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Alcohol Dementia and Thermal Dysregulation: A Case Report and Review of the Literature

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Wernicke's encephalopathy and Korsakoff's psychosis in alcoholics are thought to be due to thiamine deficiency. When the process goes untreated, patients may develop alcohol-induced persisting dementia. We review the literature on thermal dysregulation and the place of thiamine treatment in Wernicke's encephalopathy, Korsakoff's psychosis, and alcohol-induced persisting dementia. We describe a patient with alcohol-induced persisting dementia who showed thermal dysregulation which responded to parenteral but not oral thiamine. Subsequently, he developed aspiration pneumonia with associated fever reaction and expired. We describe the neuroimaging findings—diffuse cortical atrophy, ventricular dilatation, atrophy of the corpus callosum, hypothalamus, and medulla, and a probable arachnoid cyst in the left temporal tip. We conclude that thermal dysregulation was likely related to dysfunction of temperature regulatory brain centers, that thermal dysregulation was stabilized with parenteral but not oral thiamine, and that parenteral thiamine may have a role even in chronic cases of alcohol-induced persisting dementia.

Keywords: dementia; thiamine; temperature regulation; fever; hypothermia; alcohol induced persistent dementia; Wernicke's Encephalopathy; Korsakoff Psychosis

Introduction

Definition

Alcohol is a potent neurotoxic drug. Wernicke's encephalopathy (WE) is an acute neurological syndrome usually presenting with diplopia, ataxia, and confusion. Korsakoff's psychosis (KP) is a chronic condition presenting with deficits in memory and confabulations. Wernicke's encephalopathy and KP are frequently lumped together under the term Wernicke-Korsakoff syndrome (WKS). Alcohol-induced persisting dementia (AIPD) is the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) term for dementia related to alcohol consumption requiring both memory impairment and another cognitive deficit such as aphasia, apraxia, agnosia, or disturbance in executive functioning.

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Neuropathology

The most common neuropathological changes seen in alcohol-related disease include symmetric lesions of the paraventricular parts of the thalamus and hypothalamus, mamillary bodies, periaqueductal gray, and floor of the fourth ventricle.[1]

Alcohol, Temperature Regulation, and the Hypothalamus

Disorders of temperature regulation have been described in alcoholics with either acute (ie, WE) or chronic (ie, KP) brain damage. The hypothalamus, responsible for appetite control, temperature regulation, and other vegetative functions, is known to be damaged by alcohol. In animals, experimental lesions in the posterior hypothalamus resulted in hypothermia, whereas lesions in the anterior hypothalamus resulted in hyperthermia.[2,3] In patients with WE and WKS, lesions of the posterior hypothalamus have been associated with hypothermia.[4-6] Likewise, hypothalamic lesions have been associated with hypothermia in patients with Alzheimer's dementia.[7,8]

However, although hypothermia has been described after hypothalamic damage, thermal dysregulation (ThD) may be a more accurate phenomenological description than hypothermia. Lipton et al described a patient with central nervous system (CNS) sarcoid granulomas involving the hypothalamus bilaterally, with damage to the preoptic (PO) and anterior hypothalamic regions. Despite significant hypothermia, the patient remained capable of developing fever in reaction to infection. The authors hypothesized that damage to these areas results in impairment of fine temperature regulation, but "coarse" temperature regulation, subserved by a different brain center such as the medulla oblongata, remains intact, and thus thermoregulatory responses in response to infections are possible. The authors reasoned that the observed temperature changes were best described as thermolability with poor regulation against ambient heat and cold.[9] Other case reports show similar relationship between hypothalamic damage and thermoregulatory problems.[10,11] Recent reviews of the neuroscience of temperature regulation suggest that although the brain stem and spinal structures are able to sense and initiate some thermoregulatory responses, the PO region of the hypothalamus has dedicated warm and cold sensitive neurons that integrate information from local hypothalamic temperature, core body temperature, and peripheral thermoreceptors. The PO exerts thermoregulatory control over lower effector areas in the brain stem and spinal cord.[12,13]

Thiamine's Role in the Pathogenesis of WE and KP

Thiamine (vitamin B_1) is enzymatically converted to a diphosphate ester, thiamine pyrophosphate (TPP), which serves as a coenzyme to intramitochondrial enzyme complexes responsible for the metabolism of carbohydrates and lipids.[14,15] Additionally, thiamine has been associated with parasympathetic neural activity and its deficiency leads to impaired nerve conduction, nerve transmission, and nerve damage.[14] Thiamine is involved in the production of acetylcholine, γ-aminobutyric acid (GABA), glutamate, aspartate, and 5-hydroxytryptamine (5-HT) and its deficiency leads to disruption in these neurotransmitter systems.[16]

Thiamine deficiency is thought to cause the development of both WE and KP. Primary thiamine deficiency results from inadequate nutrient and vitamin intake and is primarily observed in developing countries. In contrast, secondary thiamine deficiency can occur even when there is ample thiamine in the diet. Alcohol is a major reason for secondary thiamine deficiency in developed countries where 30% to 80% of alcoholics have been found to be thiamine deficient. Alcohol leads to thiamine deficiency through a number of mechanisms—reduced food intake, reduced gastrointestinal absorption (up to 90%) of thiamine (either from food or synthetic thiamine), defective thiamine transport through the intestinal wall, decreased hepatic storage, or impaired brain metabolism of thiamine in alcoholics.[6,13,16-18] The resulting thiamine deficiency causes neuronal damage by disrupting the blood–brain barrier, increasing free radicals and disrupting normal neuronal metabolism.[16,19,20] Decreased phosphorylation of thiamine to TPP results in reductions of TPP-dependent enzymes in the brains of alcoholic patients (eg, α-ketoglutarate dehydrogenase was shown to be reduced up to 97% in the vermis of alcoholics with WKS), mitochondrial dysfunction with decreased adenosine triphosphate (ATP) synthesis and energy production dysfunction, neuronal malfunction, and selective neuronal death.[21,22]

Alcohol may also exert neurotoxic effects that are separate and independent from its effects on thiamine. Experiments with thiamine-deficient chicks have shown that memory problems resulting from thiamine deficiency improve with thiamine supplementation, whereas memory problems from both alcohol exposure and thiamine deficiency are irreversible even with thiamine replacement.[16,23]

Thiamine Treatment for Alcohol-Related ThD

Given the role of thiamine deficiency in the pathogenesis of WE and WKS, attempts have been made to correct thiamine deficiency in alcoholics. In the acute setting, thiamine is used before glucose in people with coma of unknown etiology, especially if alcoholism or malnutrition are suspected. Because of thiamine's role in glucose metabolism, increasing glucose metabolism (eg, by administering intravenous glucose) increases the demand for thiamine, which may lead to exacerbation of the thiamine deficiency and further CNS damage.[1,16,21] Owing to irregularities in gastrointestinal absorption of oral thiamine (which could be especially decreased in alcoholics), parenteral forms of thiamine have been used to treat the symptoms of WE, including hypothermia, in the acute hospital setting.[5,6] Once discharged from the hospital, patients are often

switched to oral thiamine.[6] However, due to the above described problems with absorption, transport to the neurons and enzymatic conversion of thiamine, alcoholics may not be able to fully benefit from oral thiamine therapy.[16] Most studies describe the effects of thiamine treatment on temperature regulation during the acute stages of WE. Few studies have described the presence of hypothermia or thermolability in the chronic stage of KP and the effects of oral versus parenteral thiamine on treating this symptom. Here, we present a case report of ThD in a patient with AIPD ie, KP and its treatment with both oral and parenteral thiamine.

Case Presentation

History of Present Illness, Past Psychiatric and Past Medical History

The patient was a 74-year-old white male who was admitted to our inpatient medical psychiatry unit from his skilled nursing facility (SNF). Six months prior to admission, he developed a rash, started scratching himself. Three months prior to admission, he became lethargic, was started on unknown antibiotics. Over the past 2 months, the patient had frequently been agitated and at times assaultive toward SNF staff and residents. He became hyperphagic. His speech had become unintelligible even to his ex-wife who was his conservator. The rash had spread over his entire body.

The patient had a longstanding history of using alcohol. He had a history of blackouts but no seizures. He had no history of illicit drug use. He had a 35-pack-year history of smoking.

The patient had 1 prior admission to our hospital 9 years previously. He had drunk half a bottle of vodka 1 day prior to that admission. He was noted to be confused and confabulating. His blood pressure was 134/82, heart rate was 100 to 110 beats per minute, temperature was 99°C. He was treated for alcohol withdrawal and diagnosed with KP. A computed tomography of the brain showed significant cerebral atrophy. He continued having increased heart rate and temperature throughout that hospitalization. At discharge, he was stabilized but still confabulating.

Little is known about the patient's prior history or his history for the 9 years between the 2 admissions. Per his ex-wife, the patient had been demented and resided in an SNF.

The patient had a history of hypertension, poor dentition, benign prostatic hypertrophy, and urinary incontinence. There were no known drug allergies.

Social History

The patient attended 3 years of college and worked as a salesperson for the Royal Typewriter Advertising Agency. He also worked in real estate. He retired at the age of 60 and lived in a retirement facility in West Hartford in the early 1990s.

Physical, Neurological, and Mental Status Examination

The patient was 6 feet 2 inches tall, weighed 181 pounds. He was an older-looking gentleman, restless, but in no obvious distress. He had a diffuse maculopapular blanching rash on his skin. There was no evidence of infection. There was no lymphadenopathy. Lungs were clear to auscultation bilaterally. Cardiovascular examination revealed regular rate and rhythm, without murmurs, rubs, or gallop. Abdomen was soft, nontender, positive for bowel sounds. There was evidence of some urinary incontinence. Extremities were without edema or tenderness. On neurological examination, patient ambulated without assistance. However, his gait was slightly slow and ataxic. Cranial nerves II to XII were intact. Pupils were equal and reactive to light and accommodation. There was no gross motor deficit or sensory disturbance. The patient was nonverbal. The attending physician wrote, "Alert but does not respond to his name or to questions." Because of that, his thought process and content were difficult to assess. The patient was unable to describe his mood. His affect was irritable and labile.

Laboratory Studies on Admission

Valproic acid level was 53 mg/L, hemoglobin 11.1 g/dL, hematocrit 32.7%, WBC 5200, platelets 212 000, sodium 140 mEq/L, and potassium 4.7 mEq/L.

Medications on Admission

Divalproex sodium, aspirin, lisinopril, mirtazapine, risperidone, hydroxyzine, folate, thiamine 100 mg per day by mouth, and quetiapine p.r.n.

Diagnostic Evaluation on Admission

Axis I: AIPD; alcohol dependence, in sustained full remission.
Axis II: Deferred.
Axis III: Hypertension and urinary incontinence; diffuse maculopapular rash; dementia secondary to ethanol; benign prostatic hypertrophy.
Axis IV: Longstanding dementia; lives in an SNF; current global assessment of functioning (GAF) of 15.

Hospital Course

The patient was admitted to the medical psychiatry unit. During the first week of his hospital stay, his speech was disjointed, with nonsensical sounds. Thought process and content were difficult to evaluate. He was occasionally agitated but mostly tired. The dermatology service diagnosed the patient's rash as scabies, started him on permethrin cream, corticosteroids (Methylprednisolone), and anticholinergic agents (Hydroxyzine). Subsequently, the rash completely resolved. With the improvement of the rash, the patient's behavior improved as well. He responded well to the milieu of the unit and to a low-dose quetiapine 25 mg and lorazepam 1 mg as needed for agitation. Mirtazapine, risperidone, and divalproex were continued.

During his hospital stay, the patient experienced episodes of hypothermia. His body temperatures (obtained through serial axillary and rectal temperatures) decreased to 33.3°C. He was treated using warming blankets. Body temperatures fluctuated significantly throughout the day, between 32.8°C and 36.7°C (Figure 1). Hypothesizing that these changes may be due to hypothalamic damage, we ordered a brain magnetic resonance imaging (MRI) with thin slices through the hypothalamus. The MRI showed diffuse cortical atrophy, diffuse dilatation of the ventricles, corpus callosal atrophy, and a probable arachnoid cyst in the left temporal tip measuring 4 × 3 cm. On closer examination, there was prominent atrophy of the hypothalamus as well as the medulla (Figure 2). Because the absorption of oral thiamine varies greatly and is frequently impaired in alcoholics, we decided to start the patient on 100 mg intramuscular (IM) thiamine per day for 5 days. During the IM thiamine treatment, the patient's temperature stabilized between 34.4°C and 35.6°C without the dramatic fluctuations seen before. Following the discontinuation of IM thiamine, the patient's temperature tracked downward again. We restarted 100 mg intravenous (IV) thiamine per day 2 days later (see Figure 1 for temperatures and other vital signs during hospitalization). Meanwhile, the patient had shown evidence of poor swallowing, and 2 consecutive barium swallow evaluations showed evidence of aspiration. The patient developed right lower lobe aspiration pneumonia, which brought his temperatures toward the febrile range. He became mute and noninteractive. After a discussion with the family, his resuscitation status was changed to comfort measures only. He was started on a scopolamine patch for secretions, and intravenous morphine as needed for agitation or labored breathing. Warming blankets continued to be applied when needed. The patient died a few days later. The family decided not to pursue autopsy.

Conclusions and Discussion

Our case demonstrates that the disorder of temperature regulation in this patient with AIPD is more accurately described as ThD. Because most ambient environments are colder than the body temperature, most patients with hypothalamic damage present with a picture of hypothermia. Our patient's temperature was initially quite unstable and in the hypothermic range (32.8-36.7°C), stabilized with administration of 5 days of IM Thiamine (33.9-35.6°C), trended down after discontinuation of the IM Thiamine (33.3-34.4°C), but increased to fever range (35-37.8°C) when the patient developed aspiration pneumonia (Figure 1). Thus, his thermal disorder is best described as one of ThD rather than one of inadequate temperature production. This is consistent with Lipton's case who was also able to mount a fever response to infection, so his "broad band" or "coarse" thermal regulatory system was preserved.

Our patient's temperature curve did not parallel the other vital signs curves over time. Respiratory rate and oxygen saturation remained stable throughout the hospitalization until the patient developed aspiration pneumonia when the oxygen saturation decreased to below 95%. Blood pressure and heart rate fluctuated over time, but were mostly within the normal range and their fluctuations were not clearly affected by the parenteral Thiamine or the infection.

We initially hypothesized that the hypothalamus was involved because of the history of hyperphagia and hypothermia. The brain MRI showed multiple areas of atrophy including the hypothalamus, medulla, corpus callosum, and global brain atrophy (Figure 2). Of note, the MRI showed atrophy in 2 of the areas known to be involved in temperature

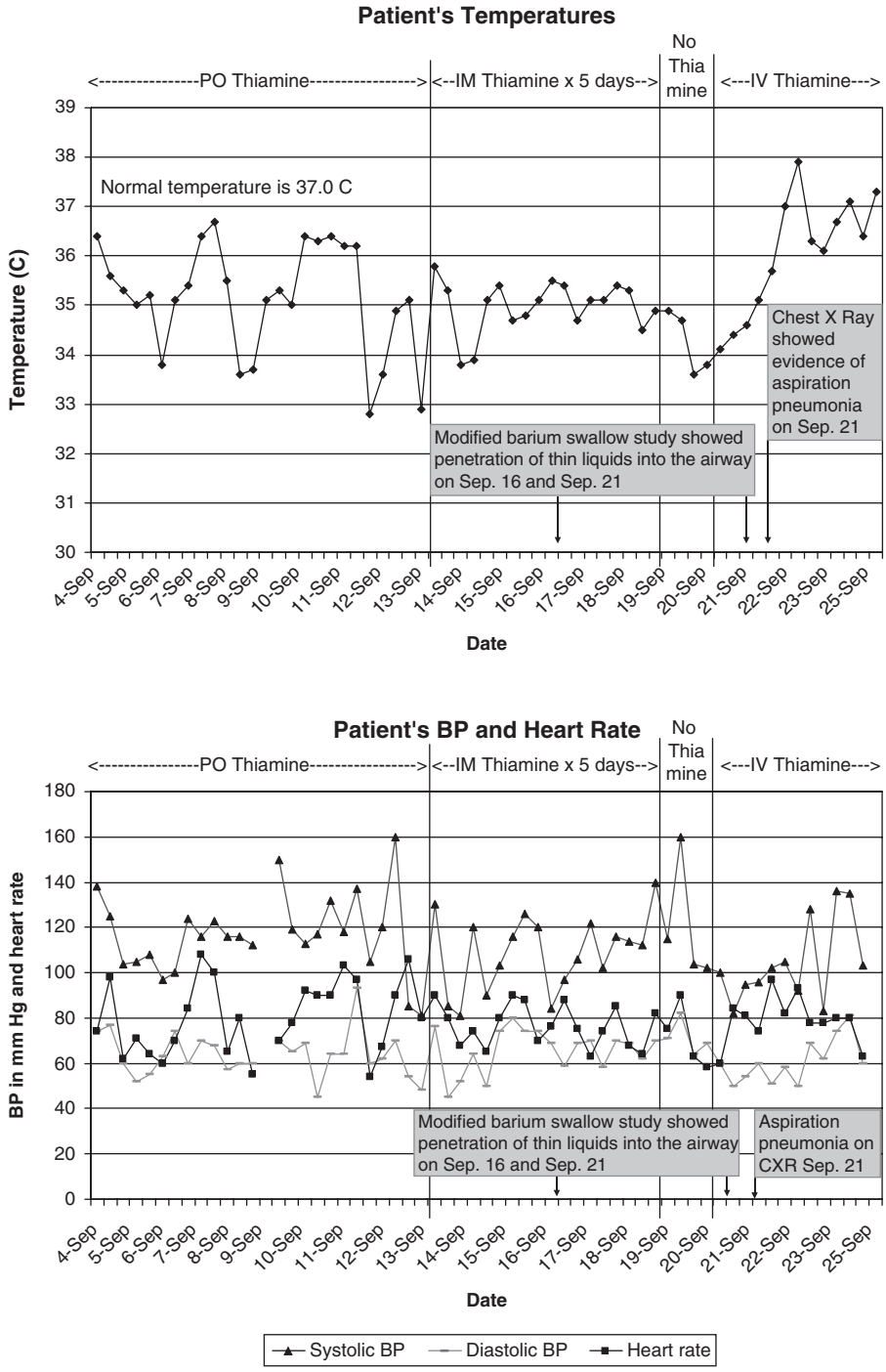

Figure 1. Temperature (in Celsius), systolic blood pressure, diastolic blood pressure, and heart rate measurements presented over the time of the patient's hospital stay. Diagnostic tests (modified barium swallow, chest radiograph) and times of oral/parenteral thiamine administration are plotted on the graph to show associations between these events and the temperature curve. BP, blood pressure; CXR, chest x-ray; HR, heart rate; IM, intramuscular; IV, intravenous; PO, by mouth; Sats, saturations.

regulation—the hypothalamus and medulla. Current thinking postulates that body temperature is regulated by the spine, brain stem, and hypothalamus in a hierarchical manner. Lower brain regions are capable of mounting a course temperature response on their own; the PO area of the hypothalamus achieves fine temperature regulation by integrating information from various sources and exerting control over lower brain effector centers. Because our patient showed the ability of mounting a fever

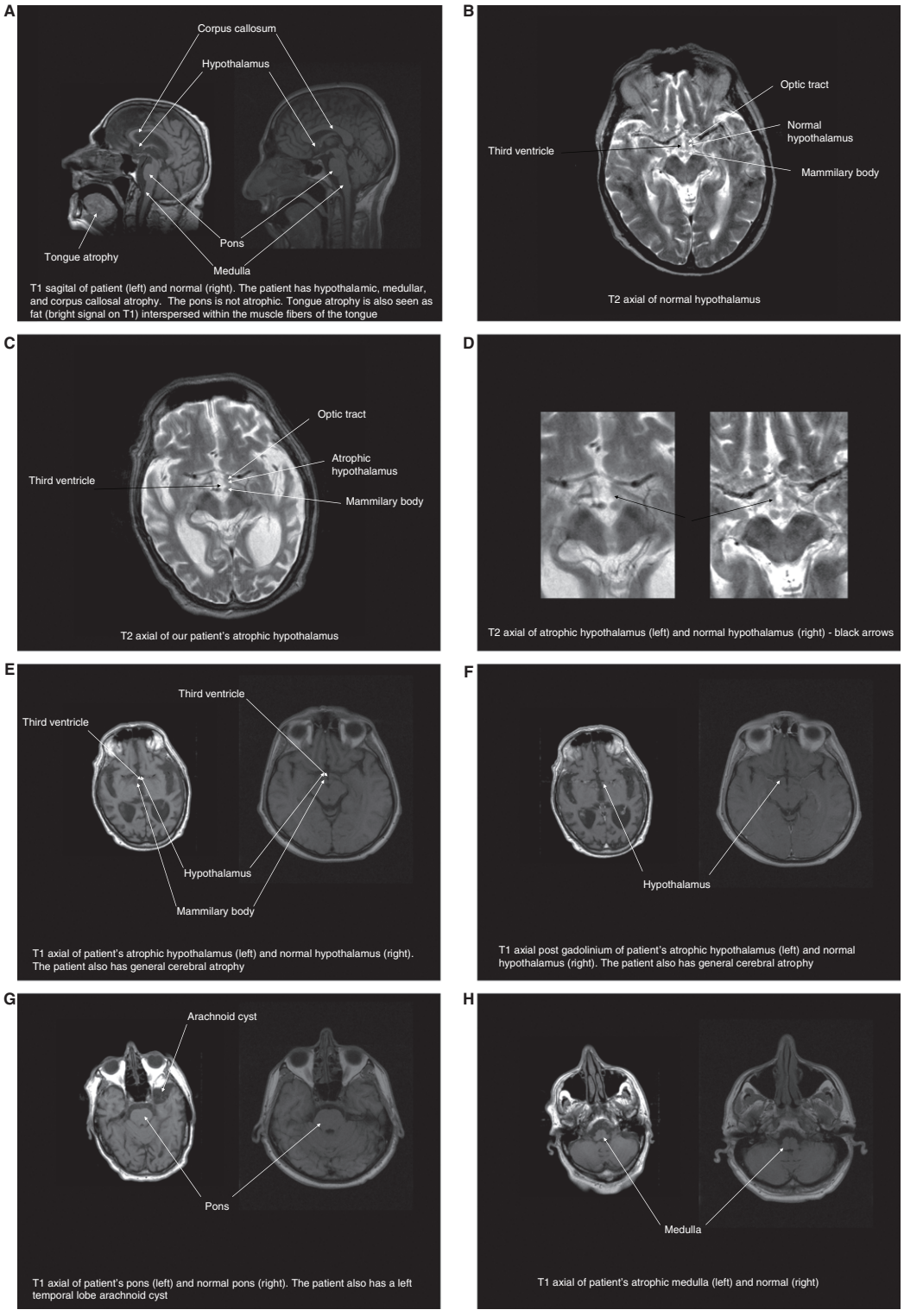

Figure 2. (A) T1 sagital of patient (left) and T1 sagital of normal (right). The patient hypothalamic, medullar and corpus callosal atrophy. The pons is not atrophic. Tongue atrophy is seen as fat (bright signal on T1) interspersed within the muscle fibers of the tongue. (B) T2 axial of normal hypothalamus. (C) T2 axial of our patient's atrophic hypothalamus. (D) T2 axial of atrophic hypothalamus (left) and normal hypothalamus (right). (E) T1 axial of patient's atrophic hypothalamus (left) and normal hypothalamus (right). The patient also has general cerebral atrophy. (F) T1 axial post gadolinium of patient's atrophic hypothalamus (left) and normal hypothalamus (right). The patient also has general cerebral atrophy. (G) T1 axial of patient's pons (left) and normal pons (right). The patient also has a left temporal lobe arachnoid cyst. (H) T1 axial of patient's atrophic medulla (left) and normal medulla (right).

response to an infection, we could hypothesize that the hypothalamic damage played a leading role in the observed ThD. This hypothesis is consistent with Lipton's and other case reports showing similar associations between hypothalamic damage and thermoregulatory problems,[9,10,11] and with neuropathological studies of alcoholics with WKS showing lesions of the hypothalamus and mamillary bodies. However, it is difficult to infer the function of a particular brain center that is part of a neural network from the ensuing dysfunction when that brain center is lesioned. It is impossible to infer its function when other parts of the network are diseased as well. Thus, we conclude that our patient's ThD was caused by dysfunction of the brain temperature regulation network including the hypothalamus and medulla, hypothesize that the hypothalamus played a leading role in ThD, and describe the MRI findings of atrophy in a number of additional brain areas.

Animal models show that hypothermia is a predictable consequence of thiamine deprivation,[24,25] and human case reports of WE show improvements in hypothermia with thiamine treatment.[11,26,27] In our case, it is possible that other factors contributed to the ThD. The multiple medications that the patient was taking could certainly have contributed to abnormal temperature responses by affecting brain neurotransmitters. Alcohol, malnutrition, vitamin B_{12} and folate deficiencies could have contributed to the development of dementia in this patient and could have directly or indirectly (through the degeneration of brain temperature regulating centers) contributed to the observed ThD syndrome in this patient. However, because none of these factors changed during the short period of treatment with parenteral Thiamine, the observed temperature stabilization cannot be explained by the above factors. Whatever the initial pathways leading toward the damage of the thermoregulatory centers, parenteral Thiamine helped stabilize them. Our case demonstrates that ThD in AIPD can be successfully stabilized with parenteral thiamine supplementation.

Our case suggests that oral and parenteral Thiamine are not equally available to the brain and that parenteral Thiamine administration may be warranted even long after the acute period of alcohol intoxication and WE. In our case, the patient had not consumed alcohol and had been in an SNF for more than 10 years. Whereas oral Thiamine did not lead to improved temperature regulation (presumably because of poor gastrointestinal absorption), parenteral Thiamine stabilized the temperature fluctuations rapidly. In nonalcoholics, absorption of oral Thiamine is limited to a maximal daily amount of 8 to 15 mg regardless of the amount available in food, and cellular uptake is mediated by a plasma membrane transporter.[15] In alcoholics, absorption, transport, and use of Thiamine may be inadequate, and higher blood/cerebrospinal fluid (CSF) concentrations may be needed to achieve adequate concentrations of thiamine in the CSF. Thiamine deprivation may not be easily replenished and discrete periods of Thiamine deprivation may over time have cumulative effects on nerve cell dysfunction.[16] These factors may not be completely resolved despite adequate initial treatment with Thiamine. Therefore, regardless of the stage of the disease, parenteral thiamine in the IV or IM route may be much more effective than oral Thiamine in the treatment of ThD.

The exact mechanism of Thiamine in stabilizing thermal regulation is unclear. Given the relatively rapid improvement in thermal regulation (within days), we would hypothesize that Thiamine exerted its effects by entering neurons, improving metabolism, mitochondrial functioning, and energy production, and thus improving the functioning of thermal regulatory centers in the hypothalamus and elsewhere.

Finally, our case has the typical limitations of a case report. Because of the single case and the multiple factors influencing the observed variables, it is difficult to postulate with certainty that any causal relationship exists between the different variables. For example, we cannot determine whether the hypothalamic and medullar atrophy was acute or chronic, although the history would suggest that it was most likely chronic. We cannot be sure of the etiology of the hypothalamic and medullar atrophy which could have been caused by the direct effects of alcohol, by longstanding malnutrition, by Thiamine or other vitamin deficiencies, by a brain degenerative process, or by other unknown factors. Although the ThD was likely associated with the hypothalamic and medullar atrophy for the reasons stated above, we cannot be sure of that. Alternative explanations would be that the temperature dysregulation was associated with other temperature-regulating brain centers, or that it happened as a result of the multiple medications the patient was taking, without a clear relationship to the brain atrophy. To know that, we would have to be able to isolate the effects of multiple variables on ThD, an analysis usually beyond the limitations of a single case report.

Whatever the pathophysiological pathway leading to hypothalamic atrophy and to the observed temperature dysregulation, parenteral Thiamine did lead to temperature stabilization, while most of the other possible contributing factors remained unchanged during that time. Therefore, the observed temperature stabilization can be reasonably attributed to the parenteral Thiamine.

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