

CASE REPORT

Middle-aged man with primary hyperparathyroidism-associated psychosis: A case report

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Abstract

Background: Primary hyperparathyroidism (PHPT) with mild hypercalcemia (Ca <12 mg/dL) often remains asymptomatic. However, PHPT may induce various psychiatric symptoms, including depression, cognitive dysfunction, and infrequently, psychotic symptoms, predominantly in older adults rather than in middle-aged or younger individuals.

Case-presentation: A 48-year-old man, with no history of physical or mental illness, experienced delusions about a suspicious car in his neighborhood, believing it was linked to criminal activity. This led to his being taken into custody after harming himself and his family. He was admitted for psychiatric evaluation and diagnosed with PHPT after mild hypercalcemia was discovered. He was initially treated medically for the mild hypercalcemia; however, only his disorientation showed improvement, and his broader psychiatric symptoms persisted. His delusions ceased only after surgical intervention. Following discharge, he remained symptom-free without requiring anti-psychotic medication.

Conclusion: This case highlights the importance of considering PHPT in patients of any age presenting with psychosis, even with mild hypercalcemia. Surgical options for patients with PHPT should be considered when medical interventions fail.

KEYWORDS

mild hypercalcemia, middle age, primary hyperparathyroidism, psychosis

BACKGROUND

Distinguishing primary psychiatric manifestations from those secondary to underlying physical illnesses, such as endocrine disorders, is crucial. Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and elevated serum parathyroid hormone (PTH) levels. It classically presents with multisystem symptoms, including skeletal, renal, gastrointestinal,

neurological, and psychiatric manifestations.¹ While PHPT typically causes nonspecific psychiatric symptoms such as depression, anxiety, and cognitive impairments, more severe manifestations like psychosis are rare.²

Mild hypercalcemia, defined as a serum calcium level of <12 mg/dL, often remains asymptomatic;³ however, it is increasingly detected owing to routine serum calcium screening.¹ Importantly, PHPT can induce psychiatric symptoms even in cases of mild

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hypercalcemia, and these symptoms do not necessarily correlate with the calcium levels.²

Older individuals are more prone to developing PHPT,⁴ with more frequent and severe psychiatric manifestations compared to younger patients.⁵ This report details a case of a middle-aged patient with mild hypercalcemic PHPT whose psychotic symptoms were alleviated by parathyroidectomy, highlighting the importance of considering PHPT in the differential diagnoses of psychosis, regardless of age. If psychosis persists despite medical therapy, surgical intervention should be contemplated.

CASE PRESENTATION

A 48-year-old Japanese man with no history of physical or mental health issues, substance use, or familial psychiatric problems was admitted for psychiatric evaluation. Employed as a corporate worker for over a decade, he had maintained stable interpersonal relationships. However, 1 month before his admission, he developed paranoia about a suspicious car in his neighborhood, believing it was linked to a reported crime. Concerned for his family's safety, he urged them to stay indoors. In a distressing decision influenced by his delusions, he attempted suicide by stabbing himself in the neck, thinking it would deter the criminal and prompt police intervention. Fortunately, he only needed to have stitches. Days later, still driven by the belief that his family was at risk of criminal involvement, he assaulted them with a blunt object to keep them at home and subsequently turned himself in to the police. After his arrest, initial evaluations suggested paranoid schizophrenia.

On admission to our hospital, he was agitated and continued to express fears for his family's safety, although he experienced no hallucinations. He was alert and oriented and had no physical symptoms. Treatment with aripiprazole 6 mg/day was initiated. Laboratory results indicated mild hypercalcemia (serum Ca 11.5 mg/dL, normal range 9.2–10.6 mg/dL) and slightly low phosphate levels (serum P 2.9 mg/dL, normal range 3.0–4.9 mg/dL). Liver, kidney, and thyroid functions were normal, but elevated PTH-intact levels of 106 pg/mL (normal range 11.0–67.0 pg/mL) suggested hyperparathyroidism. Despite treatment with 80 U/day of elcatonin by intramuscular injection for a week, his hypercalcemia persisted. Throughout the 8 days of hospitalization, his condition fluctuated; he eventually became disoriented, agitated, and delirious, prompting his transfer to Yamaguchi University Hospital for further evaluation and treatment of hyperparathyroidism. There, his laboratory data showed that hypercalcemia and elevated PTH levels persisted, and hypercalcemia was not induced by any other factor (Table 1). Diagnostic imaging was performed, including a ^{99m}Tc-methoxyisobutylisonitrile scintigram and contrast-enhanced computed tomography, which revealed an abnormality in the left inferior parathyroid gland, confirming a diagnosis of PHPT. No abnormalities were detected in the thyroid or pituitary glands. His bone mineral density was recorded at 0.882 g/cm² at lumbar vertebrae 2–4, with a T-score of -1.2 (\leq -2.5, diagnosed with

TABLE 1 Patient laboratory results after admission to Yamaguchi University Hospital.

Laboratory results	Value	Normal range
Albumin (g/dL)	3.8	3.7–4.7
Total serum calcium (mg/dL)	11.1	9.2–10.6
Phosphorus (mg/dL)	3.3	3.0–4.9
PTH-intact (pg/mL)	106	11.0–67.0
1,25 dihydroxy vitamin D ₃ (pg/mL)	41.9	
PTHrP (pmol/L)	< 1.0	0–1.1

Abbreviation: PTHrP, parathyroid hormone-related protein.

osteoporosis and surgery was recommended). Treatment with alendronate (5 mg/day) reduced his serum calcium levels to 10.5 mg/dL, which improved his disorientation and altered consciousness. Over the subsequent 4 weeks, the calcium levels remained in normal range, PTH-intact levels were elevated (104 pg/mL), and the paranoid delusions persisted. Subsequently, a left inferior parathyroidectomy was performed, revealing a parathyroid adenoma. Postoperatively, his serum calcium normalized to 9.3 mg/dL and PTH-intact to 14.3 pg/mL. His delusions resolved within 10 days and aripiprazole was reduced to 3 mg/day, eventually being discontinued 3 years later without recurrence of his symptoms. His violent actions, which were proven to be driven by PHPT-induced psychosis, were not prosecuted, and he has remained symptom-free for over a decade.

DISCUSSION AND CONCLUSION

Although depression and cognitive dysfunction are common psychiatric manifestations of PHPT, psychosis is rare. In 1988, Joborn et al. reported that of 441 patients with PHPT who underwent parathyroidectomy, 23% had had psychiatric symptoms, with only four cases exhibiting psychosis.² In March 2024, we reviewed case reports of PHPT-associated psychosis, defined as delusions or hallucinations, from PubMed (Table 2). We excluded reports with no apparent PTH elevation, histories of schizophrenia or schizoaffective disorder, drug influences (e.g., lithium), unreadable full texts, and reports in languages other than English.

The occurrence of delusions in our patient due to PHPT is significant, as it underscores the importance of considering PHPT in the differential diagnosis of middle-aged cases experiencing similar manifestations. PHPT is prevalent among older adults; Yeh et al. noted an incidence rate of 12–24 per 100,000 persons under the age of 50, and 196 in women and 95 in men aged 70–79.⁴ Psychiatric symptoms are reportedly more common in older individuals because of their decreased tolerance for serum calcium fluctuations. This increased susceptibility can manifest as severe psychiatric manifestations even with mild hypercalcemia.¹³



TABLE 2 Case reports of PHPT-related psychosis.

Case	Age/sex	Medical history	Ca (mg/dL)	PTH (pg/mL)	Medical therapy for psychiatric symptoms	Medical therapy for PHPT	Surgical intervention	Notes
Corredor-Orlandelli et al. ⁶	68/F	None	13.21	396	LMP 5 drops/day, RIS 2 mg/day, SER 50 mg/day	○; single dose of zoledronic acid IV	-	Ectopic parathyroid adenoma
El-Husari et al. ⁷	72/F	None	12.9	150	OLZ 5 mg/day and IM as needed	○; cinacalcet	-	The hallucinations persisted even after the hypercalcemia was corrected with intravenous fluids and resolved after 2 weeks of treatment with cinacalcet
Meng et al. ⁸	70/F	None	11.5	348	RIS	x; vitamin B ₁₂ IM, calcitonin SC, zoledronic acid IV	○	
Enyi et al. ⁹	68/F	None	11.2	201	OLZ	x; cinacalcet	○	
Otsuki et al. ¹⁰	68/F	None	10.4	180	QTP 37.5 mg/day, RIS 1-2 mg/day	-	○	
Nagy et al. ¹¹	58/F	None	14.4	759	OLZ 15 mg/day, GBP 300 mg/day, HAL 2 mg as needed	x; calcitonin	x	
Singh et al. ¹²	Middle age	None	12	※high	OLZ 10 mg/day SER 50 mg/day	○; pamidronate	-	※Different medical test was used. Calcium levels normalized over the few days along with her psychiatric symptoms
Park et al. ¹³	38/M	Vitamin D deficiency and osteoarthritis	11	106	RIS 1 mg/day, CZP 0.5 mg/day	-	-	Imaging tests not yet conducted. Cholecalciferol 2000 IU/day for vitamin D deficiency
Babar et al. ¹⁴	17/M	Learning disability	16.5	315		x; calcitonin IV	○	Uses marijuana about 2-3 times per week
Papa et al. ¹⁵	72/M	None	18.0	708.3	SER	x; furosemide IV, calcitonin SC	○	
Watson et al. ¹⁶	63/M	None	10.8	127	RIS 2 mg/day	○; furosemide	○	The delusions were initially relieved by medical therapy. A week later they relapsed and were resolved by surgery

Note: The unit for Ca was standardized to mg/dL. Ca levels were corrected using serum albumin.

Abbreviations: ○, improved; x, no improvement; -, not implemented; CZP, clonazepam; GBP, gabapentin; HAL, haloperidol; IM, intramuscular injection; IV, intravenous injection; LMP, levomepromazine; OLZ, olanzapine; QTP, quetiapine; RIS, risperidone; SC, subcutaneous injection; SER, sertraline.



In our review, four cases under the age of 60 were noted, including a middle-aged patient reported by Singh et al. and a 17-year-old boy who had a complex history of marijuana use and learning disabilities, and had significant hypercalcemia and psychosis that resolved post-surgery.¹⁴ Other notable cases include a 38-year-old man, suspected to have PHPT due to high PTH levels, who did not receive a definitive diagnosis because of non-compliance with medical advice,¹³ a 58-year-old woman who did not respond to medical or surgical treatment and her outcome after admission to a psychiatric hospital was unknown,¹¹ and a middle-aged woman whose auditory hallucinations and delusions improved with medical management for hypercalcemia after high PTH levels and enlarged parathyroid glands were identified.¹²

In our case, the diagnosis of PHPT was confirmed by blood tests, imaging studies, and pathological evaluation. The marked improvement in psychosis after parathyroidectomy strongly suggests an association between PHPT and psychosis.

PTH's ability to cross the blood-brain barrier and bind to PTH2 receptors on the limbic system neurons may explain the potential for inducing psychosis, independent of calcium levels.^{5,17} Generally, the correlation between psychiatric symptom severity and degree of hypercalcemia is poor.² In several cases, including ours and two cases under the age of 60, PHPT patients experienced psychosis despite having only mild hypercalcemia.^{8-10,13,16} Furthermore, in the case of El-Husari et al., the hallucinations persisted even after the hypercalcemia had improved, and the administration of cinacalcet normalized the PTH level and improved the hallucinations.⁷ In some cases, the psychosis resolved alongside the improvement in hypercalcemia,^{12,16} whereas in our case, the delusions persisted even after 4 weeks of improvement in hypercalcemia and disorientation, and they resolved after parathyroidectomy and normalization of PTH. This suggests that PTH can directly cause psychiatric symptoms and may explain why PHPT can cause psychiatric symptoms even in middle-aged people who, unlike older adults, do not have a reduced tolerance to calcium.

Nevertheless, an epidemiological study by Yeh et al. revealed that only about 32% of patients with mild hypercalcemia had their PTH levels measured,⁴ suggesting that many cases of asymptomatic PHPT may go undiagnosed. This highlights the importance of vigilant PTH measurement when diagnosing psychosis with concurrent mild hypercalcemia to rule out PHPT.

Surgical intervention can be beneficial for PHPT-related psychosis when medical therapy proves ineffective. The fifth International Workshop on the Evaluation and Management of PHPT, held in 2022, recommended surgery for asymptomatic PHPT if specific criteria are met, such as serum calcium >1 mg/dL above normal, significant skeletal or renal involvement, or if the patient is under 50 years of age.¹⁸ Given that our patient was 48 years old, we performed surgery. However, the American Association of Endocrine Surgeons suggests surgery even when only neurocognitive or neuropsychiatric symptoms are present, despite the conflicting guidelines.¹⁹ Recent systematic reviews and meta-analyses

have shown that parathyroidectomy significantly improves depression and anxiety scores,²⁰ and cohort studies have noted improvements in neurocognitive symptoms following surgery.²¹ Despite the lack of studies specifically investigating the efficacy of surgery for PHPT-related psychosis, case reports indicate variable outcomes. In our case and review, delusions persisted despite medical management but resolved following parathyroidectomy.^{8,9,14,15} Thus, surgical treatment should be considered for patients whose psychosis persists despite improved hypercalcemia through medical therapy.

In conclusion, this case report describing the clinical course of a 48-year-old man with PHPT-associated psychosis, characterized by mild hypercalcemia resistant to medical management but resolving after surgical intervention, highlights the importance of considering PHPT in the provisional diagnosis of psychosis in patients of any age presenting with hypercalcemia, regardless of its severity. It also illustrates that while medical therapy may normalize serum calcium levels, it may not suffice for alleviating psychosis, thus making surgical intervention a vital consideration. Elevated PTH levels may be involved in the mechanism of psychosis caused by PHPT in middle age. In this case, the patient was also taking an antipsychotic, so it cannot be excluded that it contributed to the improvement of the acute psychosis. As evidenced, even mild elevations in serum calcium can precipitate significant psychiatric disturbances, advocating for a thorough endocrine evaluation in the management of new-onset psychosis.

AUTHOR CONTRIBUTIONS

Kota Shinkawa performed the literature search and wrote and revised the first draft of the manuscript. Masaya Mashimoto rewrote and revised the manuscript. Hiroshi Kaneyuki interviewed and treated the patient, and rewrote and revised parts of the manuscript. Toshio Matsubara and Shin Nakagawa wrote and revised parts of the manuscript. All authors contributed to and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Not applicable as this is a case report.

ETHICS APPROVAL STATEMENT

This report was approved by the Ethics Committee of Yamaguchi Prefectural Mental Health Medical Center.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient for presentation of their clinical course.

CLINICAL TRIAL REGISTRATION

Not applicable as this is a case report.

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