

## Review Article

# Familial hypocalciuric hypercalcaemia – familial benign hypercalcaemia: a review

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## Introduction

Hypercalcaemia is frequently found during routine blood screening and often remains asymptomatic for a prolonged period until serious renal or bone complications reveal its presence.<sup>1,2</sup> Symptoms of hypercalcaemia also may be marked by nonspecific gastrointestinal or neuropsychiatric complaints. It is therefore not unexpected that routine serum calcium analysis by auto-analyser techniques is frequently the first hint for a correct diagnosis. Although the list of causes of hypercalcaemia is long, the vast majority are due either to primary hyperparathyroidism or malignancy.<sup>3</sup> In most situations, a correct clinical history and examination with simple measurements of serum calcium, phosphorus, chloride, bicarbonate, and creatinine are usually insufficient to predict the correct diagnosis with high probability. Serum parathyroid hormone estimation is often essential for distinguishing primary hyperparathyroidism from malignancy unless the cause of malignancy is clear.

Since many of these hypercalcaemic patients ultimately are considered candidates for parathyroidectomy, a correct diagnosis is required. This is especially true for patients with familial forms of hypercalcaemia, since when this familial hypercalcaemia is attributed to parathyroid adenoma or hyperplasia, surgical correction is possible, while on the contrary, these interventions have usually no success in familial benign hypercalcaemia<sup>4</sup> or familial hypocalciuric hypercalcaemia (FHH).<sup>5,6</sup> The latter syndrome is clearly different from hyperparathyroidism, either occurring as an isolated abnormality or in the context of familial multiple endocrine neoplasia

and has to be ruled out in patients presenting with hypercalcaemia.

This short review will focus on different aspects of familial hypercalcaemia.

## Clinical and biochemical features of familial hypocalciuric hypercalcaemia

The clinical spectrum of hypercalcaemia found in subjects with FHH ranges from life-threatening disorders in the case of neonatal primary hyperparathyroidism to an asymptomatic biochemical abnormality found on a routine blood test. However, symptoms due to hypercalcaemia are infrequent and most of the family members are completely asymptomatic.<sup>7,9</sup> Classical stigmata of hypercalcaemia such as lethargy, obstipation, nausea, vomiting, pruritus, polydipsia, and polyuria are seldom present in hypercalcaemic sibs<sup>8</sup> and rarely lead patients to seek medical attention. Hence, detection of the hypercalcaemia is often by routine blood examination.

Since no abnormalities of protein binding are described in FHH, both the total and ionized serum calcium concentrations are elevated in hypercalcaemic family members.<sup>4,7–10</sup> Although high penetrance of hypercalcaemia in childhood distinguishes FHH from other familial hypercalcaemic syndromes where hypercalcaemia is seldom detected before the age of 10,<sup>5,6,11</sup> it is not practical since the screening of youngsters often poses problems. The hypercalcaemia in FHH is usually not influenced by subtotal parathyroidectomy, since calcium levels quickly return to previous values,<sup>6,12,13</sup> and therefore family members often present a history of an unsuccessful parathyroid exploration or a subtotal parathyroidectomy. Serum phosphorus concentration is almost always higher than in primary hyperparathyroidism,<sup>9,10,14</sup> and in

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contrast to the latter disease the hypercalcaemia is paralleled by a disturbance in regulation of serum magnesium concentration sometimes resulting in mild hypermagnesaemia.<sup>8,10</sup> The cardinal feature of FHH is, however, a relative decrease in renal excretion of the divalent cations, calcium and magnesium.<sup>4,6,8-10,14</sup> Adjustments of urinary excretion of divalent cations for creatinine clearance, which is usually normal in FHH,<sup>6</sup> provides an even better discrimination between hyperparathyroidism and FHH.<sup>10</sup> Unlike other causes of hypercalcaemia which often result in a decreased urine concentrating ability,<sup>15</sup> the capacity to form concentrated urine after water deprivation is maintained in FHH as demonstrated by Marx *et al.*,<sup>16</sup> and it seems that renal function is well maintained despite lifelong hypercalcaemia.

Although there is disagreement about the parathyroid gland pathology,<sup>8,17,18</sup> a slight degree of parathyroid hyperplasia is often found. Immunoreactive parathyroid hormone (PTH) concentrations are lower than in typical hyperparathyroidism, and only slightly elevated or normal concentrations are found.<sup>4,8,9,19-22</sup> Bioactive parathyroid hormone is reported to be normal.<sup>20</sup> Concentrations of other calcium-regulating hormones, i.e. 25-hydroxy vitamin D<sub>3</sub>,<sup>8,9,21-24</sup> 24,25-dihydroxy vitamin D<sub>3</sub>,<sup>21</sup> and calcitonin<sup>9,12</sup> are normal in patients with FHH. The normal concentration of active vitamin D metabolites is further confirmed by Kristiansen *et al.*,<sup>24</sup> who showed that intestinal calcium absorption is normal. Reports of elevated urinary cAMP concentrations in FHH<sup>25,26</sup> suggest either an increased parathyroid activity or an increased renal response to PTH in FHH. Suggestive for this last hypothesis is that parathyroid stimulation, be it exogenous<sup>25</sup> or endogenous, induces a greater increase in urinary cAMP<sup>26</sup> concentrations in FHH than in primary hyperparathyroidism.

Although these clinical and biochemical features are different when compared to primary hyperparathyroidism, none of these parameters alone or combined can make the diagnosis in an individual. As discussed in the diagnosis section, one needs to look at the entire family to establish a diagnosis.

### Complications of FHH

Complications of hypercalcaemia often seen in primary hyperparathyroidism are seldom encountered in FHH.<sup>6</sup> Osteopenia, a frequent consequence of primary hyperparathyroidism, is not reported in FHH, and bone mineral density of the spine, and of distal and mid radius is normal.<sup>27</sup> Furthermore, there is no biochemical evidence of increased bone turnover, since alkaline phosphatase and urinary hydroxyproline excretion are normal.<sup>12</sup> The incidence of peptic ulcer disease and of nephrolithiasis in FHH is similar

to that in the general population.<sup>8,28</sup> Pancreatitis, on the other hand, seems more frequently detected than in primary hyperparathyroidism,<sup>6,22,29,30</sup> although there is no obvious explanation for this possible increased incidence. Neonatal primary hyperparathyroidism, a rare congenital disease, is also seen with increased frequency in FHH.<sup>7,31-35</sup> Marx *et al.*<sup>31</sup> suggested several possible mechanisms to explain this association. First, these neonates may be homozygous for FHH and hence suffer from a severe form expressed as neonatal primary hyperparathyroidism.<sup>31,34-36</sup> Second, the disease may be analogous to secondary hyperparathyroidism arising in a fetus with FHH who senses the normocalcaemia of the mother as too low.<sup>30</sup> A third explanation is that neonatal severe primary hyperparathyroidism represents one end of the spectrum of variation in the clinical severity of familial hypocalcaemic hypercalcaemia.<sup>31</sup> Earlier, we described the association of interstitial lung disease<sup>9,13</sup> and disturbed host defence mechanisms expressed as granulocyte dysfunction<sup>13,37</sup> in a family with FHH. FHH seems also associated with adult onset diabetes mellitus,<sup>37,38</sup> thyroid disease,<sup>38</sup> cardiovascular disorders<sup>37</sup> and chondrocalcinosis (36% in FHH vs 2-7% in a general population).<sup>6</sup> Further study, however, is needed to determine if these abnormalities are true associations or spurious phenomena.

In spite of this list of possible complications, FHH is a benign disease seldom accompanied by excess morbidity or mortality. Premature mortality is hence less frequent than in other forms of familial hypercalcaemia such as familial multiple endocrine neoplasia.<sup>6</sup>

### Diagnosis

Until more insight is gained into the pathogenesis of FHH, the diagnosis of this disorder will depend on the observation of the characteristic features in a family, and the diagnosis can therefore not be confirmed in an isolated subject. Although subjects with FHH present with significant differences in several biochemical tests, only evaluation of the entire family can clearly differentiate this syndrome from hypercalcaemia due to hyperparathyroidism. The first requirement is the familial occurrence of hypercalcaemia often associated with hypermagnesaemia and a normal or slightly increased concentration of PTH. The urinary excretion of divalent cations is relatively diminished. The hypercalcaemia is, furthermore, not accompanied by skeletal abnormalities, renal calculi, or gastric ulcer disease. In contrast to other forms of familial hypercalcaemia, this form of hypercalcaemia often can be detected already in sibs younger than age 10. An ineffective subtotal parathyroidectomy in a family member points, furthermore, in the direction of FHH. In combining these features, other causes of hypercal-

caemia and familial hypercalcaemia can be excluded. Table I presents some features which distinguish FHH from primary hyperparathyroidism, but one should be aware that none of the features cited enables one to make the diagnosis in an individual case, if one does not take the family history into account.

### Pathophysiology of FHH

Although much still has to be learned about the pathophysiology of FHH, there are arguments that the function of several organs is affected by an impaired sensitivity to and/or abnormal transport of extracellular calcium. Both kidneys and parathyroid glands are reported to be less sensitive to the extracellular calcium concentration.

Mild parathyroid hyperplasia<sup>17</sup> with blocked responses to changes in serum calcium is encountered in FHH.<sup>31,40</sup> Using calcium and EDTA infusions, we demonstrated an increased parathyroid 'setpoint' to calcium.<sup>40</sup> To suppress PTH secretion, a higher-than-normal calcium (Figure 1) concentration is needed in FHH than in normal persons. In patients with parathyroid hyperplasia and adenoma, however, the 'setpoint' is even more elevated. This *in vivo* observation correlated well with previous *in vitro* studies by Brown *et al.*, which showed that hyperplastic parathyroid glands from patients with primary hyperparathyroidism secreted more PTH than expected in view of the pre-existing hypercalcaemia.<sup>41,42</sup> The persistence of a disturbance in mineral metabolism after total parathyroidectomy in FHH<sup>7,9,22</sup> indicates that the

defect is not limited to the parathyroid gland proliferation and secretion of the parathyroid hormone.

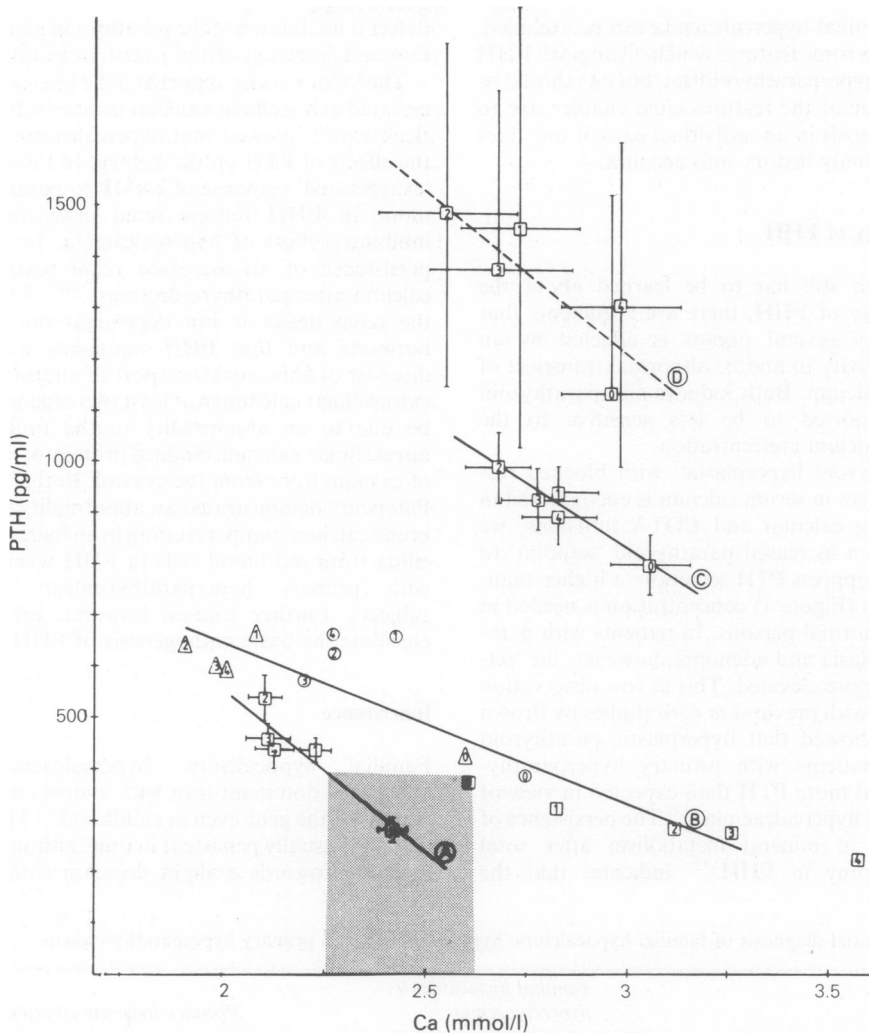
The kidney is also reported to be less sensitive to the elevated extracellular calcium concentration in FHH. Beck *et al.*<sup>43</sup> showed that hypercalcaemia attenuated the effects of PTH on the kidney. In this context, the 'exaggerated' response of cAMP to parathyroid hormone in FHH reflects renal insensitivity to the inhibitory effect of hypercalcaemia. In view of the persistence of an increased renal reabsorption of calcium after parathyroidectomy,<sup>22,44,45</sup> it is clear that the renal defect is not dependent on parathyroid hormone and that FHH represents a generalized disorder of abnormal transport of and/or response to extracellular calcium in at least two organs. This could be due to an abnormality in the function of an intracellular calcium-binding protein or in transport of calcium to or from the cytosol. Recently, Hoare & Paterson<sup>46</sup> demonstrated an abnormality in the membrane calcium pump, resulting in an increased calcium efflux from red blood cells in FHH when compared with primary hyperparathyroidism or normal subjects. Further studies, however, are needed to elucidate the basic pathogenesis of FHH.

### Inheritance

Familial hypocalciuric hypercalcaemia is an autosomal dominant trait with almost complete penetrance of the gene even in childhood.<sup>1,2</sup> The hypercalcaemia is usually persistent in time, although there is a tendency towards a slight decrease with advancing

**Table I** Differential diagnosis of familial hypocalciuric hypercalcaemia and primary hyperparathyroidism

	<i>Familial hypocalciuric hypercalcaemia</i>	<i>Primary hyperparathyroidism</i>
Sex ratio	1:1 M:F	3:1 M:F
Age at onset	birth	rare before 10
Inheritance	autosomal dominant	not inherited, unless in multiple endocrine neoplasia syndromes; then autosomal dominantly inherited
Complications	rare	peptic ulcer, nephrolithiasis, bone disease
Serum calcium	elevated	elevated
Serum phosphorus	normal	low
Serum magnesium	high normal or increased	variable
Alkaline phosphatase	normal	often increased
Serum PTH	normal or slightly increased	increased
1,25-(OH) <sub>2</sub> D <sub>3</sub>	normal	increased
Fractional urinary calcium excretion	low	normal
Hydroxyprolinuria	normal	increased
Urinary cAMP	high normal or elevated	increased
Parathyroid ultrasound	mostly normal	often abnormal
Response to partial parathyroidectomy	absent	good
Organs with primary dysfunction	several (kidney, parathyroid gland, red blood cells,?)	parathyroid



**Figure 1** Relationship between calcium and parathyroid hormone (PTH) before and at 1 to 4 h following EDTA and calcium infusions (0–4 in the symbols) in controls (A), FHH (B), parathyroid adenoma (C), and hyperplasia (D). For patients with FHH, individual values are shown ( $\square$  for patient HM during Ca infusion,  $\Delta$  for HM during EDTA infusion, and  $\circ$  for patient HI during EDTA infusion). For controls, parathyroid adenomas, and hyperplasias, means  $\pm$  s.e.m. are shown. The shaded area represents the normal ranges of both PTH and calcium. The data clearly demonstrate that the 'setpoint' of the parathyroid gland in FHH is intermediate between normal and parathyroid adenoma or hyperplasia. (Reproduced with permission of the editor. From: Auwerx *et al.*<sup>40</sup>)

age<sup>5,13</sup> (Auwerx *et al.*, unpublished results). The disease spectrum was, however, recently expanded to include variants of FHH with very wild expression in heterozygotes.<sup>36</sup> In an elegant analysis of a family with FHH and severe neonatal hyperparathyroidism, Marx *et al.* reported that the FHH gene can be expressed as mild or intermittent hypercalcaemia in some heterozygotes, while in homozygotes it is expressed as severe neonatal hyperparathyroidism.<sup>36</sup> This has been confirmed in other studies.<sup>34</sup>

A linkage of the inheritance of FHH with HLA haplotype A11Bw55Cw3DR4 was described in one family.<sup>32</sup> Additional family studies are, however, needed to draw firm conclusions about a possible HLA linkage.

#### Treatment

Since in this disorder lifelong hypercalcaemia only



leads to minimal morbidity, no treatment of the hypercalcaemia *per se* is recommended at present.<sup>6-8,12</sup> Subtotal parathyroidectomy is unsuccessful in restoring normocalcaemia, and normal calcium metabolism persists even after total parathyroidectomy.<sup>5,6,13,22,44,45</sup> Marx *et al.*<sup>28,38,44</sup> have estimated that 10% of patients with persistent hypercalcaemia after parathyroidectomy have previously unrecognized FHH. With increased awareness of FHH as a cause of hypercalcaemia, unnecessary neck exploration might be avoided.<sup>47</sup>

Regular follow-up of patients with FHH allows the detection of rare complications at an early stage. Only occasionally will intervention be necessary, i.e. for severe neonatal primary hyperparathyroidism or for pancreatitis. The procedure of choice in these cases is a total parathyroidectomy.<sup>31,32</sup>

### Conclusions

Diagnosis of FHH in a single individual is difficult and depends on the observation of characteristic features of FHH in a family. These characteristics consist of hypercalcaemia often accompanied by the occurrence of a hypocalciuria, a tendency for hypermagnesaemia, and a normal or only slightly elevated concentration of

immunoreactive parathyroid hormone (PTH). The absence of the typical complications of hypercalcaemia and the high frequency of hypercalcaemia in young family members distinguish this syndrome further. FHH is usually inherited as an autosomal dominant trait. Recently, a variant of the disease has been observed in which heterozygotes showed only mild intermittent hypercalcaemia while the homozygotes suffered from severe neonatal hyperparathyroidism. The pathophysiology of FHH is unknown but an impaired sensitivity and/or abnormal cellular transport or binding of calcium in several organs including the parathyroid glands and kidney is suggested. This results in an elevated parathyroid 'set point' for calcium and a relative hypocalciuria. Since subjects with FHH generally do not have medical problems related to this and have a normal longevity, no treatment is needed. Only in cases of FHH complicated by severe neonatal primary hyperparathyroidism or pancreatitis is total parathyroidectomy advised.

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