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Normocalcemic Primary Hyperparathyroidism

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Abstract

The prevalence and the natural history of Normocalcemic Primary Hyperparathyroidism (NCHPT) are not well known. Therefore the aim of this retrospective study was to determine the prevalence and natural history of (NCHPT).

We reviewed the electronic medical records of patients with normal serum calcium level (8-10.5 mg/dl) and elevated serum Parathyroid Hormone (PTH) level (>72 pg/ ml) over a period of 10 years (2003 to 2013), mean period of 4.6 years, ranging 1-8 years at Michigan State University outpatient clinics. During this time, no patient was sent for parathyroidectomy but simply followed. We identified 332 patients to have primary hyperparathyroidism out of which 50 were normocalcemic. Out of these twenty-seven (54%) patients were found to have vitamin D deficiency (25 Hydroxy vitamin D level< 30ng/ml), and 2 patients taking hydrocholorothiazide were excluded. Thus the prevalence of NCPHPT is 21 /332 (6.3%). Bone mineral density had been determined in 13 patients. 6/13 (46.1%) showed osteoporosis, 5/13 (38.46%) had osteopenia and 2/13 were normal. Two patients 2/21 (9.5%) had history of recurrent fractures, and 6 (28.5%) had recurrent kidney stones. Among those with Vitamin D deficiency, PTH level returned to normal only in 7 patients over a period of 3 months to 4 years after the correction of the deficiency. In 20 patients, PTH remained elevated throughout the follow up ranging from 2 months to 7 years.

This retrospective analysis shows that among all patients with hyperparathyroidism about 6.3% may have NCHPT. Our data also shows that NCPHPT is not a benign entity and may be associated with increased risk of osteopenia, osteoporosis and kidney stones.

Introduction

Normocalcemic Primary Hyperparathyroidism (NC-PHPT) is a clinical entity characterized by normal serum calcium and persistently elevated parathyroid (PTH) levels. These patients have no obvious causes for secondary hyperparathyroidism such as vitamin D deficiency and renal insufficiency [1,2-16,17]. None of the patients had clear evidence of gastrointestinal disease. Although the entity NC-PHPT is now well recognized it's natural history and the course is not well known. Therefore our aim of the study was to evaluate the prevalence and the natural course of NCPHPT. To the best of our knowledge, the term normocalcemic primary hyperparathyroidism was first used by Wills, et. al [18]. Since then, several studies have described the various aspects of this entity [1,2-16,17].

Study Design and Method

We retrospectively evaluated the medical records of patients with normal serum calcium (8-10.5 mg/ dl) and elevated serum Parathyroid Hormone (PTH) level (> 72 pg/ ml) over a period of 10 years (2003-2013) at Michigan State University outpatient clinics. We excluded the patients with chronic liver disease, kidney disease (GFR <90), vitamin D deficiency and subjects taking Lithium or Hydrochlorothiazide to exclude causes of secondary hyperparathyroidism. Subjects with previous parathyroid surgery were also excluded.

Result

We identified 332 patients to have primary hyperparathyroidism out of which 50 were normocalcemic. Out of these, twenty seven (54%) patients were found to have vitamin D deficiency (25 hydroxy vitamin D level < 30 ng/ ml) and 2 patients were taking HCTZ. These were excluded from further analysis. We therefore had 21 patients who were found to have NCHPT. Hence, the prevalence of NCPHPT appears to be 21/332 (6.32%). The baseline characteristics of these 21 patients are shown in Table 1. Out of those 21 patients, 7 had serum calcium > 10 occasionally. However, the level would rise and fall. 3 (~15%) of them eventually had serum calcium > 10.5. 1 of those 3 subsequently had normal serum calcium levels whereas 2 of them continued to have serum calcium >10.5 for the next 3 years until we could obtain the data. Although the

Table 1: Baseline characteristics of patients with NCPHT.

Age (years)	**Mean-60.9 ± 13.2**	
Gender M/ F	2/19	
Serum Albumin (gm/ dl)	Mean = 4.2 ± 0.3	Range = 3.5-4.8
Serum Calcium (mg/ dl)	Mean = 9.4 ± 1.0	Range = 8.08-11.12
Serum PTH (pg/ ml)	Mean = 118.3 ± 51.3	Range = 74.5-388.2
Vitamin D (ng/ ml)	Mean = 42.1 ± 16.1	Range = 30.9-78.6

All values are mean ± SD

initial total serum calcium level was normal in all patients, 2 (7.4%) had elevated ionized calcium, and 5 (23.8%) had normal ionized calcium. Ionized calcium was not measured in 14 (66.6%) patients. Serum albumin was normal in all. Hence, no additional albumin related adjustments were made. Bone mineral density had been determined in 13 patients. 6/13 (46.1%) showed osteoporosis, 5/13 (13.4 %) had osteopenia and 2/13 (15.3%) were normal. Two patients (9.5%) had history of recurrent fractures, and 6 (28.5%) had recurrent kidney stones. Out of 6 patients with recurrent stones only one had BMD checked which showed osteopenia.

Discussion

In this retrospective study we found the prevalence of NCPHPT to be approximately 6.3%. In prospectively studied patients the prevalence has ranged from 0.5 to 16.7% [9-11]. Garcia et al reported a prevalence of 6% in 100 postmenopausal women, which is very similar to the prevalence in our study [11].

In our study, vitamin D deficiency was the most common cause of elevated PTH level in the presence of normal serum calcium. Vitamin D deficiency is a well-known cause of secondary hyperparathyroidism [1]. An inverse relationship exists between 25-hydroxivitamin D and PTH [19]. When vitamin D decreases below the normal range, the parathyroid gland responds with increased synthesis and secretion of PTH. The level of 25-hydroxivitamin D at which this occurs is somewhere between 20 and 30 ng/ mL [19]. A recent informal consensus of investigators active in the field settled on a value of 30 ng/ ml [20]. However the mechanism by which the vitamin D deficiency increases PTH levels is not clear, at least it does not seem to be mediated through serum calcium levels because the serum calcium levels are normal and yet the PTH levels are elevated. In a very large study based on laboratory collected specimens, Valcour et al observed that 40% and 51% subjects with 25 (OH) levels below 20 and 10 ng/mL respectively had biochemical hyperparathyroidism with serum PTH level greater than 65 pg/ ml, the upper level of normal in their study [21]. However there was no threshold above which increasing levels of 25 (OH) vitamin D levels further suppressed PTH levels [21]. Unfortunately serum calcium levels were not available. Therefore it is difficult to evaluate whether the PTH response was directly related to the vitamin D levels or mediated through serum calcium levels. In another Italian study, serum PTH levels were significantly correlated with age, 25 (OH) D and calcium intake [22].

In patients where vitamin D deficiency is the cause of elevated PTH level, it is expected that PTH levels will fall into the normal range after vitamin D deficiency is corrected. However, that does not appear to be the case in all patients. In a study of Asian patients with vitamin D deficiency, PTH normalized only in 45-55% subjects [23]. In another study of secondary hyperparathyroidism in patients with osteoporosis, Yendt, et. al. [24] observed that in 1/3 of patients the standard treatment of vitamin D deficiency (1,000 unit of vitamin D_3 daily or 50,000 IU vitamin D_2 once weekly) failed to correct secondary hyperparathyroidism. In our study among those with vitamin D deficiency, PTH level returned to normal only in 7 patients over a period of 3 months to 4 years after the correction of the deficiency. In two patients, PTH levels gradually declined but did not reach normal levels despite having normal vitamin D level, for a period of 3 and 7 years. In 18 patients, PTH remained elevated throughout the follow up ranging from 2 months to 5 years.

A strict definition of NCPHPT requires that the serum calcium be in the normal range with an elevated PTH level. This for practical clinical purposes means that the albumin corrected serum calcium is in the normal range. It has been suggested that both total and serum ionized calcium should be in the normal range [12]. However; reliability of ionized calcium in clinical laboratories may be questionable. While the measurement of total calcium, albumin and total protein is available in standard laboratories, measurement of ionized calcium remains more difficult and is generally performed only in reference laboratories [25]. Several factors may affect the measurement of ionized calcium including patient posture, tourniquet, pH of the sample, and the time it takes to process the sample. Samples must be drawn anaerobically, avoiding heparin contamination, transported on ice, and must be processed within hours. These conditions, if not strictly adhered to, make the determination of ionized calcium somewhat unreliable in routine clinical laboratories [25,26].

Despite these reservations in several studies reported as NCPHPT the ionized calcium level was not reported [8,11,14,15].

The spectrum of presentation of primary hyperparathyroidism has changed over the years from symptomatic to asymptomatic after routine biochemical measurement of serum calcium became available in 1970's [27]. In 1988, Rao, et. al, [28] suggested that primary hyperparathyroidism may be a biphasic disease. During the first phase, PTH levels are elevated, but serum calcium is normal. Until recently, the first phase was subclinical because PTH levels were rarely measured when the serum calcium was normal. The second phase is the one that has traditionally been recognized because of the development of hypercalcemia.

Thus, normocalcemic PHPT may represent an early or mild form of hypercalcemic PHPT, detected when the only biochemical abnormality is an elevated PTH concentration (14). Maruani, et. al, [16] suggested that normocalcemic primary hyperparathyroidism may be due to target organ resistance to the actions of PTH. In their studies, normocalcemic subjects demonstrated inadequate suppression of PTH in response to an oral calcium load. Fasting bone turnover markers and net skeletal calcium release were also lower in the normocalcemic group compared to the hypercalcemic group.

The natural history and clinical presentation of NCPHPT is not well described. Many patients come from referral centers where PTH levels may have been obtained for other reasons, such as evaluation of osteopenia/osteoporosis or renal stones. In the cohort evaluated by Cusano, et. al, [1], at the time of diagnosis, 57% had osteoporosis by bone mineral density. 11% had fragility fractures, and 14% had nephrolithiasis. Other studies have described the prevalence of osteoporosis ranging from 46-73%,

fragility fractures 11%, and renal stones from 9-14% [7,14]. In a large study where 187 patients with NCPHPT were followed, Siporva, et. al, [3] reported that another endocrine disease was present in 76% of subjects. Reduced bone density was present in 42%, arterial hypertension in 47%, ischemic heart disease in 40%, and a history of nephrolithiasis in 4%. Diabetes mellitus was diagnosed in 13% patients. It was reported that the thyroid diseases, mainly nodular goiter, and primary hypothyroidism was the most common endocrine disorder noted in this group, but the exact frequency was not described [3]. In our study, we noted that 46.1% had osteoporosis and 13.4% had osteopenia. 9.5% had history of recurrent fractures, 28.5% had recurrent kidney stones.

Although the treatment guidelines for hypercalcemic primary hyperparathyroidism are well described [29], there are no definite therapeutic recommendations for the treatment of NCPHPT. Most of the patients are asymptomatic and a careful follow up is all that may be needed. We agree with Cusano, et. al, [1] that annual serum calcium, PTH and BMD measurements seem reasonable. If the disease progresses to the hypercalcemic phase then the guidelines of the 4th International Workshop for Surgical Management of Asymptomatic Primary Hyperparathyroidism should be followed [29].

Study Limitations

This being a retrospective study, all causes of secondary hyperparathyroidism such as age, BMI, waist circumference, calcium intake, subclinical gastrointestinal disorders, hypercalciuria, hyperaciduria etc could not be taken into account. We acknowledge that the lack of measurement of ionized calcium is an important limitation as total serum calcium level can be unreliable when there is a major shift in serum protein or PH [30]. However, we also want to emphasize that all of our patients had normal serum albumin and normal renal function. Moreover, there was no clear evidence of acid base imbalance based on the lab tests available.

Conclusion

This retrospective analysis shows that among all patients with hyperparathyroidism about 6% may have NCHPT. Vitamin D deficiency is frequently associated with elevated PTH, but normal calcium level. When vitamin D deficiency is the putative cause of elevated PTH levels, it may take several months for PTH levels to return to normal, even after the vitamin D levels have been normalized. In some patients PTH levels may not return to normal despite high doses of vitamin D. Our data is also consistent with other studies showing that NCHPT is not a benign entity and may be associated with increased risk of osteopenia, osteoporosis and kidney stones which needs to be carefully followed.

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