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Neurocognitive dysfunction: A predictor of parathyroid hyperplasia

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Abstract

Background—To determine whether a symptomatic presentation was associated with parathyroid hyperplasia, we retrospectively examined pre-operative symptom profiles of patients who underwent parathyroidectomy.

Methods—From October 2007 to July 2008, 111 patients with primary hyperparathyroidism completed a preoperative symptom questionnaire prior to parathyroidectomy. The symptom profiles of patients with and without hyperplasia were compared.

Results—Neurocognitive symptoms occurred in 51.4% of patients. Patients with 1 neurocognitive symptom had a 25% risk of parathyroid hyperplasia. Additional neurocognitive symptoms increased the risk of hyperplasia linearly, with hyperplasia occurring in 38% of patients reporting 2 neurocognitive symptoms ($P < .001$) and 61% of patients reporting 3 or more of these symptoms ($P < .001$). A negative sestamibi scan was associated with a 33% risk of hyperplasia. Coupled with at least 1 neurocognitive symptom, the risk of hyperplasia was 53.3% ($P < .001$). Of patients with 3 or more neurocognitive symptoms and a negative localizing scan, 100% were found to have parathyroid hyperplasia ($P < .001$).

Conclusion—The presence of neurocognitive dysfunction in a patient with hyperparathyroidism may be used as a predictor of hyperplastic disease. Three or more of these symptoms, coupled with a negative sestamibi scan, was 100% predictive of parathyroid hyperplasia in our cohort.

Primary Hyperparathyroidism (PHPT) is a disorder of calcium metabolism caused by increased parathyroid hormone (PTH) released by 1 or more overactive parathyroid gland(s). PHPT is the most common cause of hypercalcemia in the outpatient population and is 4 times more common in women. Most cases of PHPT are caused by a single hyperfunctioning gland (80–89%). In contrast, multigland hyperplasia is less common (10–15%) and may be associated with multiple endocrine neoplasia syndromes.¹ For both disease processes, parathyroidectomy remains the only potentially curative treatment. However, the distinction between single-gland disease and multigland hyperplasia remains necessary for optimal surgical treatment. The current treatment standard for adenomatous disease is a minimally invasive parathyroidectomy (MIP). Conversely, the surgical approach

for multigland hyperplasia involves a bilateral exploration with the removal of 3 1/2 glands or total parathyroidectomy with placement of a parathyroid implant.

Currently, the success of MIP is highly contingent on the use of pre-operative adjuncts to localize the hyperfunctioning gland(s). The most commonly used adjuncts are imaging procedures such as ultrasound and Tc(99 m)-sestamibi scans. Pre-operatively, Tc(99 m)-sestamibi scintigraphy (sestamibi) is a reliable imaging modality used to localize abnormal parathyroid tissue with a reported sensitivity of 70–90%.^{2,3} Unfortunately, sestamibi scanning has a markedly decreased sensitivity of 50–60% in localizing multigland disease, which limits its use in reliably predicting parathyroid hyperplasia.^{4,5} Using a dual-phase technique of sestamibi imaging can increase the sensitivity and specificity in localizing multi-gland disease.⁶ Some studies suggest using a combination of sestamibi and ultrasound to localize hyperplastic glands.⁷ A recent study showed the sensitivity of ultrasound imaging alone to be 57% in localizing adenomas.³ Combining ultrasound and sestamibi studies was associated with an increased sensitivity of 87% but was only accurate in 54% of cases.^{3,7} Even with both of these imaging modalities, there remain a proportion of patients with nonlocalizing scans. Although nonlocalizing scans are more common in multigland disease, most of these patients still have single-gland disease.^{4,8}

Another area of recent investigative interest has been the symptomatology of PHPT. Classically, the symptoms of PHPT have been described by the mantra, “bones, stones, moans, and groans” to reflect the effects of persistent hypercalcemia. However, the modern patient is most often diagnosed by routine biochemical testing and rarely presents complaining of these somatic symptoms. These patients are then categorized as “asymptomatic PHPT.” Recently, attention has been turned to the more vague neurocognitive symptoms frequently described in these “asymptomatic” patients. These symptoms include difficulty concentrating, memory problems, depressed mood, and anxiety. Multiple studies have concluded that parathyroidectomy is an effective cure for both the classic symptoms as well as the neurocognitive effects of PHPT.^{1,9–12}

Given the ability of parathyroidectomy to cure PHPT reliably and alleviate a myriad of symptoms caused by the disease, it is imperative to provide optimal surgical intervention to patients with PHPT. However, the surgical approach to adenomatous versus hyperplastic disease differs, and the current pre-operative imaging techniques are poor in differentiating etiology. Therefore, the aim of this study is to determine whether a symptomatic presentation could be used to predict parathyroid hyperplasia to help plan the optimal surgical intervention for the patient.

MATERIALS AND METHODS

From October 2007 to July 2008, 111 consecutive patients with PHPT completed a pre-operative symptom questionnaire prior to parathyroidectomy. Of these patients, 18 (3 male and 15 female) were diagnosed with parathyroid hyperplasia, which was confirmed at the time of operation. For all patients, data including patient demographics, gland weight, imaging study results, and laboratory values, were collected prospectively in our Endocrine Surgery Database. The presence of preoperative symptoms was obtained from a patient

questionnaire that was completed by the patients at their initial preoperative consultation. Specifically, this questionnaire asked patients whether they had any of the following problems and/or symptoms: fatigue, weakness, bone/joint pain, difficulty concentrating, memory problems, depression, anxiety, nausea, vomiting, constipation, heartburn, abdominal pain, blood in urine, nighttime urination, frequent urination, or kidney stones.

Data analysis was conducted using statistical software (SPSS Graduate Pack 10.0; SPSS Inc., Chicago, IL). In analysis of these data, Pearson χ^2 , the Fisher exact test, and a 1-way analysis of variance was used when appropriate. With regard to the results, statistical significance was defined as $P \leq .05$. The collection of patient data and subsequent analysis was approved by the University of Wisconsin Human Subjects Institutional Review Board.

RESULTS

Patient characteristics (Table I)

Of the 111 consecutive patients undergoing parathyroidectomy, 18 (16.2%) were found to have parathyroid hyperplasia, none of which were diagnosed with a multiple endocrine neoplasia syndrome. When comparing patients with parathyroid hyperplasia versus adenomatous disease (single or double adenoma), no significant difference was found regarding sex, gland weight, presence of osteoporosis, vitamin D deficiency, preoperative creatinine levels, or kidney stones. Patients with hyperplasia were significantly younger than those with adenomas, with mean ages of 55 ± 3 years versus 62 ± 1 years, respectively ($P = .025$). The 2 groups also differed significantly in pre-operative serum calcium but not in PTH levels. Hyperplastic patients had a mean serum calcium of 10.6 ± 0.1 mg/dL compared with 11.1 ± 0.1 mg/dL in patients with parathyroid adenoma(s) ($P = .006$). Mean pre-operative PTH was 87.1 ± 10.5 pg/mL in patients with hyperplasia versus 117.9 ± 7.5 pg/mL in patients with adenomatous disease ($P = .085$).

Imaging studies

All patients in this study underwent pre-operative localization with either a sestamibi scan and/or neck ultrasound. Ultrasounds were performed in 33.3% of patients, and sestamibi scans were obtained in 96.4% of patients. Between the parathyroid hyperplasia and parathyroid adenoma groups, no difference was found in the rates of ultrasound imaging use or the accuracy of the ultrasound. The ultrasound was correct in localizing abnormal glands in 60% (3/5) of patients with hyperplasia compared with 72% (23/32) of patients with adenomatous disease ($P = .46$). Conversely, a statistically significant difference was found in the rate of obtaining a negative sestamibi scan when comparing the 2 groups. The sestamibi scan was negative in 61% (11/18) of patients with parathyroid hyperplasia versus 24.7% (22/89) of patients with parathyroid adenoma ($P = .006$). Therefore, a negative sestamibi scan alone conferred a 33% (11/33) risk of parathyroid hyperplasia in this cohort (Fig 1).

Neurocognitive symptoms

Neurocognitive symptoms, including difficulty concentrating, memory problems, depression, or anxiety, occurred in 51.4% (57/111) of patients. Patients self-reporting at least 1 of these neurocognitive symptoms had a 24.6% (14/57) risk of having parathyroid

hyperplasia ($P = .014$; 78% sensitivity, 54% specificity). The absence of neurocognitive dysfunction had a negative predictive value of 92.6%. Additional neurocognitive symptoms increased the risk of hyperplasia linearly, with hyperplasia occurring in 38.2% (13/34) of patients reporting 2 neurocognitive symptoms ($P < .001$; 74% sensitivity, 77% specificity) and 61% (11/18) of patients reporting 3 or more of these symptoms ($P < .001$; 61% sensitivity, 93% specificity). Patients who reported all four neurocognitive symptoms had a 70% (7/10) risk of hyperplasia (Fig 2, A).

The predictive value of these symptoms was additive to a negative sestamibi scan. A negative sestamibi scan alone was associated with a 33% (11/33) risk of hyperplasia. A negative sestamibi scan coupled with at least one neurocognitive symptom was associated with a 53.3% (8/15) risk of hyperplasia ($P < .001$; 44% sensitivity, 93% specificity). A negative scan with at least 2 symptoms correlated with a 77.7% (7/9) risk of hyperplasia ($P < .001$; 39% sensitivity, 98% specificity). Of the patients with 3 or more neurocognitive symptoms and a negative localizing scan, 100% (6/6) were found to have parathyroid hyperplasia ($P < .001$; 34% sensitivity, 100% specificity) (Fig 2, B).

DISCUSSION

Because the development of MIP for curative treatment of primary PHPT, the necessity of accurate distinction between single versus multiple-gland disease has become increasingly important. Considering the differing surgical approaches in treating these 2 disease entities, we investigated the possible methods of determining the correct etiology pre-operatively. At our institution, 111 consecutive patients with PHPT completed a pre-operative symptom questionnaire. Of these patients, 18 were found to have parathyroid hyperplasia at the time of parathyroidectomy. In this study, we demonstrated a significant association between the presence of neurocognitive symptoms and the risk of parathyroid hyperplasia. A linear relationship was found between the number of self-reported neurocognitive symptoms and the risk of hyperplastic disease. The presence of 4 neurocognitive symptoms was associated with a 70% risk of parathyroid hyperplasia. This association was further strengthened with the addition of a nonlocalizing sestamibi scan. Of patients reporting 3 or more neurocognitive symptoms with a negative sestamibi scan, 100% were found to have hyperplastic disease.

The reason that parathyroid hyperplasia patients have more neurocognitive symptoms remains unknown. The manifestations of hyperparathyroidism may be mediated by elevated calcium levels and/or elevated PTH levels and may be related to the duration of disease. Parathyroid hyperplasia tends to present with lower elevations in serum calcium compared with adenomatous patients, as observed in this study. Also, although the results were not statistically significant in this cohort, there was a trend toward lower elevations in serum PTH in patients with hyperplasia versus patients with adenoma. Because the laboratory abnormalities in hyperplasia patients are typically not as profound and their imaging evaluation is often negative, their disease many have gone unrecognized or untreated for a longer period of time. The chronicity of their disease may lead to more chronic changes or damage that may contribute to their different symptomatology.

In this study, a negative sestamibi alone was associated with a 33% risk of hyperplasia. Our results are similar to those observed by other investigators regarding the prevalence of hyperplastic disease in patients with negative sestamibi scans.^{4,13} However, it should be noted that the utility of sestamibi localization studies in patients with parathyroid hyperplasia remains controversial. Gordon et al⁶ found relatively high sensitivity and specificity (96% and 88%, respectively) of dual-phase sestamibi scanning in patients with hyperplastic disease. Other studies have shown a favorable sensitivity of sestamibi scanning with parathyroid hyperplasia, which further supports that this modality should be the first imaging method.^{3,7} Conversely, many investigators cite the wide range of sensitivity and specificity reported with sestamibi imaging as a cause for concern when considering MIP, which urges subsequent investigation to determine accurately the true etiology of PHPT in a given patient.^{7,14}

Because most patients with a negative sestamibi study will still have a single adenoma,⁸ there has been a recent effort to more accurately determine preoperatively, which patients truly have single-gland disease and therefore may undergo MIP. Kebebew et al⁵ developed a scoring model to aid in this distinction using total serum calcium, intact PTH, positive sestamibi or ultrasound imaging showing a single enlarged gland, and concordant sestamibi and ultrasound results. This scoring model relies on the ability of imaging studies to accurately localize a single abnormal gland. Although it is useful for identifying a group of patients who are highly likely to have single-gland disease, it cannot predict accurately those patients with multigland disease.

Our study demonstrated an accurate method of predicting parathyroid hyperplasia without relying on positive localization studies. Instead, we used the presence of neurocognitive symptoms and the absence of positive imaging to select patients who are at a high risk for multigland disease. Neurocognitive symptoms are well described in patients with PHPT, but we believe that this is one of the first studies to show that those symptoms are more prevalent in patients with multigland disease versus adenomatous disease. Whereas these symptoms are somewhat vague and can be difficult to quantify, all the data collection was done preoperatively and was collected in a prospective manner. Because we did not have any preconceived idea that these symptoms might be associated with hyperplasia, and all symptom reporting was done by patient self-report, this minimizes any bias and lends further credibility to the results.

Another limitation of our study was the relatively small size of our patient cohort with a total of 111 patients with PHPT. The size of the study limits the statistical power of the results, and therefore the results may not be universally applicable. In addition, the predictive model was discovered by retrospective analysis. Consequently, the study results require prospective validation in a larger cohort before acceptance in practice.

In conclusion, this study demonstrated a method of accurately distinguishing between adenomatous versus hyperplastic disease preoperatively based on the presence of neurocognitive symptoms and a negative sestamibi scan. These results are important for many reasons. To begin, it highlights the frequency of neurocognitive dysfunction in patients with PHPT. Most patients in this cohort self-reported at least one neurocognitive symptom.

Many studies demonstrate successful parathyroidectomy can alleviate these vague symptoms and improve quality of life.^{9–12,15}

Furthermore, this study helps to identify a subset of patients that are at a high risk for multigland disease and may be at a high risk for operative failure with a MIP, especially if performed without the aid of intra-operative parathyroid hormone testing (IOPTH). IOPTH can be a reliable adjunct when performing parathyroidectomy, especially with multigland disease^{2,16,17} or when discordant imaging studies are present.¹⁸ However, the use of IOPTH can be both time consuming and costly, and some surgeons have abandoned its use or use it only selectively. This study found a reliable pre-operative method for identifying patients who are at a high risk for multigland disease. Because the pre-operative risk of hyperplasia exceeds 50%, these patients would be best served with either a bilateral exploration or MIP with the use of IOPTH to ensure a biochemical cure.

From the data presented here, it is evident that a pre-operative diagnosis of parathyroid hyperplasia is strongly suggested by a negative sestamibi scan and the presence of neurocognitive symptoms. Although this predictive model requires prospective validation, it holds promise that it may allow us to tailor our treatments to provide patients with the optimal surgical management and minimize the risk of operative failure.

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Fig 1.
Sestamibi localization versus risk of hyperplasia.

Fig 2.
(A) Neurocognitive symptoms vs risk of hyperplasia. (B) Additive effect of nonlocalizing sestamibi scan.

Table I

Patient characteristics *

	Adenoma	Hyperplasia	<i>P</i> value **
N (%)	93 (84%)	18 (16%)	
Mean age (years)	62 ± 1	55 ± 3	.025
Sex			
Male	25 (27%)	3 (17%)	.361
Female	68 (73%)	15 (83%)	
Gland weight (mg)	898 ± 235	347 ± 91	.304
Symptoms			
Osteoporosis	22 (24%)	5 (28%)	.609
Vitamin D deficiency	31 (33%)	6 (33%)	.663
Kidney stones	17 (18%)	4 (22%)	.696
Pre-operative laboratory evaluation			
Serum calcium (mg/dL)	11.1 ± 0.1	10.6 ± 0.1	.006
PTH (pg/mL)	118 ± 8	87 ± 11	.085

* Values reported as mean ± standard error of the mean.

** Pearson Chi square.