The investigation of hypocalcaemia and rickets

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Our understanding of disorders that present with hypocalcaemia has advanced rapidly in the past decade. The molecular basis of many of these disorders and conditions associated with phosphate wasting has now been established. While many children will need specialist involvement, they often will present to general paediatricians, and appropriate investigations prior to intervention will enable early diagnosis. Not all children with hypocalcaemia and low or low normal parathyroid hormone levels have isolated hypoparathyroidism, and clinicians need to be aware of the potential for misdiagnosis. Outpatient departments and paediatric wards should have a readily accessible and comprehensive list of bloods that need to be taken when a child presents with hypocalcaemia or rickets.

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E stablishing the diagnosis in patients with hypocalcaemia and rickets can be difficult. There is a wide and expanding range of underlying disorders, some of which are extremely rare. Recognition and understanding of diseases such as hypocalcaemic hypercalciuria; hypoparathyroidism, deafness, and renal dysplasia (HDR syndrome); autoimmune polyglandular endocrinopathy with candidiasis and ectodermal dystrophy (APECED); and the various forms of hypophosphataemic rickets has advanced considerably over the past decade and has made the assessment of this patient group more complex.[1–4] While this area of practice may primarily be of interest to the subspecialist, the general paediatrician will be confronted with children with hypocalcaemia and rickets, and knowledge of what constitutes an appropriate investigation and management plan is important. A definitive diagnosis will frequently not be made at the first encounter with the patient, but a comprehensive range of investigations before intervention will help to ensure that treatment is appropriate.

CALCIUM HOMOEOSTASIS

Maintenance of serum calcium levels in the physiological range is a complex process that reflects the function of, and interaction between, vitamin D, parathyroid hormone (PTH), and the calcium sensing receptor.

The calcium sensing receptor was characterised in 1993[5] and is found on the cell surface of tissues such as the parathyroid gland, kidney, and bone. A lowering of ionised calcium in extracellular fluid is detected by this receptor, and leads to enhanced PTH secretion by the parathyroid chief cell. PTH is the principle calcitropic peptide in humans; its effects on tissues like kidney, bone, and intestine are primarily mediated through the parathyroid hormone receptor (PTH/PTHrP receptor).[6] These effects can be summarised as follows:

- Increased reabsorption of calcium by the distal renal tubule.
- Mobilisation of calcium reserves from bone.
- Enhanced 1 alpha hydroxylation of vitamin D to 1,25 dihydroxyvitamin D by the kidney. This in turn increases intestinal calcium absorption and serum calcium levels.
- Increased renal phosphate excretion.

HYPOCALCAEMIA AND RICKETS

Deficiency or impaired function of one of the three main determinants of circulating calcium concentrations outlined above (vitamin D, PTH, and the calcium sensing receptor) can lead to hypocalcaemia. The main causes of hypocalcaemia include:

- Vitamin D deficiency
- Impaired vitamin D metabolism
- Calcium deficiency
- Reduced PTH production
- Impaired PTH action due to end organ resistance
- An abnormal calcium sensing receptor
- Impaired renal function.

The above can influence calcium concentrations in the newborn period, but babies are also subject to insults that can affect calcium homoeostasis, such as prematurity, asphyxia, and maternal hyperglycaemia.

Rickets is a disorder of growing children in which the newly formed bone matrix is not mineralised appropriately. It reflects a deficiency of the bone constituents, calcium, and/or phosphate. Some children with hypocalcaemia will be found to have rickets, but not all children with rickets will be hypocalcaemic. Rickets can be classified according to the underlying pathology into three main groups: vitamin D deficiency, calcium deficiency, or phosphate deficiency.

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Vitamin D deficiency or resistance
This may be caused by:

- Dietary deficiency.

- Lack of sunlight exposure.

- Malabsorption.

- Liver disease and drug associated dysfunction (e.g. phenytoin), resulting in failure to 25 hydroxylate vitamin D.

- Renal pathology with significant tubular damage. The associated 1 alpha hydroxylase deficiency leads to a failure to 1 hydroxylate vitamin D appropriately.

- An inherited deficiency of 1 alpha hydroxylase due to defects in the 1 alpha hydroxylase gene (vitamin D dependent rickets type I).[7]

- End organ resistance to vitamin D (vitamin D dependent rickets type II).[8] This disorder is usually due to mutations in the vitamin D receptor and can be associated with alopecia.

Calcium deficiency
Dietary calcium deficiency without concomitant vitamin D deficiency is described.[9][10]

Phosphate deficiency
This may be caused by:

- Renal tubular loss because of specific genetic forms of renal phosphate wasting, such as hypophosphataemic rickets (X linked[11–13] and dominant[14][15] forms exist), as well as generalised renal tubulopathies, such as Fanconi's syndrome. Occasionally phosphate wasting can be associated with benign or malignant tumours.[16][17]

- Inadequate phosphate intake, which is the main cause of osteopenia of prematurity.

PRESENTATION AND CLINICAL FEATURES

Hypocalcaemia may be an incidental finding, or it can result in symptoms such as paraesthesia or cramps. Awareness of hypocalcaemia as a cause of seizures is important because children are still treated with anticonvulsants without serum calcium concentrations being checked. Children with congenital heart defects and those with primary adrenal failure may have their calcium concentrations measured routinely because of the known association with hypoparathyroidism. Children with rickets may present with limb deformity (both genu varum and valgum), and in the case of the inherited forms of rickets this is frequently noticed when the child starts to weight bear. Some children with vitamin D deficiency can present with hypocalcemia without the typical skeletal phenotype.[18]

AN INVESTIGATIVE APPROACH TO THE CHILD WITH HYPOCALCAEMIA AND RICKETS

A detailed history documenting diet, lifestyle, family, and drug history, as well as development and hearing is important. The examination should include an assessment of skin, nails, teeth, and the skeleton, as well as the cardiovascular system. A comprehensive range of investigations should be performed at baseline, analogous to the approach to hypoglycaemia in childhood (table 1). They have been divided here into blood, urine, and other potentially useful tests.

Investigations on blood

- Calcium, phosphate, and creatinine in plasma. Ionised calcium should ideally be measured because this is the biologically active component and is more accurate than "corrected" calcium levels derived from total calcium concentrations. Calcium concentrations vary according to age, and an appropriate reference range needs to be used.

Table 1 First and second line investigations in patients with hypocalcaemia and rickets

First line	Second line
Blood	
Calcium/phosphate	Karyotype
Alkaline phosphatase	Autoantibody screen
Electrolytes and creatinine	Parental/sibling biochemistry
Bicarbonate	Maternal vitamin D status
PTH	Thyroid function
Magnesium	
Vitamin D	
"Save serum"	
Urine	
Calcium	Low molecular weight proteins
Phosphate	
pH	
Protein	
Glucose	
Other investigations	
Hand/wrist radiograph	Renal ultrasound
	EDTA sample for genetic studies
	Skull radiograph

- Alkaline phosphatase levels. An appropriate, age related reference range should be used; an individual's pubertal status needs to be considered.

- PTH.

- Plasma bicarbonate, looking for evidence of acidosis in association with Fanconi's syndrome or renal tubular acidosis.

- Magnesium levels should always be checked in hypocalcaemic patients. Severe hypomagnesaemia (<0.45 mmol/l) causes hypocalcaemia by impairing PTH secretion as well as PTH action.

- Vitamin D (25-hydroxyvitamin D).

- Save serum. This may be useful at a later date to measure 1,25 vitamin D if the picture suggests resistance to vitamin D with high 25-hydroxy vitamin D levels.

The above investigations can usually be undertaken on 4–5 ml whole blood.

PTH undergoes cleavage to a variety of smaller peptides. Only the N-terminal fragment has biological activity at the PTH/PTHrP receptor, and the low circulating concentrations combined with a short half life of 2–5 minutes mean that it can be difficult to measure. The standard approach to determining circulating PTH concentrations uses a two site immunoassay (for example, the Nichols Advantage chemiluminescence immunoassay) which measures the intact peptide. Potassium/EDTA plasma or a serum (plain clotted) sample should be collected and transported to the laboratory within one hour, or stored on ice if it is likely to be longer before the sample is separated and frozen or analysed (about 1 ml whole blood is usually adequate). Blood can be processed in this way out of normal working hours, and many biochemistry departments now provide a rapid turnaround.

Investigations on urine

- Calcium, phosphate, and creatinine in a spot urine sample. When this is being used to calculate renal tubular phosphate handling (see below), this needs to be taken within two hours of the serum sample.

- Urinalysis for pH, protein, and glucose.

The main objective of assessing urine calcium excretion is to establish whether this is inappropriately high in the presence
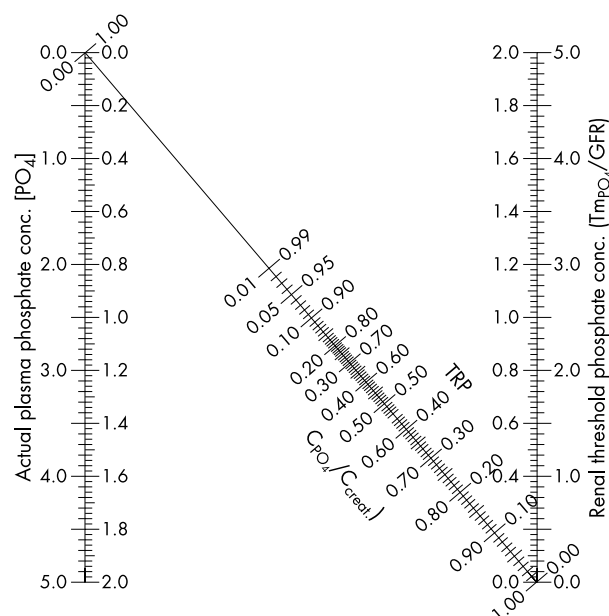
Figure 1 Calculate % TRP and then use this and the serum phosphate to calculate TmP/GFR from the nomogram: % TRP = 1 − $(U_p \times P_{crea})/(P_p \times U_{crea})$. The inner axes are mmol/l and the outer axes mg/100 ml.

of a low plasma calcium. Reference values for urine calcium/creatinine ratio in young children are not well defined and will vary according to factors such as diet. The upper limit of normal (~97th centile) for fasting urine calcium excretion in healthy children greater than 2 years of age in the United Kingdom is 0.69 mmol/mmol,[19] but values may be greater than this in infancy. In the presence of hypocalcaemia a urine calcium/creatinine ratio greater than 0.3 mmol/mmol on spot samples suggests inappropriate excretion.[20] A timed 24 hour urinary calcium excretion (collected in containers with hydrochloric acid to prevent precipitation of calcium salts) can be obtained in the older child. Hypercalciuria is suggested by values greater than 0.1 mmol/kg/day.[21] Timed urine collection can be difficult in young children, and a random spot urine calcium creatinine ratio repeated on 2–3 occasions at the same time of day is frequently the most appropriate way of assessing urine calcium excretion. The calcium:creatinine ratio on the second voided urine sample of the day after an overnight fast is most closely related to 24 hour urine calcium levels.[21]

Renal phosphate handling may be abnormal despite a serum phosphate within the quoted laboratory normal range, and should be assessed in more detail by determining the tubular maximum reabsorption threshold of phosphate per glomerular filtration rate (TmP/GFR). The TmP/GFR can be calculated using the nomogram (fig 1) or computer equation based on the work of Walton and Bijvoet and published in 1975,[22] or the following formula based on the work of Brodehl and colleagues[23]:

$$TmP/GFR = \frac{P_p - U_p \times P_{crea}}{U_{crea}}$$

P_p, U_p, P_{crea}, and U_{crea} refer to plasma and urine concentrations of phosphate and creatinine.

TmP/GFR can be calculated in both fasting and non-fasting children and should be compared with age appropriate reference ranges. British reference data calculated using the Walton and Bijvoet formula provide a reference range for 2–15 year olds of 1.15–2.44 mmol/l.[19]

Table 2 Principle causes of hypocalcaemia in childhood

Parathyroid hormone deficiency (low PTH levels)
I. Parathyroid aplasia/hypoplasia or abnormal PTH production
  As part of 22q11 deletions
  10p13 deletion
  CHARGE syndrome
  X linked hypoparathyroidism (1 family in the world to date)
  Autosomal dominant hypoparathyroidism
  Autosomal recessive hypoparathyroidism
  Syndrome of hypoparathyroidism, deafness, renal dysplasia (HDR)
II. Type 1 autoimmune polyendocrinopathy
III. Infiltrative lesions such as Wilson's disease, thalassaemia
III. Mitochondrial DNA mutations
    e.g. Kearns Sayre syndrome
IV. Magnesium deficiency
V. Neck surgery

Altered "set point" (normal or low normal parathyroid hormone levels)
VI. Calcium sensing receptor activating mutation

Hypocalcaemia associated with increased PTH production (raised PTH levels)
VII. Gsα and other signalling defects
    e.g. pseudohypoparathyroidism
VIII. Vitamin D deficiency
    Nutritional
    Malabsorption
IX. Calcium deficiency
X. Impaired vitamin D metabolism
    Enzyme deficiency—defects of the 1 alpha hydroxylase gene (vitamin D dependent rickets type I)
    End organ resistance to vitamin D (vitamin D dependent rickets type II)
XI. Renal failure
XII. Magnesium deficiency (low and high PTH levels have been reported)
XII. Osteopetrosis

Other investigations

- A hand/wrist and/or knee radiograph if rickets is suspected. A skull film may occasionally provide further information but is not necessary routinely.

- Checking the plasma and urine biochemistry of both parents and possibly siblings is crucial when inherited diseases such as hypocalcaemic hypercalciuria and hypophosphataemic rickets are suspected. It is also important to measure maternal calcium and vitamin D levels in the case of hypocalcaemia in infancy because of the link with maternal vitamin D deficiency and hyperparathyroidism. Maternal hyperparathyroidism is associated with adverse pregnancy outcome and causes transient hypocalcemia in the newborn because the fetal parathyroids are suppressed following exposure to high calcium levels in utero.

- An autoantibody screen including adrenal, parathyroid, and smooth muscle and LKM antibodies is useful in cases of isolated hypoparathyroidism and where APECED is suspected (see later).

- Renal ultrasound scan looking for evidence of nephrocalcinosis or renal dysplasia.

- Karyotype looking for 22q11 and 10p13 deletions.

THE INTERPRETATION OF BLOOD AND URINE BIOCHEMISTRY

The biochemical picture can be categorised according to the presence of undetectable, normal or high levels of PTH (table 2). In our experience the initial diagnosis in patients presenting with hypocalcaemia or rickets may be incorrect in as many as 80% of cases (unpublished data); an approach that is linked

to PTH concentrations can help to explain and understand the underlying pathophysiology and should help to improve diagnostic accuracy.

Undetectable or low PTH levels in the hypocalcaemic child

Undetectable or very low PTH values in the symptomatic child suggest hypoparathyroidism (table 2). Aplasia or hypoplasia of the parathyroids is most commonly due to the DiGeorge/velocardiofacial syndrome associated with deletion of chromosome 22q11.2. A similar phenotype including hypoparathyroidism has also been associated with deletions of chromosome 10p and, recently, the HDR syndrome (hypoparathyroidism, deafness, and renal dysplasia) was found to be due to defects in the GATA3 gene at 10p15.[2] The HDR syndrome is an autosomal dominant disorder which can present with hypocalcaemia in early life, although the diagnosis of hypoparathyroidism may be delayed by many years.[24] Defects in the PTH gene are rare and can be associated with autosomal dominant and recessive isolated hypoparathyroidism.[25][26] Mutations of the GCMB gene on the short arm of chromosome 6 can also cause recessively inherited hypoparathyroidism.[27]

Diseases such as polyglandular endocrinopathy type 1, also known as autoimmune polyglandular endocrinopathy with candidiasis and ectodermal dystrophy (APECED), can present with hypoparathyroidism in the absence of the two other major manifestations, which are candidiasis and adrenal failure.[28] There should be a high index of suspicion for this disease in all cases of hypoparathyroidism presenting in children older than 4 years.[29] Children with APECED may have other "minor" features such as malabsorption, gallstones, hepatitis, dysplastic nails and teeth, and do not always have circulating autoimmune markers. APECED has an autosomal recessive pattern of inheritance and is caused by mutations of the autoimmune regulator (AIRE) gene.[3] Screening should be considered in the siblings of affected individuals. Mitochondrial disease is a rare cause of hypoparathyroidism but is not usually an isolated finding.[30]

Detectable PTH values (low-normal or normal)

Detectable PTH values (low-normal or normal) in an asymptomatic individual raise the possibility of an abnormality of the calcium sensing receptor which can be assessed in more detail by determining urinary calcium excretion. Urine calcium excretion is typically low in longstanding hypoparathyroidism, and a relatively high urine calcium excretion (urine Ca:Cr ratio >0.3 mmol/mmol) suggests hypocalcaemic hypercalciuria.[1] Hypocalcaemic hypercalciuria is due to activating mutations of the calcium sensing receptor which downshift the set point for calcium responsive PTH release. Serum calcium levels are relatively refractory to change in response to vitamin D analogues, but urine calcium greatly increases with an associated risk of nephrocalcinosis. Magnesium levels are low in this disorder because the calcium sensing receptor also detects this cation (see table 1). Intervention can also lead to the development of symptoms in previously well patients; this may reflect PTH suppression with a resultant failure of acute "minute to minute" regulation of serum calcium. Hypocalcaemic hypercalciuria may be sporadic or have an autosomal dominant pattern of inheritance, and screening may identify an asymptomatic parent. Interestingly, mutations that fully activate the calcium sensing receptor have recently been associated with the development of Bartter's syndrome.[31] The patients reported actually had suppressed PTH levels despite hypocalcaemia, but also had hypokalaemia and a raised bicarbonate in contrast to the typical picture in hypocalcaemic hypercalciuria.

Children with hypophosphataemic rickets will frequently have normal PTH and calcium levels in contrast to vitamin D

related/calcium deficiency rickets where the PTH is almost always raised and calcium concentrations normal or reduced.

Increased PTH levels

If the serum creatinine is normal, thereby excluding renal insufficiency, then increased PTH levels point towards a diagnosis of vitamin D related/calcium deficiency rickets or pseudohypoparathyroidism (see table 1). Vitamin D deficiency is still prevalent in the Western world,[32][33] and it is important to remember that this may present with hypocalcaemia before the typical clinical phenotype develops.[34] A detailed history looking for evidence of dietary deficiency or gut dysfunction is mandatory in all children with hypocalcaemia or rickets. Physical findings of fatigue, myalgia, and weakness may accompany bony deformities. Genu valgum (knock knees) may occur as well as the more typical genu varum (bow legged) appearance. High risk groups include Asian families, where the maternal and child diet may be low in calcium and vitamin D and where exposure to sunlight can be limited.[35] Maternal vitamin D levels should always be checked in neonates with vitamin D deficiency. The diagnosis of Fanconi syndrome should be considered in any child with persistent glycosuria, phosphaturia, and acidosis. Measurement of low molecular weight urine proteins (β_2 microglobulin or retinol binding protein) should confirm the diagnosis.[36]

Pseudohypoparathyroidism is a heterogeneous disorder that is frequently associated with abnormalities of the G protein component adjacent to the PTH and other G protein coupled cell surface receptors. Patients may become hypocalcaemic despite a compensatory increase in PTH concentrations, and may have other endocrine problems, such as primary hypothyroidism and hypogonadism that are also manifestations of an abnormal signalling mechanism.[37][38] Not all patients are overweight and many are of normal intelligence.

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Learning points

- Paediatric units should have a protocol for the investigation of patients with hypocalcaemia and rickets
- The measurement of PTH should be undertaken prior to intervention
- Vitamin D deficiency may present with hypocalcaemia, without phenotypic changes of rickets
- Vitamin D deficiency needs to be excluded in patients with suspected pseudohypoparathyroidism
- A diagnosis of "isolated" hypoparathyroidism should only be made when other disorders associated with hypocalcaemia, such as APECED and HDR syndrome, have been considered
- The adult reference range for phosphate may be quoted, leading to abnormally low results being regarded as normal
- The assessment of renal phosphate handling (TmP/GFR) is the definitive way to exclude hypophosphataemic rickets

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Fetal and Neonatal Edition, May 2003

The following articles—being published in the May 2003 issue of the *Fetal and Neonatal* edition of the *Archives of Disease in Childhood*—may be of general interest to pae-diatricians.

Original articles

Long term outcome of neonatal meningitis. J P Stevens, M Eames, A Kent, S Halket, D Holt, D Harvey

Congenital brachial palsy: incidence, causes, and outcome in the United Kingdom and Republic of Ireland. G Evans-Jones, S P J Kay, A M Weindling, G Cranny, A Ward, A Bradshaw, C Hernon

Health and school performance of teenagers born before 29 weeks gestation. A Johnson, U Bowler, P Yudkin, C Hockley, U Wariyar, F Gardner, L Mutch