

## **Psychiatric Symptomatology in Patients With Primary Hyperparathyroidism**

Charlotte Joborn, Jerker Hetta, Mats Palmér, Göran Åkerström  
and Sverker Ljunghall

*Departments of Internal Medicine, Psychiatry and Surgery,  
University Hospital, Uppsala, Sweden*

### **ABSTRACT**

A retrospective investigation was made of the occurrence of psychiatric symptoms among 441 patients operated on for primary hyperparathyroidism in Uppsala in 1956-79, and of the relationship between such symptoms and age, sex and degree of hypercalcaemia. A follow-up, using a mailed questionnaire, was carried out 4-27 years postoperatively.

Psychiatric symptoms were found in 23% of the patients (102/441). The patients with these symptoms had the same sex distribution and serum calcium levels as the other patients, but were significantly older. Severe symptoms occurred more frequently in older patients. Such symptoms were noted not only in patients with very high serum calcium values but also in association with mild or moderate hypercalcaemia.

The most common symptoms were depressive and anxiety states, which occurred in 78 patients. Psychosis with hallucinations and paranoid ideas was found in four patients. Eight patients had an organic brain syndrome and a further 12 patients had minor cerebral impairment.

At the follow-up half of the patients reported an improvement after the first postoperative year. Most of them considered that this improvement was sustained at the time of follow-up.

This study indicates that psychiatric symptoms are common among patients with hyperparathyroidism and can occur even with moderate hypercalcaemia. Elderly patients seem to be more vulnerable and more often develop severe symptoms such as psychosis or organic brain syndrome.

## INTRODUCTION

The importance of the calcium ion in regulatory functions of the central nervous system has become increasingly evident. Synthesis and release of central neurotransmitters and postsynaptic receptor sensitivity, are calcium-dependent (7). Some patients with hyperparathyroidism (HPT) have displayed EEG abnormalities and in association with secondary HPT the brain content of calcium has been found to be increased (5).

It is thus conceivable that patients with derangements of the systemic calcium metabolism may have various psychiatric symptoms, and severe disturbances of mood and behaviour have occurred in patients with primary HPT (2, 17, 18). Psychiatric symptoms have been reported in 1-50% of patients with HPT (6, 9, 10, 13-15, 17, 20), but only in a few larger studies have the mental disturbances been investigated more extensively (13, 17). Nowadays there is an increased awareness of primary HPT and this disorder is diagnosed with increased frequency (9), especially in elderly patients with only mild-to-moderate elevations of serum calcium.

In the present study we have examined retrospectively the occurrence of psychiatric symptoms in a series of patients operated upon for primary HPT over a 25-year period. We have also investigated the relationship between such symptoms and age, sex and degree of hypercalcaemia. In order to estimate the effects of parathyroid surgery on the psychiatric symptoms, a follow-up was performed.

## PATIENTS AND METHODS

During the years 1956-1979, 441 patients were operated upon for primary HPT at the Department of Surgery of the University Hospital, Uppsala. Data concerning these patients were collected from the hospital records of the Departments of Surgery and Internal Medicine and, when appropriate, from the referral hospitals. Of the 441 patients, 330 (75%) were females (mean age  $60 \pm 12$  (SD) years) and 111 (25%) were males (mean age  $52 \pm 15$  years). Their mean preoperative serum calcium concentrations ranged between 2.40 and 4.95 mmol/l with a mean of  $2.87 \pm 0.30$  mmol/l. Further details regarding this material, the laboratory and surgical findings and the long-term outcome concerning the serum calcium levels have recently been presented (16, 19).

The present study deals with those patients in whom preoperative psychiatric symptoms were reported in the records. Only patients in whom such symptoms were clearly evident were included in the study. If adequate information concerning the patients' psychiatric state was not available, the patients were regarded as not having had such complaints. The recorded data were not always sufficient for a detailed psychiatric diagnosis and the patients were therefore grouped in accordance with their symptoms rather than with strict psychiatric diagnoses.

In 1983, i.e. 4-27 years postoperatively (mean  $10 \pm 4$  years), a follow-up of all patients still alive was performed. A questionnaire was mailed to all patients who, according to the records, had experienced psychiatric symptoms preoperatively. This questionnaire contained eight items (six concerning psychiatric and two somatic symptoms) on a five-grade scale. The patients were asked to report the degree of symptoms they had experienced before the operation and one year postoperatively, and the degree at present. The effects of surgery on the mental state were then evaluated from these questionnaires. An improvement was considered to have taken place only if there was an unequivocal positive effect. If the patient's opinion was uncertain, the condition was regarded as unchanged.

Conventional statistical methods were applied, namely Student's t-test for comparison of mean values and the chi-square test for comparison of proportions. All mean values are given together with the standard deviation (SD).

## RESULTS

According to the medical records 102 of the 441 patients (23%) with primary HPT had psychiatric symptoms preoperatively. In this group there were 82 women (80%) and 20 men, and thus the sex distribution was similar to that of the whole material. Psychiatric symptoms were more common among older patients and there was a higher mean age of patients with such symptoms ( $61 \pm 11$  years) than of those without ( $57 \pm 13$  years,  $p < 0.05$ ). During the first half of the study period there was a marked increase in the number of operations for primary HPT. Before 1965 only occasional patients with psychiatric symptoms were operated on, but thereafter both the number and proportion of these patients increased to levels which have since remained constant. Over the 25-year study period the mean age of the patients with psychiatric symptoms showed only minor variations (Table I).

TABLE I. Sex distribution, mean age and serum calcium ( $\pm$  SD) in HPT patients with and without psychiatric symptoms, operated on between 1956-1979. The mean serum calcium values do not include values of the eight patients with hypercalcaemic crisis. The percentage values with parentheses denote the proportion of patients with psychiatric symptoms in the whole series of patients in the corresponding period.

Primary HPT - 441 patients operated on 1956-1979						
Patients with psychiatric symptoms (n=102)					All other patients (n=339)	
Year of operation	1959	1960-1964	1965-1969	1970-1974	1975-1979	1956-1979
Total no.	1 (14%)	2 (8%)	20 (24%)	40 (24%)	39 (24%)	102 (23%)
Male/Female	0/1	0/2	5/15	8/32	7/32	20/82
Mean age (years)	66	69.5	58 $\pm$ 13	60 $\pm$ 12	63 $\pm$ 10	61 $\pm$ 11
S-calcium (mmol/l)	3.06	3.18	2.86 $\pm$ 0.33	2.84 $\pm$ 0.24	2.90 $\pm$ 0.15	2.88 $\pm$ 0.24
						2.85 $\pm$ 0.30

Eight of the 102 patients presented with a picture of hypercalcaemic crisis, i.e. a greatly elevated serum calcium level (3.18-4.96 mmol/l) and a cerebral affection. They were included in the present study because they had had psychiatric symptoms which had clearly preceded the acute crisis. Other patients with an acute hypercalcaemic crisis (including cerebral affection) but without previous psychiatric symptoms were not included. The serum calcium values of the other 94 patients with psychiatric symptoms were not significantly higher than those of patients without such symptoms and showed no apparent changes during the study period (Table I). Psychiatric symptoms occurred in association with all levels of hypercalcaemia, but a higher proportion (50%) of the occasional patients with S-Ca > 3.60 mmol/l had such symptoms.

The most common psychiatric symptoms were depressive and/or anxiety states, which occurred in 78 patients, i.e. 18% of the total material (Table II). Frequent complaints among these patients were unspecific feelings of tiredness or loss of initiative, depression, nervousness, anxiety, sleep disturbances and irritability; somatic symptoms such as tachycardia, headache, muscle weakness, oppression and dizziness were also frequent. At the time of operation half of these 78 patients were or had been receiving medication for their symptoms and 20 of them had been admitted for in-patient psychiatric care for severe depression or neurosis.

Table II. Distribution of the 102 patients with primary hyperparathyroidism and psychiatric symptoms, by type of disorder, with mean ages ( $\pm$  SD) and serum calcium levels (range and median).

Symptom	No.	Age (years)	S-Ca (mmol/l)		
			Range	(Median)	
Depressive	49	78	59 ± 11	2.45 - 4.96	(2.85)
Nervous/Anxiety	55				
Psychosis		4	69 ± 9	2.60 - 3.40	(2.83)
Organic brain syndrome		8	68 ± 8	2.60 - 4.53	(2.90)
Minor cerebral impairment		12	70 ± 6	2.79 - 4.53	(3.01)

Psychosis with delusions and hallucinations were reported in four patients. In one of them these symptoms developed together with marked hypercalcaemia (S-Ca 3.40 mmol/l) and a picture of hypercalcaemic crisis, whereas in the other three patients paranoid ideas and hallucinations occurred in association with moderately elevated serum calcium values (2.60-2.92 mmol/l). Paranoid ideas were also experienced to some degree by another seven patients, five of whom had an organic brain syndrome and two depression.

An organic brain syndrome (3) was present in a further eight patients, who were admitted from mental hospitals with a diagnosis of senile dementia. These patients have been presented in more detail elsewhere (11). Twelve other patients had similar but minor cerebral impairment, with loss of memory, slight disorientation and impaired social functioning.

The severity of the symptoms was not apparently correlated to the degree of hypercalcaemia. The serum calcium values in the 32 patients with psychiatric symptoms who had needed hospital care (severe depression or neurosis, psychosis and organic brain syndrome) showed a wide range from 2.45 to 4.96 mmol/l (median 2.85 mmol/l). It was thus evident that even patients with mild or moderate hypercalcaemia could have severe mental disorders.

Symptomatic renal stones occurred in 21% (22 patients) of the patients with psychiatric symptoms, but in 32% of those without such symptoms ( $p < 0.05$ ) (Table III). The frequency of gastric symptoms, thirst/polyuria and skeletal

Table III. Somatic symptoms among the 102 patients with primary hyperparathyroidism (HPT) and psychiatric symptoms, in comparison with HPT patients without psychiatric symptoms.

Somatic symptoms	Pat. with psychiatric symptoms (n = 102)	Pat. without psychiatric symptoms (n = 339)
Renal stones	21%	32%
Peptic ulcer/ gastric symptoms	28%	16%
Thirst/polyuria	28%	10%
Tiredness/weakness	46%	44%
Musculo-skeletal pain	28%	8%

or muscular pain, on the other hand, was higher in the former group. The operative and histopathological findings did not differ remarkably between these two groups, the frequency of adenoma being 87% in the patients with psychiatric symptoms and 80% in the other patients.

The postoperative results concerning the uncharacteristic psychiatric symptoms were difficult to evaluate from the medical records. However, in eight of the eleven patients in whom psychotic symptoms occurred preoperatively, there were no reports on such symptoms after surgery. In the other three patients the postoperative result was unclear.

In 1983 sixty-nine of the 102 patients were still alive and were sent the postal questionnaire. Their mean age at this time was  $67 \pm 8$  years. Sixty-one questionnaires were answered by the patients themselves and another seven were returned unanswered by the patients' care-takers. Of the 61 respondents 33 (54%) reported an improvement one year postoperatively, and most of them considered that this was sustained at the time of follow-up. The results for the separate symptoms are presented in Table IV. The greatest improvements were reported for tiredness, depression and states of anxiety. The improvement was not correlated to the age at operation or to the preoperative serum calcium values, neither was it restricted to any special degree of psychiatric symptomatology, i.e. both patients with mild and severe symptoms reported improvement.

Table IV. Follow-up of psychiatric symptoms in 61 patients 4 - 27 years after operation for primary hyperparathyroidism.

Symptom	Preoperative symptoms	Improved 1 year postop.	Still better at follow-up
Tiredness	48	25 (52%)	19 (40%)
Depression	47	22 (47%)	18 (38%)
Anxiety	45	23 (51%)	17 (38%)
Sleep disturbances	40	13 (32%)	11 (28%)
Pain	35	13 (37%)	11 (31%)
Impaired memory	29	11 (38%)	6 (21%)
Thirst	28	16 (57%)	12 (43%)
Renal stone	18	15 (83%)	15 (83%)

## DISCUSSION

In this study almost one-fourth of all patients operated on for primary HPT had psychiatric symptoms preoperatively. Since this figure is based on a retrospective evaluation of medical records, it is likely to represent a minimum number, as in some instances the notations were insufficient for evaluation. The varying reports on the occurrence of psychiatric symptoms among HPT patients in the literature (6, 9, 10, 13-15, 17, 20) might be due to differences in patient selection, methodological factors and criteria of psychiatric illness. Reports from recent years are in agreement, however, that psychiatric symptoms are common in patients with HPT.

During the study period the mean age and serum calcium level of patients with psychiatric symptoms undergoing parathyroid surgery remained unchanged, suggesting that the indications for parathyroidectomy in such patients have not altered. The increased number of operations is therefore presumably due to an increased awareness of HPT.

Among patients with psychiatric disorders, depressive and nervous symptoms were the most frequently reported. Similar observations have been made in previous studies of HPT patients (4, 9, 10, 14) many of whom have shown total recovery during short-term follow-up after parathyroid surgery. Disturbances of the regulation of intracellular calcium in the central nervous system have recently been implicated in the pathogenesis of affective disorders (7), and could theoretically explain the psychiatric symptoms in HPT patients. It is also likely that premorbid personality patterns are of importance for the various mental disorders developing during hyperparathyroidism. The fact that HPT, being rather a common disorder, is diagnosed by serendipity in some patients should also be considered.

Psychotic symptoms in patients with HPT are less usual than depression, but can occur in rare cases, often as part of an organic confusional state (2, 17). Most patients with such symptoms in our material were elderly and it seems that older patients are at greater risk of developing this severe condition even in association with mild to moderate hypercalcaemia.

The psychiatric symptoms were found to have occurred mainly in the older age groups. However, there was no distinct correlation between the degree of hypercalcaemia and the various symptoms. This indicates that the ageing brain becomes more susceptible to disturbances of the ionic environment.



There may also be a dissociation between central nervous and systemic calcium regulation.

In the hitherto most extensive description of psychiatric disorders in HPT patients it was reported (17) that more or less incapacitating symptoms occurred in 38 out of 46 patients. In that series, however, the mean serum calcium level was around 3.15 mmol/l and several patients had values above 3.50 mmol/l. In some of these cases the distinction from the impairment of cerebral functions associated with pronounced hypercalcaemia, i.e. a hypercalcaemic crisis, was obscure. Psychiatric affections were also common among our patients with severe hypercalcaemia. However, only 12 of the 441 patients fulfilled the criteria of hypercalcaemic crisis. In the present series psychosis and/or confusion were only rarely related to severe hypercalcaemia, but psychiatric symptoms were more frequent in the few patients with a serum calcium concentration above 3.50 mmol/l.

It should be emphasized, however, that incapacitating psychiatric symptoms sometimes occurred in patients with marginal hypercalcaemia.

In the present study the outcome of surgery could only be evaluated by a postal questionnaire, which by necessity permitted only rough assessments of the psychiatric symptoms, as experienced by the patients themselves. Since more than four years had elapsed since the operation, the possibility of placebo effects could most likely be ruled out. With these considerations in mind and in view of the fact that most patients were ten years older at the follow-up than at the time of surgery, it is remarkable that many patients reported a definite and lasting improvement. As previously reported (11), some patients with severe impairment of mental functions, classified as organic brain syndrome, can experience a considerable improvement postoperatively. Among the patients of the present study there was a wide spectrum of preoperative symptoms, ranging from organic psychosis to mild forms of anxiety. The reported postoperative improvement did not appear to be restricted to any particular type of symptom, nor was there any particular group in which parathyroid surgery was clearly ineffective.

In conclusion, this study indicates that psychiatric symptoms are common among patients with HPT and can occur even in those with moderate hypercalcaemia. Many patients report considerable and lasting improvement postoperatively. These observations, however, call for a more detailed pros-

pective study before it can be recommended that screening and operation for HPT should be carried out on wider indications than are generally accepted today.

#### ACKNOWLEDGMENTS

This study was supported by grants from the Ingrid and Einar Thuring Foundation, Stockholm, Sweden and the Swedish Medical Research Council.

#### REFERENCES

1. Agras S & Oliveau DC. Primary hyperparathyroidism and psychosis. *Canad Med Ass J* 1964;91:1366-67.
2. Alarcon RD & Franceschini JA. Hyperparathyroidism and paranoid psychosis: Case report and review of the literature. *Br J Psych* 1984; 145:477-86.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Third edition, Washington, D.C., APA, 1980.
4. Anderson J. Psychiatric aspects of primary hyperparathyroidism. *Proc Roy Soc Med* 1968;61:1123-24.
5. Cogan MG, Covey CM, Ariefi AI, Wisniewski A & Clark OH. Central nervous system manifestation of hyperparathyroidism. *Am J Med* 1978; 65:963-70.
6. Cope O. Hyperparathyroidism: Diagnosis and management. *Am J Surgery* 1960;99:394-403.
7. Dubovsky SL & Franks RD. Intracellular calcium ions in affective disorders: A review and a hypothesis. *Biological Psychiatry*, 1984;18: 781-95.
8. Fitz TE & Hallman BL. Mental changes associated with hyperparathyroidism. *Arch Int Med* 1952;89:547-51.
9. Heath III H, Hodgson SF & Kennedy MA. Primary hyperparathyroidism: Incidence, morbidity and potential economic impact in a community. *N Eng J Med* 1980;302:189-93.
10. Hecht A, Gershberg H & St. Paul H. Primary hyperparathyroidism. Laboratory and clinical data in 73 cases. *J Am Med Ass* 1975;233: 519-26.
11. Joborn C, Hetta J, Frisk P, Palmér M, Åkerström G & Ljunghall S. Primary hyperparathyroidism in patients with organic brain syndrome. *Acta Med Scand* (in press).

12. Kleinfeldt M, Peter S & Gilbert GM. Delirium as the predominant manifestation of hyperparathyroidism. *J Am Geriatr Soc* 1984;32:689-90.
13. Karpati G & Frame B. Neuropsychiatric disorders in primary hyperparathyroidism. *Arch Neurol* 1964;10:387-97.
14. Mallett LE, Bilezikian JP, Heath DA & Aurbach GD. Primary hyperparathyroidism: Clinical and biochemical features. *Medicine* 1974; 53:127-146.
15. Mundy GR, Cove DH & Fisker R. Primary hyperparathyroidism: Changes in the pattern of clinical presentation. *Lancet* 1980;1:1317-20.
16. Palmér M, Ljunghall S, Åkerström G, Adami HO, Bergström R, Grimelius L, Rudberg C & Johansson H. Temporal trends in patients with primary hyperparathyroidism operated on over a 24-year period. Clinical and laboratory findings. *J Chron Dis* (accepted for publication).
17. Petersen P. Psychiatric disorders in primary hyperparathyroidism. *J Clin Endocrinol Metab* 1968;28:1491-95.
18. Reinfrank R. Primary hyperparathyroidism with depression. *Arch Int Med* 1961;108:606-610.
19. Rudberg C, Palmér M, Åkerström G, Ljunghall S, Adami HO, Johansson H, Grimelius L, Thoren L & Bergström R. Late results of operation for primary hyperparathyroidism. *Surgery* 1985 (in press).
20. Watson L. Clinical aspects of Hyperparathyroidism. *Proc Roy Soc Med* 1968;61:1123.

Correspondence to: Sverker Ljunghall, MD  
Dept of Internal Medicine  
University Hospital  
S-75185 Uppsala  
Sweden