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LETTER TO THE EDITOR

Severe and treatment-resistant hypocalcemia in patient with bilateral COVID-19 pneumonia☆

Hipocalcemia severa y resistente al tratamiento en paciente con neumonía bilateral COVID-19

Dear Editor,

COVID-19 is a huge global health problem due to its high rate of transmission and its high morbidity and mortality rates. Among the numerous pathophysiological effects associated with the virus, endocrine and metabolic disorders stand out. However, the particular consequences on the calcium/phosphorus metabolism system are still not fully understood.

We present the case of a 76-year-old man admitted for bilateral pneumonia due to COVID-19. The patient had a history of hypertension and chronic hypocalcaemia of unclear cause, and was on regular treatment with enalapril 20 mg/day and oral supplements of calcium/vitamin D 600 mg/400 IU/day. His analysis records showed low total plasma calcium levels of around 7.5 mg/dl (range: 8.6–10.2) between 2015 and 2018, with no known cause, but no other analytical data in relation to calcium and phosphate metabolism.

When he arrived at the A&E department, his arterial blood gases were compatible with respiratory failure: pH 7.42 (range: 7.35–7.45), PCO_2 31 mmHg (range: 35–48), PaO_2 59 mmHg (range: 83–108), bicarbonate 20.1 mmol/l (range: 21–28) and lactate 1.5 (range: 0–1.3). The blood tests also showed total lymphocytes 0.83 (range: 1–4), ferritin 1147 ng/ml (range: 30–400), C-reactive protein 19 mg/dl (range: 0—0.5), D-dimer 5 μg/ml (range: 0.15—0.50) and calcium ion 3.24 mg/dl (range: 4.6–5.4), with no symptoms compatible with hypocalcaemia. Chest X-ray showed extensive bilateral consolidations with peripheral distribution and nasopharyngeal exudate was positive for COVID-19.

On admission, the patient was prescribed hydroxychloroquine 400 mg/12 h on the first day, then 200 mg/12 h, lopinavir/ritonavir 200/50 mg/2 tablets/12 h, azithromycin 500 mg/day, IV methylprednisolone 80 mg/day, low molecular weight heparin at a dose of 1 mg/kg, omeprazole 20 mg/day and his usual oral calcium supplement. Despite clinical and analytical improvement after starting treatment, the patient reported perioral and upper limb paraesthesia. The only other symptom he had was anorexia. He did not develop diarrhoea until 48 h after starting treatment with lopinavir/ritonavir. Urgent blood tests revealed total plasma calcium of 5.1 mg/dl, calcium corrected for albumin 6.14 mg/dl, plasma phosphorus 5.4 mg/dl (range: 2.5–4.5) and magnesium 2.42 mg/dl (range: 1.6–2.4). An urgent venous blood gas test showed calcium ion of 2.84 mg/dl, with normal acid-base metabolism parameters and lactate levels. A test for Trousseau's sign was performed with a positive result at 30 s. No changes on ECG were reported. Treatment was started with calcium gluconate at a dose of 225 mg of elemental calcium infused over 15 min, followed by continuous intravenous infusion at 2 mg/kg/h. The infusion had to be continued for 24 h due to the patient's persistently low blood calcium levels (calcium ion of 3.32 mg/dl in repeat test), until normal levels were finally achieved (calcium ion in blood gases 4.96 mg/dl), and treatment was changed to progressive oral supplementation up to 3 g of elemental calcium/day.

Despite the oral supplementation, the patient again developed severe symptomatic hypocalcaemia with calcium ion of 3.30 mg/dl, calcium corrected for albumin 6.48 mg/dl and hyperphosphataemia of 5.8 mg/dl, without hypomagnesaemia, requiring reintroduction of the calcium gluconate infusion. Tests were completed with PTH 23 pg/ml (range: 15–65), vitamin D 22 ng/ml (range: >30) and TSH 1.71 μU/ml (range: 0.27–4.20). It was decided to add calcitriol, initially at a dose of 0.25 μg/day, which had to be increased to 0.5 μg/day to finally achieve blood calcium levels in the safe range (calcium corrected for albumin 7.9 mg/dl) and normal phosphorus levels (3.9 mg/dl).

The presence of hypocalcaemia, hyperphosphataemia and inappropriately normal PTH for these hypocalcaemia values establishes the diagnosis of primary hypoparathyroidism. Pending completion of further tests, and in the absence of a history of irradiation or surgical interventions and other autoimmune diseases, a provisional diagnosis was made of idiopathic primary hypoparathyroidism.

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Although there are very few reports of hypocalcaemia during COVID-19 infection,[1,2] one of the main limitations of these studies has been the lack of complete analytical data due to variations in computer records between the different participating centres and, on occasions, insufficient data collected in centres with less infrastructure or specialisation. However, it has been described as a frequent complication in patients with similar viral infections, such as severe acute respiratory syndrome (SARS), where up to 70% of patients were affected while in hospital,[3] and Ebola virus disease, in which 75% were affected,[4] but without clarifying the mechanism by which these viruses may predispose patients to develop hypocalcaemia. In the case of SARS-CoV, the virus enters the cell by an endosomal pathway, binding a protein to ACE2, and for this to take place ion channels, including calcium, play an important role.[5] In the case of COVID-19, a case was recently described of bilateral myoclonus in the extremities secondary to hypocalcaemia in a patient with COVID-19.[6] In this same publication, they describe electrolyte imbalances, including hypocalcaemia, as being common in their patient cohort (7%), although not severe.[6] However, they do not specify whether blood calcium levels are corrected for albumin.

One possible cause of hypocalcaemia could be treatment with high-dose methylprednisolone, which is known to negatively affect both intestinal absorption of calcium[7] and its reabsorption in the renal tubule,[8] and could lead to long-term calcium deficiency. However, a recent study showed no decrease in calcium levels in patients with COVID-19 treated with glucocorticoids.[9] Proton pump inhibitors are also known to reduce intestinal calcium absorption.[10] Although these causes alone do not seem to explain the development of hypocalcaemia, they may contribute to triggering the crisis and making it difficult to correct with treatment in patients with underlying primary hypoparathyroidism. Additionally, we have to remember that symptoms such as anorexia and diarrhoea are common in patients with COVID-19, attributable both to the viral infection and treatment with antiretrovirals or hydroxychloroquine, and can consequently contribute to fluid-electrolytic imbalance.

In summary, COVID-19 can cause a treatment-resistant hypocalcaemia crisis in patients with underlying calcium and phosphorus metabolism disorders, as in our case of a probable asymptomatic hypoparathyroidism previously controlled exclusively with low doses of oral calcium/vitamin D supplements. We should therefore pay greater attention to alterations in calcium/phosphorus metabolism in patients with COVID-19 and monitor calcium levels more closely, particularly in those with a previous diagnosis of hypocalcaemia, in order to avoid a worsening of the condition and establish appropriate treatment at an early stage.

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