Primary and secondary uraemic hyperparathyroidism: from initial clinical observations to recent findings

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Introduction

Primary hyperparathyroidism has evolved from what was initially thought to be a very rare disease to a relatively frequent endocrine disorder. The rapid improvement in knowledge of this disease in the early part of this century is due to the observations of a small number of internists and surgeons. A parathyroid adenoma was for the first time successfully removed by Mandl in 1925 [1]. The first series of patients with primary hyperparathyroidism was published in 1934 and reported on 17 patients [2].

The present review is directed at some of the major issues of primary and secondary uraemic hyperparathyroidism to see how they have evolved during the years. Most were already recognized in the 1950s and 1960s, at a time when Mary G. McGeown became progressively interested in the endocrine disorders of the parathyroid glands.

Incidence of hyperparathyroid diseases

It has long been known that hyperparathyroidism is not a rare disease. Based on the clinical and biochemical means available in the late 1950s, Mary G. McGeown was able to document the occurrence of primary hyperparathyroidism in 55 cases over a time period of 4 years in the population of Northern Ireland which was then 1.3 million people [3]. She calculated from these data an annual incidence of ten cases per million population. Since the introduction of multi-channel autoanalysers in the late 1960s, a dramatic increase in the incidence became apparent which in the United States was estimated to be approximately 270 per million population [4]. A similar incidence was reported at that time from Great Britain and Sweden.

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Modes of parathyroid hormone (PTH) action

Initially there were two main schools of thought concerning the action of PTH, as pointed out in the interesting review on hyperparathyroidism by McGeown and Morrison [3]. The earlier view, put forward by Thomson and Collip [5] and Jaffe [6], was that the hormone acts directly on bone tissue to cause its dissolution, and that the changes in plasma electrolytes are secondary to the bone changes. In contrast, Albright and Ellsworth believed that the skeletal changes were secondary to changes in blood chemistry, the latter being secondary to the phosphaturic action of PTH and the subsequent decrease in serum phosphorus [7]. Since in their opinion a low extracellular phosphate concentration would cause less saturated body fluids this could provoke a compensatory dissolution of bone mineral, allowing restoration of the disturbed extracellular calcium phosphate equilibrium. The resulting increased serum calcium would explain the often observed increase in urinary calcium excretion which again would cause an undersaturation of the body fluids and thus perpetuate the vicious circle.

The first hypothesis of a direct PTH action at the bone level was subsequently strengthened by the demonstration that PTH was capable of inducing hypercalcaemia and bony changes in nephrectomized animals [8]. However, it proved difficult to explain the various features of hyperparathyroidism, such as disturbed gastric function [9], the neuromuscular syndrome, and pseudogout, by an action on only one target organ. Thus, the idea arose that several different target tissues must exist. Interestingly, this hypothesis could be proved only 40 years later when the PTH/PTHrp receptor was cloned [10] and subsequently found to be expressed in numerous tissues, in addition to kidney and bone [11].

Clinical presentation of primary hyperparathyroidism

It was already well recognized in the 1950s that primary hyperparathyroidism mainly presented with two
different faces, namely as a ‘bone disease’ characterized by osteitis fibrosa cystica or as a ‘stone disease’ characterized by recurrent nephrolithiasis. McGeown and Morrison therefore postulated that there should be more than one hormone to explain such contrasting phenotypes [3]. This idea again emerged 20 years later when Broadus et al. stressed the importance of an elevated serum calcitriol in the pathogenesis of hypercalciuria and renal stone formation in primary hyperparathyroidism [12]. In keeping with this, hyperparathyroid patients with predominant bone disease had lower calcitriol, but higher PTH levels [13]. However, the occurrence of these two syndromes is not mutually exclusive, and the distinction probably cannot be made on the sole basis of differences in plasma calcitriol and PTH values [14].

The potential role of calcitonin in the clinical expression of primary and secondary hyperparathyroidism has been a subject of debate for years. The increase of plasma calcitonin in uraemic patients, which was often observed in the presence of hypocalcaemia and therefore tentatively attributed to the concomitant hyperphosphataemia, could lead to a relative protection against the bone-resorbing activity of PTH, by enhancing bone formation. It could even be responsible of the patchy osteosclerosis often present in such patients [15].

**Diagnosis of parathyroid overfunction**

The diagnosis of hyperparathyroidism of mild to moderate degree has long been hampered by the absence of a reliable method for the determination of plasma PTH, as regretfully stated by McGeown in 1965 [16]. Therefore, at that time clinicians had to rely mainly on the measurement of secondary parameters such as plasma and urinary calcium and phosphorus, in the absence of pathognomonic skeletal changes. The subsequent introduction of radioimmunoassays using antibodies directed against the C-terminal, N-terminal or midregion moiety of PTH was an important step forward in diagnostic terms. This was particularly true for estimating the degree of secondary hyperparathyroidism in patients with chronic renal failure. However, the diagnosis of primary adenoma and hyperplasia remained difficult. At the end of the 1980s, the development of a double sandwich radioimmunoassay, allowing measurement of human intact PTH reliably, solved this difficulty at last. It probably has led since, on the one hand, to the avoidance of unnecessary surgery in most instances but on the other hand it has greatly helped to indicate parathyroidectomy in patients with hyperparathyroidism of moderate degree at earlier time points than was the case previously.

**Factors involved in the control of PTH secretion**

It is well established that PTH secretion is directly regulated by calcium and calcitriol at the level of the parathyroid cell [17]. Very recently it was demonstrated that phosphate also modulates PTH secretion directly [18–20], in addition to its long known indirect effects via changes in plasma calcium and calcitriol synthesis. Whereas calcitriol regulates pre-pro-PTH gene expression at the transcriptional level, calcium and phosphate appear to act mainly at post-transcriptional steps. Calcium and calcitriol have been shown to interact with specific receptors in the parathyroid cell membrane and nucleus, respectively. In contrast, it remains unclear at present by which transmembranous signalling system phosphate exerts its direct action on the parathyroid cell.

The relation between plasma Ca\(^{2+}\) and plasma PTH exhibits an inverse sigmoidal relationship, with Ca\(^{2+}\) being normally regulated at a set-point which corresponds to the midpoint of the inverse sigmoidal Ca\(^{2+}\)/PTH curve [21].

PTH is not only secreted from the glands in a basal, tonic mode but is also released in a pulsatile fashion, in the form of episodic secretory bursts [22,23]. Hypocalcaemia selectively increases pulsatile PTH release by stimulating both burst frequency and burst mass by a Ca-rate sensitive mechanism [24]. Oral calcitriol, but not i.v. calcitriol, suppresses baseline pulsatile PTH release and in addition reduces the pulsatile secretory capacity in response to hypocalcaemia [24].

**Pathophysiology of PTH hypersecretion and parathyroid hyperplasia**

In primary hyperparathyroidism excessive PTH secretion is associated with parathyroid tissue hyperplasia. Parathyroid adenomas are characterized by a monoclonal growth pattern in all cases [25] whereas in the majority of cases of primary non-familial parathyroid hyperplasia the growth pattern is polyclonal [26]. Various somatic gene mutations probably underly the transformation of normal parathyroid tissue into an adenoma, including clonal rearrangement and over-expression of the cyclin D1/PRAD1 oncogene, allelic losses on chromosome arms 1p [27] and 11q [28], and several, recently discovered deletions in chromosome regions 6q and 15q [29]. Mutations of the menin gene located on the 11q13 region are characteristic for patients with the multiple endocrine neoplasia type I (MEN-I) syndrome [30], and germline point mutations of the ret proto-oncogene are involved in the tumorigenesis of MEN-2A [31]. Finally, an inactivation of the RB tumour suppressor gene on 13q14 is common in parathyroid carcinoma, but not in primary adenoma [32].

Concerning the pathogenesis of secondary uraemic hyperparathyroidism, a number of systemic and local factors are probably involved. Thus the decrease of plasma calcium and calcitriol in early renal failure and the increase of plasma phosphate in advanced renal failure lead to a constant stimulation of PTH synthesis and/or secretion. In addition, the frequently diminished
expression of vitamin D receptor [33] and calcium-sensing receptor [34,35] in parathyroid tissue of such patients, particularly in areas of hypothetical or proved clonal growth, almost certainly contributes to the escape of PTH secretory control.

Abnormal, de novo expression of growth factors such as TGF-α may stimulate the development of parathyroid tissue hyperplasia in chronic renal failure [36]. In case of severe secondary hyperparathyroidism, we [26] and others [37] have shown that benign clonal tumours develop in a high proportion of parathyroid glands, probably favoured by the existence of polyclonal parathyroid hyperplasia for many years [38]. The molecular genetic anomalies involved in the pathogenesis of benign monoclonal or multiclonal tumours in uraemic patients with severe secondary hyperparathyroidism are still unknown. We recently found evidence of loss of heterozygosity for several genes located on human chromosome 11p in a series of parathyroid glands sampled from several such patients, possibly corresponding to monosomy of chromosome 11 in some cases [39]. Others found evidence for an allelic loss on chromosome 11q13 in 2 of 12 parathyroid glands from six patients [40].

The question of whether the apoptotic rate of parathyroid cells is modified in primary or secondary hyperparathyroidism remains controversial [41]. The problem is hampered by the fact that it has not been possible so far to determine apoptosis reliably in normal parathyroid tissue. According to our most recent, still preliminary results the rate of apoptosis is increased in primary and secondary hyperparathyroidism, compared with normal parathyroid tissue [42].

Taken together, these findings are compatible with a possible role for the inactivation of tumour suppressor genes, located on chromosome 11 and elsewhere, in the pathogenesis of benign parathyroid tumours. Probably more than one gene rearrangement or deletion are implicated in abnormal parathyroid growth. Precise knowledge of individual deletions in each parathyroid tumour could help to achieve the ultimate goal of designing specific therapeutic approaches. Alternatively, the identification of therapeutic tools capable of interfering less specifically with excessive parathyroid cell proliferation, might be a more reasonable strategy in the near future. Last not least, the specific induction of parathyroid apoptosis constitutes another theoretical approach worth considering.

References

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