Outcome Study of Psychological Distress and Nonspecific Symptoms in Patients With Mild Primary Hyperparathyroidism

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Background: Primary hyperparathyroidism is a common endocrinopathy. The appropriate management of its mild form, however, remains controversial.

Hypothesis: Mild primary hyperparathyroidism is associated with psychological distress and other nonspecific symptoms that improve following parathyroidectomy.

Design: Two-year prospective before-after study.

Setting: University hospital.

Patients: Twenty-six consecutive patients with mild hypercalcemia (<12 mg/dL [<3 mmol/L]) due to primary hyperparathyroidism, without osteitis fibrosa cystica or urolithiasis were enrolled from January 11, 1997, through April 21, 1998.

Intervention: Parathyroidectomy.

Main Outcome Measures: Primary outcome was psychological distress as measured by the 28-item version of the General Health Questionnaire. Secondary outcomes included body weight, joint pain, and occurrences of bowel movements and urination.

Results: Before surgery, 15 patients (58%; 95% confidence interval, 37%-77%) showed psychological distress (case group) while 11 patients did not (noncase group). A clinically and statistically significant reduction in the General Health Questionnaire score was detected at 3 months in the case group (−6.1; 95% confidence interval, −11.0 to −1.2), but the reduction was smaller (−1.9; 95% confidence interval, −6.9 to 3.0) at 24 months after surgery. No significant change in the General Health Questionnaire score was observed in the noncase group during the follow-up. No significant change was noted in any of the secondary outcomes.

Conclusions: Psychological distress was associated with mild primary hyperparathyroidism and was ameliorated after surgery. The improvement, however, was limited in extent and duration.

Arch Surg. 2002;137:779-783

With the increasing use of routine biochemical laboratory testing, primary hyperparathyroidism (PHPT) is frequently detected. This trend has resulted in an observed change in the clinical presentation of the disease, in that most patients show mild hypercalcemia without classical manifestations of osteitis fibrosa cystica or urolithiasis. This evolution is challenging the management of the disease, and the recommendation of surgery for such patients is open to debate. A regional survey showed that surgery was recommended as the initial management for 41% of patients diagnosed between 1965 and 1974 but for only 15% of those diagnosed between 1983 and 1992.

The US National Institutes of Health proposed criteria to recommend surgery for asymptomatic patients with PHPT; nevertheless, some physicians are more conservative than the recommendations suggest.

See Invited Critique at end of article

while others advocate parathyroidectomy for almost all patients. Among endocrine surgeons, a significant variation was noted in the threshold for recommending surgery. Some researchers claim that patients with mild hypercalcemia due to PHPT report symptoms, when questioned in detail, of depression, constipation, polyuria, weight loss, and joint pain; other investigators, however, do not
PATIENTS AND METHODS

DESIGN AND PROTOCOL

A prospective longitudinal study was conducted in patients with mild PHPT who were operated on and followed up for 2 years. The study was approved by the Ethical Committee of Tokyo Women’s Medical University. All participants in the study gave written informed consent.

PATIENTS

To be classified as having mild PHPT, patients had to fulfill all of the following conditions (inclusion criteria): albumin-corrected serum calcium level less than 12 mg/dL (<3 mmol/L), no evidence of osteitis fibrosa cystica on x-ray films of the hands, and no history or evidence of urolithiasis. Patients with 1 or more of the following conditions (exclusion criteria) were excluded: multiple endocrine neoplasia, recurrent or persistent hyperparathyroidism, concomitant thyroid diseases, or a cognitive limitation. From January 6, 1997, through April 30, 1998, 80 consecutive patients with PHPT underwent parathyroidectomy in the Department of Endocrine Surgery at Tokyo Women’s Medical University. Because 37 did not fulfill the inclusion criteria and 8 patients met at least 1 of the exclusion criteria, 35 patients were potentially eligible subjects. Among them, 26 agreed to take part in the study (participants), while 9 patients never have a chance to be asked to participate for logistical reasons (nonparticipants).

MEASUREMENTS

Psychological distress was measured using the General Health Questionnaire (GHQ).16,17 It is a self-administered screening instrument designed to detect current diagnosable psychiatric disturbances, and it focuses on disruptions in normal function rather than on lifelong traits.18 A 28-item version (GHQ-28), 1 of several shorter forms of the GHQ, was used for the present study and includes 4 subscales (somatic symptoms, anxiety, social dysfunction, and severe depression). The GHQ scoring method of assigning weights of 0, 0, 1, and 1 to 4 response columns for each of the 28 items generates a potential total score between 0 and 28.16 For the Japanese GHQ-28, a cutoff value of 6 is used for psychological case identification, designating patients with a score of 6 or higher as cases.17 Reliability and validity of the GHQ-28 have been established, with a test-retest correlation coefficient of 0.90 and sensitivity and specificity in case identification of 90% and 86%, respectively, for a cutoff value of 6.16,17 It was also demonstrated that the GHQ-28 reflects changes in the severity of psychiatric disturbances over time.18

For the secondary outcomes, participants recorded their body weight and the degree of joint pain as assessed by an 11-point numerical rating scale.19 In addition, they were asked to keep a diary in which they counted the occurrences of bowel movements and urination for 3 consecutive days at each scheduled measurement.

All outcome measures were evaluated before and at 3, 6, 12, and 24 months after parathyroidectomy. The initial assessment was performed during the hospital stay just before the planned surgery, and follow-up evaluations were conducted by postal communications.

STATISTICAL CONSIDERATIONS

Characteristics of the participants and the nonparticipants were compared using the χ² test for categorical variables and an unpaired t test for continuous variables. The mean preoperative GHQ score of the participants was compared with the reference value of the Japanese GHQ-28 (mean ± SD, 2.76 ± 2.31) using an unpaired t test.

Repeated-measures analysis of variance was used to examine the time trends in the outcomes. For the primary outcome, the GHQ total score and its 4 subscale scores were analyzed by multivariate repeated-measures analysis of variance. Multiple comparisons were made between the baseline and postoperative outcome measurements using Dunnett procedure. For occurrences of bowel movements and urination, mean values at each scheduled observation period were used for the statistical analyses.

Based on observations by Ormel et al,20 a minimally and clinically important change in the GHQ-28 score ranges between 3 and 6. When a type I error is set at 5% for a 2-tailed distribution, a sample size of 26 gives a power greater than 84% to detect that change using a paired t test, assuming that the SD of the change in the GHQ-28 score ranges between 3 and 5.20

The 95% confidence intervals (CIs) for proportions were constructed using binomial distribution. Commercially available statistical software (SPSS version 10.0J; SPSS Japan Inc, Tokyo, Japan) was used for all other analyses.21

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

Characteristics of the 26 participants, along with those of the 9 nonparticipants, are shown in Table 1. The mean ± SD level of serum calcium of the participants (10.7 ± 0.6 mg/dL [2.68 ± 0.15 mmol/L]) was significantly lower than that of the nonparticipants (11.4 ± 0.4 mg/dL [2.85 ± 0.09 mmol/L]) (P = .01). Although statistically insignificant, there were more women among the participants (23/26 [89%]) compared with the nonpar-
participants (5/9 [56%]) (P = .055). Nine participants (35%) required medications for comorbid conditions while 6 nonparticipants (67%) needed medications (P = .13).

All of the participants underwent standard unilateral neck exploration and parathyroid tumor removal without any complications. Pathological diagnoses of the tumors were all single adenomas. None of the participants developed hypocalcemia requiring calcium or vitamin D supplementation, except for 2 who took calcium lactate or calcitriol for several days for slight numbness. Serum calcium levels of all the participants were within the normal range throughout the follow-up.

PSYCHOLOGICAL DISTRESS BEFORE SURGERY

At the initial assessment, the mean GHQ-28 total score of the participants was 8.6 (95% CI, 5.5-11.7), which was significantly higher than the reference value (P < .001). Fifteen subjects (58%; 95% CI, 37%-77%) were considered to be psychological cases while others were noncases. Baseline characteristics of the case group and of the noncase group are presented in Table 2. There was no significant difference between the 2 groups in age, sex, laboratory data, or the prevalence of comorbid conditions.

CHANGES IN PSYCHOLOGICAL DISTRESS AFTER SURGERY

Three participants in the case group withdrew from follow-up evaluations of the outcomes. One took part in the preoperative assessment. The other 2 became unavailable after responding at the 3-month and 6-month evaluations, respectively (Table 3). They were excluded from the longitudinal analyses of the primary and secondary outcomes data.

Multivariate-repeated measures analysis of variance of the GHQ scores showed significant changes in the time trends in the case group (P = .01) but not in the noncase group (P = .63). Changes in the GHQ scores from the preoperative assessment are summarized in Table 4. A significant decrease in the GHQ total score was noted at 3 months after surgery in the case group (−6.1; 95% CI, −11.0 to −1.2), but the change was not sustained at 24 months (−1.9; 95% CI, −6.9 to 3.0). For the subscale scores in the case group, significant reductions were observed in somatic symptoms, anxiety, and severe depression at 3 months after surgery. The extent of these reductions, however, became smaller as time passed after surgery, except for the depression subscale, for which the reduction was maintained throughout the follow-up. At 24 months after surgery, the proportions of participants whose total scores were at the cutoff value or higher were 83% (95% CI, 52%-98%) in the case group and 27% (95% CI, 6%-61%) in the noncase group.

SECONDARY OUTCOMES

Preoperative mean ± SD values for body weight, joint pain on the 11-point numerical rating scale, and occurrences of bowel movements and urination were 56.2 ± 7.8 kg, 2.6 ± 2.5, 1.2 ± 0.7, and 6.5 ± 2.1, respectively. Follow-up evaluations revealed no significant changes in any of the secondary outcomes (Table 5).

COMMENT

Although surgery has traditionally been the definitive treatment for PHPT, a recent predominance of patients...
with mild disease has called into question the need for parathyroidectomy.5 Because an abnormal test finding of mild hypercalcemia may not in itself be an indication for parathyroidectomy, clinical outcomes of surgery were examined to try to resolve this dilemma.

Psychological symptoms are associated with PHPT, including depression, anxiety, fatigue, concentration difficulties, and sleep disturbances.22 Such observations led to the formation of a hypothesis that PHPT causes psychological distress. There are some biological explanations to support the relationship.23,24 The effect of parathyroidectomy, however, has never been fully established: some researchers23,25,26 report that surgery is associated with improvement of the symptoms, while other investigators22-24 report conflicting findings. In particular, data on patients with mild hypercalcemia are limited. A 1997 systematic review article15 revealed 3 studies that had used reliable and valid instruments to measure psychological distress in this patient population. Although PHPT with mild hypercalcemia is associated with distress, no longitudinal study with a sufficient follow-up had determined the outcome effects of surgery.15 In addition, no other study at the time of our investigation had reported on the outcomes of a study population without the classic symptoms. This prompted us to carry out a longitudinal study of this population in whom indications for surgery are controversial. In a study published in 1998, Pasieka and Parsons28 reported that patients with PHPT experienced improvements in their symptoms, including psychological ones, 1 year after surgery. This study, however, involved a population with general PHPT, not the mild form of the disease. Using the SF-36 health status questionnaire, Talpos et al29 measured quality of life in a randomized controlled trial of patients with mild PHPT who were allocated to groups with or without surgery. Although their study demonstrated that surgery provided some statistically significant improvements, it was not clear whether the observed changes in the SF-36 scores represented clinically important improvements.

The primary hypotheses for the present study were 2-fold: (1) mild PHPT is associated with psychological distress and (2) the distress is improved after parathyroidectomy. The results obtained were consistent with the hypotheses. However, because the improvement in the case group was not sustained during the follow-up, the association may not represent the causal relationship between the disease and the distress. The changes in the GHQ scores in the case group can be explained by alternative hypotheses. First, psychological symptoms may arise from stress as a general experience of having surgery.13 In a study conducted by Joborn et al, 10 patients with probable PHPT with mild hypercalcemia who had not undergone parathyroidectomy showed little distress. The explanation, however, is weakened by the find-

Table 3. General Health Questionnaire Scores of Cases Who Withdrew From Follow-up Evaluations*

<table>
<thead>
<tr>
<th>Age, y/Sex</th>
<th>Before Surgery</th>
<th>3 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>56/Female</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>56/Female</td>
<td>13</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>73/Female</td>
<td>15</td>
<td>4</td>
<td>15</td>
</tr>
</tbody>
</table>

*NA indicates not available.

Table 4. Mean Changes in the General Health Questionnaire Scores From the Preoperative Evaluation

<table>
<thead>
<tr>
<th>Score</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
<th>SEM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Group (n = 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>−6.1†</td>
<td>−3.0</td>
<td>−4.1</td>
<td>−1.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Somatic symptoms</td>
<td>−1.9†</td>
<td>−0.5</td>
<td>−1.0</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>−1.7†</td>
<td>−1.1</td>
<td>−0.8</td>
<td>−0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Social dysfunction</td>
<td>−0.8</td>
<td>0.0</td>
<td>−0.4</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Severe depression</td>
<td>−1.8†</td>
<td>−1.4</td>
<td>−1.8†</td>
<td>−1.7†</td>
<td>0.6</td>
</tr>
<tr>
<td>Noncase Group (n = 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.6</td>
<td>0.9</td>
<td>1.5</td>
<td>2.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Somatic symptoms</td>
<td>0.0</td>
<td>0.3</td>
<td>0.7</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.6</td>
<td>0.4</td>
<td>0.6</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Social dysfunction</td>
<td>0.0</td>
<td>0.3</td>
<td>0.0</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Severe depression</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
<td>0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Dunnett procedure.  
†Significant at P<.05 (Dunnett procedure).

Table 5. Mean Changes From the Preoperative Evaluation (n = 23)

<table>
<thead>
<tr>
<th>Variable</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
<th>SEM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Joint pain</td>
<td>0.5</td>
<td>−0.1</td>
<td>0.5</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Occurrences of bowel movements</td>
<td>−0.2</td>
<td>−0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Occurrences of urination</td>
<td>0.8</td>
<td>0.5</td>
<td>0.7</td>
<td>0.9</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Dunnett procedure.  
†Measured using 11-point numerical rating scale.
ing that preoperative patients with other diseases did not exhibit distress.28,30 Second, regression to the mean may play a role in the repeated measurements.31 However, the observed changes in the case group at 3 months after surgery were clinically important beyond statistical regression.20 Third, as Lundgren et al32 showed, symptoms such as joint pain, increased fatigue, loss of energy, and mental depression were commonly seen among healthy subjects; therefore, these symptoms in patients with mild PHPT may be coincidental, and the observed improvement may be a consequence of patients' expectations of the treatment. As shown in clinical studies33,34 of surgical treatment for angina pectoris, if improvements in subjective symptoms are due to such a placebo effect of surgery, the symptoms would be expected to recur several months after the operation. The 2-year follow-up in the present study was sufficient to compensate for this potential bias.

Generalizability of the present study is limited for 2 reasons. First, results from preoperative patients may not be applicable to patients who are managed conservatively. Second, the prevalence of psychological cases in the present study may be overestimated because there were more women among the participants compared with the nonparticipants. Scores on the GHQ tend to be higher in women than in men.10

Benefits of parathyroidectomy cannot be determined by conducting randomized controlled trials in which subjects are blinded to interventions, because such allocation would be unethical. Therefore, observational studies on various outcomes are necessary to establish appropriate management strategies for patients with mild PHPT.

We thank Akie Hattori for her managerial work.

This study was not supported by any external funding.

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It is generally accepted among endocrine surgeons that many, if not most, patients with primary hyperparathyroidism have a wide spectrum of physical and mental impairments, and that the severity of these impairments improves after correction of the condition by parathyroidectomy. To try to shed light on this phenomenon, Okamoto and colleagues from Japan report on the results of psychological testing, using the General Health Questionnaire, of 26 patients with primary hyperparathyroidism before and after curative operation.

The General Health Questionnaire\(^1\) has been used since 1972 as a screening instrument for the detection of diagnosable psychiatric disorders in the primary care setting. The full questionnaire has 60 questions; the authors of this study used the shorter 28-question version, which has been validated internationally and used as a screening method for identifying psychiatric illness–associated somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression, with sensitivities in the 80% to 90% range for detecting psychiatric illness. About half the patients in the study by Okamoto et al met the screening criteria for 1 or more of these dysfunctions, indicating they had possible underlying psychiatric illness. These patients showed transient improvement in scores at 3 months, with return toward baseline scores at 6 months and 2 years. If they had psychiatric illness, it was not corrected by reversing their primary hyperparathyroidism. The conclusion of Okamoto and colleagues that there is no “causal relationship between the disease and the distress,” however, may not be correct, because it fails to make a distinction between psychological distress and diagnosable psychiatric illness.

Other investigations, using the 36-item Short-Form health survey in a much larger cohort of patients, showed sustained improvement in emotional role limitation scores at 6 months.\(^2\) The chief difference between the 2 studies is in the tools that were used and in what those tools were designed to measure. One screens for psychiatric illness; the other assesses mental function more broadly. My interpretation of the 2 studies, taken together, is that the mental or emotional dysfunction associated with primary hyperparathyroidism is not evidence of psychiatric illness, but rather is evidence of a different kind of global dysfunction. This distinction may well be an important one. If true, it would force one to rethink many of the conclusions in the present study.

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