Pediatric Pellagra

Overview

Background

Pellagra is a systemic nutritional wasting disease caused by a deficiency of vitamin B3 (niacin),[1] which is an essential component of several coenzymes. Besides ingestion, niacin can be endogenously synthesized from its natural precursor, the amino acid tryptophan, a process that requires 2 other B vitamins, B2 and B6. Pellagra occurs when intake of niacin and tryptophan are low (primary) or when conversion of the essential amino acid to the coenzyme (secondary) is impaired.

Don Gasper Casal, a Spanish court physician, first described pellagra among the poor peasants of the Asturias province of Spain in 1735. In Italian vernacular, pellagra means "rough skin" and refers to the thickened skin noted in patients with the condition. Pellagra remained endemic among the maize-eating poor peasants of southern Europe for nearly two centuries before the etiology of this condition was elucidated by a physician scientist in the United States.

Pellagra was first reported in the United States in 1902.[2] Soon, pellagra and its accompanying dementia occurred in epidemic proportions in the American South. Poverty and dietary consumption of corn were the most frequently observed risk factors. Individuals with pellagra were felt to be infectious and were placed in facilities to protect the remainder of society. Dr. Joseph Goldberger of the US Public Health Service was assigned to perform research in a pellagra hospital and hypothesized that the clinical syndrome was the consequence of an inadequate diet. He then demonstrated that pellagra could be induced and prevented by dietary modification.

In 1937, Conrad A. Elvehjem, an agricultural chemist at the University of Wisconsin, discovered that nicotinic acid cured black tongue (a condition analogous to pellagra) in dogs. Human clinical trials soon followed and confirmed that nicotinic acid (a derivative of niacin) represented the key preventive factor to pellagra. Diets based on unfortified maize (corn) are pellagragenic for the following two reasons: (1) These diets are low in tryptophan, the amino acid precursor of niacin, which can be used to offset a diet low in niacin, and (2) any endogenous niacin in untreated corn is bound in a nonbioavailable form. Following the discovery of niacin, food fortification with this water soluble B vitamin became feasible. Improved socioeconomic conditions, change in dietary practices, and food fortification with niacin were all responsible for the eradication of pellagra from the post–World War II United States.

Despite subsisting on a staple diet of corn, Latin Americans have remained essentially pellagra-free. In these cultures, maize has been presoaked in alkaline lime prior to the preparation of tortillas for several centuries. This step breaks down the outer shell of the kernel, thus liberating the bound niacin. This process enhances the dietary content of maize and ensures protection against pellagra. In contrast, endemic pellagra has been noted among poor peasants of the Deccan Plateau of India who subsist on a staple diet of sorghum (millet). Although this grain contains adequate tryptophan, it also contains high levels of leucine, another amino acid that interferes with the enzymatic conversion of tryptophan to niacin.

At present, pellagra is limited to populations with a compromised dietary intake of niacin and tryptophan or an excessive intake of leucine (a natural antagonist), especially in times of stress or in unique circumstances. These situations include chronic alcohol intake, individuals with significant malabsorption, administration of specific medications, or with a few rare disease entities that impact niacin availability.

Pathophysiology

Niacin is essential for adequate cellular function because of its required roles in 2 similar but distinct coenzymes (ie, nicotinamide adenine dinucleotide [NAD] and nicotinamide adenine dinucleotide phosphate [NADP]). Both of these are cofactors that can be recycled by serving as both oxidizing (NAD, NADP) and reducing (NADH, NADPH) agents.
During the oxidation of glucose and other intermediary metabolites, a substantial amount of chemical energy is released. NAD/NADH are able to transfer electrons in a process that captures the energy by generating high-energy phosphate bonds. The synthesized ATP then provides the energy necessary for other reactions of intermediary metabolism that simultaneously regenerate NAD from the reduced NADH. A portion of this cofactor is also converted to NADP/NADPH, which plays several distinct roles. Reduced NADPH is used in reactions that detoxify reactive oxygen species, that metabolize drugs in a cytochrome P450 system, and that support lipid biosynthesis.

Because of the large range of organs and tissues impacted by niacin deficiency, the clinical expression of pellagra is diverse. Pellagra is classically defined by "the 3 Ds" (ie, diarrhea, dermatitis, and dementia.) Almost universally, GI symptoms precede the skin manifestations. Mucosal inflammation and atrophy involves most of the GI tract. Evidence of glossitis and atrophy of the papillae of the tongue are characteristic findings, along with gastritis and subsequent gastric mucosal atrophy. Acute inflammation of the small intestine and colon are also commonly noted.

Skin lesions are usually sharply demarcated and occur in areas more prone to sun exposure. Histopathologic changes include vascular dilatation, proliferation of endothelial lining, perivascular lymphocytic infiltration, and hyperkeratinization and subsequent atrophy of the epidermis. Microscopic changes in the presence of a grossly normal nervous system can be found in the brain, spinal cord, and peripheral nerves. Findings include central chromatolysis of neurons, patchy demyelination, and degeneration of the various affected parts of the nervous system.

Pellagra is often an evolving process, which, if untreated, can lead to progressive deterioration and death (the fourth "D") over a period of years.

---

**Epidemiology**

**Frequency**

**United States**

In the early part of the 20th century, pellagra was a growing epidemic in the southeastern United States and caused public alarm. However, pellagra is no longer a concern. Although the current incidence of pellagra in the United States is unknown, it appears to be limited to sporadic cases. Primary pellagra is now seen in America in individuals with alcoholism, those who participate in "fad" diets, and those with primary or secondary malabsorption states. Secondary pellagra is also rare and seen in individuals with natural or iatrogenic compromise in the transformation of tryptophan to niacin, including carcinoid syndrome.[3]

Pellagra has also been reported in relation to intake of isoniazid, ethionamide,[4] and pyrazinamide for tuberculosis.[5] These agents have structural similarity to niacin and are able to function as competitive inhibitors.

**International**

Although the exact incidence of pellagra in other countries is unknown, chronic seasonal endemic cases of pellagra are observed among the sorghum-eating population of the Deccan Plateau in India.

Recent outbreaks of pellagra have been documented during emergencies in susceptible regions, including Malawi, Mozambique, Angola, Zimbabwe, and Nepal.[6] Epidemiologist from the United Nations World Food Program have reported an unanticipated persistence of pellagra for more than one year after the civil war in Angola ended.[7] Niacin deficiency was noted in almost one third of women and 6% of children in this country, in which untreated corn is the major food staple.

**Mortality/Morbidity**

Untreated pellagra results in death from multiorgan failure. Morbidity of pellagra is related to its effects on the various organ systems involved.

- Early systemic effects of the disease include malaise, apathy, weakness, and lassitude.
- GI involvement leads to a malabsorptive state and subsequent failure to thrive. The patient can appear to have irritable bowel syndrome.
- Dermatitis tends to be painful during the acute phase and eventually becomes disfiguring.
- Neurological manifestations include anxiety, depression, delusions, hallucinations, headaches, insomnia, and stupor.
- Besides presenting as the nonalcoholic pellagra, acute pellagraic encephalopathy can present with ataxia and myoclonus as the chief symptoms.
Race

No racial predilection for the development of pellagra is recognized, other than its rate of occurrence in ethnic populations with diets deficient in niacin, tryptophan, or both.

Sex

No biological sexual predilection for the development of pellagra is recognized. The only risk factors for the development of pellagra is dietary deprivation or defective endogenous generation of niacin.

Epidemiological data collected during the pellagra epidemic in the United States demonstrated that women, children, and elderly persons of both sexes had the highest prevalence of pellagra. Infants, adolescents, and working young males were least frequently affected.[2] These disparities are believed to be secondary to an unbalanced distribution of food within households.

Age

Pellagra typically is an adult disease. The classic symptoms of pellagra are generally not well developed in infants and children.[8] Adolescents and young children could develop pellagra if exposed to a pellagragenic diet. Pellagra rarely occurs during infancy. Historically, the dermatitis of kwashiorkor has been mistaken as infantile pellagra.

Presentation

History

Pellagra can be induced experimentally in 6-8 weeks with exposure to a pellagragenic diet.

In endemic cases, pellagra tends to be seasonal and occurs during spring and early summer. Early symptoms are nonspecific. Patients express weakness, lassitude, and anorexia. Soon, classic symptoms of GI involvement, dermatitis, and disturbed mental state follow.

A small US series reported that less than a quarter of patients with pellagra had a syndrome that included diarrhea, dermatitis, and dementia.[9] Isolated dermatitis and dementia were both slightly more common, whereas a combination of dermatitis and diarrhea was seen in nearly 20%.

A small Romanian series published in 1994 also described a slightly different clinical presentation for modern pellagra.[10] Sun exposure causes the skin to rapidly move from sunburn to pigmented and parched. Parched lips and angular stomatitis were also observed. GI symptoms suggest irritable bowel syndrome, with either constipation or diarrhea and abdominal discomfort. Dementia in this cohort was characterized by an unexpressive look, abnormal facial expressions, difficulty sleeping and headaches.

- GI findings
  - Pellagra begins in the gut, where metabolically active mucosal tissue is constantly turning over.
  - Patients with pellagra tend to suffer from poor appetite, nausea, epigastric discomfort, abdominal pain, and increased salivation.
  - Gastritis can be present and may result in achlorhydria.
  - Glossitis typically causes soreness of the mouth and dysphagia.
  - Diarrhea is the manifestation of intestinal inflammation. Diarrhea is typically watery (enteritis) but is occasionally bloody and mucoid (colitis).
  - A single case has been reported of a young woman who presented with pellagra secondary to megaduodenum. [11]

- Skin findings
  - Affected skin lesions are initially erythematous and are associated with a burning sensation.
The distribution of the cutaneous eruption is typically symmetrical and bilateral in parts of the body exposed to sun. There can be acute presentation with bullae, which has been referred to as wet pellagra. Dorsum of the hands and feet, neck area, and a malar rash are typical areas of involvement.

As the dermatitis progresses, the affected skin becomes hyperpigmented and thickened.

The dermatologic findings of pellagra, which responded to niacin supplementation, have been reported as an initial presentation of Crohn disease.[12]

For more detailed information, see the Medscape Reference article Dermatologic Manifestations of Pellagra.

- Neuropsychiatric findings
  - Early neuropsychiatric symptoms of pellagra include lethargy, apathy, depression, anxiety, irritability, and poor concentration.
  - As the disease advances, patients become disoriented, confused, and delirious. Eventually, the patient becomes stuporous and comatose.
- Death: Death is the result of the depletion of the coenzyme required to generate sufficient energy to support vital body functions.

**Physical**

See the list below:

- GI symptoms
  - Anorexia and malabsorptive diarrhea lead to a state of malnutrition. The picture may initially be confusing because other B vitamin deficiencies may also be present. If severe enough, a kwashiorkor phenotype may be observed.
  - Often, the glossitis is severe and is associated with swelling and tenderness of the tongue. The tongue becomes beefy red and has a raw appearance secondary to atrophy of the papillae.

- Skin symptoms
  - Initially, the skin lesions of pellagra resemble a typical sunburn noted over parts of the body that have been exposed to the sun. They tend to be bilateral, tender and symmetrical in distribution.
  - Lesions may blister, vesiculate, and denude.
  - Eventually, the affected skin thickens and becomes hyperpigmented.
  - Parts of the body most commonly involved include the dorsum of the hands, feet, forearms, and legs. The face presents with a butterfly distribution over the cheeks, forehead, tip of the nose, and front V of the neck. The neck lesion is referred to as the Casal necklace, named after Don Gasper Casal who first described pellagra. Facial seborrheic dermatitis is noted in some patients. The scrotum, perineum[3], and pressure points may also be involved.

- Neurologic symptoms
  - Muscle weakness leads to gait problems.
  - Paraesthesia and a burning sensation are noted in some patients.
  - Mental status changes are early signs and become profound over time.

**Causes**

Dietary deficiency of bioavailable niacin and of its precursor, tryptophan, or malabsorption of these nutrients results in pellagra. Other mechanisms can lead to the deficiency by compromising conversion of tryptophan to niacin. Certain peculiar dietary amino acid imbalances can affect the body's ability to synthesize niacin and also cause pellagra.
Primary: Compromised intake of niacin or tryptophan
- Poverty
- Poor nutrition
- Chronic alcoholism
- Neglect and abuse, resulting in malnutrition
- Famine
- HIV
  - Anorexia nervosa: This association needs to be kept in mind as the relationship of these conditions is symbiotic. Deficiency of NAD leads to the manufacture of hunger–suppressive endorphins eliminating normal satiety signals making it easier to starve one self.
  - Sometimes persons with alcoholism can develop secondary issues that combine to yield pellagra.[13]

Primary: Compromised ability to absorb ingested niacin and tryptophan
- Malabsorptive states
- Prolonged diarrhea

Secondary: Altered intermediary metabolism impacting niacin synthesis
- Hartnup disease: This is an autosomal recessive disorder that compromises renal and intestinal transport of neutral amino acids.[14] The gene for this condition, which severely depletes tryptophan (the substrate for niacin synthesis), has been found by homozygosity mapping to be located on chromosome 5p15.
- Fad diets: Individuals following diets high in leucine and low in tryptophan (eg, rich in yogurt, gelatin) or groups who consume large amounts of the grain sorghum may develop pellagra.[15] Excessive leucine alters the normal metabolism of tryptophan and thereby contributes to low levels of niacin.
- Isoniazid therapy: Treatment with the antituberculosis drug isoniazid can lead to pyridoxine depletion. Pyridoxine, another B vitamin, is required as a coenzyme for the conversion of tryptophan to niacin. Isoniazid therapy is a well-recognized contributor to pellagra.
- Carcinoid tumors: Niacin and serotonin are alternative pathways of tryptophan metabolism. Normally, serotonin production only represents a small fraction of tryptophan degradation. Patients with carcinomas have excessive serotonin production. Increased diversion of tryptophan toward serotonin production results in a deficiency of substrate available for niacin synthesis.[16, 17]
- Medications: Like isoniazid, most of the medications associated with pellagra disrupt its endogenous synthesis from tryptophan. These include 5-flurouracil, pyrazinamide, 6-mercaptopurine, hydantoins, ethionamide, phenobarbital, azathioprine, and chloramphenicol.

Multifactorial, miscellaneous, or unknown mechanism
- Liver cirrhosis
- Diabetes mellitus
- Prolonged febrile illness, possibly leading to increased energy hence niacin requirements
- Human immunodeficiency virus (HIV) disease: Besides simply malnutrition, diarrhea, and febrile state, plasma tryptophan levels are decreased in patients with HIV, inducing a pellagralike state.[18] Certain authors have recommended niacin supplementation as a general therapeutic principle for HIV in the third world. However, a recent report on a cohort of well-nourished HIV positive children without diarrhea found no evidence for niacin depletion in this group.[19]
  - The clinical features in a group of patients with alcoholism and pellagra included confusion and/or clouding of consciousness, marked oppositional hypertonus (gegenhalten), and myoclonus.
Differential Diagnoses

- Acute Cutaneous Lupus Erythematosus (ACLE)
- Crohn Disease
- Discoid Lupus Erythematosus
- Drug Eruptions
- Drug-Induced Lupus Erythematosus
- Drug-Induced Pemphigus
- Drug-Induced Photosensitivity
- Pediatric Atopic Dermatitis
- Pediatric Contact Dermatitis
- Porphyria Cutanea Tarda
- Seborrheic Dermatitis
- Subacute Cutaneous Lupus Erythematosus (SCLE)
- Ulcerative Colitis

Workup

Laboratory Studies

Therapeutic response to niacin in a patient with the typical symptoms and signs of pellagra establishes the diagnosis.

Low serum niacin, tryptophan, NAD levels, and NADP levels were thought to reflect niacin deficiency and confirm the diagnosis of pellagra.

However, high-pressure liquid chromatography (HPLC) of urinary metabolites of niacin were shown to be a more sensitive investigation to identify pellagra in a cohort known to have the condition compared with measuring blood NAD and NADP levels. Concentrations in spot urine samples of 1-methyl-2-pyridone-5-carboxamide (2-PYR) and 1-methylnicotinamide (1-MN) were reported to be 91% sensitive and 72% specific in estimating niacin deficiency.[20]

While the above-mentioned assays are usually used during suspicion of pellagra, they are actually indirect tests for the dietary intake of niacin and tryptophan. If the deficiencies are short-lived, then they may not necessarily reflect clinical pellagra.

Histologic Findings

Histologically, the acute stage of dermatitis may show a variety of changes, including infiltration of the epidermis with neutrophils, intracellular edema, and intra- or subepidermal vesicle formation secondary to spongiosis or vacuolar degeneration of the basal layer. Older lesions may present with hyperkeratosis, parakeratosis, and variable acanthosis, with increased basal layer melanin.[13]

Treatment
Medical Care

Nicotinamide or niacin taken orally is usually effective in reversing the clinical manifestations of pellagra. Because patients are often malnourished and suffer from other vitamin deficiencies, provision of a high-protein diet and B-complex vitamins is needed for complete restoration of health.

A recent study conducted on a rat model of pellagra has shown that administration of the niacin precursor, L-tryptophan (L-trp) is effective in preventing pellagra, but its safety for this use in humans is yet to be established.[21]

Treating patients with alcoholism who have multiple B vitamin deficiencies with a B complex that has inadequate amounts of niacin or with thiamine and pyridoxine therapy without niacin may aggravate the neurological state or trigger the development of alcoholic pellagra encephalopathy.[22]

RDA for infants and children

The recommended intake of 6.6 niacin equivalents per 1000 kcal daily is accepted for children aged 6 months or older. For infants up to 6 months, it is accepted that breastfeeding by well-nourished mothers supplies adequate niacin equivalents to fulfil the needs (ie, 8 niacin equivalents/1000 kcal) of this age group.[8]

Diet

In order to prevent and/or treat pellagra, provide a diet high in protein and adequate in calories. The addition of meats, milk, peanuts, green leafy vegetables, whole or enriched grains, and brewers’ dry yeast can enhance the niacin intake. In patients with oral dysphagia secondary to glossitis, a liquid or a semisolid diet may be required. Long-term inclusion of milk, meat, and eggs in the diet ensures dietary adequacy of proteins essential for recovery.

Activity

Bed rest is mandatory in treatment of severe cases of pellagra.

Medication

Vitamins

Class Summary

These are organic substances required by the body in small amounts for various metabolic processes. Vitamins may be synthesized in small or insufficient amounts in the body or not synthesized at all, thus requiring supplementation.

Niacin (Vitamin B-3)

Source of niacin used in tissue respiration, lipid metabolism, and glycogenolysis. Exogenous administration cures the syndrome and, within the dosage levels prescribed, is not associated with uncomfortable flushing observed with niacin administration in other conditions (eg, hypercholesterolemia).

Follow-up

Further Inpatient Care
See the list below:

- Patients with acute cases of pellagra require bed rest during the initial phase of treatment.
- Patients with severe glossitis require a liquid or a soft solid diet to overcome the dysphagia.
- Various high-calorie drinks rich in protein and B vitamins (including niacin).
- Topical management of skin lesions with emollients may reduce discomfort.

### Deterrence/Prevention

See the list below:

- Avoid sun exposure during active phase of the disease.
- Close dietary follow-up of the patient upon recovery helps prevent recurrence of pellagra.

### Complications

See the list below:

- Dermatitis of pellagra can be distressing and disfiguring. Denudation of the vesiculated and blistered skin lesions can potentially become secondarily infected.
- Severe glossitis causes dysphagia.
- GI involvement leads to a malabsorptive state.
- Depression, anxiety, delusions, hallucinations, and coma are the neuropsychiatric complications observed among patients with pellagra.
- The malnourished state associated with pellagra results in death if untreated.

### Prognosis

See the list below:

- If pellagra is diagnosed and treated appropriately, the prognosis for recovery is excellent.

### Contributor Information and Disclosures

**Author**

Simon S Rabinowitz, MD, PhD, FAAP  Professor of Clinical Pediatrics, Vice Chairman, Clinical Practice Development, Pediatric Gastroenterology, Hepatology, and Nutrition, State University of New York Downstate College of Medicine, The Children's Hospital at Downstate

Simon S Rabinowitz, MD, PhD, FAAP is a member of the following medical societies: American Academy of Pediatrics, American Association for the Advancement of Science, American College of Gastroenterology, American Gastroenterological Association, American Medical Association, New York Academy of Sciences, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, Phi Beta Kappa, Sigma Xi

Disclosure: Nothing to disclose.

**Coauthor(s)**

Navneetha Unnikrishnan, MBBS  Resident Physician, Department of Pediatrics, State University of New York Downstate College of Medicine

**https://emedicine.medscape.com/article/985427-print**
Disclosure: Nothing to disclose.

Specialty Editor Board

Mary L Windle, PharmD Adjunct Associate Professor, University of Nebraska Medical Center College of Pharmacy; Editor-in-Chief, Medscape Drug Reference

Disclosure: Nothing to disclose.

Jatinder Bhatia, MBBS, FAAP Professor of Pediatrics, Medical College of Georgia, Georgia Regents University; Chief, Division of Neonatology, Director, Fellowship Program in Neonatal-Perinatal Medicine, Director, Transport/ECMO/Nutrition, Vice Chair, Clinical Research, Department of Pediatrics, Children's Hospital of Georgia

Jatinder Bhatia, MBBS, FAAP is a member of the following medical societies: Academy of Nutrition and Dietetics, American Academy of Pediatrics, American Association for the Advancement of Science, American Pediatric Society, American Society for Nutrition, American Society for Parenteral and Enteral Nutrition, Society for Pediatric Research, Southern Society for Pediatric Research

Disclosure: Serve(d) as a director, officer, partner, employee, advisor, consultant or trustee for: Nestle<br/>Serve(d) as a speaker or a member of a speakers bureau for: Nestle<br/>Received income in an amount equal to or greater than $250 from: Nestle.

Chief Editor

Jatinder Bhatia, MBBS, FAAP Professor of Pediatrics, Medical College of Georgia, Georgia Regents University; Chief, Division of Neonatology, Director, Fellowship Program in Neonatal-Perinatal Medicine, Director, Transport/ECMO/Nutrition, Vice Chair, Clinical Research, Department of Pediatrics, Children's Hospital of Georgia

Jatinder Bhatia, MBBS, FAAP is a member of the following medical societies: Academy of Nutrition and Dietetics, American Academy of Pediatrics, American Association for the Advancement of Science, American Pediatric Society, American Society for Nutrition, American Society for Parenteral and Enteral Nutrition, Society for Pediatric Research, Southern Society for Pediatric Research

Disclosure: Serve(d) as a director, officer, partner, employee, advisor, consultant or trustee for: Nestle<br/>Serve(d) as a speaker or a member of a speakers bureau for: Nestle<br/>Received income in an amount equal to or greater than $250 from: Nestle.

Additional Contributors

Steven M Schwarz, MD, FAAP, FACN, AGAF Professor of Pediatrics, Children's Hospital at Downstate, State University of New York Downstate Medical Center

Steven M Schwarz, MD, FAAP, FACN, AGAF is a member of the following medical societies: American Academy of Pediatrics, American College of Nutrition, American Association for Physician Leadership, New York Academy of Medicine, Gastroenterology Research Group, American Gastroenterological Association, American Pediatric Society, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, Society for Pediatric Research

Disclosure: Nothing to disclose.

Acknowledgements

Valeriya Feygina, MD, PhD Resident Physician, Department of Pediatrics, Richmond University Medical Center

Disclosure: Nothing to disclose.

Kumaravel Rajakumar, MD, Department of Pediatrics, Assistant Professor, Children's Hospital of Pittsburgh, University of Pittsburgh.

Kumaravel Rajakumar is a member of the following medical societies: Ambulatory Pediatric Association and American Academy of Pediatrics

Disclosure: Nothing to disclose.

Sujana Reddy, MD Staff Physician, Department of Pediatrics, Richmond University Medical Center, Staten Island

Sujana Reddy, MD is a member of the following medical societies: American Academy of Pediatrics

Disclosure: Nothing to disclose.
References


