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Review

Pellagra: A Health Crisis Sparked by Niacin Deficiency

Ojili Sannutha*[1], Chevuru Baby Shalini[2], Yadala Prapurnachandra[3]

[1]*Ratnam Institute of Pharmacy, Pidathapolur [V&P], Muthukur[M], SPSR Nellore District-524346*

[2,3]*Department of Pharmacy Practice, Ratnam Institute of Pharmacy, Pidathapolur[V&P], Muthukur[M], SPSR Nellore District-524346*

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Corresponding Author: *Ojili Sannutha*
Email: *sannutha0006@gmail.com*
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ABSTRACT:

Pellagra is a systemic disease caused by a severe deficiency of niacin. Primary pellagra is caused by a lack of niacin in the diet. Secondary pellagra can occur when the body is unable to absorb the niacin. In the early part of the 20th century , pellagra was a growing epidemic in the southeastern United States and caused public alarm.Primary pellagra is now seen in America in individuals with alcoholism . In dietary sources, niacin is present in fish, meats, and fortified foods such as cereal, bread, and legumes. During meat processing, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) can become hydrolyzed to free nicotinamide. The symptoms of pellagra include diarrhea, skin lesions, dementia.The gastrointestinal symptoms include vomitings, indigestion, abdominal pain etc.The neurological symptoms include memory loss, depression etc. And dermatological symptoms include rashes etc. Classic pellagra responds dramatically to oral administration of nicotinamide niacin 100-300 mg/day in three separate dose.

Keywords: Niacin deficiency, NAD, NADP, Fortified foods.

1.INTRODUCTION:

Pellagra is a systemic disease caused by a severe deficiency of niacin (via B3). It affects the whole body and can eventually leads to death.[1]

2.TYPES:

1. Primary pellagra is caused by a lack of niacin in the diet . It usually occurs in poor and food limited populations.

2 . Secondary pellagra: It can occur when the body is unable to absorb the niacin. It is a form of "malnutrition - specifically , micronutrient undernutrition. [1]

Niacin was initially referred to as the anti-black tongue factor due to niacin`s effect on dogs. In the 1700 pellagra first appeared in Italy and the name translates into "Pella", meaning skin , and "Agar" meaning rough. In the early 1900, pellagra was prevalent in the southern united states due to the low availability of corn.The primary dietary sources of niacin. Symptoms include the 4D`s dermaties , diarrhoea, dementia and death.[4]

Pellagra is a disease of poverty and social inequality(Brenton 1998). It has severely affected far more women than men. The disease results primarily from deficiencies in the B vitamin niacin and amino acid tryptophan. The first descriptions of pellagra were in the old world during the 18th century as maze was becoming more common as a staple food. This plague of corn" was rampantin some marginalized European peasant populations for centuries and prevalent among poor U.S southerners in early decades of twentieth century.[13]

3.LITERATURE REVIEW:

1.V. P. SYDENSTRICKER (1949) this article reviewed about a clinical standpoint the problems of the etiology and treatment of pellagra remain unsolved, and the mortality rates in general hospitals range between 20 and 50 per cent. In an effort to determine the most promising fields for further inquiry into the etiology of pellagra and also to determine the causes of such persistently high death rates, the records of 440 patients with this disease were analyzed. When patients were admitted to the hospital more than once, the new data were added to those previously recorded; no patient was counted twice.

2. Richard J. Castiello (1972) this article discusses that administration of niacinamide (nicotinamide; the amide form of Pellagra, a disease of niacin-deficiency, may occur in association with the carcinoid syndrome. A 63-year-old black woman had both diseases. In the carcinoid syndrome, functioning tumor cells indirectly depress endogenous niacin production by diverting tryptophan metabolism towards serotonin and away from niacin. Anorexia and diarrhea,

frequently present in the carcinoid syndrome, reduce the availability of exogenous niacin by decreasing the amount ingested and absorbed.

3. Barrett P. Brenton (2008) this article reviewed as Pellagra is generally characterized as a niacin deficiency disease. Symptoms include the four "D's" - dermatitis, diarrhea, dementia, and death. Historically, it has been linked to high maize and low protein diets. The "plague of com" was rampant in southern Europe for centuries and prevalent among U.S. Southerners in the early 1900s. Pellagra's social history is extensive and stands as a classic in the study of vitamins and nutrient deficiencies.

4. Supreeth S (2019) this article discusses that We rarely come across deficiency of niacin in the current clinical practice. Deficiency of niacin (Vitamin B3) leads to pellagra with constellation of symptoms affecting gut, skin, and nervous system. We present a case of nutritional deficiency of niacin presenting as pellagra in a 45-year-old female. The patient was treated successfully with Vitamin B3 supplementation. Pellagra shall be considered in differential diagnosis of chronic diarrhea when associated with skin lesions affecting sun-exposed areas.

4.AIM : The overview of the epidemiology, pathophysiology , and clinical manifestations of pellagra emphasizing its impact on global health.

OBJECTIVES:

- Review the risk factors for developing niacin deficiency.
- Explain the common physical exam findings associated with niacin deficiency.
- Outline the importance of collaboration and communication among the interprofessional team to improve outcomes for patients with niacin deficiency.
- To prevent complications like skin problems , gastrointestinal issues and neurological problems

5.Epidemiology of pellagra

UNITED STATES STATISTICS:

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.[4]

Primary pellagra is now seen in America in individuals with alcoholism , 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. [4]

Pellagra was endemic in Egypt until the gradual replacement of maize with wheat brought about improvements. In areas of Africa, south of the Sahara, Nyasaland.Beside Africa, a significant no of cases have been reported in Asia. The disease is endemic in the deltas of some rivers in china. However most reports related to pellagra in Asia have come from India. Pellagra is historically a disease of maize eating population, it has been reported in T.S and A.P in some segments of population who eat Juwan.[3]

Pellagra has occured in many geographical areas as one of the commonest worldwide affliction. Pellagra declined in all parts of the world. Although today the condition is rather uncommon, occasional cases are found. It is still endemic in remote areas of the world where green, vegetables, fruits, animal proteins are unobtainable. [3]

6.ETHIOLOGY:

Niacin deficiency can occur from a lack of consuming dietary sources containing niacin. In dietary sources, niacin is present in fish, meats, and fortified foods such as cereal, bread, and legumes. To a lesser extent, niacin is in coffee, tea, and nuts. During meat processing, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) can become hydrolyzed to free nicotinamide. In some foods, such as corn, niacin can be covalently bound to carbohydrates or small peptides, decreasing the bioavailability for absorption in the small intestines. Therefore, some of the earliest signs of pellagra occurred in populations consuming a high corn-based diet. In addition to dietary sources, the liver can synthesize niacin from tryptophan; thus, a diet containing both niacin and tryptophan is necessary to maintain adequate niacin levels[13]

Alcohol-induced pellagra

De Oliveira Alves reported a case a seropositive HIV patient with a history of alcohol excess who presented with systemic symptoms ,progressive disorientation and skin manifestations of pellagra. Treatment with high protein,high-calorie diet and nicotinamide at 600 mg/day and showed rapid improved in the skin lesions after three weeks of treatment [5]

Direct damage of intestinal villi may also lead to intestinal absorption of niacin and tryptophan, leading to pellagra in alcoholics. Hiraga et al reported a rare case of laryngitis, glossitis and psychosis in a chronic alcoholic as a manifestation of pellagra.[5]

DRUGS AS A CAUSE OF PELLAGRA :

The WHO recommends isoniazid for prophylaxis against tuberculosis (TB) in people treated with highly active antiretroviral therapy (HAART) in countries with a high incidence of TB.1 The risk of developing pellagra in HIV patients with latent TB who were given Isoniazid prophylaxis has been commented on. Isoniazid reduces niacin levels in two ways: it inhibits its intestinal absorption and inhibits its endogenous production from tryptophan.18 Essentially, the human body treats the structurally similar isoniazid as if it were niacin and so behaves as if niacin concentrations are sufficient.[5]

The underlying causes of primary and secondary pellagra are different:[1]

Primary pellagra occurs if a person's diet is low in niacin. The people who are most at risk of getting primary pellagra are those whose diet relies mainly on maize.[1]

It is very rare in developed countries , where manufacturers routinely fortify flour with niacin.

A person who cannot absorb vitamin B-3, despite having a diet rich in niacin, may develop secondary pellagra. A significant risk factor for secondary pellagra is alcohol use disorder.[1]

An article from 2014 suggests that alcohol use disorder can cause pellagra through malnutrition. A person may not be eating enough food containing niacin, and the alcohol can prevent the body from absorbing it.[1]

Alcohol can also stop certain proteins from turning into niacin, increasing the risk of pellagra developing. However, alcohol-induced pellagra often goes undetected because its presentation is similar to that of alcohol-withdrawal delirium.[1]

Other risk factors for secondary pellagra include:

- Malntrition from homelessness , anorexia , HIV or end stage cancer
- Crohn's disease
- Hartnup disease
- Dialysis
- Certain drugs like isoniazid for tuberculosis
- Carcinoid syndrome, a collection of symptoms due to carcinoid tumors[1]

7.**PATHOPHYSIOLOGY:**

Pellagra can develop according to several mechanisms, classically as a result of niacin (vitamin B3) deficiency, which results in decreased nicotinamide adenine dinucleotide (NAD). Since NAD and its phosphorylated NADP form are cofactors required in many body processes, the pathological impact of pellagra is broad and results in death if not treated. [9]

The first mechanism is simple dietary lack of niacin. Second, it may result from deficiency of tryptophan, an essential amino acid found in meat, poultry, fish, eggs, and peanuts, which the body uses to make niacin. Third, it may be caused by excess leucine, as it inhibits quinolinate phosphoribosyl transferase (QPRT) and inhibits the formation of niacin or nicotinic acid to nicotinamide mononucleotide (NMN) causing pellagra-like symptoms to occur.[6]

The key factor responsible for the pellagra symptoms are niacin and tryptophan defeciencies. Bearing in mind that niacin plays a central role in energy metabolism and past translation process of protein modification and gives the complexity of tryptophan catabolic pathway.[4]

Features of pellagra have been produced experimentally in animals by nutritional deprivation of niacin. It has been theorized that manifestations of pellagra results from the inadequacy of NAD and NADP levels to maintain cellular energy transfer reaction.[3]

Hence, tissue with high-energy requirements such as brain or with high turn-over rates such as skin or gut are particularly affected. Photosensitivity is a prominent and initial manifestation of pellagra. It has been postulated to occur as a result of urocanic acid deficiency, which protects the skin from ultraviolet rays by absorbing light in UVB range.[3]

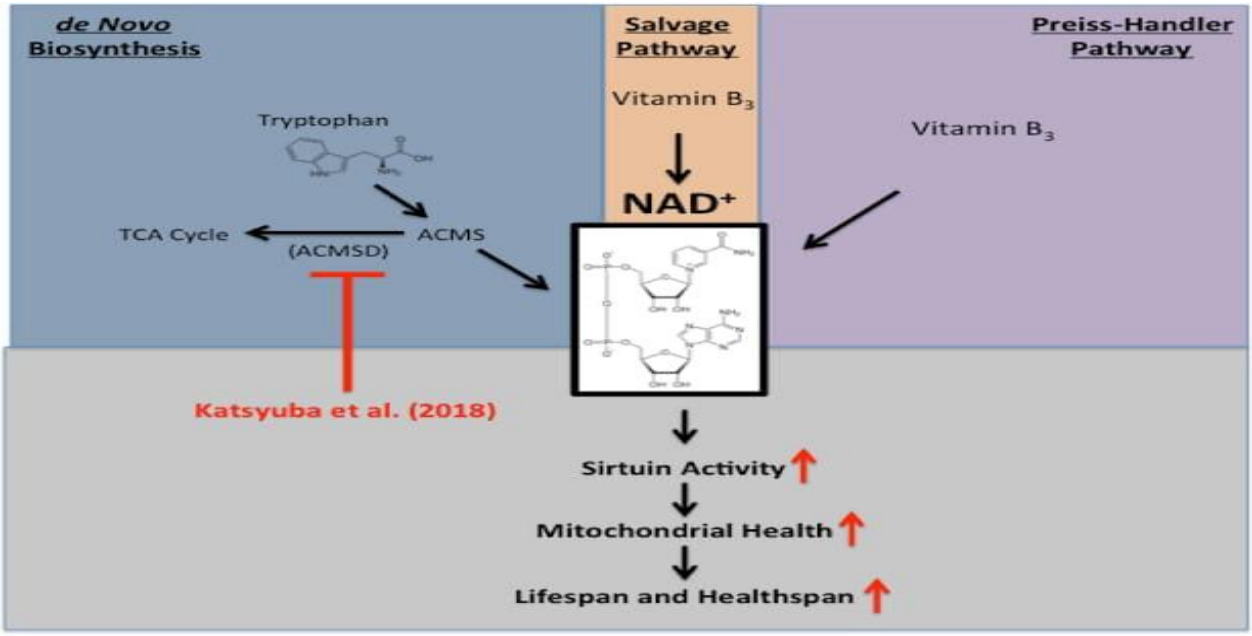

FIG-1: PATHOPHYSIOLOGY OF PELLAGRA

8.CLINICAL MANIFESTATIONS:

Pellagra is a multiple deficiency disease associated with diets providing low levels of niacin and tryptophan and often involving other vitamin B resulting in changes in the skin , gastrointestinal tract , and nervous system . [1]

The primary symptoms are :

- Diarrhea
- Skin lesions
- Dementia

GASTROINTESTINAL SYMPTOMS:(Diarrhea)

The most common gastrointestinal issue is diarrhea. Diarrhea is the passing of loose, watery stools at least three times per day.[1]

FIG-2; GIT SYMPTOMS

Diarrhea can lead to dangerous dehydration, and it can cause malnutrition over time, as it can affect the absorption of nutrients from food. It is also often the first symptom of pellagra to appear.[1]

Other gastrointestinal symptoms include:

- Vomiting
- Abdominal pain
- Nausea

- Indigestion
- Decreased appetite
- Oral ulcers

Diarrhea occurs when the mucous lining of the intestines fails to replenish itself fast enough. [5]

Without this mucosa , the intestines can't digest properly and they can't protect themselves from irritation and inflammation .[1]

Chronic inflammation affects mucous lining along the entire gastrointestinal tract , from mouth to bowels

This leads to gastrointestinal symptoms such as stomach pain and indigestion as well as symptoms of oral mucositis which include mouth sores and a red , swollen tongue.[1]

NEUROLOGICAL SYMPTOMS:(DEMENTIA)

Pellagra is a systemic disease, affecting the body as a whole as cells are deprived of the energy they need to perform bodily functions. This will eventually affect the brain and nervous system. Early symptoms may be vague. They may include lethargy, apathy and difficulty concentrating, or they may look more like anxiety or depression. Over time, symptoms progress to confusion and delusions. Severe cases may lead to permanent dementia, as well as neurological damage.[3]

Some neurological conditions, such as anxiety and depression, are early symptoms of pellagra.[1]

As pellagra advances, people may experience symptoms of dementia, including:

- memory loss
- delusions
- confusion
- In some cases, psychosis

There are three main symptoms of alcohol-induced pellagra that relate to the brain and nerves. These are:

- Intermittent confusion
- Stiff muscles that are hard to use
- Exaggerated startle responses[1]

Without treatment, pellagra can be life threatening and lead to death.

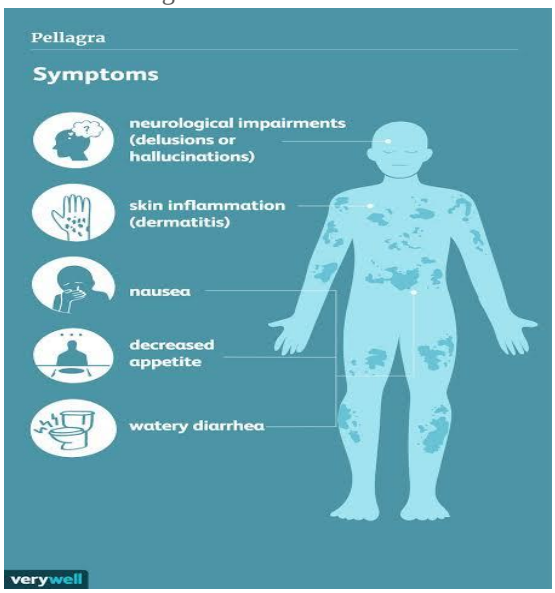

FIG-3: SYMPTOMS OF PELLAGRA

DERMATOLOGICAL SYMPTOMS:(SKIN LESIONS)

The dermatological changes called pellagra, are usually the most prominent.

The skin lesions starts with erythema resembling sunburn, which is symmetrically distributed on the parts of the body exposed to direct sunlight.[8]

The back of the hands and forearms upto the rim of the sleeves, the feet and legs upto the edge of the trousers are exposed to the sun.The genitals and pressure points may also be affected.[8]

Pellagra related dermatitis often causes thickened and scaly skin, rashes and discolouration .

FIG -4: SKIN RASHES

Complications of niacin deficiency include the condition of pellagra (associated symptoms include mental confusion, glossitis, alopecia, dermatitis, sensitivity to sunlight, enlarged heart, peripheral neuritis, and dementia). The following is a concise list of complications that can occur secondary to niacin deficiency:[8]

- Malnutrition and cachexia
- Secondary infection of the skin rashes
- Neuropsychiatric symptoms
- Coma [8]

9.CASE REPORT:

A 38-year-old woman presented with dry, cracked and hyper pigmented skin lesions over bilateral upper limb, neck and feet , since 4 months. The skin lesions were localised to sun exposed areas of the body indicating photosensitivity. The classical appearance of dermatitis and its distribution over the sun-exposed area confirms the diagnosis of pellagra. She reported burning sensations over these lesions and no diarrhoea or neurological symptoms. Her dietary habits were reported to be poor because of alcohol addiction.[14]

FIG-5: Woman with pellagra

10.DIAGNOSIS AND TESTS :

HOW IS PELLAGRA DIAGNOSED ?

Your healthcare provider will examine you and your symptoms and ask you about your medical history and diet. When they suspect pellagra, they may order a urine test to confirm it. Levels of certain chemicals in your urine can tell them if your body has enough niacin. They may also confirm pellagra by treating you with niacin supplements and seeing if that helps.[12]

Fig -6: Blood test

11.TREATMENT:

Classic pellagra responds dramatically to oral administration of nicotinamide or niacin (nicotinic acid 100-300 mg/day in three separate doses. Niacinamide is preferred because it does not cause vasomotor disturbances, like niacin. Mental changes disappear within 24–48 h but skin lesions may take 3–4 weeks. Most pellagrins require concomitant administration of riboflavin and pyridoxine, and a diet rich in calories and proteins to address malnutrition. A dosage of 40 –200 mg niacin per day is used to treat pellagra symptoms in Hartnup's disease and carcinoid syndrome. In patients with malabsorption syndromes and eating disorders, adequate nutritional supplementation can lead to the avoidance of pellagra. Early recognition of clinical features and appropriate knowledge of predisposing factors can avoid much morbidity and, sometimes, even mortality.[3]

Treating patients with excess alcohol use who have multiple vitamin B deficiencies with a B complex with insufficient amounts of niacin or with pyridoxine and thiamine therapy without niacin could aggravate the neurological clinical state or trigger the appearance of alcoholic pellagra encephalopathy.[13]

12.PREVENTION:

A well-balanced diet is the simplest way to ensure adequate nutrition. When food choices are limited, enriched foods and dietary supplements can help. A B-complex vitamin supplement provides enough niacin for most healthy adults. The recommended daily dose of niacin is about 15 milligrams [12]

The best food sources of niacin are:

- Beef liver.
- Beets
- Brewer's yeast
- Enriched bread and cereals
- Oily fish, such as salmon and tuna
- Peanuts
- Potato
- Poultry
- Rice
- Sunflower seeds
- Spaghetti sauce

If you have a chronic health condition that predisposes you to pellagra, you may need to discuss long-term prevention with your healthcare provider. This may involve diet, supplements or changes to your medications.[12]

13.CONCLUSION:

In conclusion , pellagra , a disease sparked by niacin deficiency , poses a significant threat to global health , particularly in vulnerable populations. The complex interplay between nutritional, socioeconomic, and environmental factors underscores the need for a multifaceted approach to prevention and control. Addressing niacin deficiency through dietary diversification , food fortification, and supplementation is crucial .

Moreover, enhancing public awareness access , and promoting research into the molecular mechanisms underlying pellagra are essential for mitigating this health crisis.

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