Management of patients with advanced secondary hyperparathyroidism: the Japanese approach

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Introduction

Control of secondary hyperparathyroidism is one of the main objectives in the management of uraemic bone disease [1]. Although early initiation of prophylactic measures and calcitriol pulse therapy [2] in cases with advanced hyperparathyroidism have had a positive impact on patient management, there are still difficulties to select the most appropriate therapy for the individual patient with advanced secondary hyperparathyroidism. The major problem is to identify in time the patient who cannot be controlled by calcitriol and for whom the decision has to be made whether medical management or parathyroidectomy are the most appropriate interventions [3,4]. Despite advances, such as new vitamin D sterols [5], calcimimetics [6,7] or non-aluminium, non-calcium-containing phosphate binders [8], this dilemma persists unabated.

We are of the opinion that recent insights into the pathogenetic mechanisms underlying parathyroid hyperplasia [9,10] have greatly helped to make more rational selections of therapy. It is the purpose of this brief communication, to offer to the readers of Nephrology Dialysis Transplantation some information on the unique intervention strategies that we have recently developed in Japan.

How to assess the patient

To assess the severity of hyperparathyroidism, a classical approach is measurement of the concentration of intact parathyroid hormone (PTH) as well as markers of bone turnover, such as serum total alkaline phosphatase, bone alkaline phosphatase isoenzyme and others. In addition to these markers, however, we feel that appropriate imaging of the parathyroids is very useful indeed [11,12], because it provides information that cannot be obtained from serum markers.

Which pathomechanisms underly parathyroid hyperplasia?

Two types of parathyroid hyperplasia can be distinguished in the uraemic patient, i.e. diffuse hyperplasia and nodular hyperplasia. Nodular hyperplasia is characterized by the presence of several nodules that are surrounded by fibrous capsules. This variant is seen mainly in patients exhibiting strikingly enlarged parathyroid glands [13]. Cells within the nodules exhibit a lower density of calcitriol receptors [14] and calcium sensing receptors [15,16]. Cells within the nodules also have a higher proliferative potential and there is a correlation in the sense that the higher the rate of cell proliferation, the lower the expression of these receptors [17].

The initial stage in this process is diffuse hyperplasia of the parathyroid gland. Some cells in the parathyroid with diffuse hyperplasia, particularly those exhibiting reduction of calcitriol and calcium sensing receptors, escape from cell cycle control mechanisms and proliferate vigorously. This will ultimately lead to the development of nodular transformation of the parathyroid gland (nodular hyperplasia). In advanced cases, nodules may grow so vigorously that they occupy the entire gland, which then forms one single nodule. Monoclonal cell growth was believed to underly only the more severe cases of nodular hyperplasia [18], but subsequent studies documented that cells within nodules always exhibit monoclonal proliferation, irrespective of the size of the nodule [19]. Specific gene rearrangements have been proven only in limited numbers of patients [20]. Mutations of the calcium sensing receptor or calcitriol receptor genes have never been demonstrated in uraemic patients.
either [21,22], but there is evidence of widespread gene deletions [23].

How does parathyroid gland morphology impact on patient management?

Parathyroid glands exhibiting nodular hyperplasia are usually resistant to medical therapy, as shown schematically in Figure 1. It is, therefore, important to be able to distinguish diffuse from nodular hyperplasia based on clinical data. The most informative approach is to determine the size of the parathyroid glands.

The critical size of the parathyroid gland is apparently 0.5 cm³ or 1 cm in diameter, as detected by ultrasonography. According to our clinical experience [11], patients in whom at least one gland is >0.5 cm³ (or >1 cm in diameter) are usually refractory to calcitriol in the long run, even when calcitriol is administered as pulse therapy. The cell biology of the large nodules appears to be different because Tominaga et al. [24] noted that transplanted parathyroid fragments cause relapse of hyperparathyroidism if the gland from which the fragments were derived weighed >0.5 g. Histological studies confirmed our hypothesis that nodular hyperplasia is found in >90% of parathyroid glands weighing >0.5 g [25].

Selection of therapeutic modalities according to the pattern of parathyroid hyperplasia

The patient with suspected diffuse hyperplasia

In the following we discuss the approach that has been adopted by a group of Japanese nephrologists.

When diffuse hyperplasia is suspected, we recommend that serum calcium and phosphate concentrations should be normalized and then the patient be treated by administration of ‘physiological’ doses of active vitamin D sterols. We then go on to calcitriol pulse therapy either by intravenous [26,27] or oral [28] routes. According to our clinical experience, we feel that when this approach is used, suppression of PTH secretion can be achieved early on and will usually persist in the long run.

In order to prevent the progression from diffuse to nodular hyperplasia, we feel that rigorous control of serum phosphate concentration is indispensable, based on animal experiments indicating that high phosphate concentrations stimulate the parathyroids [29,30]. It is of interest that according to Almaden et al. [31], the stimulatory effect of phosphate is more pronounced in parathyroid tissue exhibiting diffuse rather than nodular hyperplasia. A phosphate load also contributes to decreased calcium sensing receptor expression [32].

What do we do if the patient does not respond to calcitriol within 3 months? We consider two possibilities. Nodular hyperplasia may have developed in glands that are still relatively small. According to the study of Tominaga et al. [25], up to 50% of the glands weighing between 0.25 and 0.5 g exhibit nodular hyperplasia. There is also some suggestive evidence that apart from the size of the glands, the shape of the glands, as detected by advanced ultrasonography devices, may give a hint as to nodule formation within the glands [33]. Apart from size and shape, the blood supply to the glands, as detected by colour Doppler ultrasonography, may give a hint to the presence of nodular hyperplasia [25,34].

The second possibility that we have to entertain is that one or more supernumerary glands exhibiting nodular hyperplasia may have escaped detection by ultrasonography [35]. Such glands can be detected, however, using scintigraphy, computed tomography or magnetic resonance imaging [36]. Demonstration of such a gland would of course be an indication for parathyroidectomy.

The patient with suspected nodular hyperplasia

Since these patients are usually resistant to calcitriol therapy, including calcitriol pulse therapy, we do not advise prolonged therapeutic attempts because prolonged treatment implies a high risk of metastatic
calcification [37]. We agree with proposals [4] that such patients should undergo surgical parathyroidectomy, at least if they do not respond to a short course of medical intervention.

The discussion arises whether the same approach is indicated for all patients, irrespective of whether they have nodular hyperplasia of all glands or nodular hyperplasia only of selected glands.

In patients in whom three or more parathyroid glands are enlarged and provide evidence of nodular hyperplasia, there is consensus that surgical parathyroidectomy is indicated [38,39]. We prefer total parathyroidectomy, preserving fragments for autotransplantation that have been obtained from the smallest gland with the greatest chance of diffuse hyperplasia. If tissue fragments from nodular glands are used, there is a high risk of relapse [24].

In contrast, the patient with only one or two enlarged glands is not considered as an urgent indication for surgery. Should one wait until hyperplasia has progressed to a more severe stage before surgery is justified? Should one try medical management, waiting for the arrival of effective and safe vitamin D analogues or calcimimetics or their combination?

Although conventional total parathyroidectomy is advocated by many, as in patients with primary hyperparathyroidism in whom selective partial parathyroidectomy with minimal incision has become the preferred approach for single adenoma or hyperplasia [40,41], we are against this approach because of concerns that these patients ultimately will develop nodular hyperplasia of all glands, particularly if there is no chance of early kidney transplantation.

It is in these patients that two new techniques have proven quite successful in our Japanese experience. The first technique is selective percutaneous ethanol injection (PEIT) [42,43]. This implies selective destruction of glands with nodular hyperplasia by ethanol injection under ultrasonographic guidance. This is done in the hope that the remaining glands with diffuse hyperplasia are then more easily controlled by medical therapy [44] and this approach is now widely used in Japan [45]. In some patients, hyperparathyroidism may persist despite successful ablation and then one usually finds ectopic glands. Because of this possibility, whether scintigraphy, computed tomography or magnetic resonance imaging should be performed routinely before PEIT is currently under discussion.

A second recent technique is direct injection of calcitriol into the gland [46]. This approach is adopted with the rationale to achieve very high local concentrations of calcitriol within the parathyroid gland. It has been shown that subsequent to this intervention, responsiveness to medical management is restored. According to a recent report, another active vitamin D analogue, 22-oxa-calcitriol (maxacalcitol) has been injected into the gland by this technique and led to successful control of PTH secretion and parathyroid hyperplasia [47]. The success of this intervention has led to more imaginative approaches, including, at least in animal experiments, adenoviral vector delivery [48], several vitamin D analogues and calcimimetics [49]. Although nodular glands can be ablated with this technique, it would be naive to assume that this is the end of the story. Because of this concern, strict control of serum phosphate is absolutely indispensable.

A final word on the coincidence of primary and secondary hyperparathyroidism. This possibility is suggested if a patient has a markedly enlarged single parathyroid gland despite a history of only relatively short dialysis. A novel approach to distinguish primary and secondary hyperparathyroidism has been proposed by Tominaga et al. [50] by analysing the expression of cell cycle regulators. Whether this will have practical applications in the future is not yet known.

Conclusion

There is no simple, uniform approach to the management of hyperparathyroidism in the renal patient. We wish to emphasize that the most useful clinical information for the selection of interventions is derived from the results of imaging procedures. The simplest and most practical investigation is evaluation of the gland size by ultrasonography. If there is suggestive or definite evidence of nodular hyperplasia, we recommend the removal of such glands by surgery or PEIT at a relatively early stage, in an effort to avoid prolonged and potentially even harmful medical intervention, particularly high dose calcitriol pulse therapy [39].

References

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