



## Low thyroid stimulating hormone levels associated with acute psychosis in a geriatric patient and improvement with resolution of psychosis: a case report

### Practice points

- Thyroid abnormalities may be seen in acute psychiatric admissions.
- Usually these abnormalities resolve with treatment of the psychosis.
- If thyroid abnormalities persist after 2 weeks of treatment, further thyroid work-up should be considered to diagnose the cause of the dysfunction.

Thyroid function abnormalities may be seen in acute psychiatric admissions in adults and adolescents. A man in his 70s suffering from Alzheimer's dementia was admitted with symptoms of agitation, aggression and delusional behavior. He had no history of thyroid disorder. The admission thyroid stimulating hormone (TSH) level was low at 0.235 mIU/ml. Other thyroid work-up was negative. We suspected that the TSH abnormalities were possibly related to the acute psychosis. Serial measurements of TSH and assessment of treatment progress with Clinical Global Impression scale were completed. TSH level on admission was 0.235 and at discharge 0.510 mIU/ml. The global impression scale scores showed corresponding improvement. Thyroid work-up and follow-up thyroid function tests in 2 weeks should be considered before exercising treatment options for thyroid function abnormalities in acute psychotic patients, particularly in the elderly.

**Keywords:** psychosis • thyroid stimulating hormone

Thyroid function abnormalities may be seen in acute psychiatric admissions in adults and adolescents [1]. However, there is a paucity of published data in acute geropsychiatric patients.

It has long been recognized that many endocrine abnormalities, particularly thyroid dysfunction, play an important role in psychiatric illness [2]. Many symptoms of thyroid dysfunction may mimic those of psychiatric illness and *vice versa*. Thus, assessing thyroid function in geropsychiatric patients is of paramount importance.

Hyperthyroidism has been related to symptoms of anxiety, hyperactivity, mood lability, mania, transient psychosis and depression. Elderly patients with hyperthyroidism may not present with the typical clinical picture.

The presenting features may be weight loss, apathy, weakness or depression.

It is known that thyroid hormones play a direct role in regulating brain function [3], although the underlying mechanism is still unclear. Thyroid hormone concentration in the brain is usually maintained, in spite of significant peripheral fluctuations [4].

Even minor changes in the levels of thyroid hormone may cause marked affective disturbances [5]. Thyroid hormones may regulate central adrenergic neurotransmission and thus, influence brain homeostasis [6]. However, the specific relationship between thyroid hormone disturbances and psychiatric disorders remains unclear. Measurement of thyroid hormone activity in the CNS may be required, particularly in diseased states,

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because the peripheral and central regulation of thyroid hormones may be independent of each other [6], and psychiatric symptoms may persist even after thyroid abnormalities are corrected [7].

In this paper we report the case of an elderly patient who was admitted with psychotic symptoms, agitation, aggression and low thyroid stimulating hormone (TSH) level, with no history of thyroid disorder. We suspected that the TSH abnormalities were related to the acute psychosis.

### Case report

An elderly man in his 70s suffering from Alzheimer's dementia was admitted to our hospital because of agitation, aggression, and delusional behavior. He also refused to take any medications. The patient was expressing delusional thoughts. He could not give a coherent history and could not describe the events that led to his hospitalization.

On admission, the patient was poorly groomed, wearing a hospital gown loosely tied. No abnormal involuntary movements were noted. Eye contact was poor. Speech was normal. The patient was unable to verbalize his mood. Affect was irritable, constricted and incongruent with the thought content. The patient was uncooperative, guarded, grandiose and hostile. The thought process was coherent but tangential at times. Paranoid delusions, racial preoccupation and confabulation were noted. He did not appear to be experiencing perceptual disturbances. He was alert and oriented to person, but not to time or place. Insight and judgment were poor. On admission, the Clinical Global Impression (CGI) scale [8] severity of illness score was 6 (severely ill).

The patient had a history of dementia Alzheimer's type with delusional features. He had been hospitalized twice with the same diagnosis in the same year, primarily related to his lack of adherence to medications and aggressive behavior. The patient was on haloperidol decanoate 100 mg intramuscularly every 4 weeks and the last injection prior to the index hospitalization was about 3 weeks prior to admission. Patient was also prescribed aspirin 81 mg/day, amlodipine, trihexyphenidyl hydrochloride, clonidine, metoprolol tartrate and latanoprost eye drops. He had a history of glaucoma, cataract of the left eye and hypertension. No allergies were noted. There was no history of thyroid disorder.

Routine laboratory tests done on admission included complete blood count, chemistry, TSH level, free thyroxine level, triiodothyronine uptake, hemoglobin A1c, vitamin B12 and folic acid level, rapid plasma reagin test, ECG and urine toxicology. The results were all normal except for low TSH, 0.235 mIU/ml

(0.465–4.68 mIU/ml). The thyroxine (T<sub>4</sub>) level was within normal range at 5.89 µg/dl (5.53–11.0 µg/dl). T<sub>3</sub> uptake also was within the normal range, at 34.2% (22.5–37%). The CT scan of the head showed mild cerebral atrophy and small vessel changes without intracranial hemorrhage. Ultrasound of the thyroid gland showed a markedly enlarged, heterogeneous thyroid with multiple confluent nodules in both thyroid lobes. There were no physical or definitive psychiatric symptoms of subclinical hyperthyroidism in this patient. The endocrinology consultant suggested the diagnosis of hyperthyroxinemia of acute psychiatric illness with recommendation to test for thyroid auto-antibodies, and opined that there was no need for anti-thyroid medication at that time. The thyroglobulin antibody test result was <20 (range: <20 IU/ml).

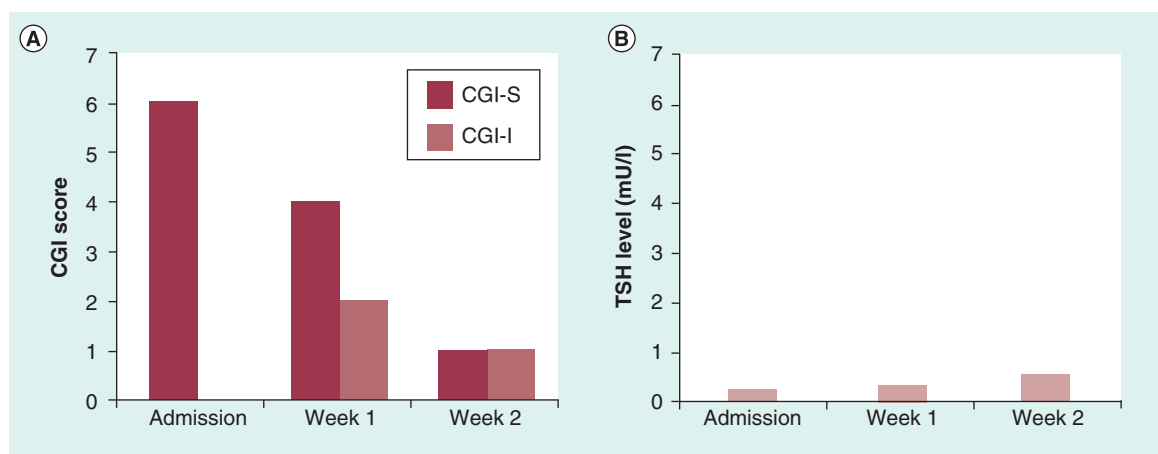
The patient was diagnosed with dementia Alzheimer's type with delusional features, and low TSH possibly secondary to acute psychosis.

The patient was treated with haloperidol up to 5 mg *per os* twice daily. However, he only took occasional doses of the oral haloperidol and therefore was given haloperidol decanoate 100 mg intramuscularly 2 days after admission. The patient's previous medications were continued except for trihexyphenidyl, which was changed to amantadine.

Treatment progress was monitored with Clinical Global Impression-Improvement (CGI-I) scale at admission, after 5 days of treatment and at discharge. Serial measurements of TSH were done every 5 days (Figure 1).

After 5 days of treatment, the patient was superficially cooperative, and less hostile and less agitated. He was taking medication after much encouragement and counseling. He was less grandiose but remained seclusive. Affect was constricted, not congruent with thought content. Thought process was more goal directed and less tangential. Delusions were less intense. Insight was limited. CGI-S done at this time was 4 (moderately ill), and the CGI-I was 2 (much improved). The TSH had increased to 0.345 mIU/l.

At discharge, after 10 days of treatment, the patient was calm and cooperative. Delusional ideation had remitted. No abnormal involuntary movements were noted. He had normal psychomotor activity. He was not seclusive, leaving his room often. The CGI-S was 1 (normal, not ill at all), the CGI-I was 1 (very much improved), and the TSH level had increased to 0.510 mIU/l (normal range: 0.500–4.700 mIU/l). The CGI-I and -S in this context refer to the behavioral complications of dementia such as the aggression and the delusions that resulted in the hospitalization, and was the focus of treatment, and not the cognitive deficits.



**Figure 1. Clinical Global Impression scale in relation to thyroid stimulating hormone levels. (A)** CGI score and **(B)** TSH level.

CGI: Clinical Global Impression; CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity; TSH: Thyroid stimulating hormone.

## Discussion

Thyroid stimulating hormone secretion is controlled primarily by the thyroid hormones triiodothyronine (T3) and thyroxine (T4) through negative feedback, while the hypothalamic secretion of thyrotropin-releasing hormone (TRH) stimulates TSH release; and various neurotransmitters may play a role in TRH secretion [9].

TSH levels may be affected by a multitude of factors such as drugs, poor caloric intake and various nonthyroidal illnesses, which may result in either suppressed or slightly elevated TSH levels [10].

### Thyroid dysfunction associated with drugs

There are several drugs that can cause changes in thyroid function, including phenothiazines, other typical and atypical antipsychotics, tricyclic and nontricyclic antidepressants, lithium, carbamazepine, valproic acid, benzodiazepines, opiate substitution drugs,  $\beta$ -blockers, orphenadrine, methylphenidate and atomoxetine, dopamine, levodopa, bromocriptine, glucocorticoids, octreotide, amphetamines, metoclopramide, amiodarone, intravenous furosemide, nonsteroidal agents, salicylates >2 g per day and phenytoin [11,12].

Discussion of the mechanisms of thyroid dysfunction of all the above medications is beyond the scope of this paper. None of the medications that the patient received, except haloperidol are known to have any effect on thyroid function. Moreover amantadine, which is a dopamine agonist, will theoretically have the opposite effect of haloperidol on the dopamine receptor. This patient was also noncompliant with oral medications, so the only medication that merits discussion is the haloperidol decanoate injection that the patient received 3 weeks prior to the index admission. This indicates that he still had haloperidol in his

system. The known effect of haloperidol is to cause a mild increase in the TSH, through hyperprolactinemia and thyroid autoantibody release specifically in females [11–13]. The fact that the patient conceivably had haloperidol in his system on admission, the negative result of thyroglobulin antibody, and that the patient is a male are pointing to the fact that it is unlikely to be related to haloperidol. Moreover the TSH was low on admission and started increasing with the improvement of psychosis, as we have conceptualized.

### Subclinical hyperthyroidism

Subclinical hyperthyroidism is characterized by a low or undetectable serum concentration of serum TSH, with levels of free triiodothyronine and free thyroxine within the normal range. Patients with subclinical hyperthyroidism may be symptomatic. The symptoms may include palpitations, tremor, heat intolerance, sweating, nervousness, anxiety, reduced feeling of well-being, fear, hostility and inability to concentrate. Our patient did not have any of these symptoms except hostility. His TSH levels also improved with resolution of psychosis as evidenced by the CGI scale changes. Previous work has shown that, of the various thyroid function abnormalities in acute psychosis, TSH abnormalities are less common, and elevated triiodothyronine uptake is more common [14].

### Thyroid dysfunction in nonthyroidal illnesses

Abnormal thyroid function tests are commonly found during starvation and in patients with systemic, nonthyroidal illness [15,16]. In euthyroid sick syndrome there is usually high or low T3, and an increase in T4 and normal TSH, however, our patient had normal T3 uptake and T4 with low TSH [15]. Decreased serum

T3 is the most frequently observed thyroid function alteration in these patients. Decreased serum T4 and decreased TSH may be present in patients with severe illness. While this phenomenon is incompletely understood, the serum thyroid hormone alterations found in nonthyroidal illness may, at least in part, result from a decrease in TSH secretion [16]. This, in turn, is associated with decreased TSH response to stimulation by TRH administration [17,18]. Although the teleological reasons for these changes in the physiology of TSH secretion are unclear, it should be noted that serum TSH routinely rises during recovery from the nonthyroidal illness [16]. While controversy exists on this point, the changes in thyroid function found in nonthyroidal illness may not necessarily represent the presence of intrinsic thyroid dysfunction.

While our patient differs in one respect from the patients with nonthyroidal illness described above, in that his serum T4 was within normal range, the pattern of decreased serum TSH with spontaneous recovery with treatment of the acute psychosis resembles the TSH pattern in systemic nonthyroidal illness, and a similar alteration in the physiology of TSH secretion may be hypothesized. As in the case of systemic illness, thyroid function test alterations found in psychiatric patients may not necessarily represent the presence of thyroid dysfunction [19–21]. The abnormal test results are transient and normalize within 5–10 days. They correlate with improvement of correction of the psychiatric illness [22].

The sensitive TSH assay is currently the best single initial test for the diagnosis of thyroid disease in outpatients [23]. However, a systematic review of literature from 1999 found that in unselected general medical, geriatric, or psychiatric inpatients, the TSH test has a low yield of true-positive and many false-positive results [24].

#### Thyroid dysfunction in geriatric & geropsychiatric patients

In a retrospective study of 197 acute geropsychiatric patients Madhusoodanan *et al.* found the prevalence of hyperthyroidism to be not significantly increased in the geropsychiatric group compared with the non-psychiatric geriatric patients [14]. These findings are in agreement with previous studies in adults over the age of 55 years [25] and in patients with acute psychiatric illness [26]. The study also found that the most common abnormalities in thyroid function tests in the study group was elevation in triiodothyronine uptake and free thyroxine index. Elevation in triiodothyronine uptake was seen in 25.3% of female and in 13.4% of male patients. Almost all of these patients were euthyroid.

In a study of 868 long-term care patients, 65 years and above, referred to psychiatry, it was found that TSH was low in 0.07%. Elevated TSH was found in 10.7% and was associated with female gender and psychosis [27].

Changes in thyroid function can be correlated with advancing age [28]. The prevalence of overt and sub-clinical hypothyroidism in older populations is as high as 20% [29]. The prevalence of subclinical hyperthyroidism also increases with age. In older populations it has a prevalence of 1–2% in iodine-sufficient areas [29,30] and 7–8% in iodine-deficient areas [3].

#### Thyroid dysfunction & psychotic disorders

In another study, psychosis was associated with hypothyroidism, especially in women; and in most of their studied cases, psychiatric symptoms were apparent before thyroid symptoms [31]. The association of hypothyroidism and psychosis was reported in other studies [32,33].

It has been shown that patients with schizophrenia have altered circadian rhythm patterns compared with the healthy population. These changes may be associated with alterations in neurotransmitters in the hypothalamus and other regions of the brain. It should be noted that serum TSH has been shown to be lower and to have a blunted response to TRH in this patient population [34,35].

#### Thyroid dysfunction & affective disorders

Other factors such as glucocorticoids have been shown to be elevated in depression. The resolution of depressive symptoms has been accompanied by decline in cortisol levels [36]. Glucocorticoids have been shown to inhibit TSH secretion and thyroid function [37,38]. Glucocorticoids cause a loss of the nocturnal surge of TSH, which is mediated in the hypothalamus and higher CNS centers [36–38].

It has been shown that lower levels of serum TSH may be a risk factor for switching over from depression into manic states in bipolar depressed patients [39]. Only patients with low levels of TSH, and none with high levels of TSH experienced a switch to manic state.

#### Thyroid dysfunction & stress

Thyroid hormone imbalances have also been associated with high levels of acute stress. TSH levels may fluctuate as a response to intense periods of stress, and even after elimination of certain stressors [40]. Our patient was admitted with symptoms of agitation, hostility and aggression – symptoms that may be associated with an increased metabolic rate and with situations in which the body reacts to a stressful situation. Stress hormones (epinephrine, norepinephrine and cortisol)

are present at high levels in these situations. Numerous studies show that chronic stress exerts an increased burden on the adrenal glands [29]. Hypothalamic and pituitary function may then be suppressed by negative feedback effects of glucocorticoids. In addition, studies have shown that during the stress response, inflammatory cytokines IL-1 $\beta$ , IL-6 and TNF- $\alpha$  are released [30]. These mediators are thought to downregulate the hypothalamopituitary axis and reduce levels of TSH [30]. It was demonstrated that in carp fish, IL-1 $\beta$  expression in the hypothalamus is upregulated following stress, as well as IL-1 receptor in the periphery (kidney). The study provided evidence for bidirectional communication between hypothalamopituitary axis and the immune system [41].

### Conclusion & future perspective

In acutely psychotic patients, thyroid function abnormalities may be present initially and resolve with treatment of the psychosis. The presence of systemic illness, malnutrition and binding protein abnormalities must also be considered as contributors to the thyroid function test abnormalities. In the absence of evidence suggesting intrinsic thyroid dysfunction,

and a normal or mildly elevated free thyroxine level, specific treatment for the thyroid dysfunction may be withheld pending monitoring of the thyroid function tests. Premature treatment of these abnormalities may be counterproductive particularly in the elderly. If thyroid function abnormalities persist after 2 weeks, further clinical evaluation should be done to diagnose the cause of thyroid dysfunction.

### Disclosure

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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