Konzo

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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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