Nutrition in Clinical Practice
Volume 0 Number 0
xxxx 2019 1–4

DOI: 10.1002/ncp.10418
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Pellagra, an Almost-Forgotten Differential Diagnosis of Chronic Diarrhea: More Prevalent Than We Think

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Abstract

Pellagra, caused by vitamin B3 (niacin) deficiency, is traditionally described as dermatitis, diarrhea, dementia (3D), and even death (4D) syndrome if not recognized and treated promptly. Although full-blown pellagra with all 3D features has become rare, pellagra still exists, especially in high-risk populations, which is actually more prevalent than we think. We report that a recently treated patient with the full spectrum of 3D clinical features of pellagra presents as chronic diarrhea of unknown etiology for 1 year. It reminds us that keeping a high index of suspicion and maintaining a broad differential diagnosis are critical for recognition and management of this potentially fatal but treatable condition. (*Nutr Clin Pract.* 2019;0:1–4)

Keywords

dementia; dermatitis; diarrhea; niacin; pellagra; vitamin deficiency

Introduction

Vitamin B3 (niacin) deficiency can cause pellagra. With fortified foods, pellagra, especially the full-blown presentation of pellagra with all 3D symptoms, has been essentially eradicated in developed countries. This statement may be misleading since pellagra still exists, especially in high-risk patients such as those experiencing alcohol abuse, anorexia nervosa, malnutrition, wasting conditions, homelessness, HIV infection, and those using medicines such as antiepileptic, azathioprine, and isoniazid.[1]

In clinical practice, pellagra is often overlooked in differential diagnoses, leading to a delay in treatment. We recently treated a patient with the full spectrum of 3D symptoms of pellagra who presented with chronic diarrhea.

Case Report

An 81-year-old Caucasian male presented with a 1-year history of chronic diarrhea, 2–3 weeks of an itchy skin rash, 2 weeks of truncal and bilateral hand coarse tremors, and 1–2 days of delirium confusion.

The patient lived alone. For the past 1 year, the patient had chronic diarrhea consisting of 6–7 loose stools daily of unknown etiology and poor oral intake, and he had experienced weight loss of 11.7 kg. The patient had a history of social alcohol use but quit 2 years prior to admission. An esophagogastroduodenoscopy (EGD) performed 9 months ago was normal except for increased gastric folds. A colonoscopy performed 4 years ago was normal.

The patient's chronic medical problems included gastroesophageal reflux disease and type 2, noninsulin-requiring diabetes mellitus. On admission, his vital signs were a temperature of 99.1°F, heart rate of 97 bpm, respiratory rate of 18 bpm, and blood pressure of 116/58 mmHg.

On exam, the patient appeared cachectic, confused, and somnolent. A skin examination revealed a symmetric well-demarcated violaceous, hyperpigmented, dry, thickened desquamating rash with scaling on the patient's anterior lower neck and clavicles, bilateral arms, and lower legs (Figure 1). A neurologic exam showed truncal and bilateral hand coarse tremors during intentional activity, minimal resting tremors, and no focal neurologic deficits.

Imaging Studies

On magnetic resonance imaging of the brain, there was no evidence of acute hemorrhage or infarction. A computed tomography scan of the chest (without contrast) did not show any evidence of thoracic malignancy. As mentioned earlier, an EGD showed thickened gastric folds. A colonoscopy revealed diverticulosis but no polyps or cancer. Pathology results from the gastrointestinal (GI) studies reported mild

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Financial disclosure: None declared.

Conflicts of interest: None declared.

This article originally appeared online on xxxx 0, 2019.

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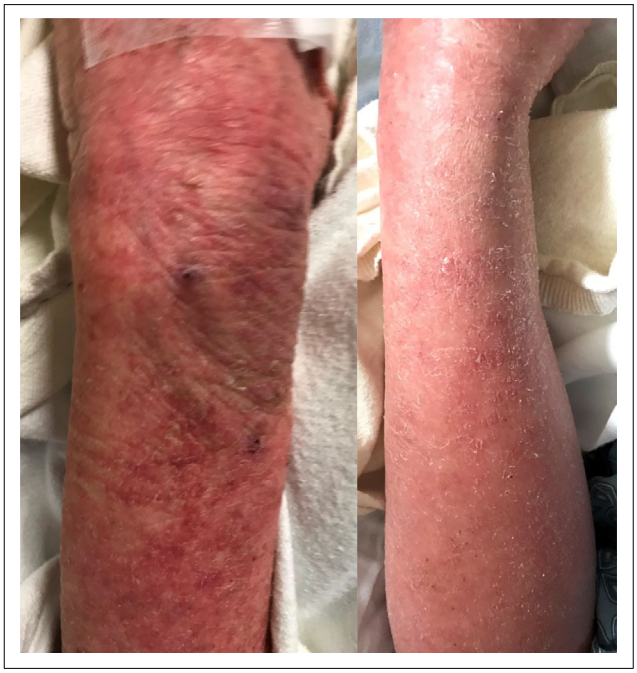

Figure 1. Skin changes on the left forearm prior to (left image) and 3 weeks post (right image) niacin supplement treatment.

chronic gastritis, intestinal metaplasia, small intestinal and colonic mucosa within normal limits, and no *Helicobacter pylori*.

Laboratory Tests

The patient's laboratory tests are summarized in Table 1. Stool *Clostridium difficile* (*C. diff*) antigen and toxin were negative. Laboratory tests ruled out celiac disease and *C. diff* infection. The collective presentation of sunburn-like hyperpigmentation dermatitis in sun exposure areas, chronic diarrhea, and delirium was suggestive of pellagra.

Additional labs revealed plasma nicotinic acid <20 ng/mL and nicotinamide 25 ng/mL, both of which were low. Vitamin B3 (niacin) in plasma is comprised of nicotinic acid and its metabolite nicotinamide; because of variability in metabolism, serum concentrations of these 2 compounds can be variable. However, this patient's serum levels were low when compared with reference ranges (nicotinic acid ranges from <20 to 30,000 ng/mL; nicotinamide ranges from fasting plasma concentration 40 to 400 ng/mL after administering nicotinic acid). This patient's low vitamin B3 levels therefore supported the diagnosis of pellagra.

Treatment

We immediately started a therapeutic trial of niacin replacement. As per World Health Organization guidelines,[2] the treatment included oral niacin at 300 mg daily in divided dose for 3–4 weeks. Three days after niacin supplement, the patient became awake and alert with significant improvement in his tremor. Six days later, the patient's diarrhea resolved, and 3 weeks later, his rash was significantly improved with skin smoothed and hyperpigmentation faded (Figure 1). Oral supplementation with nicotinamide 100 mg three times a day was continued for 4 weeks and then changed to once daily.

The correction of the clinical 3D features with niacin replacement further supported the diagnosis of pellagra.

Table 1. Serum Laboratory Results in a Patient With Pellagra.

Laboratory Test (Unit)	Results	Reference Value
White blood cells, $\times 10^9$/L	12.2	4–10
Hemoglobin, g/dL	12.4	13–17 (men)
Hematocrit, %	38.9	36–47 (men)
Platelets, 10^9/L	94	150–400
Mean corpuscular volume, μm^3	78.4	80–100
Sodium, mmol/L	145	135–145
Potassium, mmol/L	4.4	3.5–5
Chloride, mmol/L	97	95–105
Bicarbonate, mmol/L	32	23–28
Serum urea nitrogen, mg/dL	46	8–21
Creatinine, mg/dL	1.63	0.8–1.3
Glucose, mg/dL	102	65–110
Calcium, mg/dL	6.3	8.7–10.5
Ionized calcium, mmol/L	0.86	1.15–1.35
Ionized parathyroid hormone, pg/mL	24.6	14–72
Magnesium, mg/dL	0.3	1.8–2.4
25-Hydroxy vitamin D, ng/mL	29.8	30–75
Total bilirubin, mg/dL	0.4	2–20
Aspartate aminotransferase, U/L	19	5–30
Alanine aminotransferase, U/L	21	5–30
alkaline phosphatase, U/L	60	50–100
Total protein, g/dL	6.2	60–80
Serum albumin level, g/dL	4.1	3.5–5
Hemoglobin A1C, %	5.6 (10.9 9 months ago)	4–6
Iron, µg/dL	20	65–380 (men)
Total iron binding capacity, µg/dL	201	45–85
Iron saturation, %	10	
Ferritin, ng/mL	51	12–300 (men)
Vitamin B12, pg/mL	415	232–1245
Folate, ng/mL	14.3	3.4–20
Zinc, µg/dL	66	60–130
Copper, µg/dL	94	70–175
Ceruloplasmin, mg/dL	25	18–36
Vitamin B1, nmol/L	14	8–30
Gastrin, pg/mL	381	<101
Parietal cell antibody	<1:40	
Intrinsic factor blocking antibody	Negative	Negative
Transglutaminase IgA, U/mL	<3	
Immunoglobulin A, mg/dL	203	70–420
Antinuclear antibody	Negative	Negative
Alcohol, mg/dL	<10	

Discussion

Defining pellagra as a disease of the "3D syndrome" may be misleading. First, the classic dermatitis of pellagra is described as a symmetrical skin rash involving sun-exposed areas that looks like a sunburn. The rash ranges from subtle changes of photo damage to an eruption of scaling, erythematous, and hyperpigmented lesions. Although the skin lesions are usually the most prominent of the 3 "D"s, they may be minimal or absent if the skin has not been exposed to sunlight.

Second, the diarrhea in pellagra is often caused by gastroenterological mucosal inflammation throughout the entire GI system, leading to stomatitis, glossitis, nausea, vomiting, abdominal pain, and ultimately intractable diarrhea.[3,4] The diarrhea itself can contribute to ongoing malnutrition because of poor malabsorption. The diarrhea, however, is not always present. Approximately 60% of pellagra cases have stomatitis, and only about 19% have diarrhea.[2]

Third, in early stages, neurologic features manifest as psychoneurotic symptoms such as insomnia, depression, hallucinations, delirium, pellagrous encephalopathy, and psychosis; in late stages, patients with chronic pellagra can develop memory loss and dementia.[2,3] In acute niacin deficiency, psychoneurotic features closely resemble Wernicke's syndrome.[2] Furthermore, pellagra may present as an isolated delirium without the other symptoms of the triad, that is, subclinical pellagra.

Therefore, if we use the classic triad of 3D symptoms as the diagnosis criteria for pellagra, we can miss the diagnosis. Moreover, the 3D syndrome of pellagra might be better thought of as dermatitis, digestive disturbance including diarrhea, and delirium encephalopathy.[3]

Awareness of niacin deficiency has at least 2 applications in clinical practice. The first is in alcohol abuse. Vitamin B1 (thiamin) and vitamin B9 (folate) deficiency are well known in individuals who abuse alcohol. Vitamin B3 (niacin) deficiency is found to be at 27% in patients with alcoholism[3,5] but has largely been overlooked. Moreover, pellagrous encephalopathy or psychosis can present as delirium tremens, especially in treatment-resistant alcohol withdrawal.[6] Consequently, whenever individuals with chronic alcoholism exhibit certain mental, neurological, or GI symptoms, one should strongly suspect pellagra and start niacin supplement.[7]

The second is in carcinoid tumors. Niacin comes from 2 sources: oral intake and internal biochemical synthesis from tryptophan. In carcinoid tumors, it has been reported that increased diversion of tryptophan toward serotonin can cause niacin deficiency since these 2 biochemical pathways share the same substrate of tryptophan (Figure 2). Moreover, a subset of carcinoid tumor patients develops carcinoid syndrome characterized by flushing, skin abnormalities, abdominal cramps, recurrent diarrhea, asthmatic wheezing, and valvular heart disease, which overlaps with pellagra symptoms. Furthermore, niacin replacement in patients with carcinoid tumors resolves several common symptoms, such as skin lesions and diarrhea/steatorrhea.[8] Patients presenting with niacin deficiency should be screened for carcinoid tumor. In this patient, the urine 5-hydroxyindoleacetic acid (5-HIAA) was 9.7 mg/24 h (as per guideline,[9] 5-HIAA 1–15 mg/24 h was normal); therefore, this patient did not meet diagnostic criteria for carcinoid tumor-associated niacin deficiency.

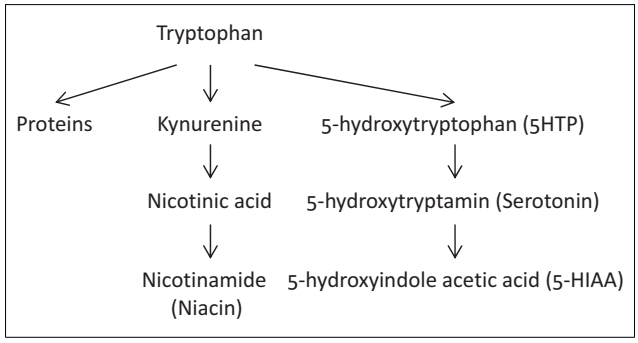

Figure 2. Niacin comes from 2 sources: oral intake and internal biochemical synthesis from tryptophan. In carcinoid tumors, increased diversion of tryptophan toward serotonin can cause niacin deficiency since these 2 biochemical pathways share the same substrate of tryptophan.

This patient's niacin deficiency likely arose from his poor oral intake and was compounded by his chronic diarrhea. He lived alone and had poor social support, poor appetite, and reduced oral intake, which was corroborated by his family. On admission, the patient's weight was 45 kg (1 year ago, it was 56.7 kg) and body mass index was 18 kg/m^2. The patient appeared cachectic and experienced weight loss of 20.6% over 1 year, consistent with severe calorie and protein malnutrition.[10] Moreover, the patient's chronic diarrhea likely worsened his malnutrition and niacin deficiency. This patient also had a history of social alcohol abuse but quit 2 years ago, suggesting his deficiency was less likely because of alcohol use.

Because niacin does not have any appreciable stores in the body, symptomatic niacin deficiency can present as soon as 60 days after insufficient dietary intake.[11] Niacin comes in 2 major forms: nicotinic acid used to increase high-density lipoprotein, which frequently has side effect of flushing,[12] and nicotinamide (nicotinic acid amide is the active form), the vitamin B3 supplement form, is a nonflushing form of niacin.[13]

Pellagra is more common than thought, especially in high-risk patients. It is critical to maintain a high index of suspicion and keep a broad differential for diagnosis.

Table 2. Pellagra and Niacin Deficiency Awareness and Clinical Applications.

Characteristics of Pellagra	Comments
The triads of pellagra: Dermatitis Diarrhea Dementia	Suggest change to: Dermatitis Digestive distress Delirium encephalopathy
Patients at high risk of niacin deficiency: Alcohol abuse Anorexia nervosa Malnutrition Wasting conditions Homelessness HIV infection Medicines: antiepileptics, azathioprine, and isoniazid	Consider niacin deficiency and start supplement appropriately
Common causes	
Alcohol abuse	Suggest adding niacin supplement to CIWA-Ar protocol
Carcinoid tumors	Suggest screening for carcinoid tumor in pellagra patients

Importantly, physicians may consider revising the traditional 3D features to dermatitis, digestive distress including chronic diarrhea, and delirium to better recognize pellagra[3] and start niacin supplement promptly (Table 2).

Statement of Authorship

S. Cao contributed to the conception and design of the research; S. Cao, X. Wang, and K. Cestodio contributed to the acquisition and analysis of the data; S. Cao, X. Wang, and K. Cestodio contributed to the interpretation of the data; and S. Cao drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

References

1. de Oliveira Alves A, Bortolato T, Bernardes Filho F. Pellagra. *J Emerg Med*. 2018;54(2):238-240.
2. World Health Organization, Office of the United Nations High Commissioner for Refugees. *Pellagra and Its Prevention and Control in Major Emergencies*. Geneva, Switzerland: World Health Organization: Office of the United Nations High Commissioner for Refugees; 2000.
3. Oldham MA, Ivkovic A. Pellagrous encephalopathy presenting as alcohol withdrawal delirium: a case series and literature review. *Addict Sci Clin Pract*. 2012;7(1):12.
4. Varella Morandi Junqueira-Franco M, Ernesto Troncon L, Garcia Chiarello P, do Rosário Del Lama Unamuno M, Afonso Jordao A, Vannucchi H. Intestinal permeability and oxidative stress in patients with alcoholic pellagra. *Clin Nutr*. 2006;25(6):977-983.
5. Ishii N, Nishihara Y. Pellagra among chronic alcoholics: clinical and pathological study of 20 necropsy cases. *J Neurol Neurosurg Psychiatry*. 1981;44(3):209-215.
6. Badawy AA. Pellagra and alcoholism: a biochemical perspective. *Alcohol Alcohol*. 2014;49(3):238-250.
7. López M, Olivares JM, Berrios GE. Pellagra encephalopathy in the context of alcoholism: review and case report. *Alcohol Alcohol*. 2014;49(1):38-41.
8. Shah GM, Shah RG, Veillette H, Kirkland JB, Pasieka JL, Warner RR. Biochemical assessment of niacin deficiency among carcinoid cancer patients. *Am J Gastroenterol*. 2005;100(10):2307-2314.
9. Maroun J, Kocha W, Kvols L, et al. Guidelines for the diagnosis and management of carcinoid tumours. Part 1: the gastrointestinal tract. A statement from a Canadian National Carcinoid Expert Group. *Curr Oncol*. 2006;13(2):67-76.
10. White JV, Guenter P, Jensen G, et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enteral Nutr*. 2012;36(3):275-283.
11. Wildman REC, Medeiros DM. *Advanced Human Nutrition*. Boca Raton, FL: CRC Press; 2000.
12. Garg A, Sharma A, Krishnamoorthy P, et al. Role of niacin in current clinical practice: a systematic review. *Am J Med*. 2017;130(2):173-187.
13. Kademian M, Bechtel M, Zirwas M. Case reports: new onset flushing due to unauthorized substitution of niacin for nicotinamide. *J Drugs Dermatol*. 2007;6(12):1220-1221.