Hypercalcemia in children: three cases report with unusual clinical presentations

Hipercalcemia em crianças: relato de três casos com apresentações clínicas incomuns

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Abstract

Hypercalcemia is a rare condition in childhood; the most common causes are primary hyperparathyroidism, malignancy, prolonged immobilisation, thyrotoxicosis, thiazide diuretic, supplements containing calcium, milk-alkali syndrome, vitamin D intoxication, infections and idiopathic. We present three cases of severe hypercalcemia of unusual causes in children. The first patient had high fever, poor general condition, weight loss and myalgia. Extensive preliminary investigation did not define the etiology, but a review of medical history revealed prolonged contact with pet bird and a positive serology for Chlamydia confirmed the diagnosis of psittacosis. The second patient had generalized lymphadenopathy and hepatosplenomegaly with fever a month ago. Paracoccidioides brasiliensis was identified in myelogram; the patient showed partial improvement with the use of co-trimoxazole, with subsequent emergence of multiple osteolytic lesions. A smear of gastric lavage was positive for Mycobacterium tuberculosis and the patient was treated with rifampicin, isoniazid, ethambutol and pyrazinamide, with improvement of clinical condition. The third patient was treated by hypercalciuria and idiopathic hypomagnesiuria with daily use of cholecalciferol; the patient had a two quilograms of weight loss in the past two months. No cause of hypercalcemia could be detected in laboratory workout. The capsules of cholecalciferol were analyzed and presented an amount of 832,000 IU of vitamin D per capsule. Acute hypercalcemia in childhood may be due to exogenous vitamin D intoxication, as well as infectious causes. The possible causal relationship between psittacosis and occurrence of hypercalcemia alert to the need for detailed investigation of the epidemiological antecedents.

Keywords: hypercalcemia; infection; psittacosis; vitamin D.

Resumo

A hipercalcemia é uma condição pouco comum na infância; dentre as causas mais comuns destacam-se hiperparatireoidismo primário, neoplasia, imobilização prolongada, tireotoxicose, diurético tiazídico, suplementos contendo cálcio, síndrome leite-álcali, intoxicação por vitamina D, infecções e causa idiopática. Apresentamos três casos de hipercalcemia grave por causas incomuns em crianças. O primeiro paciente tinha história de febre alta acompanhada de queda do estado geral, emagrecimento e mialgia. Extensa investigação preliminar não definiu a etiologia, porém uma revisão da história clínica revelou contato prolongado com ave de estimação e uma sorologia positiva para clamídia confirmou o diagnóstico de psitacose. O segundo paciente apresentava adenomegalia generalizada e hepatoesplenomegalia acompanhadas de febre por um mês, tendo sido identificado *Paracoccidioides brasiliensis* no mielograma; o paciente apresentou melhora parcial com uso de sulfametoxazol+trimetoprima, com posterior surgimento de múltiplas lesões osteolíticas. Uma baciloscopia do lavado gástrico foi positiva para *Mycobacterium tuberculosis*, tratado com rifampicina, isoniazida, pirazinamida e etambutol, com boa evolução. O terceiro paciente já era acompanhado por hipercalciúria e hipomagnesiúria idiopáticas e fazia uso diário de colecalciferol; perdeu dois quilogramas nos últimos dois meses. Nenhuma causa de hipercalcemia pôde ser detectada nos exames laboratoriais. As cápsulas de colecalciferol foram analisadas e encontrou-se uma quantidade de 832.000 UI de vitamina D. A hipercalcemia aguda na infância pode ser decorrente de intoxicação exógena por vitamina D, bem como de causas infecciosas. A possível relação causal entre psitacose e ocorrência da hipercalcemia alerta para a necessidade de investigação detalhada dos antecedentes epidemiológicos.

Palavras-chave: hipercalcemia; infecção; psitacose; vitamina D.

Introduction

Hypercalcemia is defined as serum total calcium (TCa) > 11 mg/dL or ionic Ca (iCa) > 1.4 mmol/L. TCa serum levels > 14mg/dL or > 3.5 mmol/L characterizes severe hypercalcemia and requires immediate care.[1-3] The clinical manifestations and complications of hypercalcemia are weakness, fatigue, abdominal pain, vomiting, constipation, lethargy, coma, ventricular fibrillation, polyuria, nocturia, dehydration, and acute renal injury. When hypercalcemia is persistent, it can lead to renal lithiasis, nephrocalcinosis and soft tissues calcification.[4]

It is an uncommon condition in children and the most prevalent causes include: primary hyperparathyroidism, neoplasia, prolonged immobilization, thyrotoxicosis, thiazide diuretics, supplements containing calcium, milk-alkali syndrome, vitamin-D intoxication, hypercalcemia associated with infections, and idiopathic causes.[3]

We present three cases of severe hypercalcemia of uncommon causes in children.

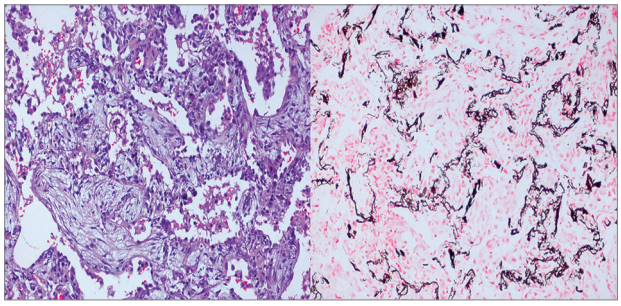
Case report

Case 1: hypercalcemia and pet

G.S.M., male, 6 years, white, previously healthy. Two weeks ago, presented with episodes of high fever lasting for 3 days, with no apparent cause. He evolved with a drop in general health, vomiting, myalgia and weight loss of 3 kg. He was taken to the emergency room, then being dehydrated and with abdominal pains. Laboratory tests showed iCa = 2.8 mmol/L; K = 2.7 mEq/L; Mg = 1.0 mEq/L; creatinine = 1.49 mg/dL; urea = 82 mg/dL; uric acid = 8.40 mg/dL; hemoglobin = 12 g/dL, leukocytes = 40,370/mm^3 (segmented = 33,870/mm^3; lymphocytes = 3,670/mm^3; monocytes = 1.930/mm^3) and platelets = 616,000/mm^3; LDH = 248 U/L; Albumin = 3.10 g/dL. Normal chest radiograph. PTH = 8.10 pg/mL; Vitamin- D = 17.0 ng/mL.

His hypercalcemia was refractory to hydration and furosemide (up to 3 mg/kg/day). He was treated with pamidronate disodium 0.5 mg/kg, with good response after 7 days (TCa = 9.1 mg/dL). During the investigation, we found a bilateral increase in renal echogenicity attributed to nephrocalcinosis due to hypercalciuria. Skeleton X-rays revealed no lytic lesions and the bone marrow biopsy was normal. Bone scintigraphy revealed areas of diffuse heterotopic calcification in the lungs and stomach. Chest CT showed areas suggesting metastatic calcification and interstitial fibrosis, confirmed later by lung biopsy (Figure 1).

Figure 1. Left (40x magnification), hematoxylin-eosin staining: important interstitial thickening by cells with clear cytoplasm, associated with hyperplasia of type-2 pneumocytes and some calcification foci. Right side (40x magnification), von Kossa staining: calcification in most alveolar septa. Upon immunohistochemistry, extensive recent interstitial fibrosis.



Serologies for cytomegalovirus, hepatitis B and C, Epstein-Barr, syphilis, toxoplasmosis, rubella, HIV and HTLV 1 and 2 were negative. The patient persisted with increased counts of total leukocytes and neutrophils. The medical interview reassessment showed prolonged contact with Nymphicus hollandicus (calopsita).

Serologies for Mycoplasma pneumoniae and Chlamydia trachomatis presented positive IgM titers. He was treated with azithromycin for 7 days, with a new calcium elevation of in this period (TCa = 14.5 mg/dL); We chose to change the antibiotic to doxycycline for 21 days, as empiric treatment for psittacosis, with excellent clinical response and normalization of calcium levels. Subsequently, there was serological confirmation of acute Chlamydia psittaci infection.

Case 2: fever, anemia and then, hyperalcemia

J.V.S., male, 6 years old, white, with high fever for 1 month, developed increased abdominal volume and skin lesions. Upon examination, he was pale and feverish, with cervical and axillary lymph node enlargement (1.0-1.5 cm, mobile), hepatosplenomegaly, and varicelliform skin lesions on the face and trunk. Laboratory tests showed hemoglobin = 6.8 g/dL; platelets = 102,000/mm^3; leukocytes = 6.060/mm^3; urea = 27mg/dL; creatinine = 0.48 mg/dL; alkaline phosphatase = 429 IU/mL and albumin = 2.2 g/dL. HIV serology was negative. Chest X-ray: peri-hilar condensation and absence of bone changes.

The myelogram ruled out leukemia, but the mycological examination identified Paracoccidioides brasilienses. The patient was started on sulfamethoxazole + trimethoprim (8 mg/kg/day). After 7 days, he progressed to leukopenia (2,950/mm^3) and thrombocytopenia (48,000/mm^3), associated with amphotericin B deoxycholate 1 mg/kg/d. He developed arthralgia, difficulty to walk, hypoactivity and dehydration associated with electrolytic disorders (TCa = 12.9 mg/dL; K = 2.2 mEq/L).

Amphotericin B was suspended on the 20th day due to decreased hepatosplenomegaly and electrolyte disorders. He maintained TCa = 14.9 mg/dL and *p* = 6.1 mg/dL, unrelated to serum PTH levels (PTH < 1 pg/mL). He evolved with calciuria (13 mg/kg/day), signs of nephrocalcinosis and nephrolithiasis, worsening renal function, and multiple lithic lesions on the clavicles, scapulae, costal arches and humerus, with bilateral humeral epiphyseal slipping.

Bone scintigraphy showed diffuse hypercaptation in these lesions. The situation persisted until the 2nd month of hospitalization, when a new myelogram showed marked hypoplasia, and a liver biopsy revealed a large amount of fungi. In addition, a culture of the gastric lavage was positive for Mycobacterium tuberculosis.

Treatment for tuberculosis was started and the treatment with amphotericin was reintroduced for another 20 days, which brought about a normalization of laboratory parameters, clinical improvement and fungus eradication. The present case was reported by Tresoldi *et al.*,[1] and it was included in a modified and summarized form in this series to provide a comparative effect with the other two cases presented.

Case 3: vitamin-D supplement prepared to-order in a specialized pharmacy

V.A.S., male, brown, 8 years old, under follow up from the 1st year of life because of recurrent microscopic hematuria, secondary to idiopathic hypercalciuria and low urinary magnesium. Under use of magnesium oxide and pyridoxine, hydrochlorothiazide and cholecalciferol 2,000 IU/day. Loss of 2 kg in the last two months, presented with postprandial vomiting, inappetence, adynamia, pain in lower limbs, polyuria and nocturia in the past week.

Laboratory tests showed: TCa = 18.5 mg/dL; Potassium (K) = 1.9 mmol/L; Creatinine = 0.8 mg/dl; Creatinine clearance = 52 ml/min, and calciuria = 439 mg/24h. After three days of hydration, K correction, use of methylprednisolone (2 mg/kg/day), spironolactone and furosemide, disodium pamidronate (two doses of 0.5 mg/kg each, on two consecutive days) were introduced, resulting in TCa Serum levels of up to 10 mg/dL.

The investigation for neoplasms (long bones, skull, hips and spine X-rays and abdominal ultrasonography) was negative. No evidence of granulomatous disease was found. The dosages of thyroid and parathyroid hormones were within the reference values. Thyroid and parathyroid glands scintigraphy did not show changes. The vitamin-D serum level was > 150 ng/ml (reference: 30 to 100 ng/mL). The capsules of the drug were submitted to a reference-laboratory analysis, the vitamin-D content was estimated at 832,000 IU per capsule.

Discussion

A recent paper describes the natural course of psittacosis as an influenza-like disease, but it can occur as pneumonia, endocarditis and encephalitis. Characteristically, peripheral blood monocytosis and pulmonary lesions with buildup of inflammatory cells are described.[5] We did not find reports of hypercalcemia associated with Chlamydia sp. in the literature. However, it is known that bacterial infections can cause bone destruction resulting from the over-generation of osteoclasts. Inflammatory cytokines such as TNF-alpha, IL-1, IL-6 act by stimulating the RANKL receptor present in the osteoblast. This, in turn, couples with the RANK present in the pro-osteoclast, which becomes a mature osteoclast, promoting bone resorption with increased calcemia.[6]

In our Case 1, we considered the epidemiological history to start the empirical treatment with doxycycline, and the clinical response could confirm, together with serology, the psittacosis diagnosis. In this case, we could not rule out the possibility of polymorphisms in the genes that regulate calcitriol degradation.

Hypercalcemia is described in granulomatous diseases (sarcoidosis, tuberculosis) and fungal infections. The association of Paracoccidioides brasilienses and hypercalcemia is rare, with few cases previously published, without elucidation regarding the hypercalcemia mechanism.[7]

The abrupt way calcemia established and normalized suggests that bone lysis was the most important factor for its genesis.[1] The

increase in calcitriol synthesis by macrophages is known in granulomatous diseases.[8-10] This mechanism has already been challenged in paracoccidioidomycosis.[11] However, in this case there was an association with tuberculosis, which may be an additional mechanism associated with the genesis of hypercalcemia.

In the last decade, there has been an increase in the prescription and use of vitamin-D supplements, motivated by association studies, aiming at taking advantage of potential pleiotropic benefits in various systems and organs.[12,13] Despite the lack of more consistent evidence in relation to vitamin-D supplementation and its impact on various diseases, it has become common to find patients with a daily intake of 800 to 4,000 IU/day of vitamin D, sometimes for years.[14,15]

Vitamin D intoxication in children and adolescents is a rare event and it is often associated with formulation errors. In case reports, the daily intake ranged from 40,000 to 560,000 IU/day, and these cases presented with severe hypercalcemia, hypercalciuria and nephrocalcinosis.[16] However, there are reports of vitamin D poisoning, even when taking the daily dose allowance.[16]

Polymorphisms in genes that regulate vitamin-D hydroxylation and the binding protein synthesis could influence serum vitamin-D levels, as in Williams syndrome, caused by mutations in CYP24A1, leading to a decrease in 24-hydroxylase synthesis, and consequently decreased degradation of calcitriol.[4,9]

Therefore, the use of vitamin D should be guided by scientific evidence and, in special cases, with periodic monitoring of serum levels of TCa, Ca, vitamin D and calciuria.[17] Prescription of formulated vitamin D should be done with caution and in pharmacies which meet quality requirements.

In conclusion, acute hypercalcemia in children may be due to several causes, including inflammatory, infectious, as well as exogenous poisoning by vitamin D. To the best of our knowledge, an unpublished fact was the possible causal relationship between psittacosis and hypercalcemia, alerting for the need for detailed investigation of the epidemiological history and, thus, early institution of the appropriate treatment.

References

1. Tresoldi AT, Pereira RM, Castro LC, Castro LC, Rigatto SZP, Belangero VMS. Hipercalcemia e lesões osteolíticas múltiplas em criança com paracoccidioidomicose disseminada e tuberculose pulmonar. J Pediatr (Rio J) 2005;81:349-52. DOI: http://dx.doi.org/10.2223/1375
2. Shane E, Berenson JR. Treatment of hypercalcemia. [Acesso 2015 Fev 1]. Disponível em: htpp://www.UpToDate.com
3. Bresolin NL, Andrade OVB. Urgências e Emergências Nefrológicas em Terapia Intensiva Pediátrica. In: Toporovski J, Mello VR, Filho DM, Benini V, eds. Nefrologia Pediátrica. 2a ed. Rio de Janeiro: Guanabara Koogan; 2006.
4. Reynolds BC, Cheetham TD. Bones, stones, moans and groans: hypercalcaemia revisited. Arch Dis Child Educ Pract 2015;100:44-51. DOI: http://dx.doi.org/10.1136/archdischild-2013-305406
5. Knittler MR, Berndt A, Böcker S, Dutow P, Hänel F, Heuer D, et al. Chlamydia psittaci: new insights into genomic diversity, clinical pathology, host-pathogen interaction and anti-bacterial immunity. Int J Med Microbiol 2014;304:877-93. DOI: http://dx.doi.org/10.1016/j.ijmm.2014.06.010
6. Kim J, Yang J, Park OJ, Kang SS, Kim WS, Kurokawa K, et al. Lipoproteins are an important bacterial component responsible for bone destruction through the induction of osteoclast differentiation and activation. J Bone Miner Res 2013;28:2381-91. DOI: http://dx.doi.org/10.1002/jbmr.1973
7. Almeida RM, Cezana L, Tsukumo DM, de Carvalho-Filho MA, Saad MJ. Hypercalcemia in a patient with disseminated paracoccidioidomycosis: a case report. J Med Case Reports 2008;2:262. DOI: http://dx.doi.org/10.1186/1752-1947-2-262
8. Abbasi AA, Chemplavil JK, Muller BF, Arnstein AR. Hypercalcemia in active pulmonary tuberculosis. Ann Intern Med 1979;90:324-8. DOI: http://dx.doi.org/10.7326/0003-4819-90-3-324
9. Bilezikian JP. Etiologies and therapy of hypercalcemia. Endocrinol Metab Clin North Am 1989;18:389-414.
10. Murray JJ, Heim CR. Hypercalcemia in disseminated histoplasmosis. Aggravation by vitamin D. Am J Med 1985;78:881-4. DOI: http://dx.doi.org/10.1016/0002-9343(85)90300-6
11. Caldwell JW, Arsura EL, Kilgore WB, Reddy CM, Johnson RH. Hypercalcemia in patients with disseminated coccidioidomycosis. Am J Med Sci 2004;327:15-8. DOI: http://dx.doi.org/10.1097/00000441-200401000-00004
12. Gröber U, Spitz J, Reichrath J, Kisters K, Holick MF. Vitamin D: Update 2013: From rickets prophylaxis to general preventive healthcare. Dermatoendocrinol 2013;5:331-47. DOI: http://dx.doi.org/10.4161/derm.26738
13. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81. DOI: http://dx.doi.org/10.1056/NEJMra070553
14. Jacobsen RB, Hronek BW, Schmidt GA, Schilling ML. Hypervitaminosis D associated with a vitamin D dispensing error. Ann Pharmacother 2011;45:e52. PMID: 21917555
15. Marins TA, Galvão TFG, Korkes F, Malerbi DAC, Ganc AJ, Korn D, et al. Intoxicação por Vitamina D: Relato de caso. Einstein 2014;12:242-4. DOI: http://dx.doi.org/10.1590/S1679-45082014RC2860
16. Vogiatzi MG, Jacobson-Dickman E, DeBoer MD; Drugs, and Therapeutics Committee of The Pediatric Endocrine Society. Vitamin D supplementation and risk of toxicity in pediatrics: a review of current literature. J Clin Endocrinol Metab 2014;99:1132-41. DOI: http://dx.doi.org/10.1210/jc.2013-3655
17. Quadros KRS, de Oliveira RB. Reposição de vitamina D nativa: indicação à luz das evidências científicas atuais. Rev Fac Ciênc Méd Sorocaba. 2016; 18:79-86.