CLINICAL PRACTICE

*Clinical Vignette*

# Wet Beriberi Associated with Hikikomori Syndrome

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Wet beriberi, characterized by high cardiac output with predominantly right-sided heart failure and lactic acidosis, is a disease caused by thiamine deficiency, and is rarely seen in modern society. However, patients with social withdrawal syndrome, also known as hikikomori syndrome, may be a new population at risk of thiamine deficiency. Hikikomori syndrome, first recognized in Japan, is becoming a worldwide issue. A 39-year-old Japanese patient was brought to our hospital, with a 3-week history of progressive shortness of breath and generalized edema. The patient had right-sided high-output heart failure, lactic acidosis, and Wernicke–Korsakoff syndrome. Because of his history of social isolation, we diagnosed hikikomori syndrome according to the Japanese government's definition, which is as follows: lifestyle centered at home; no interest or willingness to attend school or work; persistence of symptoms beyond 6 months; and exclusion of other psychiatric and developmental disorders. Considering his diagnosis of hikikomori syndrome and social isolation, we suspected malnutrition, particularly thiamine deficiency, and successfully treated him. Clinicians should be aware of the potential risk of thiamine deficiency associated with hikikomori syndrome and initiate thiamine replacement in cases of high-output heart failure associated with lactic acidosis.

*KEY WORDS:* thiamine deficiency; beriberi; heart failure; Korsakoff syndrome; high cardiac output.
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## INTRODUCTION

Hikikomori is a Japanese word meaning social withdrawal. Hikikomori syndrome is a modern problem that was first recognized in Japan and is increasing worldwide.[1] It usually affects young adults who isolate themselves from the world by staying in their home or bedroom for days, months, or even years without communicating with others.[2] As a result of their prolonged isolation, they may develop malnutrition, including thiamine deficiency, which can lead to cardiac beriberi. We report a rare case of hikikomori syndrome with wet beriberi complicated by Wernicke–Korsakoff syndrome.

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## CLINICAL PRESENTATION

A 39-year-old previously healthy man was brought by ambulance to our emergency department (ED) with a 3-week history of progressive generalized weakness. He was not able to provide reliable information, due to amnesia. His parents stated that he had worked, socialized with others, and lived with his parents until 1 year prior to admission, when he quit his job. Thereafter, he became isolated from society and started to live by himself. Although his story was incoherent, he repeatedly mentioned that he mostly consumed instant noodles. He denied a history of alcohol or illicit drug use. Three weeks prior to admission, he gradually started to feel fatigue, shortness of breath, and generalized edema, and he was unable to ambulate independently when he was brought to the ED. On arrival, his vital signs were as follows: blood pressure, 130/50 mmHg; heart rate, 115 beats/min; respiratory rate, 30 breaths/min; body temperature, 36.6 °C (97.8 °F); and oxygen saturation, 99% on room air. He had jugular vein distension and prominent generalized pitting edema, with clammy, cyanotic skin on all extremities. A III/VI systolic ejection murmur was found at the left sternal border in the second intercostal space. Breath sounds were clear bilaterally. He was alert and oriented, but he provided an incoherent history suggestive of confabulation. No external ophthalmoplegia and no sensory abnormalities were noted, but he had mildly decreased muscle strength, with hyporeflexia of the deep tendons in all extremities. Blood cell counts were normal. Metabolic panels showed electrolyte disturbance and azotemia, with sodium of 126 mmol/L, potassium of 4.7 mmol/L, chloride of 95 mmol/L, $HCO_3^-$ of 6.8 mmol/L, urea nitrogen of 41.4 mg/dL (14.8 mmol/L), and creatinine of 1.21 mg/dL (107 μmol/L). The arterial lactate level was severely elevated to 7.1 mmol/L (normal range: < 1.0 mmol/L). Thyroid function was normal. Brain natriuretic peptide (BNP) level was 236.8 pg/mL (normal range: < 18.3 pg/ml). Chest radiography showed cardiomegaly with an enlarged right heart border and prominent pulmonary trunk, with no evidence of congestion. Electrocardiogram was normal. Because of the concern for right-sided heart failure, chest CT with contrast and echocardiography were performed. CT scan showed no evidence of pulmonary embolism. Echocardiography demonstrated a hyperdynamic state, with left ventricular ejection fraction of 68%. Marked right atrial and ventricular dilation was found (Fig. 1a). Mild tricuspid

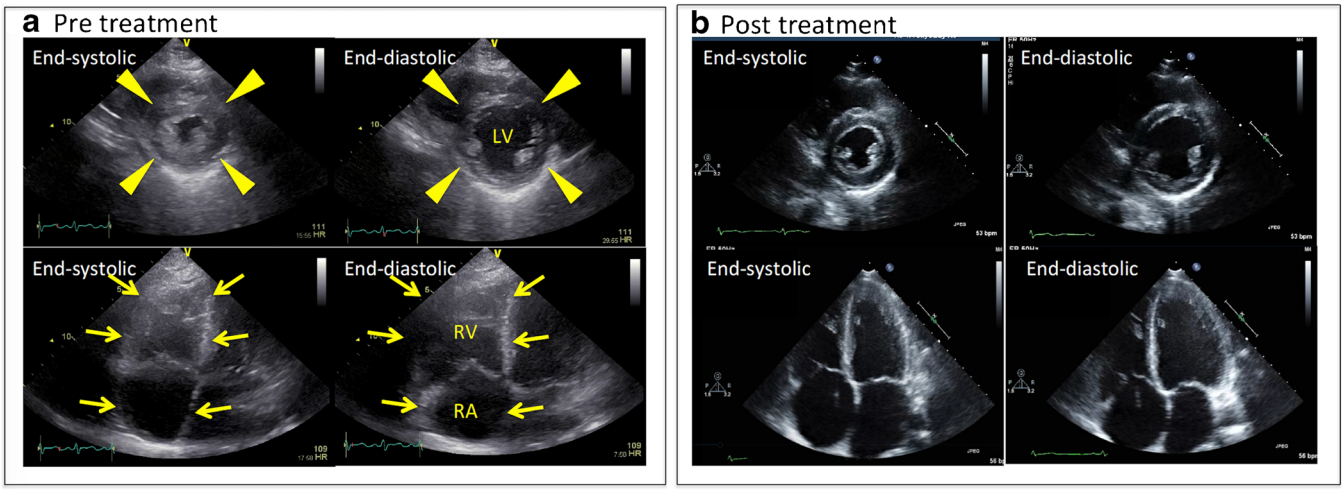


**Figure 1** Upper images show parasternal short-axis views and lower images demonstrate echocardiographic apical four-chamber views (end-diastole on the left and end-systole on the right) on arrival (a) and on day 11 after admission (b). On arrival, the left ventricle (LV) was hyperdynamic, with an ejection fraction of 68% (arrowheads). The right atrium (RA) and ventricle (RV) were enlarged (48 mm and 50 mm, respectively; (arrows). The hyperdynamic state of the left ventricle and the size of the right ventricle improved to normal after treatment with thiamine and furosemide (b).

regurgitation with an estimated systolic pulmonary artery pressure of 58 mmHg was noted. For further evaluation of his pulmonary hypertension, the patient underwent pulmonary artery (PA) catheter evaluation 10 h after arrival, which showed extremely high cardiac output of 15 L/min and low systemic vascular resistance of 343 dyne/s/cm$^{-5}$. Pulmonary artery pressure and right ventricular pressure were elevated, with normal pulmonary artery occlusion pressure and pulmonary vascular resistance. These findings were consistent with right-sided heart failure with pulmonary hypertension due to very high cardiac output (Table 1).

Because of his history of social isolation for more than 6 months, we diagnosed hikikomori syndrome according to the Japanese government's definition,[1] which is as follows: lifestyle centered at home; no interest or willingness to attend school or work; persistence of symptoms beyond 6 months; and the exclusion of other psychiatric and developmental disorders. Those who maintain personal relationships (e.g., friendships) are excluded from having this condition. Although it was difficult to rule out other psychiatric diseases in our patient, due to amnesia, he did not present with a depressive mood, hallucinations, delusion, or agitation. His parents stated that he did not have any mental development abnormalities and had previously communicated with others without difficulty.

Despite scarce knowledge of the patient's lifestyle due to amnesia, because of our suspicion of thiamine deficiency-induced wet beriberi and Wernicke–Korsakoff syndrome, empiric treatment with intravenous thiamine (vitamin B1) infusion was started, along with furosemide for edema, on the day of his admission, while waiting for his serum thiamine lab test results. A drastic improvement in edema and lactic acidosis was observed on day 2. The patient's pulmonary hypertension and hyperdynamic state were significantly improved on follow-up echocardiography on day 11. The size of the right ventricle also normalized (Fig. 1b). Blood cultures remained negative.

The patient's amnesia and confabulation gradually improved. His serum thiamine lab test result was eventually received, and was low at 1.72 mcg/dL (normal range, 2.5–7.5 mcg/dL). Based on his excellent response to thiamine administration in the setting of low serum thiamine level, thiamine deficiency was diagnosed.

**Table 1 Results of Pulmonary Artery Catheterization**

| Parameter | Value | Normal range |
|---|---|---|
| Right atrium (mmHg) | 11 | 1–5 |
| Right ventricle (systole/diastole mmHg) | 44/7 | 15–28/0–8 |
| Pulmonary artery (systole/diastole mmHg) | 41/15 (mean, 27) | 15–28/5–16 (mean, 16) |
| Pulmonary capillary wedge (mmHg) | 7 | 6–15 |
| Cardiac output (L/min) | 15.6 | N/A |
| Pulmonary vascular resistance (dyne/s/cm$^{-5}$) | 107 | 45–120 |
| Systemic vascular resistance (dyne/s/cm$^{-5}$) | 343 | 900–1400 |

*N/A not applicable*

## DISCUSSION

Hikikomori syndrome, also called social withdrawal syndrome, is a social issue originally reported in Japan.[1] It has now been reported in countries throughout the world, including the United States, France, India, Hong Kong, South Korea, Italy, Spain, and Oman.[3] It occurs in approximately 1−2% of adolescents and young adults in Asian countries.[4–6] In the United States, its prevalence has not been reported. However, the first case was reported in 2013, and a recent international survey of psychiatrists suggested that the prevalence and

features of hikikomori syndrome did not differ between Asian countries and the United States.[7,8]

The first criterion established by the Japanese Ministry of Health, Labor, and Welfare in 2003 excluded other psychiatric diseases for the diagnosis of hikikomori syndrome.[1] However, it is now considered that it could be related to multiple psychiatric diseases.[2,9] A recent epidemiological survey in Japan reported that approximately half of hikikomori patients experienced psychiatric disorders (mood, anxiety, impulse control, or substance-related) at some point in their lifetime, including before, after, or during the year of onset of hikikomori.[4] Hikikomori syndrome without and with currently recognized psychiatric disorders is called primary and secondary hikikomori, respectively. Primary hikikomori can be regarded as a new psychiatric disorder.[3,10] However, inconsistency still exists in terms of which psychiatric disorders among the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) psychiatric disorders are to be excluded in order to diagnose primary hikikomori.[3] Our patient did not have manifestations of psychiatric signs and symptoms except for amnesia; therefore, his hikikomori was thought to be of the primary type.

The etiology of hikikomori is unclear. Aversive childhood experiences, such as social exclusion, have been associated with hikikomori.[3] Risk factors can include dysfunctional family dynamics and parental rejection as well as overprotection.[3] Hikikomori patients refuse to communicate and often use the internet profusely, with approximately one-tenth of hikikomori patients reportedly meeting the diagnostic criteria of internet addiction.[2] Although there is an overlap of the two, it is unclear whether internet addiction is a risk factor for hikikomori syndrome.[2] In our case, the patient and his family denied any history suggestive of internet addiction.

A few reports from Japan have suggested that hikikomori patients are at risk of malnutrition.[11,12] However, hikikomori patients actually have a low risk of malnutrition, because they often live with family members who provide food.[1] One study, however, found that 11% of hikikomori patients were living alone, which could indicate malnutrition risk.[13] Hikikomori patients prefer to remain isolated in their own rooms as much as possible. As a result, we believe they eat many preserved foods (such as ramen, udon, and soba), as our patient did, many of which do not include enough thiamine. A case of thiamine deficiency was reported in a Japanese hikikomori patient who was eating only instant noodles.[11]

The main sources of thiamine are whole grains, cereals, meat (especially pork), vegetables, and dairy products.[14] A low intake of thiamine due to starvation, excessive and prolonged vomiting, or an unbalanced diet of preserved food can lead to deficiency.[15] Thiamine reserves in the body amount to only 30 mg and are depleted after only 20 days of inadequate oral intake.[16] Thiamine deficiency can also be induced by loss of thiamine due to the use of loop diuretics, dialysis, or parenteral nutrition.[14] In addition, high consumption of carbohydrates or alcohol[17] and stressful conditions such as infections will accelerate the Krebs cycle and thiamine utilization, which may aggravate thiamine deficiency.[18] Our patient mentioned that he was mainly eating instant noodles. Although most instant-cup type noodles now contain artificial thiamine, some noodle products still do not. A single portion of udon, soba, and ramen contains 0.1 mg, 0.37 mg, and 0.03 mg of thiamine, respectively.[19] These can be purchased as dried preserved noodles.[19] Considering that 1.1–1.5 mg of thiamine intake per day is necessary to prevent its deficiency, these noodles do not provide an adequate amount of thiamine.[16] The active form of thiamine, thiamine pyrophosphate (TPP), is an important cofactor for several enzyme reactions of cell regulatory processes, biosynthesis, and metabolism.[16] Therefore, thiamine deficiency results in defects in cell synthesis, repair, and replication, and impaired acetylcholine synthesis in the central nervous system.[16] In addition, a sufficient amount of TPP in the nerves and muscles is important for activating the transport of sodium and potassium.[16] Therefore, thiamine deficiency produces various neuromuscular manifestations.[16] TPP is also essential in the conversion of pyruvate to acetyl-CoA during the Krebs cycle. The accumulated pyruvate in thiamine deficiency will be converted to lactic acid through the anaerobic pathway.[20]

Classically, thiamine deficiency, or beriberi, is divided into two major types: dry and wet beriberi. Dry beriberi has predominant features of peripheral neuropathy such as motor weakness and areflexia.[15] Cerebral beriberi is a special form of dry beriberi that manifests with Wernicke–Korsakoff syndrome.[15] Although Wernicke's encephalopathy manifests with mental status change, ataxia, and ophthalmoplegia, only 16% of patients have all three symptoms.[21] Mental status changes can occur in the form of global confusion (disorientation, drowsiness, apathy, indifference, incoherence in speech), memory disorder (mild memory impairment, amnesia), anxiety, fear, coma, and stupor.[21] Untreated thiamine deficiency can result in Korsakoff syndrome, which is often irreversible.[21] It is characterized by impaired formation of new memories, with relative preservation of other mental functions and confabulation.[21]

Wet beriberi causes right-sided heart failure and pulmonary hypertension with high cardiac output due to vasodilation.[1] The low systemic vascular resistance (vasodilation) of wet beriberi is caused by adenosine production and opening of the arteriovenous shunt in the arterioles of the somatic musculature.[22–24] The mechanism of adenosine release in beriberi is not clearly understood, but it is believed to be caused by a decrease in the acetyl-CoA level.[25] Pulmonary hypertension with wet beriberi is considered to be caused by high blood flow to the pulmonary artery and increased rapid venous return.[26] Other causes of high-output heart failure include thyrotoxic heart, anemia, cirrhosis, and sepsis; these conditions were ruled out in our patient. Shoshin beriberi is a fulminant, pernicious, advanced form of wet beriberi that is characterized by severe biventricular failure, variable cardiac output with vascular collapse, peripheral cyanosis, and

death.[27] This type of fulminant beriberi occurs when typical right-sided wet beriberi is left untreated or when the patient has underlying left ventricle dysfunction such as alcoholic cardiomyopathy.[28]We believe that we may have prevented progression to shoshin beriberi in our patient through timely diagnosis and prompt treatment with thiamine.

Our patient was diagnosed with wet beriberi complicated by Wernicke–Korsakoff syndrome, as evidenced by his high-output cardiac failure, pulmonary hypertension with severe lactic acidosis, amnesia, and confabulation, all of which improved after thiamine administration. Hikikomori syndrome may be a new risk factor for thiamine deficiency in modern society, especially for those living alone. Because wet beriberi can easily be treated with thiamine replacement, clinicians should consider the possibility of wet beriberi in patients with high-output cardiac failure associated with pulmonary hypertension and should start thiamine replacement therapy.

**Teaching points from the vignette**

1. Hikikomori syndrome (social withdrawal syndrome) is becoming a worldwide issue and may be a risk factor for thiamine deficiency.
2. Thiamine deficiency can occur due to daily consumption of preserved foods, which are often consumed by isolated hikikomori patients.
3. Clinicians should consider empirical thiamine replacement when encountering a hikikomori patient with critical illness, such as mental status changes or heart failure with lactic acidosis.

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***Compliance with Ethical Standards:***

***Conflict of Interest:*** *The authors declare that they do not have a conflict of interest.*

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