
A Practical Approach to Hypocalcaemia in Children

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Abstract

Hypocalcaemia is one of the commonest disorders of mineral metabolism seen in children and can be a consequence of several different aetiologies. These include a failure of secretion or action of parathyroid hormone, disorders of vitamin D metabolism and abnormal function of the calcium-sensing receptor. A practical approach to the investigation, diagnosis and subsequent management of hypocalcaemic disorders is presented.

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Hypocalcaemia is one of the commonest disorders of calcium and phosphate metabolism seen in children. It may be asymptomatic or manifest with a variety of different symptoms which can vary with the age of the child. Although the differential diagnosis is quite wide the cause can usually be categorised into one of a small list of broad aetiologies. An understanding of the key determinants of the regulation of plasma calcium and the normal physiological response to hypocalcaemia will lead to an appropriate interpretation of investigations and subsequent diagnosis and management.

Physiological Response to Hypocalcaemia

A fall in plasma calcium will lead to several physiological changes which, acting in conjunction, lead to a rapid restoration of plasma calcium into the normal range. These changes take place in the three key organs that are involved in the maintenance of plasma calcium, i.e. the kidney, bone and the small intestine (fig. 1). Thus, a fall in the level of ionised calcium is detected by the calcium-sensing receptor located in the parathyroid glands and the renal tubules. In the parathyroid glands this leads to the secretion of parathyroid hormone (PTH) and the synthesis of additional parathyroid hormone. The increased circulating levels of parathyroid hormone then acts in three different ways.

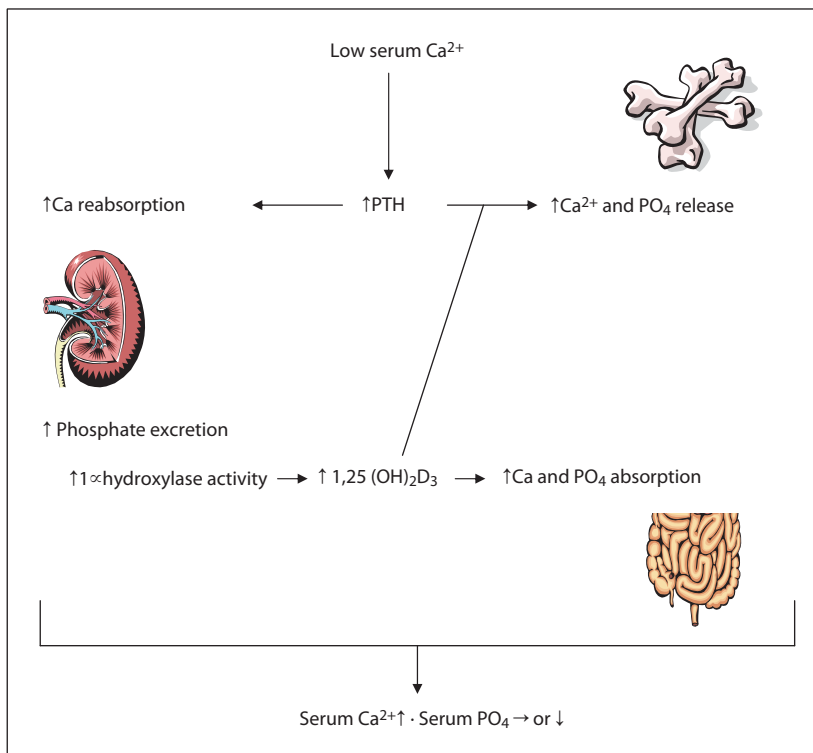


Fig. 1. Physiological response to hypocalcaemia.

- 1 It alters the renal tubular reabsorption of calcium in the kidney leading to more of the filtered plasma calcium being reabsorbed and less excretion in the urine. In doing this there is a reciprocal effect on the tubular reabsorption of phosphate with a fall in this leading to increased urinary phosphate excretion. Thus, one of the markers of a raised serum parathyroid hormone is a low plasma phosphate and tubular reabsorption of phosphate (TRP).
- 2 Parathyroid hormone acts on the skeleton stimulating osteoclasts to increase bone resorption leading to the release of calcium from bone into the circulation.
- 3 The increased circulating parathyroid hormone also stimulates the activity of the 1 α -hydroxylase enzyme in the proximal renal tubule leading to increased secretion of 1,25(OH)₂D which then increases intestinal calcium absorption.

Thus alterations in renal calcium reabsorption, bone resorption and intestinal calcium absorption result in a restoration of the ionised calcium level. Although the synthesis and secretion of parathyroid hormone is the key factor in this response, it can be appreciated that this also requires a functional calcium-sensing receptor, appropriate synthesis of 1,25(OH)₂D and a normal response of peripheral tissues to the secreted PTH.

Signs and Symptoms of Hypocalcaemia

The symptoms of hypocalcaemia often reflect the key role of calcium in the processes of nerve conduction and muscle function with a low plasma calcium resulting in increased neuromuscular excitability. Paraesthesia, a tingling sensation, usually present around the mouth, fingers and toes is a common symptom of hypocalcaemia. Muscle cramps, which in some children may progress to tetany, which is due to sustained muscle contractions, often in the hands, can be experienced. Convulsions, which may be either focal or generalised, can be a manifestation of hypocalcaemia at any age but are particularly recognised during infancy and adolescence. Other less common symptoms include laryngospasm, stridor and apnoea in neonates. Hypocalcaemia can also lead to disturbances of cardiac rhythm and prolongation of the QT interval on an electrocardiograph. Chronic hypocalcaemia can lead to calcification of the basal ganglia, subcapsular cataracts, papilloedema and dental enamel hypoplasia, particularly of the primary dentition.

Two manifestations of latent hypocalcaemia that can be evoked on clinical examination are the signs of Chvostek and Trousseau. The former consists of gentle repeated tapping with a forefinger on the lateral cheek over the course of the facial nerve 0.5–1.0 cm below the zygomatic process and 2 cm anterior to the ear lobe. A positive sign is twitching of the corner of the mouth on the ipsilateral side due to contractions of the circumoral muscles. However, it is not a reliable marker of hypocalcaemia as one study has shown it to be negative in 29% of individuals with laboratory confirmed hypocalcaemia [1]. Trousseau's sign is evoked when a sphygmomanometer cuff is inflated above systolic pressure and maintained for three minutes. A positive sign is the adoption of the 'main d'accoucheur' position with flexion of the wrist and metacarpophalangeal joints and extension of the interphalangeal joints and adduction of the fingers due to carpedal spasm. Note that this sign can be painful for the individual if sustained for too long. It is believed to be a more specific marker of hypocalcaemia than Chvostek's sign with one study showing that 94% of individuals with hypocalcaemia had a positive sign [2].

Investigations

There are several important investigations required in the management of a child with hypocalcaemia, the majority of which are biochemical in nature (table 1). It is usually the total plasma calcium that is measured in the blood although some laboratories and near patient testing facilities will measure the ionised calcium which is usually 50% of the total plasma calcium. Calcium is predominantly bound to albumin in the plasma and therefore deviation of the plasma albumin from the normal range will affect the measured total plasma calcium. Some laboratories will automatically adjust for this and quote a corrected plasma calcium. However, in the absence of this facility

Table 1. Investigations in hypocalcaemia

Plasma calcium, phosphate and magnesium
Plasma albumin
Plasma or serum alkaline phosphatase
Plasma creatinine
Plasma 25-hydroxyvitamin D
Serum parathyroid hormone
Store serum, e.g. for 1,25-dihydroxyvitamin D ₃
Send blood for DNA studies as appropriate
Urine for calcium/creatinine ratio
X-ray of wrist or knee

there are several simple correction factors that can be applied. One of the most well known is to correct the plasma calcium by 0.02 mmol/l for every 1 g/l that the plasma albumin deviates from the normal value of 40 g/l, e.g.

total plasma calcium: 2.2 mmol/l,

plasma albumin: 30 g/l,

corrected calcium: $2.2 - 0.02(30 - 40) = 2.4$ mmol/l.

A measurement of the plasma phosphate is useful as an indirect index of parathyroid hormone activity with a low phosphate reflecting a raised serum PTH and a high phosphate a reduced serum PTH. Hypomagnesaemia is a rare but important cause for hypocalcaemia and therefore plasma magnesium should be included in the list of investigations. Plasma or serum alkaline phosphatase is usually included as part of the standard bone profile provided by many laboratories as a marker of bone turnover. This is often raised when hypocalcaemia is secondary to a disorder of vitamin D and within the normal range when secondary to hypoparathyroidism. Plasma creatinine is an essential investigation to exclude the possibility of renal failure as the cause for hypocalcaemia.

Measurement of 25OHD is an important routine investigation given the frequency of disorders of vitamin D in the aetiology of hypocalcaemia in children. It is the main circulating form of vitamin D and the metabolite that best reflects an individual's vitamin D status. Although a level less than 50 nmol/l (20 ng/ml) would be regarded as consistent with vitamin D deficiency, hypocalcaemia does not usually occur until levels are less than 25 nmol/l (10 ng/ml). Once vitamin D deficiency has been excluded as a cause of the hypocalcaemia, most of the remaining causes have a genetic basis and blood should be taken for appropriate genetic analysis.

Serum PTH is the most critical investigation in determining the aetiology of hypocalcaemia and, as indicated subsequently in this chapter, this is used here as the main means of classification. There are three additional investigations that may prove to be helpful. Additional serum should be routinely obtained when the initial investigations are performed and stored in the laboratory. This can then be used for

Table 2. Aetiology of hypocalcaemia

PTH disorder

- Reduced PTH secretion
- Impaired PTH action

Vitamin D disorder

- Vitamin D deficiency
 - Impaired vitamin D metabolism
 - Impaired renal function

Abnormality of the calcium-sensing receptor

- Gain of function mutations in the gene for the calcium-sensing receptor
 - Antibodies to the calcium-sensing receptor
-

subsequent analysis, such as measurement of $1,25(\text{OH})_2\text{D}$, when the initial investigations have not clarified the aetiology of the hypocalcaemia. Attempting to measure such a metabolite at a later stage when a child has been commenced on initial treatment is often compromised by the effect of the treatment. A measurement of the urine calcium/creatinine ratio, ideally on a second morning urine sample obtained in the fasting state, is a useful marker of renal calcium excretion and conversely of renal tubular calcium reabsorption [3]. Finally an X-ray of the metaphysis of a long bone such as at the wrist or knee may identify previously unsuspected pathology, such as the presence of rickets or of a dense skeleton in an infant with osteopetrosis.

Aetiology of Hypocalcaemia – Classification

It is possible to divide the causes of hypocalcaemia into three broad categories that reflect the three main important components in the regulation of plasma calcium, i.e. serum parathyroid hormone, vitamin D and the calcium-sensing receptor (table 2). Within each of these categories, it is possible to subdivide further. Thus, the category relating to PTH would encompass a reduction of PTH secretion, as seen in hypoparathyroidism, and an impairment of PTH action as seen in pseudohypoparathyroidism. Within the category relating to vitamin D this can again be divided into a lack of the essential substrate, 25OHD , as seen in vitamin D deficiency, or an impairment of the metabolism, as in 1α -hydroxylase deficiency, or end organ action of vitamin D. The category relating to disorders of the calcium-sensing receptor encompasses congenital disorders due to mutations in the relevant gene, as seen in autosomal dominant hypocalcaemia (ADH), and acquired disorders such as antibodies to the calcium-sensing receptor.

However, a more practical approach in determining the aetiology of hypocalcaemia is to adopt a classification dependent on the level of circulating serum PTH in the presence of hypocalcaemia (table 3). Thus, a serum PTH that is either undetectable or low can be seen either in hypoparathyroidism or hypomagnesaemia. An

Table 3. Categorisation of cause of hypocalcaemia

Undetectable or low PTH

Hypoparathyroidism

Hypomagnesaemia

Normal PTH

Abnormality of the calcium-sensing receptor

Raised PTH

Pseudohypoparathyroidism

Vitamin D deficiency

Impaired vitamin D metabolism

Chronic renal failure

Osteopetrosis

inappropriately normal serum PTH is often seen when there is an abnormality affecting the function of the calcium-sensing receptor. Finally, an elevated serum PTH, which would be the normal physiological response, is seen when there is a disorder of vitamin D or a failure of end-organ action of PTH as seen in pseudohypoparathyroidism or osteopetrosis. The next section of this chapter will examine this classification in more detail with descriptions of the individual conditions.

Hypocalcaemia with Low or Undetectable PTH

Congenital Hypoparathyroidism

This may occur as an isolated defect or in association with other developmental defects. A number of genetic abnormalities have now been identified that can be broadly divided into those that encode abnormal forms of PTH, defects in intracellular transcription factors or defects that prevent normal development of the parathyroid glands.

Isolated Congenital Hypoparathyroidism

Isolated congenital hypoparathyroidism (#146200) may be sporadic or familial with autosomal-dominant (168450.0001), recessive (168450.0002) and X-linked recessive (%307700) forms being recognised. The gene for preproPTH is located on chromosome 11p15 (*168450) with homozygous mutations responsible for an autosomal-recessive form [4], whilst the autosomal-dominant inherited form is due to point mutations in the signal sequence of preproPTH preventing processing and translocation of PTH across the endoplasmic reticulum and cell membrane for exocytosis [5]. Another form of isolated hypoparathyroidism, which is inherited in an autosomal-recessive manner

has been shown to be due to mutations of the transcription factors GCMB (glial cell missing B), also known as GCM2 (glial cell missing 2), (*603716), located on chromosome 6p24.2, which is responsible for parathyroid gland development [6]. Occasionally, some heterozygous individuals also have a mild degree of hypoparathyroidism which is inherited in an autosomal-dominant manner (see chapter 15, cases 1 and 2).

The X-linked recessive form has now been identified due to an interstitial deletion-insertion involving chromosomes 2p25.3 and Xq27.1 [7]. This is thought to affect the function of SOX3, a transcription factor expressed in the developing parathyroid glands. All of these conditions present during the neonatal period or childhood without any signs of other organs being affected and treatment of the hypocalcaemia with vitamin D analogues is usually all that is required.

The 22q Deletion (Di George) Syndrome

The most well-known syndrome associated with congenital hypoparathyroidism is the Di George syndrome (DGS) (#188400) which overlaps with the velocardiofacial syndrome (#192430). It is the commonest chromosome deletion syndrome and affects 1 in 4,000–5,000 livebirths. Maldevelopment of the 3rd and 4th branchial pouches causes hypoplasia of the parathyroid glands and thymus in association with congenital conotruncal cardiac defects and a distinctive facial phenotype. Most cases are sporadic but familial cases with apparent autosomal-dominant inheritance are described. The majority are due to deletions at chromosome 22q11 although deletions at a second locus at 10p13 have been found in some patients. The deletion in chromosome 22q is hemizygous and encompasses a variable length of the chromosome. However, it seems that, when hypoparathyroidism is present, there is a common deletion of the TBX1 gene (*602054) which is a transcription factor involved in development of the pharyngeal arches, pouches and otic vesicles.

Clinical features of the DGS are variable. Hypocalcaemia may be present in the neonatal period but is often transient although it may recur at puberty or in adulthood [8] – times when growth is most rapid and the demand for calcium is greatest. Occasionally, when hypocalcaemia presents clinically at adolescence, retrospective assessment of the case history strongly suggests that symptoms have been present for several years. However, hypocalcaemia may be overlooked in the neonatal period if the condition is accompanied by serious cardiac anomalies. It is thought that up to 70% of patients who survive the neonatal period have some degree of parathyroid hypoplasia (see chapter 15, case 3).

Other Forms of Familial Hypoparathyroidism

The hypoparathyroid, deafness, renal anomalies (HDR) (#146255) syndrome is inherited in an autosomal-dominant manner and is due to mutations in the gene coding

for the transcription factor GATA3 on chromosome 10p14–10pter (*131320) which is critical for parathyroid, kidney and otic vesicle development [9]. Affected individuals usually have hypoparathyroidism in association with bilateral sensorineural deafness and renal anomalies.

Another syndrome that includes hypoparathyroidism, mental and growth retardation and dysmorphic features (HRD syndrome) (#241410) is inherited in an autosomal recessive manner. It includes the Kenny-Caffey syndrome (KCS) (#244460) (short stature, osteosclerosis and ocular abnormalities) and the Sanjad-Sakati syndrome (growth failure, ocular malformations, microcephaly and mental retardation). The genetic defect for these was localised to chromosome 1q42–q43 and was subsequently identified as due to mutations in TBCE (*604934) (tubulin-specific chaperone E), which cause loss of function and probable altered microtubule assembly in affected tissues [10].

Finally, a number of mitochondrial disorders are associated with congenital hypoparathyroidism. These include Kearns-Sayre syndrome (KSS) (#530000) (progressive external ophthalmoplegia, heartblock or cardiomyopathy), MELAS (#540000) (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes) and MTPDS (#609015) (mitochondrial trifunctional protein deficiency syndrome). As they are mitochondrial gene defects they are maternally inherited. In all of these conditions the hypoparathyroidism is often a relatively minor feature and may be overlooked in the light of the other problems present (see chapter 15, case 4).

A rare form of congenital, though not genetically mediated, hypoparathyroidism has been reported secondary to maternal hyperparathyroidism [11]. Affected infants have presented in the neonatal period with hypocalcaemia due to transient hypoparathyroidism which, on investigation of the mother, has identified previously unrecognised hyperparathyroidism which presumably suppresses the foetal parathyroid glands in utero.

Acquired Hypoparathyroidism

This can be a consequence of surgery on the thyroid gland (e.g. total thyroidectomy for thyrotoxicosis) or parathyroid glands (e.g. primary hyperparathyroidism) due to their inadvertent removal or damage to the blood supply. Rarely, in children it may be related to radical neck dissection for malignancy. It should therefore be a routine that plasma calcium is estimated following thyroidectomy in children. Hypoparathyroidism may also be a complication of iron deposition in the parathyroid glands in children with thalassaemia major who receive repeated blood transfusions. This usually presents in the second decade often in conjunction with other end organ complications such as hypogonadism and diabetes mellitus. It has also been reported as a rare complication of Wilson's disease due to copper deposition or iodine-131 therapy for thyroid disease.

Autoimmune hypoparathyroidism can be either isolated or as part of the autoimmune polyendocrinopathy type 1 syndrome (APS1) (#240300) [12]. This latter condition may be sporadic or familial with an autosomal-recessive mode of inheritance. There is a triad of principal features, mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency. Ectodermal dystrophy of the nails is often present leading to the alternative term APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy) for this syndrome. It usually presents in early childhood with mucocutaneous candidiasis (mean age 5 years) with hypoparathyroidism (mean age 9 years) being the earliest endocrine manifestation with subsequent development of adrenal insufficiency (mean age 14 years). Additional autoimmune features that may occur include malabsorption, chronic active hepatitis, thyroid disease, hypogonadism and diabetes mellitus. Antibodies against the parathyroid, thyroid and adrenal glands are present in many patients. The underlying genetic defect is due to mutations in the autoimmune regulator (AIRE) gene on Chromosome 21q22.3 (*607358) [13]. There are reports of affected individuals who have not been recognised to have this condition dying of adrenal insufficiency. It is therefore important that all children with apparent idiopathic acquired hypoparathyroidism have regular assessments of adrenal function. In affected children with APECED who are receiving treatment for hypoparathyroidism the onset of hypercalcaemia may be the first manifestation of adrenal insufficiency due to volume depletion as a consequence of mineralocorticoid deficiency. It is also important to be aware that many affected individuals have functional hyposplenism and are more vulnerable to pneumococcal infections and therefore should be immunised with Pneumovax [14].

Hypomagnesaemia

A rare but important cause of hypocalcaemia in a child is a low plasma magnesium. Magnesium is essential for PTH secretion and activation of the PTH receptor by ligand. There is an inadequate PTH response to hypocalcaemia in the presence of hypomagnesaemia which is corrected when the plasma magnesium is brought back into the normal range. This may present as a congenital defect with neonatal hypocalcaemia or may be an acquired defect in an older child. The causes for hypomagnesaemia can be broadly divided into those affecting intestinal magnesium absorption and those producing an excessive leak of magnesium from the renal tubules. In the context of a child with hypocalcaemia secondary to a low plasma magnesium, the easiest way to distinguish between these two possible causes is to assess urinary magnesium excretion with a urine magnesium/creatinine ratio on a spot urine sample for which normative paediatric data are available [3]. The normal response in the face of hypomagnesaemia is for the kidneys to reabsorb as much magnesium as possible and therefore a high magnesium/creatinine ratio would point to a renal tubular leak. Hypercalciuria is also present in some of these conditions and this is not always associated with hypermagnesuria.

Hypomagnesaemia with Hypomagnesuria

Hypomagnesaemia with secondary hypocalciuria (HOMG1) (#602014) is caused by a selective defect of magnesium absorption in the small intestine with no evidence of any additional malabsorption. Affected infants present with hypocalcaemic fits in the first few weeks of life and are found to have remarkably low plasma magnesium values of <0.5 mmol/l [15]. They may initially require parenteral magnesium treatment and can then be maintained on an oral magnesium preparation which will keep the plasma calcium in the normal range despite the fact that the plasma magnesium remains sub-normal at around 0.5 mmol/l (see chapter 15, case 5). The inheritance of this condition appears to be autosomal recessive and often occurs in consanguineous families. The genetic defect has been identified as due to mutations in TRPM6 on Chromosome 9q22 (*607009) which is expressed in intestinal epithelia and renal tubules [16] (see chapter 2 for further details). Renal calcium excretion is low in this condition.

Hypomagnesaemia with Hypermagnesuria

Associated with Hypocalciuria

Hypomagnesaemia with associated hypocalciuria (HOMG2) (#154020) is the other main congenital form of hypomagnesaemia. The hypomagnesaemia is associated with isolated renal magnesium loss with high urinary magnesium excretion. This is an autosomal-dominant disorder due to mutations in the FXRD gene on Chromosome 11q23 [17] (*601814). This gene codes for the γ -subunit of the Na^+/K^+ -ATPase on the inner membrane of the renal tubule and causes hypomagnesaemia with reduced urinary calcium excretion. The clinical manifestations are generally milder than those of HOMG1 and may not become apparent until adulthood.

Isolated recessive renal hypomagnesaemia (IRH, HOMG4) (#611718) is a rare autosomal-recessive condition caused by a mutation in the epidermal growth factor (EGF) gene (*131530) which controls magnesium reabsorption via TRPM6 (see chapter 2 for details). Isolated hypomagnesaemia is associated with normal plasma and urine calcium, but the patients have psychomotor retardation and seizures with brisk reflexes, presumably as a result of other effects of EGF.

Gitelman syndrome (#263800) has some overlap with the Bartter syndrome although it is a separate entity. Mutations in the thiazide-sensitive sodium chloride transporter (SLC12A3) (*600968) result in hypokalaemic alkalosis with salt wasting, hypomagnesaemia and hypocalciuria. Patients usually present after the age of five years with episodes of muscle weakness, lethargy, tetany and muscle cramps. Dermatitis may be present and, although Gitelman's is described as being benign, a prolonged cardiac Q-T interval may give rise to arrhythmias and syncopal attacks. Chondrocalcinosis is a feature which these patients share with others with chronic

hypomagnesaemia. Urinary calcium excretion is low. Treatment consists of correcting the biochemical abnormalities, particularly the potassium and magnesium deficiencies, with oral supplementation.

Associated with Hypercalciuria

Hypermagnesuria with hypercalciuria and nephrocalcinosis (HOMG3) (#248250) is caused by mutations in the gene for claudin 16 (Paracellin 1) (*603959), which is located in the tight junctions of the epithelium of ascending loop of Henle. As a consequence, there is excessive excretion of both magnesium and calcium. Several different homozygous or compound heterozygous mutations have been described and the severity of the condition varies according to genotype. In some cases the problem is self-limiting whilst in others renal failure may ensue. Hypocalcaemia is occasionally present.

Renal hypomagnesaemia with ocular involvement (#248190) is also autosomal recessive and is similar to HOMG3 but also includes ocular abnormalities such as coloboma, myopia and horizontal nystagmus. No mutations are found in the Claudin 16 gene but they are found in the similar claudin 19 gene (*610036). This is located mainly in the collecting ducts of the renal tubule.

Acquired Hypomagnesaemia

Hypomagnesaemia may also occur as a consequence of either malabsorption, as in Crohn's disease or Whipple's disease, or as an acquired renal defect secondary to certain drugs inducing excess renal magnesium wasting. These include the drugs cisplatin, amphotericin B, cyclosporin and tacrolimus. Severe burn injury has also been reported to cause hypocalcaemia secondary to hypomagnesaemia [18].

Hypocalcaemia with Normal Parathyroid Hormone

Familial Hypocalcaemia with Hypercalciuria

Individuals with this condition, autosomal-dominant hypocalcaemia (ADH) (included in #146200) were often previously felt to have idiopathic hypoparathyroidism with a serum PTH that was inappropriately normal in the face of hypocalcaemia. Then linkage analysis in large families with autosomal-dominant hypoparathyroidism mapped a candidate gene to a locus on chromosome 3q13 which corresponded to the region known to include the gene coding for the calcium-sensing receptor. Subsequently, it was identified that this condition was due to gain of function mutations in the gene for the calcium-sensing receptor [19] (*603959). Most of these mutations alter the set point

of the calcium-sensing receptor in the parathyroid glands and the kidneys leading to a lower plasma calcium prior to PTH release and a lowered tubular calcium reabsorption causing relative hypercalciuria (see chapter 2 for details). One mutation causes constitutive activation of the CaSR that prevents PTH secretion even at low calcium concentrations [20]. A low plasma magnesium is often also present in this condition. Many subjects with this condition are asymptomatic but some individuals, particularly children during febrile episodes or neonates, exhibit hypocalcaemic symptoms particularly seizures and neuromuscular irritability. Treatment should be reserved for symptomatic subjects only as there is a significant risk of hypercalciuria and nephrocalcinosis. Although the condition is rare it may account for a significant proportion of cases of idiopathic hypoparathyroidism. In one study of 19 unrelated cases of isolated hypoparathyroidism in France, 8 subjects (42%) had activating mutations of the calcium-sensing receptor [21]. Forty-four mutations have now been described with the majority present in the extracellular or transmembrane domains. A web site is maintained to keep track of these mutations (<http://www.casrdb.mcgill.ca/>). Thiazide diuretics have been used with effect to reduce the hypercalciuria in treated individuals. An alternative option to consider if treatment is required is the use of synthetic PTH which has been used with apparent benefit in 1 child [22] (see chapter 15, cases 6 and 7).

Antibodies to the Calcium-Sensing Receptor

A biochemical picture similar to ADH has also been reported in individuals who have been found to have antibodies to the calcium-sensing receptor often in the context of other autoimmune disease [23]. In at least one individual the hypocalcaemia was transient.

Hypocalcaemia with a High Parathyroid Hormone

Pseudohypoparathyroidism

This condition was first reported in 1942 and was the first example of hormone resistance identified in man [24]. It has similar biochemical features to hypoparathyroidism with hypocalcaemia and hyperphosphataemia with the exception that serum levels of PTH are elevated. Pseudohypoparathyroidism (PHP) refers to several distinct but related disorders in which resistance to PTH is the predominant feature. Unlike most hormone-resistant conditions, the defect is not in the PTH receptor but in the signalling protein G α which is downstream of many different G protein coupled hormone receptors and acts by stimulating the production of adenylyl cyclase which activates the second-messenger cyclic AMP. Resistance to the action of PTH in this condition appears to be mainly in the proximal renal tubule and therefore other

actions of PTH, e.g. on bone, are unaffected. Thus affected individuals can have normal levels of plasma calcium for many years despite elevated PTH levels. It will often present in mid childhood with hypocalcaemic fits or muscle spasms.

PHP is subdivided into two types dependent on the renal tubular response to infused exogenous PTH. Type I is where there is blunting of both cyclic AMP generation and urinary phosphate excretion whereas type II demonstrates impaired urinary phosphate excretion only. The category of type I PHP is subdivided into PHP types Ia, Ib and Ic.

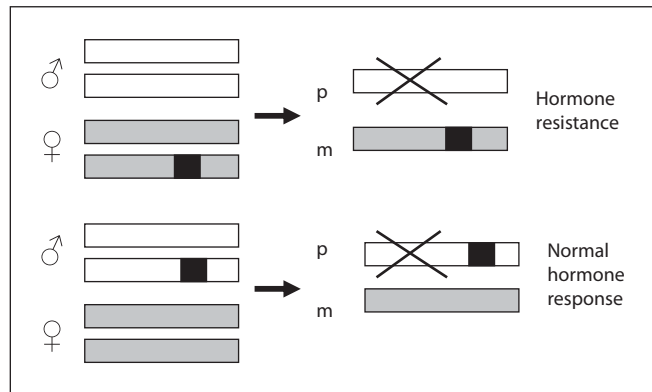
PHP Type Ia (#103580)

In this subtype affected individuals, in addition to PTH resistance, have features of Albright's hereditary osteodystrophy (AHO), which is a constellation of physical features including round face, truncal obesity, short stature, shortening of the 4th and 5th metacarpals and metatarsals, heterotopic ossification and/or mental retardation. Evidence of additional hormone resistance, particularly hypothyroidism and hypogonadism, is usually present and there may also be evidence of growth hormone deficiency due to resistance at the GHRH receptor. The underlying genetic defect is due to heterozygous mutations in the gene *GNAS* on chromosome 20q13.2 (+139320) which encodes for the *G α* subunit [25]. Skin fibroblasts and erythrocytes from affected individuals have a 50% reduction in *G α* mRNA. A related disorder is pseudopseudohypoparathyroidism (PPHP) (#612463) in which individuals have AHO features but no evidence of hormone resistance. Heterozygous mutations in the *GNAS* gene are also present and affected individuals can be found in the same kindreds as those with PHP type Ia. The phenotype expressed is dependent on the gender of the parent transmitting the gene defect with paternal transmission causing PPHP and maternal transmission PHP type Ia [26]. This is due to the imprinted nature of the *G α* protein in different tissues with the maternal allele being predominantly expressed in the proximal renal tubules, thyroid gland, gonads and pituitary. Therefore, an individual carrying a maternally transmitted *G α* mutation will exhibit hormone resistance but an individual carrying a paternally expressed mutation, which is not expressed in the proximal renal tubule, will have no hormone resistance as only the maternally expressed allele, which is normal, is expressed (fig. 2).

PHP Type Ib (#603233)

This second subtype of type I pseudohypoparathyroidism is characterised by PTH resistance in the absence of AHO features. Additional hormone actions such as those of TSH can also be impaired. Although most cases are sporadic, familial cases with autosomal-dominant inheritance are reported. The severity of the condition can vary significantly. As in PHP type Ia PTH resistance only occurs when there is maternal transmission. However, in contrast, mutations in the *GNAS* gene are not present in the majority of subjects with PHP type Ib although the disease gene maps to a region on chromosome 20q containing the *GNAS* locus. Current evidence indicates that the

Fig. 2. Schematic representation of imprinting of *Gsa* mutation expression in renal tubules (adapted from Wilson et al. [26]). The black square represents a *Gsa* mutation.



most likely cause is mutations in regulatory regions of the *GNAS* gene inherited from the mother that interfere with parent specific methylation of the gene [27].

PHP Type Ic (#612462)

These patients have the characteristic features of AHO with multiple hormone resistance but have not been shown to have mutations in the *GNAS* gene. However, it is not clear whether or not this is a separate entity.

PHP Type II (%203330)

This is a rarely reported condition with as yet no genetic basis. These patients do not have features of AHO and the resistance to PTH is confined to the phosphaturic response with a normal cyclic AMP response. It has been pointed out that a biochemical picture similar to this condition can be seen in severe vitamin D deficiency with hypocalcaemia and a high plasma phosphate despite an elevated serum PTH suggesting renal resistance to PTH [28]. As these abnormalities rapidly respond to administration of vitamin D, it has to be speculated as to whether PHP type II actually exists or may just be another manifestation of vitamin D deficiency. The genetic conditions relating to hypoparathyroidism and pseudohypoparathyroidism are summarised in table 4.

Disorder of Vitamin D Supply or Metabolism

Vitamin D Deficiency

Although vitamin D deficiency in children will usually present with rickets, symptomatic hypocalcaemia may also be the first manifestation. This is particularly the case during infancy and puberty where the rapid growth that characterises these periods may be responsible for increased requirements for calcium for bone mineralisation

Table 4. Summary of genetic causes of hypocalcaemia

Disorder	Abbreviation	OMIM	Inheritance	Gene	OMIM	Gene location
<i>Conditions associated with low PTH levels</i>						
Familial Isolated hypoparathyroidism	FIH	168450.0001	AD	prepro PTH	*168450	11p15.3-p15.1
		168450.0002	AR	PTH	*168450	11p15.3-p15.1
		168450.0003	AR	PTH	*168450	11p15.3-p15.1
		%307700	XLR deletion/ insertion AR (usually)	?SOX3 GCMB (GCM2)	*313430 *603716	Xq27.1/2p25.3 6p24.2
<i>Other forms of familial hypoparathyroidism</i>						
22q deletion (Di George) syndrome	DGS1	#188400	AD but mostly sporadic	TBX1	*602054	22q11.2
Di George-like syndrome	DGS2			?		10p13
Hypoparathyroid sensorineural deafness renal anomalies	HDR	#146255	AD	GATA3	*131320	10p15
Hypoparathyroid mental and growth retardation dysmorphic features	HRD Kenney-Caffey Sanjad-Sakati	#241410 #244460	AR	TBCE	*604934	1q42-q43
<i>Mitochondrial disorders</i>						
Progressive external ophthalmoplegia, heartblock or cardiomyopathy (Kearns-Sayre)	KSS	#530000	mitochondrial			
Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes	MELAS	#540000	mitochondrial			
Mitochondrial trifunctional protein deficiency syndrome	MTPDS	#609015	mitochondrial			
Autoimmune polyendocrine syndrome type 1	APS1 APECED	#240300	AR	AIRE	*607358	21q22.3
<i>Hypomagnesaemia with hypomagnesuria</i>						
Hypomagnesaemia with secondary hypocalciuria	HOMG1	#602014	AR	TRPM6	*607009	9q22
<i>Hypomagnesaemia with hypermagnesuria</i>						
Hypomagnesaemia with associated hypocalciuria	HOMG2	#154020	AD	FXYD2 (Na/ K-ATPase)	*601814	11q23
Isolated recessive renal hypomagnesaemia	IRH HOMG4	#611718	AR	EGF	*131530	4q25

Table 4. Continued

Disorder	Abbreviation	OMIM	Inheritance	Gene	OMIM	Gene location
Gitelman syndrome		<u>#263800</u>	AR	thiazide-sensitive NaCl transporter (SLC12A3)	<u>*600968</u>	<u>16q13</u>
Hypermagnesuria with hypercalciuria and nephrocalcinosis	HOMG3	<u>#248250</u>	AR	claudin 16	<u>*603959</u>	<u>3q27</u>
Renal hypomagnesaemia with ocular involvement		<u>#248190</u>	AR	claudin 19	<u>*610036</u>	<u>1p34.2</u>
<i>Hypocalcaemia with normal PTH</i>						
Autosomal-dominant hypocalcaemia	ADH	<u>#146200</u>	AD	CaSR	<u>+601199</u>	<u>3q13.3-q21</u>
<i>Hypocalcaemia with raised PTH</i>						
Pseudohypoparathyroidism type Ia	PHP1A	<u>#103580</u>	AD (maternally inherited) or sporadic	GNAS complex	<u>+139320</u>	<u>20q13.2</u>
Pseudohypoparathyroidism type Ib	PHP1B	<u>#603233</u>	AD (maternally inherited)	GNAS complex methylation defects	<u>+139320</u>	<u>20q13.2</u> , <u>20q13.2</u> , <u>20q13.2</u>
Pseudohypoparathyroidism type Ic	PHP1C	<u>#612462</u>	?AD maternally inherited	?GNAS complex		
Pseudopseudohypoparathyroidism	PPHP	<u>#612463</u>	AD (paternally inherited)	GNAS complex	<u>+139320</u>	<u>20q13.2</u>
Pseudohypoparathyroidism type II	PHP2	<u>%203330</u>	?	?	?	?

The OMIM numbers of the various conditions and those of their related genes, where known, are shown in columns 3 and 6, respectively. The chromosomal locations of the various genes are shown in column 7.

and longitudinal growth [29]. It is often the case in these groups that radiological evidence of rickets is absent at the time of presentation. Another phenomenon often seen in these age groups is the presence of a high plasma phosphate despite a high circulating level of PTH. This would imply that there is resistance to the action of PTH in the renal tubules. There is evidence to suggest that this occurs as a consequence of dietary calcium deficiency which corrects when adequate calcium intake is supplied [30].

Any of the additional forms of 'calciopaenic' rickets caused by defects in Vitamin D metabolism or action can have hypocalcaemia as a feature. These are described in more detail in chapter 8.

Chronic renal failure and chronic liver disease can also present with a biochemical picture of hypocalcaemia with a high circulating level of serum PTH. In the former hypocalcaemia is a consequence of the failure of adequate synthesis of $1,25(\text{OH})_2\text{D}$ and the rise in plasma phosphate due to failure to excrete a phosphate load. This is usually managed by the use of a phosphate binder such as calcium carbonate in conjunction with a vitamin D analogue such as alfacalcidol. In chronic liver disease, hypocalcaemia occurs in combination with rickets. It is primarily because of malabsorption of vitamin D and calcium rather than a failure of activity of the 25-hydroxylase enzyme in the liver which only occurs with end stage liver failure. This is often treated with a vitamin D analogue such as alfacalcidol or calcitriol.

Osteopetrosis

A rare but important cause of hypocalcaemia presenting in the neonatal period is infantile osteopetrosis [31]. In this condition there is a failure of osteoclast action and therefore a lack of bone resorption. There have been several reports of infants with this condition who initially present with neonatal hypocalcaemic convulsions indicating the importance of bone resorption to maintain adequate levels of plasma calcium in the neonatal period. Affected infants usually have raised levels of serum PTH which is unable to produce bone resorption due to the osteoclast defect as another form of PTH resistance. An X-ray of a wrist or knee will demonstrate the characteristic dense bones. It is an important condition to diagnose early as preservation of eyesight is dependent on the timing of diagnosis and the availability of bone marrow transplantation (see chapter 12 for a more detailed description of the various forms of osteopetrosis).

Treatment

The treatment of hypocalcaemia is dependent on two factors:

- 1 whether the hypocalcaemia is causing severe symptoms such as convulsions, and
- 2 the underlying cause for the hypocalcaemia.

If urgent correction of the plasma calcium is required, an intravenous bolus of 10% calcium gluconate 0.5 ml/kg (0.11 mmol/kg) to a maximum of 20 ml/kg over 5–10 min should be administered, followed by a continuous intravenous infusion over 24 h of 1.0 mmol/kg (maximum 8.8 mmol). It is important to note that extravasation of intravenous calcium can cause a considerable reaction and subsequent scarring in the skin and subcutaneous tissues and therefore the infusion site should be regularly checked. In addition, once the severe symptoms have resolved, the intravenous route should be discontinued in favour of oral calcium supplements. For a child where urgent correction of the plasma calcium is not required oral calcium

supplements 0.2 mmol/kg to a maximum of 10 mmol should be administered four times daily.

In the management of hypoparathyroidism or pseudohypoparathyroidism the use of a vitamin D analogue such as 1α -hydroxyvitamin D (alphacalcidol) or $1,25(\text{OH})_2\text{D}_3$ (calcitriol) in a dose of 25–50 ng/kg/day is the most appropriate way of increasing intestinal calcium absorption. The aim is to maintain the plasma calcium at the lower end of the normal range between 2.0 and 2.2 mmol/l as the renal calcium reabsorption will be low in these conditions due to the lack of action of PTH with the risk of hypercalciuria. Monitoring should include periodic assessment of a urine calcium/creatinine ratio and renal ultrasonography to detect nephrocalcinosis. In theory recombinant PTH could be used instead of a vitamin D analogue but would require daily parenteral injection and therefore the oral route is preferred.

Hypomagnesaemia will usually respond to an oral magnesium supplement such as magnesium glycerophosphate in a dose of 0.2 mmol/kg three times daily. The use of oral magnesium salts is sometimes limited by diarrhoea. If hypomagnesaemic symptoms are severe and do not respond to oral magnesium supplements, intramuscular injection of a 50% solution of magnesium sulphate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$) can be given. This contains 2 mmol/ml.

Vitamin D deficiency should be treated with ergocalciferol (D_2) or colecalciferol (D_3) as the fastest way to replenish deficient stores of 25OHD. There is a liquid preparation suitable for infants and young children containing 3,000 units per ml. A dose of 3,000 units daily for infants less than 6 months and 6,000 units daily for age 6 months to 12 years given for an initial period of 6 weeks is often adequate. In the adolescent with hypocalcaemia secondary to vitamin D deficiency there is a capsule of ergocalciferol containing 10,000 units. Calcium supplements may also be required in the initial management of these disorders until the plasma calcium has returned to the normal range.

Conclusions

As can be seen from this chapter, there are many different disorders that can cause hypocalcaemia in a child. It is important that all the appropriate investigations are undertaken prior to the initiation of any treatment. A stepwise logical approach in the interpretation of the relevant investigations will often lead to the correct diagnosis. Some of these conditions are congenital in origin, e.g. congenital hypoparathyroidism, infantile osteopetrosis and are likely to present early in life, whereas some of the conditions are acquired, e.g. vitamin D deficiency, autoimmune polyendocrinopathy and can therefore present at any time during childhood or adolescence. Some of the conditions have important associated features, e.g. adrenal insufficiency and hypoplasia in autoimmune polyendocrinopathy which need to be watched for in the long-term management of the condition. Finally, many of the disorders have a genetic

basis which has now been identified and therefore it is important, once a provisional diagnosis is made, to undertake genetic studies so as to confirm the suspected diagnosis and to inform appropriate genetic counselling.

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