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Hypercalcemia of the newborn: etiology, evaluation, and management

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Abstract Hypercalcemia in infants is uncommon but has potentially serious sequelae. This review examines four cases of neonatal hypercalcemia, emphasizing appropriate investigations and treatment of acute and chronic hypercalcemia. The paper provides additional information as to the mechanisms of calcium dysregulation in idiopathic infantile hypercalcemia, Williams syndrome, vitamin D intoxication, and parathyroid and parathyroid-related protein disturbances.

Key words Hypercalcemia · Infant · Etiology · Management

Introduction

Hypercalcemia in the newborn period is very uncommon. However, its sequelae are serious, particularly the renal consequences, which include nephrocalcinosis with distal tubular dysfunction, nephrolithiasis, and renal insufficiency. These infants must be promptly investigated and treated.

Four cases of neonatal hypercalcemia

Iatrogenic

This patient was born prematurely at 24 weeks' gestational age, weighed 440 g, and was being fed parenterally. At the age of 4 weeks, his creatinine had rapidly increased to 262 µmol/l (3.0 mg/dl). This was initially attributed to hypoperfusion secondary to a patent ductus arteriosis (PDA), as well as treatment with indomethacin for this lesion.

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However, his serum calcium level was incidentally found to be 5.2 mmol/l (20.8 mg/dl) and his ionized calcium was 3.1 mmol/l (12.4 mg/dl).

His major clinical finding was polyuria. Immediately, his i.v. fluids were switched to normal saline, from parenteral nutrition, eliminating any further calcium and vitamin D intake. Calcitonin, furosemide, hydrocortisone, and continued volume expansion normalized his calcium by 60 h. His evaluations demonstrated a normal serum phosphate, 1.6 mmol/l (5.0 mg/dl), suppressed parathyroid hormone (PTH), 4 pg/ml, normal 25-hydroxyvitamin D level, 52 nmol/l (normal 25–103 nmol/l), suppressed 1,25-dihydroxy-vitamin D, <24 pmol/l (normal 36–108 pmol/l), and a low vitamin A level 0.36 µmol/l (normal 0.7–1.5 µmol/l). He remained eucalcemic and demonstrated no further hypercalciuria or nephrocalcinosis on follow-up.

Because we could find no other reason for this hypercalcemia and because it resolved completely after stopping his parenteral fluids, we concluded that his hypercalcemia was due to his i.v. calcium supplementation, in association with indomethacin treatment for the PDA. He became hypercalcemic as he was unable to excrete his i.v. calcium load [1].

Neonatal severe hyperparathyroidism

Shortly after delivery, an infant girl presented with tachypnea, respiratory distress, and marked hypotonia. After initial cardiorespiratory stabilization, she was found to be hypercalcemic, with an ionized calcium of 1.5 mmol/l (6.0 mg/dl) and a total calcium of 2.85 mmol/l (11.4 mg/dl). A chest X-ray revealed diffuse undermineralization, subperiosteal bone resorption, and multiple rib fractures. On the 2nd day of life, her total calcium had increased to 3.2 mmol/l (12.8 mg/dl), with an ionized calcium of 1.7 mmol/l (6.8 mg/dl), and she had low renal calcium excretion (calcium/creatinine ratio 0.2 mmol/mmol=0.07 mg/mg). A concurrent phosphorus level was low at 0.8 mmol/l (2.5 mg/dl) and her alkaline phosphatase level was 398 U/l (normal 68–217 U/l). Given the significant elevation of her serum calcium, with evidence of hyperparathyroidism, intact PTH was assayed and found to be 990 pg/ml (normal 10–60 pg/ml). Despite therapy with saline hydration, calcitonin, and glucocorticoids, the child's serum calcium progressively rose, and the phosphorus fell. On day 5 of life, a neck exploration revealed four enlarged parathyroid glands. Following total parathyroidectomy, with autotransplantation of a small fragment of one gland in her left arm, this infant remained eucalcemic. Her parents were found to have asymptomatic hypercalcemia and relative hypocalciuria, matching the description of familial hypocalciuric hypercalcemia (FHH). The family underwent genetic testing, which revealed homozygous mutations in the calcium sensing receptor in the infant and heterozygous mutations in the parents [2].

Williams syndrome

A 6-week-old infant presented to the emergency room with dehydration and failure to thrive. Her weight had not increased since birth and her serum creatinine was elevated at 84 μmol/l (0.95 mg/dl). She had a total calcium of 3.2 mmol/l (12.8 mg/dl) and an ionized calcium of 1.8 mmol/l (7.2 mg/dl). Her urine calcium/creatinine ratio was markedly elevated at 4.2 mmol/mmol (1.5 mg/mg), reflecting a urine calcium excretion of 10 mg/kg per day. Her urinanalysis demonstrated pyuria, and mild bilateral nephrocalcinosis was noted by ultrasonography. Overnight, after discontinuing feeds, i.v. normal saline resuscitation, calcitonin, and glucocorticoids, her calcium value returned to normal. She had initially been hypertensive and was found to have supravalvular aortic and renal artery stenoses. Her physical examination was otherwise normal.

Her laboratory examination demonstrated a suppressed intact PTH, 8 pg/ml, a normal 25-hydroxyvitamin D, 44 nmol/l (normal 25–103 nmol/l), and a markedly elevated 1,25-dihydroxyvitamin D value, 342 pmol/l (normal 36–108 pmol/l). The putative diagnosis of Williams syndrome was made based on the constellation of hypervitaminosis D, hypercalcemia, and arterial stenoses. She was treated with a diet low in calcium and in vitamin D. Her monthly serum calcium and urine calcium/creatinine ratios normalized. Her pyuria disappeared and monthly renal ultrasonography demonstrated no additional nephrocalcinosis. Her distal tubular function remained intact, indicating no renal tubular acidosis.

Currently, at the age of 9 months, her altered calcium homeostasis is resolving as her 1,25-dihydroxyvitamin D level has returned to the normal range, and she has more easily recognized physical features of the syndrome (elfin facies, blue eyes with a stellate pattern in the iris). Fluorescent in situ hybridization analysis demonstrated complete deletion of one of her elastin genes, consistent with the diagnosis of Williams syndrome [3].

Idiopathic

The patient was born with a cleft lip and palate. He was given parenteral nutrition post delivery until he was better able to feed from a bottle. At the age of 2 weeks, when he was exclusively drinking regular infant formula, he was found to have an elevated calcium of 2.97 mmol/l (11.9 mg/dl). This remained persistently elevated. He was also found to have a mildly increased serum creatinine 52 μmol/l (0.6 mg/dl) and a normal alkaline phosphatase. His urine calcium/creatinine ratio was consistently greater than 2.0 mmol/mmol (0.7 mg/mg) and he had mild pyuria. Renal ultrasonography was normal.

His intact PTH level was suppressed, 4 pg/ml, parathyroid hormone related protein (PTHrP) was undetectable, <0.1 pmol/l, normal <0.1 pmol/l, and his vitamin D metabolite levels were low/normal: 25-hydroxyvitamin D level, 12 nmol/l (normal 25–103 nmol/l), 1,25-dihydroxyvitamin D, 53 pmol/l (normal 6–108 pmol/l). A skeletal X-ray survey was normal. He was treated with a diet reduced in calcium and in vitamin D, which he tolerated well. At the age of 4 months, his tubule reabsorption of phosphate decreased, his alkaline phosphatase rose slightly, his PTH rose just above the upper limit of normal, and his serum calcium dropped slightly. The special formula was mixed with increasing proportions of normal formula. By the age of 6 months, he was taking regular formula and regular infant solids, and his calcium status was completely normal. At a year of age he continues to have normal calcium homeostasis and his clinical presentation was consistent with idiopathic infantile hypercalcemia (IIH).

Diagnosis, clinical and laboratory findings

Hypercalcemia is defined as an ionized calcium that exceeds the upper limit of normal, 1.35 mmol/l (5.4 mg/dl), with or without an elevated total calcium, greater than 2.7 mmol/l (10.8 mg/dl). Most infants are asymptomatic when diagnosed, with mildly elevated levels detected on routine testing. Occasionally newborns may present with symptoms resulting from strikingly elevated values [4, 5]. These babies fail to thrive, secondary to vomiting, poor feeding, irritability, and polyuria. Alternatively, they may present with seizures.

Clinically, these infants can have bradycardia, a short QT interval, and hypertension. They are often dehydrated, lethargic, and hypotonic. Their physical examination is usually otherwise normal, except for the infants with subcutaneous fat necrosis, Williams syndrome, Jansen metaphyseal chondrodysplasia, and hypophosphatasia.

Renal function is often reduced, which further compromises renal calcium elimination. The serum creatinine is frequently elevated, as a consequence of the effects of calcium on blood vessel tone and nephrogenic diabetes insipidus. Urine calcium excretion is elevated and consequently hematuria and pyuria are common.

Etiology

The causes of hypercalcemia are diverse and uncommon (Table 1). The most-common cause is iatrogenic, usually when the baby is receiving excess calcium salts, generally in the i.v. form [1]. The hypercalcemia is transient and usually mild. The second most-common cause is IIH, which is a diagnosis of exclusion. This syndrome was formerly divided into two subgroups, mild and severe. The latter is now known as Williams syndrome.

Table 1 Causes of hypercalcemia

Iatrogenic (calcium salts)
Idiopathic infantile hypercalcemia
Williams syndrome
Vitamin D
Vitamin D intoxication
Subcutaneous fat necrosis
Granulomatous diseases
Parathyroid related
Hyperparathyroidism
Neonatal severe hyperparathyroidism
Secondary hyperparathyroidism
Familial hypocalciuric hypercalcemia
PTHrP
tumour related
PTH receptor mutation – Jansen's metaphyseal chondrodysplasia
Miscellaneous
Hypophosphatasia
Hypophosphatemia
Vitamin A intoxication
Blue-diaper syndrome
Other medications – hydrochlorothiazide

PTH, Parathyroid hormone; PTHrP, parathyroid hormone related protein

Idiopathic infantile hypercalcemia

"Mild" or the Lightwood variant IIH is a heterogeneous disorder. It was originally described in the 1950s in England, during a period of high-dose vitamin D fortification. Lowering the supplementation has dramatically decreased the incidence [6]. Infants usually diagnosed with this disorder present with thirst, dehydration, and polyuria. The mechanisms responsible for the hypercalcemia are not uniform. Some of these infants have elevated vitamin D metabolites, suggesting vitamin D intoxication and/or subtle renal dysregulation of vitamin D metabolism, both of which would account for the increased intestinal calcium absorption. In others, the vitamin D levels are normal, suggesting an increased sensitivity to their vitamin D, again accounting for increased gut absorption [7]. Lately, some infants have been found to have elevated PTHrP levels at the time of the hypercalcemia. When the children achieved eucalcemia, the levels of PTHrP were normalized [8]. As the duration of the hypercalcemia is variable, the infants must be closely followed to re-institute dietary calcium and vitamin D. Generally, their hypercalcemia resolves by 12 months of age and the prognosis is good [7].

Williams syndrome

Williams syndrome is a multisystem developmental disorder caused by the deletion of contiguous genes on chromosome 7. Hemizygosity of the elastin gene defect is seen in over 90% of cases [3]. The deletion of the elastin gene itself can account for the vascular and connective tissue abnormalities, but the genes that contribute to the features such as hypercalcemia, dysmorphic facies, and mental retardation remain to be identified.

Two-thirds of the infants are small for gestational age and may have distinct facial features (depressed nasal bridge, epicanthal folds, and/or prominent lips). With time, they become more prominent as the children acquire "elfin facies" and a loquacious manner [9]. The hypercalcemia, if initially present, rarely persists to the end of the 1st year. The pathogenesis is unknown, although elevated levels or 1,25-vitamin D have been observed in some infants; in others, it is felt that they have increased sensitivity to "normal" metabolite concentrations [10]. Additionally, the hypercalcemia has been reported to recur during puberty [11].

Vitamin D intoxication

Infants may develop hypercalcemia secondary to elevated levels of circulating vitamin D metabolites. Excessive endogenous synthesis of 1,25-dihydroxyvitamin D occurs in such conditions as subcutaneous fat necrosis and granulomatous diseases. In the former, red-violaceous plaques, often located on the back or on pressure points, are sites of 1,25-dihydroxyvitamin D synthesis [12]. The increased levels of 1,25-dihydroxy-vitamin D usually remit quickly after birth, but in some infants this can persist for 1–2 years.

Hypercalcemia may also be provoked by excessive exogenous vitamin D due to the inappropriate choice of infant formula or errors in vitamin D supplementation of milk or formula. In such cases, the 25-hydroxyvitamin D levels are elevated [13–15].

Primary or secondary hyperparathyroidism (secondary to altered maternal calcium homeostasis)

Severe neonatal hyperparathyroidism is caused by homozygosity for inactivating mutations of the calcium sensing receptor [2]. These babies have extreme hypercalcemia, very elevated PTH concentrations, and require urgent medical control of the serum calcium followed by parathyroidectomy. Without surgery, the mortality rate is high [16]. The heterozygous parents have FHH, a syndrome of modest asymptomatic hypercalcemia. The parents do not need any medical intervention, except genetic counselling [2, 17].

There are other cases of neonatal primary hyperparathyroidism in the literature, although most were described prior to the discovery of the calcium sensing receptor. In most cases, the episodes were transient, did not require surgery, and, in retrospect, were likely cases of FHH [18]. A Japanese kindred was documented to have three infants with self-limited hyperparathyroidism and hypercalciuria [19]. To date, the molecular basis has not been identified. Thus, there may be other causes of neonatal primary hyperparathyroidism.

In secondary hyperparathyroidism, the baby's serum calcium and PTH concentration may be increased if the maternal calcium homeostasis is deranged. A medical history and an assessment of the mother's serum calcium will clarify the diagnosis. These infants do not require a parathyroidectomy, but only symptomatic treatment of the hypercalcemia until the disorder remits [20].

Parathyroid hormone related protein

PTHrP is found in normal tissue and is associated with hypercalcemia of malignancy in adults [5], although this may not be the sole factor accounting for the hypercalcemia of malignancy. Hypercalcemic infants harboring tumours have been found to have increased levels of PTHrP, which was felt to be the causative agent of the hypercalcemia [21–23].

Jansen metaphyseal chondrodysplasia

Jansen metaphyseal chondrodysplasia arises from a heterozygous mutation in the PTH/PTHrP receptor [24]. The receptor is found in kidney, bone, and growth plate. The constitutive activity in bone causes hypercalcemia

due to increased bone resorption, and is lifelong. The aberrant receptor in the growth plate alters its function, resulting in postnatal-onset short-limbed dwarfism. As infants, they are of normal length and appearance. However, in childhood the phenotype becomes more apparent: prominent hypertelorism, mandibular hypoplasia, and progressive and disproportionate short stature. At birth, these infants have obvious bony lesions on X-ray, consisting of rachitic changes, radioluciencies, and irregularities of the metaphyses of the long bones [24].

Others

Hypophosphatasia is an autosomal recessive condition in which there is a deficiency of the alkaline phosphatase enzyme. This disorder presents with a spectrum of clinical manifestations. The severest form presents with polyhydramnios, extreme skeletal hypomineralization, and short deformed limbs, and fetal death. Less-severe forms are carried to term, but the infant has hypercalcemia, severe rachitic changes, and undermineralized bone on X-ray. This less-severe form is generally lethal, early in life. Additionally, there are more-mild forms that present later in infancy or in childhood [25].

Hypophosphatemia can provoke hypercalcemia, primarily in small preterm infants fed a diet relatively deficient in phosphorus. Hypophosphatemia can directly increase synthesis of 1,25-dihydroxyvitamin D, which in turn increases gut absorption of calcium and phosphorus, resulting in hypercalcemia. Supplying a diet adequate in phosphorus corrects and avoids such situations [26].

Vitamin A toxicity is rare and can cause severe hypercalcemia. Usually the child has ingested a large dose of the vitamin or vitamin A was administered during renal failure. As vitamin A is metabolized by the kidney, renal insufficiency causes toxic accumulation, which probably directly acts on the bone to cause increased resorption and hypercalcemia [27, 28]. Infants with congenital hypothyroidism have been reported to have hypercalcemia. The mechanism for this has yet to be thoroughly clarified [29]. Lastly, the blue-diaper syndrome is a selective defect in tryptophan intestinal transport. These infants present with fever, irritability, and hypercalcemia. The diagnosis is made by analyzing urine indoles [30].

Investigations

All infants with persistent mild hypercalcemia or those with profound hypercalcemia require urgent investigation (Table 2). Figure 1 outlines how these analyses assist with the diagnosis of the underlying illness. Measurement of an intact PTH level, at the time of hypercalcemia, is pivotal. If the PTH level is low, then additional calcitrophic hormones must be assayed. If it is high, then the infant must be thoroughly investigated for the cause of the hyperparathyroidism, and may require urgent surgical evaluation.

Table 2 Evaluation of infants with persistent hypercalcemia

Blood	Total and ionized calcium, pH, phosphorus, alkaline phosphatase, creatinine, intact PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D
Urine	Calcium/creatinine ratio, tubular reabsorption of phosphate
Renal ultrasonography	
Other tests that can be performed, if the above do not yield a diagnosis	
PTHrP	
Vitamin A	
Parents' serum calcium and urine calcium	
Long bone X-rays	

Identifying the abnormal calcitrophic hormone can allow diagnosis of a specific syndrome, elucidation of the mechanism for the hypercalcemia, and definition of its optimal treatment. It may also be used to guide the duration of therapy.

Treatment

For persistent mild hypercalcemia, the baby can be managed with dietary modification, close follow-up, and, if needed, the addition of therapeutic agents. However, for a moderate-to-severe hypercalcemic infant, prompt investigation and therapy must be instituted. The therapy has four main goals: correction of dehydration, enhancement of renal excretion of calcium, inhibition of intestinal absorption or bone resorption, and treatment of the underlying disorder.

Moderate to severe hypercalcemia

The initial steps are non-specific and effective for all causes of hypercalcemia: discontinue all forms, oral and i.v., of calcium and vitamin D. IV normal saline expansion of the extracellular fluid compartment with 150–250 ml/kg per 24 h (1.5–2.5 X maintenance) will help to encourage calcium excretion. Subsequently, furosemide at 0.5–1.0 mg/kg i.v. every 6 h will further encourage calciuresis. It is important to ensure continuing adequate hydration during this therapy. To avoid iatrogenic disturbances, attention should be paid to the infant's serum sodium, potassium, magnesium, phosphorus, and calcium levels and urine calcium/creatinine ratio.

Specific therapies

Adjuvant therapies in the acute phase are calcitonin, glucocorticoids, and dialysis. *Calcitonin* is given subcutaneously every 6 h at a dose of 4–8 IU/kg and should be initiated as soon as possible. This promptly reduces the serum calcium, but its effectiveness abates after a few days. For this reason, it is not an ideal drug for chronic therapy. High-dose *glucocorticoids* reduce the absorption of calcium in the gut and may decrease bone resorption

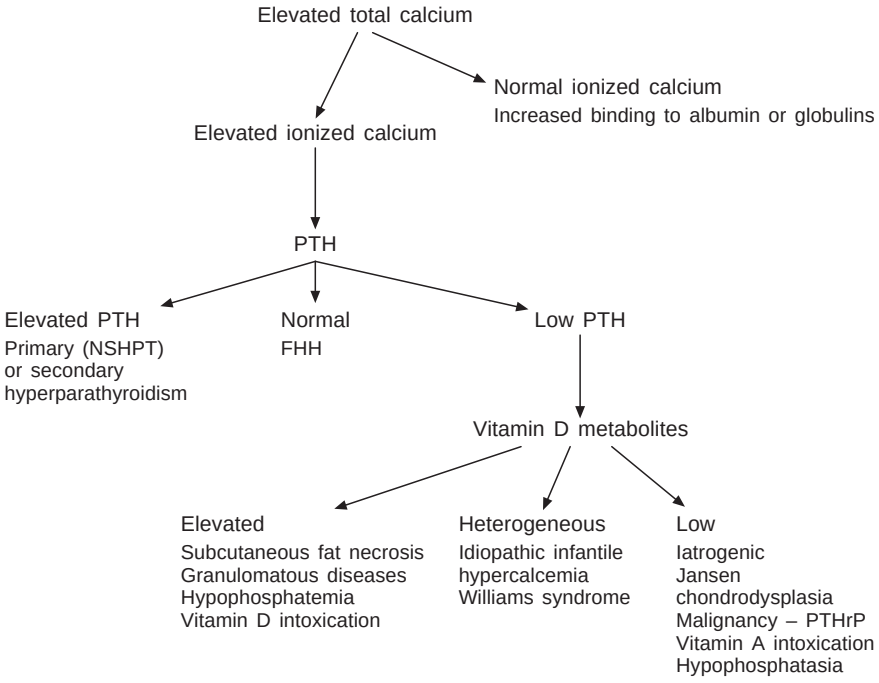

Fig. 1 Analyses to assist with the diagnosis of the underlying illness in neonatal persistent hypercalcemia. *PTH*, Parathyroid hormone; *NSHPT*, neonatal severe hyperparathyroidism; *FHH*, familial hypocalciuric hypercalcemia

and liberation of calcium. Methylprednisolone (1 mg/kg per 24 h i.v.), hydrocortisone (1 mg/kg i.v. every 6 h) or its equivalent is effective but is not recommended for long-term use, as it has many undesirable side effects.

Bisphosphonate therapy is used in adults and children for PTH-mediated hypercalcemia and vitamin D intoxication [31, 32]. We have used a single dose of pamidronate (0.5 mg/kg i.v.) in this setting [33], but experience in infants is limited, and the drug cannot be recommended for routine use until its safety profile is better understood. In theory, pamidronate may be the ideal agent to stabilize cases of neonatal severe primary hyperparathyroidism prior to parathyroidectomy. Oral or i.v. phosphorus is not recommended in the face of a normal serum phosphorus as it only leads to heterotopic mineralization.

Dialysis, either hemodialysis (HD), if the infant is hemodynamically stable, or peritoneal dialysis (PD), should be prescribed with a low-calcium dialysate (1.25 mmol/l) in the face of severe and unremitting hypercalcemia. Although, HD will more rapidly normalize the serum calcium, it is technically more difficult in infants (a suitable neonatal, acute, dual-lumen HD catheter is available from Med Comp., Harleysville, Pa., USA).

With both HD and PD, attention to serum phosphorus and magnesium is essential to avoid iatrogenic depletion in patients with normal renal function. If progressive hypophosphatemia occurs as eucalcemia is achieved, Fleet enemas (Merck Frosst, West Point, Pa., USA) can be added to the HD bicarbonate stock solution, as needed. Supplemental phosphorus can be given to patients treated with PD, either orally or i.v. Sodium phosphate can also be added to the peritoneal dialysate solution, not to exceed 0.75 mM. The bags should be inspected hourly for evidence of crystals and fresh solutions should be prepared every 8 h.

Chronic therapy

For newborns requiring prolonged therapy, a diet low in calcium and vitamin D is the mainstay of treatment. As most causes of hypercalcemia, whether mediated through PTH, vitamin D, or unknown factors, have increased intestinal absorption of calcium, limiting the dietary intake is a rational approach. CalciloXD (Ross Laboratories, North Chicago, Ill., USA) contains minimal calcium and no vitamin D. As the hypercalcemia resolves, usual infant formula or breast milk can be mixed with the CalciloXD to ensure increasing amounts of calcium. Close follow-up is required with these infants, in order to prevent long-term rickets or hypocalcemia. Serum calcium and urinary calcium excretion are analyzed every 2 weeks for the 1st month, and monthly, thereafter. Renal ultrasonography should be performed periodically to assess nephrocalcinosis.

If the dietary restriction is inadequate, chronic glucocorticoids can be added to the regimen [34]. Cellulose phosphate binders have been occasionally used in children but there is limited experience in neonates and they may contain unwanted free phosphate [35].

Summary

Hypercalcemia in the newborn period is rare. This article explores the diverse etiologies, outlines diagnostic evaluations, and acute and chronic management strategies. It is extremely important to diagnose and aggressively treat these infants to prevent serious long-term sequelae, such as nephrocalcinosis which can lead to renal insufficiency.

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