Micronutrient deficiencies

Introduction

Malnutrition refers to deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients. Malnutrition covers 2 broad groups of conditions. One is 'undernutrition'—which includes stunting (low height for age), wasting (low weight for height), underweight (low weight for age) and micronutrient deficiencies or insufficiencies (a lack of important vitamins and minerals). The other is overweight, obesity and diet-related noncommunicable diseases (such as heart disease, stroke, diabetes and cancer).

WHO defines malnutrition as follows: Malnutrition refers to a number of diseases, each with a specific cause related to one or more nutrients (e.g. protein, iodine or iron) and each characterized by cellular imbalance between the supply of nutrients and energy on the one hand, and the body's demand for them to ensure growth, maintenance, and specific functions, on the other.

Consequences of malnutrition

Malnutrition affects people in every country. Around 1.9 billion adults worldwide are overweight, while 462 million are underweight. An estimated 41 million children under the age of 5 years are overweight or obese, while some 159 million are stunted and 50 million are wasted. Adding to this burden are the 528 million or 29% of women of reproductive age around the world affected by anaemia, for which approximately half would be amenable to iron supplementation.

Many families cannot afford or access enough nutritious foods like fresh fruit and vegetables, legumes, meat and milk, while foods and drinks high in fat, sugar and salt are cheaper and more readily available, leading to a rapid rise in the number of children and adults who are overweight and obese, in poor as well as rich countries. It is quite common to find undernutrition and overweight within the same community, household or even individual – it is possible to be both overweight and micronutrient deficient.

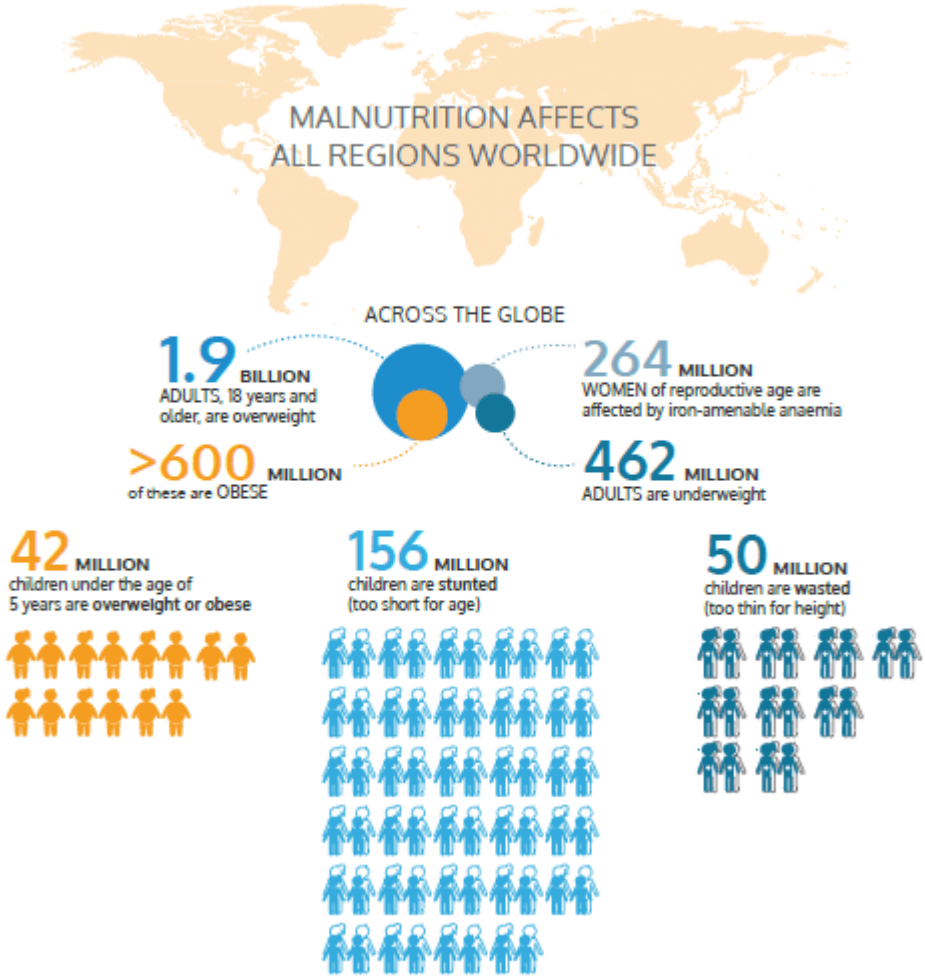

Image: WHO

Protein-energy malnutrition

Undernutrition is sometimes used as a synonym of protein–energy malnutrition (PEM). While other include both micronutrient deficiencies and protein energy malnutrition in its definition.https://en.wikipedia.org/wiki/Malnutrition – cite_note-Jones2011-12 The term “severe malnutrition” or “severe undernutrition” is often used to refer specifically to PEM. PEM is often associated with micronutrient deficiency. Two forms of PEM are kwashiorkor and marasmus, and they commonly coexist.

Kwashiorkor

Kwashiorkor is mainly caused by inadequate protein intake. The main symptoms are oedema, wasting, liver enlargement, hypoalbuminemia, steatosis, and possibly depigmentation of skin and hair. Kwashiorkor is further identified by swelling of the belly, which is deceiving of actual nutritional status. The term means 'displaced child' and is derived from a Ghana language of West Africa, means "the sickness the older one gets when the next baby is born," as this is when the older child is deprived of breast feeding and weaned to a diet composed largely of carbohydrates.

Marasmus

Marasmus ('to waste away') is caused by an inadequate intake of protein and energy. The main symptoms are severe wasting, leaving little or no oedema, minimal subcutaneous fat, severe muscle wasting, and non-normal serum albumin levels. Marasmus can result from a sustained diet of inadequate energy and protein, and the metabolism adapts to prolong survival.https://en.wikipedia.org/wiki/Malnutrition – cite_note-Clinical_Nutrition_in_Practice_(2011)-26 It is traditionally seen in famine, significant food restriction, or more severe cases of anorexia. Conditions are characterized by extreme wasting of the muscles and a gaunt expression.

Undernutrition, hunger

Undernutrition encompasses stunted growth (stunting), wasting, and deficiencies of essential vitamins and minerals (collectively referred to as micronutrients). The term hunger, which describes a feeling of discomfort from not eating, has been used to describe undernutrition, especially in reference to food insecurity.

Micronutrients

Micronutrients are essential elements required by organisms in small quantities throughout life to orchestrate a range of physiological functions to maintain health. Micronutrient requirements differ between organisms; for example, humans and other animals require numerous vitamins and dietary minerals, whereas plants require specific minerals. For human nutrition, micronutrient requirements are in amounts generally less than 100

milligrams per day, whereas macronutrients (carbohydrate, protein and fat) are required in gram quantities daily.

The minerals for humans and other animals include 13 elements that originate from Earth's soil and are not synthesized by living organisms, such as calcium and iron. Plants are the primary origin of nutrients for humans and animals and some micronutrients may be available in low levels and deficiencies can occur when dietary intake is insufficient, as occurs in **malnutrition**.

Trace minerals	Vitamins	Essential fatty acids	Essential amino acids
Boron	Vitamin B complex • Vitamin B1 (thiamine) • Vitamin B2 (riboflavin) • Vitamin B3 (niacin) • Vitamin B5 (panthothenic acid) • Vitamin B6 group (pyridoxine, pyridoxal-5-phosphate, pyridoxamine) • Vitamin B7 (biotin) • Vitamin B8 (ergadenylic acid) • Vitamin B9 (folic acid) • Vitamin B12 (cyanocobalamin) • Choline	Alpha-linolenic acid	Histidine
Cobalt	Vitamin A (retinol, retinal, retinoic acid and provitamin A carotenoids (mainly beta carotene))	Linolenic acid	Isoleucine
Chlorine	Vitamin C (ascorbic acid)		Leucine
Chromium	Vitamin D (ergocalciferol, cholecalciferol)		Lysine
Copper	Vitamin E (tocopherol)		Methionine
Iodine	Vitamin K (phylloquinone, menaquinone complices)		Phenylalanine

Iron	Carotenoids (alpha carotene, beta carotene, cryptoxanthin, lutein, lycopene, zeaxanthin)		Threonine
Lithium			Tryptophan
Manganese			Valine
Molybdenum			
Selenium			
Sodium			
Zinc			

Table: Essential Micronutrients

There are 4 essential nutrients: essential mineral (nutrient)s, vitamins, essential fatty acids, and essential amino acids. An alternative method of classifying nutrients as either type I or type II. This classification is based on the way in which the body responds to a nutrient deficiency. A type I response is characterised by specific physical signs of deficiency as a result of a reduced tissue concentration of the nutrient. For example, if the diet is deficient in a type I nutrient such as iron, there is an initial consumption of body stores followed by clinical signs characteristic of iron deficiency. The concentration of iron in the tissues is markedly reduced, but there is no effect on growth or body weight. In contrast, a type II response is characterised by reduced growth rate or weight loss in the absence of specific deficiency signs. For example, if the diet is deficient in a type II nutrient like zinc, growth stops, followed by weight loss. Protein and energy (derived from carbohydrates and fat) are classified as type II nutrients.

Type I nutrients	Type II nutrients
Iodine	Sodium
Iron	Potassium

Folic acid	Zinc
Calcium	Magnesium
Selenium	Nitrogen
Copper	Sulphur
Manganese	Phosphorous
All vitamins	Water
	Essential amino acids
	Energy (carbohydrates, fats)

Table: Type I and type II nutrients

The type I and II classification is important because it emphasises that poor growth is not caused solely by protein-energy malnutrition but can result from other nutrient deficiencies which may not be recognised and so appropriately treated. Furthermore, it demonstrates the importance of a wide range of nutrients in causing poor growth or weight loss, and therefore the need for a nutritionally balanced diet.

In much of the developed world, such micronutrient deficiencies are rare; this is due to (1) an adequate supply of food and (2) the addition of vitamins and minerals to common foods (fortification).

Micronutrient deficiencies are widespread in developing countries and affect approximately 2 billion people worldwide which is equivalent to more than one-third of the total world population. The most common deficiencies are due to lack of iron (anaemia), vitamin A (xerophthalmia) and iodine (goitre and cretinism). Outbreaks of deficiency disorders, which are rarely seen in normal circumstances, have also occurred in emergencies among populations entirely dependent on food aid. These include deficiencies of vitamin C (scurvy), niacin (pellagra) and thiamine (beri beri). The general ration provided in emergencies by agencies like WFP and ICRC are frequently lacking in some essential micronutrients, which means that populations always require other foods (or in some cases micronutrient

supplements) to complement the rations. Donor agencies can assist populations to maximise their intake of micronutrient-rich foods by adopting a number of different strategies which, in preferred order, include: promoting the production of vegetables and fruit; providing fresh food items in the ration; adding a food to the ration which is rich in a particular vitamin or mineral; providing fortified foods; and supporting the distribution of nutrient supplements.

Vitamins

Vitamins have a special place in the history of medicine. At the end of the 19th century, it was thought that infectious diseases could explain most of the illnesses of mankind. It took a while to show that nutritional deficiencies were responsible for certain ailments, instead of a particular infection. The study of thiamine deficiency earned its author the Nobel Prize (Eijkman 1929). The research connected with vitamin C was likewise awarded this prestigious prize (Haworth and Szent-Gyorgyi, 1937).

A vitamin is an organic molecule (or related set of molecules) which is an essential micronutrient — that is, a substance which an organism needs in small quantities for the proper functioning of its metabolism but cannot synthesize, either at all or in sufficient quantities and therefore must obtain through its diet. Vitamins can fulfil different biochemical functions. Some function as regulators of cell and tissue growth and differentiation (e.g. vitamin A), other serve as cofactors/coenzymes (B complex). Vitamin D and vitamin E/C serve as hormone-like regulators of mineral metabolism and antioxidants.

The name vitamin refers to “vital amine” (amine of life), even though not all vitamins (in particular vitamin A) have an amine components. As the word was already ubiquitous by the time it was shown that not all vitamins are amines, the final “e” was dropped to deemphasize the “amine” reference.

Humans must consume vitamins periodically but with differing schedules, to avoid deficiency. Body stores for different vitamins vary widely; vitamins A, D, and B_{12} are stored in significant amounts, mainly in the liver, and an adult’s diet may be deficient in vitamins A and D for many months and B_{12} in some cases for years, before developing a deficiency condition. However vitamin B_3 (niacin and niacinamide) is not stored in significant amounts, so stores

may last only a couple of weeks. For vitamin C, the first symptoms of scurvy in experimental studies of complete vitamin C deprivation in humans have varied widely, from a month to more than six months, depending on previous dietary history that determined body stores.

A primary vitamin deficiency occurs when an organism does not get enough of the vitamin in its food. A secondary deficiency may be due to an underlying disorder that prevents or limits the absorption or use of the vitamin, due to a “lifestyle factor”, such as smoking, excessive alcohol consumption, or the use of medications that interfere with the absorption or use of the vitamin. People who eat a varied diet are unlikely to develop a severe primary vitamin deficiency. In contrast, restrictive diets have the potential to cause prolonged vitamin deficits, which may result in often painful and potentially deadly diseases.

Well-known human vitamin deficiencies involve vitamin A deficiency, thiamine (beriberi), niacin (pellagra), vitamin C (scurvy), and vitamin D (rickets). These specific deficiencies will be discussed as well as iodine deficiency disorder. The description of other micronutrient deficiencies is beyond the scope of these lecture notes.

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Vitamin A deficiency

Summary

- Vitamin A deficiency (VAD) can be caused by insufficient intake through food or by increased need in case of infection
- Leading cause of preventable childhood blindness
- Causes xeropthalmia: dryness of conjunctiva and cornea, Bitot spots, keratomalacia and night blindness
- Is associated with excess mortality
- Treatment with large and repeated doses, lower doses in pregnancy
- Prevention can be achieved with diet change, periodic supplementation and fortification

Epidemiology

Vitamin A deficiency (VAD) or hypovitaminosis A is a shortage of vitamin A in blood and tissues. It is the leading cause of preventable childhood blindness and is related with child mortality. VAD affects about one-third of children under five worldwide and claims the live of more than 500.000 children annually, mainly in Southeast Asia and Africa. An estimated 250.000 to 500.000 children go blind each year due to vitamin A deficiency and half of them die within a year of becoming blind. VAD prevalence in high among pregnant women in many developing countries and contributes to maternal mortality. VAD affects the immune system and infectious diseases such as measles have higher fatality rates. Even subclinical deficiency can be a problem as it may increase child's risk of developing respiratory and diarrhoeal infections, decrease growth rate (stunting), slow bone development and decrease likelihood of survival from serious illness. Periodic, high-dose vitamin A supplementation is a proven, low-cost intervention which has been shown to reduce all-cause mortality by 12 to 24 percent. Globally, around 65% of all children aged 6 to 59 months received two doses of vitamin A, fully protecting them against VAD.

However between 2015 and 2016 vitamin A supplementation coverage dropped by more than half in countries with the highest under-five mortality rates, the countries where it is needed most. This caused an increase of children aged 6 to 59 months left unprotected from 19 to 62 million. Two-thirds of at risk countries have no VAD data of use data that are > 10 years old, challenging vitamin A supplementation programs.

Vitamin A metabolism and pathophysiology

The term vitamin A should be used as the generic descriptor for retinoids exhibiting the qualitative biological activity of retinol. The main molecular structure contains a cyclic part and a non-cyclic chain with 5 double bonds in the all-trans position. A functional group is found at the end of the non-cyclic part which can be an alcohol (retinol), an aldehyde (retinaldehyde), a palmitate (retinolpalmitate), etc. The term *provitamin A carotenoid* should be used as the generic descriptor for all carotenoids exhibiting qualitatively the biological activity of beta-carotene.

Vitamin A is fat soluble and is absorbed in the gut in the chylomicron fraction and then

transported via the lymphatics, to the liver. The availability of fats in the intestine will influence the fraction of the available vitamin that will be absorbed. Vitamin A (retinol) is ingested as either retinyl esters or carotenoids and metabolized to active compounds such as 11-cis-retinal, which is important for vision, and all-trans-retinoic acid, which is the primary mediator of biological actions of vitamin A. Once stored in the liver as retinolpalmitate it will be transported to the target organs bound to a protein, the retinol binding protein (RBP). Zinc and an adequate intake of proteins are required for normal production of RBP. Transthyretin (TTR= transports thyroxine and retinol) is a transport protein in the serum and cerebrospinal fluid that carries the thyroid hormone thyroxine (T_4) and retinol-binding protein bound to retinol. The liver secretes transthyretin into the blood, and the choroid plexus secretes TTR into the cerebrospinal fluid. If retinol is not needed, it is instead stored in liver stellate cells in the form of retinyl esters.

Rhodopsin, the light-sensitive pigment in rods of the eye, is formed when 11-cis-retinal combines with the protein opsin. Absorption of light energy causes rhodopsin to decompose by a series of photochemical reactions to all-trans-retinal and opsin. As this occurs, a visual signal is transmitted to the central nervous system. Night blindness is an early symptom of vitamin A deficiency. In night blindness, the small amount of light at night does not elicit an adequate response because the amounts of 11-cis-retinal and rhodopsin that can be formed are depressed. Another important function of vitamin A is regulation of growth and differentiation of cells. In the absence of vitamin A: 1) proper stem cell differentiation does not occur; 2) growth and development of embryos are altered; 3) epithelial cellular development with ciliary function is deficient, and the barrier to infection is decreased; 4) cells involved in innate and acquired immune function are decreased; 5) xerophthalmia develops because of abnormalities in corneal and conjunctiva development; 6) normal bone growth and tooth development do not occur, contributing to stunting.

Vitamin A in skin creams

Companies that produce skin creams often juggle with terms as '*Pro-retinol A',...* The creams contain pro-retinols (precursors to retinols) that break down to retinol on exposure to the skin. Vitamin A itself is what does all the work. As well as being the precursor to retinal, it is also a chemical messenger, one function of which is to instruct cells to begin

multiplying more uniformly, and to produce more elastin and collagen, two protein building materials essential in healthy, young-looking skin cells.

Causes of vitamin A deficiency

Both an insufficient input and an increased need can result in the deficiency. Insufficient intake is seen when following food items are lacking the diet:

- Animal sources of vit A: milk – butter – fish oils – liver – meat – egg yolk
- Vegetables: green leafy vegetables – carrots
- Fruits: mango – papaya
- Oils: palm oil

Infections of the gut, malabsorption, worm infestations and particularly giardiasis that provokes steatorrhea decrease vitamin A absorption. Infections can increase vitamin A demands dramatically. Some investigators even calculated the increase during infections in the order of 3000 IU per day. Particularly children with measles are very likely to develop a very fast progressing keratomalacia.

Recommended daily intake

Adult:	750 µg
Pregnancy:	750 µg
Breastfeeding:	1200 µg
Children:	
< 1 yr:	300 µg
1-4 yr:	250 µg
4-6 yr:	300 µg
7-9 yr:	400 µg
10-12 yr:	575 µg

13-15 yr:	725 µg

Note: 1 IU = 0,3 mcg retinol

There is a very strong association of vitamin A deficiency with malnutrition (PEM). Both are diseases of the poorer people of the population and of the deprived. They will have an overall lower food intake but particularly of meats and milk products, sources rich in vitamin A and of oils and fats, which are necessary for the vitamin A absorption. These children will also have more frequent infections, increasing their demands and interfering with the absorption at the level of the gut. Once their serum protein levels decrease like in severe malnutrition the necessary enzymes for absorption and transportation to the target organs will diminish further aggravating the deficiency.

Clinical aspects

VAD is an important contributing factor in mortality which is still very high in the majority of the third world countries. This can for a large extend be explained by the role vitamin A has in maintaining the immunological response and the differentiation and maintenance of epithelial surfaces, like the skin, bronchi, gut and genito-urinal tract, which are more prone to invasion by bacteria in a vitamin deficiency state. A higher frequency of diarrhoea, ARTI (acute respiratory tract infection) and otitis media have been noted. These effects are present well before there are overt clinical signs at the level of the eye.

Xerophthalmia

Although xerophtalmia literally means (xeros= dry ; ophthalmos = eye) dryness of the eye and is used as such by the ophthalmologists, it is used in a broader sense in the public health context of vitamin A deficiency. Here it means all lesions, internal and external, attributable to the deficit of vitamin A: dryness of conjunctiva and cornea, Bitot spots, keratomalacia and night blindness. Xeroderma is another expression of xerosis.

The natural course of the disease progresses from night blindness to dryness of the cornea,

sometimes with Bitot spots, to keratomalacia, although many children will not pass through this sequence. In a community where children have eye signs, there will be many other children who are vitamin A deficient but who have completely normal eyes and vision. Children with eye signs due to VAD are only the 'tip of the iceberg' explaining why community approaches to control VAD are important. Some eye signs reflect long-standing VAD, whereas other eye signs reflect severe, acute, sudden-onset VAD. A child who is vitamin A deficient, but who does not have eye signs, may develop immediately corneal ulcers as a result of infections or diarrhoea. Children with any of the eye signs of VAD are at high risk of dying.

Grade of xerophthalmia		Peak age group (years)	Type of deficiency	Risk of death
XN	Night blindness	2–6; adult women	Long standing. Not blinding	+
X1A	Conjunctival xerosis	3–6	Long standing. Not blinding	+
X1B	Bitot's spot	3–6	Long standing. Not blinding	+
X2	Corneal xerosis	1–4	Acute deficiency. Can be blinding	++
X3A	Corneal ulcer/ <1/3 cornea	1–4	Severe acute deficiency. Blinding	+++
X3B	Corneal ulcer/keratomalacia ≥1/3	1–4	Severe acute deficiency. Blinding	++++
XS	Corneal scarring (from X3)	>2	Consequence of corneal ulceration	+/–
XF	Xerophthalmic fundus	Adults	Long standing. Not blinding. Rare	–

Table: WHO classification of vitamin A deficiency and the age groups most affected

Night blindness

- Nyctalopia or night blindness is not always perceived because it is a subjective sign; on the one hand and because its perception is very much influenced by the availability of electricity on the other hand. The child has an inability to see in poor lighting conditions like those which prevail at the end of the day when the evening is setting. A longer adaptation of vision to the dark is needed, like when one is getting from a light to a darker environment. Children will usually not complain and mothers should be asked if they stumble over objects in the house in the evening or that their children can't find the parents anymore in the house in the evening. The child might become less active and may be fearful of moving around. Night blindness is quantifiable through a dark adaptation test,

but it is difficult to evaluate objectively in children.

Historical note: Xeropthalmia and Vitamin A

The Eber's Papyrus describes night blindness in ancient Egypt. Physicians treated the condition by squeezing the ''juices'' of a grilled lamb's liver into the eyes of afflicted patients. In 1971, George Wolff speculated that these topically applied ''drops,'' rich in retinol, probably drained into the lachrymal sac, where they were absorbed into the systemic circulation and thereby reached the retinal cells. Perhaps that was the case, but Alfred Sommer observed the treatment of a young boy in rural Indonesia that was described in exactly the same fashion, but provided a more direct explanation for the way in which ''liver juices,'' applied topically, could reach the back of the eye. At the conclusion of the ceremony, after juice from a goat liver had been squeezed onto the boy's eyes, the traditional healer fed the child the remaining liver! The healer did not consider eating the liver part of the treatment; he fed the child the liver so as not to waste precious food.

Modern concepts of xeropthalmia date from the early 1800s, when dogs that were "starved" on sugar and distilled water developed perforating corneal ulcers resembling those in "ill-nourished infants". One hundred years elapsed before investigators realized that these changes were caused by lack of a specific nutrient "fat soluble A", present in the lipid fraction of milk, eggs, butter and cod-liver oil, and -as provitamin A carotenoids- in dark-green leafy vegetables and certain coloured fruits. Bloc -studying the growth and development of children in a Danish orphanage, noted that vitamin A-deficient children were far more likely to develop urinary tract infections, grew less and were less likely to develop xeropthalmia, and that vitamin A treatment cured the condition. By 1928, Green and Mellanby dubbed vitamin A the "anti-infective factor".

In 1932 Ellison administered daily vitamin A to one-half of the cases of measles admitted to the Grove fever hospital outside London. Those given vitamin A had only half the case-fatality rate of those restricted to standard therapy. Vitamin A was finally crystallized in 1937.

Conjunctival- and corneal xerosis

VAD causes squamous metaplasia and keratinization in the eye. Conjunctival xerosis can be difficult to detect. One can see a slight wrinkling of the conjunctiva. In corneal xerosis glands in the conjunctiva no longer function normally, leading to loss of tears and mucous with an increased risk for infections. The light reflex of the cornea loses its well-defined appearance and becomes mottled and hazy. The cornea becomes dry, less translucent and more opaque.

Bitot spots are unpainful, triangular, whitish, pearly coloured spots, usually found on the lateral side of the conjunctiva, which are pathognomonic for VAD. They consisting of keratin accumulations, often intermixed with an overgrowth of Corynebacterium xerosis, which result from epithelial (squamous) metaplasia: the conjunctival cells become more like skin than a mucous membrane. The white foamy deposits can be wiped away partially, but they don't disappear completely, even when the deficiency is reversed.

Corneal ulcer and keratomalacia

If the acute VAD is not treated promptly, the cornea can become ulcerated and melt away. The liquefaction necrosis of the cornea varies from small ulcerations to softening and rupture of the cornea, with resulting loss of anterior chamber fluid and collapse of the eye. Keratomalacia indicates that more than one-third of the cornea is affected. In just a few days the cornea can be completely destroyed and secondary infection is common. As long as there is no superinfection, there is no pain or redness. The end result is corneal scarring, staphylomas (bulging of a badly damaged cornea) or phthisis bulbi (a shrivelled up eye). Children with keratomalacia are often malnourished, but previously healthy appearing children can develop keratomalacia following measles infection or diarrhoea. It is important to screen young children from the same family and community.

Diagnosis

Clinical

In low resource settings the diagnosis of individual patients is usually made clinically. Fundus examination can be useful to detect xerophthalmic fundus, which is more present in adults. Small white spots are found on the retina. This moderate form of VAD (night blindness, conjunctival dryness) will disappear after 2-4 days of treatment without leaving any lesions or

sequelae.

Plasma levels and Hepatic reserves

The problem with measuring plasma retinol levels is that they only change after a prolonged period of vitamin deficit, due to the buffering action of the liver. Their use is limited to research evaluations of vitamin A deficiency and of very little practical use in real life situations. Hepatic reserves can be determined with a liver biopsy, which is only done on an experimental and research basis. The reserves can be estimated: after administration of a small dose of retinol (1.800 IU) the plasma retinol levels are measured again and compared with the retinol concentrations before the administration. If the concentration increases by more than 20 % then this indicates reserves are low.

Plasma retinol	
>= 30 mcg/100 ml	Normal
30-20 mcg/100 ml	Mild deficiency
20- 10 mcg/100 ml	Associated with night blindness, Bitot spots Moderate deficiency
< 10 mcg/100 ml	Severe deficiency

Impression cytology

Impression cytology is a technique to detect the degree of metaplasia of the conjunctiva. The lack of differentiation and the decrease or absence of goblet cells is looked for. It is not a routine diagnostic test.

Vital staining

Vital staining detects the degree of conjunctival metaplasia by putting dye (Lissamon green or Bengal rose) on the conjunctiva. This method lacks specificity.

Treatment

The presence of clinical signs of vitamin a deficiency should be considered an emergency. The most urgent are those infants with corneal signs. Large and repeated doses are therefore given. Associated illnesses should always be treated.

In an endemic zone, all children with PEM and measles need vitamin A treatment.

Treatment dosage

Children < 1 yr	Children > 1 yr and adults except pregnant women
100.000 IU immediately 100.000 IU after 24 hrs 100.000 IU after 14 days	200.000 IU immediately 200.000 IU after 24 hrs 200.000 IU after 14 days

Below one year or below 8 kg the dose is half of the dose delivered in the vitamin A high dosage capsules. These contain 6 drops; to administer throw away tree drops and give the remainder.

Although teratogenic in animals, a clear correlation between ingestion of large doses of vitamin A and congenital malformations has not been established. As a precautious measure, **pregnant women** should not receive large doses of vitamin A due to the possible teratogenic effect. Smaller doses up to 10.000 IU per day are safe. A total dose of 200.000 IU should be aimed at. **Lactating women** should receive 200.000 IU in the first month postpartum. One month after delivery again smaller doses up to 10.000 IU per day are preferred. This because one month after delivery there is the possibility of recurrent pregnancy.

Xerophthalmia is treated with topical antibiotics and padding of the eye. Topical steroids should be used with caution. Corneal grafting and conjunctival reconstruction using a flap are out of scope for most settings where VAD is prevalent.

Prevention

“Appropriateness” is a basic premise for vitamin A intervention. Two conditions dictate whether a program, designed to prevent vitamin A deficiency, is appropriate:

- A substantial segment of the population is “at risk” of developing clinical or biochemical vitamin A deficiency of sufficient severity to be considered of Public Health importance.
- The problem is serious enough to warrant the diversion of scarce resources toward a program to control vitamin A deficiency versus other preventable diseases or community projects within the country.

Currently vitamin A prophylaxis is approached through one of the three major intervention strategies:

1. A change in diet directed toward achieving a continuous intake of vitamin A rich foods.
2. Administration of a single, large dose of vitamin A administered on a periodic basis.
3. Fortification of an appropriate dietary vehicle with vitamin A.

Change in dietary intake

Different strategies have been applied to increase dietary intake. Promotion of breastfeeding is effective in entirely breastfed children, provided the mother has adequate daily intakes of vitamin A. They have a lower prevalence of mild and severe xerophthalmia during early childhood. Nutritional education, kitchen gardening programs, larger scale agricultural programs and income generating programs are possibilities to achieve a higher vitamin A intake. Diet adaptation is the most sustainable solution and avoids the risk of hypervitaminosis. This approach de-medicalizes a food related condition. Challenges can be the availability of vitamin A rich products. These products must also be culturally accepted and land suitable.

Distribution of large dose vitamin A capsules

Large doses of 200.000 IU are distributed at regular intervals, most frequently every six months. The seasonal distribution approach is used to protect children in the higher

prevalence seasons, reduces cost while maintaining the same impact. There are three possible delivery strategies: the ‘medical’ or ‘therapeutic’ approach, which offers treatment to children who present to a health facility with an illness episode. They will be given a dose of vitamin A according to a set of pre-set criteria of high risk of developing vitamin A deficiency. The ‘targeted’ distribution covers groups within the larger general target population; e.g., residents of a high prevalence neighbourhood, those attending mother and child health clinics, etc. The ‘universal’ distribution in which all pre-school children and not pregnant lactating mothers in a prescribed region are dosed at prescribed intervals by single or multipurpose workers in the community.

Vitamin A fortification

Fortification of Mono-sodium Glutamate in the Philippines and of sugar in Guatemala has been highly successful. Other possible vehicles are wheat and milk. Vitamin A is light- and heat sensitive so it must be protected from light and stored in a cooler environment. The success of this type of program depends on the identification of a suitable vehicle, which has to be consumed by all and particularly the population at risk, and in a continuous and constant fashion. Fluctuations between people and in time should be as small as possible. The cost of the program on a national scale is usually high enough to raise the question as to who is going to bear it; the government, the industry or the consumer. Disagreement over this last point has led to the discontinuation of some fortification programs.

Vitamin A toxicity

Acute hypervitaminosis

Ingestion of large dose can give rise to transient signs and symptoms of toxicity, which are self-limiting and completely reversible. No deaths have been reported after the ingestion of the doses used in treatment and prevention. Intracranial pressure rises giving rise causing headaches and a bulging fontanel in young children. Nausea, vomiting, dizziness, headaches have been described in adults. Desquamation of the skin, bone pains and hair loss can occur in the following days.

Chronic hypervitaminosis

Ingestion of large doses on a regular basis can lead to hepatitis, cirrhosis, hair loss, dry scaling skin, hyperpigmentation, hyperostosis and bone pains, hepato-splenomegaly and anaemia. It is therefore recommended not to exceed a daily intake of 3000 µg (10.000 IU) in children and 7500 µg (20.000 IU) in adults. Why does the liver get damaged in chronic hypervitaminosis A? The liver gets a double blood supply: arterial via the arteria hepatica and venous via the portal vein. The blood vessels branch until they form a capillary-like network, the so-called liver sinusoids. These vessels are rather different from ordinary capillaries and containing large fenestrations. They do not rest upon a basal membrane but are surrounded by reticuline fibers. The sinusoids contain, apart from vascular endothelial cells, also Kupffer cells, monocyte-derived phagocytes. Outside the sinusoids is the space of Disse (German anatomist, Joseph Disse; 1852–1912). This space contains the microvilli of hepatocytes as well as Ito cells (syn. stellate cells; Japanese physician Toshio Ito: 1904–1991). Ito cells store fat and fat soluble vitamins, like vitamin A. Excessive intake of vitamin A leads to pathologically enlarged Ito cells. When damaged, Ito cells can change into an activated state. These are responsible for secreting collagen scar tissue. This leads to fibrosis, cirrhosis and portal hypertension.

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Rickets

Summary

- Vitamin D in food: sequentially converted in the skin (sunlight), liver and kidneys
- Calcitriol needed for mineralization of osteoid and calcium uptake in the intestine
- Deficiency in children (epiphyseal plate still open) leads to rickets
- Deficiency in adults (epiphyseal plate closed) leads to osteomalacia
- Irregularly frayed, wide, cup-shaped distal ulna and radius, rachitic rosary, hypocalcaemia
- Pseudofractures, bone deformities, gait disturbance

- Rapid recovery after deficiency correction, except if end-organ resistance
- Do not confuse rickets with rickettsiosis

Rickets: Historical Note

For centuries, rickets – despite being common – was a mysterious disease. In 1650, Francis Glisson, a Cambridge physician published in Latin a treatise on rickets titled “De Rachitide.” Glisson’s treatise addresses the clinical features of rickets in a scientific tone, but lapses into medieval mysticism while discussing the aetiology of rickets. Glisson ascribed the aetiology of rickets to “cold distemper, that is moist and consisting of penury or paucity of and stupefaction of sprits.” Despite his affirmation of mysticism in the cause of rickets, Glisson was convinced that rickets was neither contagious nor heritable. Glisson’s suggested treatments for rickets included: cautery, incisions to draw out bad humours, blistering and ligature of soft wool around the limb to retard the return of blood. For correction of bony deformities, Glisson proposed splinting and artificial suspension of the affected infant: “The artificial suspension of the body is performed by the help of an instrument cunningly made with swathing bands, first crossing the breast and coming under the armpits, then about the head and under the chin, then receiving the hands by two handles, so that it is a pleasure to see the child hanging pendulous in the air, and moved to and fro by the spectators. This kind of exercise is thought to be many ways conducible in this affect, for it helped to restore the crooked bones, to erect the bended joints, and to lengthen the short stature of the body.”

After Glisson’s discoveries, no advances were made in the study of rickets for 2 centuries. At the turn of the 20th century, rickets was rampant among the underprivileged infants residing in industrialized cities of North in the United States and several polluted cities in Europe. In 1919, Edward Mellanby, an English physician, conducted the earliest definitive experimental study exploring the role of diet in the aetiology and treatment of rickets. Puppies between 5 and 8 weeks of age were exposed to 1 of 4 natural diets. All 4 diets were rachitogenic after a variable period of exposure. Rickets was severe and developed easily in dogs that grew well on the rachitic diets. Neither yeast (antineuritic vitamin) nor orange juice (anti-scorbutic vitamin) hindered the development of rickets. Various foods were added to the rachitic diets and their effect on development of rickets was studied.

Foods rich in fat-soluble vitamin A (cod-liver oil, butter, and whole milk) were able to prevent rickets. Mellanby postulated, “It therefore seems probable that the cause of rickets is a diminished intake of an antirachitic factor which is either fat-soluble A, or has a somewhat similar distribution to fat-soluble A. Mellanby’s work clearly established the role of diet in the cause of rickets.

McCollum was now confronted with same question faced by Mellanby, whether fat-soluble A was anti-rachitic by itself or if there was another substance with specific anti-rachitic function with similar distribution as fat-soluble A. McCollum and Mellanby were aware of F. G. Hopkins’ report that oxidation destroyed fat-soluble A. Mellanby found oxidized butter fat had lost its anti-rachitic effect, but similarly treated cod-liver oil still retained its protective action against the development of rickets. Mellanby stated “this difference can be explained by the fact that cod-liver oil contains greater quantity of antirachitic vitamin than butter, or that the destructive change takes longer time, or whether some other explanation must be sought. McCollum and his coworkers were soon able to explain the preservation of anti-rachitic function in oxidized cod-liver oil. Unlike Mellanby, they chose to explore the anti-xerophthalmic and anti-rachitic functions of oxidized butter fat and oxidized cod-liver oil. They chose “diet 3143,” which was adequately restricted with regard to fat-soluble A to cause severe rickets but still able to prevent the onset of xerophthalmia, to induce rickets in rats. Using the “line test,” the anti-rachitic potency of several fish liver oils, vegetable oils, and butter fat were tested. Oxidized cod-liver oil had lost its anti-xerophthalmic function, but still retained its calcium-depositing properties. Untreated coconut oil had no anti-xerophthalmic property, but had minimal anti-rachitic function. McCollum and his coworkers concluded that the anti-rachitic substance found in certain fats was distinct from fat-soluble vitamin A and its “specific property was to regulate the metabolism of the bones.” In the sequence of discovery of vitamins, the newly discovered antirachitic substance was the fourth; hence it was called vitamin D.

In 1890, addressing the aetiology of rickets, Palm studied the relationship between incidence of rickets and its geographical distribution and concluded that rickets was caused by lack of exposure to sunlight. Palm was able to point out that, despite a superior diet and relatively better sanitary condition, infants residing in Britain were more at risk for rickets than infants living in the tropics. Exposure to plenty of sunshine, which was the norm for infants residing in the tropics, was responsible for their protection against rickets.

Palm recommended “systematic use of sun-baths as a preventive and therapeutic measure in rickets.”

The bridging of the knowledge that photosynthesized vitamin D and vitamin D in cod-liver oil were similar was responsible for the eventual conquest of rickets. By the 1930s, the use of cod-liver oil in the treatment and prevention of rickets became common place. The eventual public health prevention initiative of fortification of milk with vitamin D led to eradication of rickets.

Source: Vitamin D, Cod-Liver Oil, Sunlight, and Rickets: A Historical Perspective; K. Rajakumar, Pediatrics Vol. 112 No. 2 Aug 2003

Vitamin D metabolism and calcium homeostasis

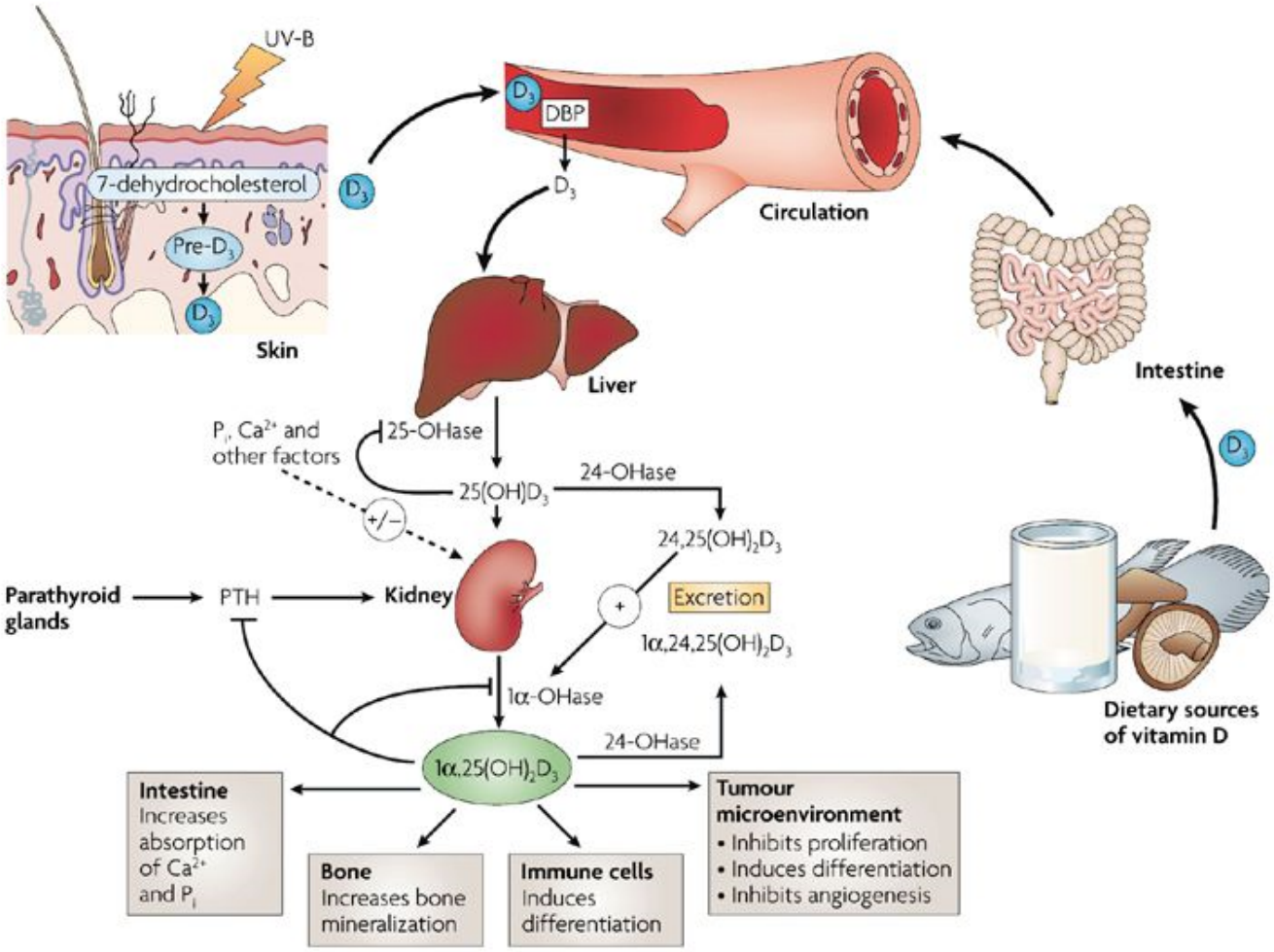

Figure: Vitamin D Metabolism (source: Nature Reviews Cancers 7, 684-700_2007)

Vitamin D is present in food as a fat-soluble provitamin. Vitamin D is regarded as a sterol, although the B ring of the molecular steroid skeleton is open. A photochemical conversion and two hydroxylations take place in the body before the final form is reached. The absorption of vitamin D is determined by the fat content of the food; by the proper functioning of the pancreas (lipase) and by the presence of sufficient bile. After absorption in the intestine, the provitamin is first transported to the skin, where a photochemical conversion takes place via ultraviolet light. Vitamin D_3 (= cholecalciferol = calciol) is formed. This compound can also be produced via UVB radiation from an endogenous precursor, 7-dehydrocholesterol or pre-vitamin D3. Sunlight breaks the B ring of the cholesterol structure

to form pre-D_3. Pre-D_3 then undergoes a thermal induced rearrangement to form D_3. Continued irradiation of pre-D_3 leads to the reversible formation of lumisterol and tachysterol (isomers of pre-vitamin D_3) which can revert back to pre-D_3 in the dark. Vitamin D_3 is subsequently bound to a carrier protein and transported to the liver, where an initial hydroxylation takes place with the formation of 25-OH-D_3. In the kidneys, 25-OH-D_3 (calcidiol) is further hydroxylated to the metabolically much more active form 1,25-$(OH)_2$-D_3 (calcitriol). A similar hydroxylation takes place in the placenta. Extra-renal synthesis of 1,25-$(OH)_2$-D_3 may occur in pathological conditions, such as sarcoidosis and other granulomatous disorders.

It is important to maintain calcium concentrations at a constant level to preserve a normal neurological function, muscular contractility and bone mass. In the extracellular compartment calcium is always in equilibrium with phosphate. Their product has to remain constant, otherwise the calcium-phosphate complexes will precipitate. If calcium increases, phosphate will decrease. The biggest reservoir of those two minerals is the bone. When the calcium concentration drops, the parathyroid glands secrete the parathyroid hormone PTH. This stimulates the production of 1,25(OH)2D. The receptor of 1,25-$(OH)_2$-D_3 is located in the cytoplasm of the cell. After binding, the complex migrates to the cell nucleus where (as a transcription factor) it mediates the expression of various genes. As a result of this (1) the active absorption of calcium in the intestine is stimulated, (2) the loss of calcium through the kidneys is decreased (resorption is stimulated) with increase in phosphate excretion and (3) bone cells (osteoclasts) are stimulated to resorb bone minerals and release calcium in the extra-cellular compartment. As a result of this the calcium concentration will rise and the secretion of PTH decrease.

Rickets, causes

Rickets and osteomalacia develop when there is insufficient vitamin D, when its metabolism is disturbed or when the tissues are resistant to its activity (e.g. mutation of the vitamin D receptor). By following the metabolic chain that leads to the active 1,25-$(OH)_2$-D_3 the various causes of osteomalacia/rickets can be visualized. For instance, the food may contain too few precursors. If there is insufficient fat in the diet, or there is insufficient bile and the fat is not absorbed (steatorrhoea), a deficiency of fat-soluble vitamins (ADEK) will occur. Prolonged treatment with cholestyramine is a risk factor. Insufficient exposure to sunlight is also an aetiological possibility. Dark-skinned people residing for a long time in the northern

hemisphere are a high-risk group. This also applies to those who wear protective clothing and people who spend most of their time indoors (elderly people and Islamic women and children are high-risk groups). For instance, rickets/osteomalacia is not uncommon in Indian and Pakistani immigrants in Britain. A lack of direct sunlight and calcium (chelation of calcium by the phytates in their traditional diet and low intake of milk) contributes to the problem. There are several diseases that may be associated with vitamin D deficiency, such as chronic renal failure (lack of 1-25-$(OH)_2$-D_3 and hyperparathyroidism), hypoparathyroidism, genetic diseases such as hereditary hypophosphataemia, or vitamin D-resistant rickets.

Clinical nutrition and bone disease	
Vitamin D	Rickets, osteomalacia
Vitamin C	Scurvy
Copper	Fractures (in premature infants with parenteral nutrition)
Calcium	Osteoporosis

Vitamin D content of food (µg/100 g)

Cereals	
Grain, flours, starches	0
Milk & milk products	
Cow's milk	0.01-0.03
Human milk	0.04
Dried milk	0.21
Cream	0.1-0.28
Cheese	0.03-0.5
Yoghurt	Trace-0.04
Eggs	
Whole	1.75
Yolk	4.94
Fats and oils	
Butter	0.76
Cod liver oil	210
Margarines and spreads*	5.8-8.00
Meat & meat products	
Beef, lamb, pork, veal	Trace
Poultry, game	Trace
Liver	0.2-1.1
Fish and fish products	
White fish	Trace
Fatty fish	Trace-25
Crustacea & molluscs	Trace
Vegetables	0

* Added during production (Vitamin D_2).

Source : Holland et al 1991

Table: Vitamin D content in foods

Pathophysiology

Osteomalacia refers to a disorder in which there is abnormal bone mineralization and the ratio of mineral to matrix is diminished due to an excess of unmineralized osteoid. This in contrast to osteoporosis where there is a reduction in quantity of bone mass per unit of volume. Osteomalacia in children is known as rickets, and because of this, use of the term “osteomalacia” is often restricted to the milder, adult form of the disease.

Crystallization of minerals in osteoid requires adequate concentrations of ionized calcium and phosphate. Vitamin D influences these levels after its dihydroxylation into calcitriol (hepatic position 25 and renal position 1). When concentrations are too low crystallization does not proceed normally.

Vitamin D disrupts mineralization because it normally regulates and enhances the absorption of calcium in the intestine. A lack of vitamin D causes plasma calcium concentrations to fall. Low plasma calcium levels stimulate parathyroid hormone (PTH). PTH raises calcium concentration but also increases renal clearance of phosphate. When phosphate decreases below a critical level, mineralization cannot proceed normally. On top of this, hypophosphatemia causes a disturbed apoptosis of chondrocytes, leading to an excess of unmineralized osteoid.

Rickets in the strict sense of the term is a disease caused by any interference with the process of enchondral bone formation (calciumphospate deposition in cartilaginous bone), the cascade of events normally taking place in the epiphyseal growth plates and resulting in gain in length of long bones. In children, the abnormalities are clearest in the areas of most active growth, i.e. the epiphyses. In chronic deficiency there is resorption of trabecular and cortical bone, which is not compensated by mineralization of osteoid. Adequate treatment with vitamin D causes a rapid reversal of this situation.

Normal enchondral bone formation is resumed. In adults, the changes are similar but are not

limited to the extremities of the long bones. As a consequence, the skeleton will be affected in its two main functions as the mechanical support for the other organs and the major reservoir of calcium to serve a large array of physiologic functions.

Clinical aspects

The clinical picture is one of bone deformities ranging from mild signs to very distinctive bone deformities. Clinical and radiological bone lesions predominate in the areas of rapid bone growth, namely the long bone epiphyses and the costochondral junctions. Thus the clinical manifestations are most striking at the time of greatest velocity. The maximum frequency of signs is usual found between 4-12 months with most of the signs seen in children below 18 months. Bone changes, visible on X-rays, precede clinical signs, becoming evident in the 3rd or 4th month of life (more common 6-9 months)- sometimes even at birth if the mother is severely vitamin D deficient. Bone changes in rickets are most evident at the distal ends of the radius and ulna. The bony ends lose their sharp, clear outline. They are cup-shaped and show a spotty or frayed outline. Later, the distance between the ends of the radius and ulna and the metacarpal bones appears to be increased because the noncalcified ends are invisible on the X-ray. This increase in the width of the epiphyseal cartilages can also be seen at the distal extremities of the tibia and fibula(“erlenmeyer deformity”). As healing begins, a thin white line of calcification appears at the epiphysis, becoming denser and thicker as calcification proceeds.

Kyphoscoliosis may develop and walking is delayed. Older children and adolescents experience walking as painful and in extreme cases develop bowlegs or knock-knees.

Maternal osteomalacia leads to changes in the bones of the foetus and even to tetany or seizures in the newborn (hypocalcaemia). Young infants with vitamin D deficiency are restless and sleep poorly. They have reduced mineralization of the skull (craniotabes = “wasting of the skull) and frontal bossing can be seen. On the thorax, palpable lumps develop at the costochondral junctions: costochondral beading (rachitic rosary). Harrison’s groove, corresponding to the costal insertion of the diaphragm, may be present.

In adults, osteomalacia occurs particularly in the vertebrae, pelvis and legs. Fine lines appear in the cortex: ribbon-like areas of demineralization, the so-called pseudofractures or Looser’s

lines.

Histologically they consist of focal accumulations of non-calcified osteoid. Preferential localizations for pseudofractures are the lateral edge of the scapula, femur neck, medial femoral shaft, ribs and ramus pubis. Looser's lines are usually symmetrical, extending perpendicularly to the cortex; are manifestly shorter than the diameter of the bone and display no callus formation. As the bones soften, body weight may cause bowing of the long bones, vertical shortening of the vertebrae and flattening of the pelvic bones, which narrows the pelvic outlet. This may subsequently cause difficulties in childbirth.

Rickets: clinical signs in babies

1. Aspecific restlessness and irritability
2. Head sweating
3. Skeletal signs (ricketsial thoracic rosary at 6-9 months of age). Disturbed bone maturation with wide epiphyseal plates and fraying of metaphysis. Frontal bossing and soft osseous borders of cranial vault (craniotabes) with or without widened fontanelles.
4. Delayed teething, enamel hypoplasia and numerous caries
5. Hypotonia: muscle flabby or muscle cramps (eventual seizures, tetany, laryngeal spasms)
6. Higher risk of upper respiratory tract infections due to muscle weakness and thoracic cage deformities
7. Anaemia (von Jacksch-Luzet syndrome) due to marrow space fibrosis. If severe, extramedullary production of red cells in liver and spleen can lead to hepatosplenomegaly

Human breast milk contains very little vitamin D (approx 25 IU per litre). Prolonged breast feeding by mothers who don't take extra vitamin D, followed by sudden switch to milk formula (containing lots of phosphate) can precipitate overt hungry bone syndrome, sometimes presenting with signs of acute or subacute hypocalcemia (e.g. convulsions).

Diagnosis

In the blood there is approximately 500 times more 25-OH-D_3 present than 1,25-$(OH)_2$-D_3 and the half-life of 25-OH-D_3 is 15-45 days, constituting a factual reservoir of the vitamin. As a

consequence, serum level of 25(OH)D is the laboratory test ordered to indicate whether or not a person has vitamin D deficiency or insufficiency.

The half-life of 1,25-dihydroxyvitamin D is short (4 to 6 hours). The levels of this compound can remain normal (or even raised) even when a person may be vitamin D deficient, depending on the activity of the 1-alpha-hydroxylase that converts 25-hydrovitamin D to 1,25-dihydroxyvitamin D, which in turn depends on the current blood concentration of calcium, phosphate and parathyroid hormone.

Measuring the active form of vitamin D (1,25-dihydroxyvitamin D) lacks utility in the routine evaluation of suspected vitamin D deficiency.

In healthy people, normal levels are 25 to 40 ng/mL (62 to 100 nmol/L) for 25-OH-D_3 and 20 to 45 pg/mL (48 to 108 pmol/L) for 1,25-$(OH)_2$-D_3. In nutritional rickets and osteomalacia, 25-OH-D_3 levels are very low.

Hypophosphatemia and high serum alkaline phosphatase are characteristic. Calcium is low or normal, depending upon the effectiveness of parathormone (secondary hyperparathyroidism) in restoring serum calcium to normal.

It is also considered reasonable to treat at-risk persons with vitamin D supplementation without checking the level of 25(OH)D in the serum, as vitamin D toxicity is very rare.

Differential diagnosis

A review of the patient's history may suggest nutritional problems. Rickets must be distinguished from infantile scurvy (cfr. scorbutic rosary), congenital syphilis (serologic tests) and from chondrodystrophy (large head, short extremities, thick bones; normal calcium, phosphate and alkaline phosphatase levels). Frontal bossing can be a sign of congenital lues, hemolytic anemia (thalassemia's, sickle cell disease), Hurler syndrome, achondroplasia). Yaws (= Pian = Framboesia) can give rise to sabre tibia.

Osteogenesis imperfecta, cretinism, congenital dislocation of the hip, hydrocephalus and

poliomyelitis should be readily distinguishable. Tetany must be distinguished from convulsions due to other causes.

Vitamin D-resistant rickets may be caused by severe renal damage, as in chronic renal tubular acidosis (e.g. Fanconi's syndrome or X-linked hypophosphataemia). Osteomalacia must be distinguished from other causes of bone decalcification, such as hyperparathyroidism, senile or postmenopausal osteoporosis; osteoporosis of hyperthyroidism, steroid use, Cushing's syndrome and atrophy of disuse.

Treatment

The World Health Organization defined an "International Unit" of vitamin D_3 as 0.025 micrograms (or one microgram = 40 IU).

Treatment usually consists of vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol), in addition to dietary advice and sunlight exposure. While there is evidence that vitamin D_3 raises 25(OH)D blood levels more effectively than vitamin D_2, other evidence indicates that D_2 and D_3 are equal for maintaining 25(OH)D status. Treating vitamin D deficiency depends on the severity of the deficit. An initial high-dosage treatment phase until the required serum levels are reached, is followed by the maintenance of the acquired levels. The lower the 25(OH)D serum concentration is before treatment, the higher is the dosage that is needed in order to quickly reach an acceptable serum level. The initial high-dosage treatment can be given on a daily (1000 IU for newborns, 1000 to 5000 IU for 1-12 months old infants and 5000 IU for patients older than 1 year) or weekly basis or can be given in form of one or several single doses orally or intramuscular (200,000 IUI), especially when there are concerns about compliance. Maintenance supplementation of 400 IU per day is recommended, with double doses for premature infants, dark-skinned infants and children residing in areas of limited sun exposure.

It is important to make sure that the children are receiving enough calcium. A daily intake of 800 mg in infants and children, and 1 g in adults, is the required minimum during the first month of treatment. Milk and dairy products can easily supply this, but when this does not seem possible, calcium supplementation must be provided.

The first radiological signs of healing will appear after 2-4 months.

Vitamin D intoxication

When accidental or intentional high doses of vitamin D are taken, the clinical picture is dominated by hypercalcaemia. The rate at which the symptoms develop depends upon the dose and duration of excess vitamin D intake. The first symptoms are anorexia, nausea, vomiting, polyuria, polydipsia and pruritus. Polyuria is secondary to a massive increase of urinary calcium excretion. Complications consist of metastatic calcifications (nephrocalcinosis!) and renal failure.

Patients sometimes complain of eye irritation. Physical examination may reveal a bandlike grey-white opacity across the corneal surface: band keratopathy. Treatment consists of stopping further administration of vitamin D and giving corticosteroids. Urinary acidification is recommended. Diuretics serve no useful purpose. Bisphosphonates such as pamidronate (an osteoclast inhibitor) may be used in extreme cases.

Prevention

With the major source of vitamin D derived from the skin, exposure to sunlight is the best prevention. In high latitude countries, supplements or fortification may be needed. Human breast milk is deficient in vitamin D (1.0 µg/L = 40 IU/L), whereas fortified cow’s milk contains ten times as much. Breastfed infants should therefore be given a supplement of vitamin D (400 IU)/day) from birth to 6 months, at which time they are given a more diversified diet. Large doses of 200.000 IU (5 mg) can also be given every 3 months. This dose is not always well absorbed. The safest is to give daily small doses. Bottle feeds have already adjusted levels of vitamin D. Food fortification of margarine and cow’s milk has eradicated rickets in Europe and the United States.

The elderly are a particular group at risk. Many older people stay indoors most of the time and get very little exposed to sunlight. The can develop demineralization of the bone with bone pains and fractures. Daily supplements can be necessary.

LAST UPDATED BY ADMIN ON JANUARY 29TH, 2025

Beriberi

Summary

- Thiamine = vitamin B1, water-soluble, heat-labile
- Deficiency caused by lack of thiamine intake
- Deficiency caused by thiaminases
- Symptoms may develop acutely
- Dry beriberi: peripheral neuritis with paralysis and loss of sensation
- Wet beriberi: high-output heart failure
- Cerebral beriberi: ophthalmoplegia, mental confusion, ataxia
- Infantile beriberi: aphonia, areflexia and heart failure
- Diagnosis by empirical treatment

Thiamine

Thiamine (Vitamin B1) is an essential micronutrient with dual co-enzymatic and non-co-enzymatic functions. It is involved in carbohydrate and branched-chain amino acid metabolism; as well as in the production of neurotransmitters, myelin, and nucleic acids. There is also evidence that thiamine plays a role in immune and anti-inflammatory processes and gene regulation. Thiamine is a water-soluble, heat-sensitive and very unstable vitamin which is present in many foods: meat, grain products, potatoes, beans, nuts and yeast. The richest sources are cereal grains and pulses. Green vegetables, fish, meat, fruit and milk all contain useful quantities. The refining of sugar, rice and grain products reduces the thiamine content. Whole grain rice requires more chewing and is heavier, but polishing of brown rice (removal of the dry outer layer) reduces the content of vitamin B1 to practically zero.

Thiamine resists temperatures up to 100°C, but it tends to be destroyed if heated further (e.g. if fried in a hot pan or cooked under pressure). It is often washed away with the cooking water, which can be avoided by preparing food with just the amount of water that will be absorbed in cooking, or by using water that is left over in soups or stews. Cassava contains only about the same low quantity as polished, highly milled rice. It is surprising that beriberi is not common among the many people in Africa, Asia and Latin America whose staple food is

cassava, although underdiagnosis might play a role. Some nutrients contain thiaminases which have the ability to break down vitamin B1 in the food: raw fish, coffee and tea leaves. Certain plants, such as bracken (especially the young fern fiddleheads) contain thiaminases and are consequently toxic (cfr. the disease called “staggers” in horses eating these ferns).

This thiaminase is destroyed by cooking. The uptake of thiamine takes place in the proximal small intestine. A small amount is stored in muscle tissue. In Asian countries such as China, Indonesia, Japan, Malaysia, Myanmar, the Philippines and Thailand beriberi used to be a major cause of morbidity and mortality in those whose diet consisted mainly of rice. In contrast, people in many parts of the Indian subcontinent were relatively protected from beriberi because they consumed mainly parboiled rice, which conserves enough thiamine.

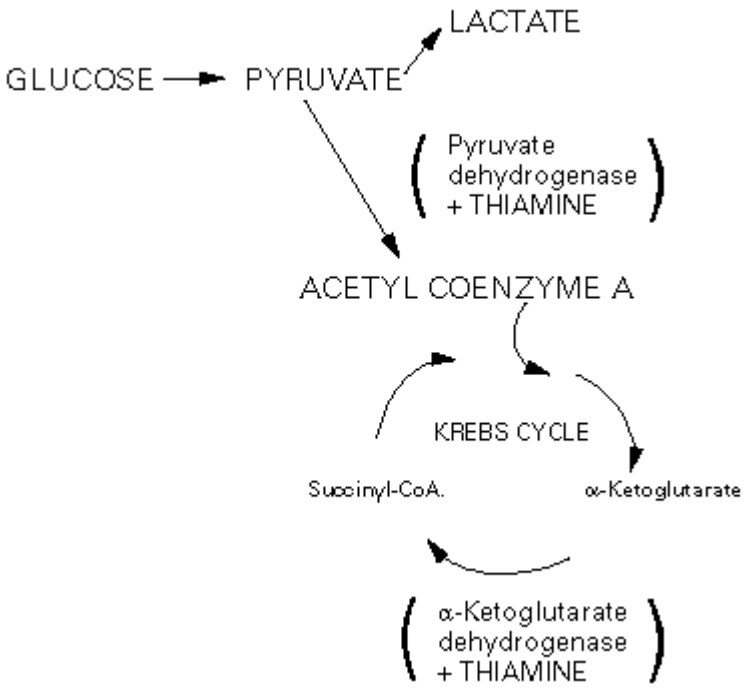

Fig: Thiamine is a co-enzyme in the conversion from pyruvate to acetyl-CoA and in the conversion of alpha-ketoglutarate to succinyl-CoA. Non availability of thiamine leads to lactic acidosis

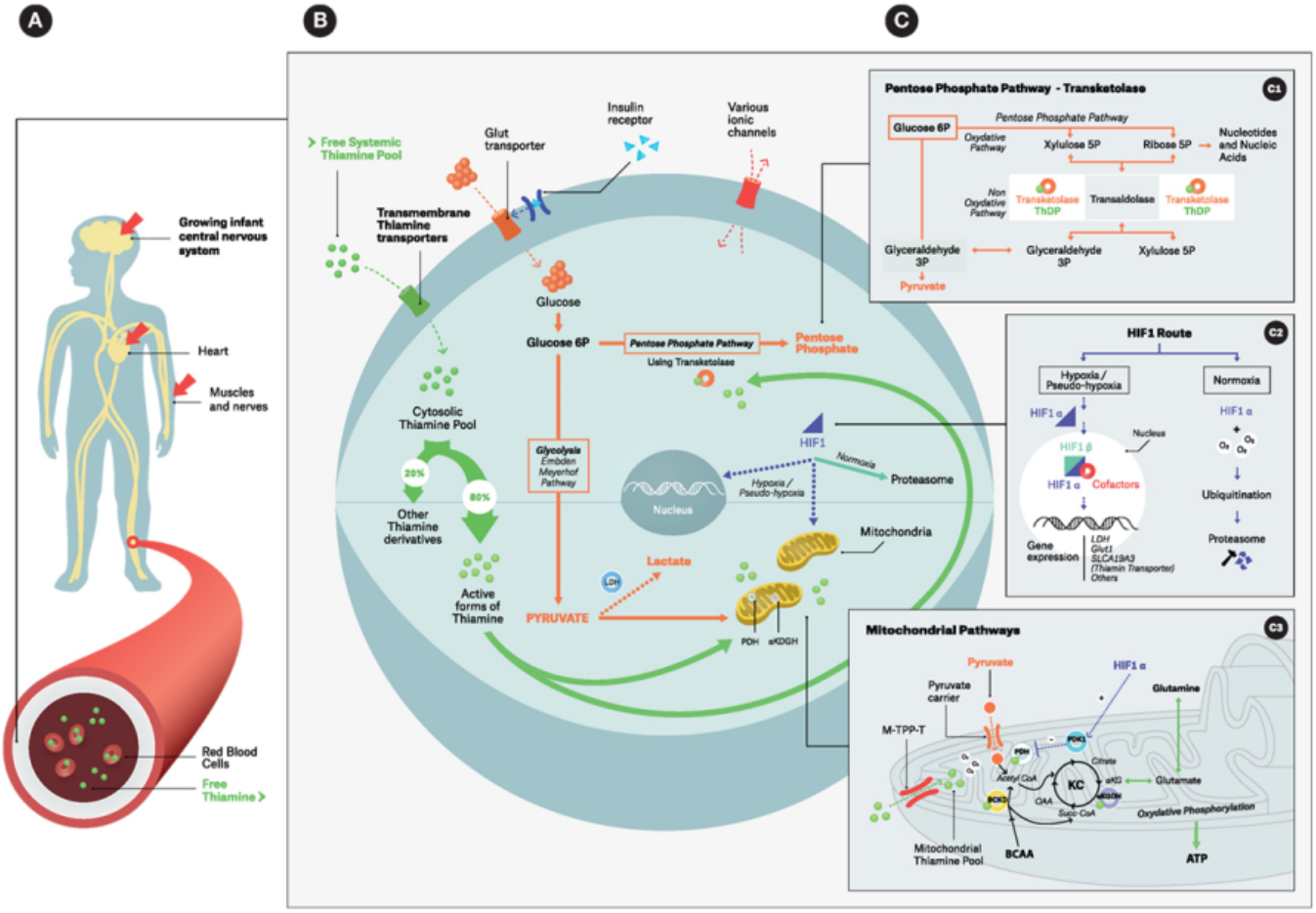

Fig: overview of thiamine intracellular action: focus on co-enzymatic functions. (A) Infant thiamine distribution with its three main target organs; (B) thiamine cellular metabolism with its main pools and thiamine-related metabolic pathways; (C) zooming boxes: (C1) – cytosolic pentose phosphate pathways using transketolase, (C2) – HIF-1 alternative routes, (C3) – mitochondrial events (source: Frontiers in Nutrition June 2016, Volume 3, Article 16)

Thiamine pyrophosphate (= thiamine diphosphate) is the co-enzyme of several enzymes of carbohydrate metabolism:

1. Pyruvate dehydrogenase, which is needed to convert (decarboxylate) pyruvate to acetyl CoA (Krebs cycle).
2. Transketolase: involved in the pentose phosphate pathway. This pathway generates NADPH which is essential for reductive biosynthesis, e.g. production of myeline.

3. 2-Oxo-glutarate dehydrogenase (= alpha ketoglutarate dehydrogenase), needed for the Krebs cycle (converting into succinyl-CoA via decarboxylation and production of NADH) and the synthesis of some neurotransmitters, e.g. GABA.

Thiamine is important for neural cell membranes and it has a modulating function in neuromuscular transmission.

Beriberi, historical overview

At the end of the 16th century, the first reports emerged of a new disorder in the Far East. In Indonesia this disease was called beriberi. The etymology of the word is not clear. Dr. Jacobus Bontius reported that beriberi is similar to the local name for sheep, and was believed to refer to the peculiar gait of that animal. Together with Nicolaas Tulp from Holland (cf. the painting “The Anatomy Lesson of Dr. Tulp” by Rembrandt, 1632) he gave the first European description of the disease. In Hindi, the term ‘bharbari’ means swelling; in Arabic the term ‘burh’ means shortness of breath; and ‘bahri’ means marine. In Singhalese, ‘bhayree’ means weakness. Beriberi was found to be a ravaging disease which occurred with varying frequency. This was dramatically illustrated in 1883 when a training ship of the Japanese navy sailed to Hawai via New Zealand and South America for over nine months. Of the crew of 376 sailors and officer cadets, 169 fell ill with beriberi and 25 died of the disease. On the recommendation of the Japanese medical officer Takaki, a different diet was used, with more meat, fish, barley and beans and less rice on a new voyage with the ship Tsukuba that was undertaken the following year. On this voyage there were only 14 cases of beriberi and no fatalities. Takaki observed that beriberi was common among low-ranking crew who were often provided free rice and thus ate little else, but not among crews of Western navies, nor among Japanese officers who consumed a more varied diet. These findings prompted the Japanese Navy to change its staple diet. More barley was used instead of rice, with a drastic reduction of beriberi as a result. However, the physicians of the time concluded that it was not the different diet that was responsible but the improved hygiene. During the Russian-Japanese war of 1904-1905, no fewer than 90,000 cases of beriberi were diagnosed in Japanese soldiers.

The disease occurred in communities that ate white rice, but not in all individuals and the

disorder was also seen (to a lesser extent) outside rice-growing areas. The Dutch doctor Christian Eijkman, who won the Nobel Prize in 1929, was working in Indonesia and he used chickens as an animal model for beriberi. He noticed the symptoms of beriberi in some chickens used in his laboratory when their feed had been altered for a few months. During that time, chickens in the laboratory had been fed leftover rice from military rations, until a new cook refused to allow military rice to be fed to civilian animals. Rice was then purchased from another source, and the birds soon recovered. During the months that the chickens developed beriberi, the feed had been polished rice, and when the birds' diet was switched back to unpolished rice, the birds recovered in a few days. Eijkman surmised that polished rice lacked a dietary component found in unpolished rice, and that beriberi was caused by depriving the body of this component, which he called "the anti-beriberi factor". Subsequently, Eijkman was able to prove that the disease was not caused by blood contamination, respiratory metabolism, perspiration, or seasonal or temperature variation. He suspected the disease was caused by an unknown bacteria. The Polish researcher Casimir Funk isolated the antiberiberi factor and established that it was an amine. He coined the term 'vitamin' for 'vital amine'. As a result of his discovery, research into deficiency diseases gained momentum. It wasn't until 1936, however, that the correct chemical structure of the antiberiberi factor was finally revealed. Funk was sure that more than one substance like Vitamin B1 existed, and in his 1912 article for the Journal of State Medicine, he proposed the existence of at least four vitamins: one preventing beriberi ("antiberiberi"); one preventing scurvy ("antiscorbutic"); one preventing pellagra ("antipellagric"); and one preventing rickets ("antirachitic").

Rice bran and thiamine

Rice bran is a tiny covering membrane that entirely encloses brown rice. It comprises several thin layers. On the outside of the kernel is the fused testa-pericarp (seed coat and fruit wall) and immediately below is the aleurone layer, which is rich in fat and protein. This layer plays an important role in the germination of rice. When an intact grain of rice is exposed to a moist environment, the central core of the grain (embryo) absorbs water. As a consequence, the embryo secretes a plant hormone (gibberellin) that diffuses into the aleurone layer. This layer subsequently secretes amylase, which converts the starch in the endosperm ('the grain') into sugars that can then be absorbed by the embryo. The endosperm is rich in starch but poor in thiamine and other compounds. The embryo and

the bran, on the other hand, are rich in proteins, fats and thiamine. The high oil content of bran makes it subject to rancidification, one of the reasons that it is often separated from the grain before storage or further processing. Bran is often heat-treated to increase its longevity. In white rice the bran and embryo have been removed, as a result of which the rice becomes rancid less quickly but is also deficient in thiamine. When brown rice is steeped in water and partly cooked (parboiled) before preparation, the thiamine in the aleurone layer is able to diffuse into the starchy endosperm. When the rice is then polished, the grain still contains some of the vitamin. This is why beriberi was absent in those regions where the people ate parboiled rice. Parboiling makes it easier to remove the husk but a lot of people don't like the rather musty taste that this treatment gives the rice. In most cultures this thin membrane is removed without parboiling by mechanical polishing, beating or shaking.

Causes

Thiamine in the human body has a half-life of 18 days and is quickly exhausted, particularly when metabolic demands exceed intake. A biochemical deficiency can become apparent rather quickly, even after just 7 days. The course of the disease is usually somewhat slower. A daily intake of 1 mg of thiamine is sufficient for a moderately active man and 0.8 mg for a moderately active woman. Pregnant and lactating women may need more. FAO and WHO recommend an intake of 0.4 mg per 1 000 kcal for most persons. Deficiency may develop in alcoholics, elderly people, malabsorption, use of diuretics, prolonged administration of antacids, dialysis, folate deficiency, diets with a high content of refined grain products lacking fruits and vegetables and ingestion of thiaminase-containing food. Refugees, victims of famine, prisoners and alcoholics are especially at risk for beriberi.

Because thiamine is involved in carbohydrate metabolism, a person whose main supply of energy comes from carbohydrates is more likely to develop signs of thiamine deficiency if their food intake is decreased. With a deficient diet, clinical complaints often develop in strong young males because they have a high glucose metabolism. Increased thiamine consumption may develop in seriously ill patients, hyperthyroidism, pregnancy, lactation and fever. Chronic malabsorption (chronic diarrhoea) leads to reduced uptake. Clinically particular attention should be paid when people are at risk of deficiency and are temporarily receiving

no food (persistent vomiting, hyperemesis gravidarum). Especially when a glucose solution is administered quickly by intravenous injection and the metabolism suddenly has to cope with additional substrate, symptoms of acute deficiency may be induced. In practice such a situation can arise when a confused alcoholic with suspected hypoglycemia is admitted to hospital and a sudden deterioration of the clinical condition is observed after glucose administration.

In infants, refeeding syndrome is a potentially fatal complication of SAM management, especially when the introduction of food is too fast. Rapid initiation of nutritional rehabilitation also increases intracellular thiamine turnover which, on a background of pre-existing low whole body thiamine status, can precipitate the onset of true thiamine deficiency and may contribute to the mortality linked with refeeding syndrome.

Clinical aspects

The energy used by the nervous system is derived entirely from carbohydrate, and a deficiency of thiamine blocks the final utilization of carbohydrate, leading to a shortage of energy and lesions of the nervous tissues and brain. Deficiency causes degeneration of peripheral nerves, the thalamus, mammillary bodies and the cerebellum. The cerebral blood flow is markedly reduced and vascular resistance is increased. The heart may become dilated, muscle fibers become swollen, fragmented and vacuolized with interstitial spaces dilated by fluid. Vasodilation occurs and can result in oedema in the feet and legs. Arteriovenous shunting of blood increases and eventually high-output heart failure may occur.

Deficiency signs may initially be very limited. Muscular cramps and paraesthesia may develop. Tiredness is already present but is often camouflaged: deficient patients often do normal activities with less movement. Anaesthesia over the shin is one of the first clinical signs. In more severe deficiencies, cardiovascular problems may develop (Wet beriberi). This concerns a high-output heart failure with peripheral pitting oedema, low peripheral resistance, warm extremities, full pulse, “pistol shot” heart tones, swollen neck veins, slight cyanosis and lactate acidosis. Quick deterioration with sudden death may occur. When neurological symptoms are prominent, this is called ‘Dry beriberi’. This term indicates a mixed motor-sensory neuropathy with pain, paraesthesia, hyporeflexia and muscle atrophy.

Nocturnal muscular pain in the calves may develop. The symptoms are more pronounced in the legs than in the arms. Frequently the patient is unable to get up from the squatting position without assistance and wrist drop or drop foot can develop. Patients often succumb due to infectious complications (TB, decubitus) when they become bedridden.

Acute Wernicke's syndrome manifests by horizontal nystagmus, ophthalmoplegia with diplopia, fever (dysfunction of the hypothalamus), ataxia, confusion and coma. Frequently there are autonomous disorders, both sympathetic hyperactivity with tremor and agitation and hypoactivity with hypothermia and low blood pressure. Acute cerebellar ataxia may develop. During alcohol abstinence with simultaneous thiamine deficiency an acute delirium tremens may develop. Retrograde amnesia, confabulation, psychosis and learning difficulties are signs of Korsakoff's syndrome (psychosis). This develops in 80% of Wernicke patients.

Infantile beriberi is manifested by aphonia, areflexia and heart failure. Breast-fed babies of thiamine-deficient mothers – who often have no overt signs – become restless between 2 and 5 months of age, cry frequently (a loud piercing cry) and often refuse breastfeeding. They soon become debilitated and cry soundlessly. Soshin beriberi, a fulminant form of congestive heart failure with cyanosis and oedema; lactic acidosis is also documented in infants. Administration of thiamine IV results in very rapid recovery, often with noticeable improvement in less than 24 hours. Due to the non-specific presentation, thiamine deficiency is often overlooked or misdiagnosed as typhoid fever, sepsis, malaria, pneumonia or decompensated congenital cardiomyopathy in infants.

Diagnosis and treatment

The diagnosis of thiamine deficiency is initially a clinical one.. A practical and easy test to determine the thiamine status does not exist. Since the vitamin is cheap and not toxic if suspicious of deficiency a trial of therapy is reasonable. A high level of clinical suspicion should be demonstrated in the following situations: suspicion of infantile beriberi; unexplained neurological signs, encephalitis, and cardiac failure; early clinical deterioration after initiation of feeds in malnutrition; sepsis (including in SAM); severe burns; major trauma; hypoxia; and unresponsive lactic acidosis. In acute situations a dose of 100 mg thiamine is administered IV. It is best to add 2 ml of a 50% magnesium sulphate solution, since magnesium is a cofactor for transketolase an associated hypomagnesaemia is frequently

observed. The clinical response in heart failure is usually very dramatic and fast. Improvement can already be observed just a few hours after administration. The patient is subsequently treated with 20 mg thiamine daily together with a multivitamin and efforts are made to eliminate the cause of the deficiency (diet, including avoidance of thiaminases, treatment of alcoholism, absorption problems, antiemetics, etc.). Central lesions usually do not fully recover. In the case of peripheral neural lesions, the degree of recuperation depends upon the duration and severity of the damage.

Prevention

A balanced diet, sufficiently rich in vitamins, is essential. Food supplements may be given to high-risk groups. An unbalanced diet (e.g. based on polished rice) should be avoided. Lactating mothers in endemic regions should preferably take thiamine.

Thiamine deficiency in alcoholics

Although classical beriberi is uncommon in industrialized countries, thiamine deficiency is by no means a rarity. It is prevalent in the alcoholic population worldwide. Alcoholism is an increasingly prevalent condition, and several clinical features previously believed to be due to chronic alcoholic intoxication are now known to be the result of nutritional deficiencies. The most common of these conditions is probably alcoholic polyneuropathy, which has similarities to neuritic beriberi and is believed to result mainly from thiamine deficiency. Alcoholics who get much of their energy from alcoholic drinks often consume insufficient food and do not get adequate amounts of thiamine and other micronutrients. They may develop a peripheral neuritis, which can influence both the motor and the sensory systems, often affecting the legs more than the arms. The various manifestations include muscle wasting, abnormal reflexes, pain and paresthesia. These symptoms often respond to treatment with thiamine or B-complex vitamins taken orally.

Another condition resulting from thiamine deficiency in alcoholics is Wernicke-Korsakoff syndrome. Wernicke’s disease is characterized by eye signs such as nystagmus (rapid involuntary oscillation of the eyeball), diplopia (double vision arising from unequal action of the eye muscles), paralysis of the external rectus (one of the muscles of the eyeball)

and sometimes ophthalmoplegia (paralysis of the muscles of the eye due to lesions in the nuclei of cranial nerve III and VI). It is also characterized by ataxia (loss of coordination of body movements) and mental changes. Korsakoff's psychosis involves a loss of memory of the immediate past and often elaborate confabulation which tends to conceal the amnesia. Korsakoff syndrome (KS) is a late neuropsychiatric manifestation of Wernicke encephalopathy (WE). They are two different syndromes, each representing a different stage of the disease. Wernicke encephalopathy (WE) is an acute syndrome requiring emergent treatment to prevent death and neurologic morbidity. Korsakoff syndrome (KS) refers to a chronic neurologic condition that usually occurs as a consequence of WE. It is now generally agreed that any distinction between Wernicke's disease and Korsakoff's psychosis in the alcoholic patient may be artificial; Korsakoff's psychosis may be regarded as the psychotic component of Wernicke's disease. This view is supported by the fact that many patients who appear with ocular palsy, ataxia and confusion, and who survive, later show loss of memory and other signs of Korsakoff's psychosis. Similarly, psychiatric patients with Korsakoff's psychosis often show the stigmata of Wernicke's disease even years after the illness. Pathological evidence also indicates the unity of the two conditions.

That Wernicke-Korsakoff syndrome is caused by thiamine deficiency and not by chronic alcohol intoxication is shown by the fact that the condition responds to thiamine alone, even if the patient continues to consume alcohol. Of overriding importance in this syndrome is the rapid occurrence of irreversible brain damage; early recognition and treatment are therefore vital. A patient suspected of having the syndrome should immediately receive 500 mg of thiamine by injection (500 mg IV 3x/d for 3 days followed by 250 mg IV/IM per day for 4 days), even before a definitive diagnosis is made.

Prevention

The prevention of Wernicke-Korsakoff syndrome calls for considerable public health ingenuity. Several possible measures have been suggested:

· the "immunization" of alcoholics with large doses of thiamine at regular intervals (the development of a suitable depot carrier to reduce the frequency of these injections would be very helpful);

· the fortification of alcoholic beverages with thiamine;

· a provision by public health authorities that thiamine-impregnated snacks be made available on bar counters.

The cost of any of these measures would almost certainly be less than the present enormous expenditure on institutional care of those who have suffered from Wernicke-Korsakoff syndrome.

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Pellagra

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.

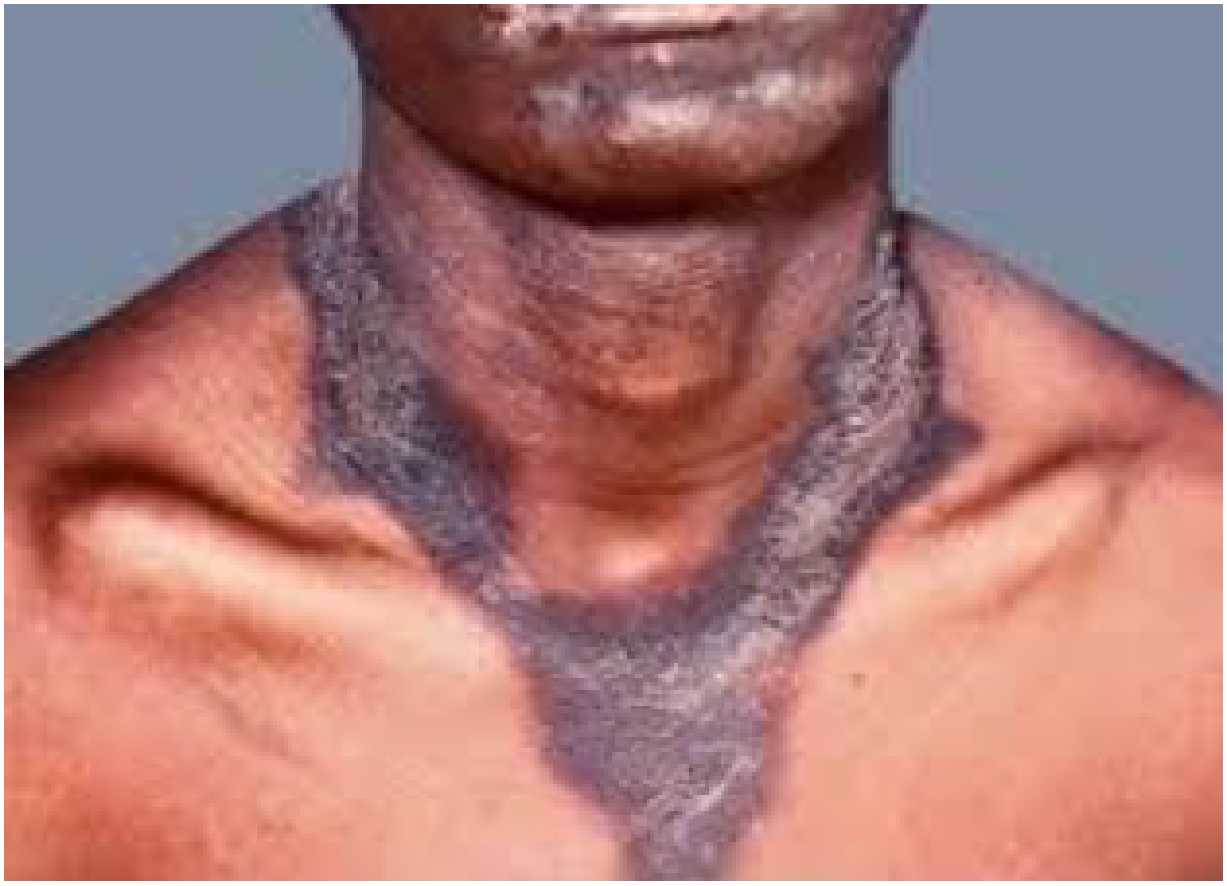
Clinical aspects

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.

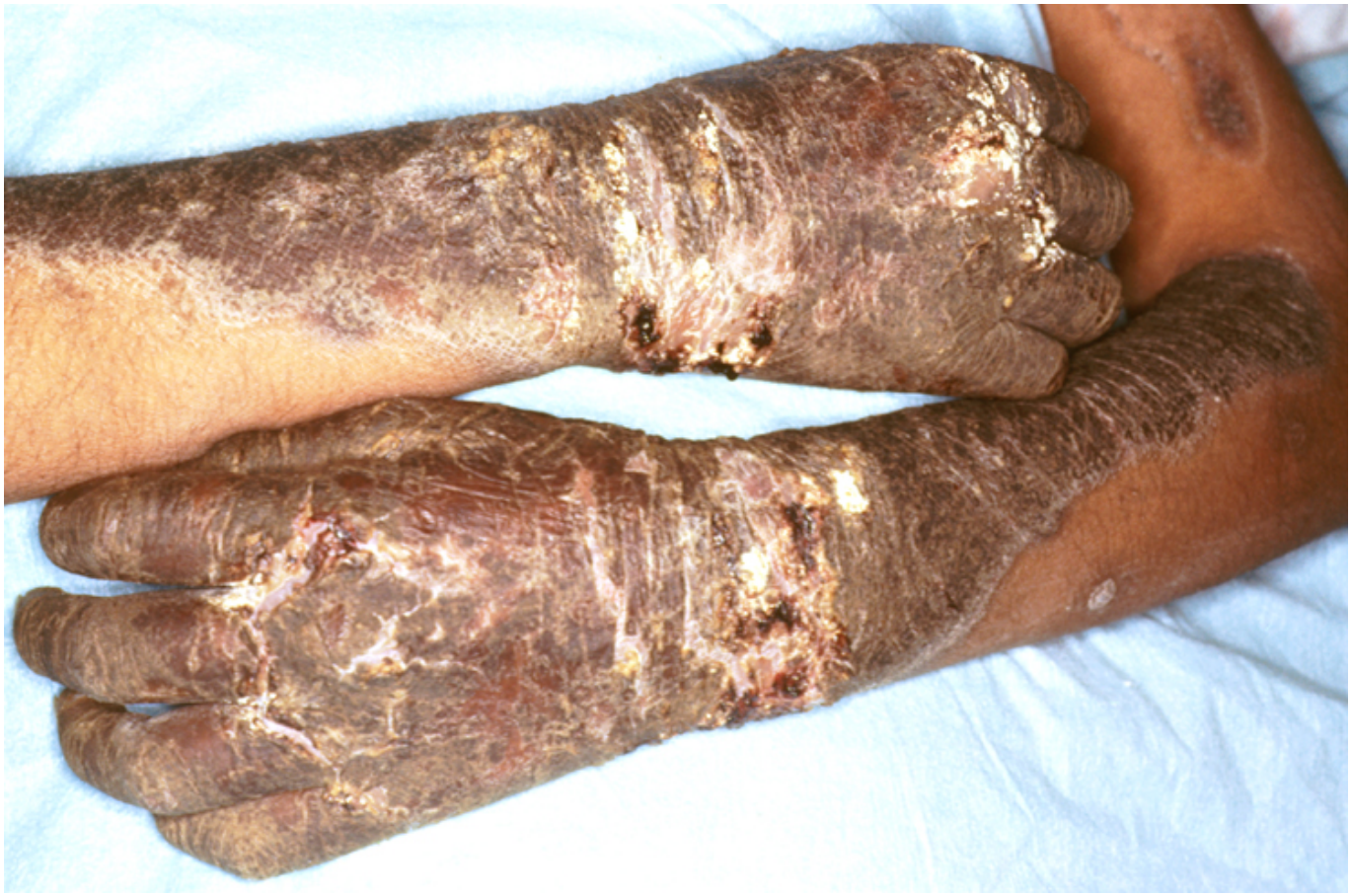
Skin lesions occur symmetrically on areas of the skin exposed to sunlight, such as the face, the back of the hands, the neck, the forearms and exposed portions of the leg. Patients initially present with deepening of the pigmentation. The hyperpigmented areas lose the oily

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.

LAST UPDATED BY ADMIN ON JANUARY 30TH, 2025

Scurvy

Summary

- Deficiency of ascorbic acid leads to poor quality collagen
- Hemorrhages and bone abnormalities dominate the clinical picture
- Barlow's disease (infantile scurvy) with periosteal hemorrhage)
- Rapid improvement with vitamin C tablets or fresh fruit and vegetables

Introduction

Scurvy is a disease caused by lack of vitamin C. The condition was a common ailment aboard European seagoing ships in the early days of world exploration and was a serious problem on long voyages. In 1497, Vasco da Gama, in his epic trip from Portugal to India and back, lost no fewer than 100 of his original crew of 160 to scurvy. Magellan's expedition of circumnavigation of the world (1519-1521) lost 200 of his original crew of 218. Of the 110 crew members of Jacques Cartier's exploration of the St Laurence river (Canada), 100 were affected during the winter of 1535-1536. A quarter died, the rest recovered with grounded cedar bark, a native Indian remedy. Aboard the ships there was a systematic lack of fresh fruit and vegetables.

In the nineteenth century, scurvy began to occur among infants receiving the newly introduced preserved milk instead of breastmilk or fresh cows' milk. The preserved milk contained adequate carbohydrate, fat, protein and minerals, but the heat used in its processing destroyed the vitamin C, so the infants got scurvy. Nowadays, scurvy only occurs in the event of an unbalanced diet with nutritional deficiency, as in some elderly people and alcoholics. Scurvy is sometimes seen in persistent problematical situations in the tropics (refugees, starvation), certainly in warm and dry regions where there is a lack of fresh fruit and vegetables. In a population living in stable conditions, scurvy is rare.

Ascorbic acid

For a long time the origin of scurvy was a mystery. Before vitamin C was identified, however, a form of empirical treatment and prophylaxis had been discovered, but the nature of the compound that cured scurvy was not clear. A breakthrough came with the discovery that guinea pigs could develop scurvy. Guinea pigs, fruit-eating bats and higher primates (Old and New World monkeys, apes and humans) – unlike most mammals – are unable to synthesize ascorbic acid. Lower primates or prosimians, such as lemurs, loris and tarsiers have active L-gulunolactone acid oxidase, and so make their own vitamin C. Humans have an inactivating mutation in this enzyme, which leads to an afunctional pseudogene and therefore the inability to synthetize vitamin C. One could say that the entire human race has an inborn error of metabolism. When the defect in guinea pigs was discovered, scientists had an animal model and an in vivo assay for measuring the antiscorbutic activity of different food products.

It was demonstrated that drying, cooking and prolonged exposure to air destroyed the active ingredient. During his research at Cambridge University in 1928, the Hungarian biochemist Szent-Gyorgyi isolated vitamin C. He isolated the compound from lemons, oranges, cabbages and adrenal cortex. After his return to Hungary, he continued his work on paprikas, as befits a good Hungarian. It turned out that paprikas are very rich in vitamin C. He received the Nobel Prize for Medicine in 1937. He initially proposed to name his crystalline sample “ignose”, indicating its relationship to sugars while at the same time underlining his ignorance of its true nature. The editor of the *Biochemical Journal* where he wanted to publish his findings, did not like jokes and reprimanded him. A second suggestion “godnose” was judged to be equally unacceptable. Szent-Györgyi finally accepted the more prosaic “hexuronic acid”, since the molecule had 6 carbons and was acidic. Haworth suggested the term “ascorbic acid,” acknowledging the antiscorbutic nature of the compound.

Subsequently it became evident that vitamin C occurs in numerous food products. Vegetables such as broccoli and tomatoes, but also potatoes and citrus fruit have large concentrations of vitamin C. Sir Walter Norman Haworth discovered an efficient synthesis method for the preparation of vitamin C based on a carbohydrate precursor. Sir Norman

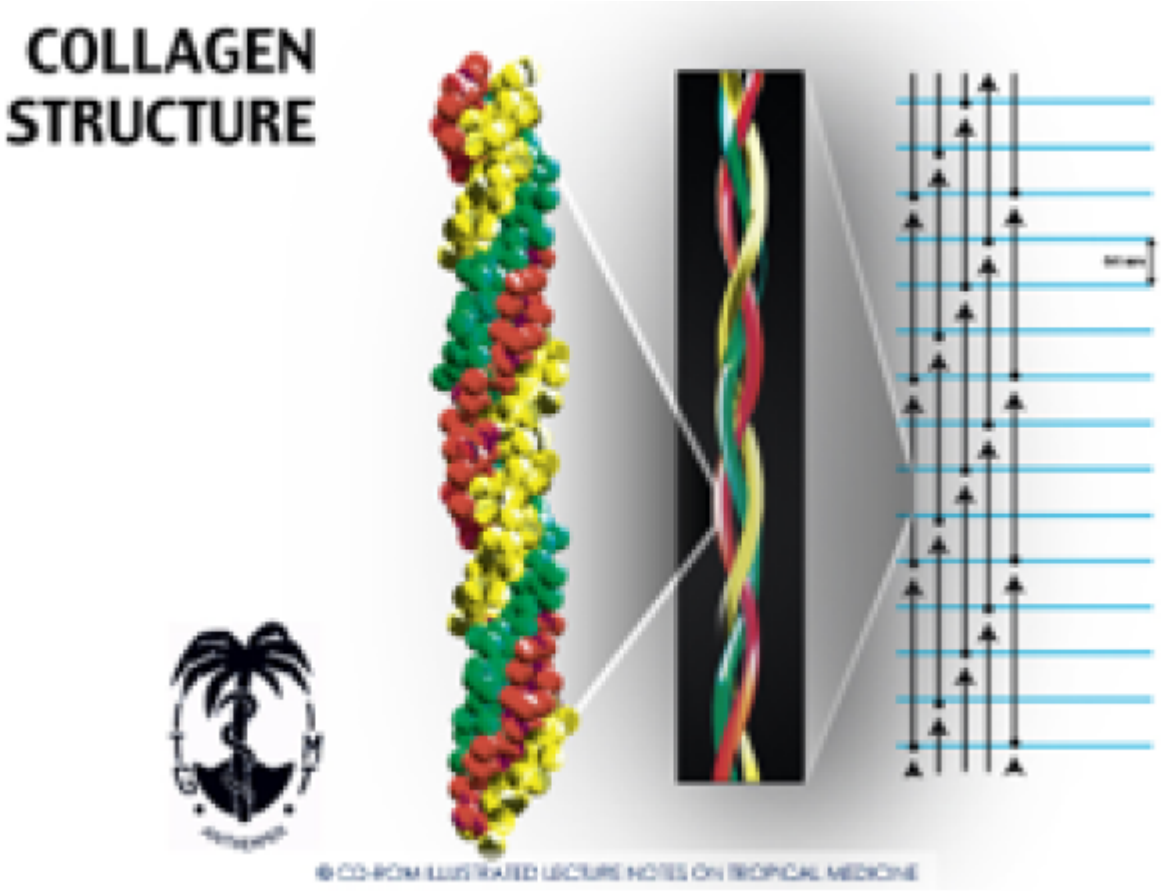
Haworth and Paul Karrer (Switzerland) were jointly awarded the Nobel Prize for Chemistry for their work in 1937.

The name ascorbic acid refers to ‘antiscorbutic’ (from the Low German term for scurvy: *schorbock*). Vitamin C is essential for the production of mature collagen. It is a highly reducing compound and is capable of undergoing reversible oxidation. In consequence, it fulfils a role in redox reactions in the body. Vitamin C is the L-enantiomer of ascorbate; the D-enantiomer is not physiologically active. Vitamin C promotes the uptake of iron in the intestine and protects folic acid reductase. Vitamin C regenerates antioxidants such as vitamin E, flavonoids and glutathione. It plays a role in the synthesis of steroids and the production of carnitine.

Collagen

Vitamin C is important in redox reactions. At least 8 different enzymes use vitamin C as a cofactor (maturation of collagen, production of several peptide hormones and neurotransmitters, synthesis of carnitine). Several symptoms of scurvy can be traced back to defective collagen. Collagen is the commonest protein in the animal kingdom. Large amounts of unusual amino acids are found in collagen: hydroxylysine and hydroxyproline. These are essential for the chemical stability of collagen. The conversion of proline into hydroxyproline is stimulated by the enzyme proline hydroxylase. For this purpose it uses a Fe^{2+}ion, which is converted during the reaction into Fe^{3+}. This inactivates the enzyme. Enzyme regeneration takes place by an interaction with ascorbate, in which vitamin C is converted into dehydroascorbic acid. For a better understanding of scurvy, we briefly sketch the normal production of the commonest form of collagen. Individual collagen polypeptide chains are synthesized on the ribosomes of the rough endoplasmatic reticulum. The strands are released in the lumen of the endoplasmic reticulum as large precursor molecules, the so-called pro-alpha chains. Signal peptides are still present at front and rear. In the lumen, selected proline and lysine residues are hydroxylized to hydroxyproline and hydroxylysine. Every pro-alpha chain subsequently combines with two other chains to form a triple-strand helix via hydrogen bridges, the fibrillar procollagen. This is subsequently secreted. Procollagen is converted extracellularly into tropocollagen

by enzymatic cleavage (with the exception of collagen IV in the basal lamina). Tropocollagen subsequently develops further into mature collagen. Normal collagen is broken down slowly by extracellular collagenases. In scurvy, defective pro-alpha chains are formed (the formation of hydroxy-amino acids is disrupted). They do not form a triple helix and are quickly degraded. The consequences are first noticed first in the tissues where collagen turnover is fastest, such as blood vessels. Owing to the gradual loss of the existing collagen, the blood vessels become progressively fragile.



Collagen structure. This is disturbed in osteolathyrism and in scurvy (vitamin C deficiency). Drawing by JP Wenseleers, copyright ITM

Aetiology

Primary deficiency is due to an unbalanced diet, i.e. a diet containing less than 10 mg vitamin C per day. There is little agreement on the minimal daily dose to avoid scurvy. Pregnancy,

lactation, smoking, surgical procedures, thyrotoxicosis, burns and chronic inflammation increase the body's requirements up to 70-90 mg/day. In achlorhydria and chronic diarrhoea, less vitamin C is absorbed. Ascorbic acid is unstable in the presence of heat and prolonged cooking of food considerably reduces the quantity of active vitamin C. Scurvy is uncommon nowadays but outbreaks can be seen in refugee camps, during famines and occasionally in prisons.

Clinical aspects

The highest concentrations of vitamin C are found in white blood cells, the lens and the brain. The total body pool of vitamin C is approximately 1500 mg. The excess is excreted. There is a turnover of 3% per day, which gives a half-life of approximately 18 days. This explains the latency period of 3 to 6 months for symptoms to occur after starting a diet without vitamin C.

Ascorbic acid is necessary for the proper formation and maintenance of intercellular material, particularly collagen. In simple terms, it is essential for producing part of the substance that binds cells together, as cement binds bricks together. In a person suffering from scurvy, the endothelial cells of the capillaries lack normal solidification. They are therefore fragile, and haemorrhages take place. Similarly, the dentine of the teeth and the osteoid tissue of the bone are improperly formed. The patient first complains of pronounced fatigue, general debility of slow onset, irritability, weight loss and vague myalgia and joint pain. Sometimes the first symptom is stiffness in the calves, due to local haemorrhages. Because of the pain in the legs, children may present with pseudoparalysis. In many cases they spontaneously adopt an antalgic posture, with bent knees and hips: frog-leg posture as described by Thomas Barlow. This is usually seen in babies born prematurely when they reach about 6-12 months of age if they have been fed deficient artificial food: Barlow's disease or infantile scurvy. Splinter haemorrhages beneath the fingernails may occur as in infective endocarditis. Haemorrhages around the eyes, ears, neck and on the roof of the mouth may occur. Spontaneous bleeding may occur anywhere in the body, including bleeding leading to palpable subperiosteal haemorrhages. Hyperkeratotic hair follicles and perifollicular petechiae (scorbutic purpura) are quasi pathognomonic. Corkscrew hairs is a typical scorbutic feature. The poor cell-binding also explains the poor scar formation and slow healing of wounds manifest in persons deficient in ascorbic acid. Old scars might break open. The gums become swollen, purple and spongy and bleed easily. Often there will be secondary infection.

In advanced scurvy, teeth fall out spontaneously. Endochondral bone development ceases because osteoblasts no longer produce osteoid. A fibrous area is formed between diaphysis and epiphysis. The costochondral junctions enlarge. This is clinically palpable as a scorbutic rosary (not to be confused with rachitic rosary). Other symptoms include femoral neuropathy and oedema of the legs. Microcytic hypochromic anaemia may develop as vitamin C is needed to absorb iron.
Sudden cardiac failure and death can occur in a patient with above mentioned symptoms, even if the person does not appear seriously ill.

Differential diagnosis

Scorbutic rosary on the thorax and bone abnormalities must be distinguished from rachitic rosary (vitamin D deficiency). Scorbutic gingivitis must be distinguished from other causes such as candidiasis, herpes, trench mouth, syphilis, pemphigus and Behçet's syndrome. Scorbutic haemorrhages must be distinguished from other bleeding diatheses. Subperiosteal haemorrhage with periosteal elevation should be distinguished from congenital syphilis.

Diagnosis

The vitamin C content in peripheral blood can be measured in specialized laboratories, although plasma vitamin C levels quickly normalize with enteral intake of ascorbic acid and do not reflect tissue levels. A level of less than 11 µmol/liter is diagnostic for scurvy. Measurement in leukocytes – a storage pool for ascorbic acid – is more precise. A capillary fragility test will be positive. When this is measured using the sphygmomanometer, it is called the Hess capillary test. The regular haemostasis parameters (platelets, coagulation times) are normal. Findings on X-rays of the legs include a lucent transverse metaphyseal band with an adjacent dense sclerotic band, metaphyseal spurring and nonspecific evidence of diffuse osteopenia and cortical thinning. Radiographs may reveal periosteal fluid consistent with haemorrhage.

Treatment

The treatment of scurvy consists of administering extra vitamin C (at least 100 mg three times daily for two weeks) and adjusting the daily diet with plenty of fresh fruit and vegetables. Clinical improvement may be expected within one to two weeks. Chronic

gingivitis and extensive subcutaneous haemorrhages take longer to heal. Increased intake of vitamin C with meals can have a manifest effect on the absorption of iron. In many iron-deficient populations, increasing vitamin C intake will help reduce the incidence and severity of iron deficiency anaemia.

Treatment: historical note on James Lind and Captain Cook

Various therapies were used in ancient times but as long as the cause remained unknown, no rational treatment could be suggested. Some people believed that certain plants could be used as a remedy for scurvy. For instance, *Cochlearia officinalis* (Family: Cruciferae) is known as common scurvy grass. Naval surgeon James Lind was on board the *Centurion*, a British gunship which had been put to sea in 1740 in order to give a hard time to the Spanish. After three years he had gained considerable experience with scurvy. In 1747, he conducted a kind of clinical trial ahead of its time. He had 12 patients with scurvy on board. They were divided into six groups and each group received a different treatment: (1) one glass of cider a day, (2) 25 drops of an elixir of vitriol three times a day, (3) two spoonfuls of vinegar three times a day, (4) half a pint of sea water three times a day, (5) a mixture of garlic, mustard, horseradish and balsam of Peru three times a day, (6) two oranges and a lemon each day. The two men who were given citrus fruit made a spectacular recovery. Cider also brought some improvement, although to a more limited extent. Lind published his findings. In July 1772, Captain Cook set out from Plymouth on board *HMS Resolution* on an expedition that was to last three years. He didn't lose a single member of the crew to scurvy. A paper that he presented on the prevention of scurvy won for Cook the Royal Society's Copley Gold Medal. He ordered the crew to eat sauerkraut twice a week and gave a malt potion and an orange and lemon to everyone who showed the first signs of scurvy. Furthermore he made sure that the ship was provisioned with fresh fruit and vegetables each time they made landfall. He also demanded strict hygiene on board, which was very unusual at the time. The Royal Navy implemented Captain Cook's regimen regarding hygiene and ordered that on voyages lasting longer than two weeks, everyone on board was to be given a spoonful of lemon juice and sugar each day. This mixture was incorrectly described as 'lime juice', and to this day, British sailors are known as 'Limeys'. Unfortunately, limes (*Citrus medica* var *acidum*) were sometimes used instead of lemons (*Citrus medica* var *limonum*). Limes contain much less vitamin C than

lemons so that fatalities sometimes occurred and the use of lemon juice was regarded with suspicion. After 1860, only lemons were officially allowed for antiscorbutic use. The reason why scurvy was banished from the long-distance sailing ships of the Chinese Ming dynasty (1368-1644) was due to the fact that the crew were regularly given fresh, germinated soya beans to eat, as part of their traditional food. Unlike non-germinated seeds, these shoots are rich in vitamin C. The importance of the absence of scurvy is not to be underestimated, since the voyages of the Chinese admiral Zheng He (1421) led to world maps, which were obtained by the Portuguese crown and were a crucial element for the major discovery expeditions of Henry the Navigator, opening the world for the West, a fundamental turning point in history.

Prevention

A sufficiently varied diet containing fruit and green vegetables will prevent the development of scurvy. Prolonged cooking of all food should be avoided. Vitamin C 60-100 mg/day PO provides protection against scurvy. Some people use vitamin C megadoses in the hope of preventing colds and other ailments. There is little evidence to support this but no definitive conclusion has yet been reached.

Vitamin C is metabolized to oxalate. When megadoses vitamin C are consumed on a daily basis, this might facilitate the formation of oxalate kidney stones but there is no consensus on this. Excess ascorbate is normally excreted in the urine, but in patients with renal failure, it is retained and converted to insoluble oxalate and can accumulate in multiple organs.

LAST UPDATED BY ADMIN ON JANUARY 30TH, 2025

Iodine deficiency disorders

Summary

- Iodine deficiency disorders (IDD) are most prevalent in mountainous, alluvial plains and areas far away from oceans due to low iodine intake
- About 2 billion people in the world have low iodine intake

- Cretinism is only the tip of the iceberg of IDD manifestations
- Iodine deficiency is the most frequent cause of avoidable mental retardation
- Goitrogenous factors like thiocyanate and selenium deficiency contribute to goiter formation
- Neurological cretinisme is irreversible
- Myxoedematous cretinisme can be reversed when treated early
- Prevalence of endemic goiter, urinary iodine concentrations, TSH dosage and prevalence of cretinism determine endemicity of IDD
- Salt, water or oil are used for iodine fortification

Introduction

Iodine is an oligo-element that is present in the human body in a very small quantity (15 to 20 mg for adults). Its only known function is as essential element in the production/composition of the thyroid hormones T3 and T4. These hormones have a specific role in the metabolism of all cells of the organism and in the growth process of most organs, in particular the brain. In a situation of iodine shortage, thyroid hormone synthesis and availability is reduced, with numerous health consequences. In the past the deficiency was called “endemic goitre”, related to the most prominent sign of the deficiency “the goitre”, but the health problems due to iodine deficiency are far more important than goitre alone. It is now replaced by “iodine deficiency disorders” or “IDD”.

Epidemiology

At present there are no exact figures on the prevalence iodine deficiency disorders available: in 1990 it has been estimated that among the 1572 million people in the world exposed to iodine deficiency (28.9 % of the world population), 11.2 million were affected by overt cretinism, the most extreme form of mental retardation due to the deficiency and that another 43 million people were affected by some degree of mental impairment. It therefore appeared that iodine deficiency was the leading cause of preventable mental retardation. A WHO report of 2007 concludes that global progress in controlling iodine deficiency has been made, but still 2 billion people (of which 266 million school-aged children) have insufficient iodine intake. This report warns that more than adequate or even excessive iodine intake in 34 countries.

Although present in 95 countries, the problems due to iodine deficiency occur most in mountainous regions: the mountain chains of the Himalayas, the Andes (where the neurological form is dominant), the mountainous regions of Vietnam, etc. Regions that are situated at a low level, far away from the oceans, like the central part of the African continent (where the myxoedematous form is dominant) and to a lesser degree the European continent, are also affected as well as the high plains of China and Australia. The groups with the highest risk for iodine deficiency are in order of importance the fetus, the newborn, the pregnant and nursing woman, the young child. The prevalence increases with age until puberty, and is higher among women than among men.

The real problem of the iodine deficiency, from a public health point of view, is not goitre itself, but the mental retardation secondary to the thyroid deficiency that is present in fetal life and in the beginning of postnatal life. The socio-economic consequences (high number of disabled, learning difficulties in children, infant death in children with cretinism) are quite important and they are a real obstacle to the development.

Aetiology

1. Low iodine intake

Several arguments confirm that iodine deficiency is the main cause of the observed problems: there is an inverse relation between the prevalence of goitre and the urinary excretion of iodine over 24 hours, used as an indicator of iodine intake. The correction of the iodine deficiency decreases the prevalence of endemic goitre, cretinism and of hypothyroidism. Low iodine intake can be explained by 2 phenomena:

Geography

A soil that is poor in iodine produces water and foods, poor in iodine. The ocean is the essential reservoir for iodine. The iodized ions are oxidized in elementary iodine on the surface of the water by the sunlight. The iodine is volatile and diffuses in the atmosphere and returns to the soil by rain. So it’s brought along by rivers, running water and melting ice. The poorest soils in iodine are found in mountainous regions: these were covered by the glaciers of the Quaternary and because these melted the underlying iodine was swept away with the

erosion. Most mountainous districts in the world have been or are still endemic goitre regions. The disease may be seen throughout the Andes, in the whole sweep of the Himalayas, in the Alps where iodide prophylaxis has not yet reached the entire population, in Greece and the Middle Eastern countries, in many foci in the People's Republic of China, and in the highlands of New Guinea. The iodine content of the drinking water is low, as is the quantity of iodide excreted each day by residents of these districts.

Non-mountainous regions, far away from the oceans can have poor iodine concentrations in their soils. Plants absorb iodine from the ground, plants are eaten by animals and plants and animals are eaten by humans, so the iodine concentration in food is often a good reflection of the distance from the sea.

Examples of iodine deficient low-land regions are the belt extending from the Cameroon grasslands across northern DRC and the Central African Republic to the borders of Uganda and Rwanda, Holland, Central Europe and the interior of Brazil.
Last, a wash-away effect in soils that are regularly flooded can be seen, like the alluvial plains in deltas of big rivers.

Isolation

Food diversity and the mobility of the populations bring along a spontaneous reduction of the prevalence of the endemic goitre. Isolation leads to poor food exchanges and diversification. The phenomenon of opening isolated regions, observed in the last decades, explains as much of the decrease in the prevalence of IDD as the iodination campaigns. It is also the reason for the observed spontaneous historical reduction of the prevalence of IDD in most countries.

2. Goitrogenous factors

The role of additional factors playing a role the aetiology of IDD has been suspected because goitre exists in regions where the iodine intake is adequate. The additional role of goitrogens from food origin or in the environment has been looked into and has been proved in a number of regions in the world.

Thiocyanates inhibit the iodine pump and increase the renal clearance of iodide. They are derived from manioc, in a variable quantity that depend on the nature of the soil, the type of cassava that is cultivated, the way of preparation and consummation of cassava. DRC, Mozambique and Indonesia are countries where thiocyanate can be found. Thiocyanate is derived from intestinal breakdown linamarin – a cyanogenic glycoside – from cassava and its conversion to thiocyanate by the liver. Thiocyanate is a competitive inhibitor of the Na/I symporter in thyroid follicular cells. A reciprocal relationship exists between iodide and thiocyanate in that increasing amounts of iodide protect increasingly against the thiocyanate derived from the cassava. It now seems well established that cassava may contribute to the severity of endemic goitre and probably the incidence of endemic cretinism, but there are many severe endemics where cassava is not eaten. In these regions, it is possible that other goitrogens in the local food may contribute to the effects of a prevailing iodine deficiency. Thiocyanate may cross the human placenta and affect the thyroid of the fetus.

Thioureas act on the level of the oxidation and metabolism of iodine in the thyroid.

3. Selenium deficiency

It has been shown that selenium deficiency may have profound effects on thyroid hormone metabolism and possibly also on the thyroid gland itself. In this situation the function of type I deiodinase (a selenoprotein) is impaired. Type I deiodinase plays a major role in T4 deiodination in peripheral tissues like kidney, liver and gut. It has been shown that when in an area of combined iodine and selenium deficiency, only selenium is supplemented, serum T4 decreases. This effect is explained by restoration of type I deiodinase activity leading to normalization of T4 deiodination and conversion to T3, while T4 synthesis remains impaired because of continued iodine deficiency.
Selenium deficiency also leads to a reduction of the selenium containing enzyme glutathione peroxidase. Glutathione peroxidase detoxifies H_2O_2 which is abundantly present in the thyroid gland as a substrate for the thyroperoxidase that catalyzes iodide oxidation and binding to thyroglobulin, and the oxidative coupling of iodotyrosines into iodothyronines. Reduced detoxification of H_2O_2 may lead to thyroid cell death. Elevated H_2O_2 levels in thyrocytes may be more toxic under situations of increased TSH stimulation such as is present in areas with severe iodine deficiency. Finally decreased availability of glutathione peroxidase impairs

thyroid hormone synthesis in the thyroid gland, a fact that could also contribute to decreased T4 synthesis. Selenium deficiency certainly plays a role in the aetiology of the type of myxedematous endemic cretinism seen in Central Africa but does not by itself constitute a cause of endemic goitre. Extensive epidemiological data collected in China indicated that all selenium-deficient areas were IDD-endemic areas. However, the reverse is not true: IDD can be very severe in many selenium-rich areas.

Iodine needs

The physiologic needs are equal to the hormonal quantity of iodine that is produced every day. This means 50 to 100 ug/day for an adult. The quantity starts increasing in puberty certainly among women. Among the girls of 11 to 12 years a slight increase in the volume of the thyroid body is not rare (transitory hypertrophy).

RECOMMENDED INTAKE	ug/day	
0 - 6 months	35	8 ug/kg 5 ug/100ml of milk 7 ug/100 kcal
6 - 12 months	45	
1 - 10 years	60 – 100	
>= 11 years	100 - 115	
pregnancy – lactation	125 - 150	

Table: Recommended daily intake of iodine (µg/day)

Pathophysiology

Goitre

Because of a deficiency of iodine, the synthesis of the thyroid hormones is reduced. A low level of thyroxin in the blood stimulates the hypophysis to free TSH. This results in a hyperplasia of the cells of the thyroid gland with increase in thyroid volume (goitre). This in turn makes a higher captivation of circulating iodine possible. If the normal production of

thyroid hormones cannot be maintained, hypothyroidism appears.

However, efficient adaptation to iodine deficiency is possible in the absence of goitre as demonstrated in nongoitrous patients in endemic goitre areas such as New Guinea and the Congo. Moreover, adequate adaptation to iodine deficiency has been demonstrated in areas of severe iodine deficiency in the absence of endemic goitre. This clearly indicates that goitre is not required for achieving efficient adaptation to iodine deficiency. Rather in these conditions, efficient adaptation to iodine deficiency is possible thanks to a high iodide trapping capacity but with only a slight enlargement of the thyroid. At this stage, the characteristic hyperplastic picture includes abundant parenchyma, high follicular epithelium and rare colloid.

On the contrary in large goitres, the major part of the gland is occupied by extremely distended vesicles filled with colloid with a flattened epithelium. The mechanism responsible for the development of colloid goitre is not fully understood but it does not appear to be TSH hyperstimulation. It must be the consequence of an imbalance between thyroglobulin synthesis and hydrolysis, i.e. secretion. In these conditions, iodide is diluted while thyroglobulin is in excess, resulting in a lesser degree of iodization of thyroglobulin and consequently a decrease in iodothyronine synthesis and secretion. Hydrolysis of large amounts of poorly iodinated thyroglobulin will result in an important leak of iodide by the thyroid and enhanced urinary loss of iodide, further aggravating the state of iodine deficiency. Therefore, large colloid goitres in endemic iodine deficiency represent maladaptation instead of adaptation to iodine deficiency because they may produce a vicious cycle of iodine loss and defective thyroid hormones synthesis.

Iodine deficiency in the fetus

The fetus and the new born are more sensitive than the adult to the effects of low levels of circulation thyroid hormone seen in iodine deficiency or goitrogenous substances. There is an immaturity of the adaptation mechanisms and iodine reserves are small. The period of growth, pregnancy and lactation increases the needs and make the individual more vulnerable.

The human brain develops during its fetal life until the end of the third life-year. Consequently an iodine and/or thyroid hormone deficiency during this critical period of life causes irreversible changes in the development of the brain. Iodine deficiency in the fetus is the result of iodine deficiency in the mother. The consequence of iodine deficiency during pregnancy is impaired synthesis of thyroid hormones by the mother and the fetus. An insufficient supply of thyroid hormones to the developing brain may result in mental retardation.

The physiologic role of thyroid hormones can be defined as to insure the timed coordination of different developmental events through specific effects on the rate of cell differentiation and gene expression. Thyroid hormone action is exerted through the binding of T3 to nuclear receptors which regulate the expression of specific genes in different brain regions following a precise developing schedule during fetal and early postnatal life. The T3 which is bound to the nuclear receptors is primary dependent on its local intracellular production from T4 via type II deiodinase and not from circulating T3.

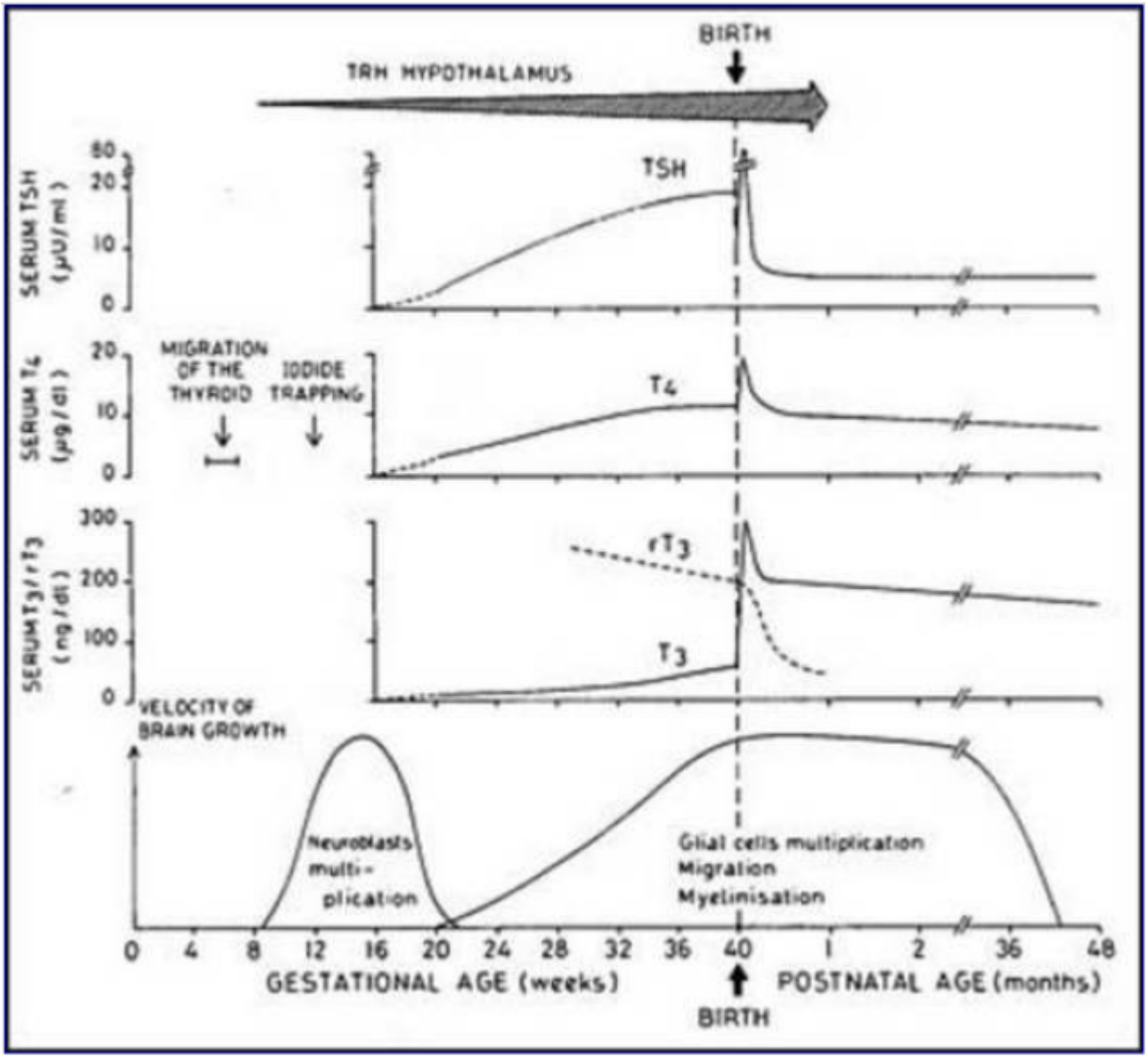


Figure: Ontogenesis of thyroid function and regulation in humans during fetal and early postnatal life

Brain growth is characterized by two periods of maximal growth velocity. The first one occurs during the first and second trimesters between the third and the fifth months of gestation. This phase corresponds to neuronal multiplication, migration and organization. The second phase takes place from the third trimester onwards up to the second and third years postnatally. It corresponds to glial cell multiplication, migration and myelinization. The first

phase occurs before fetal thyroid has reached its functional capacity. It is now largely agreed that during this phase, the supply of thyroid hormones to the growing fetus is almost exclusively of maternal origin while during the second phase, the supply of thyroid hormones to the fetus is essentially of fetal origin. Thyroid hormones are transferred from mother to fetus both before and probably after the onset of fetal thyroid function, contrasting with the previous dogma that this transfer is minimal or does not exist. Nuclear T3 receptors and the amount of T3 bound to these receptors increase about six to tenfold between 10 and 16 weeks, also before the secretion of hormones by the fetal thyroid. This transfer is decreasing but persists during later gestation. Up to 30 % of serum T4 in cord blood at birth could be of maternal origin.

Clinical aspects

The term Iodine Deficiency Disorders (IDD) refers to all the ill-effects of iodine deficiency in a population that can be prevented by insuring that the population has an adequate intake of iodine. These effects are listed in in the table below.

Fetus Abortions	Stillbirths Congenital anomalies Increased perinatal mortality Endemic cretinism
Neonate Neonatal goitre	Neonatal hypothyroidism Endemic mental retardation Increased susceptibility of the thyroid gland to nuclear radiation
Child and goitre	Adolescent (subclinical) hypothyroidism Impaired mental function Retarded physical development Increased susceptibility of the thyroid gland to nuclear radiation

Adult goitre with its complications	Hypothyroidism Impaired mental function Spontaneous hyperthyroidism in the elderly Iodine-induced hyperthyroidism Increased susceptibility of the thyroid gland to nuclear radiation

The Spectrum of Iodine Deficiency Disorders, IDD, Adapted from Hetzel, Laurberg et al.; Stanbury et al.

Goitre

Goitre is an increase in thyroid volume of four to five times that can cause aesthetic problems or compression of the oesophagus and trachea. Goitre can be associated with hypothyroidism, but also Iod-Basedow (not to be confused with Basedow's disease which is the same as Graves' disease) hyperthyroidism can occur in a patient with an endemic goitre due to iodine deficiency relocates to an iodine-abundant geographical area. Cancer is a rare complication of goitre.

Cretinism

Cretinism exists in two extreme forms, but most presentations are intermediate forms. **Neurological** cretinism is be secondary to a state of maternal and fetal hypothyroidism supervening in the beginning of fetal life. The child is euthyroid but presents with spastic diplegia (symmetrical paralysis), deaf-muteness, strabismus and serious mental retardation. This condition is irreversible. **Myxedematous** cretinism is the long-term consequence of a permanent, earlier unknown hypothyroidism; it begins during the fetal or neonatal period if mothers are deprived of iodine during the later process of pregnancy. Myxedematous cretinism has a picture of hypothyroidism with important stature and variable mental retardation. This condition can still respond to thyroid hormone replacement therapy and early detection and treatment is crucial to safeguard the baby's prognosis.

The mental deficiency is the iceberg of which cretinism is only the top. Retardation of

intellectual development was noted in up to 5% of the total population in an endemic zone. This makes iodine deficiency the most frequent cause of avoidable mental retardation. These people often have a clinically and biologically euthyroid aspect since the retardation is a consequence of a transient hypothyroidism during the critical phase of the cerebral development which resolved spontaneously.

Iodine deficiency in the neonate

Miscarriages are more frequent in iodine deficient regions. An increased perinatal mortality due to iodine deficiency has been shown in DRC from the results of a controlled trial of iodized oil injections alternating with a control injection given in the latter half of pregnancy. There was a substantial fall in infant mortality with improved birth weight following the iodized oil injection. Low birth weight of any cause is generally associated with a higher rate of congenital anomalies and higher risk of death throughout childhood. Apart from mortality the importance of the state of thyroid function in the neonate relates to the fact that the brain of the human infant at birth has only reached about one third of its full size and continues to grow rapidly until the end of the second year. The frequency distribution of IQ in apparently normal children in such conditions is shifted towards low values as compared to matched controls who were not exposed to iodine deficiency during the critical period of brain development because of correction of the deficiency in the mothers before or during early gestation.

More globally, in a meta-analysis of studies on neuromotor and cognitive functions in conditions of moderate to severe iodine deficiency, iodine deficiency resulted in a loss of 13.5 IQ points at the level of the global population.

Iodine deficiency in the adult

A high degree of apathy has been noted in populations living in severely iodine deficient areas. This may even affect domestic animals such as dogs. It is apparent that reduced mental function due to cerebral hypothyroidism is widely prevalent in iodine deficient communities with effects on their capacity for initiative and decision making. This indicates that iodine deficiency can be a major block to the human and social development of

communities living in an iodine deficient environment and constitutes a major teratogen at the community level. In addition to this impact to brain and neurointellectual development, iodine deficiency at any period in life, including during adulthood, can induce the development of goitre with mechanical complications and/or thyroid insufficiency. Another consequence of longstanding iodine deficiency in the adult but also in children is the development of hyperthyroidism, especially in multinodular goitres with autonomous nodules. It is now accepted that hyperthyroidism is one of the disorders induced by iodine deficiency.

Treatment

The prolonged administration of iodide or of T4 reduces the volume of goitre. Surgical treatment is rarely indicated. Unfortunately, these individual treatments are frequently impossible to apply on the whole population because of the magnitude of the problem and of the lack of medical infrastructure. The logical medical attitude is to focus all efforts on the prevention. The principle is simple: the prevention of iodine deficiency = a regular and stable iodine administration.

Prevention

Diagnosis of endemicity

Several factors can be taken into consideration when determining and quantifying the endemicity of the problems related to iodine deficiency:

1. Prevalence of endemic goitre

Its determination is based on the percentage of people with a goitre in a specific population. During field inquiries, the best method consists in examining the whole population of the region. In case of difficulties, it is allowed to limit these inquiries to children from 6 to 12 years. By palpation, a thyroid is considered goitrous when each lateral lobe has a volume greater than the terminal phalanx of the thumbs of the subject being examined. However, palpation of goitre in areas of mild iodine deficiency has poor sensitivity and specificity. In such areas, measurement of thyroid volume by ultrasound is preferable.

Classification	Description
Grade 0	No palpable or visible goitre.
Grade 1	A goitre that is palpable but not visible when the neck is in the normal position (i.e. the thyroid is not visibly enlarged). Thyroid nodules in a thyroid which is otherwise not enlarged fall into this category.
Grade 2	A swelling in the neck that is visible when the neck is in a normal position and is consistent with an enlarged thyroid when the neck is palpated.

Revised classification of goitre according to WHO/UNICEF/ICCIDD

2. Dosage of urinary iodine

It is difficult to measure precisely the food iodine content. When in nutritional balance, the intake of iodine equals the urinary excretion of iodine. Urinary iodine excretion is a good marker of the very recent dietary intake of iodine and therefore is the index of choice for evaluating the degree of iodine deficiency and of its correction. Iodine concentrations in casual urine specimens of children or adults provide an adequate assessment of a population iodine nutrition, provided a sufficient number of specimens is collected. Twenty four hours samples are difficult to obtain and are not necessary. Relating urinary iodine to creatinine is expensive and unnecessary. However the median urinary iodine is often misinterpreted. Individual iodine intakes and therefore a spot urinary iodine concentration are highly variable from day-to-day, and a common mistake is to assume that all subjects with a spot UI <100 µg/L are iodine deficient.

For epidemiological studies, the population distribution of urinary iodine is required rather than individual levels. Because the frequency distribution of urinary iodine is usually skewed towards elevated values, the median is considered instead of the mean as indicating the status of iodine nutrition.

Median urinary iodine (µg/l)	Iodine intake	Iodine nutrition

< 20	Insufficient	Severe iodine deficiency
20-49	Insufficient	Moderate iodine deficiency
50-99	Insufficient	Mild iodine deficiency
100-199	Adequate	Optimal
200-299	More than adequate	Risk of iodine-induced hyperthyroidism following introduction of iodized salt in susceptible groups
> 300	Excessive	Risk of adverse health consequences: iodine-induced hyperthyroidism, auto-immune thyroid diseases

Table: Epidemiological criteria for assessing iodine nutrition based on median urinary iodine concentrations in school-aged children

3. TSH dosage (thyroid stimulation hormone)

TSH level in the serum are elevated in cases of iodine deficiency. However difficulties are often encountered in obtaining venous blood samples in populations due to apprehension about blood collection and operational difficulties. Therefore these measurements are not routinely recommended in routine assessment and monitoring. In spite of the difficulties in blood collection, it has to be kept in mind that the final objective of correction of iodine deficiency is not only to increase the access of the population to iodized salt and to normalize the urinary iodine concentration but mostly to normalize thyroid function tests. Elevated serum TSH, unless exceptional pathological situations, indicates an insufficiency in the saturation of the T3 receptor in the brain, whatever the level of serum thyroid hormones. Therefore, elevated serum TSH constitutes an indicator of the potential risk of iodine deficiency on brain development. Serum T4 and T3 are less specific indicators of iodine deficiency because they are modified usually only in conditions of at least moderate iodine deficiency. Moreover these levels are largely influenced by age and sex. Elevated serum T3 in spite of low serum T4 is considered as a protective mechanism to most parts of the body, except the brain, where T3 is produced locally and not derived from the circulating T3.

The use of whole blood from finger pricks spotted on filter paper cards can be used at least for the measurement of serum TSH as indicators of thyroid hyperstimulation. A frequency distribution of serum TSH in neonates shifted to high values is a particularly sensitive index of the risk of potential damage of the developing brain due to iodine deficiency. In normal conditions, less than 3 % of neonatal TSH are above the critical threshold of 5 mU/L whole blood. However because of technical and financial limitations the use of this variable has been recommended only in countries and areas where a program of systematic neonatal hypothyroid screening is already implemented.

4. Prevalence of cretinism

The study of the prevalence of cretinism can be completed by a study of the light forms (deaf muteness) when necessary. The prevalence of the cretinism can be up to 10 % of the whole population in certain regions.

Criteria on the intervention level

An operational definition of endemicity based on the experiences and a consensus between the experts has been refined and allows identification of the need for interventions in a formal manner. A zone is arbitrarily defined as affected by endemic goitre when more than 10 % of the children between 6 to 12 years suffer from goitre.

Iodine Deficiency	Severe	Moderate	Mild
Number of cases of goitre among school children Visible goitre Total goitre	 > 50 % > 10 %	 20-49 % 5-9 %	 10-19 % 1-5 %
Urinary iodine (median, µg/l)	< 20 %	20-49 %	50-99 %
Prevalence of cretinism	> 1 %	< 1 %	0 %

Indicators of iodine status at population level

In case of suspicion of endemic disease a fast inquiry on the prevalence among school children from 6 to 12 years old will give a first approximation of the magnitude of the problem. The consultation of a specialist is recommended for the following stages which will consist in refining the endemicity diagnosis and in deciding if an intervention is a good idea and what sort of intervention is needed.

Intervention strategies

1. Iodized salt

The iodination of salt is one of the most simple, least expensive and most efficient measures, in nutrition as well as in public health. It was used for the first time in 1917 in the United States. Since then its efficiency has been recognized in several countries: Guatemala, Argentina, Brazil, and Switzerland. It is a simple technology with an ignorable risk for toxicity. Iodine is added to the salt under the form of potassium iodide or, in humid tropical regions, potassium iodate because of its increased stability. The proposed concentration varies between 1/25.000 and 1/100.000 in function of certain criteria like the consummation of salt by the population and the severity of the deficiency. The cost averages 0.20 US$/person/year and the efficiency of the program depends on:

- the control and monitoring of the iodine quantity
- the resistance of the producers of salt
- the geographical distribution of the production sites
- the distribution in the risk zones
- the accessibility of the iodized salt and the by-passes

Iodized salt is considered as the most appropriate measure for iodine supplementation. The advantage of supplementing with iodized salt is that it is used by all sections of a community irrespective of social and economic status. It is consumed as a condiment at roughly the same level throughout the year. Its production is often confined to a few centres which means that processing can occur on a larger scale and with better controlled conditions. However this is often not the case in developing countries.

The packaging of the iodized salt is very important. Jute bags have been used extensively but

in humid conditions salt absorbs moisture. The iodate dissolves and will drop out of the bag if it is porous with a heavy loss. This has been found to reach 75% over a period of nine months. To avoid this waterproofing is required, achieved by a polythene lining inside the jute bag or else a plastic bag. The additional cost of a plastic bag (50-80% more) would be justified by reduced losses and their resale value.

2. Iodination of water

Water is really a good means of transportation with a large distribution and it is easy to adjust. There are no negative effects and costs are moderate. It can be done by iodizing the water distribution system or wells with slow release capsules. As salt, it is a daily necessity and thus the iodization will reach the most vulnerable groups.

3. Iodized oil

An iodized oil supplementation program is necessary when other methods have been found ineffective or can be considered to be inapplicable. Iodized oil can be regarded as an emergency measure for the control of severe IDD until an effective iodinated salt program can be introduced. Spectacular and rapid effects of iodized oil in reducing goitre can be expected. Iodized oil can be given in injections (Lipiodol®) or orally. Protection of an oral dose is around one year, that of an injection four to five years.

The possibility of linking up an iodized oil program with childhood vaccination and antenatal care has been considered in the past. Diversification and modification of food habits in endemic zones is another preventive measure, but is challenging as it often requires importation of sea food to remote areas.

Monitoring

In the countries that have begun iodized salt programs, sustainability is a major focus. These programs are fragile and require a long-term commitment from governments. In several countries where iodine deficiency had been eliminated, salt iodization programs fell apart and iodine deficiency recurred.

The indicators used in monitoring and evaluating IDD control programs include:

1) Indicators to monitor and evaluate the salt iodization process (Process indicators)
2) Indicators to monitor the impact of salt iodization on the target populations (Impact indicators).

The impact indicators include in order of priority the determinations of urinary iodine, of the prevalence of goitre and of the serum levels of TSH and thyroid hormones. It is now considered that iodine deficiency has been eliminated from one particular country when the access to iodized salt at household level is at least 90 %, together with a median urinary iodine of at least 100 µg/L and with less than 20 % of the samples below 50 µg/L.

Side effects of iodine supplementation

The effect of iodine on the thyroid gland is complex with a U shaped relation between iodine intake and risk of thyroid diseases as both low and high iodine intake are associated with an increased risk. It is stated that normal adults can tolerate up to about 1000 µg iodine/day without any side effects.

However this upper limit of normal is much lower in a population which was exposed to iodine deficiency in the past. The optimal level of iodine intake to prevent any thyroid disease may be a relatively narrow range around the recommended daily intake at 150 µg.

The possible side effects of iodine excess are as follows:

1. Iodide goitre and iodine-induced hypothyroidism

When the iodine intake is chronically high, as for example in coastal areas of Japan and China due to the chronic intake of seaweeds rich in iodine such as laminaria or in Eastern China because of the high iodine content of the drinking water from shallow wells, the prevalence of thyroid enlargement and goitre is high as compared to normal populations and the prevalence of subclinical hypothyroidism is elevated. The mechanisms behind this impairment of thyroid function are probably both iodine enhancement of thyroid

autoimmunity and reversible inhibition of thyroid function by excess iodine (Wolff-Chaikoff effect) in susceptible subjects. However, this type of thyroid failure has not been observed after correction of iodine deficiency, including in neonates after the administration of huge doses of iodized oil to their mothers during pregnancy.

2. Iodine-induced hyperthyroidism

Iodine-induced hyperthyroidism (IIH) is the main complication of iodine prophylaxis. It has been reported in almost all iodine supplementation programs. Iodine deficiency increases thyrocytes proliferation and with the development of multifocal autonomous growth. These nodules become autonomous and can result in hyperthyroidism after iodine supplementation. A multicentre study conducted in seven African countries, including Zimbabwe and Congo showed that the occurrence of IIH in the last two countries was due to the sudden introduction of poorly monitored and excessively iodized salt in populations which had been severely iodine deficient for very long periods in the past.

The conclusion of the multicentre study was that the risk of IIH is related to a rapid increment of iodine intake resulting in a state of acute iodine overload.

It thus appears that IIH is one of the Iodine Deficiency Disorders. It appears to be largely unavoidable in the early phase of iodine supplementation. It affects principally the elderly with long lasting autonomous nodules. Its incidence reverts to normal or even below normal after one to ten years of iodine supplementation.

3. Iodine-induced thyroiditis

Another possibility is the aggravation or even the induction of autoimmune thyroiditis by iodine supplementation. However, no large surveys have been performed which have analyzed the impact of large scale programs of iodine supplementation on the occurrence of clinically significant iodine-induced thyroiditis with public health consequences on thyroid function.

4. Thyroid cancer

Although in animal studies the chronic stimulation of the thyroid by TSH is known to produce thyroid neoplasms, in humans correction of iodine deficiency rather decreases the risk of and morbidity from thyroid cancer.

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Konzo

Summary

- Acute hypertonic paraparesis
- Cyanide intoxication caused by badly processed bitter cassava (manioc)
- Other factors such as deficiency of sulphur-containing amino acids seem to be important

Definition

Konzo is characterised by an epidemic acute isolated and symmetrical hypertonic paraparesis, which is permanent but non-progressive. The condition is to date only known in poor regions of Africa. In the Yaka valley konzo means “bound legs”, a good description of the hypertonic gait. This is the name used in Congo and is now the official term for this motor neuron disorder.

Epidemiology

Two large epidemics have been reported, each of more than 1000 cases. The first was in the Bandundu region in Congo (1936-37) and the second in the Nampulla province of Mozambique (1981). Outbreaks that are related to households living in absolute poverty that have sustained themselves for weeks or months on insufficiently processed bitter cassava, have been reported from 6 countries: Congo (esp Bandundu region), Mozambique, Tanzania, the Central African Republic, Cameroon and Angola. The total number of reported cases up to 2009 was 6788, but most cases are never reported and there are estimates of 100,000 cases in DRC alone. The majority of cases of konzo occur in the dry season, chiefly during a long drought. Sporadic cases of konzo also occur. Children who are being breastfed are not

affected. Familial clustering is common.

Aetiology

The aetiology of konzo has not yet been fully clarified. At present a toxic/nutritional aetiology is assumed. There is an epidemiological connection between konzo and eating bitter cassava. Nevertheless, konzo only occurs in 1% of the cassava consuming population. Consumption of bitter cassava is a precondition, but not in itself sufficient to induce konzo. Cassava contains very little sulfur and shortage of sulfur-containing amino acids are probably contributory, since these are essential for the detoxification in the body of cyanide to thiocyanate, which is removed in the urine. People of the same ethnic group living only 5 km away from those with konzo might have a near zero konzo prevalence which is related to different protein intake through fish or bushmeat. It is possible that as yet unidentified components also play a role. Due to its clinical similarity to neurolathyrism, a search for the neurotoxin beta-ODAP was performed but turned up negative. Epidemics coincide with periods of food shortage, drought, intense trading in cassava and war. These are circumstances in which people may be inclined to shorten the long preparation which bitter cassava requires. If shortcuts are taken to process the cassava quickly, large amounts of cyanogens may remain in the food. The disorder is regarded as a form of cyanide intoxication, although the final word on this has not yet been spoken.

Cassava

Cassava originated in South America and was first cultivated by the Maya in Yucatán. It was introduced in Africa by Portuguese traders from Brazil in the 16th Century and around the same era it arrived in Asia with Portuguese and Spanish ships. There are various species, all belonging to the Euphorbiaceae: *Manihot esculenta, M. aipi* and *M. utilissima*. Over the last 400 years, the plant has become a staple for millions of Africans, especially those in areas with marginal land where few other crops survive. Cassava is known by several names in tropical and subtropical countries: manioc, yuca, mandioca, Brazilian arrowroot. It is named tapioca when it is dried to a powdery extract. Food items such as the gelatinous porridge “fufu” in West- and Central Africa and the bammy of Jamaica come from cassava. Cassava is a woody shrub and is extensively cultivated as an annual crop

for its edible starchy tuberous root, a major source of carbohydrates. The young leaves and shoots may be eaten as vegetables ("saka saka"). Cassava is the third-largest source of food carbohydrates in the tropics, after rice and maize. It is a major staple food in the developing world, providing a basic diet for over half a billion people. It is very drought-tolerant and grows on marginal soils where other crops do not grow well. It is usually harvested after 18 months. Cassava roots are poor in protein, but the leaves are a good source of protein rich in lysine. The cassava roots, when they are still attached to the stalk, remain good for many months if stored under the earth. Once harvested deterioration begins quite quickly. There is an unwanted conversion of starch to sugar and a number of enzymatic reactions occur which cause discoloration of the product and reduces its value. Bacterial and fungal deterioration also occur. Drying the roots to a moisture content of less than 14% prolongs their storage life considerably.

Apart from its nutritional value, cassava has several other uses: alcoholic beverages made from cassava have distinct local names (cauim and tiquira (Brazil), kasiri (Guyana, Suriname), impala (Mozambique), masato (Peruvian Amazonia chicha), parakari or kari (Guyana), nihamanchi (South America) also known as nijimanche (Ecuador and Peru), ö döi (chicha de yuca, Ngäbe-Bugle, Panama), sakurá (Brazil, Suriname), tarul ko jaarh (Darjeeling, Sikkim, India)); ethanol biofuel made from cassava is increasingly used in China; cassava serves as a good roughage source for ruminants such as cattle and manioc starch diluted in water can be sprayed over clothing before ironing to stiffen collars. It was claimed that cassava has anti-cancer activity but a report from the American Cancer Society states that "there is no convincing scientific evidence that cassava or tapioca is effective in preventing or treating cancer". Nigeria is the world's largest producer of cassava producing 57 million tons or 21% of the world total, while Thailand is the largest exporter of dried cassava.

There are "sweet" and "bitter" varieties, indicating the absence or presence of toxic cyanogenic glucoside levels, respectively. In particular the bitter form survives well under dry conditions. Bitter cassava produces up to 1 g/kg of cyanide, especially during prolonged dry seasons. This is 50 times more than the sweet variety. The more toxic varieties of cassava are a fall-back resource (a "food security crop") in times of famine or food insecurity in some places. Farmers often prefer the bitter varieties because they deter pests and animals. If large amounts of bitter cassava are eaten for long periods,

without special precautionary measures being taken to remove the toxin from the plant, and if there is a deficiency in sulphur-containing amino acids Konzo results.

Pathophysiology

The capacity to produce toxic hydrogen cyanide is present in more than 2000 plant species, classified into over 100 plant families. In all cases the HCN is not stored as such in the cells. The plant produces complex molecules, generally glucosides (e.g. amygdalin) but also some lipids. From these, HCN can enzymatically be released. The enzyme that accelerates this reaction is physically separated from the cyanogenic substance. If the plant is crushed and its structural integrity is threatened, the enzyme comes into contact with the cyanogenic substance and the reaction can then take place. It can be assumed that the cyanide is intended to protect the plant from damage.

In cassava, above mentioned process is mirrored as follows. The bitter varieties contain large amounts of the two cyanogenic glucosides linamarin and lotaustralin, in a ratio of 10 to 1. Linamarin is found in vacuoles in the cytoplasm. The concentrations are highest in the peel. Linamarase, the enzyme which breaks down linamarin, is found in the cell wall. When the cells burst (accidental crushing of the plant, being eaten by insects or during processing), the linamarin comes into contact with linamarase. This enzyme splits linamarin into glucose and acetone cyanohydrin. The latter spontaneously releases acetone and HCN. This reaction may be accelerated by the cassava enzyme hydroxynitril lyase. Once HCN has been produced, it spreads in the air as gas (boiling point of HCN =25.7°C).

Cyanides are rapidly acting toxic substances. Cyandide (CN^-) inhibits cellular respiration by binding to the trivalent iron (Fe^{3+}) of cytochrome oxidase, a component of the mitochondrial electron transport chain. This impairs the energy-generating function of the mitochondria, leading to cell death.

Cyanide (CN^-) is normally converted in humans to the less toxic thiocyanate (SCN^-) by the enzyme rhodanase (also written as rhodanese). This is a mitochondrial enzyme which is widely present throughout the human body, with the highest concentrations in the liver and kidneys. Thiocyanate is the chief metabolite of cyanide. Thiocyanate itself has a goitrogenic

effect if there is a shortage of iodine in the diet. The body uses sulphur-containing amino acids to render cyanide harmless. If the diet is deficient in sulphur, cyanide will be converted to cyanate (OCN^-), which induces neurogenerative disease in both animals and humans. The cells which are most affected are Betz' cells in the motor cortex.

Clinical aspects

Konzo begins abruptly, without prodromal signs. In 90% of cases the onset of symptoms takes less than one day. The initial symptoms are described as tremor, cramps, a heavy feeling and/or weakness in the legs, a tendency to fall down and difficulty remaining upright. There is a visible hypertonic gait when walking or running. Occasionally there will be lower back pain, blurred vision, speech difficulties and/or paraesthesia of the legs, but they disappear within a month. During the first two days the majority of patients have general muscular weakness and are confined to bed. Hypertonicity is present from day one. Flaccid paralysis of the limbs does not occur. Since this is an upper motor neuron disorder, very brisk reflexes are found in the legs and Babinski's sign is present. Pronounced clonus occurs, or may be triggered by physical examination, e.g. dorsiflexion at the ankle joint. Later there is a slight partial improvement. Finally the affected person develops a stable hypertonic paraparesis, which persists for the remainder of life, or might improve a little. After onset the neurological signs remain constant or improve minimally if no further cyanide is ingested, unlike for example HTLV-1 infection in which further deterioration takes place. Some sufferers will later have a second attack with deterioration of their condition, possibly with dysarthria, abnormalities of eye movement, hypertonicity of the arms.

Konzo, symmetrical spastic paraparesis; ©Studio Leyssen 14; winner 'Best Medical picture 2017, the Lancet'

Differential diagnosis

Lathyrism is a neurological disease cause by eating large quantities of the Lahyrus grain that has high concentrations of the neurotoxin β-oxalyl-L-α,β-diaminopropionic acid (ODAP). It causes paralysis due to upper motor neuron damage. It is mainly seen in Bangladesh, India, Nepal and Ethiopia. Tropical spastic paraparesis has symptoms similar to konzo, but the onset is much slower. Polio can be easily distinguished as it provokes an asymmetrical flaccid paralysis.

Chronic, low-level cyanide exposure can lead to the tropical ataxic neuropathy (TAN) that manifests with polyneuropathy, ataxic gait, optic atrophy and sensory deafness. It was first described by Osuntokun among the Ijebu speaking Yorubas in south western Nigeria in 1968.

Till today TAN remains an enigmatic disease with no effective treatment. The exact pathogenesis remains unresolved, and several factors have been proposed including malnutrition, vitamin B deficiencies, malabsorption, poor protein consumption, chronic cyanide and nitrile toxicity, with a strong geospatial endemic prevalence in areas of cassava cultivation.

Motor neuron disease

The term “motor neuron disease” includes disorders in which (1) both the upper and the lower motor neurons are affected (amyotrophic lateral sclerosis), (2) disorders in which only the lower motor neurons are abnormal (spinal muscular atrophies, post-poliomyelitis, Guillain-Barré syndrome, botulism, trauma) and (3) disorders of exclusively the upper motor neurons (neurolathyrism, konzo, hereditary spastic paraplegia, primary lateral sclerosis, stroke, multiple sclerosis, cerebral palsy, trauma).

Symptoms of upper motor neuron disease (= lesion above the anterior horn cell of the spinal cord or the motor nuclei of cranial nerves): muscle weakness, spasticity, clasp-knife response, Babinski sign present, increased deep tendon reflexes.
Symptoms of lower motor neuron diseases (= lesion in nerves distal from the anterior horn op the spinal cord or lesion in fibres from the cranial motor nuclei to the muscles): muscle paresis or paralysis, fasciculations, hypotonia, hyporeflexia, muscle wasting.

Diagnosis

The following criteria are used for the diagnosis of konzo:

1. A visible symmetric hypertonic gait when walking or running
2. The onset of the disease takes less than one week and then remains stable
3. Bilateral brisk knee and Achilles tendon reflexes without signs of vertebral lesions
4. Eating bitter cassava and no consumption of grass peas (*Lathyrus sativus*)

Urinary concentrations of thiocyanate and linamarin are elevated. The patient is HTLV-1 negative.

Treatment

There is no known etiological treatment for konzo. Treatment with sodium thiosulphate ($Na_2S_2O_3$), a cyanide antidote, gave disappointing results. A good and varied diet, high dose multivitamins and physical rehabilitation with walking aids are advised. Since the sufferers have no cognitive defects, affected children should be encouraged to continue their education. Some children have been operated with an elongation of the Achilles tendon which improved the position of the foot but the long term outcome remains uncertain.

Prevention

Konzo is not a large public health problem when Africa is regarded as a whole. It is, however, a real problem in the communities affected and of course for the individual patient. The message should be that (1) konzo is not infectious in order to avoid sufferers becoming socially isolated, (2) cassava should be processed correctly without missing out any steps (shortcuts in processing are to be avoided), (3) a varied diet is important. Including maize (corn) flour when making porridge, or including other sulphur-containing food product, such as onions in the diet, is advised; but food habits take a long time to change. The tubers can be made safe by correct processing. As a first step the cells should be burst in order to bring the linamarin into contact with the endogenous glucosidase. In a second step (drying or heating) cyanohydrin is converted to hydrogen cyanide which then evaporates (this is faster at a higher temperature). One of the following precautionary measures should be taken when preparing cassava:

- Fermenting by immersion in water, followed by drying in the sun or cooking, (sufficient time necessary, usually 3 days or longer if the water is cold)
- Grating and fermenting of fresh pulp followed by drying with heat (3 days needed).
- Direct drying of the roots in the sun (less effective)

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