

Pellagra May Be a Rare Secondary Complication of Anorexia Nervosa: A Systematic Review of the Literature

Jonathan E. Prousky, ND, FRSH

Abstract

Pellagra is a nutritional wasting disease attributable to a combined deficiency of tryptophan and niacin (nicotinic acid). It is characterized clinically by four classic symptoms often referred to as the four Ds: diarrhea, dermatitis, dementia, and death. Prior to the development of these symptoms, other nonspecific symptoms insidiously manifest and mostly affect the dermatological, neuropsychiatric, and gastrointestinal systems. A review of the literature reveals several case reports describing pellagra in patients with anorexia nervosa. The most common features of pellagra in patients with anorexia nervosa are cutaneous manifestations such as erythema on sun-exposed areas, glossitis, and stomatitis. Health care providers might consider a trial of 150-500 mg niacin if anorexic patients exhibit these cutaneous findings. Pellagra can be diagnosed if cutaneous symptoms resolve within 24-48 hours after oral niacin administration. To further corroborate a diagnosis of pellagra in anorexic patients, specific 24-hour urine tests for niacin metabolites and 5-hydroxy-indoleacetic acid could be run prior to treatment with niacin being instituted. Other factors, such as mycotoxins, excessive dietary leucine intake (although not in anorexia), estrogens and progestogens, carcinoid syndrome, and various medications, might also lead to the development of pellagra. Although pellagra appears to be a rare, yet possible, secondary complication of anorexia nervosa, it should be considered in the work-up of patients who

exhibit cutaneous manifestations subsequent to sunlight exposure.

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Introduction

A review by Patrick covered the etiology and well-known nutritional deficiencies associated with anorexia, bulimia, and atypical eating disorders.¹ The comprehensive article did not, however, cover the possible connection of pellagra and anorexia. In this article, four case reports from the medical literature demonstrating pellagra in patients with anorexia nervosa are reviewed.

Classic pellagra is a nutritional wasting disease characterized by combined deficiency of the essential amino acid tryptophan and the vitamin niacin (nicotinic acid).²

Bicknell and Prescott described the history of pellagra in great detail.³ The word pellagra means rough skin and was coined by Frapolli in 1771. Frapolli was the first investigator to note the appearance of skin lesions in response to sunlight exposure. The disease was first identified in Spain and Italy, but soon was found to be widespread in other European countries. Although first described in North America in 1864, it made its presence known prior to this date. In 1937 it was discovered that black tongue, a disease in canines similar to human pellagra, was cured through the

Jonathan E. Prousky, ND, FRSH – Associate Naturopathic Medical Officer; Assistant Professor of Clinical Nutrition, The Canadian College of Naturopathic Medicine.
Correspondence address: The Canadian College of Naturopathic Medicine, 1255 Sheppard Avenue East, Toronto, Ontario M2K 1E2
E-mail: jprousky@ccnm.edu

use of niacin. Soon after, niacin was used in humans with good results, but was not completely curative. In 1947 the complexity of pellagra was resolved.² It was found that the essential amino acid tryptophan, a metabolic precursor to the nicotinamide coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), could cure or prevent pellagra. In the 1950s, studies demonstrated that 60 mg of tryptophan provided the equivalent of 1 mg of niacin.⁴ Considering the typical Western diet provides approximately 1 gram of tryptophan daily from protein sources and other foods, the daily niacin requirements can generally be met from diet alone.² Thus, it was determined that the best way to treat or prevent pellagra was to administer preformed niacin or ensure an adequate intake of dietary protein.

Although pellagra is characterized by the four classic symptoms (four Ds) – diarrhea, dermatitis, dementia, and death – other symptoms insidiously manifest earlier. Such symptoms include achlorhydria, anorexia, anxiety psychosis, cheilosis, constipation, delirium, dermatitis occurring on sun-exposed areas, diminished strength, glossitis, intermittent stupor, melancholia, nausea, paralysis of extremities, peripheral neuritis, stomatitis, weight loss, and vomiting.²⁻⁶ Bicknell and Prescott report the gastrointestinal symptoms of pellagra precede the other symptoms.³ Hoffer, by contrast, has reported the earliest symptoms of pellagra in its subclinical form manifest as modern mood disorders (e.g., anxiety, depression, fatigue, and vague somatic complaints) followed by the development of other symptoms.⁷ Despite differing reports about the initial symptoms of this wasting disease, pellagra is characterized by diverse clinical manifestations mainly involving the dermatological, gastrointestinal, and neurological systems.

Methods

Literature Search

A search was conducted of English and non-English language articles in the following databases: MEDLINE (1966-March 2003), AMED (1995-March 2003), and Alt HealthWatch

(1990-March 2003). To be included in the final review an article had to (1) report the results of a case of anorexia nervosa and pellagra, (2) describe methods by which a diagnosis of pellagra was established, (3) report a diagnosis of pellagra in a patient having a current or previous diagnosis of anorexia nervosa, (4) not involve other medical conditions such as alcoholism or depression, and (5) attempt to determine if an association existed between anorexia nervosa and pellagra. Of eight potential articles screened,⁸⁻¹⁵ four were included for this systematic review.

Case Report #1

The first reported case of pellagra in a patient with anorexia nervosa was in 1938 and involved a 38-year-old female with symptoms of weakness, headaches, and undernourishment.¹² She had been unwell the past 11 years and unable to work. When she was admitted to the hospital, she developed complete anorexia and exhibited neuropsychiatric symptoms of hostility, disorientation, and suspicious and violent behaviors. Pertinent findings on physical examination revealed an emaciated patient weighing 73 pounds, without any dermatitis, but with moderate glossitis and stomatitis. She was also combative throughout the examination, had thin extremities with some bruising, and refused all food and drink. Two weeks later she required forced feeding and was given 500 mg niacin in divided doses with her feedings. Within 24 hours she took food voluntarily. Four days later she was rational, agreeable, and cooperative. Within a month her weight had increased to 85.5 pounds. No mention was made regarding the frequency of forced-feedings, and whether she was given psychiatric medications, other vitamin supplements, or other medications or psychiatric interventions that could have contributed to her recovery.

Case Report #2

The second report involved a 20-year-old female admitted to the Medical Service at UCLA in January 1982 for evaluation of weight loss.¹³ Physical examination revealed a weight of 43 kg and a pulse rate of 80 that increased to 108 on

standing. She had normal thyroid function, ketonuria (2+), and mild diffuse ST-T wave changes. She was diagnosed with anorexia nervosa after psychiatric consultation and discharged. She was prescribed oral desipramine hydrochloride, 50 mg at night for 2-3 weeks. During the next few months the patient did well while continuing outpatient psychiatric care. Although she remained out of school, she was able to work at a part-time job indoors. In May 1982, she presented with dermatological symptoms that had begun four weeks earlier when studying outside in the sun. The dorsa of her hands and extensor aspects of her distal forearms had involved pruritic eruptions made worse when exposed to sunlight. A skin biopsy showed changes consistent with a diagnosis of pellagra. Light testing at her low back revealed a minimal erythema dose no different from other patients and subjects. Her 24-hour urinary niacin metabolites were low, indicating niacin deficiency. Her pellagra-associated dermatological symptoms resolved when niacin was administered orally at 100 mg three times daily for approximately three weeks. By the third week only residual pigmentary changes remained. Repeated urine studies performed one month later revealed niacin metabolites had returned to normal. She was able to tolerate sunshine without any more dermatological symptoms, had maintained her weight at 45 kg, and continued to undergo intermittent psychiatric care. The patient's history of pruritic eruptions upon sunlight exposure increased the likelihood she had pellagra. The fact that niacin metabolites were low prior to treatment and normalized one month after treatment further supported a diagnosis of pellagra in this case.

Case Report #3

The third reported case occurred in a 19-year-old female with a history of anorexia nervosa and prominent photosensitivity of 10 months duration.¹⁴ She had had no previous problems with tanning or sunburn. The onset of photosensitivity occurred following a sunlamp session in which the lamp exploded while being used. The subsequent erythema involved her face and anterior trunk only. Subsequently, 5-10 minutes of mid-

day sun produced erythema in the sun-exposed areas and in areas covered by light clothing. Over the previous six months, she had lost 30 kg weight, and had recurrent postprandial epigastric pain, vomiting, and occasional diarrhea. She had a past history of asthma and epilepsy, but was not currently being treated for either condition. On physical examination, the patient had erythema and slight scaling of the face, neck, upper limbs, and V-neck region. She also had slight hyperpigmentation and desquamation of her anterior trunk that did not involve the bikini areas. A work-up was performed including a complete blood count, electrolytes, liver function tests, B12, folate, anti-nuclear antibodies, porphyrin screens, chest X-ray, gastroscopy, and photopatch testing. The only notable laboratory finding was a decreased level of 24-hour urinary 5-hydroxy-indole-acetic acid (5-HIAA), which authors (of this case report) suggest might be useful as a potential diagnostic test for pellagra when unable to provide testing of plasma tryptophan or urinary N¹-methyl-nicotinamide (NMN). She was given niacin orally at 150 mg daily along with psychiatric care and dietary counseling. Within 48 hours her symptoms resolved and she remained well at follow-up several months later. No mention was made of the patient's weight at the time of diagnosis and follow-up, the specific symptoms that resolved 48 hours following niacin treatment, or whether 5-HIAA levels normalized.

Case Report #4

Cleary and Cleary comment on four cases of anorexia nervosa and one case of bulimia nervosa that were "relieved" through the use of oral niacin at 500 mg daily.¹⁵ Although no case descriptions were provided in the report, they theorize that anorexia nervosa is a form of subclinical pellagra sustained by hunger-suppressive endogenous endorphins. They purport that a deficiency of NAD leads to the manufacture of hunger-suppressive endorphins, eliminating normal satiety signals, thus making it easy to starve oneself. Since loss of appetite is a common feature of both pellagra and anorexia nervosa, Cleary and Cleary hypothesize that adequate niacin brings NAD levels

to normal, eliminating the addiction to endogenous endorphins resulting in a return of normal hunger signals and eating behaviors within 24 hours. Unfortunately, vital information was lacking in this report, such as more thorough case descriptions, including information pertaining to cutaneous findings among the anorexic patients. Also lacking was the meaning of “relieved,” and follow-up in terms of care and outcomes among patients months later.

Discussion

The cutaneous changes were among the first symptoms of pellagra to appear in anorexia nervosa patients. This contrasts with other reports of mood or gastrointestinal symptoms arising before the development of classic pellagra.^{3,7} All the case reports, except case report #2 lacked laboratory data such as testing niacin metabolites before and after treatment. If cutaneous improvements were clearly specified following niacin treatment, more validity might have been ascribed to the case reports. However, cutaneous improvements following niacin treatment further support the diagnosis of pellagra in anorexic patients. Table 1 summarizes the cutaneous improvements that occurred in patients given an oral dose of niacin.

Considering the complexity of anorexia nervosa and the many clinical manifestations of the disease, it is difficult to determine which initial symptoms might be reflective of pellagra. Nevertheless, consideration appears to be warranted when investigating the possibility of pellagra in anorexic patients. Although it might simply be happenstance that an isolated vitamin deficiency is brought out in response to sunlight exposure, pellagra should be suspected when the history of an anorexic patient reveals cutaneous manifestations following sunlight exposure.

To corroborate a clinical suspicion of pellagra, a healthcare provider might want to consider treating empirically with 150-500 mg niacin in divided doses daily, and monitor for cutaneous improvements 24-48 hours later. If cutaneous improvements occur then a presumptive diagnosis of pellagra can be made. If laboratory testing is desired, the easiest method would be 24-hour urine

testing of the breakdown products of niacin coenzymes (such as NMN) along with measurements of the pyridone turnover products (N¹-methyl-2-pyridone-5-carboxamide and N¹-methyl-4-pyridone-3-carboxamide).⁵

An untested and more experimental approach would be a 24-hour collection of 5-HIAA in the urine. When niacin or protein intake is inadequate there is a loss of feedback inhibition on the kynurenine pathway, diverting more tryptophan to the kynurenine pathway, making less substrate available for serotonin synthesis, and resulting in decreased levels of urinary 5-HIAA.¹⁴ Additional support for this association can be found in a rat study where the administration of 20 mg niacin resulted in increased levels of 5-HIAA and decreased levels of xanthurenic acid via the kynurenine pathway.¹⁶ In spite of the practicality and cost-effectiveness of these urinary tests, assessing niacin metabolites and possibly 5-HIAA levels would certainly help when evaluating for pellagra in patients with anorexia nervosa.

Besides a deficient intake of niacin and/or protein, other factors might lead to cutaneous features and/or clinical manifestations of pellagra in anorexic patients. For example, riboflavin and/or pyridoxine deficiencies can impair the biosynthesis of niacin from tryptophan. Riboflavin is the coenzyme for kynurenine hydroxylase and pyridoxine is the coenzyme for kynureninase – both enzymes that enable the *in vivo* conversion of tryptophan to niacin.² If a deficiency of any one of these vitamins exists clinical features of pellagra might develop.

Factors such as mycotoxins, excessive dietary leucine intake (which would not be seen in anorexia), estrogens and progestogens, carcinoma syndrome, and various medications might also lead to the development of pellagra.² Mycotoxins deplete tissue stores of niacinamide (the amide of niacin) and might be an etiological factor in the development of pellagra. Estrogen metabolites are competitive inhibitors of kynureninase, whereas progesterone might reduce the activity of kynurenine hydroxylase, even though *in vitro* work had shown that progesterone or its conjugates did not have any influence on

Table 1. Cutaneous Improvements Experienced by Three Anorexic Patients Taking Oral Doses of Niacin for Pellagra

Reference	Cutaneous Manifestations at Presentation	Dose of Oral Niacin Treatment	Cutaneous Improvements after Oral Niacin Treatment
12	Moderate glossitis and stomatitis without any dermatitis	500 mg in divided doses daily	Complete resolution, but the cutaneous improvements were not specified
13	Pruritic eruptions on the dorsa of the hands and distal forearms	100 mg three times daily	Residual pigmentary changes remained after three weeks of niacin
14	Erythema and slight scaling of the face, neck, upper limbs and V-neck region, and slight hyperpigmentation and desquamation of the anterior trunk sparing the bikini areas.	150 mg daily	Complete resolution, but the cutaneous improvements were not specified

this enzyme. Carcinoid syndrome, a tumor of the enterochromaffin cells of the gastrointestinal tract, diverts most of the tryptophan from NAD synthesis to serotonin synthesis. Lastly, medications such as Isoniazid, Benserazide and Carbidopa are associated with niacin depletion. Even though these factors are not likely to be the cause of pellagra in anorexic patients, it is important for the clinician to consider them when evaluating anorexic patients.

Conclusion

Even though pellagra seems to be a rare, yet possible secondary complication of anorexia nervosa, it ought to be considered in the work-up of patients with cutaneous manifestations following sunlight exposure. While resolution of the cutaneous manifestations of pellagra occurred 24-48 hours after oral niacin administration, the improvements among the anorexic patients were primarily of the dermatological system. Since no other marked improvements among other physiological systems were clearly evident from niacin administration, it appears to be a specific therapy

for a very small minority of patients with anorexia nervosa. These findings justify further investigations into the use of niacin in treating cutaneous manifestations of anorexia nervosa. More case reports, research, and rigorous controlled trials are needed to properly evaluate its therapeutic effectiveness, safety, and mechanisms of action as part of a comprehensive nutritional plan for anorexia nervosa.

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