Summary

- Disease caused by lack of vitamin PP (niacin) or tryptophan
- High risk if unbalanced maize based diet
- 3 D's clinical signs: dermatitis, diarrhea and dementia
- Treatment by nicotinamide supplements/vitamin B complex and a balanced diet

Introduction

For many years, chiefly in regions where maize is the staple diet, a condition has been known which was characterized by cutaneous, mucosal and neurological abnormalities. This condition is known as pellagra. The disease derives its name from an old Italian description. It had been established that prisoners on a prolonged diet consisting solely of maize developed a skin problem. The etymology of the word is based on the Italian "pelle" (skin) and "agra" (rough). In the 18th century the inexpensive polenta, based on maize meal, was a staple of many rural regions of Italy. It was initially thought that the disease was caused by a fungal toxin in the food. In 1796, Dr Casper Casal, of Oviedo (Spain), described the disease mal de la rosa. The illustration in his work shows manifest skin lesions of the neck. Since that time, this symptom has been known as Casal's necklace.

Pellagra, historical note

In the early 20th century, pellagra was a major problem among the poor Southerners of the USA. The work of the American scientist Joseph Goldberger represented a milestone in the history of epidemiology when he discovered that orphans whose diet consisted mainly of maize with molasses developed pellagra and that others (who had a more varied diet) were not affected by the disease. None of the staff ever contracted the disease (they had the first choice of the food). He injected himself and several volunteers with blood from pellagra patients. Not one of them developed the disease. Even eating faecal matter of the patients (!) was likewise unable to induce the disease in these intrepid volunteers, which was a strong argument against an infectious origin. After milk, eggs and meat were put on the menu of the orphanages, pellagra disappeared. A controlled experiment at a State Prison Farm in Mississippi manifestly demonstrated that pellagra only develops after living on an

unbalanced diet. An animal model was developed using dogs that were fed on maize and subsequently developed so-called ‘black-tongue’.

In 1937 Conrad A. Elvehjem an agricultural chemist at the University of Wisconsin, discovered that nicotinic acid cures black tongue. It was discovered that the disease has its origins in a deficiency of a compound present in small quantities in food. The compound was designated as vitamin PP (pellagra preventing factor). Sometimes the term vitamin B3 is used. The identification of pellagra as a deficiency disease was not evident. There were sometimes apparently contradictory data. Early in the 20th century, for instance, pellagra was rife in the maize-eating population of Romania. Paradoxically, however, their maize contained more niacin than the food of the indigent population of India, where pellagra did not occur. The explanation was only discovered later when it became clear that maize contained very little tryptophan and that much of the niacin in maize is present as a bound form called niacytin (which is not absorbed in the intestine). The reason why pellagra did not occur in the indigenous maize-eating population of Central America was found to be based on the fact that they used alkali in the preparation of their maize meal, which released niacin from niacytin. They also had a more varied diet, which included a lot of beans (i.e. another food that contains niacin). It should be noted that white bread contains much less niacin than maize, but the niacin in maize is not fully available because it is in a bound form.

The highest prevalence in recent times has probably been in southern Africa, where conditions for some agricultural and industrial workers until 1994 were not unlike those in the southern United States between 1900 and 1920. A report from South Africa suggested that 50 percent of patients seen at a clinic in the Transvaal had some evidence of pellagra, and that the majority of adults admitted to the mental hospital in Pretoria had the disease. Pellagra regrettably has also been widely reported in refugee camps and in famine situations where maize has been the relief food and relief agencies have given too little attention to providing a balanced diet or adequate micronutrient intakes.

Niacin

Niacin is also known as nicotinic acid, although the latter term is avoided in order not to evoke an association with tobacco and thus make people suspicious. The amide is likewise active (nicotinamide).

Niacin is absorbed from food in the stomach and small intestine. A small quantity of niacin is produced endogenously from tryptophan, an essential amino acid. Food that is rich in tryptophan and deficient in niacin will not give rise to clinically manifest deficiency. Alcoholics and people with hyperthyroidism are at higher risk of contracting pellagra. The conversion from tryptophan to niacin is more difficult in people with vitamin B2 (riboflavin) and B6 (pyridoxine) deficiency.

Niacin is required for adequate cellular function and metabolism as an essential component of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). NAD and NADP are the active forms of niacin and are coenzymes for many dehydrogenases that play an important role in glycolysis, protein and amino acid metabolism, pyruvate metabolism, pentose biosynthesis, generation of high-energy phosphate bonds, glycerol metabolism, and fatty acid metabolism. In case of deficiency, all sorts of cell functions become deranged. High energy requirements (brain) or high turnover rate (gut, skin) organs are most susceptible to deficiency.

Aetiology

On average, a person needs approximately 20 mg niacin on a daily basis. Primary pellagra may be caused by niacin and/or tryptophan deficiency in the diet. A generally poor balance of amino acids in the diet could also give rise to pellagra. For instance, pellagra frequently affects people who eat sorghum (millet) as a staple food. This grain crop contains high concentrations of leucine. Although this grain contains adequate tryptophan, excessive concentrations of leucine interfere with tryptophan metabolism and subsequent niacin synthesis. Zein the main protein in maize (= corn) – which is the staple food in many parts of the world- contains very small amounts of tryptophan. Niacin in maize is chemically bound and is not absorbed in the intestine unless the food is treated with alkalis as lime water. An example of the latter is the tortilla. Food products that contain large quantities of niacin are liver, kidney, groundnuts and yeast and, to a lesser extent, wheat and green vegetables. The bioavailability of niacin from meat, milk, beans and eggs is excellent.

Secondary deficiency may develop in persistent chronic diarrhoea with malabsorption, liver cirrhosis and alcoholism and in the event of prolonged parenteral nutrition being given without vitamin supplements. During treatment with isoniazid (INH) the drug is substituted

for nicotinamide in the synthesis of NAD. The resulting molecule is inactive. In prolonged treatment with INH (tuberculosis) it is possible for iatrogenic induced pellagra to be provoked. On top of that, INH tends to bind to vitamin B_6 and reduce niacin synthesis, since B_6 (pyridoxine) is a required cofactor in the tryptophan-to-niacin reaction. There are also several situations where tryptophan metabolism is disrupted. For instance, pellagra may develop in carcinoid syndrome due to the conversion of tryptophan into serotonin (5-hydroxytryptamine). Beware the cluster abdominal pain, diarrhoea, flushing, variable blood pressure, pulmonary valve stenosis and intermittent wheezing in carcinoid syndrome.

Clinical aspects

Clinically, the disease is identified by the so-called classical three Ds: dermatitis, diarrhoea and dementia. Mucositis should also be added to these characteristic symptoms. The symptoms may develop alone or in combination. People suffering from pellagra usually appear poorly nourished with weakness and underweight.

Skin lesions occur symmetrically on areas of the skin exposed to sunlight, such as the face, the back of the hands, the neck, the forearms and exposed portions of the leg. Patients initially present with deepening of the pigmentation. The hyperpigmented areas lose the oily sheen of healthy skin and become dry, scaly and eventually cracked. There is usually a definite line of demarcation between these lesions and the healthy skin, and this line can be felt as the affected area is rough to the touch. The skin condition may remain static, heal or progress. If it progresses, desquamation commonly occurs; there may be deep cracking and fissuring and the skin becomes thick and rough; occasionally the skin may blister. The blisters contain a colourless exudate. In white subjects the skin lesions initially look like the erythema of sunburn. In both black and white patients, the lesions of pellagra produce burning sensations and pain when exposed to the direct rays of the sun, just as sunburn does in a person with pale skin.

The most conspicuous is a sharply defined symmetrical, desquamating rash in the neck (Casal’s necklace) and on the forearms. A butterfly-shaped rash may appear on the face, which must be distinguished from skin abnormalities in SLE patients. Secondary infection may develop, including wound myiasis. Skin lesions may be associated with acute intertrigo with erythema, maceration and abrasion; superinfection may develop in the predilection

areas (folds of the groin, genitals). Pellagra sometimes occurs without skin lesions (*pellagra sine pellagra*).



Casal’s necklace



Pellagra dermatitis with hyperpigmentation, drying, cracking and fissuring of the skin

Mucositis develops in the mouth, vagina and urethra. A red tongue and stomatitis are characteristic of acute deficiency. The tip and edges of the tongue are the first to be affected. This is followed by a generalized painful, burning glossitis, with swelling of the tongue and hypersalivation. Lip and tongue ulcers may develop. The area around the parotid duct orifice may become necrotic (the area opposite the molar teeth). Deeper mucosae may be affected, with sore throat and oesophageal damage with dysphagia and abdominal pain. Some patients report loose stools but these complaints are not usually predominant. Caution: chronic malabsorption in itself may induce niacin deficiency. Gastrointestinal hyperemia, ulceration and proctitis may lead to bloody diarrhoea. When angular stomatitis is present this usually indicates an associated riboflavin deficiency (vitamin B2).

Neurological symptoms are due to an organic encephalopathy. Psychosis may occur with sleep and memory disorders, anxiety, agitation, rapid irritability, disorientation, confusion

and confabulation (compare this with Wernicke-Korsakoff's syndrome in thiamine deficiency). Mania, delirium, paranoia and depression occur in later stages of the disease. At one time many pellagra patients were incarcerated in mental institutions. Muscular rigidity may develop together with a cogwheel phenomenon, hyperreflexia and a positive Babinski's sign. In the motor cortex, lysis of Betz's cells and to a lesser extent, lysis of Purkinje's cells are found. In the spinal cord, the posterior columns are chiefly affected (proprioception tracts; cfr vitamin B12 deficiency). In peripheral nerves there is myelin degeneration, but to what extent this overlaps with the findings in beriberi is unclear (nutritional deficiencies are often mixed). Post-mortem examination may reveal cardiac, adrenal gland, liver and spleen atrophy.

Dracula and Pellagra

Dracula was not the first time a vampire appeared in literature, but it's truly the book that established vampires as a horror staple. The question is, where did the author Bram Stoker gain inspiration for the vampiric flaws and habits of Dracula? The origins may be surprising.

In 1735, pellagra was a newly recognized disease in Europe. In the 18th and 19th centuries, a big change to the European diet occurred – Corn. Corn is a crop that originated in the Americas, domesticated by Native Americans over the course of many generations. Corn could produce more calories per acre than traditional European staple crops, and corn cultivation slowly spread. However, corn is lacking in many vital nutrients. Where corn cultivation went, pellagra was soon to follow.

To societies with little medical knowledge, pellagra was a spooky illness indeed. People with pellagra (called pellagrins) developed a hypersensitivity to sunlight. Avoidance of sunlight is a classic vampire trait and one of the foremost symptoms of pellagra. The tongues of pellagrins became swollen and beefy red. Lips became red and cracked. The reddened mouth and tongue might have led to suspicions of blood drinking. In Dracula, the count himself is described as having very red lips. Mental problems also plagued pellagrins. The lack of niacin led to degradation of the neurons, causing dementia in sufferers. Insomnia is a fairly common symptom of this, leading pellagrins to adopt the vampire-like habit of staying awake into the night. Increased levels of irritability and aggression occurred as well. Did this

lead their neighbours to fear attack from red-lipped people in the dead of night?

Death was the end result of pellagra for many unfortunate people in those times. After one person died from pellagra their family members might have appeared to be wasting away due to sustained supernatural attack. In traditional vampire folklore, the vampire returns night after night to slowly drain its victim of life. However, the real reason for entire families declining was the result of shared poor dietary conditions. If one family member died from pellagra, it was likely that the other family members were sickened as well.

When Bram Stoker researched for Dracula, he delved into the folklore of the communities most affected by pellagra. With this in mind, it doesn't seem like a coincidence that Stoker's description of vampires bears resemblance to the symptoms of pellagra. Vampire legends may have arisen as an explanation for a frightening illness that people back then encountered every day. So what's the best way to defeat a vampire? Maybe it's time to put away the crosses and holy water and instead feed the vampire some chicken and eggs.

Diagnosis

When all symptoms and signs are present; the clinical diagnosis is simple. In most cases there are only a few symptoms present. Especially in non-endemic settings the linkage of the different symptoms can be very challenging contributing to an additional "D": delay in diagnosis. The diagnosis is confirmed by measuring serum niacin or the urinary excretion of N´-methylnicotinamide (NMN). NMN excretion of <0.8 mg/day suggests niacin deficiency. Patients with pellagra also have increased urinary excretion of coproporphyrins. In clinical practice a successful trial of therapy will confirm the original diagnosis.

Treatment

As there is seldom a deficiency of only one vitamin, treatment should include a polyvitamin preparation in addition to a balanced diet. The diet should contain at least 100 g per day of good protein (if possible, meat, fish, milk or eggs; if not, groundnuts, beans or other legumes) and should be high in energy (3 000 to 3 500 kcal per day). Specifically for pellagra, nicotinamide (precursor of niacin) is given as a supplement in a dose 300 mg daily using divided doses. If niacin itself were to be administered, the patient would complain of flushing,

paresthesia and a burning sensation. If no oral supplement can be given (severe stomatitis, severe diarrhoea, uncooperative patient), 100 to 250 mg can be injected SC twice daily. In the acute phase the patient should avoid exposure to sunlight. Pellagra is often a very gratifying disease to treat. Violent, almost uncontrollable mental patients can become normal, rational, peaceful human beings within a few days of taking a few tablets of nicotinamide. In persons with severe skin lesions, a sore mouth and severe diarrhoea with frequent watery stools, dramatic improvements occur within 48 hours. The skin redness and pain on exposure to sunlight improves; pain in the mouth abates and eating becomes a pleasure for the patient; and most gratifying for the patient, the intractable diarrhoea disappears. Neurological improvement is rather slow.

Prevention

A balanced diet is essential for prophylaxis and reliance on maize as the sole staple food should be discouraged. In some countries flour is systematically enriched with extra niacin. Niacin tablets should be administered in prisons and institution in areas where pellagra is endemic and to refugees in famine relief.

Nicotinic acid and hyperlipidemia

Nicotinic acid has been in use as a lipid-lowering drug for several decades. It is effective in lowering low-density lipoprotein (LDL)-cholesterol, triglycerides, and lipoprotein (a), and in increasing high-density lipoprotein (HDL)-cholesterol. All these effects are pronounced, and at present greater increase of HDL-cholesterol cannot be obtained by any other drug. Patients with hypertriglyceridaemia/low HDL-cholesterol despite being treated with a statin, are the most suitable candidates for being treated with this drug. However, more recent studies have delivered disappointing results, leading to the conclusion that no further benefit is achieved by adding niacin to existing statin therapy in patients with high cardiovascular risk. Moreover, in these studies, several adverse effects of the treatment were observed and niacin for hyperlipidemias is not recommended anymore.