L) from 2016 through 2019. The patient was diagnosed with primary hypoparathyroidism and was treated with Alphacalcidol 0.5 μg × 1/daily, calcium 500 mg × 4 the first day followed by 400 mg × 2 and magnesium 360 mg × 3, which induced rapid clinical recovery with dissolvement of muscular pain and biochemical improvement. This case study suggests that further studies are needed to investigate the added value of routine monitoring for hypocalcemia as part of clinical follow-up of people living with HIV.

1. Introduction

Hypocalcemia can severely impair quality of life and has many putative causes. The most severe forms are often caused by hypoparathyroidism (Mannstadt et al., 2017). Acquired hypoparathyroidism is rare and typically a complication to total thyrodectomy or due to autoimmune hypoparathyroidism (Sandhu et al., 2018). Autoimmune hypoparathyroidism may in some cases be part of the autoimmune polyglandular syndrome (Eisenbarth and Gottlieb, 2004) or isolated hypoparathyroidism with anti-parathyroid gland or calcium sensing receptor (CaSR) antibodies (Blizzard et al., 1966). Among people living with human immunodeficiency virus (HIV) there has been a focus on hyponatremia that occurs often in these patients (Kuehn et al., 1999).

Calcium status is to the best of our knowledge not monitored regularly in most centers as disorders in calcium homeostasis are not a frequent finding in people living with HIV (PLWH). Nonetheless severe hypocalcemia has been reported to be induced by a direct destructive effect of the HIV virus on the parathyroid gland (Kuehn et al., 1999). However, the most common causes of hypocalcemia in PLWH are vitamin D deficiency and pharmacotherapy and not viral influence on parathyroid hormone (PTH) production (Sandhu et al., 2018). We report a case of a 67-year-old male suffering from severe symptomatic hypocalcemia most likely due to persistent HIV-induced hypoparathyroidism.

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https://doi.org/10.1016/j.bonr.2021.101119
Received 2 June 2021; Received in revised form 10 August 2021; Accepted 14 August 2021
Available online 20 August 2021
2. Case presentation

A 67-year-old male living with HIV for the past 20 years, presented at an emergency department with persistent muscular pain, dehydration and acute moderate renal failure following a period of prolonged nausea, vomiting and diarrhea. The patient had no fever. Previous medical history of importance included acute myocardial infarction, peripheral artery disease, hiatus hernia and esophagitis. There was no history of neck surgery, radiation therapy or large infections in the head and neck area. He denied having any symptoms of hypocalcemia during childhood, including cramps, fasciculations, muscle twitches or any family history of hypocalcemia, or other autoimmune diseases. His medication at the time of admission consisted of combined antiretroviral therapy (Efavirenz, Emtricitabine and Tenofovir), cardiovascular medication (Nitroglycerin, Acetylsalicylic acid, Rosuvastatin and Sildenafil) and analgesics (Tradalol). Tenofovir was paused during admission due to gastrointestinal symptoms and dehydration, while Efavirenz and Emtricitabine were continued as Tenofovir has previously been shown to exert a more potent effect on calcium homeostasis (Van Welsen et al., 2019). Tenofovir was reinstated at the time of discharge from the hospital without reemergence of the symptoms of hypocalcemia and no drop in serum calcium.

Due to the patient’s gastrointestinal symptoms, there were performed several tests to determine whether he had bacterial or viral gastroenteritis, but no positive tests were detected except for Streptococcus dysgalactiae in the urine, for which he was treated with Penicillin 1 million units × 4 for 3 days. It cannot be excluded that the gastrointestinal symptoms were adverse effects of the antiretroviral medication, but the symptoms passed during hospital admission. At the time of admission, the patient presented with massive muscular pain particularly in his lower extremities making it impossible for the patient to walk longer distances. Vital signs as well as biochemical infection markers such as total leukocyte count and CRP were all normal. However, the levels of ionized calcium were low at 0.98 mmol/L (ref. 1.18–1.32 mmol/L) (Table 1). Interestingly, the patient presented with chronic hypocalcemia, which was persistent at this low level since the first measurement of ionized calcium in 2016, in contrast to serum phosphate that remained near normal in most samples (Table 1). Unfortunately, the patient was diagnosed with primary hypoparathyroidism. Treatment with Alphacalcidol 0.5 μg × 1 daily, calcium 500 mg × 4 the first 24 h followed by 400 mg × 2, and magnesium 360 mg × 3 were initiated and induced a rapid clinical recovery with dissolution of muscular pain in addition to a biochemical improvement with an increase of ionized calcium to 1.0 and total calcium to 1.70 in January 2020 (Fig. 1). The patient was discharged fully mobilized four days after the diagnosis of hypoparathyroidism and treatment initiation. Follow-up in the endocrine outpatient clinic was initiated to exclude genetic or other hereditary reasons for hypoparathyroid hypocalcemia. Exon sequence test of calcium sensing receptor (CasR) – AP2S1 and GNA11 – revealed no mutations that could explain the phenotype. CT and parathyroid scintigraphy were without signs of cervical masses or pathology and a “24h-urine calcium and phosphate collection” was performed twice with normal calcium excretion. Following discharge and repeated visits in the clinic, the cause of hypoparathyroidism is still not verified. The patient had increased light chains of both kappa and lambda chains and underwent bone marrow biopsy that was normal, as well as a PET-CT scan revealing multiple costa fractures and PET negative sclerotic foci.

3. Discussion

Hypocalcemia is a relatively common condition that may be asymptomatic or, as reported here, a severe condition that hampers life quality and ultimately may be life-threatening (Hypocalcemia: diagnosis and treatment – endotext, 2020). The most frequent causes of hypocalcemia are related to disorders of vitamin D and/or PTH metabolism, particularly vitamin D and/or magnesium deficiency. Less frequent causes include rare inherited diseases, autoimmune or acquired conditions. Hypocalcemia is not recognized as a common problem following the spontaneous course of HIV-infections or as a result of the antiviral treatment. Most cases reporting low serum total calcium concentrations in PLWH were caused by hypoalbuminemia as ionized calcium was normal. Hypocalcemia as an adverse effect of antiviral therapy may predominantly be caused by Tenofovir that decreases bone mineral density, induces hypocalcemia and increases PTH. Alternatively, treatment of opportunistic infections with medications like Foscarnet that complex binds calcium or Ketoconazole that inhibit CYP-enzymes and thereby inhibits activation of vitamin D (Perazella and Brown, 1994). The mechanism of Tenofovir-associated hypophosphatemia is both renal Fanconi syndrome as well as an increase in FGF23. Recent studies have shown increased prevalence of hypocalcemia in PLWH due to a high prevalence of vitamin D deficiency (Moges et al., 2014; Kuehn et al., 1999).

Our patient had severe hypocalcemia with concomitant low serum PTH levels despite adequate vitamin D and magnesium levels, indicating that hypoparathyroidism was the underlying cause. The patient had no issues during childhood or early adulthood and no previous neck surgery, strongly supporting that the proposed hypoparathyroidism is acquired. Available case reports on direct HIV-caused hypoparathyroidism are sparse (Lehmann et al., 1994). However, one study did show decreasing PTH levels in PLWH, but the decline have not been related to a direct infection or infiltration of the parathyroid gland (Sandhu et al., 2018; Jaeger et al., 1994a). It is likely that the virus in some cases may infect the gland or more likely induce an immune response that leads to glandular destruction (Beltrán et al., 2003). One study showed expression of the CD4-molecule at the surface of parathyroid gland cells using a monoclonal antibody recognizing CD4, which enables direct binding and inhibition of the parathyroid gland by the HIV-infection (Helm et al., 1996). A possible direct link is supported by a study showing that 4/21 PLWH with low ionized calcium had normal serum PTH, which implies that the parathyroid glands may have a diminished response, which was supported by showing that the maximal secretion of PTH

| Table 1 | Blood sample overview of patient. |
|---------|----------------------------------|
| Reference interval | 05/2016 | 06/2017 | 06/2018 | 06/2019 | 12/2019 | 01/2020 |
| Ionized Ca (mmol/L) | (1.18–1.32) | 0.79 | 0.90 | 0.85 | 0.69 | 0.97 | 1.0 |
| PTH (pmol/L) | (2.0–8.5) | - | - | - | - | 1.3 | 1.5 |
| 25OHD (mmol/L) | (60–160) | 73 | 135 | 114 | 112 | 88 | - |
| Magnesium (mmol/L) | (0.71–0.94) | - | - | - | 0.64 | 0.63 | - |
| Phosphate (mmol/L) | (0.71–1.23) | 1.45 | 1.21 | 1.34 | 1.10 | 0.52 | 0.72 |
| eGFR | (≤90) | 73 | 73 | 75 | 59 | 58 | 49 |
| - not available. |
after EDTA-induced hypocalcaemia was reduced in patients with AIDS compared with HIV-negative controls (Jaeger et al., 1994b). The increased light immune chains are unexplained as the plasma cells in the bone marrow were normal, but a pathogenetic influence is possible as this would also affect the renal function. Irrespective of a direct or an indirect glandular destruction/inhibition – the initial treatment is the same, with either active vitamin D and calcium supplementation or recombinant PTH. In this case we supplemented the patient with Alpha-calciol and calcium that rapidly improved the symptoms. The patient gradually improved over the coming months.

The most frequent causes of hypocalcemia in PLWH are most likely similar to the risks for developing hypocalcemia in other patient populations particularly malnutrition, low vitamin D status or due to pharmacotherapy related to HIV or other infections, or as in our patient most likely due to the HIV-infection. We cannot provide any evidence for HIV infection of the gland or destruction of the gland secondary to the HIV infection as it could be due a yet unidentified autoimmune cause. However, the time of onset – the severity, the lack of timing with existing therapy and no other identifiable cause supports that HIV could be the etiology behind the acquired hypoparathyroidism. Irrespective of whether the HIV-infection is the direct cause of the calcium disorder, this case study outlines the importance of monitoring ionized calcium, vitamin D and PTH levels in PLWH.

4. Conclusion

While uncommon, HIV may induce primary hypoparathyroidism that may result in severe symptomatic hypocalcemia. This case study suggests that further studies are needed to investigate the added value of routine monitoring for hypocalcemia as part of clinical follow-up of people living with HIV.

Funding

This work was supported by Novo Nordisk Foundation, FSS, BII.

Consent

There has been obtained oral and written informed consent from the patient to publish this case report.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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