Working together to eliminate cyanide poisoning, konzo and tropical ataxic neuropathy (TAN).

CCDN News

Cassava Cyanide Diseases Network

Issue Number 12, December 2008

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Differential diagnosis of konzo from other tropical diseases: a review

Konzo with its upper motor neurone manifestations can be confused with other diseases and differential diagnosis is important. Using the WHO criteria, konzo by its spastic paraparesis can easily be distinguished from causes of flaccid paraplegia such as poliomyelitis, leprosy or trauma.[1] The commonest neurological diseases to be considered in its differential diagnoses include neurolathyrism, Tropical Ataxic Neuropathy (TAN) and Tropical Spastic Paraparesis/ HTL V-I Associated Myelopathy (TSP/HAM) (see Table 1).

Konzo is clinically very similar to neurolathyrism but differs from TAN and TSP/HAM.[2-5] The socio-economic conditions of konzo and neurolathyrism patients are very similar as well. Both diseases can be considered a sign of poverty, monotonous unbalanced diet and illiteracy.[6] Neurolathyrism only differs from konzo with the somewhat higher age of onset, predominance of males among the affected, sphincter involvement in some cases and the absence of cranial nerve involvement.[2] There is no geographical overlap between the consumption of grass pea seed and cassava roots and therefore there is no geographical overlap of the two diseases. Combination of grass pea and cassava in the diet could even amplify the risk. It would be difficult to make a differential diagnosis between neurolathyrism and konzo if both disorders occurred in the same population.[2,5]

Konzo and TAN have been attributed to dietary cyanide exposure from consumption of insufficiently processed cassava roots, but rates of exposure differ in both diseases.[7] In contrast to konzo, TAN is a progressive disorder with slow onset that mainly affects older adults. Furthermore, konzo involves damage to upper motor neurones without sensory involvement, whereas TAN is mainly caused by damage of sensory neurons in the spinal cord resulting in ataxia. TAN rarely progresses to inability to walk, whereas walking difficulties are the primary symptom of konzo and a high proportion of the konzo-affected subjects are unable to walk. About half of the TAN cases have optic atrophy which is rare among konzo cases. About one in five TAN cases has exaggerated reflexes, a sign that occurs in all konzo cases.[1,2]

TSP/HAM is clinically possible to distinguish from both konzo and neurolathyrism, although the clinical features of TSP/HAM include typical signs that are similar to both diseases such as weakness in the legs, hyperflexia, clonus and extensor plantar responses. TSP/HAM is characterised by a chronic progressive spastic paraparesis with sphincter disturbances, urinary incontinence and impotence. There is mild to no sensory loss and absence of spinal cord compression. Most but not all cases of TSP/HAM are seropositive for HTLV-1.[3,4,8,9]

Table 1 :*Characteristic features of four tropical myeloneuropathies (Tylleskär et al, 1994b)*

	Konzo	**Tropical ataxic neuropathy**	**Neurolathyrism**	**HTLV-I associated myelopathy**
Geographical area	Africa	Africa	Asia/ Africa	Worldwide
Occurrence	Epidemic and endemic	endemic	epidemic and endemic	endemic
Highest prevalence	3 %	3 %	3 %	0.1 %
Familial clustering	yes	yes	yes	yes
Type of onset	acute	slow	acute	slow
Course	permanent	progressive	permanent	progressive
High incidence age group	< 40	> 40	< 40	> 40
Main neurological findings:				
Gait abnormality	Spastic paraparesis	Ataxia	Spastic paraparesis	Spastic paraparesis
Peripheral neuropathy	no	yes	no	common
Sphincter involvement	no	no	rare	yes
Optic atrophy	rare	yes	no	no
Deafness	no	common	no	no
Etiology	Attributed to weeks of high cyanide exposure from cassava	Attributed to prolonged, varying cyanide exposure from cassava	Caused by months of high grass pea (*Lathyrus sativus*) consumption	Caused by chronic HTLV-I infection

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Comparison of cassava flour and gari

Cassava flour is the major stable product made from cassava roots in Eastern, Southern and Central Africa, whereas gari is the main stable product made from cassava roots which is used in West Africa and also in southern Mozambique.

Processing. Table A gives a comparison of the preparation of these two products.[1] Sun drying of cassava roots is a very simple method that requires no mechanised equipment and is carried out by women at home. By comparison gari is normally produced in a factory using a mechanical grinder to grate the peeled cassava roots, a press for dewatering and the roasting process is done by women.

Cassava flour in water is neutral (pH about 6.5), whereas gari in water is acidic (pH 4.1), due to lactic acid fermentation that occurs during prolonged processing of the wet cassava mash. The long processing allows the enzyme linamarase to hydrolyse linamarin completely to acetone cyanohydrin, which is unstable above pH 5,[2] and most of it breaks down spontaneously to acetone and hydrogen cyanide (HCN) gas which partly escapes to the air. The remainder of the HCN and nearly all the acetone cyanohydrin is removed in the roasting process, but some remains in the final gari, which has a slightly sour taste because of the lactic acid present.

Total cyanide content. The sun drying of peeled cassava roots does not allow the enzyme linamarase to come into intimate contact with linamarin, as occurs during gari production, and hence linamarin is only partially broken down in the flour, which is found to contain linamarin at average levels of 45 ppm.[3] During a drought the cassava plant produces greatly increased amounts of linamarin[4] and the total cyanide content of flour increases 2-4 fold to >100 ppm.[5] The World Health Organisation (WHO) safe level for total cyanide in cassava flour is 10 ppm.[6] Levels of total cyanide in gari (present as acetone cyanohydrin) range from 0-40 ppm with mean values of 15-20 ppm.[5]

Availability of cyanogens in the body. Acetone cyanohydrin is completely decomposed to cyanide under the alkaline conditions present in the human gut, whereas linamarin is stable under these conditions and only about 50% is absorbed in the body.[7] Thus the total cyanide absorbed by the body from cassava flour under non-drought conditions is about 22.5 ppm and from gari about 15-20 ppm

Methods to reduce cyanide. The total cyanide content of cassava flour is reduced 3-6 fold by mixing it with water, spreading it in a thin layer on a

basket and leaving in the shade for five hours. This allows linamarase present to hydrolyse linamarin to acetone cyanohydrin which breaks down spontaneously at pH 6.5 with liberation of HCN gas.[8-10] The method was checked out in northern Mozambique and found to be very acceptable to rural women. Unfortunately over the 2-3 years since its discovery there has been very little use of the wetting method in flour processing areas. Acetone cyanohydrin in gari is stable at pH 4.1 and does not breakdown at ambient temperatures[8] or in the sun.

Konzo and tropical ataxic neuropathy (TAN). Konzo occurs under conditions of high cyanide intake over a relatively short period due to drought or to war.[10,11] However konzo is endemic (persistent) in certain locations in Nampula Province of Mozambique.[12] TAN is also persistent in Nigeria[13] and this is probably due to long term comsumption of cyanide from gari at sub-lethal levels. TAN has also been reported from a wide range of other cassava-growing countries including Tanzania, West Indies and southern India.[10,14]

The key to the removal of these cyanide-induced diseases is a considerable reduction in the cyanide intake from cassava. The universal introduction of the wetting method would reduce cyanide intake from cassava flour and could remove konzo altogether. Clearly it is also important to develop methods to reduce the cyanide content of gari, that may also lead to a reduction of the incidence of TAN.

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Table A

	Gari	Cassava flour
Where used	West Africa & southern Mozambique	Eastern, southern & central Africa
Method of Production	Peeled root is grated & the mash fermented for 2-3 days in a hessian bag, dewatered, sieved & heated in a metal dish with stirring to remove cyanogens	Peeled root sun dried for ca 7 days then pounded to a powder & sieved. In heap fermentation peeled roots are heaped up in the shade for ca 4 days & then sun dried.
PH of product	ca 4.1 due to lactic fermentation	neutral, about 6.5
Major cyanogen present	acetone cyanohydrin	linamarin
Total cyanide content in ppm	range 0-40 ppm mean 15-20 ppm	mean 45 ppm rising to >100 ppm in a drought year
Availability of cyanogens	100%	about 50%
Simple method to remove cyanogens	Wetting method does not work because pH is too low	Wetting method. Mix flour with water & leave in thin layer in shade for 5 hours. Total cyanide content reduced 3-6 fold

Outbreak of konzo disease in health region No. 2 of the Central African Republic

Rev Neurol (Paris). 2008 Dec 9. [Epub ahead of print]

[Article in French]

INTRODUCTION: Konzo is a neuromyelopathy characterized by permanent spastic paraparesis, linked to a subacute poisoning by cyanide found in cassava. The purpose of the study is to describe the epidemiological aspects of konzo in health region No. 2 in the Central African Republic. METHOD: A descriptive cross-sectional study was conducted among patients collected during a one-month period (July 16 to August 16, 2007) of active surveillance for acute flaccid paralysis. RESULTS: Eighty-one cases of konzo were identified during the study period, representing a prevalence of 10 per 100,000. Mean age of patients was 10.7+/-7.7 years. Children and women were most affected. The main warning signs were fatigability (97.6%), tremor (88.9%), walking difficulty (100.0%), dysarthria (67.9%) and a loss of visual acuity (65.4%). The predominant neurological signs were lower limb paresis (90.0%) and hyperesthesia (66.7%). CONCLUSION: Konzo is a serious public health problem in this region of the Central African Republic. A prevention program should be set-up.

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Endomyocardial fibrosis: cause still unknown.

A recent review article concluded that the cause of endomyocardial fibrosis (EMF) is still a mystery[1]. EMF is a severe chronic heart disease in which the inner layer of the heart becomes fibrous and thickens. Most patients present with advanced heart failure. The outlook is poor, with a high incidence of sudden death.

The disease is common in some tropical areas, with estimates that around 10 million people are affected.[2] Most cases have been reported from Uganda, Ivory Coast, Nigeria and India.[3]. EMF is usually limited to specific geographical areas. Most studies are based in clinics; a recent community-based study in a known high prevalence area in Mozambique gave an estimated prevalence of 19.8%.[2]

The disease is commoner in children and young adolescents, but also occurs in adults. Male preponderance has been described in Kerala and Nigeria, and female preponderance in Brazil and Uganda.[3] In the Mozambican community-based study,[2] the prevalence rate (28.1%) was highest in 10-19 years old and the male prevalence rate (23.0%) was higher than female (17.5%). Only 22.7% of cases had symptoms.

Many causes have been suggested including worm infestation, malaria, genetic susceptibility, cerium or thorium in monazite deposits in the soil, and prolonged ingestion of cassava associated with a low protein diet. No single cause explains EMF in all the areas where it has been reported.[3]

Regarding cassava as a possible cause, a case-control study in Uganda showed an association between the disease and markers of poverty, including a cassava-based diet.[4] Experiments by Sezi[5] found that monkeys fed on a cassava-based diet developed heart lesions, while those fed on a banana diet did not.

The review authors state that “despite the known role of cyanogens from improperly processed cassava in konzo, an upper-motor neuron disease reported from Central and East Africa, cardiac manifestations have not had a part in these outbreaks”.

As far as we know, no-one has searched thoroughly for endomyocardial fibrosis in populations affected by konzo.

Although cassava has never been excluded as a possible cause, there are many other stronger candidates: But despite investigation into these causes, nobody has come up with a definite conclusion. The search continues.

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CCDN News is the Newsletter of the Cassava Cyanide Diseases Network (CCDN). The CCDN is a free, worldwide network commenced in June 2001, which is working towards the elimination of konzo, TAN and other cassava cyanide diseases.
CCDN News will consider for publication short articles and letters (1-3 pages A 4 double spaced) written in English
Because CCDN News is a newsletter, full-size original papers or reviews cannot be considered for publication.

Posters (in several languages) explaining how to reduce the poison in cassava flour can be found at www.anu.edu.au/BoZo/CCDN