Asymptomatic hyperparathyroidism: A medical misnomer?

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The diagnosis of primary hyperparathyroidism (PHPT), a complex endocrinopathy involving calcium metabolism and increased parathyroid hormone (PTH) secretion, is confirmed by documenting increased or inappropriately elevated PTH secretion in the setting of high normal or elevated serum calcium. Approximately 100,000 patients with recently diagnosed PHPT are documented each year in the United States. Automated, multichannel, routine screening of total serum calcium concentrations in the early 1970s led to a dramatic increase in the recognition of this disease. As a result, in the current era of advanced technology, the diagnosis is usually made at an earlier stage of the disease process. Whereas the classic and time-honored manifestations of “bones, stones, abdominal moans, and psychic groans” are not typical of the modern presentation of the disease, most reports suggest that many patients with PHPT discovered in the course of routine biochemical screening may have symptoms that are both vague and extremely nonspecific.

At present in the United States, more than 80% of patients with PHPT in fact present with a myriad of nonclassical, subclinical signs and symptoms of this disease. These patients are identified as those whose disease process has yet not evolved to a severe degree but who still exhibit subjective, identifiable symptoms believed to be typical of PHPT. These patients are often referred to in the literature as having “asymptomatic” PHPT. The differences in both clinical and biochemical presentation over the past several decades, which has changed from the overtly symptomatic high serum calcium and PTH levels to “asymptomatic” patients with lower serum calcium concentrations, have created much controversy over the timing of surgical intervention, which remains the only available definitive treatment. Historically, the recommendation for surgical intervention has been reserved for those patients whose disease process had advanced to a “symptomatic” level of objective symptoms manifested by nephrolithiasis, pancreatitis, and osteoporosis. Because of the variety of vague symptoms that are difficult to quantify, questions have arisen as to the possible benefit that patients might receive relative to these subjective symptoms after successful parathyroidectomy.

In the last decade, the guidelines of the National Institutes of Health (NIH) for treating PHPT did not offer a clear definition of “asymptomatic” PHPT. Indeed, many patients (and also many physicians) do not realize that their symptoms may be a manifestation of their disease until these symptoms diminish or wondrously disappear after...
parathyroidectomy. These nonspecific symptoms have been particularly difficult to study in a qualitative manner, and the literature has not led to any clear conclusions. Patients frequently display clinical signs of mental depression, poor general health, low energy levels, decreased ability to complete daily tasks at home or at work, decreased social interaction, and pain, particularly in the legs. Often improvements, particularly in the neuromuscular manifestations, occur after biochemical cure, even in those patients considered “asymptomatic.” Presumably, then, these nonspecific signs and symptoms have a negative impact on health-related quality of life, but systematic studies in this area are limited. Consistent improvement from prior baseline in patients’ perceptions of their general health or health-related quality of life, particularly in reduced bodily pain, improved vitality, and better emotional and physical functioning, has been reported. Specific improvement pertaining to forgetfulness, irritability, headaches, and weakness after successful parathyroidectomy was reported by Pasieka et al. These authors’ results demonstrate an impressive 60% increase in patients’ general health that persisted at 1 year but was most marked within 10 days after parathyroidectomy. Quiros et al also reported that parathyroidectomy is associated with improvement in patient’s perception of general health, muscle strength, energy level, and mood, and concluded that these subjective symptoms are valid indications for parathyroidectomy.

No report has documented that the degree of increase in serum calcium level correlates directly with symptomatology for all patients. In fact, in a 1991 study by Harrison and Wheeler, symptomatic and asymptomatic patients had similar preoperative serum calcium concentrations, suggesting that serum calcium concentrations alone were not responsible for the clinical severity of PHPT. Another study demonstrated that increased long-term mortality occurred even in patients with minimal hypercalcemia. More recently, a prospective study of patients who did not initially undergo operation found no reliable predictors determining who would eventually require surgical intervention before complications developed. In addition, the increased risk of bony fractures in females that begins approximately 10 years before surgical intervention disappears less than 1 year after operation. A Swedish cohort of more than 102,515 person-years demonstrated that the hyperparathyroid state is also associated with increased mortality.

A meta-analysis of the neuropsychologic aspects of this disease revealed that thorough systematic studies in this area are limited. Various studies have demonstrated that successful parathyroidectomy offers a possibility of improving these neuropsychologic symptoms, however. Brown et al suggested that cognitive dysfunction is present in patients with PHPT, but improvement in cognition is not observed within 6 months of parathyroidectomy. Numann et al reported improvements in neuropsychologic functioning across subsets, specifically in logical memory and associative learning. Goyal et al also examined the neuropsychiatric manifestations of PHPT exhibiting pronounced psychiatric symptoms and found that they were significantly improved after parathyroidectomy. Of particular note, these authors found no correlation between serum calcium concentration and the degree of neuropsychiatric symptoms. More recently, Talpos et al, using the SF-36 Health Survey in a randomized controlled clinical trial, found that social behavior and emotional role functioning improved after operation even in those patients without marked or severe symptoms of PHPT. These authors speculated that these domains might represent the initial clinical changes that patients experience before the development of a clearly identifiable state. Our own preliminary data suggest that functional magnetic resonance imaging may be a feasible tool for assessing these patients and some day may be ideal for highlighting functional brain changes. Our studies have focused on the anterior cingulate gyrus, the portion of the brain that concentrates on attention and concentration. Results from these studies, although preliminary, are encouraging.

Blood pressure is also known to correlate with serum PTH concentration, consistent with the induction of hypertension in humans exposed to chronic PTH infusion. The normal circadian rhythm of heart rate is blunted in patients with hyperparathyroidism, providing evidence of an imbalance in cardiac autonomic regulation and suggesting that diminished responsiveness to autonomic input to the heart or modification of this input by decreased vagal activity or increased sympathetic activity nocturnally can alter circadian rhythm. Imai et al reported a disturbance in any portion of the hierarchy of factors that regulate the circadian rhythm of sympathetic neural tone, which seems to disturb the circadian rhythm in blood pressure. Nilsson et al reported that circadian dysfunction of cardiac autonomic nerves in PHPT improved after parathyroidectomy. Another study of 20 individuals with mild PHPT who were age- and sex-matched with healthy subjects suggested that modulation of adrenergic control of circulation seems to be associated with
cycles of sleep stages 3 and 4.

Serum PTH levels to occur every 100 minutes and are related to thyroidism) found that peaks in plasma PTH tend evaluating 7 normal subjects (without hyperparathyroidism) with PHPT have altered circadian rhythms and in cardiovascular disease, and increased long-term survival after cure of PHPT. These findings also help make the case for the active treatment in PHPT.14,15

Our studies have revealed marked alterations in sleep patterns of patients with PHPT. Joborn et al. first noted reduced sleep on a single-item battery of 40 questions from a comprehensive psychopathologic rating scale (CPRS). To our knowledge, no further study of the relationship of sleep patterns and PHPT has been performed to date. Nonetheless, endocrine signals appear to play a prominent role in communication within the circadian system, and in fact neuroendocrine secretion itself appears to be under circadian control. The characteristic pattern of endocrine gland secretion is episodic or pulsatile and depends on the stage of sleep and the time of day. Age-related changes in both the endocrine and neuroendocrine circadian systems have also been well documented in humans. In normal patients (without PHPT), the 24-hour PTH profile is influenced by a sleep process with a circadian component. We believe that the altered circadian rhythm noted in cardiovascular studies of patients with PHPT supports the hypothesis that patients with inappropriately increased PTH levels have altered circadian rhythms and thus altered sleep patterns, which in turn may account for some of the multitude of subjective symptoms that they experience. What scant information that is available on the role of serum PTH and sleep remains unsettled. One older study evaluating 7 normal subjects (without hyperparathyroidism) found that peaks in plasma PTH tend to occur every 100 minutes and are related to cycles of sleep stages 3 and 4.17 Serum PTH levels and calcium concentrations were more closely related to sleep stages than to one another, suggesting that the regulation of serum PTH and calcium is complex and may involve interactions with neural neurohormonal systems.17 During baseline conditions in normal healthy male controls, serum PTH levels followed a bimodal diurnal rhythm, with an average amplitude of 4.2 pg/mL. The serum PTH levels followed a diurnal rhythm that persisted during the circadian rhythm, suggesting that a large component of this rhythm reflects an endogenous circadian rhythm.

Studying sleep cycles in patients with inappropriate PTH overproduction may support growing evidence linking sleep with behavior, mood, and cognitive skills. At the recent National Institutes of Health National Sleep Conference in March 2004, the Surgeon General stated that “the depth and breadth of sleep problems is not fully appreciated.” Sleepiness and fatigue contribute to lapses in attention, slowed reaction times, errors in working memory, reduced ability to learn, difficulties with problem solving, and deficits in executive function. Such performance problems have serious consequences. These problems resemble the subjective complaints of patients with PHPT, suggesting that chronic sleep dysfunction could be the underlying mechanism leading to the “preclinical” complaints of patients with chronically elevated PTH. Advances in the technology of sleep imaging are enabling new research into the neurophysiology and neurocircuitry associated with sleep and wakefulness. The neuromodulators that mediate neural signaling, their hierarchy in this process, and the role of complex hormones need to be better understood.

Another issue of particular interest today is the geriatric population, the group most at risk for developing PHPT. The incidence of PHPT in the general US population is 1.54 per million and increases with ages in both sexes, exceeding 1.5 per 100 in elderly Americans. The impact of chronic disease in these older adults, the most likely group to have coexisting cardiovascular problems and age-associated physiologic changes as sources of muscular weakness, is not fully understood. Due to the lack of understanding regarding this disease process, nonclassical symptoms are often overlooked in the elderly. Nonclassical symptoms may be discounted and erroneously assumed to be related to the aging process, depression, or a manifestation of Alzheimer’s disease or dementia. This population is often not readily referred for surgical evaluation despite the fact that “subclinical” symptoms may be major contributors to disability and functional decline in older adults with PHPT. A New Zealand study found that the delay between diagnosis and referral for surgery ranged from 8 days to 10 years, and exceeded 2 years in 24% of patients.18 Pitzenmeyer et al.19 evaluated symptoms associated with PHPT in patients age 76 to 98 years and found that neuropsychiatric manifestations (most commonly confusion and depression) were present in 73%. Chronic disease and age-associated physiologic changes are vitally important factors associated with the onset and progression of disability and eventual institutionalization of older adults.

Although the benefits of parathyroidectomy for primary hyperparathyroidism with advanced symptomatology are well known, the degree to which
older adults in particular may benefit from earlier intervention, and the extent to which this may reduce the long-term impact of later treatment of this disease, remain unknown. More rigorous studies need to be developed to determine whether early treatment for this condition will reduce the progression of disability in this growing segment of the population.

Despite these findings, controversy remains as to the extent of benefits experienced from parathyroidectomy in “asymptomatic” PHPT patients. In spring 2002, the “Workshop on Asymptomatic PHPT: A Perspective on the 21st Century” convened at the NIH. Leaders in the field discussed how a better understanding of the issues facing patients with PHPT has changed perceptions and led to changes in the recommendations for physicians caring for patients with asymptomatic PHPT. The summary statement emphasized the need for prospective studies to document postoperative improvement and encouraged studies regarding nontraditional aspects of PHPT. Recommendation guidelines were published. Indications for operation were limited to patients with serum calcium concentration 1.0 mg/dL above the upper limit of normal, urinary calcium concentration of 400 mg/24 hr, a reduced creatinine clearance of 30%, a T score below −2.5 at any bony site, or age under 50 years. We maintain that the definition of “asymptomatic” PHPT remains unclear even today. Neuropsychologic “symptoms” were not defined or included, despite the fact that health-related quality of life is widely recognized as a multidimensional concept encompassing physical, psychologic, social, and other domains of functioning. Improved health-related quality of life is clearly translatable and can be repeated. The summary statement failed to mention the use of objective neuropsychologic measurement scales or instruments to measure the impact of the disease on quality of life, the efficacy of cure, or the overall health status of an individual patient or this specific group of “asymptomatic” patients. The summary statement suggested monitoring serum calcium concentrations every 6 months and obtaining bone density studies every 3 years, a potentially costly and prolonged follow-up. Recently, Mahadevia et al. noted substantial variation in the clinical management of PHPT. They reported that endocrinologists’ practice patterns were not influenced by the published consensus guidelines. The diverse thresholds for surgical referral suggest a lack of agreement about the clinical management of this disease. A recent article by Eigelberger et al. questions whether these guidelines are too restrictive. These authors’ own study demonstrated equal improvement in patients who did meet and those who did not meet NIH criteria for operative intervention. The authors question whether the consensus criteria should be used when determining which patients should undergo operative treatment. Many surgeons agree that parathyroidectomy in patients with mild PHPT is justified because it results in subjective and objective benefits, as evidenced by improved quality of life, and can be performed with minimal morbidity and high cure rates.

Is “asymptomatic PHPT” truly a medical misnomer? We believe that it may be. Virtually all patients benefit symptomatically and metabolically. Moreover, the improved survival supports our contention that most, if not all, patients with PHPT should be offered surgical intervention by an experienced endocrine surgeon.

REFERENCES


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