

# Late-onset mania with psychosis associated with hypothyroidism in an elderly Chinese lady

Tor P C, Lee H Y, Fones C S L

## ABSTRACT

**Late-onset bipolar disorder is rare and can be precipitated by organic brain disorders. While the association between hyperthyroidism and mania is well described, mania or hypomania precipitated by hypothyroidism is rare. The authors present late-onset bipolar disorder in a 72-year-old woman presenting with mania and psychosis, which appear to have been precipitated by autoimmune hypothyroidism. This case shows the importance of ascertaining the thyroid status in patients with mood and psychotic disorders, especially in elderly patients and in patients lacking prominent signs of thyroid disease.**

**Keywords: bipolar disorder, hypothyroidism, mania, psychosis, quetiapine**

*Singapore Med J 2007; 48(4):354–357*

## INTRODUCTION

Bipolar disorder is a chronic, relapsing condition that usually presents in patients between 17 and 21 years of age.<sup>(1)</sup> Although often diagnosed after a manic or hypomanic episode, bipolar disorder not uncommonly presents initially with an episode of depression,<sup>(2,3)</sup> with manic episodes unreported by patients or missed by treating physicians. Late-onset bipolar disorder is rare,<sup>(1)</sup> and may be precipitated by organic brain disease like hyperthyroid states.<sup>(4)</sup> Equally rare is mania or hypomania associated with hypothyroidism, with only four other reported cases in the available literature.<sup>(5–8)</sup> In these cases, the patients were mostly young women in the reproductive age group. The more common association between depression or depressive psychosis and hypothyroidism is well known.<sup>(9)</sup> The classic paper on “myxoedematous madness” by Asher<sup>(10)</sup> describes acute psychosis in the setting of advanced hypothyroidism. We present a case of late-onset bipolar disorder presenting with mania and psychosis associated with autoimmune hypothyroidism with minimal signs of thyroid disease.

## CASE REPORT

A 72-year-old Chinese woman was brought by her adopted daughter and son-in-law to the emergency department (ED). She had forced them to lend her money to go to a Christian retreat and take her shopping that same day. During the shopping trip, she was irritable, disinhibited and verbally abusive towards the shopkeepers, her daughter and son-in-law. When forced by her daughter to go to the ED, she lay on the ground and refused to move. At the car park, she was opening car doors of strangers and claiming her son-in-law was trying to abandon her and had to be physically restrained.

The patient was agitated, and was physically restrained and sedated with 15 mg intravenous (IV) diazepam and 15 mg IV haloperidol. Despite this, she still struggled against the restraints and spat at the medical staff. A quick mental state examination revealed a large elderly Chinese woman with greying hair and wearing large black-rimmed spectacles. She was relevant and oriented to time, place and person, but uncooperative and demanded to be released. She did not have pressure of speech or flight of ideas but her mood was agitated and expansive. She displayed some grandiose thoughts about her relationship with God, saying that she was being held back from fulfilling God’s plans. However, she did not display any formal thought disorder. She did have auditory hallucinations, claiming that God spoke directly to her and gave her instructions to comply with. A formal cognitive assessment was not conducted due to the patient’s agitation.

Further history was sought from her daughter and son-in-law. They had noticed a change in the patient’s behaviour over the past two months. She had become increasingly preoccupied with money matters, and became irritable and curt towards them. Her premorbid personality was described as friendly, caring and warm. The daughter also noticed that the patient was sleeping much less than before and was “always up at night doing something”. She had recently started an aromatherapy business on the advice of church friends. This turned out to be unsuccessful and had to be wound up. In addition, the patient had recently taken up trading on the margins market, a risky and complex enterprise

Department of  
Psychological  
Medicine,  
National University  
Hospital,  
5 Lower Kent  
Ridge Road,  
Singapore 119074

Tor PC, MBBS  
Medical Officer

Fones CSL, MBBS,  
MMed, FAMS  
Head

Department of  
Anaesthesia,  
Alexandra Hospital,  
378 Alexandra Road,  
Singapore 159964

Lee HY, MBBS  
Medical Officer

Correspondence to:  
Dr Tor Phern Chern  
Tel: (65) 6772 4511  
Fax: (65) 6777 2191  
Email: torphernchern  
@gmail.com

that had managed to deplete almost all of the patient's savings. The daughter also reported that when she questioned the patient why she was involved in so many risky and new activities at her age, the patient always replied that God told her to do so.

The patient was known to have a history of depression with psychotic features three years before the current manic episode. At that time, she was brought to the hospital by her daughter for paranoid symptoms and odd behaviour for two weeks. She suspected that her phone lines were tapped, and she forbade her daughter from leaving the house as she felt people were watching and following her. She also spent many hours searching for lost house keys. She was also hyper-religious and worried that God would punish her and make her suffer. She had symptoms of poor sleep and appetite, anhedonia and low mood. The mental state examination then showed a Chinese woman with psychomotor retardation and low mood. She did not have auditory or visual hallucinations. Extensive investigations were done to exclude an organic cause of her psychotic depression. Imaging of the brain (magnetic resonance imaging and computed tomography), electroencephalography, electrocardiography, full blood count, renal panel, liver panel, thyroid function, calcium levels, syphilis screen, and Vitamin B12/folate tests were all normal. The erythrocyte sedimentation rate (ESR) was raised at 57 mm/hour. The patient did not respond well to medication and was given a course of ten electro-convulsive therapies, which improved her mood and cognition. She was discharged with quetiapine 50 mg OM, 100 mg ON and followed-up for six months at the outpatient clinic where her medicine was gradually tailed off. She was discharged from follow-up as she was well without the medication.

During this admission, a complete neurological, cardiovascular, abdominal and respiratory examination of the patient was normal. Few signs of thyroid disease were detected. The patient did have dry skin and had complained of some hair loss in recent years. There was no pitting oedema, cold intolerance, constipation, dramatic weight gain, thinned eyebrows, slow movement, lethargy, tiredness, bradycardia, slow speech or delayed tendon reflexes. Further investigations were done for the patient. The full blood count, renal panel and liver panel were normal. However, the free levothyroxine (T4) was low at 2.7 pmol/L (normal range, 10–20 pmol/L) and thyroid stimulating hormone (TSH) grossly elevated at 79.4 mIU/L (normal range, 0.45–4.5 mIU/L). The ESR was also raised at 74 mm/hour (normal range, 5–15 mm/hour). Her thyroid function tests taken previously were normal (free T4 19.6 pmol/L and TSH 3.19 mIU/L) and her ESR then was 57 mm/hour.

Additional tests were done to assess the thyroid status. The anti-thyroglobulin antibodies were grossly elevated at 2,507 IU/ml (normal 0–40 IU/ml) and anti-thyroid peroxidase antibodies at the upper limit of normal at 50 IU/ml (normal 0–50 IU/ml). Free triiodothyroxine was also low at 1.9 pmol/L (normal 4.3–8.3 pmol/L). A mini-mental state examination was performed four days after admission and she scored 29 out of 30. A referral was made to the endocrinology team, which suggested that the quetiapine taken by the patient three years ago could have caused the autoimmune thyroiditis<sup>(11)</sup> and the current hypothyroid state. The initial decision was to delay thyroid replacement to ascertain the reversibility of the thyroid status. The patient was started on haloperidol 1.5 mg ON and within two days, the patient's mood and behaviour had normalised. She was euthymic, pleasant and cooperative in the ward. She ceased to have auditory hallucinations. However, her sleep remained poor in the ward, with frequent awakenings in the night due to recurrent intrusive thoughts about money and debts. However, she was not tired and did not experience these thoughts during the day.

Further input from the endocrinology team was that the patient would be likely to require thyroxine replacement, in view of the severity of hypothyroidism and the need for antipsychotic therapy that could worsen thyroid function. Thyroxine 50 µg OM was started and the patient responded favourably to this with improved sleep and decreased intrusive, disturbing thoughts. She was discharged after two weeks. The patient was followed-up in the outpatient clinic and continued on low dose haloperidol and thyroxine with good control of her psychiatric and thyroid status. Her mood remained euthymic and her TSH value dropped in the three months after discharge. The endocrine team planned to gradually tail off thyroxine replacement in the outpatient setting.

## DISCUSSION

Mania usually presents early in a person's life.<sup>(1)</sup> Late-onset mania is more likely to have an organic basis. This patient was documented to have a normal thyroid status three years before the manic episode. The high levels of anti-thyroid antibodies and lack of physical signs of hypothyroidism in the current manic state suggest a recent onset of thyroiditis and hypothyroidism. This temporal relationship suggests that the hypothyroid status could have precipitated the manic episode. The diagnosis of bipolar disorder was not made in her initial admission as she presented with symptoms of depression (psychomotor retardation, low mood, anhedonia) and a history of elevated mood was not elicited. Even during the current admission, the patient

denied any episodes of expansive or elevated mood in the past. This is not uncommon as studies have shown that a depressive episode is the usual reason for presentation to the medical service in patients with bipolar disorder.<sup>(2,3)</sup>

The symptoms of hypothyroidism in the elderly are varied and typically include fatigue, cold intolerance, dry skin, hair loss, menstrual irregularities and constipation. Signs include hoarse voice, bradycardia, nonpitting oedema, facial puffiness, slow speech and delayed relaxation of the deep tendon reflexes. It is interesting not only that the patient did not have obvious signs of hypothyroidism, but that her manic symptoms were also not picked up for almost two months. The patient lived alone and spent most of her time interacting with her church friends. The adopted daughter reported that the church friends found her behaviour to be normal during the two months when she was sleeping less, spending large sums of money on stocks and new businesses, and displaying hyper-religiosity. The delay in seeking treatment could possibly be explained by the lack of insight of the patient into her condition and the reluctance of the adopted daughter to bring the patient to see a psychiatrist again.

The association between thyroid dysfunction and psychotic or mood disorders is well-described.<sup>(10,12)</sup> The mental state examination may reveal a wide range of dysfunction, ranging from mild attentional impairment to significant agitated delirium or psychosis. Between 5%–15% of myxoedematous patients have some form of psychosis,<sup>(13)</sup> although no typical constellation of psychotic symptoms is likely in the myxoedematous patient with a variety of clinical case reports in the literature.<sup>(14-16)</sup> Psychosis typically emerges after the onset of physical symptoms, often after a period of years or months.<sup>(17)</sup>

The association between bipolar disorder and hypothyroidism has been documented in studies showing thyroid autoimmunity to be more prevalent in bipolar patients than population and psychiatric controls (28% versus 3%–18%), with this being independent of risk factors for hypothyroidism.<sup>(18)</sup> Epidemiological support for this association is seen in a study showing patients hospitalised with hypothyroidism having a greater risk of readmission with depression or bipolar disorder than control patients.<sup>(19)</sup>

The exact mechanism behind thyroid dysfunction and bipolar disorder is unclear but has been postulated to be related to thyroid hormone regulation of central nervous system catecholamine receptor sensitivity. Surplus thyroid hormones can possibly lead to mania by promoting the action of catecholamines at central receptor sites and conversely, low thyroid levels can

lead to depression.<sup>(9)</sup> It has also been suggested that rapid alteration in the level of circulating thyroxine from severe excess to normal levels and the effects of this change on cerebral catecholamines could cause psychosis.<sup>(4)</sup> The brain appears to have unique sensitivity to the thyroid hormone and to utilise thyroid hormone differently from other organ systems.<sup>(20,21)</sup> High concentrations of T<sub>3</sub> receptors are found in the amygdala and hippocampus.<sup>(22)</sup> In hypothyroidism, the utilisation of available thyroid hormone favours the brain.<sup>(23)</sup> In rats rendered hypothyroid, an increase in cerebral dopamine is observed along with an increase in tyrosine hydroxylase activity.<sup>(24)</sup> Thyroid hormones have been shown in human and animal studies to increase  $\beta$ -adrenergic receptor sensitivity. This does not account for hypothyroidism leading to mania but this could just reflect a lack of understanding about the relationship between thyroid states and catecholamine receptor sensitivity.

Alternative possibilities include a transient hyperthyroid state caused by the thyroiditis, resulting in the manic episode. This is unlikely given the amount of time required for TSH to rise, in relation to low thyroid hormone levels.<sup>(25)</sup> Another hypothesis is that the hypothyroid status resulted in a disruption to the regulation of biological rhythms,<sup>(26,27)</sup> which precipitated the episode of mania. This has also been suggested by studies<sup>(28)</sup> that show a higher incidence of rapid-cycling bipolar disorder in hypothyroid patients. However, the same study reports that the degree of severity of hypothyroidism does not appear to correlate strictly with the severity or occurrence of the psychiatric disorder.<sup>(28)</sup> The susceptibility of the patient to psychiatric disorders may play a role in their precipitation by hypothyroid states. In this case, the patient had an episode of severe depression with psychotic features three years prior to the development of mania and would have been at a higher risk of further mood disturbances. Another related point to consider is the relative contribution of the hypothyroid state to the development of mania with psychotic features. The patient improved significantly with antipsychotics despite an initial lack of thyroid replacement, although thyroxine replacement was eventually required for optimal control of her psychiatric symptoms. In follow-up, the patient's thyroid status was well controlled with thyroxine replacement but she still required antipsychotics to control her psychiatric symptoms.

In conclusion, this case highlights the importance of screening for organic causes of psychiatric symptoms presenting for the first time in older patients as well as the importance of ascertaining thyroid function in patients with affective and behavioural symptoms. Since psychiatric complaints may be one

of the earliest manifestations of hypothyroidism, they are often misdiagnosed as functional psychiatric disorders. This confusion can lead to delayed treatment and the possibility of increased morbidity. Clinicians must also remember that most cases of bipolar disorder present with a depressive episode and that a history of elevated mood or energy should be rigorously looked for in all patients presenting with depression.

#### ACKNOWLEDGEMENT

The authors would like to acknowledge the help and support from the Department of Psychological Medicine, National University Hospital in preparing this case report.

#### REFERENCES

- Gelder M, ed. *Shorter Oxford Textbook of Psychiatry*. 4th ed. Oxford University Press Inc: New York, 2001: 303.
- Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. *Psychiatr Clin North Am* 1999; 22:517-34, vii.
- National Institute of Mental Health (NIMH): Bipolar Disorder [online]. Available at: [www.nimh.nih.gov/publicat/index.cfm](http://www.nimh.nih.gov/publicat/index.cfm). Accessed August 10, 2005.
- Lishman WA, ed. *Organic Psychiatry: The Psychological Consequences of Cerebral Disorder*. 3rd ed. Boston: Blackwell Scientific Science, 2004:509.
- Ballin J, Berggren U, Rybo E, Kjellbo H, Lindstedt G. Treatment-resistant mania with primary hypothyroidism: a case of recovery after levothyroxine. *J Clin Psychiatry* 1987; 48:490-1.
- Levitte SS. Coexistent hypomania and severe hypothyroidism. *Psychosomatics* 1993; 34: 96-7.
- Mahendran R. Hypomania in a patient with congenital familial hypothyroidism and mild mental retardation. *Singapore Med J* 1990; 40:425-7.
- Stowell CP, Barnhill JW. Acute mania in the setting of severe hypothyroidism. *Psychosomatics* 2005; 46:259-61.
- Whybrow PC, Prange AJ Jr. A hypothesis of thyroid-catecholamine-receptor interaction. Its relevance to affective illness. *Arch Gen Psychiatry* 1981; 38:106-13.
- Asher R. Myxedematous madness. *Br Med J* 1949; 2:555.
- Feret BM, Caley CF. Possible hypothyroidism associated with quetiapine. *Ann Pharmacother* 2000; 34:483-6.
- Heinrich TW, Grahm G. Hypothyroidism presenting as psychosis: myxedema madness revisited. *Prim Care Companion J Clin Psychiatry* 2003; 5:260-6.
- Hall RC. Psychiatric effects of thyroid hormone disturbance. *Psychosomatics* 1983; 24:7-18.
- Granet RB, Kalman TP. Hypothyroidism and psychosis: a case illustration of the diagnostic dilemma in psychiatry. *J Clin Psychiatry* 1978; 39:260-3.
- Davis AT. Psychotic states associated with disorders of thyroid function. *Int J Psychiatry Med* 1989; 19:47-56.
- Madakasira S, Hall TB 3rd. Capgras syndrome in a patient with myxedema. *Am J Psychiatry* 1981; 138:1506-8.
- Logothetis J. Psychotic behaviour as the indicator of adult myxedema. *J Nerv Ment Dis* 1963; 136:1561-8.
- Kupka RW, Nolen WA, Post RM, et al. High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. *Biol Psychiatry* 2002; 51:305-11.
- Thomsen AF, Kvist TK, Andersen PK, Kessing LV. Increased risk of developing affective disorder in patients with hypothyroidism: a register-based study. *Thyroid* 2005; 15:700-7.
- Thompson CC, Potter GB. Thyroid hormone action in neural development. *Cereb Cortex* 2000; 10:939-45.
- Dratman MB. Cerebral versus peripheral regulation and utilization of thyroid hormones. In: Joffe RT, Levitt AJ, eds. *The Thyroid Axis and Psychiatric Illness*. Washington, DC: American Psychiatric Press, 1993:3-94.
- Ruel J, Faure R, Dussault JH. Regional distribution of nuclear T3 receptors in rat brain and evidence for preferential localization in neurons. *J Endocrinol Invest* 1985; 8:343-8.
- Dratman MB, Crutchfield FL, Gordon JT, Jennings AS. Iodothyronine homeostasis in rat brain during hypo- and hyperthyroidism. *Am J Physiol* 1983; 245:E185-E193.
- Sato T, Imura E, Murata A, Igarashi N. Thyroid hormone-catecholamine interrelationship during cold acclimation in rats. Compensatory role in catecholamine for altered thyroid states. *Acta Endocrinol (Copenh)* 1986; 113:536-42.
- Martini L, ed. TSH. In: *Encyclopedia of Endocrine Diseases*. New York: Elsevier, 2004: 303-13.
- Cowdry RW, Wehr TA, Zis AP, Goodwin FK. Thyroid abnormalities associated with rapid-cycling bipolar illness. *Arch Gen Psychiatry* 1983; 40:414-20.
- Stancer HC, Persad E. Treatment of intractable rapid-cycling manic-depressive disorder with levothyroxine. Clinical observations. *Arch Gen Psychiatry* 1982; 39:311-2.
- Bauer MS, Whybrow PC, Winokur A. Rapid cycling bipolar affective disorder. I. Association with grade I hypothyroidism. *Arch Gen Psychiatry* 1990; 47:427-32.