

Case Report

Myxedema madness: exploring a reversible psychosis with case review and discussion

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ABSTRACT

Myxedema madness is a rare but severe neuropsychiatric manifestation of profound hypothyroidism, frequently mistaken for primary psychiatric illness due to its striking psychotic symptoms. We present the case of a 52-year-old woman with no prior psychiatric history who developed progressive persecutory delusions, auditory hallucinations, cognitive impairment, and psychomotor slowing over three months. Despite initial treatment with antipsychotics, her symptoms persisted. A broader clinical assessment, prompted by systemic features including weight gain, cold intolerance, constipation, menorrhagia, and generalized swelling, led to the diagnosis of severe hypothyroidism (TSH >100 mIU/L, free T4 <0.3 ng/dL) due to Hashimoto's thyroiditis. Levothyroxine replacement therapy resulted in the complete resolution of both psychiatric and systemic symptoms within six weeks. This case emphasizes the necessity of thyroid function screening in atypical psychosis, underscoring how early recognition can prevent misdiagnosis and unnecessary psychiatric treatment. A comprehensive discussion contextualizes this case within the existing literature, reinforcing its clinical significance.

Keywords: Myxedema madness, Hypothyroidism, Psychosis, Thyroid hormone replacement, Reversible

INTRODUCTION

Hypothyroidism, a common endocrine disorder, can present with a spectrum of symptoms ranging from subtle fatigue and weight gain to dramatic neuropsychiatric disturbances.¹ Among these, "myxedema madness" stands out as a rare but striking phenomenon where severe hypothyroidism manifests as florid psychosis, historically documented yet frequently overlooked due to its close resemblance to primary psychiatric disorders such as schizophrenia or major depressive disorder with psychotic features.²

The pathophysiological basis of this condition involves complex alterations in neurotransmitter metabolism, reductions in cerebral perfusion, and neuroinflammatory processes, although these mechanisms are not yet fully elucidated.³ Given its complete reversibility with appropriate thyroid hormone replacement therapy, early recognition is paramount to prevent unnecessary

psychiatric interventions and prolonged patient morbidity.⁴ This case report aims to illuminate the clinical presentation, diagnostic challenges, and therapeutic outcomes of myxedema madness, complemented by an extensive literature review to enhance clinical understanding and awareness.

CASE REPORT

Case history

A 52-year-old woman with no prior psychiatric history presented with a three-month course of progressively worsening neuropsychiatric symptoms. Her family reported a gradual decline in cognition, characterized by increasing confusion, memory impairment, and a significant reduction in verbal output. The patient exhibited persecutory delusions, firmly believing that her neighbours were conspiring against her, alongside auditory hallucinations consisting of threatening, non-

command voices. Psychomotor retardation was also noted, with marked sluggishness and a blunted affect. She had initially sought medical attention at a local clinic, where she was empirically prescribed antipsychotic medication (specific agent and dosage undisclosed). However, her symptoms persisted without significant improvement.

A more comprehensive history uncovered a year-long progression of systemic manifestations suggestive of hypothyroidism, including unexplained weight gain, cold intolerance, chronic constipation, prolonged menorrhagia, and generalized non-pitting edema. There was no history of head trauma, substance use, autoimmune disorders, or prior psychiatric illness in the patient or her family.

Given the constellation of neuropsychiatric and systemic symptoms, further evaluation was pursued to investigate an underlying organic etiology.

Physical examination findings

Upon physical examination, the 52-year-old female patient presented with a temperature of 35.8°C, a pulse of 54 beats per minute, blood pressure of 110/70 mmHg, a respiratory rate of 14 breaths per minute, and an oxygen saturation of 98% on room air, indicating mild hypothermia and bradycardia. She appeared disoriented, with coarse, dry skin and periorbital puffiness suggestive of myxedema, alongside non-pitting edema noted on her skin, consistent with hypothyroidism.

Neurologically, she exhibited slowed speech, delayed deep tendon reflexes, mild cognitive impairment with a mini-mental state examination (MMSE) score of 22 out of 30, and cerebellar ataxia, reflecting significant neurological involvement.

Her cardiovascular examination confirmed bradycardia without murmurs, while psychiatrically, she displayed blunted affect, poverty of speech, and persistent persecutory delusions, underscoring her psychotic state. Respiratory and gastrointestinal examinations were unremarkable, showing no additional systemic abnormalities beyond those linked to her hypothyroid condition.

Provisional diagnoses

The constellation of neuropsychiatric symptoms prompted a broad differential, including late-onset schizophrenia, major depressive disorder with psychotic features, dementia, autoimmune encephalitis, vitamin deficiencies, metabolic encephalopathy, and hypothyroidism.

Investigations

To refine the diagnosis, a comprehensive panel of laboratory tests and imaging studies was conducted.

The results revealed a markedly elevated thyroid-stimulating hormone (TSH) level exceeding 100 mIU/l and an undetectable free thyroxine (T4) level (<0.3 ng/dL), confirming severe hypothyroidism. Elevated anti-thyroid peroxidase (anti-TPO) antibodies suggested an autoimmune etiology, likely Hashimoto's thyroiditis. Mild pericardial effusion, a recognized complication of hypothyroidism, was observed on echocardiogram, while a normal brain MRI ruled out structural pathology.

Differential diagnoses

Schizophrenia or primary psychotic disorder

The acute onset of persecutory delusions and hallucinations initially raised suspicion for a primary psychotic disorder. However, the absence of prior psychiatric history, along with systemic hypothyroid symptoms such as bradycardia, Myxedema, and cognitive slowing, made this diagnosis unlikely.

Major depressive disorder with psychotic features

The patient's psychomotor retardation could have been mistaken for depression with psychotic features. However, the presence of profound cognitive impairment and myxedematous facies strongly suggested hypothyroidism as the primary cause rather than a primary mood disorder.

Autoimmune encephalitis

Given the neuropsychiatric presentation, autoimmune encephalitis was considered. However, negative autoimmune markers and a normal MRI effectively ruled out an underlying neuroinflammatory process.

Metabolic encephalopathy

Hepatic, uremic, or severe electrolyte-related encephalopathies were considered as possible explanations for the altered mental status. However, normal liver and kidney function tests, with only mild hyponatremia, made this diagnosis unlikely.

Vitamin B12 or folate deficiency

Deficiency-related neuropathies and dementias can present with cognitive dysfunction and neuropsychiatric symptoms. However, normal serum B12 and folate levels excluded this as a contributing factor.

Paraneoplastic syndromes

The presence of psychosis and cognitive impairment warranted consideration of an underlying malignancy-associated paraneoplastic process. However, comprehensive imaging and tumour marker studies showed no evidence of malignancy.

Final diagnosis

The final diagnosis of Myxedema madness was established based on the patient's clinical presentation, laboratory confirmation of severe hypothyroidism, and striking response to thyroid hormone replacement therapy.

Treatment and outcome

The patient was initiated on levothyroxine 100 mcg/day, with gradual titration based on serial thyroid function tests. Supportive measures included electrolyte correction, fluid balance monitoring, and nutritional optimization. Antipsychotic medications were

discontinued, as thyroid hormone replacement was expected to resolve the psychiatric symptoms.

Within two weeks, significant improvements were observed in cognitive function, affect, and orientation. By six weeks, the patient achieved a euthyroid state, with complete resolution of psychotic symptoms.

Follow-up

Follow-up assessments at three and six months confirmed normalization of TSH and free T4 levels. Neurocognitive evaluations demonstrated a full return to baseline function, with no residual psychiatric disturbances.

Table 1: Hematologic, metabolic and radiologic investigations of the patient.

Test	Patient value	Reference range
TSH	>100	0.4-4.2 mIU/l
Free T4	<0.3	0.8-1.7 ng/dl
Anti-TPO Antibody	Positive (3+)	Negative
Haemoglobin/WBC/Platelets	10.5/6,500/220,000	12-16 g/dl/4,000-11,000/150,000-450,000
MCV	89	80-100 fl
ESR / CRP	18/2.1	<20 mm/hr/<5 mg/l
Bilirubin/AST/ALT/ALP	0.8/30/25/90	0.1-1.2/8-40/7-56/30-120U/l
Creatinine/BUN	0.9 / 15	0.6-1.3/7-20 mg/dl
Na/K/Ca/Phos/Mg	133/4.2/9.1/3.8/2.0	135-145/3.5-5.1/8.5-10.5/2.5-4.5/1.7-2.4 mmol/l
Cortisol/PTH	12/35	5-25 mcg/dl/10-65pg/ml
Vitamin B12/D3	450/22	200-900/30-100 pg/ml
Fasting Glucose / HbA1c	92/5.3	70-100 mg/dl/ 4.0-5.6%
Chol/LDL/HDL/TG	190/120/45/130	<200/<130/>40/<150 mg/dl
Ferritin/Iron/TIBC	110/75/310	20-300 ng/ml/60-170/250-400 mcg/dl
HIV/HBsAg/HCV	Negative	Negative
Urinalysis (Protein/RBC/WBC)	Negative/0-1/1-2	Negative/<3/<5 per HPF
MRI Brain/EEG	Normal	
Echocardiogram	Mild pericardial effusion	

Table 2: Comparison table of some previous studies.

Study	Key symptoms	Findings	Treatment	Outcome
Krüger et al¹⁶ (Literature review)	Psychosis, cognitive impairment	Low T3/T4, high TSH	Levothyroxine	Recovery in most cases
Mohamed et al¹⁷ (Systematic review)	Delusions, mood changes	Severe hypothyroidism	Thyroid replacement	Significant improvement
Parikh et al¹⁸ (Case report)	Persecutory delusions, hallucinations	High TSH	Levothyroxine 100 mcg/day	Resolved in 2 weeks
Omri et al¹⁹ (Case report)	Psychotic features, paranoia	Hypothyroidism, bradycardia	T3/T4 + psych support	Full recovery
Thappa et al²⁰ (Case report)	Suicidal thoughts, paranoia	Profound hypothyroidism	Levothyroxine + psych care	Gradual recovery

DISCUSSION

Myxedema madness exemplifies the profound neurological and psychiatric effects of severe hypothyroidism.² Its rarity, combined with its striking

mimicry of primary psychiatric disorders, often leads to misdiagnosis and significant delays in appropriate treatment. The pathophysiology of this condition is not fully elucidated but is believed to involve multiple intricate mechanisms that disrupt normal brain function.

Thyroid hormones play an essential role in maintaining neuronal excitability, neurotransmitter homeostasis, and cerebral metabolism.⁵ A deficiency in thyroxine (T4) leads to widespread brain dysfunction through several pathways.

Neurotransmitter dysregulation

Hypothyroidism reduces serotonin and dopamine synthesis, contributing to depression-like symptoms, while impaired catecholamine activity may precipitate psychosis.⁴

Blood-brain barrier dysfunction

Thyroid hormones regulate the integrity of the blood-brain barrier (BBB); hypothyroidism weakens this barrier, allowing toxic metabolites and inflammatory mediators to accumulate in the central nervous system.⁶

Cerebral hypoperfusion

Studies using functional imaging have demonstrated decreased cerebral blood flow in hypothyroid patients, particularly in the frontal lobes, which are critical for cognition and behavior regulation.⁷

Glial cell dysfunction and neuroinflammation

Thyroid hormone deficiency impacts astrocytes and microglia, leading to neuroinflammation and impaired synaptic function, which can manifest as psychosis and cognitive dysfunction.^{8,9}

This case stands out due to its predominant presentation of persecutory delusions and auditory hallucinations, contrasting with the more frequently reported depressive features in the literature. Additionally, the patient's TSH level exceeding 100 mIU/l highlights the severity of hypothyroidism as a driver of these neuropsychiatric symptoms, emphasizing the need for thyroid function testing in atypical psychiatric presentations.¹⁰

Comparison with other endocrinopathies

Myxedema madness shares some overlapping features with other endocrine disorders that can precipitate neuropsychiatric symptoms, necessitating careful differentiation. Hyperthyroidism, for example, can present with agitation, anxiety, or even psychosis, but it is characterized by tachycardia, heat intolerance, and elevated thyroid hormone levels, findings diametrically opposed to our patient's hypothyroid profile.¹¹ Cushing's syndrome may mimic hypothyroidism with cognitive slowing and depression, but it is distinguished by hypertension, central obesity, and elevated cortisol levels, none of which were present here.¹²

Addison's disease, another endocrine condition, can cause fatigue and hyponatremia similar to our patient's

mild sodium imbalance, but it was excluded by normal cortisol levels.¹³ These comparisons highlight the critical role of a comprehensive hormonal panel in distinguishing myxedema madness from other endocrine mimics, reinforcing its unique feature of complete reversibility with thyroid hormone replacement.¹⁴

Broader clinical implications

The initial misdiagnosis of this case as a primary psychiatric disorder, leading to the use of antipsychotics without benefit, reflects a broader challenge in clinical practice. Psychiatric symptoms often dominate the clinical picture, overshadowing subtler systemic clues such as cold intolerance, weight gain, or bradycardia, which can delay endocrine evaluation. This aligns with previous reports noting unnecessary psychotropic interventions in myxedema madness, a pitfall that unnecessarily prolongs patient suffering and increases healthcare costs.^{4,5,15} This case underscores the need for routine thyroid function screening in patients presenting with acute psychosis, particularly in middle-aged women demographic at heightened risk for autoimmune hypothyroidism like Hashimoto's thyroiditis, as suggested by our patient's elevated anti-TPO antibodies. Enhanced awareness among clinicians could prevent such diagnostic errors and expedite appropriate therapy.

Comparative analysis with previous studies

The comparative analysis of previous studies on Myxedema madness and our current case highlights both commonalities and unique aspects. Most studies, including ours, report a strong association between severe hypothyroidism and psychotic symptoms such as paranoia, hallucinations, and cognitive dysfunction. Biochemical findings across all cases consistently show elevated TSH with low T3/T4 levels, reinforcing the role of thyroid hormone deficiency in neuropsychiatric manifestations.

Treatment with levothyroxine has universally resulted in symptom resolution, though the speed of recovery varies depending on the severity and duration of untreated hypothyroidism. While earlier studies have documented similar psychiatric presentations, our study adds a more detailed investigation, including neuroimaging and extended follow-up, to assess the course of recovery. Furthermore, our case emphasizes the importance of early thyroid screening in unexplained psychosis, as delayed diagnosis can prolong symptom resolution. This study, therefore, aligns with existing literature while providing additional insights into the variability of presentation, diagnostic challenges, and long-term outcomes in Myxedema madness.

Future perspectives

The rarity of myxedema madness poses significant challenges for systematic study, yet its full reversibility

offers substantial hope for improved patient outcomes with increased clinical awareness.^{4,8,14,16,19} Future research could explore the use of biomarkers to enhance diagnostic precision and elucidate the condition's underlying mechanisms. For instance, functional imaging studies, such as single-photon emission computed tomography (SPECT), could quantify cerebral blood flow changes in affected patients, providing a measurable correlate to the observed hypoperfusion.⁷

Similarly, analysis of cerebrospinal fluid for inflammatory markers might clarify the role of neuroinflammation in symptom genesis.⁸ Prospective cohort studies examining the prevalence of subclinical or overt hypothyroidism in psychiatric populations could provide critical data on how frequently this condition is missed, potentially refining screening guidelines and reducing diagnostic delays.⁹ From a therapeutic perspective, investigating adjunctive treatments, such as anti-inflammatory agents to address neuroinflammation alongside levothyroxine, could accelerate recovery in severe cases, offering a novel approach to management.⁶

The integration of point-of-care thyroid function testing into standard psychiatric workups could further streamline diagnosis, minimizing the time from presentation to effective treatment.¹⁰ Educational initiatives targeting primary care physicians and psychiatrists could bridge the existing knowledge gap, ensuring that myxedema madness is routinely considered alongside more common differentials like schizophrenia or bipolar disorder. Such efforts could transform clinical practice, making this reversible condition a standard part of the diagnostic lexicon.

Public health relevance

Given the global burden of undiagnosed hypothyroidism, particularly in regions with iodine deficiency, myxedema madness may be more prevalent than currently recognized.^{10,20} Its complete reversibility stands in stark contrast to the chronicity of primary psychiatric disorders, positioning it as a critical target for public health screening initiatives.¹ Enhanced collaboration between endocrinologists and psychiatrists could lead to the development of integrated diagnostic algorithms, reducing the likelihood of misdiagnosis and its associated costs, both financial and human.³ By prioritizing early detection and treatment, healthcare systems could improve patient quality of life, decrease reliance on long-term psychiatric medications, and optimize resource allocation.

CONCLUSION

Myxedema madness remains an underrecognized but fully reversible cause of psychosis that demands greater clinical awareness. Routine thyroid function screening should be a standard practice in all patients presenting with acute or atypical psychiatric symptoms, particularly

in middle-aged individuals who may be at higher risk for hypothyroidism. Early diagnosis and thyroid hormone replacement therapy lead to complete symptom resolution, preventing unnecessary antipsychotic use and prolonged morbidity. This case underscores the vital intersection of endocrinology and psychiatry, with future research and educational efforts poised to enhance recognition and management of this treatable condition.

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