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# The Clinical Picture

## Encephalopathy despite thiamine repletion during alcohol withdrawal



**FIGURE 1.** The patient had an erythematous, scaly rash on his face and a nonhealing sunburn on the left forearm.

**M**ANAGING A PATIENT WITH chronic alcohol abuse who is beginning to withdraw is a situation in which to expect the unexpected.

A 61-year-old man with a 40-year history of alcohol abuse was admitted to the hospital after presenting with a 6-month history of weakness and increasing frequency of falls, as well as a 2-day history of myalgias and fatigue. He had anorexia and chronic diarrhea, and he reported an unintentional 100-lb weight loss over the past year. He consumed at least three to five alcoholic drinks daily, including a daily “eye-opener,” and his diet was essentially devoid of meat, bread, fruits, and vegetables. His last drink had been on the morning of admission.

On physical examination, his vital signs were notable for marked orthostatic hypotension. He had angular cheilitis, an erythematous, scaly facial rash, and poorly healing severe sunburn on the dorsal surface of the left forearm, acquired 1 month earlier after minimal sun exposure while driving his car (**FIGURE 1**).

The neurologic examination noted decreased sensation in a stocking distribution, reduced proprioception in both great toes, and an intention tremor. His upper extremities were slightly hyperreflexic, he had down-going toes, he did not have clonus, and his gait was wide-based.

Laboratory results were notable for mild anemia, with an elevated mean corpuscular volume of 109.2 fL and a normal thyrotropin level. Urinalysis and urine culture were normal. Stool testing for *Clostridium difficile* toxin was negative. Computed tomography of the head was unremarkable.

He was placed on the Clinical Institute Withdrawal Assessment for Alcohol revised protocol,<sup>1</sup> and he was started on careful fluid, electrolyte, and nutritional management, including intravenous supplementation with thiamine 100 mg daily, folic acid 1 mg twice daily,

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and an oral multivitamin. Despite these interventions, he became delirious and developed horizontal nystagmus, visual hallucinations, dizziness, and increasing weakness. Benzodiazepine toxicity, which may cause similar findings, was thought unlikely, as he had received only a maximum of 4 mg of lorazepam in any single 24-hour period. His ongoing confusion, orthostatic hypotension, ataxia, and nystagmus raised concern for Wernicke encephalopathy. Thiamine was increased to 500 mg intravenously three times daily for 2 days, followed by 500 mg daily for 2 days, as recommended for acute Wernicke encephalopathy by the Royal College of Physicians.<sup>2</sup>

Although his ocular findings resolved and his blood pressure improved with high-dose thiamine, he remained confused. Other causes of delirium were considered, including other micronutrient deficiencies. He was evaluated for magnesium deficiency, as magnesium is a necessary cofactor in thiamine metabolism,<sup>3</sup> but his level was within normal limits. The constellation of symptoms, including persistent delirium, diarrhea, and skin findings, appeared to be consistent with pellagra, and niacin deficiency became a concern.

## ■ PELLAGRA AND ALCOHOL ABUSE

Niacin is a water-soluble vitamin converted to two important coenzymes involved in carbohydrate metabolism and fatty-acid synthesis.<sup>4</sup> Body stores are minimal, although the liver can convert tryptophan to niacin.<sup>4</sup>

In the United States, pellagra has become rare since niacin enrichment of bread and flour began in the 1940s. However, the risk is increased in those with chronic alcohol dependency, metabolic disease such as carcinoid syndrome, and malabsorptive states such as Crohn disease.<sup>5</sup> Alcohol abuse is commonly associated with micronutrient deficiencies. Even in alcoholics with sufficient food intake, their ability to absorb niacin may be impaired both directly and indirectly because of the toxic effects of alcohol on the gastrointestinal tract.<sup>5</sup>

### The three D's of niacin deficiency

The clinical picture of pellagra includes the three "D's" of niacin deficiency—diarrhea, dementia, and dermatitis—representing the organ

systems most commonly affected (ie, the gastrointestinal tract, nervous system, and skin). Gastrointestinal signs and symptoms may include anorexia, diarrhea, stomatitis, and abdominal discomfort.<sup>4</sup> Neurologic signs and symptoms are the most frequent clinical manifestations of pellagra but are often overlooked in alcoholics with altered mental status.<sup>5,6</sup> Early neurologic findings may include apathy, depression, paresthesias, dizziness, and falling.<sup>4,5</sup> Later findings may include hallucinations, seizures, and psychosis.<sup>4,5</sup> If severe enough, this may progress to coma and to a fourth "D"—death—if left untreated.

Skin findings, if present, are typically the most characteristic of pellagra.<sup>5,6</sup> They include a photosensitive eruption that most commonly appears on the face, arms, and the "V" of the neck ("Casal's necklace").<sup>3,6</sup> Erythema develops on areas of sun-exposed skin and may be painful or pruritic.<sup>6</sup> It may take up to four times as long to resolve as a normal sunburn.<sup>6</sup> On repeated exposure, the skin becomes thickened, hyperkeratotic, and hyperpigmented.<sup>6</sup>

## ■ DIAGNOSIS AND TREATMENT OF PELLAGRA

Suspicion of pellagra should be high in any patient with chronic alcohol abuse with changes in mental status.<sup>5</sup> Pellagra is typically diagnosed clinically. Although testing of serum levels of niacin or urine levels of niacin metabolites can be performed,<sup>4,5</sup> these tests are not commonly used, as they are neither widely available nor reliable.<sup>3,4</sup> Because there is little downside to giving niacin, treatment should be started if there is clinical suspicion of pellagra.<sup>3,4</sup> The diagnosis is confirmed by clinical improvement after niacin replacement begins.<sup>4</sup>

Pellagra is easy and inexpensive to treat once the diagnosis has been established. Supplementation can be given orally at 50 mg to 100 mg three times daily, with a maximum of 500 mg daily for 3 to 4 weeks.<sup>3,5</sup> The multivitamin our patient initially received provided only 30 mg of niacin, which was insufficient to treat his deficiency.

Other micronutrient deficiencies are also common in pellagra, such as the suspected thiamine deficiency in this patient. Although rare in adults, pyridoxine deficiency should be considered because pyridoxine plays an important

**Micronutrient deficiencies are common in chronic alcoholism**

role in niacin metabolism, and in patients such as this, the signs and symptoms of pellagra will not resolve with niacin administration alone.<sup>3,4</sup>

Neurologic symptoms can begin to resolve as soon as 24 to 48 hours after replacement therapy is started, although skin symptoms take longer to respond.<sup>6</sup>

## ■ OUR PATIENT'S MANAGEMENT AND LESSONS LEARNED

Our patient was treated with extended-release niacin 500 mg daily. He was significantly less confused within 24 hours, and 2

days later he was no longer delirious. His diarrhea resolved, but his peripheral neuropathy improved only modestly, and we believe that this was the result of his long history of alcohol abuse.

Although there are guidelines to help with the management of patients undergoing alcohol withdrawal, our experience with this patient illustrates that important clinical conditions, including micronutrient deficiencies, can easily be overlooked or misattributed, with potentially dangerous consequences. It is crucial to be mindful of these considerations. ■

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