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.

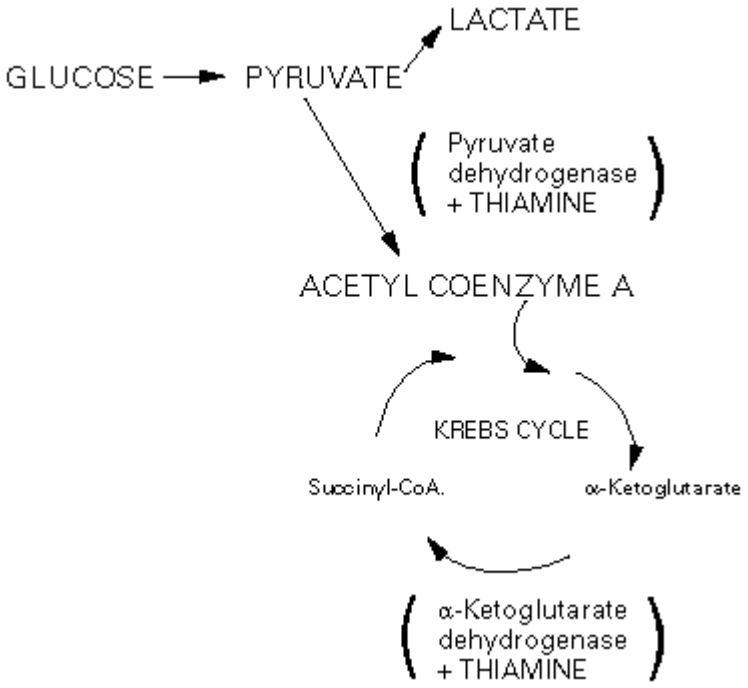

Fig: Thiamine is a co-enzyme in the conversion from pyruvate to acetyl-CoA and in the conversion of alpha-ketoglutarate to succinyl-CoA. Non availability of thiamine leads to lactic acidosis

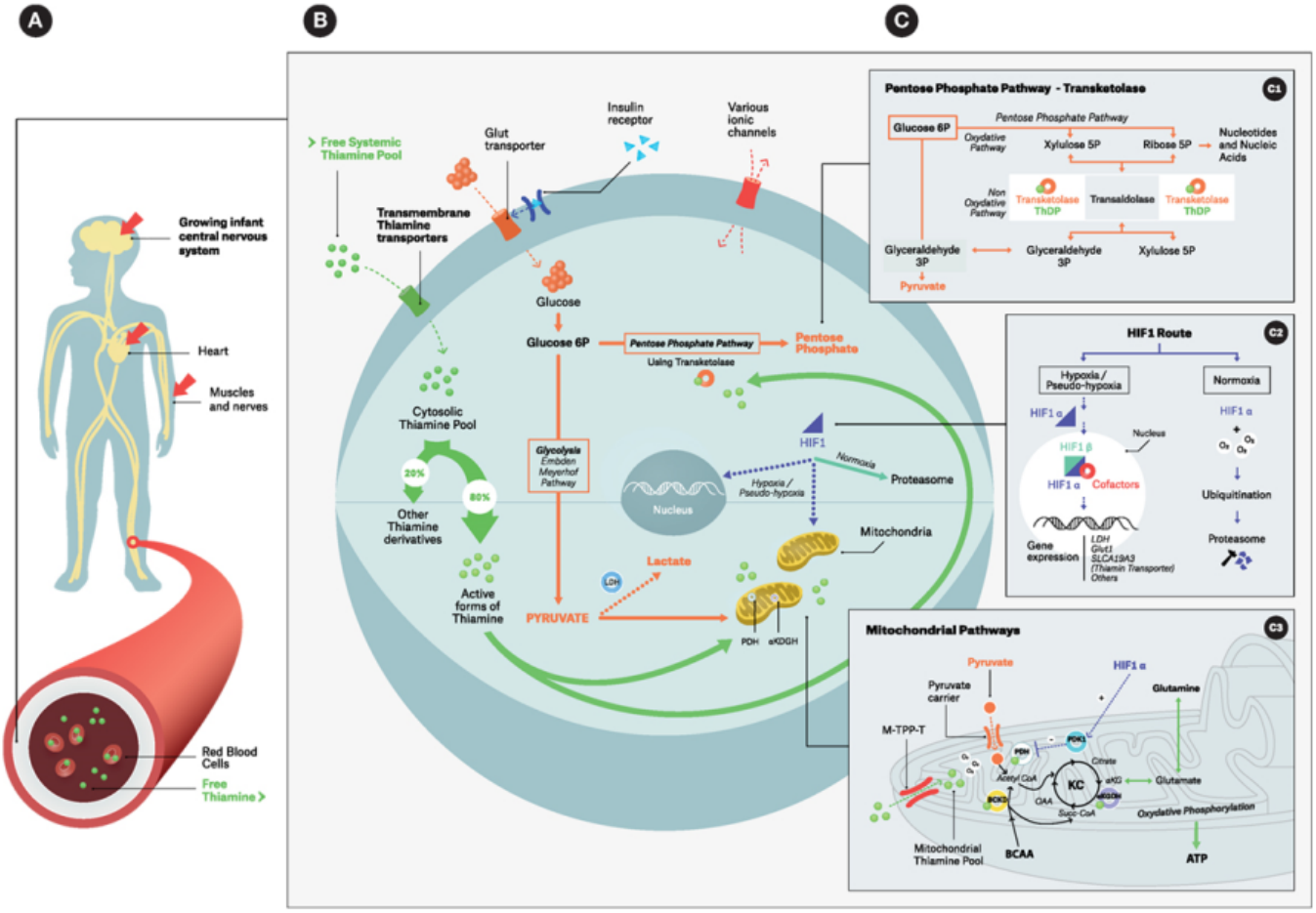

Fig: overview of thiamine intracellular action: focus on co-enzymatic functions. (A) Infant thiamine distribution with its three main target organs; (B) thiamine cellular metabolism with its main pools and thiamine-related metabolic pathways; (C) zooming boxes: (C1) – cytosolic pentose phosphate pathways 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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