

Idiopathic infantile hypercalcemia or an extrapulmonary complication of tuberculosis?

Resul YILMAZ, Ahmet Afşin KUNDAK, Taner SEZER, Samet ÖZER, Haluk ESMERAY,
Nafia Özlem KAZANCI

Gaziosmanpaşa Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Tokat.

ÖZET

İdiyopatik infantil hiperkalsemi mi, tüberkülozun ekstrapulmoner komplikasyonu mu?

Kalsiyum metabolizma bozukluklarına çocukluk çağında sık rastlanır. Bebeklik döneminde hiperkalsemi genellikle hiperparatiroidizm, ailesel hipokalsiürik hiperkalsemi, cilt altı yağ nekrozu, total parenteral nütrisyon, hipertiroidizm ve adrenal yetmezliğe bağlı olarak ortaya çıkar. Tüberküloz ve sarkoidoz gibi granülatöz hastalıklar nadir olarak hiperkalsemi nedeni olarak saptanır. Nefrokalsinöz, beyin, göz, arter kalsifikasyonları ve ensefalopatik özellikler hiperkalseminin hayatı tehdit eden sonuçlarından bazılarıdır. Ciddi hiperkalsemi bulguları veren ve miliyer tüberküloz saptanan yedi aylık kız çocuğu hasta sunulmuştur.

Anahtar Kelimeler: Hiperkalsemi, tüberküloz, nefrokalsinöz, bebeklik, etyoloji.

SUMMARY

Idiopathic infantile hypercalcemia or an extrapulmonary complication of tuberculosis?

Resul YILMAZ, Ahmet Afşin KUNDAK, Taner SEZER, Samet ÖZER, Haluk ESMERAY,
Nafia Özlem KAZANCI

Department of Children's Health and Diseases, Faculty of Medicine, Gaziosmanpasa University, Tokat, Turkey.

Calcium metabolism disturbances are common in childhood. In infancy, hypercalcemia generally occurs due to hyperparathyroidism, familial hypocalciuric hypercalcemia, subcutaneous fat necrosis, total parenteral nutrition administration, hyperthyroidism, and adrenal insufficiency. Granulomatous disorders such as tuberculosis and sarcoidosis are rarer cause of hypercalcemia. Hypercalcemia outcomes including nephrocalcinosis, brain, eye, artery calcifications and encephalopathic features are life-threatening. We report a seven-month-old girl with miliary tuberculosis who presented with severe hypercalcemia.

Key Words: Hypercalcemia, tuberculosis, nephrocalcinosis, infancy, etiology.

Tuberk Toraks 2013; 61(1): 43-46 • doi: 10.5578/tt.536

Yazışma Adresi (Address for Correspondence):

Dr. Resul YILMAZ, Gaziosmanpaşa Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, 60030
TOKAT - TÜRKİYE

e-mail: drresul@hotmail.com

INTRODUCTION

Calcium metabolism disorders are common in children. Hypercalcemia is a relatively rarer condition than hypocalcemia (1). The most common causes of hypercalcemia in older children and adults are primary hyperparathyroidism, malignancy and granulomatous diseases (2). In infancy subcutaneous fat necrosis, hyperparathyroidism, familial hypocalciuric hypercalcemia, total parenteral nutrition administration, blue diaper syndrome, congenital hypothyroidism, hyperthyroidism, adrenal insufficiency and chronic hepatic diseases are the most frequent causes of hypercalcemia (1).

In infancy and the early childhood period, conditions of the mother such as hypoparathyroidism, thyrotoxicosis, thiazide diuretics, lithium and excessive vitamin D3 intake can lead to hypercalcemia. Therefore, in this period both mother and infant must be investigated together (1).

Hypercalcemia is defined as serum total calcium levels above 10.82 mg/dL (2.7 mmol/L) or serum ionized calcium above 5.4 mg/dL. A child with mild (total serum calcium < 12 mg/dL) or chronic hypercalcemia frequently goes undiagnosed. The preponderant manifestation may be failure to thrive with arrest of weight gain. In moderate hypercalcemia (total serum calcium 12-13.5 mg/dL) generalized weakness, anorexia, constipation and polyuria are usually present. In severe hypercalcemia (total serum calcium > 13.5 mg/dL) nausea, vomiting, dehydration and encephalopathic features, including coma and seizure, may occur (1).

The management of hypercalcemia is built on the severity of the serum calcium and cause of hypercalcemia. When hypercalcemia is inconsiderable and there are no symptoms, no initial treatment may be necessary and clinician must give importance to reach an exact diagnosis. When hypercalcemia is serious or there are cardiac, gastrointestinal and central nerve system dysfunction signs and symptoms, immediate intervention is expedient (3,4).

Idiopathic infantile hypercalcemia and tuberculosis associated hypercalcemia in infancy are rare conditions (1-4). We report on a seven-month-old girl with miliary tuberculosis who presented with severe hypercalcemia.

CASE REPORT

A-7-month-old girl was referred to our pediatric clinic with fever, low appetite and excessive crying. She was not given any multivitamin supplements. Her vaccination program was ongoing. She had three doses of DTP,

OPV and Hib and a dose of BCG. On physical examination; blood pressure was 100/60 mmHg, body temperature was 36.5°C, pulse rate was 132 beats/minute and respiration rate was 32 breaths/minute. Body weight, height and head circumference measurements were under the three percentiles. Neuromotor development was appropriate to her age. She did not have any abnormal face appearance. Thorax auscultation revealed diffuse rales. The rest of her examination was normal.

On admission the patient's laboratory findings were as follows: white blood cell count 17.500/mm³, red blood cell count 4.61 x 10⁶/mm³, hemoglobin 9.1 g/dL, hematocrit 26.9%, platelet 612.000/mm³. Biochemical analysis of blood revealed the following; total calcium 16.1 mg/dL, magnesium 1.9 mg/dL, aspartate aminotransferase 40 IU/mL, alanin aminotransferase 23 IU/mL, blood urea nitrogen 8 mg/dL, serum creatinine 0.6 mg/dL, albumin 3.6 g/dL, serum total protein 6.9 g/dL, C-reactive protein 14.1 mg/dL. The parathyroid hormone (PTH) level was slightly depressed (6.12 pg/mL). Thyroid function tests, 25-OH-vitamin D3 (10.58 ng/mL) and blood gas analysis were in normal range. A urine analysis showed increased leukocyte count. The viral markers were negative for herpes virus, Epstein-Barr virus, cytomegalovirus, hepatitis B and C and human immunodeficiency virus. Blood, urine and stool cultures were negative for all pathogens. Urinary pH was 7, spot urine calcium 7.8 mg/dL, spot urine protein 23.1 mg/L, spot urine creatinine 11.5 mg/dL, calcium/creatinine ratio was 0.63 (normal < 0.85). A 24 hours urine study showed that calcium excretion was within normal range. Renal ultrasonography showed bilateral increased echogenicity in medullary pyramids which indicates nephrocalcinosis. Her family reported no history of tuberculosis and her Mantoux test was 1 mm.

On the basis of clinical and laboratory findings, pneumonia, urinary tract infection and idiopathic infantile hypercalcemia were diagnosed. Sulbactam-ampicillin, intravenous hydration, furosemid and glucocorticoid therapies were administered. On day 10, her clinical and laboratory findings became normal and she was discharged.

Two months after she was discharged, she was admitted to another facility with generalized tonic-clonic convulsions and fever. On admission she was unconscious and her light reflex was weak positive. Biochemical analysis of blood was normal including calcium (serum total calcium: 8.8 mg/dL). A computed tomography (CT) of the brain showed hydrocephalus and multiple abscess formation. A cerebrospinal fluid (CSF) examination performed by transepidermal puncture revealed

a lymphocytic picture (69 leucocyte/mm³, 67 erythrocyte/mm³) with a protein of 48.5 mg/dL, glucose 42 mg/dL (simultaneously performed serum glucose was 115 mg/dL) and chloride 1.5 mmol/L. Acid resistant bacilli screening from CSF was negative. Thorax CT revealed multiple aciner infiltration areas and diffuse micronodular densities in the pulmonary area. A diagnosis of miliary tuberculosis was made and ethambutol, rifampicin, morphazinamide, INAH medications for tuberculosis treatment were initiated. She was lost to follow-up.

DISCUSSION

Calcium metabolism disturbances are one of the most common metabolic disorders in childhood. Hypercalcemia presents with neurological, gastrointestinal and renal disturbances such as low appetite, vomiting, constipation, polyuria, and polydipsia (1-4). If proper treatment is not given, survey of soft tissues may reveal calcifications on any part of the body such as nephrocalcinosis, basal ganglion calcifications, and band keratopathy (4). Our patient was admitted with non-specific complaints including low appetite and fever. There was no evidence of calcification.

On admission our case's serum total calcium level was 16.1 mg/dL. As an infant, both she and her mother were investigated together. There was no history of excessive vitamin D3 intake or other drug use in her mother. Laboratory tests including serum total calcium, thyroid function tests and urinary calcium excretion were normal.

Severe hypercalcemia is seen with Williams syndrome. This syndrome is characterized by elfin face, mental retardation and supravalvular aortic stenosis. Other clinical features include teeth abnormalities, low birth weight, short stature and microcephalus (1,3-5). In our case there are no dysmorphic features of Williams syndrome and echocardiogram examination was normal.

Other most common cause of hypercalcemia in infancy is excessive vitamin D3 intake. When PTH levels are adequately suppressed in the presence of hypercalcemia, elevated 25-OH-vitamin D3 levels would suggest vitamin D3 intoxication (1-5). Our patient was not given any vitamin preparation including vitamin D3 and her serum 25-OH-vitamin D3 level was in normal range.

Hyperparathyroidism is one of the most common causes of hypercalcemia in adults, but it is a relatively uncommon disorder in neonates and children. Hyperparathyroidism is diagnosed when hypercalcemia is accompanied by elevated PTH levels (1-5). In our case

PTH level was suppressed so hyperparathyroidism was ruled out.

Renal tubular acidosis was excluded because the blood gas analysis of our case and her mother were normal (6).

Idiopathic infantile hypercalcemia is known as first year's disease and is divided into two groups. Mild variant is known as Lightwood variant IHH and severe variant is related to Williams syndrome. Mild or Lightwood variant IHH is a heterogeneous disorder and symptoms related to hypercalcemia initially are seen during the two to nine month old period. Which mechanisms are responsible for this syndrome is not well known. Some of the patients have elevated vitamin D3 metabolites, while others have increased sensitivity to vitamin D3. Other groups showed elevated PTH related peptide levels. Prognosis of mild variant IHH is good and hypercalcemia resolves by 12 months of age (1,3,6).

Granulomatous disorders such as tuberculosis, sarcoidosis and leprosy may cause hypercalcemia. There are few reports defining the association of hypercalcemia and tuberculosis in childhood (7,8). In these disorders inappropriate production of vitamin D3 by activated monocytic cells and granulomas is responsible for hypercalcemia (9). Early diagnosis is very important in tuberculosis to prevent the spread of organism and diffusion of the disease. However it was shown that more than three month period of time is required to determine the diagnosis. In our case, the diagnosis of miliary tuberculosis was delayed due to negative sputum smear and Montoux test and lack of abnormal findings on chest X-ray films. It takes a one to two month period of time for nodules to be noticed on X-ray films. We suggested that our patient was contaminated with tuberculosis bacilli on admission but lacked signs and symptoms of tuberculosis and corticosteroid therapy might have retarded granuloma formation (10,11).

The preliminary stages of hypercalcemia treatment are non-specific and to interrupt calcium and vitamin D intake is the first step. Hydration will increase calcium excretion afterwards starting loop diuretics. Persistent hypercalcemia could be improved with glucocorticoids, calcitonin, diphosphanates and plicamycin (1,3,4,6). Our case was improved with low calcium diet, intravenous hydration, furosemid and glucocorticoid as conventional therapy. She did not need calcitonin or any other adjuvant agents.

The World Health Organization (WHO) has reported that 8 million people develop tuberculosis each year and almost 2 million people die because of this lethal, contagious disease (12). Neglect and general ignoran-

ce of tuberculosis for two decades led to an increase in incidence of tuberculosis after a steady decline during the last century. Faced with this situation, the WHO recognized tuberculosis as a major public health problem and reinvigorated a particular challenge around prevention, diagnosis and treatment of tuberculosis (13).

In conclusion, based on the case we presented, it is suggested that disseminated tuberculosis should be considered in patients who have severe hypercalcemia even in the absence of other clinical and laboratory findings of tuberculosis. Full importance must be given for early and proper management of tuberculosis because of the high mortality and morbidity rate it causes.

CONFLICT of INTEREST

None declared.

REFERENCES

1. Diaz R. Calcium disorders in children and adolescents. In: Lifshitz F (ed). *Pediatric Endocrinology Volume 2*. 5th ed. New York: Informa Healthcare USA Inc, 2007: 475-95.
2. Fisker RA, Heath DA, Somers S, Bold AM. Hypercalcaemia in hospital patients. *Clinical and diagnostic aspects. Lancet* 1981; 24; 202-7.
3. Rodd C, Goodyer P. Hypercalcemia of the newborn: etiology, evaluation, and management. *Pediatr Nephrol* 1999; 13: 542-7.
4. Diaz R. Abnormalities in calcium homeostasis. In: Radovick S, Mc Gillivroy MH (eds). *Pediatric Endocrinology A Practical Guide*. 1st ed. New Jersey: Humana Press, 2003: 344-63.
5. Parlar A, Kavaklı K. Williams syndrome (Elfin face syndrome). *Ege Universitesi Tıp Fakültesi Dergisi* 1990; 29: 471-3.
6. Sakallıoğlu O, Hacıhamdioğlu B, Balamtekin N, Kalman S, Gök F. Idiopathic infantile hypercalcemia and renal involvement. *Int Urol Nephrol* 2008; 40: 535-7.
7. Gerritsen J, Knol K. Hypercalcaemia in a child with miliary tuberculosis. *Eur J Pediatr* 1989; 148: 650-1.
8. Okascharoen C, Nuntnarumit P, Sirinavin S. Neonatal tuberculosis associated with shock, disseminated intravascular coagulation, hemophagocytic syndrome, and hypercalcemia: a case report. *J Perinatol* 2003; 23: 79-81.
9. Sharma OP. Hypercalcemia in granulomatous disorders: a clinical review. *Curr Opin Pulm Med* 2000; 6: 442-7.
10. Kim JH, Langston AA, Gallis HA. Miliary tuberculosis: epidemiology, clinical manifestations, diagnosis, and outcome. *Rev Infect Dis* 1990; 12: 583-90.
11. Sbarbaro JA. Kochi's tuberculosis strategy article is a "classic" by any definition. *Bull World Health Organ* 2001; 79: 71-5.
12. WHO. *Global tuberculosis control: surveillance, planning, financing*. Geneva: World Health Organization, 2006: 242.
13. Lönnroth K, Raviglione M. Global epidemiology of tuberculosis: prospects for control. *Semin Respir Crit Care Med* 2008; 29: 481-91.