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Etiology of Konzo, epidemic spastic paraparesis associated with cyanogenic glycosides in cassava: Role of thiamine deficiency?

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ABSTRACT

Konzo is a syndrome of symmetrical, non-progressive, non-remitting spastic paraparesis occurring in epidemic and endemic forms in several countries in Africa, invariably associated with monotonous consumption of inadequately processed bitter cassava roots (*Manihot esculenta*) with very minimal protein supplementation. Despite numerous epidemiological, clinical and biochemical studies by authors in several countries aimed at elucidating the etiological mechanisms of Konzo, the etiology remains unknown. High cyanide consumption with low dietary sulfur intake due to almost exclusive consumption of insufficiently processed bitter cassava roots was proposed as the cause of Konzo, but there has been no evidence of a causal association between cyanide consumption and Konzo.

In this paper a new etiological mechanism of thiamine deficiency is presented, based on detailed review of the epidemiological, clinical and biochemical features of Konzo. It is postulated that in Konzo patients, a severe exacerbation of thiamine deficiency results from the inactivation of thiamine that occurs when, in the absence of dietary sulfur-containing amino acids; the sulfur in thiamine is utilized for the detoxification of cyanide consumed in improperly processed bitter cassava. Thiamine is known to be rendered inactive when the sulfur in its thiazole moiety is combined with hydrogen cyanide.

This hypothesis may stimulate studies examining the role of thiamine in the etiology of Konzo, and may lead to the formulation of strategies for the prevention and treatment of this debilitating disease.

1. Introduction

Konzo is an upper motor neuron disease, characterized by abrupt onset of symmetrical, non-progressive, non-remitting spastic paraparesis [1] occurring in epidemic and endemic forms in several countries in eastern, central and southern Africa. Epidemics of Konzo have been reported from Tanzania [2], from the Central African Republic [3] and from Mozambique [4,5]; where it was referred to as *Mantakassa* [6]. Epidemic outbreaks and sporadic, endemic cases have also been reported from Zaire [7]. By 1994, almost 4000 cases of Konzo had been confirmed in studies and reports from Africa [8], with more than 1000 cases in one epidemic in Mozambique [6]. Several hundreds of cases have been reported since [9,10], and the disease still continues to be prevalent in endemic areas [11].

The diet in patients who succumb to Konzo in all countries from where it has been described is uniformly similar. There are several weeks of almost exclusive, monotonous consumption of improperly processed bitter cassava roots, with very minimal protein supplementation; often associated with famine or war. Eighty percent of Konzo patients in Zaire denied eating animal protein prior to succumbing to the disease [7]. The frequency of food intake during the epidemics may approach starvation levels, with some families eating only once a day [12].

Despite several studies aimed at elucidating the etiological mechanisms of Konzo, the etiology remains unknown. High cyanide and low sulfur dietary intake due to exclusive consumption of insufficiently processed bitter cassava roots have been proposed as the cause of Konzo, [2,8,13] but as discussed below; there has been no clear evidence of a causal association.

Cyanide may be metabolized to cyanate [14]. Tor-Agbidye et al. demonstrated a significant increase in the plasma cyanate concentrations of sulfur amino acid-deficient rats treated with potassium cyanide [15]. Prolonged cyanate treatment is known to induce neuropathologic abnormalities in primates and humans [16,17]. It therefore appeared plausible that the metabolism of cyanide to cyanate may lead to the development of neurological disease in cassava-dependent populations. It has however been suggested that the predominantly myelinotoxic effects of cyanate toxicity [16] are more closely related to cassava-associated ataxic myelopathy than to Konzo [15].

An etiological role for retroviral infection in Konzo was suggested [18], with one report suggesting that cyanide exposure may trigger the myelopathic effects of HTLV 1 infection [19]. However, HTLV-1 associated myelopathy is characterized by paraparesis of gradual

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onset and progressive course, while the paraparesis in Konzo is clinically different with a sudden onset and a non-progressive course. Human retroviruses have been conclusively shown to be uninvolved in the causation of Konzo [20].

A nutritional deficiency was considered, given that cassava was a poor source of vitamin B. This consideration was however dismissed because there were no muco-cutaneous abnormalities suggestive of riboflavin deficiency detected on physical examination in Konzo patients [18]. Vitamins B12 and B6 were tested as part of an extensive battery of hematological and biochemical tests in patients with Konzo and found to be unremarkable [1].

There is no known prevention or treatment for Konzo, since the etiology is unknown. The need for therapy and prevention is of particular importance and urgency, given the fact that Konzo is a severe disease with very significant disability, preferentially affecting children between 4 and 12 years and women of reproductive age [6,18]. It is the most common cause of gait disability in these age groups in the affected areas.

Evidence from the literature against a causal role for cyanide intoxication in the etiology of Konzo is discussed in this paper. A new etiological hypothesis of thiamine deficiency is presented, and evidence supporting a role for thiamine deficiency in the etiology of Konzo is discussed.

2. Cassava diet and cyanide consumption in patients with Konzo

Cassava produces linamarin, a cyanogenic glycoside which is located in the plant vacuole. The parenchyma of cassava roots contains different amounts of linamarin, depending on the plant variety. Bitter cassava species have high linamarin content in the root parenchyma and have to be processed properly prior to eating. The enzyme linamarase, located in the cell wall; catalyzes the hydrolysis of linamarin to form acetone cyanohydrin, which is then hydrolyzed to hydrogen cyanide and acetone. Cyanide is converted to thiocyanate, a reaction that involves sulfur as a rate-limiting co-factor for the enzyme rhodanese [15].

During drought conditions, the cassava plant produces more linamarin than usual, leading to higher amounts of cyanide [11,21]. The consumption of inadequately processed cassava (occasioned by famine or war) also leads to high cyanide levels. In one study, individuals who consumed cassava roots soaked for just one day had high dietary cyanide exposure; with urinary thiocyanate levels of 757 μmol/l compared with a level of 50 μmol/l in individuals that ate cassava soaked for 3 days prior to consumption [22].

The urinary level of inorganic sulfate has been shown to be low in cases of Konzo, in unaffected household members of cases, and in unaffected households, indicating a widespread low intake of the sulfur amino acids needed for cyanide detoxification [22,23] in the susceptible population.

3. Evidences against the etiological hypothesis of cyanide intoxication

The cyanide hypothesis suggested that Konzo is caused by cyanide intoxication from insufficiently processed bitter cassava in combination with a sulfur amino acid-deficient diet [8,13,22], with the high cyanide intake indicated by high serum and urinary thiocyanate levels. Several arguments can be advanced against the cyanide hypothesis:

i. Thiocyanate levels are similar in cases and controls

High serum and urinary thiocyanate levels, while supporting the fact that the consumption of inadequately processed bitter cassava results in exposure to cyanide which is detoxified to thiocyanate, did not indicate that cyanide toxicity was the cause of Konzo. Indeed, high levels of thiocyanate excretion are more indicative of effective detoxification of cyanide than of increased risk of toxicity from cyanide. Further, both the patients with Konzo and their family members who did not succumb to the disease have been shown to be exposed to similar levels of cassava consumption, with both groups having high thiocyanate levels with no correlation between disease severity and thiocyanate level [6].

ii. Clinical features of cyanide intoxication are not compatible with Konzo

Consumption of cassava and cassava products containing large amounts of cyanide can cause acute intoxication with symptoms of dizziness, nausea, vomiting, abdominal pains, renal failure and death from cardiopulmonary arrest [24]. Sub-lethal acute intoxications may result in parkinsonian symptoms induced by basal ganglia damage [25]. Spastic paraparesis, the clinical hall mark of Konzo is not a known clinical manifestation of cyanide toxicity; and has not been associated with cyanide exposure from any other source. Thus, while the consumption of high levels of cyanide in bitter cassava may be a precondition or facilitator, it does not appear in itself sufficient to cause Konzo.

Since Konzo does not present with the known clinical effects of cyanide, it was hypothesized that perhaps acetone cyanohydrin (the aglycone of linamarin) may be the cause of Konzo. However, a study designed to test this hypothesis showed that rats exposed to acetone cyanohydrin showed acute signs of toxicity but did not show any persistent motor deficits [26]. Acetone cyanohydrin caused selective neuronal degeneration in discrete thalamic nuclei, but those affected areas were not those expected in an animal model of Konzo [26].

It has been suggested that a specific neurotoxic effect of linamarin, rather than the associated general cyanide exposure may be the cause of Konzo [23]. A study suggested that linamarin could be transported to the cytoplasm of neural cells where it could cause degeneration [27]. There is however no evidence to suggest that putative neurodegeneration by linamarin may lead to the motor deficits seen in Konzo.

4. A new hypothesis of thiamine deficiency

It is postulated in this paper that Konzo is a thiamine-deficiency state resulting from the inactivation of thiamine that occurs when, in the absence of dietary sulfur-containing amino acids; the sulfur in thiamine is utilized for the detoxification of cyanide consumed in improperly processed bitter cassava.

4.1. Putative mechanism of thiamine deficiency in Konzo

Following consumption, cyanide is converted to thiocyanate by the enzyme rhodanese, a reaction that involves sulfur as a rate-limiting co-factor [15]. The concentration of sulfur is normally dependent on the availability of sulfur amino acids from dietary proteins. However, rhodanese has wide substrate specificity, with respect to both sulfur donor and acceptor. Therefore, sulfur compounds other than sulfur amino acids may function as sulfur donors [28]. Available sulfur is preferentially utilized for cyanide intoxication, even in protein malnutrition. In cyanide-treated rats fed a sulfur amino acid-free diet [15], a marked loss of body weight occurred concurrent with a dramatic rise in urinary thiocyanate, suggesting the mobilization of endogenous sulfur. In Konzo patients, the low urinary sulfur concentrations in the presence of high serum thiocyanate levels indicated dietary sulfur shortage and the mobilization of endogenous sulfur from sulfur compounds other than sulfur amino acids [13].

Thiamine is one such sulfur compound whose sulfur can be mobilized during shortage of dietary sulfur amino acids. The thiamine molecule is composed of a pyrimidine moiety and a sulfur-containing