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Neurobehavioral Symptoms in Mild Primary Hyperparathyroidism: Related to Hypercalcemia but not Improved by Parathyroidectomy

Gregory G. Brown, PhD,* Richard C. Preisman, MD,* and Michael Kleerekoper, MD†

The neurobehavioral symptomatology of severe primary hyperparathyroidism (PHPT) has been thoroughly described. Less is known about more mild cases. We evaluated 34 patients with mild PHPT and followed 19 for an average of six months. Of those cases followed, ten had parathyroidectomy (PTX). Patients with no neurobehavioral abnormalities had the lowest serum calcium levels (10.9 ± 0.88 mg/dL), patients with signs of affective disorder had intermediate levels (11.25 ± 0.66 mg/dL), and patients with signs of cerebral dysfunction had the highest levels (12.17 ± 1.17 mg/dL). Serum calcium significantly correlated with motor speed, psychomotor speed, fluid intelligence, and short-term memory. However, in the follow-up of patients, PTX seemed to have no effect on their behavior. Serum calcium correlates with both type and severity of the neurobehavioral abnormalities found in mild PHPT. However, most of the evidence indicates that PTX does not produce any improvement of these abnormalities, even when the hypercalcemia elevation is corrected. (Henry Ford Hosp Med J 1987;35:211-5)

A variety of neurobehavioral symptoms have been associated with primary hyperparathyroidism (PHPT) since Nielsen drew attention to this phenomenon in the mid 1930s and early 1940s (1,2). Lethargy, drowsiness, depressive mood, neurasthenia, paranoid delusions, hallucinations, disorientation, confusion, and memory deficits all have been reported in a series of case studies (3-8). However, group studies have not always found a greater occurrence of psychiatric symptoms in PHPT than would be expected among medically ill patients in general (9-20). As shown in the Table, prevalence rates from case-series studies range from 1% to 65%. The validity of many of these rates is difficult to evaluate, since most investigators obtained data through retrospective chart review, did not state how patients were sampled, or failed to describe the method used to investigate the presence of psychiatric symptoms. Only two studies (12,20) reported their methods in sufficient detail to enable us to determine that a consecutive series was examined, and only three studies (17,18,20) described their method of psychiatric evaluation.

With the advent of routine biochemical screening, a dramatic increase has occurred in the detection of cases of hypercalcemia with few or no other symptoms of PHPT (21). Many patients presenting with mild hypercalcemia have neurobehavioral complaints as their only symptoms. Whether surgical correction of PHPT is indicated in these patients is a question that the aforementioned literature does not convincingly answer. Several authors have claimed that mental changes may occur at mild calcium elevations and clear with parathyroidectomy (PTX) (22-24). These authors at least implicitly endorse surgery for correction of these mental changes, even at mild levels of hypercalcemia.

Questions even more fundamental than response to PTX are still in need of research: How often do neurobehavioral abnormalities occur in PHPT? What variations occur in these symptoms? What is the relationship between these neurobehavioral abnormalities and serum calcium?

In this paper we present our findings on a group of patients with PHPT in whom neurobehavioral assessment was performed shortly after the diagnosis had been made and again after successful PTX or after medical follow-up, if surgery was not performed.

Methods

Subjects

Thirty-four patients with no previous history of parathyroid disease were evaluated over a 30-month period. These cases, referred for neurobehavioral assessment from the Bone & Mineral Division, represented slightly more than half of the PHPT cases seen in the clinic during this period. Not all of the physicians in the Bone & Mineral Division were enrolling patients when the study began. Any bias introduced into the sample studied was due to differences in the practices of the physicians who referred patients and those who did not. All patients who were referred to the study, 23 women and 11 men, were evaluated. Their mean age was 52.5 ± 12.3 years (mean ± standard deviation), and on the average they had high school educations (12.0 ± 2.7 years). Patients were excluded from the study if they had a history of substance abuse, secondary hyperparathyroidism, or coincidental neurological diagnosis. As a group, these patients had mild

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tests primarily measure the effects of fluid intelligence, which involves intellectual abilities necessary for the rapid solving of novel problems. The Trail Making Test is a general indicator of speed. The version of the STM Distractor Test that we used required subjects to remember a word during a 10- or 20-second period of subtracting backwards by threes from a three-digit number. Adequate performance on this test presupposes normal visual scanning, concentration, and psychomotor speed. The version of the STM Distractor Test that we used required subjects to remember a word during a 10- or 20-second period of subtracting backwards by threes from a three-digit number. Patients were also tested after a no-delay interval, but only the average of the 10- and 20-second conditions was used in the data analysis. The STM Distractor Test has been shown to be sensitive to memory deficits in patients with classical amnesias (eg, bilateral hippocampectomy, or alcoholic Korsakoff amnesia) (30). The psychiatric interview included an assessment of orientation, immediate memory, verbal reasoning, and constructional ability, in addition to an evaluation of thinking style, delusions, affect, mood, and hallucinations. The patient's history and medical record were used to estimate the duration of neuropsychological symptoms.

**Procedures**

To evaluate personality functioning and mental status, each patient received a battery of neuropsychological tests and/or a psychiatric interview; seven had psychological testing alone, while three had the interview alone. Differences in how the patients were evaluated were due to the temporary unavailability of the neuropsychologist or psychiatrist for inpatients who had brief hospitalizations. The brief neuropsychological battery assessed amnestic, intellectual, motor, psychomotor, and personality functioning. The battery was composed of the Similarities, Block Design, and Digit Symbol subtests from the Wechsler Adult Intelligence Scale (25), the Trail Making Test (26), the Short-Term Memory (STM) Distractor Test (27), Halstead's Finger Oscillation Test (28), and the Minnesota Multiphasic Personality Inventory (MMPI) (29). The mean of the three IQ subtests was used in the data analysis. These IQ subtests primarily measure the effects of fluid intelligence, which involves intellectual abilities necessary for the rapid solving of novel problems. The Trail Making Test is a general indicator of cerebral dysfunction, taken from the Halstead-Reitan Neuropsychology Battery. Adequate performance on this test presupposes normal visual scanning, concentration, and psychomotor speed. The version of the STM Distractor Test that we used required subjects to remember a word during a 10- or 20-second period of subtracting backwards by threes from a three-digit number. Patients were also tested after a no-delay interval, but only the average of the 10- and 20-second conditions was used in the data analysis. The STM Distractor Test has been shown to be sensitive to memory deficits in patients with classical amnesias (eg, bilateral hippocampectomy, or alcoholic Korsakoff amnesia) (30). The psychiatric interview included an assessment of orientation, immediate memory, verbal reasoning, and constructional ability, in addition to an evaluation of thinking style, delusions, affect, mood, and hallucinations. The patient's history and medical record were used to estimate the duration of neuropsychological symptoms.

**Results**

**Group studies**

*Initial findings*—To extend the analysis to patients who had either a psychiatric interview or a neuropsychological evaluation, but not both, we examined the degree of concordance between the two methods for classifying patients into three groups—1) no behavioral disorders, 2) affective disorders, and 3) neuropsychological signs of brain dysfunction. Independent judgments of each patient's classification revealed an 82% agreement (κ = 0.73) between the psychiatric interview and neuropsychological evaluation methods and the serum calcium level difference, which indicated that serum calcium levels were averaged over the entire hospitalization period. Only 29% of patients who had psychiatric evaluations showed a serum calcium level difference, which indicated that serum calcium levels were averaged over the entire hospitalization period. These patients had a variety of personality disorders, of which hypertension was the most common. In general, patients with a serum calcium level greater than 11.5 mg/dL were referred for elective surgery, but this procedure was not always followed, and not all patients referred for surgery agreed to proceed.

PHPT with a mean calcium of 11.5 ± 1.05 mg/dL. Of the entire sample, 21% had no physical symptoms directly referable to hyperthyroidism or hypercalcemia; only 10% had renal stones, and another 7% had peptic ulcers. The remaining patients had incidental medical diseases, of which hypertension was the most common. In general, patients with a serum calcium level greater than 11.5 mg/dL were referred for elective surgery, but this procedure was not always followed, and not all patients referred for surgery agreed to proceed.

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evaluation. We reconciled the few differences between the two methods and then classified the remaining cases.

Only 29% of our sample were clearly normal in their neuro-behavioral function; 32% had signs of affective disorder, while 39% had signs of cerebral dysfunction. Included in this latter group was a small number of patients who displayed paranoid features in addition to cognitive abnormalities. Comparisons of the serum calcium for the three groups indicated a significant difference, \( F(2,28) = 4.86, P < 0.05 \). Planned comparisons indicated that the group judged to be normal had lower mean calcium levels (10.9 ± 0.88 mg/dL) than the other two groups combined, \( t(28) = -2.15, P < 0.05 \). An additional planned comparison indicated that the patients with affective disorders had a lower mean calcium (11.25 ± 0.66 mg/dL) than patients with signs of brain dysfunction (12.17 ± 1.17 mg/dL), \( t(28) = 2.32, P < 0.05 \).

These analyses suggest that qualitative differences in neuro-behavioral dysfunction occurred as a consequence of increasing calcium levels. Subsequent analyses showed that the intensity of neurobehavioral impairment, as measured by tests of motor speed, psychomotor speed, intelligence, and short-term memory, was also correlated with serum calcium. The correlations were: -0.33, \( P < 0.05 \), for the mean tapping score averaged over the two hands; -0.45, \( P < 0.01 \), for fluid intelligence; -0.36, \( P < 0.05 \), for STM; and 0.39, \( P < 0.05 \), for the Trail Making Test. The direction of all four correlations indicated that poorer performance was associated with higher calcium levels. Only the depression scale of the MMPI failed to significantly correlate with serum calcium.

**Effects of PTX**—Nineteen patients had repeat testing of neuro-behavioral function. Ten patients had testing repeated approximately six months after successful PTX (mean preoperative serum calcium was 11.7 ± 1.0 mg/dL, and mean serum calcium at follow-up was 9.2 ± 0.94 mg/dL). Repeat testing was performed in the remaining nine patients six months after the initial evaluation (mean serum calcium at initial testing was 11.0 ± 0.98 mg/dL, and mean serum calcium at follow-up was 10.7 ± 0.82 mg/dL). A significant difference occurred in the amount of change in serum calcium between the surgical and nonsurgical groups, \( F(1,16) = 7.63, P < 0.01 \), with the nonsurgical group displaying no significant reduction in serum calcium. While PTX lowered serum calcium, nonsurgical treatment did not.

At the initial evaluation, the surgical and nonsurgical groups did not differ regarding age, education, sex, and serum calcium. The two groups did not differ on the interval between the two evaluations. Despite the significant reduction in the serum calcium following PTX, we observed no differential improvement in functioning for those behavioral domains that were correlated with the serum calcium at the initial testing.

**Case Reports**

Serum calcium was associated with type and severity of neuro-behavioral dysfunction. However, the modest size of the correlations suggested that factors other than calcium contributed to a patient’s behavioral condition. The following cases are examples of patients whose psychopathology was long-standing. PTX had little effect on the long-term outcome of their behavioral disorder.

**Case 1**
A 49-year-old woman underwent surgery for an adenoma; her calcium level nearest the interview was 11.4 mg/dL. Her history suggested several episodes of fatigue and depression throughout her adult life. She had attempted suicide by overdose nine years before surgery. Pre-operative mental status examination revealed a compulsive personality style and euthymic mood. Chart review revealed documentation of “severe anxiety” three years after surgery, and psychiatric treatment was advised.

**Case 2**
A 60-year-old woman worried about “becoming crazy” after surgery. The calcium level near her interview was 11.2 mg/dL. Biopsy diagnosed adenomata of two glands, with hyperplasia of the biopsied remaining two glands; postoperative calcium level was normal. She described lifelong anxiety, and the mental status examination revealed mild dysphoria, a compulsive behavioral style, and mild anxiety. The patient subsequently suffered three episodes of major depressive disorder beginning one year after surgery. Treatment with tricyclic antidepressants was successful, and she returned to a euthymic state.

**Case 3**
A 73-year-old woman had moderate anxiety in her preoperative interview. Her calcium level near the interview was 10.9 mg/dL. An adenoma was removed during surgery, but 16 months later chart notes revealed that the patient experienced continued fatigue with normal calcium levels.

**Case 4**
The examination of a 59-year-old woman revealed paranoia, intellectual deficits, and forgetfulness. Her calcium level near the interview was 12.5 mg/dL, and an adenoma was removed at surgery. Chart review revealed a schizophreniform psychosis six months postsurgery with psychiatric hospitalization. A 14-year presurgical history of recurrent psychosis was discovered.

**Discussion**
As indicated in the Table, several studies address the problem of neurobehavioral symptoms in PHPT. Most of these studies were based on retrospective chart review, and details of the method of evaluation were scant in several reports. These case-series studies also varied on the amount of detail provided about types of psychiatric symptoms. Several investigators employed vague and general terms when describing their patients. This vagueness not only reduces the relevance of these studies for current practice, but also raises questions about the sensitivity of these investigations to the presence of subtle or atypical behavioral disorders. As the Table indicates, those investigators who distinguished among various types of psychiatric symptoms uniformly reported higher rates than those who used global terms such as “emotional symptoms” or “emotional disturbance.” Many of the earlier studies in particular are flawed by overly diffuse analyses of psychiatric symptomatology, which would bias them toward overly conservative estimates of rates of psychopathology.
In outpatient medical settings psychiatric illness prevalence ranges from 10% to 20% (31). The prevalence of psychological morbidity in this study is at least 3.5 times higher than expected. Even when allowing for different methods of investigation among studies, the literature indicates that psychiatric morbidity is considerably higher in PHPT than would be expected among general medical outpatients.

The types of neurobehavioral symptoms found in this study were similar to those reported by other investigators. We found mild to severe affective disorder, paranoid ideation, anxiety, lethargy, impaired motor and psychomotor speed, disorientation, impairment of memory, impaired fluid intelligence, and constructional dyspraxia for both drawings and block constructions. The range of neurobehavioral syndromes seen in PHPT is fairly well established and includes affective disorder, psychotic symptoms, particularly paranoid ideation, and mild to severe organic brain syndrome.

Serum calcium correlated with both the type and severity of the neurobehavioral abnormalities observed. Affective disorders seemed to lie midway between normal functioning and impairment of cognitive functioning, while a few of the patients who displayed signs of cognitive deficits also had paranoid delusions. Further, serum calcium formed small but significant correlations with measures of motor and psychomotor speed, memory functioning, and fluid intelligence. Based on his review of earlier cases and on his own work, Peterson (17) suggested that hypercalcemia between 12 and 16 mg/dL was associated with personality changes, while organic psychosis and confusional states occurred when hypercalcemia was between 16 and 19 mg/dL. Above 19 mg/dL, somnolence and coma occur. Our results and those of others, including Peterson's, suggest that this scheme is oversimplified. Personality changes can occur below the 12 mg/dL range, while signs of organic psychosis can appear at the 12 to 16 mg/dL range. Further, elevations above 20 mg/dL do not lead to coma and somnolence in an obligatory manner. Hanes (32) and Frame et al (33) reported on patients who were "cheerful and uncomplaining" despite a serum calcium level of 20 mg/dL. A weak, general relationship exists between hypercalcemia and the type and intensity of neurobehavioral dysfunction. However, individual differences play a major role in moderating this relationship.

Although patients with signs of affective disorder tended to have calcium elevations midway between those of the non-involved patients and those with cognitive changes, some elements of depression in these cases were independent of calcium levels. This independence surfaced in the failure to find a correlation between the depression scale on the MMPI and the initial calcium levels. Further, chart reviews indicated that some of these patients continued to be depressed following correction of the hypercalcemia.

Depression was related to cognitive impairment, suggesting that depression and hypercalcemia might make somewhat independent contributions to the prediction of cognitive deficits in patients with PHPT. When findings from the depression scale of the MMPI were combined with presurgical serum calcium, the multiple correlation of this pair of variables with our remaining neurobehavioral tests improved considerably over the correlation with calcium alone. This finding was particularly strong for tests of memory and psychomotor speed. The multiple correlation between calcium and depression, on the one hand, and the Trail Making Test, on the other hand, was 0.52. The multiple correlation with performance on the STM Distractor Test was 0.65.

As noted, in some patients emotional symptoms long predicated PHPT, raising the possibility that emotional disorder might contribute to the risk of developing PHPT. However, several studies failed to find an increased incidence of PHPT in psychiatric populations (34,35). Small increases in calcium have been observed to occur in the "switch" phenomena from depression to mania (36,37). Also, lithium carbonate-induced hyperparathyroidism has been reported (38), indicating that some treatments of emotional disorders can increase the risk of PHPT.

Fluctuations in serum calcium are associated with behavioral changes in a variety of diseases, suggesting an important role for calcium in modulating behavior (39-41). Changes in calcium could influence behavior through a large number of biochemical pathways. Calcium is essential for the release of neurotransmitters and hormones. Consequently, calcium can have direct and indirect effects on neuronal functioning. The neuronal effects of calcium, occurring through hormonal release, are particularly varied. Over 30 neuropeptides, some with hormone-like structure, are known to act as neurotransmitters (42). Receptors for 1,25-dihydroxyvitamin D₃ are thought to be present in rat brain (43). The discovery of endorphins and other endogenous opiates has led to speculation about their possible role in psychopathology (42). β-endorphins might play a role in calcium flux and neurotransmitter release (44).

Surgery did not lead to differential improvement in cognitive functioning. Our results agree with the negative findings of Cogan's group (45). Numann and colleagues (46) did find some improvement in memory and verbal reasoning following surgery. Although many of the neurobehavioral tests that we used were also included in the Numann study, we used a different approach to assess verbal memory (STM Distractor Test versus Wechsler Memory Scale). This difference in method could be the basis of the different results of the two studies. However, Cogan's group, like Numann et al, used the Wechsler Memory Scale to assess memory and failed to find any significant postoperative improvement in seven patients with PHPT. Numann and colleagues reported improvement on the Similarities subtest of the Wechsler Adult Intelligence Scale, and the absence of such improvement in the present study is even more difficult to understand. The failure to replicate Cogan et al's findings cautions against using them to build a rationale for performing PTX as a treatment of neurobehavioral symptoms in mild PHPT. Treatment studies involving larger samples are needed to determine which of the results previously mentioned are most reliably replicated. PTX has not consistently led to improvement in behavioral functioning among patients with mild PHPT. However, there may be subgroups of patients whose neurobehavioral symptoms could be ameliorated by PTX. Joborn and colleagues (47) reported improvement in the cognitive functioning of eight elderly patients with an early onset of progressive dementia following PTX for treatment of their PHPT.

Future research of the neurobehavioral effects of PTX should include methodologies for identifying particularly responsive subgroups.

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