Pathophysiology and clinical management of pellagra — a review

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Abstract: Pellagra is a rare disease caused by niacin deficiency or a disruption of its metabolism. Its manifestations are dermatitis with pronounced photosensitivity, gastrointestinal symptoms, and neuropsychiatric ailments. Currently pellagra is developed in people who chronically abuse alcohol or are treated with medications from specific pharmacological groups (immunosuppressive and anti-tuberculosis drugs).

Although the root cause of the disease was established in the mid-twentieth century, a detailed explanation of the processes leading to the development of symptoms has not yet been proposed. They include complex abnormalities at the molecular, metabolic, and immunological levels.

Diagnostics is based primarily on the clinical presentation of the disease, while auxiliary tests play secondary role. The low prevalence of the disease, meaning that physicians are unfamiliar with its recognition, often leads to delays in diagnosis and appropriate treatment. The therapy is causal and based on administering niacinamide. Failure to implement treatment in the early stages of the disease leads to the patient’s death.

The aim of this literature review is to summarize the current state of knowledge on the pathomechanisms of pellagra, highlighting the clinical implications, and key elements of diagnostic and therapeutic management that are important in the treatment of pellagra patients.

Keywords: pellagra, niacin, vitamin B₃, tryptophan.

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**Introduction**

Pellagra (from Italian *pella agra*, i.e., rough skin) is a disease triggered by abnormalities in the metabolism of niacin (known also as: nicotinic acid (and nicotinamide), vitamin B₃, and vitamin PP (Pellagra Preventing factor)). The historical cause of the disease was an unbalanced diet, such as consumption of mainly corn products [1, 2].

The clinical manifestation of pellagra is elucidated by the acronym 3D’s—dermatitis, diarrhea, and dementia. Then the fourth letter D, which means death, is commonly added, as the improper treatment leads to patient’s death during multi-organ failure [3–5]. Due to the low prevalence of pellagra in developed countries (it is mainly observed in patients in specific risk groups), proper diagnosis and treatment are often delayed.

In turn, the incidence of pellagra in the countries of Africa and East Asia ranges from 5% to 35% (e.g., in Angola, Malawi, Tanzania or India), posing a serious challenge for public healthcare there [6].

The aim of this work is to systematize and summarize the current state of knowledge about the pathomechanisms responsible for the development of pellagra symptoms and the crucial aspects of the diagnostic and therapeutic procedure.

**Pathophysiology — biochemical background of pellagra**

*Niacin and tryptophan*

The key factor responsible for the pellagra symptoms are niacin [7] and L-tryptophan (Trp) deficiencies [8]. Bearing in mind that niacin plays a central role in energy metabolism and post-translational processes of protein modification, and given the complexity of tryptophan catabolic pathway (Fig. 1), a unified theory explaining the characteristic symptoms of the disease is difficult to propose.

Incorporation of niacin into the metabolic pathways requires its conversion to nicotinamide adenine dinucleotide (NAD⁺) (which acts as coenzyme) with the consumption of adenosine triphosphate (ATP) catalyzed by nicotinic acid phosphoribosyltransferase and NAD⁺ synthetase. In the NAD⁺ form, niacin is engaged in hundreds of metabolic reactions, in which it is capable of: (1) acting as a hydride acceptor (H⁻; oxidation-reduction reactions) and transferring it to the mitochondrial respiratory chain; (2) being phosphorylated to form NADP⁺ [9], involved in most biosynthetic pathways; (3) functioning as a donor of the ADP-ribosyl group, which modifies numerous proteins after attachment by poly-ADP-ribosylases (PARPs) [10].

L-tryptophan is an essential amino acid which side chain contains an aromatic indole bicycle residue. Its interaction with niacin metabolism results from being constantly converted to NAD⁺ in the kynurenine pathway, which utilizes ~95% of the
available Trp. It was estimated that a dietary intake of 60 mg of Trp per day is sufficient for the endogenous synthesis of 1 mg of niacin [11]. To maintain balance between above mentioned process and its side reactions (resulting in useless or even harmful end-products), the kynurenine pathway is regulated by the availability of coenzymes derived from other vitamins, in particular: flavin adenine dinucleotide (FAD, vitamin B₂), pyridoxal 5’-phosphate (PLP, vitamin B₆) and tetrahydrofolate (THF, vitamin B₁₁). The hepatic enzyme that controls the metabolites flux through the kynurenine pathway, i.e., tryptophan 2,3-dioxygenase (TDO), contains a heme moiety in its active site, thus linking Trp metabolism to heme biochemistry. Under physiological conditions, only ~1% of the available Trp undergoes peripheral conversion to serotonin (5-hydroxytryptamine, 5-HT) by monooxygenase.

The average daily requirement for niacin in adults is 15 mg. In children, these values are correspondingly lower depending on body mass (for small children about 4–8 mg per day), but during pregnancy they increase by ~20% [12]. Approximately 100 g of protein contains the amount of Trp needed to cover the daily requirement for...
vitamin B₃. The products most abundant in this amino acid are meat, milk, eggs, and some plant products (oats, sesame, sunflower, soy). The historical form of pellagra induced by improper diet stemmed from the dominant role of maize as an energy source. This plant contains a scarcity of Trp (~40 mg/g of nitrogen), and niacin in a non-digestible form (covalently bound to hemicellulose) [13]. The process of nixtamalization in an alkaline environment increases the bioavailability of vitamin B₃ from corn.

Niacin deficiency

Changing nutritional habits resulted from the improved availability of high-protein products and extended heterogeneity of agricultural crops. Therefore, insufficient supply of niacin is now a sparse cause of pellagra in highly developed countries [14]. Currently, pellagra develops mainly because of ethyl alcohol abuse. Excessive consumption of ethanol severely impairs niacin metabolism — not only by means of insufficient intake and disturbed absorption of nutrients and group B vitamins, but also through direct modification of kynurenine pathway enzymes by ethyl alcohol molecules (TDO inhibition, disturbance of available PLP — as consequence of its reaction with ethanol-derived acetaldehyde) and overlapping with other mechanisms that produce pellagra symptoms (i.e., γ-aminobutyric acid (GABA) receptors activity, see below) [12].

The second most common cause of pellagra are the adverse effects of immuno-suppressive drugs, i.e.: azathioprine, 6-mercaptopurine and 5-fluorouracil (mechanism involves depletion of Langerhans cells, which absence in the epidermis is one of the hallmarks of pellagra [15]), and anti-tuberculosis drugs: isoniazid, pyrazinamide, ethionamide (vitamin B₆ antimetabolites) [16]. Abnormal intestinal absorption of niacin and Trp may also lead to the development of pellagra, for example in the course of inflammatory bowel diseases and chronic diarrhea (including human immunodeficiency virus (HIV) infection) [17]. In 1956, a rare autosomal recessive genetic disorder, known as Hartnup’s disease, was described (named after the first family in which it was recognized). The loss of the function mutation in gene encoding the SLC6A19 channel, which enables the transport of Trp (and other neutral amino acids) through the intestinal epithelium and renal tubules, results in significant impairment in Trp absorption [18]. Symptoms of niacin deficiency may also appear in anorexia nervosa.

The considerable expression of the kynurenine pathway enzymes was identified only in hepatocytes [11]. For this reason, chronic liver disease is another condition predisposing to pellagra (especially if accompanied by a reduced supply of niacin). The abnormal metabolism of Trp is also a characteristic feature of the carcinoid syndrome, in which up to 99% of Trp is converted to 5-HT [19].
Factors uncoupling Trp metabolism also encompass the excessive supply of L-leucine (Leu). The first reaction of catabolism of this amino acid requires a specific aminotransferase, thus reducing the available pool of vitamins B₆ (being bound by the aminotransferase) and lowering the activity of kynureninase. Furthermore, Leu was shown to interfere with the formation of NAD⁺, by blocking the nicotinic acid phosphoribosyltransferase. The role of Leu is particularly emphasized in the development of neuropsychiatric symptoms of pellagra, because it competes with other neutral amino acids (e.g., Trp) for binding by transporters located in the glial cell membrane – disrupting the process vital for the transfer of Trp through the blood-brain barrier (BBB) [20].

**Relationship of niacin and tryptophan deficiencies with pellagra**

The main symptoms of pellagra are defined by the forementioned 3D triad of dermatitis, dementia, and diarrhea. Although it is currently proposed to redefine the individual components of the disease definition [2], the statement that skin and nervous system symptoms precede those of the gastrointestinal tract remains unchanged. The pellagrous dermatitis is characterized by pronounced photosensitivity (skin lesions are located almost exclusively on surfaces exposed to sunlight). The UV radiation elicits accelerated formation of reactive oxygen species (ROS), which oxidize lipids, proteins, and nucleic acids. The consequences are an increased production of inflammatory mediators and the formation of dysfunctional crosslinks in macromolecules, the formation of thymidine dimers and oxidation of purine bases [21]. Depending on the wavelength of the radiation, the detailed mechanism of the development of inflammatory state seems to be different. UVA with a length of 350–380 nm induces phototoxicity in keratinocytes, depending on the excitation of the intermediates of the kynurenine pathway (especially kynurenic acid). Their concentration in blood and tissues also elevates in case of blocking the activity of kynureninase (for example, in a deficiency of vitamin B₆). An analogous photosensitizing effect of 5-aminolevulinic acid (5ALA) (accumulating in the case of vitamin B₆ deficiency too) has also been postulated.

An additional mechanism related to the increase in 5ALA-dependent phototoxicity stems from the deficiency of picolinic acid (PA), a molecule facilitating the absorption of zinc (Zn) in the gastrointestinal tract [12]. Zinc is a micronutrient needed for the proper course of the heme synthesis process, especially catalysis led by ALA dehydratase.

In recent studies on the pathophysiology of pellagra, prostaglandin E2 (PGE₂) was identified as a critical mediator of UVB-induced photoinflammation (280–320 nm). The produced ROS induces type 2 cyclooxygenase (COX-2) in keratinocytes, and the resulting PGE₂ acts on EP4 receptors. The activity of EP4 directly correlates with
the intensity of inflammation in the skin [21]. Another evidence of oversensitivity to UVB radiation is a decrease in the epidermal population of Langerhans cells (apart from the surrounding of the hair follicles), with a simultaneous increase in the CD1a+ population of pro-inflammatory cells showing functional features of macrophages [15].

It is plausible that the lack of energy (in the form of NADH) or the reduction force required to remove ROS (i.e., NADPH), directly determines the high susceptibility of the skin to damage, as it is tissue with particularly high cell turnover [22]. Moreover, NAD+ is necessary for poly-ADP-ribosylation of sirtuins and enzymes repairing DNA double strand breaks, providing their proper functioning [10].

So far, no validated hypothesis has been proposed to explain the increased skin dryness in pellagra. The idea of the role of decreased urocanate (due to insufficient histidase activity in Zn deficiency) had been considered for decades, however, was rejected because patients with congenital histidinemia do not develop skin symptoms of pellagra at all [23]. The increase in Trans Epidermal Water Loss (TEWL) observed in pellagrous skin may simply be the result of extensive damage to the epidermal barrier and higher permeability for water molecules.

The mechanisms of the symptoms from the gastrointestinal tract (GIT) in patients with pellagra are similar to found in skin, because GIT also comprises tissue with a high cellular turnover. In GIT, various damaging factors act, instead of UV radiation: food (containing preservatives or dyes), bacterial toxins, etc. Usually (60% of cases) extensive inflammation develops, often affecting the mucosa of the entire GIT [2].

Neuropsychiatric disorders characteristic of pellagra (depression, schizophrenia, dementia) are the result of an impaired transformation of Trp to 5-HT (usually the conversion rate is reduced, except for carcinoid syndrome) or inappropriate activity of N-methyl-D-aspartate (NMDA) and GABA receptors [12]. Under physiological conditions, Trp transport through BBB accounts for approximately 8% of the total pool of transferred neutral amino acids (expressed as the ratio: [Trp]/[CAA]; Competing Amino Acids), while in pellagra it drops to 3%. The role played by niacin in the development of psychopathological symptoms seems unquestionable, accounting for that a recent GWAS study showed that the NAPRT1 (nicotinic acid phosphoribosyltransferase) is a major susceptibility gene for schizophrenia [20].

The reduced flux of metabolites through the kynurenine pathway leads to a decrease in the ratio of quinolinic acid and kynurenic acid (quotient [QA]/[KA]), resulting in an abnormally low activity of NMDA receptors. Moreover, the accumulating 5ALA activates presynaptic GABA receptors, thus reducing GABA release by 50%. Such a constellation of receptor activity predisposes to schizophrenia. Since Trp abnormal transformation (e.g., due to vitamin B₆ deficiency) plays a pivotal role in the pathophysiology of neuropsychiatric symptoms, it is possible to develop neuropsychiatric form of pellagra with sufficient niacin consumption but low Trp intake [24].
Clinical presentation of pellagra

Cutaneous manifestations

Pellagra is classified into the group of photodermatoses. The eruptions are symmetrical and visibly confined to the areas exposed to UV radiation (photodistribution). Common localizations include: the dorsal surface of the hands (affected in more than 95% of cases), the face, and the neck. Additionally, lesions may develop in the sites of bony prominences, and around the perineum and scrotum, usually forming erosions [1, 2, 16, 25, 26]. The eruptions are accompanied by burning pain that intensifies on palpation. Gradually, the erythematous changes become hyperpigmented (mahogany, or cinnamon color). Considerable dryness and intense exfoliation of the epidermis make the skin parchment-like look. Ultimately, the evolution of lesions ends in lichenification with excessive, abnormal keratosis (scales formation) and the development of fissures on the hands and feet surface (goose skin symptom) [1, 2]. Another term used to describe skin lesions morphology in pellagra is ‘shellac-like appearance’ [3].

The characteristic distribution of changes on the dorsal surfaces of the hands and forearms is called the gauntlet (or glove) sign. On the lower extremities, eruptions can develop following an identical pattern — on the dorsal surface of the foot and the anterior surface of the shins (referred to as the boot sign). In countries of a temperate climate, where the footwear is worn most of the time, the sandal sign is more widespread — changes appear only on the exposed surface of the foot [1, 3]. On the face, the rash localizes in the region of the anatomical course of the trigeminal nerve branches [3]. Erythematous patches on the surface of the nose and cheeks sometimes resemble those observed in systemic lupus erythematosus (butterfly sign, or malar rash). The skin of eyelids and auricles is usually not affected.

The eruptions surrounding the base of the neck are called the Casal’s collar (or the Casal’s necklace). Most often they cover the area of C3 and C4 dermatomes [1, 3, 26, 27], but sometimes they also extend to the skin of the sternum region (cravat sign). The eponym honors the author of the first historical description of pellagra, Don Gaspar Casal (1735).

In some patients, vesicles, and blisters (the form known as wet pellagra) appear within the lesions, frequently undergoing impetiginization. Due to impairment of skin healing, they tend to resolve with scarring. Such a clinical picture is mainly observed in the relapsing form of pellagra, referred to as pemphigus pellagrous [1, 3, 28, 29].

Disfiguring skin lesions contribute to the social stigma of the patient, significantly reducing the quality of life [30, 31].
**Gastroenterological symptoms**

Early gastrointestinal symptoms include loss of appetite, nausea, and vomiting. In one third of patients the area around the lips is swollen, accompanied by inflammation of the oral mucosa [3, 16]. About 60% of patients develop cheilitis, and glossitis with lingual hypertrophy and multiple erosions (causing dysphagia) [3, 28]. Another common symptom is gastritis with achlorhydrina [2, 3, 6, 32].

Diarrhea is reported in 20% of patients, as well as blood and mucus in the stool [1, 3, 28]. Intestinal inflammation aggravates malabsorption, which leads to malnutrition and cachexia, and exacerbates the other symptoms of pellagra (vicious cycle).

**Neuropsychiatric symptoms**

Neuropsychiatric symptoms of pellagra may occur even several years after the onset of skin lesions [1]. In the early stages, their character is nonspecific (fatigue with loss of concentration, nervousness and headaches). Then disturbances of sleep and wake rhythm, of mood (including depression) and anxiety develop [1–3, 6, 25, 33]. The most severe manifestations include schizophrenia and progressive dementia with memory loss, hallucinations, and delirium [2, 25, 34]. Less common are sensorimotor neuropathy, parkinsonism, and optic neuritis with photophobia [1–3].

Awareness should be raised during the management of patients with chronic alcohol abuse, because in exacerbation of pellagra, neuropsychiatric symptoms might resemble those of Wernicke’s encephalopathy [2, 5, 32]. A rare cause of sudden death in pellagra is central pontine myelinolysis [1].

The isolated neuropsychiatric pellagra (without accompanying skin and gastrointestinal disorders) was reported too [2].

**Auxiliary testing**

The diagnosis of pellagra is based on the data obtained from the anamnesis and physical examination (especially dermatological and neurological). Information about eating habits, chronic alcohol abuse and medications is particularly important. Moreover, the diagnostic procedure should cover the etiological factors of the secondary pellagra (Table 1).

**Table 1.** The risk factors of pellagra.

<table>
<thead>
<tr>
<th>Nutritional deficiencies</th>
<th>Malabsorption</th>
<th>Pharmacotherapy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>a diet based on a high consumption of corn</td>
<td>chronic alcohol abuse</td>
<td>isoniazid</td>
<td>AIDS</td>
</tr>
<tr>
<td>anorexia nervosa</td>
<td>chronic diarrhea</td>
<td>azathioprine</td>
<td>carcinoma syndrome</td>
</tr>
</tbody>
</table>
None of the available laboratory methods is characterized by sufficient sensitivity and specificity to be utilized for making definitive diagnosis. In case of diagnostic difficulties, measurement of Trp, NAD and NADP concentrations in whole blood and urine may be considered. The excretion of less than 0.8 mg of N\textsuperscript{1}-methylnicotinamide (NNMT) in the 24-hour urine collection is suggestive of pellagra [1, 3, 27]. To assess niacin metabolism, the “niacin number” ([NAD]/[NADP] \times 100) might be calculated. A value lower than 130 indicates a niacin deficiency [35].

Determination of 5-hydroxyindoleacetic acid in the 24-hour urine sample allows to exclude carcinoid syndrome in which this metabolite drastically raises (normal range: 1–15 mg/d). Oppositely, values below the normal range may indicate the sequestration of tryptophan to the synthesis of niacin, which is the result of insufficient exogenous supply of this vitamin.

Macrocytic anemia is frequently observed in the complete blood count. Other, non-specific, findings obtained in pellagra include hypoproteinemia and elevated liver enzymes [2, 36].

Histopathological features of pellagra include hyperkeratosis and parakeratosis with a slight spongiosis, increased melanin retention in the basal layer and dilated capillaries of the dermis with extravasated erythrocytes. The number of Langerhans cells is severely reduced. The less specific features of the disease included enlarged keratinocytes, oedema of the skin papillae, and subtle lymphocytic infiltrates (rarely neutrophilic) around the blood vessels. Intra-epidermal or sub-epidermal blisters are less common. Occasionally, advanced lesions present fibroblast proliferation and increased fibrosis, as well as atrophy of skin appendages [3, 36].

Table 1. cont.

<table>
<thead>
<tr>
<th>low socio-economic status</th>
<th>inflammatory bowel disease</th>
<th>ethionamide</th>
<th>liver cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a gluten-free (unenriched) diet</td>
<td>malignancy</td>
<td>6-merkaptopurine</td>
<td></td>
</tr>
<tr>
<td>insufficient supply of vit. B\textsubscript{2} and vit. B\textsubscript{6}</td>
<td>Hartnup’s disease</td>
<td>estrogens</td>
<td></td>
</tr>
<tr>
<td>gastroenterostomy</td>
<td>anticonvulsants</td>
<td></td>
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<tr>
<td>gastrectomy</td>
<td>chloramphenicol</td>
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<td></td>
<td>phenobarbital</td>
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</table>
**Differential diagnosis**

Typical cases of pellagra manifest skin lesions with a characteristic morphology. However, patients with a different course were described, which symptoms were limited only to GIT or the nervous system. As a malignancy might also be the cause of such presentation, it is justified to perform imaging (X-ray of the chest, CT of the chest and abdomen) and endoscopic examinations (gastroscopy and colonoscopy).

The other disease entities that should be considered in the differential diagnosis of pellagra are summarized in Table 2.

**Table 2. Differential diagnosis of pellagra.**

<table>
<thead>
<tr>
<th>Disease Entity</th>
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<tbody>
<tr>
<td>photosensitivity reaction</td>
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<tr>
<td>polymorphic light eruption (chronic)</td>
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<tr>
<td>kwashiorkor</td>
</tr>
<tr>
<td>deficiency of B vitamins, other than vit. B₃ (in particular B₁, B₂, B₁₂)</td>
</tr>
<tr>
<td>cutaneous lupus erythematosus (CLE)</td>
</tr>
<tr>
<td>drug-induced skin inflammation</td>
</tr>
<tr>
<td>atopic dermatitis</td>
</tr>
<tr>
<td>porphyria cutanea tarda</td>
</tr>
<tr>
<td>variegate porphyria</td>
</tr>
<tr>
<td>Wernicke’s encephalopathy</td>
</tr>
<tr>
<td>inflammatory bowel disease</td>
</tr>
</tbody>
</table>

**Treatment**

The standard treatment of pellagra is oral nicotinamide (niacinamide) supplementation. The commonly accepted dosage regimen is 300 mg daily divided into 3–4 doses. Therapy should last 3–4 weeks [37]. Improvement usually occurs within a few days, with skin lesions subsiding as first [4]. It is vital to administer preparations of other group B vitamins as well, because patients with pellagra often suffer from multivitamin deficiencies. This is particularly true for chronic alcohol abusers.

Nicotinamide therapy is also effective in Hartnup’s disease. An important difference is the necessity to supplement niacinamide for the rest of life, adjusting the dosage to the clinical response (usually 50–300 mg per day) [38]. Some patients with Hartnup’s disease might avoid pellagra by keeping a proper diet as the only preventive measure.

Zinc supplementation may be considered too [12]. This micronutrient is required for the phosphorylation of pyridoxine to PLP (important in the metabolism of Trp). Often concomitant excessive alcohol consumption contributes to the development of zinc deficiency [39].
It is also possible to treat pellagra with nicotinic acid, but its use is justified only if nicotinamide is unavailable. Adverse reactions of this medication include flushing and itching of the skin, severe headaches, and dyspeptic ailments, which negatively affect the patient’s compliance during treatment.

Topical treatment is based on the application of emollients (to reduce skin dryness) and photoprotection, according to the commonly accepted principles. It is of high importance to educate each patient on the rules of using preparations containing UV filter [40].

It should be stipulated that it is possible to effectively treat pellagra with tryptophan [41]. However, such approach can only be considered if other treatment methods are unavailable, as tryptophan is a factor possibly causing eosinophilia-myalgia syndrome (EMS) [42].

The fundamental of maintenance therapy and the prevention of disease relapses is a properly composed diet. Foods particularly rich in niacin include yeast, eggs, meat and fish, peanuts, bran, legumes, and seeds. Moreover, it is important to consume enough (about 100–150 g/day) of wholesome protein contained, for example, in dairy and meat products [43]. Food rich in B vitamins, e.g., yeast, is also beneficial.

In the case of drug-induced pellagra, discontinuation of the preparation responsible for the symptoms usually leads to a significant improvement. However, it is worth emphasizing that niacinamide treatment, without resignation of pharmacotherapy, might be effective. This is of great importance when the underlying disease requires continuous, intensive treatment (e.g., with immunosuppressive drugs) [44].

For pellagra developing due to alcohol abuse or eating disorders (e.g., anorexia nervosa), appropriate causal treatment includes proper specialist consultations, and, ultimately, addiction therapy or psychotherapy, respectively.

**Summary**

Pellagra’s 3D’s syndrome is a revelator of abnormalities in the complex metabolic pathways of niacin and Trp. Awareness of the most common risk factors contributing to the development of the disease enables targeted diagnostics. Since treatment implemented at an early stage of pellagra results in a complete resolution of its symptoms, the nosological diagnosis itself is the most critical stage of the management.

Therefore, a holistic approach to the patient’s health state is warranted, covering both a detailed anamnesis (particularly in scope of eating habits, alcohol consumption, and pharmacotherapy), as well as a comprehensive dermatological and neurological examination.

By following these rules, helping people suffering from pellagra is within the reach of every doctor.
Conflict of interest

None declared.

References