The importance of recognizing pellagra (niacin deficiency) as it still occurs

The case presented recently in *Nutrition* by Naveen et al. described a child with pellagra, a condition considered rare in childhood [1]. This study is a timely reminder that pellagra is fortunately seen infrequently in clinical practice in affluent societies. However, it is wise for clinicians to always remain vigilant, especially as certain patient groups may be more at risk for developing this condition.

Pellagra is due to a deficiency in niacin (vitamin B3 or nicotinic acid) and it is important that clinicians do not miss this condition, particularly because it is easily treatable. Niacin can be derived from various food products including eggs, milk, beans, and fortified flour. Niacin absorption occurs importantly in the small intestine and is principally stored in the liver. However, niacin also can be synthesized in humans from the essential amino acid tryptophan [2].

The amide of niacin is nicotinamide, which is the active component of nicotinamide adenine dinucleotide (NAD⁺) and its phosphate derivative (NADP⁺), which are essential cofactors in oxidation–reduction (redox) reactions. NAD⁺ and NADP⁺ and their reduced forms are mandatory for glycolysis, oxidative phosphorylation, DNA regulation, and many metabolic synthetic processes. Nicotinamide deficiency is an important factor in evoking pellagra. Body stores of nicotinamide are short-lived and thus are susceptible to nutritional depletion.

The well-known mnemonic of the “four Ds”—dementia, dermatitis, diarrhea and death—may help to remind practitioners of the clinical features of pellagra, although three more “Ds” can be added to the list—depression, delirium, and dilated cardiomyopathy.

Dementia, associated with delusions, may be preceded by irritability and depression. Dermatitis usually presents in an erythema form, and may be especially severe in areas exposed to sunlight, with pigmentation and thickening of the skin; indeed pellagra means, “rough skin.” Casals’ necklace is named after the Spanish physician Don Casals who was probably one of the first to describe pellagra and these skin lesions are clearly depicted in the case report previously mentioned [1]. The associated diarrhea is probably caused by widespread inflammation of the mucosal membranes of the gastrointestinal (GI) tract and anorexia and weight loss may subsequently occur. Other clinical features of pellagra may include achlorhydria, ataxia, glossitis, neuropathy, stomatitis, and vaginitis [3–9].

Dietary deficiency of nicotinamide is rare in affluent communities but should still be considered in areas of poor nutrition as in the case presented in this journal [1]. Individuals consuming high corn diets, which are typically low in niacin and tryptophan, are also more susceptible to developing pellagra. Pellagra is more common in those with risk factors for undernutrition such as those with anorexia nervosa, AIDS, and chronic alcohol intake and those living in poverty. In the case of chronic alcohol intake a pellagrous encephalopathy has been described [10–13].

Hartnup’s disease is a rare autosomal recessive disorder involving the renal, intestinal, and other cellular transport processes for the monoamino–monocarboxylic amino acids including tryptophan. The causative gene, *SLC6A19*, is located on chromosome 5 and this condition can result in niacin deficiency [14]. The abnormal transporter is normally present in the renal tubules and small intestine and its malfunction results in loss of tryptophan via the feces and aminoaciduria. Patients with Hartnup’s disease may present with features of pellagra that can be relieved by giving oral nicotinamide [15]. The child presented in the study cited here apparently did not have aminoaciduria [1].

Dietary niacin intake may not be sufficient to provide the body’s needs over prolonged periods of time, particularly if endogenous tryptophan is reduced [2]. A similar clinical picture has been reported as an unusual complication of the carcinoid syndrome (a rare tumor of the enterochromaffin cells generally of the GI tract) when tryptophan is diverted to the synthesis of large amounts of 5-hydroxytryptamine (serotonin), thereby leading to niacin deficiency [16,17].

Tryptophan turnover also may be impaired in pregnancy and with certain drugs. Pyridoxine is a coenzyme for kynureninase and riboflavin is a coenzyme for kynurenine hydroxylase and both these enzymes are essential for the conversion of tryptophan to niacin. Isoniazid, azothioprine, benserazide, and carbidopa may cause niacin depletion; some estrogen metabolites are competitive inhibitors of kynureninase [2–9].

If nicotinamide therapy has not already been initiated, the diagnosis of pellagra often can be made by measuring urinary N-methyl-nicotinamide concentration, which is low in niacin deficiency. Low urinary 5-hydroxyindoleacetic acid (5-HIAA) concentrations, a metabolite of serotonin, may also indicate niacin deficiency, as may abnormal erythrocyte niacin or NAD⁺/NADP⁺ concentrations. Where such specialized assays are not available, empirical treatment with oral nicotinamide resulting in clinical improvement (e.g., of the cutaneous lesions) may be a useful pointer to pellagra [2–9].

The recommend daily allowance for niacin is about 16 mg/d for adult males and 14 mg/d for non-pregnant adult females. Treatment of pellagra is usually with oral nicotinamide of ~100 to 200 mg thrice daily until symptoms and signs disappear generally after a couple of weeks [2–9]. However, niacin in high
dosages of ~1 to 2 g/d can be used for the treatment of certain dyslipidemias when it can lower both serum low-density lipoprotein cholesterol and triglyceride concentration and raise serum high-density lipoprotein cholesterol. The mechanisms whereby niacin exerts these lipid-modifying effects are in part through its action on a specific G protein-coupled receptor (GPR109 A/GPR109 B) and also activating the hydroxyl carboxylic acid (HCA) receptor 2. Niacin also inhibits diacylglycerol acyltransferase-2 and yet stimulates the ABCA1 transporter involved in high-density lipoprotein cholesterol metabolism. Niacin can cause various side effects, particularly when given at high dose for treating dyslipidemias. Side effects include cutaneous flushing, GI disturbance, impaired glucose tolerance, macular edema, and hepatic dysfunction. Nicotinamide usually causes fewer side effects than niacin and is the preferred treatment option for pellagra [18].

In summary, primary causes of pellagra can be poor intake of niacin or tryptophan. Secondary causes may be the result of malabsorption or failure to process niacin or tryptophan, such as seen in inflammatory bowel disease, excessive alcohol consumption, liver cirrhosis, carcinoid syndrome, and use of certain drugs (See Table 1). As Stratigos and Katsambas remarked, “pellagra is a still existing disease and as such its presence should not be forgotten by clinicians” [19]; wise words indeed as the case presented in this journal portrays [1].

### Table 1

<table>
<thead>
<tr>
<th>Some causes of niacin deficiency</th>
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<td>AIDS</td>
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<td>Alcohol dependency</td>
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<td>Anorexia nervosa</td>
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<td>Carcinoid syndrome</td>
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<td>Drugs; e.g. azathioprine, benzerazide, carbidopa, chloramphenicol, isoniazid</td>
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<td>Hartnup’s disease</td>
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<td>Liver cirrhosis</td>
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<td>Malabsorption states e.g. inflammatory bowel disease</td>
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<td>Poor dietary intake; e.g. predominantly corn diets</td>
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### References


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