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Non-traditional Manifestations of Primary Hyperparathyroidism

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Abstract

Classical primary hyperparathyroidism was previously a multi-systemic, symptomatic disorder not only with overt skeletal and renal complications, but also with neuropsychological, cardiovascular, gastrointestinal and rheumatic effects. The presentation of primary hyperparathyroidism has evolved and today most patients are "asymptomatic". *Osteitis fibrosa cystica* is rarely seen today and nephrolithiasis is less common. Gastrointestinal and rheumatic symptoms are not part of the clinical spectrum of modern PHPT. It remains unclear whether neuropsychological symptoms and cardiovascular disease, neither of which are currently indications for recommending parathyroidectomy, are part of the modern phenotype of primary hyperparathyroidism. A number of observational studies suggest that mild PHPT is associated with depression, decreased quality of life, and changes in cognition but limited data from randomized, controlled trials have not indicated consistent benefits after surgery. The increased cardiovascular morbidity and mortality in severe PHPT has not been definitively demonstrated in mild disease, though there is some evidence for more subtle cardiovascular abnormalities, such as increased vascular stiffness, among others. Results from observational studies that have assessed the effect of parathyroidectomy upon cardiovascular health have been conflicting. The single randomized controlled trial in this area did not demonstrate that parathyroidectomy was beneficial. Despite recent progress in these areas, more data from rigorously designed studies are needed in order to better inform the clinical management of patients with asymptomatic primary hyperparathyroidism.

Introduction

Classical primary hyperparathyroidism (PHPT) was dubbed a disease of "stones, bones, abdominal groans". Nephrolithiasis, *osteitis fibrosis cystica*, gastrointestinal and rheumatic complaints, cardiovascular disease, and neuropsychological symptoms were prominent manifestations of the disease in the past. Today, hypercalcemia, often an incidental finding on routine biochemical screening, is usually within 1 mg/dl above the upper limit of normal. Hyperparathyroid bone disease has also evolved, and overt skeletal involvement is rarely seen. Likewise, nephrolithiasis has become less frequent. Rheumatic and gastrointestinal disease including gout, pseudogout, peptic ulcer disease and pancreatitis, are not observed in sporadic PHPT (1, 2). Less clear is whether cognitive and psychologic symptoms as well as cardiovascular disease are part of the modern, generally "asymptomatic" form of PHPT that is so common today. At the last International Workshop on Asymptomatic PHPT held in 2008 (3), experts concluded that those with asymptomatic PHPT had psychological and

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cognitive complaints, but that data regarding their precise nature and reversibility were inconsistent. Additionally, it was determined that data regarding the extent and nature of cardiovascular involvement in those with asymptomatic PHPT were too limited to provide a comprehensive picture. The International Workshop identified the need for more data in these areas. Increased serum calcium and parathyroid hormone (PTH), the biochemical hallmarks of PHPT, have the potential to affect the cardiovascular system and to produce psychiatric and cognitive symptoms. There is evidence of such involvement in those with severe hypercalcemia. It is also possible that coexisting vitamin D insufficiency, common in patients with PHPT, could in part explain increased cardiovascular risk as well as changes in cognition, weakness and fatigue. There are, however, limited data regarding these specific associations with vitamin D deficiency in PHPT.

Most recent investigations on the non-classical manifestations of PHPT have focused on psychological and cognitive symptoms and the cardiovascular system. This review will summarize available data in these areas with an emphasis on randomized, controlled trial (RCT) data. While current concepts regarding the associations between PHPT and arthritis, energy and glucose metabolism as well cancer will be summarized briefly, comprehensive review of these areas is beyond the scope of this article.

Psychological and Cognitive Symptoms and Quality of Life

In the mild form of PHPT seen commonly today, many patients report nonspecific symptoms, including weakness, easy fatigability, depression, intellectual weariness, memory loss, decreased concentration, loss of initiative, anxiety, irritability, and sleep disturbance. However, the 2008 Workshop on Asymptomatic PHPT did not add psychiatric and cognitive symptoms to the list of criteria for parathyroidectomy (PTX) (4). Despite associations of such symptoms with PHPT, experts concluded there were insufficient data on their precise nature and reversibility to warrant a separate indication for PTX.

A number of studies have attempted to further characterize the psychiatric and cognitive features that accompany mild PHPT, as well as their reversibility with surgical cure (5–15). Most studies have investigated psychological symptoms and quality of life rather than cognition. Many studies are limited by their observational design, small sample sizes, inclusion of subjects with symptomatic hyperparathyroidism, or lack of appropriate control groups and objective measures. Most observational studies, but not all, suggest that there are psychological features of the disease that improve with surgery. A recent relatively large prospective case-control study assessed the prevalence of depression in mild PHPT and the benefit of PTX (16). In 169 PHPT patients, depression was twice as common compared to non-PHPT controls. PTX resulted in greater improvement in depressive symptoms compared to those who were observed and compared to thyroid surgery patients.

Improvement in depression after PTX was inconsistently seen in several other recent smaller case-control studies (14, 17, 18).

In addition to depression, quality of life (QOL) has been evaluated by a number of recent observational studies. Pasieka et al investigated the effect of PTX on 203 patients with PHPT in comparison to a thyroid surgery control group, and found a significant improvement in global health related quality of life (HRQL) after parathyroid but not thyroid surgery (19). Two others reported post-PTX improvement in emotional health and energy/fatigue in 43 “asymptomatic” patients (20) and improved perception of health status as well (21). Despite improvement in QOL after PTX, former PHPT patients still had lower QOL compared to healthy controls in a recent Danish investigation (22).

Since the benefit of surgery in observational studies could be due to baseline differences between the surgical and observation groups, or to biases introduced by their nonrandomized designs, more rigorously designed trials have been a priority. Three randomized studies of surgery vs. observation upon social and psychological function in PHPT patients with mild hypercalcemia have been published. All three used the Short Form-36 general health survey (SF-36), which measures functional health and well-being.

The group of Rao and Talpos (23) randomized 53 patients to PTX or observation. It is notable that unlike previous studies, Rao et al. found no difference in baseline SF-36 scores between PHPT patients and normal subjects. Surgery was associated with a significant benefit in social functioning and emotional role function on the SF-36. On the SCL-90, which quantifies psychological distress in 9 dimensions, surgery was associated with lower anxiety and phobia scores in comparison with those who did not have surgery, while there were no differences in the dimensions of depression, somatization, aggression, obsessive-compulsive, interpersonal sensitivity, paranoid ideation and psychoticism. No significant differences between groups were noted in the 3 composite scores (Global Severity Index, Positive Symptom Distress Index, Positive Symptom Total), or in any or the 9 individual or 3 composite scores in the observational group alone over time.

In the second RCT, Bollerslev et al. (24) reported on a large, multinational, trial in Scandinavia. Although biochemical and BMD data were included, the end-points of the study were the effect of PTX on quality of life and psychiatric symptoms in the 191 patients randomized to medical observation or PTX. In addition to the SF-36, they used the Comprehensive Psychopathological Rating Scale (CPRS), which measures 65 items and can be used to screen for the presence and severity of psychotic, mood, and neurotic disorders. Their report represented an interim analysis, with data available on 191 at baseline, 119 patients at 1 yr and 99 patients at 2 yr. In comparison with a large, age- and sex-matched reference population at baseline, those with PHPT scored lower in all psychological domains and the mental component summary of the SF-36, and had more psychiatric symptoms as determined by the CPRS. At 2 yr, SF-36-assessed physical function worsened in the observation group, although this parameter did not improve after PTX. Similarly, surgery provided no consistent improvement in psychological domains of functioning or psychiatric symptoms. Thus, although the preliminary results of this study suggest that impaired quality of life and psychiatric symptoms are present in mild PHPT, they do not demonstrate any clear benefit of surgery.

Most recently, Ambrogini et al reported on a RCT of surgery versus observation in 50 patients who met none of the NIH Guidelines for Surgery in asymptomatic PHPT (25). This study assessed quality of life and psychosocial well-being using the same tools used by Rao et al (SF-36 and SCL-90) before and after one year of follow-up. As in the Rao study but not the Bollerslev report, baseline differences between PHPT and a normal control data were minimal. Randomization to surgery resulted in a significantly higher emotional role function score. Emotional role function did not improve after surgery as it did in the Rao study; if anything, a relative improvement was noted in the non-operated group in whom scores came to resemble those of the operated group by 12 months. Overall, however, a between group analysis did demonstrate a beneficial effect of PTX in the following domains: bodily pain, general health, vitality and mental health. No differences were noted in any of the other SF-36 or SCL-90 domains between the two groups, and no worsening in the non-operated group was noted.

In addition to studies investigating psychological manifestations of PHPT, there have been several observational studies examining aspects of cognitive function (5, 11, 13, 14, 18) that have also yielded inconsistent results regarding improvement with PTX. This variability

may be due to variation in the aspects of cognition that have been investigated, as well as to differences in study design. Some are difficult to evaluate because of the very limited number of patients, limited breadth of cognitive testing or lack of controls (13, 26–29). Chiang et al. reported on 20 PHPT patients with an appropriate surgical control group (18). There were no differences between groups on cognitive testing in 4 domains, and no within group improvement after surgery, although findings may have been obscured by a highly variable follow-up interval (30–380 days in PHPT and 14–162 days after surgery in controls) and the small sample size. In 2009, Walker et al. found that those with mild PHPT (n=39) performed worse on tests of verbal memory and non-verbal abstraction compared with 89 non-PHPT controls (17). Non-verbal abstraction and some aspects of verbal memory improved after PTX such that scores were no longer different than controls. Both baseline differences and postoperative improvement were independent of anxiety and depressive symptoms.

Perrier et al. performed the only randomized, controlled study of PTX versus observation on cognition in asymptomatic PHPT (30). This small study (n =18) also assessed sleep and brain function using functional magnetic resonance imaging (fMRI). Though there were no differences in change in sleep time (which correlated with change in PTH) between treatment groups, daytime sleepiness decreased temporarily in those who underwent PTX vs. observation (at 6 weeks post-operatively), but differences were no longer significant at 6 months. Additionally, there were no between-group differences in changes in cognition. There were no changes in fMRI voxel counts, though the change in PTH level was associated with change in voxel activity in the left precentral gyrus.

In summary, most studies that have assessed psychological and cognitive symptoms in PHPT have design limitations that prevent definitive conclusions. The three randomized controlled trials of surgery versus observation on psychological function and quality of life in mild PHPT do not show consistent findings. The larger Bollerslev study but not the others strongly support the existence of more psychological symptoms in those with PHPT. The Bollerslev study also differed from the others in not finding an improvement with PTX. Furthermore, the specific domains noted to be abnormal and to improve or worsen over time differed among the studies despite the fact that the same assessment tools were used. Although all the authors raise the possibility of a placebo effect of surgery, the balance of data in these studies does support a marginally beneficial effect of PTX on quality of life and psychological functioning. However, given the variability of results, no specific improvement can be expected in a given patient.

Cardiovascular Disease

There is considerable debate regarding the cardiovascular effects of PHPT, with conflicting data concerning their extent and clinical significance. Many of the inconsistencies in the literature may be related to the evolution of the clinical presentation of PHPT from a once highly symptomatic disorder to a minimally symptomatic disease in most cases. As a result, studies of the cardiovascular system in PHPT have enrolled populations with varying disease severity, often leading to discrepant findings. Studies assessing the effect of PHPT on the cardiovascular system have investigated mortality, hypertension, cardiac and non-cardiac vascular abnormalities, as well as more subtle functional changes in the cardiovascular system.

Mortality

The increase in cardiovascular mortality in patients with severe and moderately severe PHPT has been well documented in studies from Scandinavia (31–35). The higher mortality rate declines with time from PTX, but persists long after surgical cure, suggesting that PHPT

may cause enduring damage to the cardiovascular system (36). The data on those with asymptomatic PHPT are limited, but several studies of patients with mild disease have not found mortality to be adversely impacted (37, 38). PHPT patients diagnosed in Rochester, Minnesota between 1965 and 1992 (mean calcium 10.9 mg/dl) had no increase in overall mortality. Indeed, a significantly lower than expected cardiovascular death rate was seen in patients with PHPT (relative risk 0.6) (38). This study did find that higher maximal serum calcium levels were an independent predictor of mortality.

One explanation for these incongruent mortality data is that more patients in the American studies (37, 38) had milder disease, with lower serum calcium levels and fewer symptoms than patients in the European studies (31–34, 36). This hypothesis is supported by a Swedish study investigating mortality over a 30 year time period in 10,995 patients who underwent PTX (39). While an increased risk of cardiovascular mortality was observed in the overall cohort, this risk dissipated in those enrolled in later years when calcium levels were lower. Another study reported that survival after PTX improved in those with a more recent calendar year of surgery (40, 41). The decline in death risk paralleled the decrease in mean preoperative serum calcium level over time (40). In contrast, a recent retrospective population-based observational study in PHPT patients with serum calcium mean calcium 10.5 mg/dl (1997–2006) indicated both cardiovascular morbidity (95% CI 1.54–1.87) and mortality ratios (95% CI 2.34–3.05) were increased compared to those without PHPT (42). Moreover, cardiovascular mortality was higher in those who were more recently diagnosed and who actually had lower calcium levels. However, data on a number of confounding factors were not available.

While most available data suggest that the decline in mortality in more recent years is due to lower calcium levels, it is also possible that increased cardiovascular mortality in PHPT is reversed by earlier diagnosis and intervention, advances in therapy for cardiovascular disease or that there was a change in the referral pattern for PTX. Finally, it must be noted that there are no population studies of mortality in mild PHPT surveying cohorts as large as those studied in patients with more severe disease.

Hypertension

Hypertension is frequently seen in association with PHPT, even those with asymptomatic disease. In those with PHPT as part of the Multiple Endocrine Neoplasia syndrome, hypertension is often cured by the surgical resection of pheochromocytomas. In those with sporadic PHPT, some studies have shown a reduction in blood pressure after PTX but most have not (43–45). In the recent RCT of PTX versus observation from Bollerslev et al.(46), there were no between-group differences in change in blood pressure. Given the preponderance of data, hypertension is not currently an indication for PTX.

Coronary Artery Disease

There are very limited data regarding coronary artery disease in PHPT. The autopsy study of Roberts and Waller (47) concluded that hypercalcemia and PHPT (which affected only half of the patients studied) caused coronary atherosclerosis. The range of calcium in that report was 16.8–27.4 mg/dl, making it impossible to generalize these data to patients with mild hyperparathyroidism. More recently, data from Vestergaard et al. support an increased incidence of coronary artery disease in PHPT patients with more moderate hypercalcemia (mean serum calcium 11.8 mg/dl) (41) although the risk of death was related to traditional cardiovascular risk factors rather than to severity of hypercalcemia or extent of elevation of parathyroid hormone. Coronary artery calcification, as measured by electron beam computed tomography, was not increased in 20 PHPT patients compared with population-based controls (48). On the other hand, Nilsson et al. reported reversible signs of myocardial

ischemia in those with PHPT (mean serum calcium 11.9 mg/dl), with less ST-segment depression during exercise after PTX (49). Similarly, a recent study in 22 PHPT patients demonstrated lower regional coronary flow reserve compared to 7 controls (50); time from PHPT diagnosis correlated with the degree of impairment. More data regarding the risk of coronary artery disease are needed in patients with mild PHPT before definitive conclusions can be made.

Valvular and Myocardial Calcification

Myocardial and valvular calcifications have clearly been demonstrated in PHPT patients with marked hypercalcemia (51). Studies in patients with more modest increases in serum calcium are limited. While one study in those with mild PHPT did not indicate any increase in valvular or myocardial calcifications (52), evaluation was qualitative (presence/absence). A recent study that quantitatively assessed aortic valve calcification area in mild PHPT (mean calcium 10.4 mg/dl) demonstrated increased calcification area in those with PHPT compared to non-PHPT controls (53). Moreover, PTH levels were positively associated with aortic valve calcification area. Once again, more data are needed in those with asymptomatic PHPT.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH), a strong predictor of cardiovascular mortality, has been associated with PHPT in many, but not all (54, 55) studies. Data suggest that LVH is independent of hypertension, and is instead, associated with PTH level (52, 56, 57). Many older studies, however, did not take into account other cardiovascular risk factors. Two recent studies with appropriate adjustment for or exclusion of those with cardiovascular risk factors found no evidence of increased left ventricular mass index (LVMI) in mild PHPT compared to non-PHPT controls (58, 59). While mean LVMI was not higher in PHPT in one study, higher LVMI was associated with lower 25-hydroxyvitamin D levels. These results suggest that vitamin D deficiency may be a previously unrecognized cardiovascular risk factor in PHPT, which could in part explain some of the variability between studies (59). LVH has been found to regress following PTX in some but not all observational studies, mainly in patients with severe PHPT (52, 54, 56, 57). Very limited RCT data are available. In the Bollerslev study, a subset of participants underwent echocardiogram at baseline and after 2 years of follow-up. The observed decrease in LVMI in those who had PTX compared with those followed without surgery failed to reach statistical significance, but mean LVMI was normal at baseline and the study had limited power to detect some clinically relevant differences (46). A larger RCT with longer follow-up may be necessary to fully evaluate the benefit of PTX upon LVMI.

Cardiac Conduction Abnormalities and Arrhythmia

Most, but not all studies, in those with moderate to severe hypercalcemia (mean calcium 11.3– 2.1 mg/dl) suggest that QT shortening is present in PHPT and improves after PTX (60–63). No increases in arrhythmias or AV block have been reported. Data in those with mild hypercalcemia are lacking.

Cardiac Functional Abnormalities

Diastolic dysfunction has been documented in many but not all studies, although the interpretation of some data is limited due to higher blood pressure in the PHPT group (52, 54, 57, 64). Two recent studies in mild PHPT in which relevant cardiovascular risk factors were known showed no increase in diastolic function in PHPT (58, 65). Data on improvement with PTX are also conflicting. The only randomized clinical trial in this area did not reveal a benefit of PTX upon diastolic function (46). Though most studies have not

suggested systolic dysfunction in PHPT, a recent small study suggests that left ventricular asynchrony may be present in PHPT (66).

Carotid Atherosclerosis

Carotid intima-medial thickness (IMT), a strong predictor of systemic atherosclerosis and cerebrovascular events, has been shown to be elevated in one study of patients with severe PHPT (54). A recent study in mild PHPT (mean calcium 10.5 mg/dl) also indicated increased carotid IMT compared with non-PHPT population-based controls after adjustment for cardiovascular risk factors (65). Other studies in mild disease that show no effect of PHPT or its cure on IMT have been limited by their small sample sizes and by methodological flaws (67–70).

Vascular Function

Endothelial dysfunction, an early and important step in atherogenesis, has been reported to be both normal and abnormal in those with severe PHPT (calcium 12.0 mg/dl) using differing methodologies (67, 71, 72). In those with somewhat lower calcium levels (mean 11.6 mg/dl), Baykan et al. also found impaired flow mediated (endothelial) dilation that negatively correlated with calcium levels (73). No data are available in mild disease. Data on markers of endothelial dysfunction in PHPT are currently preliminary.

Four studies have reported increased vascular stiffness, an independent marker of cardiovascular risk in patients with mild PHPT (74–77). Indeed, in one study, PHPT was a stronger predictor of increased aortic stiffness than many traditional cardiovascular risk factors, and was associated with the extent of elevation in PTH levels (77). Two of the aforementioned studies evaluated the effect of PTX upon aortic stiffness. While pulse wave velocity improved after PTX in both, this effect persisted in one and not the other after adjustment for changes in blood pressure post-operatively (74, 75). Carotid stiffness has also been demonstrated to be increased in mild PHPT with higher PTH levels predicting higher stiffness (65). Therefore, increased vascular stiffness appears to be the most consistent cardiovascular abnormality identified in those with mild PHPT and several studies indicate associations with PTH.

Cardiovascular risk factors

Some studies report increased body mass index (78), dyslipidemia (79), glucose intolerance (80), insulin resistance and diabetes mellitus (42) to be more common in those with versus without PHPT. A link between PHPT and glucose metabolism is in fact biologically plausible, as serum calcium levels could affect insulin levels by regulating intracellular free calcium concentrations. There may also be an association of PTH levels with fat mass, possibly mediated by leptin (81). One study indicated that those with severe PHPT were more likely to have cardiovascular risk factors compared to those with mild PHPT and that calcium level predicted the presence of metabolic syndrome (82). However, most studies have not found surgical intervention to consistently reduce risk (79, 83–85). RCT data do not suggest that PTX is beneficial in ameliorating cardiovascular risk factors in asymptomatic PHPT. No improvement was seen in, body mass index, glucose, insulin resistance, cholesterol, adipokines or markers of inflammation (86).

In summary, while cardiovascular mortality appears to be increased in severe PHPT, this finding has not been confirmed in those with mild disease. Data from observational studies also suggest a number of subclinical cardiovascular abnormalities, with increased vascular stiffness being the most consistent finding in mild PHPT. Cardiovascular improvement after PTX has been variable in observational studies and the single RCT in this area did not indicate a benefit. More data in these areas from rigorously, designed studies are necessary.

Rheumatic Disease

Classical PHPT was rarely associated with hyperuricemia, gout and calcium pyrophosphate crystal deposition disease (87–89). Pseudogout, a complication of calcium pyrophosphate crystal deposition disease in which calcium pyrophosphate crystal deposition causes synovitis, has been reported after the surgical cure of PHPT, though the mechanism of this association is unclear (90). Overt rheumatologic manifestations are mainly a historical phenomenon and not part of the clinical spectrum of modern disease (2).

Gastrointenstinal Disease

While no clear causal association exists between sporadic PHPT and peptic ulcer disease, this is not the case in patients with multiple endocrine neoplasia type 1 (MEN1). Gastrinoma is more severe in those with coexisting PHPT, and Zollinger-Ellison Syndrome improves with treatment of PHPT. Pancreatitis is virtually never observed as a complication of modern PHPT given its mild degree of hypercalcemia (91). Recent work indicates that patients with celiac disease are at increased risk for developing PHPT (92). It is unclear whether this association is causal.

Cancer

There are inconsistent data regarding whether cancer is more common in patients with PHPT. Several studies report increased risk of cancer and cancer deaths (42, 93, 94) with some suggesting that risk persists even after parathyroidectomy (95). Several types of cancer have been associated with PHPT including gastrointestinal and genitourinary malignancies, multiple myeloma, as well as breast and thyroid cancer, among others. The single American epidemiologic study of PHPT found a reduced, rather than increased, risk of death from cancer with a relative risk ratio of 0.58 (38). It is important to consider that the associations observed between PHPT and cancer in some investigations might not be causal, but secondary to confounding. For example, radiation exposure could lead to greater risk for both PHPT and malignancy.

Conclusions

Gastrointestinal and rheumatic manifestations are no longer observed in the modern form of PHPT. Although patients with mild PHPT seem to have neuropsychological symptoms including depression and decreased quality of life, data from RCTs have not indicated consistent benefits after PTX. The increased cardiovascular morbidity and mortality in severe PHPT has not been definitively demonstrated in mild disease, though there is some evidence for more subtle cardiovascular abnormalities that need to be more clearly defined. Further RCTs assessing cardiovascular health in PHPT are necessary.

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