Hypercalcemic Disorders in Children

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Abstract

Hypercalcemia is defined as a serum calcium concentration that is greater than 2 standard deviations above the normal mean, which in children may vary with age and sex, reflecting changes in the normal physiology at each developmental stage. Hypercalcemic disorders in children may present with hypotonia, poor feeding, vomiting, constipation, abdominal pain, lethargy, polyuria, dehydration, failure to thrive and seizures. In severe cases renal failure, pancreatitis and reduced consciousness may also occur and older children and adolescents may present with psychiatric symptoms. The causes of hypercalcemia in children can be classified as parathyroid hormone (PTH)-dependent or PTH-independent, and may be congenital or acquired. PTH-independent hypercalcemia, i.e. hypercalcemia associated with a suppressed PTH, is commoner in children than PTH-dependent hypercalcemia. Acquired causes of PTH-independent hypercalcemia in children include hypervitaminosis; granulomatous disorders and endocrinopathies. Congenital syndromes associated with PTH-independent hypercalcemia include idiopathic infantile hypercalcemia (IIH); William's syndrome; and inborn errors of metabolism. PTH-dependent hypercalcemia is usually caused by parathyroid tumors, which may give rise to primary hyperparathyroidism (PHPT) or tertiary hyperparathyroidism, which usually arises in association with chronic renal failure and in the treatment of hypophosphatemic rickets. Acquired causes of PTH-dependent hypercalcemia in neonates include maternal hypocalcemia and extra-corporeal membrane oxygenation. PHPT usually occurs as an isolated non-syndromic and non-hereditary endocrinopathy, but may also occur as a hereditary hypercalcemic disorder such as familial hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, and familial isolated primary hyperparathyroidism, and less commonly, as part of inherited complex

syndromic disorders such as multiple endocrine neoplasia (MEN). Advances in identifying the genetic causes have resulted in increased understanding of the underlying biological pathways and improvements in diagnosis. The management of symptomatic hypercalcemia includes interventions such as fluids, anti-resorptive medications and parathyroid surgery. This article presents a clinical, biochemical and genetic approach to investigating the causes of pediatric hypercalcemia.

INTRODUCTION

Hypercalcemia in children is less common than in adults, but it nevertheless is more likely to be of clinical significance (1). The differential diagnosis of hypercalcemia in children (Table 1) and adults is similar, but there are marked differences in the frequencies with which they occur. Thus, congenital causes are more frequent in children than acquired causes, such as malignancy, which are more common in adults (Table 1) (1). The causes of the hypercalcemia also depend on the age of the child, with congenital anomalies being more common in neonates, and with adolescents being affected by conditions typically seen in adults. Establishing the causes of hypercalcemia in a child may be challenging and this article reviews these etiologies and proposes a clinical algorithm to facilitate their diagnosis.

DEFINITION AND PRESENTATION OF HYPERCALCEMIA

Hypercalcemia is defined as a serum calcium concentration that is greater than 2 standard deviations above the normal mean, and this in adults is usually an ionised calcium above ~1.32 mmol/L (normal range 1.16-1.32 mmol/L) (Table 2), and a total serum calcium, which comprises 55%-60% ionised calcium plus 40%-45% protein bound (mainly to albumin) calcium, of ~2.60 mmol/L (normal range 2.20-2.60 mmol/L, 8.5-10.5 mg/dl). It is important to distinguish true hypercalcemia from an increased total calcium level secondary to an increase in protein binding, as the two conditions may also overlap. For example hypercalcemia can cause severe dehydration that in turn may result in hyperalbuminemia, resulting in a concurrent increase in calcium binding. The total calcium adjusted for albumin is calculated by the formulae: adjusted calcium = total calcium - albumin + 4.0, where calcium is in mg/100 ml and albumin in g/100 ml (2); or adjusted calcium = total calcium + ({40-albumin}x 0.02), where calcium is in mmol/L and albumin in g/L (equivalent to 0.02 mmol/L calcium for every 1g/L albumin 40g/L). Moreover, ionised and total serum calcium concentrations may vary with age and sex, reflecting changes in the normal physiology at each developmental stage and reference ranges have been established for the different age groups (Table 2). Generally, ionised and total serum calcium concentrations are higher in preterm and full-term neonates, where ionised calcium is above the 95% reference limits for adults from about the third day until at least 2 weeks post-partum (3).

The presentation of hypercalcemia in children may range from an incidental asymptomatic biochemical finding to symptoms of hypotonia, poor feeding, vomiting, constipation, abdominal pain, lethargy, failure to thrive, polyuria, dehydration and seizures (4, 5) . In severe cases, renal failure, pancreatitis and reduced consciousness may also occur, and older children and adolescents may present with psychiatric symptoms (6). Clinical history and examination may provide diagnostic clues and guide further investigations. The presence or

absence of symptoms of hypercalcemia may indicate a particular diagnosis, and the urgency with which investigations should be pursued. For example, mild non-progressive asymptomatic hypercalcemia may potentially indicate a diagnosis of familial hypocalciuric hypercalcemia (FHH), whereas, severe hypercalcemia associated with fractures and respiratory distress is suggestive of the life-threatening disorder of neonatal severe primary hyperparathyroidism (NSHPT) (7). In addition, a dietary assessment, details of existing medical problems and medications (including over-the-counter supplements), and a family history may help to reveal the cause of the hypercalcemia. Physical examination should include an assessment for dysmorphic features, which may reveal a genetic syndrome, and for sequelae of hypercalcemia, such as bony deformities. Finally, the clinical details of the parents should be assessed as the neonate's condition will have been influenced by the *in utero* environment. In addition, it is important to measure the serum calcium concentrations of the parents, because a hypercalcemic neonate may have inherited FHH from the mother, or be at a high risk of developing transient NSHPT if inheritance of FHH, due to an inactivating calcium sensing receptor (CaSR) mutation, is from the father and the mother is normocalcemic (8).

CLASSIFICATION OF HYPERCALCEMIA AND PATHOPHYSIOLOGY

There is no formal classification or grading system for defining the severity of hypercalcemia. However, the severity of clinical symptoms are more likely to be associated with greater elevations in plasma calcium concentrations, and hypercalcemia is generally considered to be mild, moderate and severe for total serum calcium concentrations <12mg/dL (3.00 mmol/L), between 12 and 14 mg/dL (3.00 to 3.50 mmol/L), and >14mg/dL (3.50 mmol/L), respectively (9). A classification of hypercalcemia that is useful in identifying the

underlying etiologies can also be based on an understanding of the pathophysiological mechanisms. Thus, hypercalcemia may arise through increased bone resorption (e.g. from lytic bone lesions), increased gastrointestinal absorption of calcium (e.g. through enhanced $1,25(OH)_2D_3$ production), and decreased renal excretion of calcium (e.g. through the action of thiazides) (Figure 1). Hypercalcemia may result from more than one mechanism; for example excessive PTH causes increased gut absorption of calcium through enhanced $1,25(OH)_2D_3$ production, and also stimulates calcium resorption in bone and renal tubules. The causes of hypercalcemia may also be classified by whether the circulating PTH concentrations are elevated, i.e. hypercalcemia that is PTH-dependent (e.g. as occurring in parathyroid tumors), or reduced, i.e. hypercalcemia that is PTH-independent (e.g. through excessive production of PTHrP by a cancer, or an excess production of downstream mediators such as $1,25(OH)_2D_3$) (Table 1 and Figure 2). Primary hyperparathyroidism (PHPT) and malignancy, which account for >90% of hypercalcemia in adults (10) , are rare in children and likely account for <5% of hypercalcemia in children, in whom other causes, especially those that are PTH-independent and due to genetic abnormalities, are more likely (Table 1). A careful history (e.g. for vitamin D ingestion, drugs, renal disease) and examination (e.g. for dysmorphology, endocrinopathies, granulomatous diseases), together with appropriate investigations will help to establish the diagnosis.

PTH-INDEPENDENT HYPERCALCEMIA

PTH-independent hypercalcemia, which is commoner in children than PTH-dependent hypercalcemia, may be due to many and diverse causes which may be genetic or acquired (Table 1) and include hypervitaminosis D and A; drugs; malignancies; granulomatous disorders; endocrinopathies; renal tubular disorders; chronic inflammatory disorders; infections; immobilisation; congenital syndromes; and inborn errors of metabolism. These disorders, some of which may be associated with either high plasma concentrations of $25(OH)D_3$ or $1,25(OH)_2D_3$ concentrations, will be reviewed (Figure 2).

HYPERCALCEMIA ASSOCIATED WITH HIGH PLASMA $25(OH)D_3$ CONCENTRATIONS

Hypercalcemia following vitamin D intoxication may occur due to incorrect prescriptions or accidental overdosing (11-14). For example, in the summer of 2016, >70 children were reported to develop hypercalcemia after receiving a vitamin D preparation that contained 75 times higher levels than those recommended (15, 16). Hypercalcemia may also complicate the use of single high dose vitamin D therapy (600,000 i.u. vitamin D_3, also known as Stoss (from the German "to shove") therapy), that is utilised by some centres for the treatment of vitamin D insufficiency or deficiency in children with rickets or cystic fibrosis (17-20). The precise mechanism by which high doses of $25(OH)D_3$ can cause hypercalcemia remains unclear. In normal physiology, $25(OH)D_3$ binds to the vitamin D receptor (VDR) with very low affinity in contrast to its active metabolite, $1,25(OH)_2D_3$. In $25(OH)D_3$ toxicity, $25(OH)D_3$ precursors and metabolites are elevated but $1,25(OH)_2D_3$ is usually normal, thereby suggesting that the hypercalcemia is not due to the actions of $1,25(OH)_2D_3$. It has been proposed that the high concentrations of circulating $25(OH)D_3$ displace $1,25(OH)_2D_3$ from the vitamin D binding protein, thereby increasing the free concentrations of

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1,25(OH)$_2$D$_3$ which then stimulate gene transcription via the VDR (21). It is important to note that excessive exposure to sunlight does not pose a risk of vitamin D toxicity, because the UVB light stimulates production and destruction of vitamin D$_3$. Thus, 7-dehydroxyxholesterol is converted to previtamin D$_3$ under UVB, and previtamin D$_3$ is then converted to vitamin D$_3$ at the plasma membrane; however, UVB light also degrades previtamin D$_3$ and vitamin D$_3$, thereby allowing an equilibrium to be reached and thereby preventing excessive vitamin D$_3$ production (22).

HYPERCALCEMIA ASSOCIATED WITH HIGH PLASMA 1,25(OH)$_2$D$_3$ CONCENTRATIONS

High circulating 1,25(OH)$_2$D$_3$ concentrations may arise because of excessive renal synthesis associated with phosphate depletion, extra-renal activation of the 1α-hydroxylase enzyme with overproduction of 1,25(OH)$_2$D$_3$, or because of impaired renal catabolism of 1,25(OH)$_2$D$_3$ to its inactive metabolite 1,24,25(OH)$_3$D$_3$ (Figure 1).

Increased renal synthesis of 1,25(OH)$_2$D$_3$ in association with phosphate depletion
Vitamin D metabolism is affected by phosphate homeostasis and the actions of the phosphate hormone fibroblast growth factor (FGF23) which are to inhibit and stimulate the activities of the renal 1α-hydroxylase (CYP27B1) and 1,25-dihydroxyvitamin D-24-hydroxylase (CYP24A1), respectively (Figure 1). Renal phosphate reabsorption in the proximal tubule involves the sodium-phosphate cotransporters 2A (NaPi-IIa) and 2C (NaPi-IIc), and phosphate reabsorption by NaPi-IIa is controlled by FGF23 and PTH (23). Loss of phosphate transport activity due to defects of NaPi-IIa, encoded by the solute carrier 34A1 gene (SLC34A1), results in phosphate depletion with a decrease in circulating FGF23

concentrations, that releases the inhibition of the 1α-hydroxylase and causes inappropriate excessive production of $1,25(OH)_2D_3$ (23), which leads to hypercalcemia, hypercalciuria and nephrocalcinosis, a combination of features seen in children with idiopathic infantile hypercalcemia (IIH). IIH classically presents in the first year of life with failure to thrive, vomiting, dehydration and lethargy, and may be fatal. The hypercalcemia usually resolves by 1 year of age, but in some individuals it may persist into adulthood (24). In addition, some patients may later develop hypercalciuria and be at risk of developing renal stone disease and osteoporosis, such that long-term surveillance is recommended for these patients (25). IIH is an autosomal recessive disorder, and two types of IIH (IIH1 and IIH2) are recognised, and are due to homozygous, or compound heterozygous mutations of the CYP24A1 and SLC34A1 genes (26)(23)(27).

Extra-renal synthesis of $1,25(OH)_2D_3$ in malignant and granulomatous diseases

Lymphomas and ovarian dysgerminomas can be extra-renal sites of 1α-hydroxylase activity, and hypercalcemia due to elevated production of $1,25(OH)_2D_3$ may occur in 15% and 5% of patients with non-Hodgkins and Hodgkins lymphoma, respectively (28, 29). Similarly, macrophages represent an extra-renal site that can have substantial 1α-hydroxylase activity. Sequestration of macrophages in granulomatous and inflammatory tissues (e.g. sarcoidosis, tuberculosis, HIV immune reconstitution syndrome, leprosy, fungal granuloma including coccidiomycosis, cat scratch fever, Crohn's disease, CMV, histoplasmosis and subcutaneous fat necrosis of the newborn) can cause dysregulated production of $1,25(OH)_2D_3$ leading to hypercalcemia (30-36). Subcutaneous fat necrosis of the newborn (SFN) is an unusual form of lobular panniculitis that typically affects newborns born at term or post-term, often with a preceding history of birth trauma or birth asphyxia, and may occur from birth up until the first 6 weeks of life. SFN may also be associated with hypothermia or therapeutic cooling,

and I̶t̶ is characterised by single or multiple erythematous violaceous plaques and nodules that can evolve into calcifications and tend to occur on the back, face, buttocks and shoulders (31, 32). It is associated with hypercalcemia that can be life threatening and the severity and duration of hypercalcemia are associated with the extent of the skin lesions (31). It has been proposed that an insult on the immature fat cells, such as exposure to cold (e.g. therapeutic hypothermia for hypoxia-ischemia encephalopathy or hypoperfusion) (31), may result in the development of necrosis and the development of a granulomatous infiltrate in the necrotic areas. In keeping with this, abundant levels of 1α-hydroxylase have been found in affected tissues, which may lead to increased production of $1,25(OH)_2D_3$ with associated hypercalcemia as reported in other granulomatous disorders (37).

Impaired degradation of $1,25(OH)_2D_3$

Loss-of-function mutations of 1,25-dihydroxyvitamin D_2 24-hydroxylase, encoded by cytochrome P450 family 24 subfamily A member 1 (*CYP24A1*), resulting in impaired catabolism of $25(OH)D_3$ and $1,25(OH)_2D_3$ to their inactive metabolites $1,24,25(OH)_3D_3$ and $24,25(OH)_2D_3$, may be associated with elevated circulating levels of the active metabolites and the disorder IIH (25, 38).

HYPERCALCEMIA NOT ASSOCIATED WITH ALTERED VITAMIN D CONCENTRATIONS

PTH-independent hypercalcemia may arise without alterations in circulating $25(OH)D_3$ or $1,25(OH)_2D_3$ concentrations, and the causes for this form of hypercalcemia include: malignancies that may produce parathyroid hormone-related peptide (PTHrP); drugs and

vitamins; endocrinopathies; renal tubular disorders; congenital and hereditary syndromes and skeletal diseases; inborn errors of metabolism; and specific neonatal disorders.

Drugs and vitamin A toxicity

Drugs such as thiazides and vitamin A (retinol), vitamin A derivatives (e.g. its active metabolite, retinoic acid), and inappropriate doses of calcium carbonate and sodium bicarbonate to patients with chronic renal failure resulting in milk alkali syndrome can cause hypercalcemia (39-44). Thus, thiazides act to increase renal calcium reabsorption, which may cause hypercalcemia or unmask hypercalcemia from other causes that had been compensated for by hypercalciuria (40, 43, 44). Isotretinoin (13-cis-retinoic acid), which is used for treatment of severe acne and neuroblastoma, may also cause hypercalcemia by increasing osteoclastic bone resorption (41, 45). However, vitamin A toxicity is a rare cause of hypercalcemia and may occur in children with malabsorptive conditions such as cystic fibrosis (39) given supplements containing preformed vitamin A of which 70-90% is absorbed, thereby making children particularly sensitive to overdose. It is important to note that vitamin A toxicity does not occur with high intake of provitamin carotenoids from fruit and vegetables as conversion to the active form of vitamin A is required, and this rarely occurs when large quantities of foods such as fish or animal liver that contain a bioavailable form (retinol) are ingested.

Malignancy and PTHrP

Cancers associated with hypercalcemia in children include hematological malignancies (e.g. leukemias, lymphomas, and myeloma), neurological tumors including neuroblastoma, rhabdomyosarcoma, hepatic tumors (e.g. hepatoblastoma and hepatocellular carcinoma), and dysgerminomas (46-50). Hypercalcemia is associated with malignancy in <1% of children

(4), and may be caused by: osteolysis due to metastases or leukemias; or osteoclastic bone resorption stimulated by hormones (e.g. PTHrP) that are produced by the tumor. PTHrP acts as a paracrine and intracrine hormone to regulate bone development, but some tumors (e.g. renal cell carcinomas, squamous cell carcinomas, dysgerminomas, ovarian and breast carcinomas, pheochromocytoma (51, 52), benign congenital mesoblastic nephroma (53)), multicystic dysplastic kidney disease (54) and renal dysplasia (55, 56)) may secrete PTHrP systemically, and the actions of circulating PTHrP on the type 1 PTH/PTHrP receptor cause hypercalcemia.

Endocrinopathies

Endocrine disorders, such as pheochromocytoma, Addison's disease, thyrotoxicosis and severe congenital hypothyroidism may be associated with development of hypercalcemia in children. The hypercalcemia associated with pheochromocytoma may be due to secretion of PTHrP (51, 52). In Addison's disease the hypercalcemia may be due to increased intestinal calcium absorption (57), that is possibly aggravated by volume depletion due to lack of mineralocorticoid hormone. Thyroid hormone in children increases bone resorption and skeletal growth; however, in thyrotoxicosis there is also premature fusion of growth plates, resulting in short stature (57), which leads to a negative balance between bone formation and resorption (58) and this may possibly explain the development of hypercalcemia. Severe congenital hypothyroidism in neonates may be associated with mild hypercalcemia in <40% of children (59), although it is rarely symptomatic and the mechanisms remain unknown. Moreover, levothyroxine treatment in children with congenital hypothyroidism (59) may also lead to an increase in circulating levels of $1,25(OH)_2D_3$ and hypercalciuria, and

hypercalcemia has been reported to only occur in neonates with congenital hypothyroidism who were treated with levothyroxine and vitamin D supplementation, although the hypercalcemia was not correlated with circulating vitamin D concentrations or metabolites of vitamin D (60).

Renal tubular disorders

Distal renal tubular acidosis has been reported to be associated with hypercalcemia (61). In addition, Bartter syndrome type 1 (neonatal), which is characterized by metabolic alkalosis, renal hypokalemia and secondary hyperaldosteronism (62), and is due to mutations in the sodium-potassium-chloride co-transporter-2 gene (*SLC12A1*), has also been reported to be associated with hypercalcemia, hypercalciuria and nephrocalcinosis (62-64). However, the hypercalcemia was associated with increased circulating PTH concentrations, which may be explained by an inappropriate response to hypocalcemia secondary to hypercalciuria (63) and is consistent with marginally increased circulating PTH concentrations that have been reported in other, older children with Bartter syndrome (64).

Inborn errors of metabolism

Inborn errors of metabolism that are reported to be associated with hypercalcemia include hypophosphatasia (HPP), congenital lactase deficiency (CLD), disaccharide intolerance and blue diaper syndrome. HPP is characterised by reduced bone mineralization due to loss-of-function mutations in tissue-nonspecific alkaline phosphatase (TNSALP), encoded by the *Alkaline Phosphatase Liver/Bone/Kidney* (*ALPL)* gene. HPP is classified into 6 forms, and each is characterised by age of onset and severity of symptoms, ranging from severe perinatal (lethal), where respiratory distress from a hypoplastic chest is the main cause of death, to milder odontohypophosphatasia, where only dental manifestations are seen (65). Patients

present perinatally or in childhood and >30% may have hypercalcemia (66). The hypercalcemia is seen in the infantile form of HPP, and may resolve spontaneously within the first year of life (67), or following targeted asfotase alfa enzyme replacement therapy (68). However, hypercalcemia may occur in adults with HPP who have been immobilized (69). In CLD, the severely reduced or absent activity of the gut enzyme lactase, leads to an inability to breakdown dietary lactose, which results in osmotic diarrhoea, dehydration and weight loss shortly after feeding commences, and patients typically have hypercalcemia with nephrocalcinosis. CLD, an autosomal recessive disorder (70-73), is caused by a mutation of the lactase-phlorizin hydrolase gene, with a reported incidence of 1:60,000 newborns in Finland (73), although it can occur in other populations (70-73). Hypercalcemia in CLD usually resolves within weeks after starting a lactose-free diet, whereas nephrocalcinosis may persist for years (74). The hypercalcemia in CLD may be secondary to, or exacerbated by, dehydration and a metabolic acidosis, or be by a direct action of lactose on the gut (74). Hypercalcemia and nephrocalcinosis may also complicate the presentation of *sucrose-isomaltase deficiency* (75), and it is thought that there may be a similar underlying mechanism to CLD. *Blue diaper syndrome* is due to an abnormality of tryptophan metabolism that results in diarrhoea in association with excessive urinary excretion of indole derivatives (76). The characteristic "blue diaper" is caused by the high levels of indecan formed when high levels of unabsorbed tryptophan in the intestine are metabolised by bacteria (76). The mechanisms causing hypercalcemia in blue diaper syndrome, which is associated with hypercalciuria and nephrocalcinosis, are not known. Hypercalcemia in the absence of renal dysfunction may also be a rare complication of primary oxalosis (77) and has also been reported in IMAGe Syndrome (characterized by Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital anomalies) (78).

Immobilisation

Immobilisation hypercalcemia may occur in 10-23% of children with spinal cord injuries, in association with suppressed plasma PTH concentrations, within 4-8 weeks of the injury (79), and be preceded by hypercalciuria, which may develop within the first week and continue for up to 18 months (79). Immobilisation hypercalcemia also occurs in some children after single limb fractures (80). The hypercalcemia is more common in adolescents and males, possibly because of increased bone turnover associated with rapid growth, and a higher bone mass, respectively (79). The mechanism is not understood but is thought to result from increased osteoclastic activity and reduced osteoblastic activity due to a lack of mechanical stimulation (79).

Congenital syndromes and diseases

Hypercalcemia is more likely to be genetic in children than in adults, and may occur as part of congenital syndromes that are associated with dysmorphism and/or skeletal abnormalities. These disorders, which include Williams syndrome, Jansen's disease and Down syndrome are often detected early in life. However, in some cases dysmorphia may be subtle or missed, and therefore the diagnoses should not necessarily be ruled out on the basis of age alone.

Williams syndrome

Williams syndrome affects approximately 1 in 7,500-10,000 individuals (81) and is characterised by elfin-like facies, learning disabilities, supravalvular aortic stenosis, nephrocalcinosis, urinary tract abnormalities, and endocrinopathies including hypercalcemia, which affects 5 to 50% of patients (81-83). It usually occurs sporadically, but may be inherited in an autosomal dominant manner (84). The mechanisms causing hypercalcemia, which may resolve spontaneously within days to weeks (83), remain unknown, but abnormal

$1,25(OH)_2D_3$ metabolism and decreased calcitonin production have been implicated (81, 83, 85), although no abnormality has been consistently demonstrated. Hemizygosity due to a microdeletion of chromosome 7q11.23 involving the *ELASTIN* and *LIM-KINASE* genes, which may explain the respective cardiovascular and neurologic features, have been reported in Williams syndrome. However, the calcitonin receptor gene, located on chromosome 7q21 and close to the region deleted in Williams syndrome, was not involved in the deletion in four patients, indicating that it is unlikely to be implicated in the hypercalcemia of such children. Another, as yet uncharacterised gene that is within this contiguously deleted region is likely to be involved to explain the abnormalities of calcium metabolism.

Jansen's Disease

Jansen's metaphyseal chondroplasia is an autosomal dominant disease characterised by short limbed dwarfism in association with severe hypercalcemia and hypercalciuria, despite normal or undetectable PTH and PTHrP concentrations. These abnormalities are associated with heterozygous mutations of the PTH-PTHrP receptor, causing constitutive ligand independent activation (86).

Down syndrome

Down syndrome, which is due to trisomy 21, is one of the most frequent genetic causes of dysmorphism, and occurs in 1 in 690 live births (87). Down syndrome has been reported in association with hypercalcemia and nephrocalcinosis in 6 patients (88). The mechanisms causing the hypercalcemia are unknown, although the hypercalcemia does appear to respond to dietary calcium restriction suggesting increased intestinal absorption as a possible etiology (88).

Acquired causes of neonatal hypercalcemia

Nutritional

Enriched formula and/or phosphate depletion can cause hypercalcemia in preterm newborns (89) and, less frequently, in newborns born at term (90). Phosphate depletion may suppress secretion of FGF-23, alleviating the inhibitory effect of FGF-23 on $1,25(OH)_2D_3$ production (Figure 1), causing an increase in $1,25(OH)_2D_3$ levels resulting in hypercalcemia. The data on plasma PTH concentrations from such babies is scant and it has been suggested that as the hypercalcemia is associated with hypophosphatemia and increased plasma $1,25(OH)_2D_3$ concentrations, then the plasma PTH is likely to be low (90). The hypercalcemia in these very low birth weight babies fed breast milk, which has a relatively high calcium to phosphate content, can be ameliorated by early administration of phosphate supplements (89).

PTH-DEPENDENT HYPERCALCEMIA

PTH-dependent hypercalcemia is usually caused by parathyroid tumors, which may give rise to PHPT or tertiary hyperparathyroidism (Table 1 and Figure 2). PHPT usually occurs as an isolated non-syndromic non-hereditary endocrinopathy and less commonly, as part of inherited complex syndromic disorders such as multiple endocrine neoplasia (MEN) and hyperparathyroid jaw-tumor syndrome (HPT-JT) (91). Tertiary hyperparathyroidism usually arises in association with chronic renal failure, and may also occur in the treatment of children with hypophosphatemic rickets (92).

The main non-parathyroid tumor related cause of PTH-dependent hypercalcemia in children is gestational maternal hypocalcemia (Table 1). This acquired cause of hypercalcemia may be apparent from the clinical history and preliminary investigations,

whereas the causes associated with parathyroid tumors, which include genetic abnormalities may be more challenging, and will be reviewed further.

GENETIC CAUSES OF HYPERCALCEMIA

PHPT may occur as a hereditary familial disorder or sporadically, i.e. as non-familial disease (93-95); however, distinguishing between sporadic and non-familial forms may sometimes be difficult. Sporadic PHPT may be the result of a *de novo* germline mutation in the patient or due to an inherited mutation with an absent family history, for example if family members have not been investigated or have died before developing symptoms (91). Both *de novo* and inherited mutations resulting in PHPT will lead to an increased risk of hereditary PHPT in the children of the patient (93-96). Studies of patients with both syndromic and non-syndromic forms of PHPT have shown that >10% will harbor a germline mutation in one of 12 genes (Table 3) (55, 93, 94, 97, 98). The non-syndromic forms, which include familial hypocalciuric hypercalcemia (FHH), neonatal severe primary hyperparathyroidism (NSHPT), and familial isolated primary hyperparathyroidism (FIHP), are likely to be more frequent than the syndromic disorders of MEN and HPT-JT.

Syndromic PHPT

Multiple Endocrine Neoplasia (MEN)

Multiple Endocrine Neoplasia (MEN) is an autosomal dominant disorder in which patients develop 2 or more endocrine tumors. Four types of MEN (MEN1-4) are recognised with each associated with a distinct set of endocrine tumors; however, parathyroid tumors occur in all of the MEN syndromes. Thus, in MEN1 patients, parathyroid tumors occur in 95% of

patients in association with pancreatic islet cell tumors (~40% of patients), anterior pituitary tumors (~30% of patients) and adrenocortical tumors (~40% of patients) (96). In MEN1, parathyroid tumors causing hypercalcemia are the first manifestation of the disease in 90% of patients, and parathyroid tumors may develop as early as 8 years of age, although only 17% of cases below 21 years of age will be symptomatic with urolithiasis, fatigue and bone pain, with the youngest symptomatic case being aged 8 years with urolithiasis (99). In MEN1, hyperparathyroidism is typically a multigland disease affecting all 4 parathyroid glands and patients who undergo subtotal parathyroidectomy usually develop recurrent hypercalcemia within a decade (100, 101). In MEN2, parathyroid tumors occur in ~20% of patients, in association with medullary thyroid carcinoma (MTC) (~99% of patients) and pheochromocytomas (~50% of patients) (96, 101). In MEN3, MTC and pheochromocytomas are also common, but parathyroid tumors are rarely seen; instead patients have other features such as a Marfanoid habitus, mucosal neuromas, medullated corneal nerve fibres and intestinal autonomic ganglion dysfunction leading to multiple diverticula and megacolon. Only a few patients with MEN4 have been described; all have parathyroid tumors in association with other tumors affecting the adrenals, pituitary and gonads (102). MEN1 is caused by a mutation in the tumor suppressor *MEN1* gene encoding menin; MEN2 and MEN3 are caused by mutations in the proto-oncogene *RET,* encoding a tyrosine kinase receptor; and MEN4 is caused by mutations of *CDNK1B*, encoding p27 (96, 101).

Hyperparathyroidism-Jaw Tumor (HPT-JT) syndrome

The HPT-JT syndrome, an autosomal dominant disorder, is characterised by the development of multiple parathyroid tumors, which may be carcinomas, and fibro-osseous tumors of the maxilla and mandible (94). Some families also have increased risk of developing renal tumors and affected women have greater risk of developing uterine tumors (94). However, in

some families the affected individuals may have developed only parathyroid tumors without other tumors or jaw tumors, and this may cause confusion with other hereditary hypercalcemic disorders such as MEN1, FHH and FIHP (93). HPT-JT is due to mutations of the Cell Division Cycle 73 (*CDC73*) gene, which is a tumor suppressor encoding parafibromin that is involved in transcriptional and post-transcriptional pathways (94). Parathyroid tumors with hypercalcemia occur in >70% of individuals with *CDC73* mutations, with the onset being typically in late adolescence or early adulthood (103-106). The youngest patient reported with hypercalcemia is 7 years old (103), and the youngest patient reported with parathyroid carcinoma is 20 years old (107). Germline pathogenic *CDC73* mutations have also been reported in patients with apparently sporadic: parathyroid carcinoma; parathyroid adenoma; or ossifying fibromas of the jaw (108). Due to the potential for early onset of tumors, biochemical surveillance for PHPT, starting from age 5-10, is recommended in individuals known to be at risk (103).

Non-Syndromic PHPT

Familial Hypocalciuric Hypercalcemia (FHH)

FHH is characterized by lifelong elevations of serum calcium concentrations, elevated or inappropriately normal plasma PTH concentrations, and low urinary calcium excretion resulting from PTH–independent reduced calcium excretion in the kidneys (109). The hypercalcemia of FHH is considered to be primarily due to inappropriate conservation of calcium in the kidney rather than being driven by an inappropriate PTH concentration (109). The mean calcium: creatinine clearance ratio (CCCR) (measured in either molar units or mass units) is typically <0.01 in FHH. However, more than 20% FHH patients have a CCCR >0.01, and such patients are at risk of being misdiagnosed with PHPT (110-112). In contrast

to PHPT, the hypercalcemia in FHH is generally benign and is not corrected by parathyroidectomy, therefore distinguishing between PHPT and FHH is important to avoid unnecessary surgery in FHH patients.

FHH is an autosomal dominant, genetically heterogeneous disorder with 3 clinically indistinguishable variants (FHH1-3) (111, 113). FHH1 comprises ~65% of FHH patients and is due to loss-of-function mutations of the calcium-sensing receptor (CaSR), a G-protein-coupled receptor (GPCR). FHH2 comprises <5% of all FHH patients and is due to loss-of-function mutations of $GNA11$, which encodes G-protein subunit α-11 (Gα$_{11}$) (111). FHH3 may occur in ~20% of FHH patients without CaSR mutations (9) and is due to loss-of-function mutations of the adaptor-related protein complex 2, sigma 1 subunit ($AP2S1$) gene. The $AP2S1$ gene encodes the adaptor-protein 2 sigma (AP2σ) subunit that forms a heterotetramer with other subunits, and plays a central role in clathrin-mediated endocytosis of plasma membrane constituents such as GPCRs (9).

As FHH is usually asymptomatic, the age of diagnosis will be variable, with individuals with concurrent medical problems or hypercalcemic symptoms being detected earlier. The youngest age of diagnosis of FHH1 is in a 4.5 month old Greek infant who had a urinary tract infection with incidental hypercalcemia (114). The youngest age for diagnosis of FHH3 is in a Japanese infant who aged 49 days presented with poor weight gain and had an $AP2S1$ mutation (115). FHH3 children are more likely than FHH1 children to be symptomatic, and to have additional phenotypic features, and thus may present earlier (116). For example, four FHH3 children, aged <1 to 11 years, have been reported to have learning difficulties (LD); one aged 14 years had LD, pancreatitis and short stature (SS); and one aged 15 years had LD, an atrial septal defect, and SS (116).

Neonatal Severe Primary Hyperparathyroidism (NSHPT)

Neonatal severe primary hyperparathyroidism (NSHPT) usually presents at birth with marked hypercalcemia, hypotonia, respiratory distress and bone demineralisation, and is usually fatal by 3 months if untreated. Bone demineralization occurs due to osteoclast over-activity and can result in bone deformities and fractures presenting at birth. Respiratory difficulties may arise from rib cage involvement. Most cases are associated with homozygous or compound heterozygous loss-of-function CaSR mutations (117) and some may occur in FHH families, either through inheriting two mutated copies of the *CASR* gene as in consanguineous families, or one copy together with a *de novo CASR* mutation. Urgent parathyroidectomy is life saving and the treatment of choice, but pamidronate or cinacalcet have been used for treatment whilst awaiting surgery (118). Cinacalcet is a positive allosteric modulator of the CaSR and will ameliorate signalling disturbances associated with most loss-of-function CaSR mutations; however if both *CASR* alleles have mutations whereby the CaSR is not expressed e.g. with a homozygous deletion in exon 5 (c.1392_1404del13), then cinacalcet will be ineffective (119). Some centres distinguish between NSHPT and neonatal hyperparathyroidism (NHPT) on the basis of homozygous and heterozygous CaSR mutations, respectively. NHPT may be associated with less marked and symptomatically transient hypercalcemia than NSHPT, with some patients developing symptom-less FHH, and therefore not requiring parathyroid surgery (120). This highlights the value of *CASR* mutational analysis in distinguishing NSHPT from NHPT.

Familial Isolated Primary Hyperparathyroidism (FIHP)

FIHP is characterized by hereditary PHPT occurring without the association of other tumors and has been described in >100 families (91, 93). The diagnosis of FIHP is based on excluding other hereditary disorders associated with PHPT such as MEN1, MEN2, MEN4, HPT-JT and FHH, and by screening for mutations in known causative genes, such as *MEN1, RET, CDKN1B, CDC73,* and *CASR* respectively (91). In the majority of these families the

genetic etiology of FIHP remains unknown (121, 122). However patients with activating mutations of glial cells missing 2 (*GCM2)*, a parathyroid-specific transcription factor, have been reported (123), as well as one PHPT patient who had a nonsense mutation of the *PTH* gene (124). Approximately 10% of patients presenting under the age of 45 years with sporadic PHPT will have a *de novo* germline *MEN1, CDC73, GCM2* or *CASR* mutation (93-95, 125, 126), and this has implications for their future management, to ensure appropriate screening for complications associated with the specific syndrome, and for screening first-degree relatives. The finding of a mutation in *MEN1, RET, CDC73* or *CDKN1B* in an apparent FIHP kindred would lead to a revised diagnosis of one of the associated syndromes with incomplete penetrance (93) and, in some families, FIHP may represent an incomplete manifestation of a syndromic form of PHPT caused by an as yet undiscovered mutation (93, 127, 128). Some patients diagnosed as having FIHP have later been reported to develop features of MEN1 (93-97, 127) and, in addition, some FIHP kindreds have associated *MEN1* mutations and may represent an allelic variant of MEN1 (127).

FIHP may be distinguished from MEN1, FHH and HPT-JT through clinical, histological and genetic findings. Over 90% of MEN1 and HPT-JT patients develop hypercalcemia as their first manifestation of the disease, and distinguishing between MEN1 and HPT-JT patients at this early stage from FIHP patients can be difficult (91, 93, 98). It is important to distinguish FIHP from HPT-JT, as HPT-JT patients are at higher risk for developing parathyroid carcinomas (129-132). The presence of ossifying fibromas of the jaw is an important distinguishing feature of HPT-JT and the identification of renal, pancreatic, thyroid, and testicular abnormalities may also help to identify HPT-JT patients. The jaw tumors in HPT-JT differ from the brown tumors observed in some PHPT patients and do not resolve after parathyroidectomy (133). Similarly, the occurrence of pancreatic, pituitary or adrenal tumors in the patient or family will suggest a diagnosis of MEN1 rather than FIHP.

FIHP may be distinguished from FHH on the basis of plasma and urinary calcium findings. In FHH, serum calcium levels are elevated from the neonatal period, whereas in FIHP, hypercalcemia rarely occurs until after the first decade (98, 127). FIHP patients are likely to have associated hypercalciuria, unlike FHH patients who usually have a CCCR <0.01 (116). However, there are considerable clinical overlaps between these disorders, and genetic testing is advisable for making the correct diagnosis.

Genetic testing in patients with syndromic and non-syndromic forms of PHPT

Genetic testing for mutations in PHPT patients is worthwhile as >10% of patients with PHPT will have a mutation in one of 13 genes (Table 3) and therefore benefit from an accurate diagnosis (91). Thus, genetic testing may provide confirmation of the clinical diagnosis (i.e. syndromic or non-syndromic PHPT) and allow appropriate screening for associated tumors to be undertaken, with implementation of appropriate treatment, e.g: early parathyroidectomy for HPT-JT patients who are at increased risk of developing parathyroid carcinomas; appropriate parathyroid surgery in MEN1 patients who generally have multigland disease requiring open neck exploration; and avoidance of unnecessary parathyroidectomies in FHH patients (91). Asymptomatic mutation carriers should receive screening for associated tumors to facilitate appropriate treatment, and the 50% of family members who do not harbor the germline mutation can be reassured and alleviated of the anxiety of developing the condition (93-95), thereby reducing costs to the individuals, and also to the health services in avoiding unnecessary biochemical and radiological investigations (93-95, 98).

Indications for genetic testing in PHPT patients include: 1) young age of presentation, i.e. <45 years of age; 2) multigland disease; 3) parathyroid carcinoma or atypical parathyroid adenomas (e.g. with fibrous bands or cysts); 4) being a first-degree relative of a known mutation carrier; and 5) being an index case with 2 or more MEN syndrome associated

tumors (93-95, 98, 126, 134). Patients should be offered genetic counselling prior to testing, and genetic testing should use non-tumor cells, (e.g. DNA obtained from leukocytes, salivary cells, skin cells or hair follicles), as DNA from parathyroid tumors may contain multiple mutations in addition to the germline mutation and therefore is not clinically useful (91). Individuals with PHPT identified to have a germline mutation should enter into an appropriate screening programme, e.g. for MEN and HPT-JT associated tumors (93, 94). If no genetic abnormalities are found within the 13 genes (Table 3), and clinical manifestations of hereditary or syndromic forms of PHPT are absent, then the likelihood of a MEN syndrome, HPT-JT or FHH is low (i.e. <5%) (93-95, 98). The first-degree relatives of PHPT patients, including children, with a germline mutation should be offered genetic counselling and appropriate gene testing, and any affected individuals subsequently identified should also enter into an appropriate screening programme, even if asymptomatic (93-95, 134). First-degree relatives who have not inherited the causative mutation require no further follow-up and can be reassured (93, 94).

Patients who present with PHPT at a later age, i.e. >45 years, and who have an underlying syndromic etiology for their PHPT, are more likely to have manifested other associated features that may be revealed during clinical evaluation. A detailed family history for PHPT (i.e. FIHP), MEN syndrome, HPT-JT or FHH should be undertaken, and gene testing should then be offered to determine the etiology of the PHPT (93-95, 110, 124, 134). However, up to 5% of patients >45 years of age with sporadic PHPT due to a solitary parathyroid adenoma may have a germline mutation involving *CDKN1A*, *CDKN2*, or *CDKN2C* (91), and this may have implications for their children. Such first-degree relatives of a patient with a mutation in *CDKN1A*, *CDKN1B* or *CDKN1C* who are also found to be mutation carriers should then have periodic screening to detect the onset of hypercalcemia in

order to facilitate appropriate earlier treatment aimed at preventing the skeletal and renal complications of PHPT (93, 95, 97, 98).

ACQUIRED CAUSES OF NEONATAL HYPERCALCEMIA

Neonatal hyperparathyroidism

Neonatal hyperparathyroidism may be an adaptation to maternal hypocalcemia due to hypoparathyroidism, vitamin D deficiency, pseudohypoparathyroidism or renal tubular acidosis (4), although in the latter, PTH is often high with normal calcium. Maternal hypervitaminosis D does not usually affect the neonate, as $1,25(OH)_2D_3$ is inactivated by the placenta, so excessive maternal $1,25(OH)_2D_3$ consumption should not cause hypercalcemia in the newborn. However, there have been case reports of excessive maternal intake of $1,25(OH)_2D_3$ and $25(OH)D_3$ causing hypercalcemia in the neonate (135, 136).

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is a technique used in pediatric resuscitation as a way of providing tissue oxygenation in cases of refractory hypoxemia to allow time for treatment of the underlying cause of the disorder to take effect. It is associated with metabolic disturbances including hypercalcemia (137-139), although the mechanisms for this are not known, but may be related to increased circulating PTH concentrations (138).

MANAGEMENT OF HYPERCALCEMIA

The management of hypercalcemia involves establishing the underlying diagnosis in parallel with lowering serum calcium levels. Medications, which may cause or exacerbate the hypercalcemia, such as calcium and vitamin D preparations should be stopped. Symptomatic

hypercalcemia may require fluid administration to rectify intravascular volume contraction caused by hypercalcemia-induced nephrogenic diabetes insipidus (140). Normal (0.9%) saline given intravenously is effective at rehydrating the patient, thereby diluting serum calcium concentrations (5). Moreover, normal saline lowers serum calcium concentrations by promoting urinary calcium excretion from the proximal renal tubule and Loop of Henle (140). Loop diuretics such as furosemide can also enhance urinary calcium excretion (140), but should be used cautiously, as they may exacerbate the intravascular volume contraction and lead to renal impairment (4). Subcutaneous calcitonin is an effective anti-resorptive agent for symptomatic hypercalcemia, however its effects are short-lived due to tachyphylaxis (4). The use of I-V bisphosphonates leads to a more sustained reduction in serum calcium concentrations, and pamidronate (0.5-1.0 mg/kg) is used most commonly in children (140). Patients should be adequately hydrated prior to receiving I-V bisphosphonates in order to minimise the potential risk of nephrotoxicity, which has been widely reported in adults (141). Glucocorticoids such as prednisolone are effective at rectifying hypercalcemia caused by granulomatous disorders, although long-term use may increase skeletal fragility and impair linear growth (4) (140). Cinacalcet, which is a CaSR positive allosteric modulator, has been successfully used to manage life-threatening hypercalcemia in some NSHPT probands (142). However, the effectiveness of cinacalcet for NSHPT will depend on the underlying CaSR mutation, and patients harboring biallelic truncating CaSR mutations will be unlikely to respond to this calcimimetic agent (143). Parathyroidectomy remains the treatment of choice for children with primary hyperparathyroidism or NSHPT, as it represents a curative procedure for these disorders (144). Hypocalcemia due to hungry bone syndrome or postsurgical hypoparathyroidism represents the most common complication of parathyroidectomy, and close monitoring of serum calcium concentrations is required following surgery (140, 144).

CONCLUSIONS

The majority of causes of hypercalcemia in children are similar to those in adults, but occur at different frequencies across the age spectrum from birth to maturity. Hypercalcemia has a broad differential diagnosis (Table 1), and comprehensive clinical assessment followed by step-wise use of investigations is necessary to elucidate the underlying cause (Figure 2). Determining the etiology of hypercalcemia is critical for successful treatment, and for ensuring the child's growth and development.

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Table 1. Causes of hypercalcemia in children

	PTH-dependent hypercalcemia	PTH-independent hypercalcemia
Genetic	• FHH1-3 • nsPHPT • *NSHPT* • FIHP • MEN 1,2, 3 and 4 • HPT-JT	• IIH • Williams syndrome • Down syndrome • Hypophosphatasia • Jansen's disease • *Inborn errors of metabolism, e.g. CLD, Bartter syndrome, blue diaper syndrome, sucrose-isomaltase deficiency, primary oxalosis, IMAGe syndrome*
Acquired	• Tertiary hyperparathyroidism due to chronic renal failure or treatment for hypophosphatemic rickets • *Gestational maternal hypocalcemia*	• Hypervitaminosis D and A • Malignancies causing osteolysis (e.g. ALL, AML), or secreting PTHrP (e.g. lymphoma, medulloblastoma, rhabdomyosarcoma, hepatoblastoma or hepatocellular carcinoma), or secreting $1,25(OH)_2D_3$ (e.g. lymphoma or ovarian dysgerminoma) • Drugs, e.g. thiazides, chemotherapy including 13-cis-retinoic acid, milk-alkali syndrome • Granulomatous disease, e.g. *subcutaneous fat necrosis of the newborn*, tuberculosis, sarcoidosis, HIV immune reconstitution syndrome, cat scratch fever, histoplasmosis, coccidiomycosis, leprosy • Endocrinopathies, e.g. thyrotoxicosis, *congenital hypothyroidism*, Addison's disease, pheochromocytoma • Distal renal tubular acidosis • Multicystic dysplastic kidney disease and renal dysplasia • Chronic inflammatory disorders, e.g. Crohn's disease • Infection, e.g. *disseminated CMV* • Immobilisation • *Nutritional and phosphate depletion in preterm neonates*

Causes more likely to be contributing to neonatal or infantile hypercalcemia are shown in italics.
Abbreviations:
Primary hyperparathyroidism (PHPT)
Familial hypocalciuric hypercalcemia types 1, 2, and 3 (FHH1, FHH2, FHH3)
Neonatal severe primary hyperparathyroidism (NSHPT)
Familial isolated hyperparathyroidism (FIHP)
Non-syndromic primary hyperparathyroidism (nsPHPT)
Multiple endocrine neoplasia types 1, 2, 3 and 4 (MEN1, MEN2, MEN3 and MEN4)
Hyperparathyroid jaw-tumour syndrome (HPT-JT)
Idiopathic infantile hypercalcemia (IIH)
Congenital lactase deficiency (CLD)
Syndrome characterized by Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital anomalies (IMAGe Syndrome)
Acute lymphoblastic leukaemia (ALL)
Acute myeloid leukaemia (AML)
1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$)

Cytomegalovirus (CMV)
Human Immunodeficiency Virus (HIV)

Table 2. Age-specific reference intervals for serum total and ionized calcium concentrations

Age range	Total calcium[a]		Ionized calcium[b]	
	mg/dL	mmol/L	mg/dL	mmol/L
Cord blood	8.2-11.2	2.05-2.80	5.20-6.40[b]	1.30-1.60[b]
Neonate (24h)	NR	NR	4.40-5.44[b]	1.10-1.36[b]
Neonate (5d)	NR	NR	4.88-5.92[b]	1.22-1.38[b]
Birth to 90d	8.0-11.3[a]	2.00-2.80[a]	NR	NR
91-180d	8.9-11.2[a]	2.20-2.80[a]	NR	NR
181-364d	9.0-11.3[a]	2.30-2.80[a]	NR	NR
1-3y	8.9-11.1[a]	2.20-2.80[a]	4.80-5.52[b]	1.20-1.38[b]
4-11y	8.7-10.7[a]	2.20-2.70[a]	4.80-5.52[b]	1.20-1.38[b]
12-18y	8.5-10.7[a]	2.10-2.70[a]	4.80-5.52[b]	1.20-1.38[b]
>19y	8.5-10.5[a]	2.20-2.60[a]	4.64-5.28[b]	1.16-1.32[b]

[a]Serum total calcium measured in vitamin D replete children and young adults, excluding those from renal, endocrine and critical care unit; thus these individuals likely had a plasma albumin in the

normal range (with serum $25(OH)D_3$ concentrations of 30-80 mg/dL or 75-200 nmol/L) and adapted from Roizen et al. J Clin Endocrinol Metab (1). [b]Cord blood calcium concentrations and serum ionized calcium concentrations adapted from Tietz Clinical Guide to Laboratory Tests. 4th Edition. Author: Alan Wu. Imprint: Saunders. Copyright 2006. h, hours; d, days; y, years; NR, not reported.

Table 3 - Genetic disorders associated with primary hyperparathyroidism

Disorder[a]	Chromosomal location	Gene
FHH 1	3q21.1	*CASR*
FHH 2	19p13	*GNA11*
FHH 3	19q13.2-q13.3	*AP2S1*
NSHPT	3q21.1	*CASR*
nsPHPT	11p15.3-p15.1, 6p24.2	*PTH*[b]*, GCM2*[c](116)
FIHP	11q13, 1q31.2, 3q21.1, 6p21.2, 9p21, 1p32, 6p24.2	*MEN1, CDC73, CASR, CDKN1A, CDKN2B, CDKN2C, GCM2*
MEN 1	11q13	*MEN1*
MEN 2 / MEN3	10q11.2	*RET*
MEN4	12p13	*CDKN1B*
HPT-JT	1q31.2	*CDC73*

[a]Inheritance of all disorders is autosomal dominant, but NSHPT can be recessive
[b]A nonsense PTH mutation has been reported in one patient
[c]Activating mutations of GCM2
Familial hypocalciuric hypercalcemia types 1, 2 and 3 (FHH1, FHH2, FHH3)
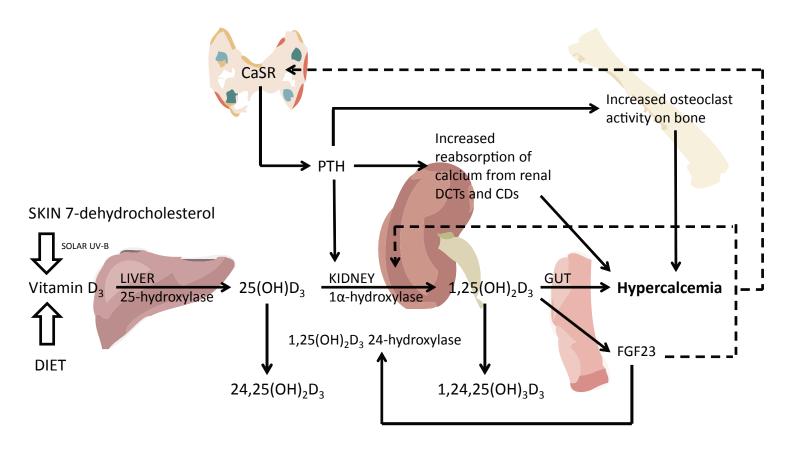Neonatal severe primary hyperparathyroidism (NSHPT)
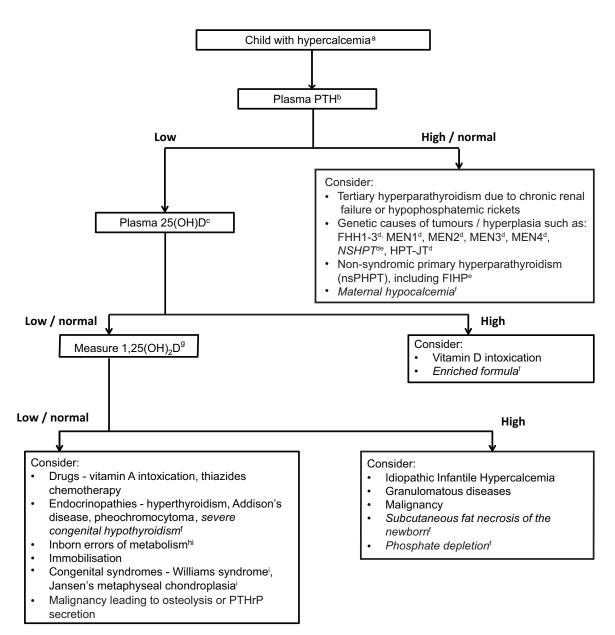Familial isolated hyperparathyroidism (FIHP)
Non-syndromic primary hyperparathyroidism (nsPHPT)
Multiple endocrine neoplasia types 1, 2, 3 and 4 (MEN1, MEN2, MEN3 and MEN4)
Hyperparathyroid jaw-tumour syndrome (HPT-JT)

Figure 1. Hormonal regulation of extracellular calcium homeostasis. Parathyroid hormone (PTH) is the principle calcitropic hormone, and acts to elevate calcium levels by promoting osteoclastic activity on bone, increasing reabsorption of calcium from renal distal tubules and collecting ducts, and stimulating renal enzyme 1alpha-hydroxylase (1α-hydroxylase) conversion of 25-hydroxyvitamin D_3 (25(OH)D_3) into the active 1,25-hydroxyvitamin D_3 (1,25(OH)$_2D_3$). 25(OH)D_3 is produced from vitamin D_3, formed by the action of solar UV-B on the skin or taken in through the diet, by the liver enzyme 25-hydroxylase. 1,25(OH)$_2D_3$ is released into the circulation and stimulates calcium uptake from the gut. Rising serum calcium levels are detected by the calcium-sensing receptor (CaSR), which facilitates a negative feedback on the parathyroid glands and PTH secretion attenuates to maintain homeostasis. 1,25(OH)$_2D_3$ is also regulated by Fibroblast Growth Factor-23 (FGF-23), the main function of which is to regulate plasma phosphate concentrations. It is secreted by osteocytes in response to an elevated 1,25(OH)$_2D_3$ concentration and acts on the kidney proximal tubules to inhibit reabsorption and increase excretion of phosphate. It also inhibits 1α-hydroxylase, thereby exerting a negative feedback on 1,25(OH)$_2D_3$ and promotes the action of 1,25(OH)$_2D_3$ 24-hydroxylase, leading to lower levels of 1,25(OH)$_2D_3$ and reduced calcium absorption from the gut.

CaSR

Increased osteoclast activity on bone

PTH

Increased reabsorption of calcium from renal DCTs and CDs

SKIN 7-dehydrocholesterol

SOLAR UV-B

Vitamin D_3

LIVER 25-hydroxylase

25(OH)D_3

KIDNEY 1α-hydroxylase

1,25(OH)$_2D_3$

GUT

Hypercalcemia

DIET

1,25(OH)$_2D_3$ 24-hydroxylase

24,25(OH)$_2D_3$

1,24,25(OH)$_3D_3$

FGF23

Figure 2. Clinical approach to investigation of causes of hypercalcemia in a child

Child with hypercalcemia[a]

Plasma PTH[b]

Low

High / normal

Consider:
- Tertiary hyperparathyroidism due to chronic renal failure or hypophosphatemic rickets
- Genetic causes of tumours / hyperplasia such as: FHH1-3[d,] MEN1[d], MEN2[d], MEN3[d], MEN4[d], *NSHPT*[de], HPT-JT[d]
- Non-syndromic primary hyperparathyroidism (nsPHPT), including FIHP[e]
- *Maternal hypocalcemia*[f]

Plasma 25(OH)D[c]

Low / normal

High

Consider:
- Vitamin D intoxication
- *Enriched formula*[f]

Measure 1,25(OH)$_2$D[g]

Low / normal

High

Consider:
- Drugs - vitamin A intoxication, thiazides chemotherapy
- Endocrinopathies - hyperthyroidism, Addison's disease, pheochromocytoma, *severe congenital hypothyroidism*[f]
- Inborn errors of metabolism[hi]
- Immobilisation
- Congenital syndromes - Williams syndrome[i], Jansen's metaphyseal chondroplasia[i]
- Malignancy leading to osteolysis or PTHrP secretion

Consider:
- Idiopathic Infantile Hypercalcemia
- Granulomatous diseases
- Malignancy
- *Subcutaneous fat necrosis of the newborn*[f]
- *Phosphate depletion*[f]

[a]Confirm hypercalcemia, defined as plasma (or serum) adjusted calcium >10.5mg/dL (2.60mmol/L) or ionized calcium >5.25mg/dL (1.32 mmol/L) (see Table 2)

[b]PTH – parathyroid hormone

[c]25(OH)$_2$D – 25-hydroxyvitamin D

[d]FHH1-3 – Familial Hypocalcaiuric Hypercalcemia types 1-3; MEN1 – Multiple Endocrine Neoplasia type 1; MEN2 – Multiple Endocrine Neoplasia type 2; MEN3 – Multiple Endocrine Neoplasia type 3; MEN4 – Multiple Endocrine Neoplasia type 4; NSHPT – Neonatal Severe Hyperparathyroidism; HPT-JT – Hyperparathyroid-Jaw Tumour syndrome

[e]Familial Isolated Hyperparathyroidism

[f]Conditions affecting neonates (shown in italics)

[g]1,25(OH)$_2$D – 1,25-dihydroxyvitamin D

[h]Inborn errors of metabolism, e.g. Hypophosphatasia[i], Congenital Lactase Deficiency (CLD) and blue diaper syndrome

[i]These syndromes may be associated with dysmorphic features, e.g. Williams syndrome, Jansen's metaphyseal chondroplasia, Hypophosphatasia