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Konzo risk factors, determinants and etiopathogenesis: what is new? A systematic review

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HIGHLIGHTS

- Dietary cyanide poisoning and protein malnutrition are major risk factors of konzo.
- Thiocyanate may underestimate the level of cyanide poisoning in konzo patients.
- Konzo etiopathogenesis probably results from an interplay of multiple factors.
- Geo-environmental and psycho-emotional factors are plausible determinants of konzo.
- New insights on the etiology of konzo are raised, but more are still needed.

ABSTRACT

Konzo is a toxico-nutritional upper motor neuron disease causing a spastic paraparesis in schoolchildren and childbearing women in some African countries. Almost a century since the first description of konzo, its underlying etiopathogenic mechanisms and causative agent remain unknown. This paper aims at refreshing the current knowledge of konzo determinants and pathogenesis in order to enlighten potential new research and management perspectives. Literature research was performed in PubMed and Web of Science databases according to the PRISMA methodology. Available data show that cassava-derived cyanide poisoning and protein malnutrition constitute two well-documented risk factors of konzo. However, observational studies have failed to demonstrate the causal relationship between konzo and cyanide poisoning. Thiocyanate, the current marker of choice of cyanide exposure, may underestimate the actual level of cyanide poisoning in konzo patients as a larger amount of cyanide is detoxified via other unusual pathways in the context of protein malnutrition characterizing these patients. Furthermore, the appearance of konzo may be the consequence of the interplay of several factors including cyanide metabolites, nutritional deficiencies, psycho-emotional and geo-environmental factors, resulting in pathophysiologic phenomena such as excitotoxicity or oxidative stress, responsible for neuronal damage that takes place at sparse cellular and/or subcellular levels.

Keywords: Konzo; motor neuron disease; cassava; cyanide intoxication; malnutrition.

1. Introduction

Konzo is a neurological disease characterized by a sudden onset of symmetrical, non-progressive and irreversible spastic paraparesis due to selective upper motoneuron damage (World Health Organization, 1996). It mostly affects children from 2 years of age and childbearing women (Chabwine et al., 2011; Siddiqi et al., 2020; Tylleskär et al., 1995), causing gait difficulties. The typical spastic gait rapidly develops within a few hours up to one week (Ministry of health Mozambique, 1984; Tylleskär et al., 1995; World Health Organization, 1996). Konzo is an exclusively African disease involving less than ten countries: the Democratic Republic of the Congo (DRC) (Banea et al., 2015b, 1997b, 1992a; Carton et al., 1986; Chabwine et al., 2011; Lucasse, 1952; Okitundu et al., 2014; Tylleskar et al., 1991), Mozambique (Cliff et al., 2011, 1997; Ernesto et al., 2002; Essers et al., 1992; Ministry of health Mozambique, 1984; Nhassico et al., 2016), Tanzania (Howlett et al., 1990; Mlingi et al., 2011, 1991), Cameroon (Ciglenečki et al., 2011; Lantum, 1998), Angola (Allen, 2010), Central African Republic (Mbelesso et al., 2009; Tylleskar et al., 1994) and Zambia (Kasonde, 2015; Siddiqi et al., 2020). More than a half of all konzo cases have been reported from the DRC (Bonmarin et al., 2002), and the country contains zones at the highest risk. Occurrence of konzo epidemics peaks during drought (mostly between June and September), famine or war (Banea et al., 2015a, 1992a; Chabwine et al., 2011; Tylleskar et al., 1991). In some countries, sporadic cases occur outside epidemic periods (Banea et al., 1997a; Chabwine et al., 2011; Ernesto et al., 2002; Tylleskar et al., 1994).

Konzo was reported for the first time in 1938 by Trolli et al. in the Congolese province of Bandundu (Carton et al., 1986; Lucasse, 1952), although the anthropological literature suggests that it was known from the late 1800s (Kashala-Abotnes et al., 2018). The prevalence of konzo is most probably underestimated (report of 6788 cases in 2009 (Nzwalo and Cliff, 2011), while the National Program of Nutrition gave an estimate of 100,000 in the DRC (Cliff, 2010; Diasolua Ngudi, 2005)). Konzo remains a poorly known disease that cannot be properly diagnosed by most local health practitioners (Nzwalo and Cliff, 2011). Furthermore, affected communities are poor, live in remote areas, have a low education level, and hold several cultural and religious beliefs regarding konzo. As a result, patients with konzo do not resort to health structures (Chabwine et al., 2011; Nzwalo and Cliff, 2011).

Although the number of konzo patients seems low worldwide, its prevalence in locally affected areas can be as high as 20 % (Boivin et al., 2013; Rosling et al., 1988). Moreover, konzo irreversibly handicaps an active portion of the population, yielding a heavy economic and social burden on the community. Thus, konzo constitutes a major public health problem and one of the most prevalent

34 neurological diseases in affected areas (Tylleskar et al., 1991). However, despite major impact on
35 local communities, konzo can be considered as a neglected disease because it is overlooked most
36 of the time and ignored by local and national health structures, as well as by the scientific
37 community, while diseased people do not receive appropriate health care and are stigmatized for
38 being handicapped. Noticeably, konzo is not even mentioned in the World Health Organization
39 (WHO) list of neglected diseases (World Health Organization, 2010).

40 Konzo occurs in food-deprived communities exposed to dietary cyanide from insufficiently
41 processed toxic cassava (*Manihot esculenta*) (Tylleskar et al., 1991). Cassava is a starchy, tuberous
42 root which constitutes a staple food and a major caloric source for about 800 million people mainly
43 residing in tropical regions (Food and Agriculture Organization, 2013). However, cassava protein
44 content, especially sulfur amino acids (SAA) such as methionine and cysteine, is very low
45 (Montagnac et al., 2009a). Thus, populations relying on an exclusive and monotonous cassava-
46 based diet (such as in konzo-affected areas) run a high risk of suffering from protein malnutrition
47 (Chabwine et al., 2011). Indeed, protein malnutrition and cassava-derived cyanide poisoning are
48 well documented as konzo risk factors since the very first reports (Cliff et al., 1985; Ministry of
49 health Mozambique, 1984), whereas causal factor and underlying etiopathogenic mechanisms
50 remain unknown (Kassa et al., 2011; Siddiqi et al., 2020).

51 In the 1980's until late 1990's, several studies were conducted to identify the etiology of konzo and
52 underlying mechanisms. Subsequently, many hypotheses were proposed, including infections such
53 as the human immunodeficiency virus (HIV) and the human T-lymphotropic virus (HTLV),
54 vitamin deficiencies, toxic agents (cyanide and its metabolites), environmental and genetic factors,
55 etc. (Kashala-Abotnes et al., 2018; Oluwole, 2015). However, all failed to be confirmed as causal
56 agents of konzo. On the other hand, none of the studied experimental animal models succeeded in
57 reproducing the clinical picture of konzo. New theories have recently emerged (Kashala-Abotnes
58 et al., 2018; Tshala-katumbay et al., 2016) but have not yet been integrated in the current conceptual
59 frame of thinking regarding the pathogeny of konzo.

60 Thus, the aim of this paper was to refresh the current knowledge of konzo determinants and
61 pathogenesis in order to enlighten potential new research and management perspectives. In
62 particular, the implications of cyanide metabolites, nutritional deficiencies, and contribution of
63 psycho-emotional and non-climatic geo-environmental factors in the appearance of konzo are
64 discussed.

65 **2. Methods**

66 **2.1 Study design**

67 We performed a systematic review of the literature following the Preferred Reporting Items for
68 Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

69 **2.2. Data sources and search strategies**

70 Literature search was conducted in PubMed and Web of Science databases until June 30, 2020.
71 Relevant publications found among references of the selected articles were also manually searched
72 for additional studies. We searched for all references containing the key word “konzo” in their title
73 or abstract, and from the retrieved results, we selected both observational and experimental studies
74 concerning the risk factors, the etiologies or the pathogenic mechanisms involved in konzo.

75 Two authors (MB and FN) independently screened the titles and abstracts of all the articles from
76 the search results to determine the articles for full-text review and applied protocol inclusion and
77 exclusion criteria to the full-text publications. Any disagreements were resolved by consensus.

78 The articles selection process is summarized in Figure 1.

79 [\[Figure 1\]](#)

80 **3. Results and discussion**

81 **3.1. Clinical presentation of konzo**

82 Konzo presents as a symmetric spastic paraparesis (or a tetraparesis in severely affected patients)
83 of abrupt onset and non-progressive course (World Health Organization, 1996). It usually occurs
84 in healthy children, who suddenly present difficulties to wake up and to walk in the morning
85 (Ministry of health Mozambique, 1984). Sometimes, especially in childbearing women, the disease
86 may appear after a physical effort such as a long walk or hard work (Ministry of health
87 Mozambique, 1984; World Health Organization, 1996). The paraparesis is immediately spastic,
88 with no initial phase of flaccidity and reaches its maximal intensity in less than one day in about
89 90 % of patients (World Health Organization, 1996). On neurological examination, patients
90 typically have a spastic (scissor) gait, associated with bilaterally exaggerated knee and/or ankle
91 reflexes and sometimes bilateral ankle clonus (Banea et al., 2016; Tshala-katumbay and Spencer,
92 2007), all signs of a bilateral pyramidal syndrome. On this basis, the WHO has defined simple
93 clinical diagnostic criteria, using the presence of 4 of the following elements: a visible symmetric

94 spastic abnormality of gait while walking or running; a history of onset of less than 1 week followed
95 by a non-progressive course in a formerly healthy person; bilaterally exaggerated knee or ankle
96 jerks without signs of disease of the spine, and the absence of consumption of grass pea (World
97 Health Organization, 1996). The absence of symptoms related to a spinal cord lesion indicates
98 damage to the upper motor neuron (Ali Ekangu et al., 2015; Mwanza et al., 2003; D Tshala-
99 Katumbay et al., 2002), even though existing data have failed to localize the exact site of the lesion
100 (Kashala-Abotnes et al., 2018). The spastic paresis sometimes extends to all four limbs, resulting
101 in a tetrapyramidal syndrome (Kassa et al., 2011; Nzwalo and Cliff, 2011; World Health
102 Organization, 1996).

103 Although in most cases, symptoms associated with konzo appear suddenly and are limited to spastic
104 paraparesis, without apparent announcing symptoms, some patients report general symptoms such
105 as pain (especially in the legs), headache, dizziness, vomiting and rarely fever (Carton et al., 1986;
106 Ministry of health Mozambique, 1984), a few days before the onset of the paraparesis. In other
107 cases, the motor deficit is associated with other signs such as pseudobulbar dysarthria, visual
108 complaints and vestibular or sensory symptoms, thereby overlapping with tropical ataxic
109 neuropathy (TAN), another disease associated with consumption of toxic cassava, but with a
110 different geographical distribution (Nigeria, Sierra Leone, India and Cuba) (Adamolekun, 2011;
111 Oluwole, 2015; Osuntokun et al., 1968), except for one report in Tanzania 50 years ago (Makene
112 and Wilson, 1972). Finally, recent studies have shown an association between konzo and impaired
113 neurocognition, especially in children (Boivin et al., 2017, 2013; Bumoko et al., 2014; Luwa E-
114 Andjafono Daniel Okitundu et al., 2018; Rivadeneyra-Domínguez and Rodríguez-Landa, 2020),
115 although it is not yet clear whether the underlying mechanisms are related to cassava toxicity or
116 other coexisting factors.

117 Differential diagnosis in the presence of typical symptoms of konzo can be made with other
118 diseases of the central nervous system causing predominant bilateral pyramidal syndrome. For this
119 reason, spinal cord macroscopic lesions should primarily be excluded because their presence
120 conceptually excludes konzo (Tshala-katumbay and Spencer, 2007; World Health Organization,
121 1996). This probably also applies to brain lesions affecting motor pathways, but available data on
122 brain structure and function of konzo patients are limited (D Tshala-Katumbay et al., 2002; Desire
123 Tshala-Katumbay et al., 2002; Tshala-Katumbay et al., 2001, 2000; Tshala-katumbay and Spencer,
124 2007). Also, consumption of grass pea has to be thoroughly searched for, as it is associated with
125 neurolethyrism, a disease with similar symptoms. (Tshala-katumbay and Spencer, 2007; World
126 Health Organization, 1996). The latter is a toxico-nutritional disease associated with a selective

127 damage of the upper motor neuron, caused by the prolonged ingestion of grass pea (*Lathyrus*
128 *sativus*) in a context of protein malnutrition (Ngudi et al., 2012). Even if the main symptoms of
129 *neurolethyrism* and *konzo* resemble each other (i.e. spastic paraparesis, appearance in food-
130 deprived conditions), some epidemiological and clinical characteristics allow differentiation
131 between them: while *konzo* mainly occurs in children and childbearing women, *neurolethyrism*
132 mostly affects male adults (Oluwole, 2015; Spencer et al., 1986). Furthermore, these 2 diseases do
133 not occur in the same geographic areas (Ethiopia, Spain, India, Bangladesh for *neurolethyrism*
134 (Tshala-katumbay and Spencer, 2007; Woldeamanuel et al., 2012)), and grass pea, the drought
135 tolerant legume involved in the occurrence of *neurolethyrism*, is neither cultivated nor consumed
136 in regions where *konzo* cases are reported. Neurological symptoms occur in a less abrupt manner
137 in *neurolethyrism* (with weakness appearing in most cases after 10–15 days, sometimes up to 3
138 months, following prodromal symptoms of myalgia, cramps and stiffness (Getahun et al., 2002;
139 Woldeamanuel et al., 2012)). In *konzo*, 90 % of patients have an onset of weakness in less than one
140 day (World Health Organization, 1996)).

141 In summary, diagnosis of *konzo* is easy, based on well-defined clinical criteria (spastic paraparesis)
142 in the presence of the two risk factors, i.e., consumption of toxic cassava products and protein
143 malnutrition. However, a careful differential diagnosis has to be made to search for (eventually
144 treatable) central nervous system lesions and other toxico-nutritional diseases related to cassava
145 (TAN) or grass pea consumption (*neurolethyrism*). Lesion should be understood here as
146 “identifiable by currently available tools or published reports”, since cellular or subcellular
147 damages below sensitivity of standard diagnostic techniques cannot be excluded (Kashala-Abotnes
148 et al., 2018; Sreeja et al., 2003). Other differential diagnoses possibly involved in or associated
149 with *konzo* (e.g., vitamin deficiencies) will be more appropriately discussed in the section 3.5.
150 below.

151 **3.2. The lesion site in *konzo***

152 It is now well established that the disease mainly affects the upper motoneuron (Donaghy, 1999).
153 However, the exact site of the neuronal damage is still unknown, as the few structural
154 investigations performed in the central nervous system (two autopsies by Trolli in 1937 (Tshala-
155 katumbay and Spencer, 2007; Tylleskar, 1994) and two magnetic resonance imaging in
156 1991 (Tylleskar et al., 1993)) of *konzo* patients failed to show any macroscopic lesion. This is
157 consistent with findings in most motor neuron diseases (MND), such as amyotrophic lateral
158 sclerosis, primary lateral sclerosis, or progressive muscular atrophy. The diagnosis of these diseases
159 is currently mainly based on a correct clinical examination searching for signs of the motor neuron

160 involvement, and exclusion of other neurological conditions that might mimic motor neuron
161 dysfunction by neuroimaging (which is usually normal in MND) (Kassubek et al., 2012; Sawalha
162 et al., 2019). Although no single test can confirm the diagnosis of motor neuron disease,
163 electrophysiological investigations may be useful to support the diagnosis of MND (Rocha et al.,
164 2005). Electrophysiological measurements (especially sensorimotor and visual evoked potentials)
165 in konzo patients have confirmed motor pathways involvement, but additionally suggested optic
166 nerve lesion and, to a lesser extent, sensory pathways dysfunction (Ali Ekangu et al., 2015;
167 Kashala-Abotnes et al., 2018; Mwanza et al., 2003; D Tshala-Katumbay et al., 2002).

168 The pathogenic processes underlying MND are not yet fully elucidated (Shaw, 2005). Several
169 mechanisms (such as excitotoxicity, oxidative stress, proteins alterations, or genetic factors) are
170 involved in the neurodegeneration observed in MND (Cluskey and Ramsden, 2001; Rocha et al.,
171 2005; Shaw, 2005). A study by Kassa et al. has reported alterations in the expression of proteins
172 involved in many cellular processes (such as the maintenance of the cytoskeleton integrity, control
173 of vesicular trafficking, or regulation of oxidative mechanisms) in rats receiving one daily injection
174 of linamarin (50-200 mg/kg body weight) or sodium cyanate (200 mg/kg body weight) (Kassa et
175 al., 2011). Additionally, these alterations were further emphasized in rats on a SAA-deficient diet.
176 These observations suggest that the motor neuron degeneration induced by konzo may result from
177 neuronal damage at cellular or molecular levels.

178 **3.3. Dietary cyanide poisoning and its detoxification pathways**

179 In all communities where konzo is reported, people rely on cassava roots as the main staple food,
180 particularly during periods of drought, famine, war or other humanitarian disasters (Chabwine et
181 al., 2011). During these hard times the bitter varieties of cassava are preferred because they
182 withstand harsh climatic conditions and pestilence (Imakumbili et al., 2019; Kimani, 2011) and
183 have a better yield (Cliff et al., 1997; Howlett et al., 1990; Imakumbili et al., 2019; Tylleskär et al.,
184 1995). The bitter taste is due to a high content of cyanogenic glucosides, mainly linamarin (about
185 95 %) and a small quantity of lotaustralin (a methyl-linamarin species) (Montagnac et al., 2009b).
186 Because of their high cyanogenic compounds content and unpleasant taste, the bitter varieties of
187 cassava have to be adequately processed to ensure safety and acceptable taste before consumption
188 (Padmaja, 1995; Szabo et al., 2010).

189 Most traditional processing methods used in communities consuming cassava, including water-
190 soaking or heap-fermentation of cassava roots, proved to be efficient (Adamolekun, 2011) in
191 reducing cyanogen rates below the toxic threshold of 10 ppm (= mg of total cyanide per kg of

192 cassava) established by the Food and Agriculture Organization (FAO) and the WHO (Joint
193 FAO/WHO Food Standards Programme. Codex Alimentarius Commission, 2009). During the
194 processing, root integrity is altered, allowing linamarase, an enzyme contained in the root cell
195 walls, to hydrolyze linamarin into glucose and acetone cyanohydrin (Adamolekun, 2011). In
196 specific conditions of temperature ($>30^{\circ}\text{C}$), humidity and pH ($\text{pH}>6$), acetone cyanohydrin
197 spontaneously breaks down into acetone and free cyanide that can easily evaporate without any
198 other manipulation (Oluwole, 2015; Tshala-katumbay and Spencer, 2007).

199 However, in difficult situations leading to food shortage, people not only rely more exclusively on
200 cassava as caloric source but they also often shortcut the processing of cassava products (Banea et
201 al., 1992b; Essers et al., 1992; Tylleskar et al., 1991). As a result, the obtained cassava products
202 contain high quantities of acetone cyanohydrin and linamarin (Banea et al., 1992b; Teles, 2002).
203 Once ingested, the major part of linamarin contained in this insufficiently processed cassava food
204 is eliminated unchanged in the urine (Carlsson et al., 1999; Mlingi et al., 1995; Teles, 2002). A
205 small amount of linamarin is broken down by glucosidases of intestinal flora to form cyanide
206 (Padmaja, 1995; Szabo et al., 2010; Tshala-katumbay and Spencer, 2007). Acetone cyanohydrins
207 obtained from this chemical reaction is rapidly transformed in the alkaline environment of the gut
208 into the highly toxic cyanide (Banea et al., 1992b). Cyanide is known as one of the most powerful
209 poisons for human beings (Teles, 2002): a dose as low as 2 mmol (54 mg) can be fatal for a 70 kg
210 adult (Padmaja, 1995; Szabo et al., 2010; Teles, 2002). Cyanide easily diffuses into tissues where
211 it rapidly combines with metallic ions (such as iron and copper) of the mitochondrial cytochrome
212 oxidase and other metalloenzymes (Bhattacharya and Flora, 2015; Teles, 2002). Resulting stable
213 complexes block the cell respiration chain by inhibiting oxygen use, leading to cell death
214 threatening the consumer's life (Bhattacharya and Flora, 2015; Lavigne et al., 2004; Padmaja,
215 1995). It is worth mentioning that acute fatal cyanide intoxication from cassava food is exceptional
216 in areas of cassava consumption (including konzo areas), most likely due to traditional knowledge
217 of its fatal risks (Teles, 2002). This finding raises the question about the required dose of cyanide
218 poisoning for konzo; hence the hypothesis of "sublethal" poisoning evoked at times by some
219 authors (Egekeze and Oehme, 1980). This could be subsequent either to ingestion of lower cyanide
220 amounts, to partially effective processing of toxic cassava, or to existing detoxification pathways
221 in vivo.

222 After its release in the organism, cyanide (in this case, predominantly originating from metabolism
223 of cassava cyanogenic glucosides) is metabolized following one major and a few minor pathways
224 detailed in figure 2. In brief, cyanide is first trapped by methemoglobin in the form of

225 cyanmethemoglobin (Pimenta et al., 2010; Schulz, 1984), but this non-enzymatic pathway is
226 rapidly saturated. The excess cyanide undergoes enzymatic reactions with thiosulfate (SSO_3^{2-}) to
227 produce thiocyanate (SCN^-) and inorganic sulfate (Nambisan, 2011; Oluwole, 2015; J Tor-
228 Agbidye et al., 1999). The rhodanese enzyme being abundantly present in the body (Schulz, 1984),
229 the main rate-limiting factor for this detoxification pathway is the availability of a sulfane sulfur
230 compound (thiosulfate) (J Tor-Agbidye et al., 1999).

231 The conversion of cyanide into thiocyanate represents up to 80 % of the in vivo detoxification
232 mechanism (Egekeze and Oehme, 1980). Thiocyanate is more than 100-fold less toxic than cyanide
233 and is easily and rapidly eliminated from the body mainly via the urine (Pimenta et al., 2010;
234 Schulz, 1984). Due to this rapid conversion into thiocyanate, high but sublethal doses of cyanogenic
235 glycosides can be consumed over extended periods without clinical symptoms of intoxication
236 (Egekeze and Oehme, 1980). Thiocyanate is the major cyanide metabolite, even in patients with a
237 low protein diet (Oluwole and Oludiran, 2013a). It has a short elimination half-life
238 (approximately 2.7 days (Pimenta et al., 2010; Schulz, 1984)) and remains stable in urine; thus
239 urinary thiocyanate concentration represents a good surrogate measure of daily cyanide poisoning
240 during the few preceding days (Lundquist et al., 1995a; Tshala-katumbay and Spencer, 2007).
241 Cheap, but accurately sensitive and specific measuring methods of urinary thiocyanate are
242 effectively used in resource-limited countries (Banea et al., 2013; Haque and Bradbury, 1999;
243 Lundquist et al., 1995a; Tshala-katumbay and Spencer, 2007). Thus, urinary thiocyanate remains
244 to date the biomarker of choice for cyanide exposure in konzo areas (Oluwole and Oludiran,
245 2013a), where smoking (that could affect measurements (Madiyal et al., 2018)) is not common.
246 However, thiocyanate synthesis largely relies on SAA that are mainly provided by dietary protein
247 intake (Brosnan and Brosnan, 2006; Nimni et al., 2007). Since konzo patients are nutritionally
248 compromised due to poor protein intake (including SAA (Banea et al., 1997a; Cliff et al., 1985)),
249 using thiocyanate as an indicator of cyanide exposure is likely to underestimate the level of cyanide
250 poisoning from toxic cassava.

251 Alternatively, in the absence of sufficient sulfane sulfur availability, the cyanide anion can be
252 eliminated by other minor pathways, such as oxidation into cyanate (OCN^-) (Kassa et al., 2011; J
253 Tor-Agbidye et al., 1999) or reaction with cystine to form L-cysteine and beta-thiocyanoalanine
254 in order to be transformed into 2-Aminothiazoline-4-Carboxylic Acid (ATC), which is deemed
255 metabolically inert and is eliminated in the urine (Kassa et al., 2011; Lundquist et al., 1995b; Nunn
256 et al., 2011). Up to 15 % of potassium cyanide intraperitoneally administered to rats was found to
257 be eliminated as ATC (Egekeze and Oehme, 1980; Lundquist et al., 1995b). A study has reported

258 that cyanide may also react with glutathione in order to be transformed into 2-aminothiazoline-4-
259 oxoaminoethanionic acid (Gyamfi et al., 2019).

260 [\[Figure 2\]](#)

261 **3.4. Risk factors of konzo**

262 ***3.4.1. High dietary cassava-derived cyanide exposure***

263 Implication of improperly processed cassava in the occurrence of konzo was already suspected
264 during the very first outbreaks (Cliff et al., 1985; Ministry of health Mozambique, 1984; Tylleskar
265 et al., 1991). Indeed, cassava products contain up to 20-30 times higher amounts of cyanogenic
266 compounds than the WHO safety threshold (10 ppm) during konzo epidemics (Chabwine et al.,
267 2011; Ngudi et al., 2003). In agreement with this observation, all subsequent studies conducted in
268 konzo areas, and especially during outbreaks, demonstrated very high thiocyanate levels in konzo
269 patients (up to 500 $\mu\text{mol/L}$ in serum (Banea et al., 1992a) and 1720 $\mu\text{mol/l}$ in urine (Cardoso et al.,
270 2004; Kambale et al., 2017; Mlingi et al., 1991; Okitundu et al., 2014)), suggesting a dietary
271 cyanide poisoning. Furthermore, within areas affected by konzo, patients displayed higher urinary
272 thiocyanate levels compared to healthy individuals and to populations from konzo-free areas or
273 from regions where cassava is not frequently consumed (Cliff et al., 1985; Tylleskär et al., 1992).
274 Thus, in the absence of another cyanide source, it is now widely agreed that the origin of high
275 cyanide exposure in the context of konzo outbreaks is linked to dietary improperly processed
276 cassava products (Howlett et al., 1990). In general, as stated above, these populations are
277 undergoing difficult conditions such as drought and war, that lead to a monotonous diet based
278 principally on cassava products (Cliff et al., 1985; Nzwalo and Cliff, 2011). Food deprivation due
279 to these difficult living conditions further pushes these populations to introduce short-cuts in
280 cassava processing, which leads to residual high cyanide concentrations in derived cassava
281 products (Banea et al., 1992b; Cliff et al., 1997).

282 However, there are still a number of unanswered questions regarding etiopathogenic mechanisms
283 and causal factors of konzo. First, whether cyanide exposure occurs during the outbreak or at any
284 other time outside the epidemic peak remains unclear. In fact, high thiocyanate levels are found at
285 any time in populations living in konzo areas (Banea et al., 1997a; Cliff et al., 2011; Tylleskär et
286 al., 1992), but appear to be even higher during epidemic peaks (Cliff et al., 1985). Second, except
287 for one study in Bandundu (DRC) where konzo patients displayed high urinary thiocyanate levels
288 compared to controls (Boivin et al., 2017), most data collected from konzo affected regions failed
289 to show a significant difference between the urinary thiocyanate levels in konzo patients and

290 individuals without konzo within the same area (Banea et al., 1997a; Tylleskär et al., 1992).
291 However, caution should be taken in drawing such conclusion as these results might be biased by
292 the method used to evaluate cyanide exposure, which is based on thiocyanate, of which synthesis
293 requires sulfur-containing amino-acids that konzo patients are likely deficient for (see below).

294 **3.4.2. Protein malnutrition**

295 Next to cyanide exposure from incompletely processed cassava processing products, malnutrition
296 is the second important risk factor identified for konzo (Banea et al., 2016; Chabwine et al., 2011).
297 One study conducted in Bandundu (DRC) found indeed that stunted children had significantly
298 higher odds of being affected by konzo, compared to non-stunted children, with an odds ratio of
299 6.1 (95% CI: 2.80–13.25) (Bumoko et al., 2015). Thus, malnutrition has constantly been mentioned
300 as a risk factor of konzo (Banea et al., 2016; Chabwine et al., 2011). As previously mentioned, the
301 main cyanide detoxification pathway requires the presence of thiosulphate, mainly provided by
302 dietary SAA (Nambisan, 2011; J Tor-Agbidye et al., 1999). Accordingly, konzo patients have been
303 often described as being deficient in SAA, as indirectly documented by measurements of urinary
304 concentration of inorganic sulphate, a valid and reliable surrogate for plasma concentration of these
305 SAA (Cliff et al., 1985; Cole and Evrovski, 2000). Plasma SAA concentrations have not been
306 specifically measured in konzo patients. However, patients suffering from TAN, another disease
307 related to cyanide intoxication from improper cassava, were found to have very low plasma levels
308 of SAA, with some of them even completely lacking cysteine (Osuntokun et al., 1968). In general
309 people living in konzo areas have been found to have lower excretion of inorganic sulphate
310 compared to people from konzo-free areas (Banea et al., 1997a; Cliff et al., 1985), with konzo
311 patients having even lower levels than unaffected subjects (Cliff et al., 1985).

312 SAA deficiency constitutes a risk factor for konzo and given its role in synthesizing thiocyanate
313 (the cyanide metabolite used to measure cyanide exposure in the context of konzo), the accuracy
314 of this measurement should be questioned as there could be a high risk of underestimation. Thus,
315 konzo patients could actually be more intoxicated than non-affected individuals, despite the similar
316 thiocyanate levels observed in most studies (see above) (Banea et al., 1997a; Tylleskär et al., 1992).
317 Thus, there is a need to find a more accurate method to assess cyanide exposure in exposed people
318 such as konzo patients who are suffering protein malnutrition, particularly SAA deficiency.

319

320 **3.4.3. Towards etiological factors of konzo**

321 Cyanide exposure from a monotonous improperly processed cassava-based diet and protein
322 malnutrition (in particular SAA deficiency) are now acknowledged as risk factors for konzo.
323 However, although patients as well as supposedly healthy subjects seem to display markers of high
324 cyanide exposure in regions witnessing konzo outbreaks (Banea et al., 1997a; Tylleskär et al.,
325 1992), association between high dietary cyanide exposure from poorly processed cassava and
326 occurrence of konzo has not been confirmed in several studies (Adamolekun, 2011). Moreover, the
327 influence of each risk factor has not been precisely determined. In addition, konzo is only described
328 in some specific regions of Africa (Figure 3 and Table 1) while the prevalence of malnutrition is
329 high in many developing countries worldwide (Spencer and Palmer, 2012), as well as the
330 consumption of cassava (and presumably improper cassava products due to frequent humanitarian
331 disasters in these regions). It thus appears that the presence of both risk factors is not enough to
332 trigger the appearance of konzo, although the epidemiological link is robust (Nzwalo and Cliff,
333 2011; Tylleskar et al., 1991). It is most likely that konzo occurs as a result of the combination of
334 these two risk factors with other parameters at the community level, in terms of individual
335 susceptibility (Kashala-Abotnes et al., 2018) and/or possibly from the environment (Oluwole,
336 2015), further explaining why konzo occurs only in geographically well-defined areas and affects
337 only a small portion of the population.

338 [\[Figure 3\]](#)

339 **3.5. Konzo determinants and etiopathogenic factors**

340 **3.5.1. The role of dietary cassava-derived cyanide and cyanogenic metabolites**

341 Based on a well-documented epidemiological link (Nzwalo and Cliff, 2011; Tylleskar et al., 1991),
342 it is now widely accepted that toxic cassava varieties containing high levels of cyanogenic
343 molecules (mainly linamarin) and yielding toxic cyanide concentrations, play a role in the
344 occurrence of konzo. The few studies investigating serum cyanide levels (Tylleskär et al., 1992) or
345 urinary linamarin (Banea et al., 1997a; Cliff et al., 1999, 1997) found high concentrations both in
346 konzo patients and healthy controls in konzo areas. As detailed above, urines (or sometimes blood)
347 thiocyanate levels that usually indicate cassava-derived cyanide poisoning, similarly showed high
348 concentrations in the whole population living in konzo-affected areas (Banea et al., 1997a;
349 Tylleskär et al., 1992). Existence of high concentrations of cyanogenic glucosides, cyanide or
350 cyanide metabolites in communities affected by konzo in comparison to people living in konzo-
351 free areas led to the hypothesis that cyanide or one of its derivatives might be the causal agent of

352 konzo (Adamolekun, 2011). Indeed, linamarin (Kassa et al., 2011; Rivadeneyra-Dominguez et al.,
353 2016; Rivadeneyra-Domínguez et al., 2013; Sreeja et al., 2003; Umoh et al., 1985), acetone
354 cyanohydrin (Rivadeneyra-Domínguez et al., 2015; Soler-martín et al., 2010), cyanide (Kimani et
355 al., 2014b, 2014a; Maiorka and Go, 2002) and cyanate (Kassa et al., 2011; Kimani et al., 2014b,
356 2014a; Shaw et al., 1974; John Tor-Agbidye et al., 1999) were experimentally tested in animal
357 models and could induce neuronal lesions correlated with neurological symptoms. However, none
358 of them could properly mimic the clinical picture of konzo. Nonetheless, interesting observations
359 can be made from the existing data.

360 A large portion of linamarin, the main cyanogenic compound that determines the rate of cassava
361 toxicity (see above), once ingested, is mostly eliminated unchanged in the urine (Carlsson et al.,
362 1999; Mlingi et al., 1995; Sreeja et al., 2003; Teles, 2002). One study has suggested that
363 unmetabolized linamarin could be transported to the brain neural cells via a glucose transporter and
364 possibly cause direct toxicity to the brain (Sreeja et al., 2003), but this hypothesis has never been
365 verified in vivo. Only a small part of linamarin is transformed into cyanide (Padmaja, 1995; Szabo
366 et al., 2010; Tshala-katumbay and Spencer, 2007). Acetone cyanohydrin, on the other hand, is
367 easily broken down into cyanide owing to the warm, humid and alkaline environment of the
368 intestines (Banea et al., 1992b). For this reason, it is suggested that symptoms related to acetone
369 cyanohydrin ingestion may be attributed to cyanide release rather than to the direct effect of acetone
370 cyanohydrin (National Research Council (US) Committee on Acute Exposure Guideline Levels;
371 National Research Council (US) Committee on Toxicology, 2009). Cyanide is a very powerful
372 poison which has to be immediately eliminated from the organism to prevent death. Dietary cyanide
373 exposure at a high dose leads to acute poisoning with headache, dizziness, weakness, visual
374 disturbance, diarrhea, vomiting, nausea, and sometimes death, as observed in some parts of the
375 world (Mlingi et al., 1992). Spastic paraparesis, the key clinical feature of konzo, has never been
376 reported in the context of acute cyanide poisoning. But at a sublethal dose, diverse detoxification
377 pathways can be engaged (see Figure 2), transforming cyanide into less toxic metabolites (Egekeze
378 and Oehme, 1980). Overall, it is unlikely that linamarin, acetone cyanohydrin or cyanide itself are
379 the causative agents of konzo. Instead, cyanide metabolites such as cyanate, thiocyanate, or another
380 so far unknown and possibly transient metabolite might be involved.

381 Under normal conditions, cyanate is produced in trace amounts during the cyanide detoxification
382 process (Kassa et al., 2011). However, in the case of malnutrition (in particular SAA deficiency),
383 experimental animal data show increased serum cyanate production following cyanide exposure (J
384 Tor-Agbidye et al., 1999), suggesting that the same would happen in nutritionally compromised

385 humans (especially those lacking SAA) who are chronically exposed to cyanide poisoning, such as
386 most people living in konzo areas. On the other hand, cyanate is a protein-carbamylating agent
387 (Alter et al., 1974; Kassa et al., 2011; Kimani et al., 2013) reducing nerve conduction velocity
388 (John Tor-Agbidye et al., 1999). This is probably the mechanism by which experimental
389 administration of cyanate induced hind limb paralysis in rats (Alter et al., 1974; Kassa et al., 2011),
390 as well as spastic quadriplegia in rhesus monkeys (Shaw et al., 1974). Accordingly, sickle-cell
391 anemic patients who received sodium cyanate as treatment, witnessed motor impairments (Peterson
392 et al., 1974). Thus, cyanate appears to impair motor function through defective carbamylation,
393 especially in the presence of protein (SAA) deficiency, thereby becoming a candidate potential
394 causative agent of konzo (Kassa et al., 2011).

395 Thiocyanate is the most important cyanide metabolite derived from the cyanide detoxification
396 process, even in people with low dietary protein intake (Egekeze and Oehme, 1980; Nambisan,
397 2011; Oluwole and Oludiran, 2013b). Although being up to 100-fold less toxic than cyanide,
398 thiocyanate may be harmful to the nervous system at high doses (German et al., 1949), causing
399 symptoms such as hyperreflexia, muscular fatigue, motor aphasia, convulsive twitching and mental
400 disturbances (Burke and Mutnick, 1994; German et al., 1949). One mechanism underlying these
401 neuropathological features could be the enhancement of glutamate binding to AMPA (α -amino-3-
402 hydroxy-5-méthyl-4-isoxazolepropionique) receptors (Hawkinson and Espitia, 1997; Murphy et
403 al., 1987), which in turn would induce cellular depolarization via calcium and/or sodium entry
404 (Wang and Qin, 2010), and trigger the excitotoxicity cascade and neuronal death (Spencer, 1999).
405 If we consider hyperreflexia observed in animal models as being the minimal equivalent of the
406 spastic paraparesis syndrome found in konzo patients, it could be hypothesized that thiocyanate-
407 induced excitotoxicity contributes to the pathogeny of konzo through upper motor neuron damage.
408 In support of this assumption, beta-N-Oxalylamino-L-alanine (L-BOAA, the toxic agent found in
409 grass pea (Ngudi et al., 2012) and incriminated in neurolathyrism) is a stereospecific agonist of
410 AMPA receptors in rodents and humans (Spencer and Palmer, 2012) and induces excitotoxic upper
411 motor neuronal death, thereby leading to spastic paraparesis (Ross et al., 1989; Spencer, 1999; M.
412 Van Moorhem et al., 2011; Marijke Van Moorhem et al., 2011). These observations further support
413 thiocyanate as a plausible candidate contributing to the pathogeny of konzo.

414 So, despite lack of experimental and clinical data, cyanate and thiocyanate appear as potential
415 konzo etiological agents. In contrast, linamarin, as well as cyanide and acetone cyanohydrin, do
416 not seem to be involved. In order to further investigate these hypotheses, appropriate experimental
417 and clinical studies should be conducted, having in mind that there might be additional mechanisms

418 as epidemiological studies have failed to show differentiation between konzo patients and non-
419 affected people regarding thiocyanate and cyanide levels.

420 ***3.5.2. Any role for infectious agents in konzo?***

421 Based on its epidemics occurrence, familial clustering (Carton et al., 1986), and on its prominent
422 symptoms that evoked some known viral infections, konzo was thought to be an infectious disease
423 for many years (Carton et al., 1986; World Health Organization, 1996).

424 Table 2 summarizes all studies that investigated the potential infectious origin of konzo. HTLV-1,
425 a virus belonging to the oncovirus family of retroviruses, is the most documented pathogen in
426 konzo (Bangham et al., 2015). Like most retroviruses, HTLV-1 is transmitted by sexual contact,
427 breastfeeding or blood transfusions (Gessain and Mahieux, 2012) and induces in about 1% of
428 infected people, a chronic slowly progressive myelopathy called HTLV-I associated myelopathy
429 or tropical spastic paraparesis (HAM/TSP) (Bangham et al., 2015; Zaninovic, 1999). HAM/TSP-
430 like syndromes have also been reported in patients infected by other retroviruses such as the HTLV-
431 2 and the Human Immunodeficiency Virus (HIV-1 and HIV-2) (Casseb et al., 2008; Posada-
432 Vergara et al., 2006; Zaninovic, 1999). However, in contrast with konzo, HAM/TSP displays a
433 slow onset and progressive course spanning from years to several decades. Furthermore, in addition
434 to spastic paraparesis, other myelopathic symptoms such as sensory deficits, pain, urinary and
435 sexual disturbances are linked with well-defined spinal cord lesions (Bangham et al., 2015).
436 Although the presence of these retroviruses and konzo may coexist in the same regions, there is to
437 date no evidence for a potential association between konzo occurrence and retroviral infections, as
438 more than 99 % of konzo patients display either negative tests for those types of infections
439 (Tylleskar et al., 1996) and the few existing case-control studies found a similar frequency of
440 positive serologic tests in konzo patients and healthy controls (Banea et al., 1992a; Howlett et al.,
441 1990; Tylleskar et al., 1996; Tylleskär et al., 1992). One study in the DRC reported a HIV-positive
442 patient fulfilling the WHO diagnostic criteria of konzo (Chabwine et al., 2011). Some studies
443 investigating other infections, like syphilis (Howlett et al., 1990; Tylleskar et al., 1993), hepatitis
444 A, B and C (Tylleskar et al., 1993) and even schistosomiasis (Howlett et al., 1990), found no
445 evidence of their involvement in the occurrence of konzo. Altogether, the current state of
446 knowledge reasonably rules out an infectious origin of konzo.

447 ***3.5.3. Any role for nutritional deficiencies and oxidative stress?***

448 As already mentioned above, most studies show similar levels of markers of cyanide exposure
449 between konzo patients and non-diseased individuals within konzo areas. Thus, there could be

450 factors (for example nutritional, metabolic or genetic) that determine individual susceptibility to
451 konzo (Kashala-Abotnes et al., 2018).

452 It is well established that nutritional status can significantly influence the neurotoxic action of some
453 chemical agents, or even may be a prerequisite for neurotoxicity to develop, as discussed earlier
454 regarding protein (SAA) deficiency (Spencer and Palmer, 2012). Additionally, oligo-elements
455 deficiency including vitamins might also be involved in the disease occurrence. A role for heavy
456 metal poisoning is also possible, especially in some konzo areas where mining activity is intensive
457 (Weyns et al., 2016). However, none of these hypotheses has been investigated but deserve further
458 attention as being potentially involved in konzo.

459 As previously stated, SAA deficiency observed in konzo patients can contribute to oxidative stress.
460 Indeed, it has been found that methionine and/or cysteine deficiency could lead to glutathione
461 depletion in the central nervous system (Nunn et al., 2011; Spencer and Palmer, 2012). Glutathione,
462 in addition to its prominent antioxidant potency, is involved in xenobiotics detoxication (Spencer
463 and Palmer, 2012; John Tor-Agbidye et al., 1999). It has been reported that glutathione may
464 contribute to cyanide detoxification by reacting with cyanide to form 2-aminothiazoline-4-
465 oxoaminoethanionic acid (Gyamfi et al., 2019). Furthermore, glutathione depletion enhances in vitro
466 excitotoxicity in cultured cortical neurons (John Tor-Agbidye et al., 1999). Other antioxidant
467 agents such as selenium have been found to be depleted in konzo patients (Bumoko et al., 2015),
468 further supporting the possible role of oxidative stress in konzo.

469 Thiamine (vitamin B1) is an essential oligo-element, i.e. mainly provided through dietary intake
470 (Martel et al., 2020). People living in konzo areas are at risk of thiamine deficiency, as they mainly
471 rely on a cassava (a poor source of thiamine)-based diet, with poor animal proteins intakes
472 (Adamolekun, 2010). Accordingly, studies on people living in areas with high konzo prevalence,
473 have confirmed a markedly low intake of vitamin B1, including in the majority of supposedly
474 “healthy” subjects (Barclay et al., 2003). Thiamine acts as a coenzyme for several enzymes
475 involved in energy metabolism, and participating in many biochemical and physiological processes
476 (Chauhan et al., 2018). Its deficiency is associated with oxidative stress and neurodegeneration in
477 brain tissue (Chauhan et al., 2018; Liu et al., 2017). At a clinical level, vitamin B1 deficiency
478 symptoms overlap with less studied konzo symptoms such as cognitive impairment (Johnson and
479 Fox, 2018; Pourhassan et al., 2019) and visual disturbances (Adamolekun, 2011; Gratton and Lam,
480 2014), without evident involvement in spastic paraparesis. A few studies have investigated the
481 levels of other group B vitamins (pyridoxin, folic acid and cyanocobalamin) in konzo (Banea et al.,
482 1992a, 1992b; Tylleskar et al., 1993) and TAN patients (Adamolekun, 2011), and found them to

483 be within normal to high ranges. To our knowledge, no study has investigated the status of vitamin
484 A in konzo patients. However, a study in Nigeria has reported the absence of vitamin A deficiency
485 in women and schoolchildren eating cassava (De Moura et al., 2015). Also, vitamin A deficiency
486 and konzo do not share any common symptoms except for visual disturbance, making vitamin A
487 deficiency unlikely to have a causative role in konzo.

488 It appears that the toxicity of cyanide metabolites could, at an individual level, be directly or
489 indirectly (through oxidative stress) favored or enhanced by different nutritional deficiencies and
490 exacerbated by the state of oxidative stress (Bumoko et al., 2015). However, their putative role in
491 konzo remains to be confirmed.

492 ***3.5.4. Geographic clustering and environmental factors are important in the occurrence of*** 493 ***konzo.***

494 For almost a century, konzo outbreaks and sporadic cases have been reported in less than 10
495 countries in central, eastern, and southern Africa (Table 1 and Figure 3). Even within these
496 countries, konzo is unevenly distributed and remains clustered in some restricted areas. As an
497 illustration, in the DRC, which bears the highest prevalence of konzo, regardless of epidemics,
498 cases have been reported only in two provinces: Bandundu in the West (Boivin et al., 2013;
499 Bumoko et al., 2015; Kambale et al., 2017; Luwa E-Andjafono Daniel Okitundu et al., 2018; Luwa
500 E-Andjofono Daniel Okitundu et al., 2018; Okitundu et al., 2014) and South-Kivu in the East
501 (Chabwine et al., 2011). In South-Kivu, which is located more than 1000 km away from Bandundu,
502 konzo appeared only in Burhinyi, a small remote village, and in Uvira (~ 100 km from Burhinyi)
503 (Chabwine et al., 2011).

504 There is an overlap between the geographical clustering of konzo and the agroecology of cassava
505 in Africa. Up to the early 1990s, the then known five African rural areas affected by konzo figured
506 on a list of 12 areas of high cassava consumption, where more cassava was grown than predicted
507 (Carter and Jones, 1993; Howlett et al., 1992; Tylleskar, 1994). In addition, six of the seven
508 countries affected by konzo so far (see the map on Figure 3) are among the first 20 major cassava
509 production countries worldwide (FAO, 2019). However, the sole agroecology of cassava cannot
510 fully explain this geographic distribution of konzo.

511 Environmental conditions may also play a major role in the geographic clustering of konzo cases.
512 A strong relationship was established between low precipitation and konzo epidemics in DRC,
513 Mozambique, and Tanzania (Oluwole, 2015). However, persistence of sporadic cases of konzo
514 outside periods of drought, suggests that additional geo-environmental factors might also be

515 involved in appearance of konzo (Imakumbili et al., 2019), like in TAN. In a study conducted in
516 Nigeria, a significant association was found between the cyanogenic content of cassava cultivars,
517 prevalence of TAN and altitude (Oluwole and Oludiran, 2013b). The characteristics of soils where
518 cassava is grown may also impact the total amount of cyanogenic compounds in cassava roots
519 (Imakumbili et al., 2019). Given the role of cassava-derived cyanide exposure in konzo, these
520 factors are likely to also play a role in konzo, but this assumption should be further explored.

521 The seasonality of konzo also strongly suggests the influence of the environment in the occurrence
522 of konzo, as most konzo epidemics occur during dry seasons (Banea et al., 2015a, 1992a; Chabwine
523 et al., 2011; Tylleskar et al., 1991). In a survey conducted in an area affected by konzo in Tanzania,
524 farmers reported increased bitterness of cassava roots during the dry season (Imakumbili et al.,
525 2019). This may result from an increase in the amount of cyanogenic glucosides in cassava roots
526 due to natural water stress conditions favored by the structure of soils and by the seasonal changes
527 (Imakumbili et al., 2019; Santisopasri et al., 2001; Tan, 1995). These observations are also
528 consistent with findings from studies by Ernesto et al. in northern Mozambique (Ernesto et al.,
529 2002) and by Banea et al. in Bandundu (Banea et al., 1997a), who noted a seasonal distribution of
530 urinary thiocyanate levels in subjects from areas affected by konzo, with higher values during the
531 dry season. And that also coincided with peak konzo incidence (Banea et al., 2015b, 1992a; Cliff
532 et al., 1985; Ministry of health Mozambique, 1984).

533 **3.6. Limitations and concluding remarks**

534 Konzo is a toxico-nutritional disease with a selective damage of the upper motoneuron, which
535 affects thousands of patients in seven African countries. Throughout the years, even if its clinical
536 picture is already definitely drawn, its risk factors well established and enough knowledge has been
537 gathered to rule out an infectious origin of the disease, little progress has been made in the
538 understanding and the prevention and management of this disease. Almost one century after its
539 identification, many questions remain unanswered: 1° its distribution in person (preferential
540 involvement of children and childbearing women), place (only specific regions in a few countries),
541 and time (mostly during dry season); 2° the causative agent of the disease, and 3° the pathogenic
542 mechanisms leading to the motoneuron damage.

543 With no anatomical lesion identified through the whole central nervous system of konzo patients,
544 it seems that the mechanisms involved in the occurrence of konzo take place at sparse cellular
545 and/or at subcellular levels. This is the case also for many other motor neuron diseases (Cluskey
546 and Ramsden, 2001; Rocha et al., 2005; Shaw, 2005). Like other motor neuron diseases, two

547 interconnected pathophysiologic phenomena seem to be particularly involved in konzo: oxidative
548 stress (Bumoko et al., 2015) and excitotoxicity (Spencer, 1999). But more studies are needed to
549 identify their role in konzo. The lack of an appropriate animal model constitutes an important
550 limiting factor in the understanding of the pathogenesis of konzo. Furthermore, because konzo is a
551 rare disease, it is very difficult to conduct a large cohort study which can longitudinally follow a
552 population at risk for konzo and find what really happens at the onset of the disease. Except for one
553 study which evaluated blood cyanide and thiocyanate levels in three patients at disease onset
554 (within 90 h) (Tylleskär et al., 1992), all available data on konzo were so far gathered from patients
555 at the sequelae phase of the disease, very often many months or years after the onset of the paresis,
556 making the understanding of the disease complicated.

557 Available observational studies have failed to demonstrate the causal relationship between konzo
558 and cyanide poisoning. However, even if thiocyanate remains currently the gold standard to
559 measure cyanide exposure, it may not be the best marker in konzo areas and may underestimate
560 the level of cyanide poisoning in konzo patients, as a larger amount of cyanide is detoxified via
561 other unusual pathways in the context of protein malnutrition (Kassa et al., 2011; J Tor-Agbidye et
562 al., 1999). Furthermore, the compromised nutritional status of affected patients and the oxidative
563 stress may constitute a condition which enhances the neurotoxicity of cyanide compounds.

564 Geographic and environmental factors probably constitute other factors of susceptibility to the
565 disease, as shown by the clustering of konzo cases in a few specific regions in central, eastern, and
566 southern Africa. Climatic variations have been demonstrated to play a major role in the outbreaks
567 of konzo. According to available data, other geo-environmental factors such as altitude and soil
568 characteristics may also be involved in the occurrence of the disease (Imakumbili et al., 2019;
569 Oluwole and Oludiran, 2013b). But such factors are still to be further investigated in konzo affected
570 areas.

571 Finally, it is to notice that all konzo affected regions have gone through different humanitarian
572 disasters (war, prolonged insecurity with mass population displacements, drought, famine...)
573 before the occurrence of cases (Chabwine et al., 2011; Ministry of health Mozambique, 1984;
574 Nzwalo and Cliff, 2011). All these situations can lead to changes in dietary habits but they may
575 also have a direct biological impact on subjects leaving in concerned areas (Stanke et al., 2013). In
576 fact, these disorders can lead to psycho-emotional distress and anxiety (Stanke et al., 2013) which,
577 in turn, can shorten the length of chromosome telomeres (Malouff and Schutte, 2017; Wang et al.,
578 2017). The length of telomeres is an indicator of human health and aging (Malouff and Schutte,
579 2017; Sanders and Newman, 2013) and shorter telomers are associated with an increased risk of

580 neurological and cardiovascular diseases, cancers and even high mortality (Malouff and Schutte,
581 2017). In addition, many individual factors, such as genes, age or gender, can modulate the
582 susceptibility of telomeres to different physical or psychosocial factors (Malouff and Schutte,
583 2017). Finally, telomeres are very sensitive to oxidative stress (Ahmed and Lingner, 2018; Sanders
584 and Newman, 2013). Whether changes in telomere length are observed in konzo patients and could
585 in turn be used as markers of the disease progression remain speculative. If confirmed, this could,
586 at least partially, explain the geographic, and maybe the individual, clustering of the disease.

587 In conclusion, almost a century since the description of konzo, its pathogenesis is still unelucidated.
588 However, it affects yearly thousands of patients in specific poor regions in Africa. Konzo
589 occurrence results in an irreversible handicap in the most active portion of the population. For these
590 communities, konzo is a major public and societal health problem. To date, no specific treatment
591 for konzo patients is available due to a gap in the knowledge on konzo. New insights on its etiology
592 are now arising, and, in that context, more research is needed.

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596 **Appendix A. Supplementary data**

597 The following is the supplementary data to this article: Detailed data for Figure 3.docx.

598 **REFERENCES**

- 599 Adamolekun, B., 2010. Etiology of Konzo, epidemic spastic paraparesis associated with
600 cyanogenic glycosides in cassava: Role of thiamine deficiency? *Bola. J. Neurol. Sci.* 296,
601 30–33. <https://doi.org/10.1016/j.jns.2010.06.016>
- 602 Adamolekun, B., 2011. Neurological disorders associated with cassava diet: A review of putative
603 etiological mechanisms. *Metab. Brain Dis.* 26, 79–85. [https://doi.org/10.1007/s11011-011-](https://doi.org/10.1007/s11011-011-9237-y)
604 9237-y
- 605 Ahmed, W., Lingner, J., 2018. Impact of oxidative stress on telomere biology. *Differentiation* 99,
606 21–27. <https://doi.org/10.1016/j.diff.2017.12.002>
- 607 Ali Ekangu, R., Kambale Kikandau, J., Vumbi Lelo, G., Kalala Lunganza, R., Yandju Marie-
608 Claire, M., Takaisi Kikuni, P., Okitundu Luwa E-Andjafono, D., Mumba Ngoyi, D., Boivin,
609 J.M., Tshala- Katumbay, D., 2015. Analysis of motor pathway involvement in Konzo

disease. *J. Neurol. Sci.* 357, e496–e497. <https://doi.org/10.1016/j.jns.2015.09.287>

Allen, T.J., 2010. Konzo in Angola. *Cassava Cyanide Dis. Neurolathyrism Netw.* 3–4. <https://doi.org/10.1371/journal.pntd.0000487>

Alter, B.P., Kan, Y.W., Nathan, D.G., 1974. Toxic Effects of High-Dose Cyanate Administration in Rodents. *Blood* 43, 69–77. <https://doi.org/10.1182/blood-2015-06-651331>

Banea, J.P., Bikangi, N., Nahimana, G., Nunga, M., Tylleskar, T., Rosling, H., 1992a. High prevalence of konzo associated with a food shortage crisis in the Bandundu region of zaire. *Ann. Soc. Belg. Med. Trop.* (1920). 72, 295–309.

Banea, J.P., Bradbury, J.H., Mandombi, C., Nahimana, D., Denton, I.C., Foster, M.P., Kuwa, N., Tshala Katumbay, D., 2015a. Konzo prevention in six villages in the DRC and the dependence of konzo prevalence on cyanide intake and malnutrition. *Toxicol. Reports* 2, 609–616. <https://doi.org/10.1016/j.toxrep.2015.03.014>

Banea, J.P., Bradbury, J.H., Mandombi, C., Nahimana, D., Denton, I.C., Kuwa, N., Tshala Katumbay, D., 2013. Control of konzo by detoxification of cassava flour in three villages in the Democratic Republic of Congo. *Food Chem. Toxicol.* 60, 506–513. <https://doi.org/10.1016/j.fct.2013.08.012>

Banea, J.P., Bradbury, J.H., Nahimana, D., Denton, I.C., Foster, M.P., Mekob, N., Kuwa, N., Bokundabi, G., Foley, W.J., 2016. Health factors associated with persistent konzo in four villages in the Democratic Republic of Congo (DRC). *African J. Food Sci.* 10, 1–6. <https://doi.org/10.5897/AJFS2015>.

Banea, J.P., Bradbury, J.H., Nahimana, D., Denton, I.C., Kuwa, N., 2015b. Survey of the konzo prevalence of village people and their nutrition in Kwilu District, Bandundu Province, DRC. *African J. Food Sci.* 9, 43–50. <https://doi.org/10.5897/AJFS2014.1206>

Banea, J.P., Poulter, N.H., Rosling, H., 1992b. Shortcuts in cassava processing and risk of dietary cyanide exposure in Zaire. *Food Nutr. Bull.* 14, 137–143.

Banea, J.P., Tylleskar, T., Gitebo, N., Matadi, N., Gebre-Medhin, M., Rosling, H., 1997a. Geographical and seasonal association between linamarin and cyanide exposure from cassava and the upper motor neurone disease konzo in former Zaire. *Trop. Med. Int. Health* 2, 1143–1151.

Banea, J.P., Tylleskär, T., Rosling, H., 1997b. Konzo and Ebola in Bandundu region of Zaire. *Lancet* 349, 621. [https://doi.org/10.1016/S0140-6736\(05\)61569-3](https://doi.org/10.1016/S0140-6736(05)61569-3)

Bangham, C.R.M., Araujo, A., Yamano, Y., Taylor, G.P., 2015. HTLV-1-associated myelopathy/tropical spastic paraparesis. *Nat. Rev. Dis. Prim.* 1. <https://doi.org/10.1038/nrdp.2015.12>

644 Barclay, D. V., Mauron, J., Blondela, A., Cavadini, C., Verwilghen, A.M., Van Geert, C., Dirren,
645 H., 2003. Micronutrient intake and status in rural Democratic Republic of Congo. *Nutr. Res.*
646 23, 659–671. [https://doi.org/10.1016/S0271-5317\(03\)00027-7](https://doi.org/10.1016/S0271-5317(03)00027-7)

647 Bhattacharya, R., Flora, S.J.S., 2015. Chapter 23 - Cyanide Toxicity and its Treatment, in: Gupta,
648 R.C.B.T.-H. of T. of C.W.A. (Second E. (Ed.), *Handbook of Toxicology of Chemical*
649 *Warfare Agents* (Second Edition). Academic Press, Boston, pp. 301–314.
650 <https://doi.org/https://doi.org/10.1016/B978-0-12-800159-2.00023-3>

651 Boivin, M.J., Okitundu, D., Makila-Mabe, B., Sombo, M.T., Mumba, D., Sikorskii, A.,
652 Mayambu, B., Tshala-Katumbay, D., 2017. Cognitive and motor performance in Congolese
653 children with konzo during 4 years of follow-up: a longitudinal analysis. *Lancet Glob. Heal.*
654 5, e936–e947. [https://doi.org/10.1016/S2214-109X\(17\)30267-X](https://doi.org/10.1016/S2214-109X(17)30267-X)

655 Boivin, M.J., Okitundu, D., Makila-Mabe Bumoko, G., Sombo, M.-T., Mumba, D., Tylleskar, T.,
656 Page, C.F., Tamfum Muyembe, J.-J., Tshala-Katumbay, D., 2013. Neuropsychological
657 effects of konzo: a neuromotor disease associated with poorly processed cassava. *Pediatrics*
658 131, e1231-9. <https://doi.org/10.1542/peds.2012-3011>

659 Bonmarin, I., Nunga, M., Perea, W.A., 2002. Konzo outbreak, in the south-west of the
660 Democratic Republic of Congo, 1996. *J. Trop. Pediatr.* 48, 234–238.

661 Brosnan, J.T., Brosnan, M.E., 2006. The Sulfur-Containing Amino Acids: An Overview. *J. Nutr.*
662 136, 1636S-1640S. <https://doi.org/10.1093/jn/136.6.1636S>

663 Bumoko, G.M., Sombo, M.T., Okitundu, L.D., Mumba, D.N., Kazadi, K.T., Tamfum-Muyembe,
664 J.J., Lasarev, M.R., Boivin, M.J., Banea, J.P., Tshala-Katumbay, D.D., 2014. Determinants
665 of cognitive performance in children relying on cyanogenic cassava as staple food. *Metab.*
666 *Brain Dis.* 29, 359–366. <https://doi.org/10.1007/s11011-014-9492-9>

667 Bumoko, G.M.M., Sadiki, N.H., Rwatambuga, A., Kayembe, K.P., Okitundu, D.L., Mumba
668 Ngoyi, D., Muyembe, J.T.J.T., Banea, J.P., Boivin, M.J., Tshala-katumbay, D., Ngoyi,
669 D.M., Muyembe, J.T.J.T., Banea, J.P., Boivin, M.J., Tshala-katumbay, D., 2015. Lower
670 serum levels of selenium, copper, and zinc are related to neuromotor impairments in
671 children with konzo. *J. Neurol. Sci.* 349, 149–153. <https://doi.org/10.1016/j.jns.2015.01.007>

672 Burke, T.G., Mutnick, A.H., 1994. Treatment of Cyanide and Thiocyanate Toxicity Secondary to
673 Sodium Nitroprusside. *J. Pharm. Technol.* 10, 207–209.

674 Cardoso, A.P., Ernesto, M., Nicala, D., Mirione, E., Chavane, L., N'zwalo, H., Chikumba, S.,
675 Cliff, J., Mabota, A.P., Haque, M.R., Bradbury, J.H., 2004. Combination of cassava flour
676 cyanide and urinary thiocyanate measurements of school children in Mozambique. *Int. J.*
677 *Food Sci. Nutr.* 55, 183–190. <https://doi.org/10.1080/09637480410001725265>

678 Carlsson, L., Mlingi, N., Juma, A., Ronquist, G., Rosling, H., 1999. Metabolic fates in humans of
679 linamarin in cassava flour ingested as stiff porridge. *Food Chem. Toxicol.* 37, 307–312.
680 [https://doi.org/10.1016/S0278-6915\(99\)00015-0](https://doi.org/10.1016/S0278-6915(99)00015-0)

681 Carter, S.E., Jones, P.G., 1993. A model of the distribution of cassava in Africa. *Appl. Geogr.* 13,
682 353–371. [https://doi.org/10.1016/0143-6228\(93\)90037-2](https://doi.org/10.1016/0143-6228(93)90037-2)

683 Carton, H., Kayembe, K., Kabeya, Odio, Billiau, a, Maertens, K., 1986. Epidemic spastic
684 paraparesis in Bandundu (Zaire). *J. Neurol. Neurosurg. Psychiatry* 49, 620–627.
685 <https://doi.org/10.1136/jnnp.49.6.620>

686 Casseb, J., de Oliveira, A.C.P., Vergara, M.P.P., Montanheiro, P., Bonasser, F., Meilman
687 Ferreira, C., Smid, J., Duarte, A.J. da S., 2008. Presence of tropical spastic
688 paraparesis/human T-cell lymphotropic virus type 1-associated myelopathy (TSP/HAM)-
689 like among HIV-1-infected patients. *J. Med. Virol.* 80, 392–398.
690 <https://doi.org/10.1002/jmv.21111>

691 Chabwine, J., Masheka, C., Balol’ebwami, Z., Maheshe, B., Balegamire, S., Rutega, B., Wa Lola,
692 M., Mutendela, K., Bonnet, M.-J., Shangalume, O., Balegamire, J.M., Nemery, B., 2011.
693 Appearance of konzo in South-Kivu, a wartorn area in the Democratic Republic of Congo.
694 *Food Chem. Toxicol.* 49, 644–649. <https://doi.org/10.1016/j.fct.2010.07.050>

695 Chauhan, A., Srivastva, N., Bubber, P., 2018. Thiamine Deficiency Induced Dietary Disparity
696 Promotes Oxidative Stress and Neurodegeneration. *Indian J. Clin. Biochem.* 33, 422–428.
697 <https://doi.org/10.1007/s12291-017-0690-1>

698 Ciglenc̆ki, I., Eyema, R., Kabanda, C., Taafo, F., Mekaoui, H., Urbaniak, V., 2011. Konzo
699 outbreak among refugees from Central African Republic in Eastern region, Cameroon. *Food*
700 *Chem. Toxicol.* 49, 579–582. <https://doi.org/10.1016/j.fct.2010.05.081>

701 Cliff, J., 2010. Konzo Count. *Cassava Cyanide Dis. Neurolathyrisms Netw. News* 15, 4.

702 Cliff, J., Lundqvist, P., Martensson, J., Rosling, H., Sorbo, B., 1985. Association of high cyanide
703 and low sulphur intake in cassava-induced spastic paraparesis. *Lancet (London, England)* 2,
704 1211–1213.

705 Cliff, J., Muquingue, H., Nhassico, D., Nzwalo, H., Bradbury, J.H., 2011. Konzo and continuing
706 cyanide intoxication from cassava in Mozambique. *Food Chem. Toxicol.* 49, 631–635.
707 <https://doi.org/10.1016/j.fct.2010.06.056>

708 Cliff, J., Nicala, D., Saute, F., Givragy, R., Azambuja, G., Taela, A., Chavane, L., Gani, A., 1999.
709 Ankle Clonus and Thiocyanate, Linamarin, and Inorganic Sulphate Excretion in School
710 Children in Communities with Konzo, Mozambique. *J. Trop. Pediatr.* 45, 139–142.

711 Cliff, J., Nicala, D., Saute, F., Givragy, R., Azambuja, G., Taela, A., Chavane, L., Howarth, J.,

712 1997. Konzo associated with war in Mozambique. *Trop. Med. Int. Health* 2, 1068–1074.
713 <https://doi.org/10.1046/j.1365-3156.1997.d01-178.x>

714 Cluskey, S., Ramsden, D.B., 2001. Mechanisms of neurodegeneration in amyotrophic lateral
715 sclerosis. *J. Clin. Pathol. - Mol. Pathol.* 54, 386–392. <https://doi.org/10.1136/mp.54.6.386>

716 Cole, D.E., Evrovski, J., 2000. The clinical chemistry of inorganic sulfate. *Crit. Rev. Clin. Lab.*
717 *Sci.* 37, 299–344. <https://doi.org/10.1080/10408360091174231>

718 De Moura, F.F., Moursi, M., Lubowa, A., Ha, B., Boy, E., Oguntona, B., Sanusi, R.A., Maziya-
719 Dixon, B., 2015. Cassava Intake and Vitamin A Status among Women and Preschool
720 Children in Akwa-Ibom, Nigeria. *PLoS One* 10, e0129436.
721 <https://doi.org/10.1371/journal.pone.0129436>

722 Diasolua Ngudi, D., 2005. Konzo and cassava toxicity: a study of associated nutritional factors in
723 the Popokabaka District, Democratic Republic of Congo. Ph D. thesis. Universiteit Gent,
724 Belgium.

725 Donaghy, M., 1999. Classification and clinical features of motor neurone diseases and motor
726 neuropathies in adults. *J. Neurol.* 246, 331–333. <https://doi.org/10.1007/s004150050358>

727 Egekeze, J.O., Oehme, F.W., 1980. Cyanides and their toxicity: a literature review. *Tijdschr.*
728 *Diergeneeskd.* 105. <https://doi.org/10.1080/01652176.1980.9693766>

729 Ernesto, M., Cardoso, A.P., Nicala, D., Mirione, E., Massaza, F., Cliff, J., Haque, M.R.,
730 Bradbury, J.H., 2002. Persistent konzo and cyanogen toxicity from cassava in northern
731 Mozambique. *Acta Trop.* 82, 357–362. [https://doi.org/10.1016/S0001-706X\(02\)00042-6](https://doi.org/10.1016/S0001-706X(02)00042-6)

732 Essers, A.J.A., Alsen, P., Rosling, H., 1992. Insufficient processing of cassava induced acute
733 intoxications and the paralytic disease konzo in a rural area of mozambique. *Ecol. Food*
734 *Nutr.* 27, 17–27. <https://doi.org/10.1080/03670244.1992.9991222>

735 FAO, 2019. FAOSTAT [WWW Document]. URL <http://www.fao.org/faostat/en/#data/QC>
736 (accessed 12.1.20).

737 Food and Agriculture Organization, 2013. Save and Grow : Cassava - A guide to sustainable
738 production intensification. Roma.

739 German, W.F., Messinger, E., Herman, M., 1949. Toxicity of thiocyanates used in treatment of
740 hypertension. *Ann. Intern. Med.* 30, 1054–1059. [https://doi.org/10.7326/0003-4819-30-5-](https://doi.org/10.7326/0003-4819-30-5-1054)
741 1054

742 Gessain, A., Mahieux, R., 2012. Tropical spastic paraparesis and HTLV-1 associated
743 myelopathy: Clinical, epidemiological, virological and therapeutic aspects. *Rev. Neurol.*
744 (Paris). 168, 257–269. <https://doi.org/10.1016/j.neurol.2011.12.006>

745 Getahun, H., Lambein, F., Vanhoorne, M., Stuyft, P. Van Der, 2002. Pattern and associated

746 factors of the neuroleptism epidemic in Ethiopia 7, 118–124.

747 Gratton, S.M., Lam, B.L., 2014. Visual loss and optic nerve head swelling in thiamine deficiency
748 without prolonged dietary deficiency. *Clin. Ophthalmol.* 8, 1021–1024.
749 <https://doi.org/10.2147/OPHTH.S64228>

750 Gyamfi, O.A., Bortey-Sam, N., Mahon, S.B., Brenner, M., Rockwood, G.A., Logue, B.A., 2019.
751 Metabolism of Cyanide by Glutathione To Produce the Novel Cyanide Metabolite 2-
752 Aminothiazoline-4-oxoaminoethanoic Acid. *Chem. Res. Toxicol.* 32, 718–726.
753 <https://doi.org/10.1021/acs.chemrestox.8b00384>

754 Haque, M.R., Bradbury, J.H., 1999. Simple method for determination of thiocyanate in urine.
755 *Clin. Chem.* 45, 1459–1464.

756 Hawkinson, J.E., Espitia, S.A., 1997. Effects of thiocyanate and AMPA receptor ligands on (S) -
757 5-fluorowillardiine, (S) -AMPA and (R,S) -AMPA binding. *Eur. J. Pharmacol.* 329, 213–
758 221. [https://doi.org/10.1016/S0014-2999\(97\)89182-0](https://doi.org/10.1016/S0014-2999(97)89182-0)

759 Howlett, W.P., Brubaker, G., Mlingi, N., Rosling, H., 1992. A geographical cluster of konzo in
760 Tanzania. *J. Trop. Geogr. Neurol.* 2, 102–108.

761 Howlett, W.P., Brubaker, G.R., Mlingi, N., Rosling, H., 1990. Konzo, an epidemic upper motor
762 neuron disease studied in Tanzania. *Brain* 113 (Pt 1, 223–235.

763 Imakumbili, M.L.E., Semu, E., Semoka, J.M.R., Abass, A., Mkamilo, G., 2019. Farmers’
764 perceptions on the causes of cassava root bitterness: A case of konzo-affected mtwara
765 region, Tanzania. *PLoS One* 14, 1–14. <https://doi.org/10.1371/journal.pone.0215527>

766 Johnson, J.M., Fox, V., 2018. Beyond Thiamine: Treatment for Cognitive Impairment in
767 Korsakoff’s Syndrome. *Psychosomatics* 59, 311–317.
768 <https://doi.org/10.1016/j.psych.2018.03.011>

769 Joint FAO/WHO Food Standards Programme. Codex Alimentarius Commission, 2009. Codex
770 Committee On Contaminants In Foods. Third Session. Discussion Paper On Cyanogenic
771 Glycosides.

772 Kambale, K.J., Ali, E.R., Sadiki, N.H., Kayembe, K.P., Mvumbi, L.G., Yandju, D.L., Boivin,
773 M.J., Boss, G.R., Stadler, D.D., Lambert, W.E., Lasarev, M.R., Okitundu, L.A., Mumba
774 Ngoyi, D., Banea, J.P., Tshala-Katumbay, D.D., 2017. Lower sulfurtransferase
775 detoxification rates of cyanide in konzo—A tropical spastic paralysis linked to cassava
776 cyanogenic poisoning. *Neurotoxicology* 59, 256–262.
777 <https://doi.org/10.1016/j.neuro.2016.05.016>

778 Kashala-Abotnes, E., Okitundu, D., Mumba, D., Boivin, M.J., Tylleskär, T., Tshala-Katumbay,
779 D., 2018. Konzo: a distinct neurological disease associated with food (cassava) cyanogenic

780 poisoning. *Brain Res. Bull.* 0–1. <https://doi.org/10.1016/j.brainresbull.2018.07.001>

781 Kasonde, J.M., 2015. Ministerial Statement On Konzo - Presented to parliament by the Minister
782 of Health.

783 Kassa, R.M., Kasensa, N.L., Monterroso, V.H., Kayton, R.J., Klimek, J.E., David, L.L.,
784 Lunganza, K.R., Kayembe, K.T., Bentivoglio, M., Juliano, S.L., Tshala-Katumbay, D.D.,
785 2011. On the biomarkers and mechanisms of konzo, a distinct upper motor neuron disease
786 associated with food (cassava) cyanogenic exposure. *Food Chem. Toxicol.* 49, 571–578.
787 <https://doi.org/10.1016/j.fct.2010.05.080>

788 Kassubek, J., Ludolph, A.C., Muller, H.P., 2012. Neuroimaging of motor neuron diseases. *Ther.*
789 *Adv. Neurol. Disord.* 5, 119–127. <https://doi.org/10.1177/1756285612437562>

790 Kimani, S., Moterroso, V., Lasarev, M., Kipruto, S., Bukachi, F., Maitai, C., David, L., Tshala-
791 Katumbay, D., 2013. Carbamoylation correlates of cyanate neuropathy and cyanide
792 poisoning: Relevance to the biomarkers of cassava cyanogenesis and motor system toxicity.
793 *Springerplus* 2, 1–8. <https://doi.org/10.1186/2193-1801-2-647>

794 Kimani, S., Moterroso, V., Morales, P., Wagner, J., Kipruto, S., Bukachi, F., Maitai, C., Tshala-
795 Katumbay, D., 2014a. Cross-species and tissue variations in cyanide detoxification rates in
796 rodents and non-human primates on protein-restricted diet. *Food Chem. Toxicol.* 66, 203–
797 209. <https://doi.org/10.1016/j.fct.2014.01.047>

798 Kimani, S., Sinei, K., Bukachi, F., Tshala-Katumbay, D., Maitai, C., 2014b. Memory deficits
799 associated with sublethal cyanide poisoning relative to cyanate toxicity in rodents. *Metab.*
800 *Brain Dis.* 29, 105–112. <https://doi.org/10.1007/s11011-013-9459-2>

801 Kimani, S.T., 2011. Neurotoxicity of cassava cyanogens in rodents and non-human primates.
802 University of Nairobi.

803 Lantum, H., 1998. Spastic paraparesis konzo in the Garoua Boulai Health District, East Province
804 - Cameroon: a hidden endemic disease. Monograph 85.

805 Lavigne, J., Roy, L., Lefebvre, L.F., 2004. Section B - 1 : Les cyanures, in: *Guide Toxicologique*
806 *Pour Les Urgences En Santé Environnementale.* p. 25.

807 Liu, D., Ke, Z., Luo, J., 2017. Thiamine Deficiency and Neurodegeneration: the Interplay Among
808 Oxidative Stress, Endoplasmic Reticulum Stress, and Autophagy. *Mol. Neurobiol.* 54,
809 5440–5448. <https://doi.org/10.1007/s12035-016-0079-9>

810 Lucasse, C., 1952. Le Kitondji : une paralysie spastique. *Ann Soc Belge Med Trop* 33, 391–401.

811 Lundquist, P., Gedal, B.K., Nilsson, L., 1995a. An Improved Method for Determination of
812 Thiocyanate in Plasma and Urine 1). *Eur. J. Clin. Chem. Clin. Biochem.* 33, 343–349.
813 <https://doi.org/10.1515/cclm.1995.33.6.343>

814 Lundquist, P., Kågedal, B., Nilsson, L., Rosling, H., 1995b. Analysis of the cyanide metabolite 2-
815 aminothiazoline-4-carboxylic acid in urine by high-performance liquid chromatography.
816 *Anal. Biochem.* <https://doi.org/10.1006/abio.1995.1310>

817 Madiyal, A., Ajila, V., Babu, S.G., Hegde, S., Kumari, S., Madi, M., Achalli, S., Alva, P., Ullal,
818 H., 2018. Status of thiocyanate levels in the serum and saliva of non-smokers, ex-smokers
819 and smokers. *Afr. Health Sci.* 18, 727–736. <https://doi.org/10.4314/ahs.v18i3.31>

820 Maiorka, P.C., Go, S.L., 2002. Neuropathologic study of long term cyanide administration to
821 goats 40, 1693–1698.

822 Makene, W.J., Wilson, J., 1972. Biochemical studies in Tanzanian patients with ataxic tropical
823 neuropathy. *J. Neurol. Neurosurg. Psychiatry* 35, 31–33.

824 Malouff, J.M., Schutte, N.S., 2017. A meta-analysis of the relationship between anxiety and
825 telomere length. *Anxiety, Stress Coping* 30, 264–272.
826 <https://doi.org/10.1080/10615806.2016.1261286>

827 Martel, J.L., Kerndt, C.C., Franklin, D.S., 2020. Vitamin B1 (Thiamine), in: *StatPearls. Treasure*
828 *Island (FL).*

829 Mbelesso, P., Yogo, M.-L., Yangatimbi, E., Paul-Senekian, V. de, Nali, N.M., Preux, P.-M.,
830 2009. Outbreak of konzo disease in health region No. 2 of the Central African Republic.
831 *Rev. Neurol. (Paris)*. 165, 466–470. <https://doi.org/10.1016/j.neurol.2008.10.020>

832 Ministry of health Mozambique, 1984. Mantakassa: an epidemic of spastic paraparesis associated
833 with chronic cyanide intoxication in a cassava staple area of Mozambique. 1. Epidemiology
834 and clinical and laboratory findings in patients. Ministry of Health, Mozambique. *Bull.*
835 *World Health Organ.* 62, 477–484.

836 Mlingi, N., Kimatta, S., Rosling, H., 1991. Konzo, a paralytic disease observed in southern
837 Tanzania. *Trop Doct* 21, 24–25. <https://doi.org/10.1177/004947559102100110>

838 Mlingi, N., Nkya, S., Tatala, S., Rashid, S., Bradbury, H., 2011. Recurrence of konzo in southern
839 Tanzania: rehabilitation and prevention using the wetting method. *Food Chem. Toxicol.* 49,
840 673–677. <https://doi.org/10.1016/j.fct.2010.09.017>

841 Mlingi, N., Poulter, N., Rosling, H., 1992. An outbreak of acute intoxications from consumption
842 of insufficiently processed cassava in Tanzania. *Nutr. Res.* 12, 677–687.

843 Mlingi, N.L. V, Bainbridge, Z.A., Poulter, N.H., Rosling, H., 1995. Critical stages in cyanogen
844 removal during cassava processing in southern Tanzania. *Food Chem.* 53, 29–33.
845 [https://doi.org/10.1016/0308-8146\(95\)95782-2](https://doi.org/10.1016/0308-8146(95)95782-2)

846 Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic
847 reviews and meta- analyses: the PRISMA statement. *Ann. Intern. Med.* 151, 264–269.

- 848 Montagnac, J.A., Davis, C.R., Tanumihardjo, S.A., 2009a. Nutritional value of cassava for use as
849 a staple food and recent advances for improvement. *Compr. Rev. Food Sci. Food Saf.* 8,
850 181–194. <https://doi.org/10.1111/j.1541-4337.2009.00077.x>
- 851 Montagnac, J.A., Davis, C.R., Tanumihardjo, S.A., 2009b. Processing techniques to reduce
852 toxicity and antinutrients of Cassava for use as a staple food. *Compr. Rev. Food Sci. Food*
853 *Saf.* 8, 17–27. <https://doi.org/10.1111/j.1541-4337.2008.00064.x>
- 854 Murphy, D.E., Snowhill, E.W., Williams, M., 1987. Characterization of quisqualate recognition
855 sites in rat brain tissue using DL-[3H]α-amino-3-hydroxy-5-methylisoxazole-4-propionic
856 acid (AMPA) and a filtration assay. *Neurochem. Res.* 12, 775–781.
857 <https://doi.org/10.1007/BF00971514>
- 858 Mwanza, J.-C., Lysebo, D.E., Kayembe, D.L., Tshala-Katumbay, D., Nyamabo, L.K., Tylleskar,
859 T., Plant, G.T., 2003. Visual evoked potentials in konzo, a spastic paraparesis of acute onset
860 in Africa. *Ophthalmol. J. Int. d’ophtalmologie. Int. J. Ophthalmol. Zeitschrift fur*
861 *Augenheilkd.* 217, 381–386. <https://doi.org/73066>
- 862 Nambisan, B., 2011. Strategies for elimination of cyanogens from cassava for reducing toxicity
863 and improving food safety. *Food Chem. Toxicol.* 49, 690–693.
864 <https://doi.org/10.1016/j.fct.2010.10.035>
- 865 National Research Council (US) Committee on Acute Exposure Guideline Levels; National
866 Research Council (US) Committee on Toxicology, 2009. *Acute Exposure Guideline Levels*
867 *for Selected Airborne Chemicals: Volume 7.*
- 868 Ngudi, D.D., Kuo, Y.-H., Lambein, F., 2003. Cassava cyanogens and free amino acids in raw and
869 cooked leaves. *Food Chem. Toxicol.* 41, 1193–1197. [https://doi.org/10.1016/S0278-](https://doi.org/10.1016/S0278-6915(03)00111-X)
870 [6915\(03\)00111-X](https://doi.org/10.1016/S0278-6915(03)00111-X)
- 871 Ngudi, D.D., Kuo, Y.-H., Van Montagu, M., Lambein, F., 2012. Research on motor neuron
872 diseases konzo and neuroletharism: trends from 1990 to 2010. *PLoS Negl. Trop. Dis.* 6,
873 e1759. <https://doi.org/10.1371/journal.pntd.0001759>
- 874 Nhassico, D., Bradbury, J.H., Cliff, J., Majonda, R., Cuambe, C., Denton, I.C., Foster, M.P.,
875 Martins, A., Cumbane, A., Siteo, L., Pedro, J., Muquingue, H., 2016. Use of the wetting
876 method on cassava flour in three konzo villages in Mozambique reduces cyanide intake and
877 may prevent konzo in future droughts. *Food Sci. Nutr.* 4, 555–561.
878 <https://doi.org/10.1002/fsn3.317>
- 879 Nimni, M.E., Han, B., Cordoba, F., 2007. Are we getting enough sulfur in our diet? *Nutr. Metab.*
880 *(Lond).* 4, 24. <https://doi.org/10.1186/1743-7075-4-24>
- 881 Nunn, P.B., Lyddiard, J.R.A., Christopher Perera, K.P.W., 2011. Brain glutathione as a target for

882 aetiological factors in neuroletharism and konzo. *Food Chem. Toxicol.* 49, 662–667.
883 <https://doi.org/10.1016/j.fct.2010.08.037>

884 Nzwalo, H., Cliff, J., 2011. Konzo: from poverty, cassava, and cyanogen intake to toxico-
885 nutritional neurological disease. *PLoS Negl. Trop. Dis.* 5, e1051.
886 <https://doi.org/10.1371/journal.pntd.0001051>

887 Okitundu, Luwa E-Andjofono Daniel, Ayanne, M.-T.S., Makila-Mabe, G.B., Banea, J.-P.M.,
888 Ngoy, D.M., Boivin, M., Tamfum-Muyembe, J.-J., Tshala-Katumbay, D., 2018. Konzo
889 global neurological index: a clinical marker of susceptibility and severity of neurocognitive
890 deficits in children living in konzo-affected areas. *African J. Neurol. Sci.* 37, 51–62.
891 Okitundu, Luwa E-Andjafono Daniel, Ayanne, M.T.S.S., Makila-Mabe, G.B., Mayambu, J.P.B.,
892 Ngoyi, D.M., Boivin, M., Tamfum-Muyembe, J.J., Tshala-Katumbay, D., 2018.
893 Socioemotional disorders in children living in Konzo-affected areas, an epidemic paralytic
894 disease associated with cyanide poisoning from food in sub-Saharan Africa. *Pan Afr. Med.*
895 *J.* 31, 1–11. <https://doi.org/10.11604/pamj.2018.31.118.11640>

896 Okitundu, L.E.-A.D., Bumoko, M.-M.G., Sombo, M.T.S.A., Kambale, J.K., Mashukano, N.,
897 Kazadi, K.T., Mumba, N.D., Boivin, M.J., Tamfum-Muyembe, J.-J., Banea Mayambu, J.-P.,
898 Tshala-Katumbay, D., 2014. Persistence of konzo epidemics in Kahemba, Democratic
899 Republic of Congo. phenomenological and socio-economic aspects. *Pan Afr. Med. J.* 18,
900 213. <https://doi.org/10.11604/pamj.2014.18.213.4572>

901 Oluwole, O.S.A., 2015. Cyclical konzo epidemics and climate variability. *Ann. Neurol.* 77, 371–
902 380. <https://doi.org/10.1002/ana.24334>

903 Oluwole, O.S.A., Oludiran, A., 2013a. Normative concentrations of urine thiocyanate in cassava
904 eating communities in Nigeria. *Int. J. Food Sci. Nutr.* 64, 1036–1041.
905 <https://doi.org/10.3109/09637486.2013.825697>

906 Oluwole, O.S.A., Oludiran, A., 2013b. Geospatial association of endemicity of ataxic
907 polyneuropathy and highly cyanogenic cassava cultivars. *Int. J. Health Geogr.* 12, 41.
908 <https://doi.org/10.1186/1476-072X-12-41>

909 Osuntokun, B.O., Durowoju, J.E., McFarlane, H., Wilson, J., 1968. Plasma Amino-acids in the
910 Nigerian Nutritional Ataxic Neuropathy. *Br. Med. J.* 3, 647–649.
911 <https://doi.org/10.1136/bmj.3.5619.647>

912 Padmaja, G., 1995. Cyanide Detoxification in Cassava for Food and Feed Uses. *Crit. Rev. Food*
913 *Sci. Nutr.* 35, 299–339. <https://doi.org/10.1080/10408399509527703>

914 Peterson, C.M., Tsairis, P., Onishi, A., Lu, Y.S., Grady, R., 1974. Sodium cyanate induced
915 polyneuropathy in patients with sickle-cell disease. *Ann. Intern. Med.* 81, 152–158.

916 <https://doi.org/10.7326/0003-4819-81-2-152>

917 Pimenta, E., Calhoun, D.A., Oparil, S., 2010. Hypertensive Emergencies, Second Edi. ed, Cardiac
918 Intensive Care. Elsevier Inc. <https://doi.org/10.1016/B978-1-4160-3773-6.10028-X>

919 Posada-Vergara, M.P., Montanheiro, P., Fukumori, L.M.I., Bonasser, F., Duarte, A.J.D.S.,
920 Penalva De Oliveira, A.C., Casseb, J., 2006. Clinical and epidemiological aspects of HTLV-
921 II infection in São Paulo, Brazil: Presence of tropical spastic paraparesis/HTLV-associated
922 myelopathy (TSP/HAM) simile diagnosis in HIV-1-co-infected subjects. *Rev. Inst. Med.
923 Trop. Sao Paulo* 48, 207–210.

924 Pourhassan, M., Angersbach, B., Lueg, G., Klimek, C.N., Wirth, R., 2019. Blood Thiamine Level
925 and Cognitive Function in Older Hospitalized Patients. *J. Geriatr. Psychiatry Neurol.* 32, 90–
926 96. <https://doi.org/10.1177/0891988718819862>

927 Rivadeneyra-Domínguez, E., Rodríguez-Landa, J.F., 2020. Preclinical and clinical research on
928 the toxic and neurological effects of cassava (*Manihot esculenta* Crantz) consumption.
929 *Metab. Brain Dis.* 35, 65–74. <https://doi.org/10.1007/s11011-019-00522-0>

930 Rivadeneyra-Dominguez, E., Rodriguez-Landa, J.F., Article, O., 2016. Motor impairments
931 induced by microinjection of linamarin in the dorsal hippocampus of Wistar rats. *Neurologia*
932 31, 516–522. <https://doi.org/10.1016/j.nrl.2014.10.018>

933 Rivadeneyra-Domínguez, E., Vázquez-Luna, a., Díaz-Sobac, R., Eduardo Briones-Céspedes, E.,
934 Rodríguez-Landa, J.F., 2015. Contribution of hippocampal area CA1 to acetone
935 cyanohydrin-induced loss of motor coordination in rats. *Neurologia* 32, 1–6.
936 <https://doi.org/10.1016/j.nrl.2015.11.010>

937 Rivadeneyra-Domínguez, E., Vázquez-Luna, A., Rodríguez-Landa, J.F., Díaz-Sobac, R., 2013.
938 Neurotoxic effect of linamarin in rats associated with cassava (*Manihot esculenta* Crantz)
939 consumption. *Food Chem. Toxicol.* 59, 230–235. <https://doi.org/10.1016/j.fct.2013.06.004>

940 Rocha, J.A., Reis, C., Simões, F., Fonseca, J., Mendes Ribeiro, J., 2005. Diagnostic investigation
941 and multidisciplinary management in motor neuron disease. *J. Neurol.* 252, 1435–1447.
942 <https://doi.org/10.1007/s00415-005-0007-9>

943 Rosling, H., Gessain, A., de Thé, G., Ebondo, N., Banea, M., Bikangi, N., Kinjanja, K., Nunga,
944 K., 1988. Tropical and epidemic spastic paraparesis are different. *Lancet* MAY 28, 1222–
945 1223.

946 Ross, S.M., Roy, D.N., Spencer, P.S., 1989. β -N-Oxalylamino-L-Alanine Action on Glutamate
947 Receptors. *J. Neurochem.* 53, 710–715. <https://doi.org/10.1111/j.1471-4159.1989.tb11762.x>

948 Sanders, J.L., Newman, A.B., 2013. Telomere length in epidemiology: A biomarker of aging,
949 age-related disease, both, or neither? *Epidemiol. Rev.* 35, 112–131.

950 <https://doi.org/10.1093/epirev/mxs008>

951 Santisopasri, V., Kurotjanawong, K., Chotineeranat, S., Piyachomkwan, K., Sriroth, K., Oates,
952 C.G., 2001. Impact of water stress on yield and quality of cassava starch. *Ind. Crops Prod.*
953 13, 115–129. [https://doi.org/10.1016/S0926-6690\(00\)00058-3](https://doi.org/10.1016/S0926-6690(00)00058-3)

954 Sawalha, K., Gonzalez-Toledo, E., Hussein, O., 2019. Role of Magnetic Resonance Imaging in
955 Diagnosis of Motor Neuron Disease: Literature Review and Two Case Illustrations. *Perm. J.*
956 23, 1–7. <https://doi.org/10.7812/TPP/18-131>

957 Schulz, V., 1984. Clinical Pharmacokinetics of Nitroprusside, Cyanide, Thiosulphate and
958 Thiocyanate. *Clin. Pharmacokinet.* 9, 239–251. [https://doi.org/10.2165/00003088-](https://doi.org/10.2165/00003088-198409030-00005)
959 [198409030-00005](https://doi.org/10.2165/00003088-198409030-00005)

960 Shaw, C., Papayannopoulou, T., Stamatoyannopoulos, G., 1974. Neuropathology of Cyanate
961 Toxicity in Rhesus Monkeys 176, 166–176.

962 Shaw, P.J., 2005. Molecular and cellular pathways of neurodegeneration in motor neurone
963 disease. *J. Neurol. Neurosurg. Psychiatry* 76, 1046–1057.
964 <https://doi.org/10.1136/jnnp.2004.048652>

965 Siddiqi, O.K., Kapina, M., Kumar, R., Ngomah Moraes, A., Kabwe, P., Mazaba, M.L.,
966 Hachaambwa, L., Ng'uni, N.M., Chikoti, P.C., Morel-Espinosa, M., Jarrett, J.M., Baggett,
967 H.C., Chizema-Kawesha, E., 2020. Konzo outbreak in the Western Province of Zambia.
968 *Neurology* 94, E1495–E1501. <https://doi.org/10.1212/WNL.00000000000009017>

969 Soler-martín, C., Riera, J., Seoane, A., Cutillas, B., Ambrosio, S., Boadas-vaello, P., Llorens, J.,
970 2010. The targets of acetone cyanohydrin neurotoxicity in the rat are not the ones expected
971 in an animal model of konzo ☆. *Neurotoxicol. Teratol.* 32, 289–294.
972 <https://doi.org/10.1016/j.ntt.2009.11.001>

973 Spencer, P.S., 1999. Food toxins, ampa receptors, and motor neuron diseases. *Drug Metab. Rev.*
974 31, 561–587. <https://doi.org/10.1081/DMR-100101936>

975 Spencer, P.S., Palmer, V.S., 2012. Interrelationships of undernutrition and neurotoxicity: Food
976 for thought and research attention. *Neurotoxicology* 33, 605–616.
977 <https://doi.org/10.1016/j.neuro.2012.02.015>

978 Spencer, P.S., Roy, D.N., Ludolph, A., Hugon, J., Dwivedi, M.P., Schaumburg, H.H., 1986.
979 Lathyrism: evidence for role of the neuroexcitatory aminoacid BOAA. *Lancet* 2, 1066–1067.
980 [https://doi.org/10.1016/s0140-6736\(86\)90468-x](https://doi.org/10.1016/s0140-6736(86)90468-x)

981 Sreeja, V.G., Nagahara, N., Li, Q., Minami, M., 2003. New aspects in pathogenesis of konzo:
982 neural cell damage directly caused by linamarin contained in cassava (*Manihot esculenta*
983 *Crantz*). *Br. J. Nutr.* 90, 467–472. <https://doi.org/10.1079/BJN2003902>

- 984 Stanke, C., Kerac, M., Prudhomme, C., Medlock, J., Murray, V., 2013. Health Effects of
985 Drought: A Systematic Review of the Evidence. *PLoS Curr.* 1–36.
986 <https://doi.org/10.1371/currents.dis.7a2cee9e980f91ad7697b570bcc4b004>
- 987 Szabo, E.A., Jansson, E., Miles, D., Hambridge, T., Stanley, G., Baines, J., Brent, P., 2010.
988 Responding to Incidents of Low Level Chemical Contamination in Food, First Edit. ed,
989 Ensuring Global Food Safety. Elsevier Inc. [https://doi.org/10.1016/B978-0-12-374845-](https://doi.org/10.1016/B978-0-12-374845-4.00024-2)
990 [4.00024-2](https://doi.org/10.1016/B978-0-12-374845-4.00024-2)
- 991 Tan, S.L., 1995. Factors affecting cyanide content in cassava (*Manihot esculenta* Crantz). *J. Trop.*
992 *Agric. Food Sci.* 23, 121–131.
- 993 Teles, F.F.F., 2002. Chronic poisoning by hydrogen cyanide in cassava and its prevention in
994 Africa and Latin America. *Food Nutr. Bull.* 23, 407–412.
- 995 Tor-Agbidye, J., Palmer, V.S., Lasarev, M.R., Craig, A.M., Blythe, L.L., Sabri, M.I., Spencer,
996 P.S., 1999. Bioactivation of cyanide to cyanate in sulfur amino acid deficiency: relevance to
997 neurological disease in humans subsisting on cassava. *Toxicol. Sci.* 50, 228–235.
- 998 Tor-Agbidye, John, Palmer, V.S., Spencer, P.S., Craig, A.M., Blythe, L.L., Sabri, M.I., 1999.
999 Sodium cyanate alters glutathione homeostasis in rodent brain: Relationship to
1000 neurodegenerative diseases in protein-deficient malnourished populations in Africa. *Brain*
1001 *Res.* 820, 12–19. [https://doi.org/10.1016/S0006-8993\(98\)01343-2](https://doi.org/10.1016/S0006-8993(98)01343-2)
- 1002 Tshala-Katumbay, D., Edebol Eeg-Olofsson, K., Kazadi-Kayembe, T., Fällmar, P., Tylleskär, T.,
1003 Kayembe-Kalula, T., 2002. Abnormalities of somatosensory evoked potentials in konzo--an
1004 upper motor neuron disorder. *Clin. Neurophysiol.* 113, 10–15.
- 1005 Tshala-Katumbay, Desire, Eeg-Olofsson, K.E., Kazadi-Kayembe, T., Tylleskär, T., Fällmar, P.,
1006 2002. Analysis of motor pathway involvement in konzo using transcranial electrical and
1007 magnetic stimulation. *Muscle and Nerve* 25, 230–235. <https://doi.org/10.1002/mus.10029>
- 1008 Tshala-Katumbay, D., Eeg-Olofsson, K.E., Tylleskar, T., Kazadi-Kayembe, T., 2001.
1009 Impairments, disabilities and handicap pattern in konzo--a non-progressive spastic
1010 para/tetraparesis of acute onset. *Disabil. Rehabil.* 23, 731–736.
- 1011 Tshala-Katumbay, D., Lukusa, V.M., Eeg-Olofsson, K.E., 2000. EEG Findings in Konzo: A
1012 Spastic Para/Tetraparesis of Acute Onset. *Clin. EEG Neurosci.* 31, 196–200.
1013 <https://doi.org/10.1177/155005940003100408>
- 1014 Tshala-katumbay, D.D., Ngombe, N.N., Okitundu, D., David, L., Westaway, S.K., Boivin, M.J.,
1015 Mumba, N.D., Banea, J., 2016. Cyanide and the human brain : perspectives from a model of
1016 food (cassava) poisoning 1378, 50–57. <https://doi.org/10.1111/nyas.13159>
- 1017 Tshala-katumbay, D.D., Spencer, P.S., 2007. Toxic disorders of the upper motor neuron system,

1018 in: Handbook of Clinical Neurology. pp. 361–370.

1019 Tylleskar, T., 1994. The Causation of Konzo. Studies on a Paralytic Disease in Africa. Uppsala
1020 University.

1021 Tylleskar, T., Banea, M., Bikangi, N., Fresco, L., Persson, L.A., Rosling, H., 1991.
1022 Epidemiological Evidence From Zaire for a Dietary Etiology of Konzo, an Upper Motor-
1023 Neuron Disease. Bull. World Health Organ. 69, 581–589.

1024 Tylleskär, T., Banea, M., Bikangi, N., Nahimana, G., Persson, L.Å., Rosling, H., 1995. Dietary
1025 determinants of a non-progressive spastic paraparesis (konzo): A case-referent study in a
1026 high incidence area of Zaire. Int. J. Epidemiol. 24, 949–956.
1027 <https://doi.org/10.1093/ije/24.5.949>

1028 Tylleskar, T., Banea, M., Bottiger, B., Thorstensson, R., Biberfeld, G., Rosling, H., 1996. Konzo,
1029 an epidemic spastic paraparesis in Africa, is not associated with antibodies to HTLV-I, HIV,
1030 or HIV gag-encoded proteins. J. Acquir. Immune Defic. Syndr. Hum. Retrovirology 12,
1031 317–318.

1032 Tylleskar, T., Howlett, W.P., Rwiza, H.T., Aquilonius, S.M., Stalberg, E., Linden, B., Mandahl,
1033 A., Larsen, H.C., Brubaker, G.R., Rosling, H., 1993. Konzo: a distinct disease entity with
1034 selective upper motor neuron damage. J. Neurol. Neurosurg. Psychiatry 56, 638–643.

1035 Tylleskar, T., Legue, F.D., Kpizingui, E., 1994. Konzo in the Central African Republic.
1036 Neurology 44, 959–961.

1037 Tylleskär, T., Rosling, H., Banea, M., Bikangi, N., Cooke, R.D., Poulter, N.H., 1992. Cassava
1038 cyanogens and konzo, an upper motoneuron disease found in Africa. Lancet 339, 208–211.
1039 [https://doi.org/10.1016/0140-6736\(92\)90006-O](https://doi.org/10.1016/0140-6736(92)90006-O)

1040 Umoh, I.B., Ogunkoya, F.O., Maduagwu, E.N., Oke, O.L., 1985. Effect of thiamin status on the
1041 metabolism of linamarin in rats. Ann. Nutr. Metab. 29, 319–324.

1042 Van Moorhem, Marijke, Decrock, E., De Vuyst, E., De Bock, M., Wang, N., Lambein, F., Van
1043 Den Bosch, L., Leybaert, L., 2011. L-β-N-oxalyl-α,β-diaminopropionic acid toxicity in
1044 motor neurons. Neuroreport 22, 131–135. <https://doi.org/10.1097/WNR.0b013e3283433027>

1045 Van Moorhem, M., Lambein, F., Leybaert, L., 2011. Unraveling the mechanism of β-N-oxalyl-
1046 α,β-diaminopropionic acid (β-ODAP) induced excitotoxicity and oxidative stress, relevance
1047 for neurolathyrism prevention. Food Chem. Toxicol. 49, 550–555.
1048 <https://doi.org/10.1016/j.fct.2010.03.054>

1049 Wang, X., Sundquist, K., Hedelius, A., Palmér, K., Memon, A.A., Sundquist, J., 2017. Leukocyte
1050 telomere length and depression, anxiety and stress and adjustment disorders in primary
1051 health care patients. BMC Psychiatry 17, 1–10. <https://doi.org/10.1186/s12888-017-1308-0>

1052 Wang, Y., Qin, Z.H., 2010. Molecular and cellular mechanisms of excitotoxic neuronal death.
1053 Apoptosis 15, 1382–1402. <https://doi.org/10.1007/s10495-010-0481-0>

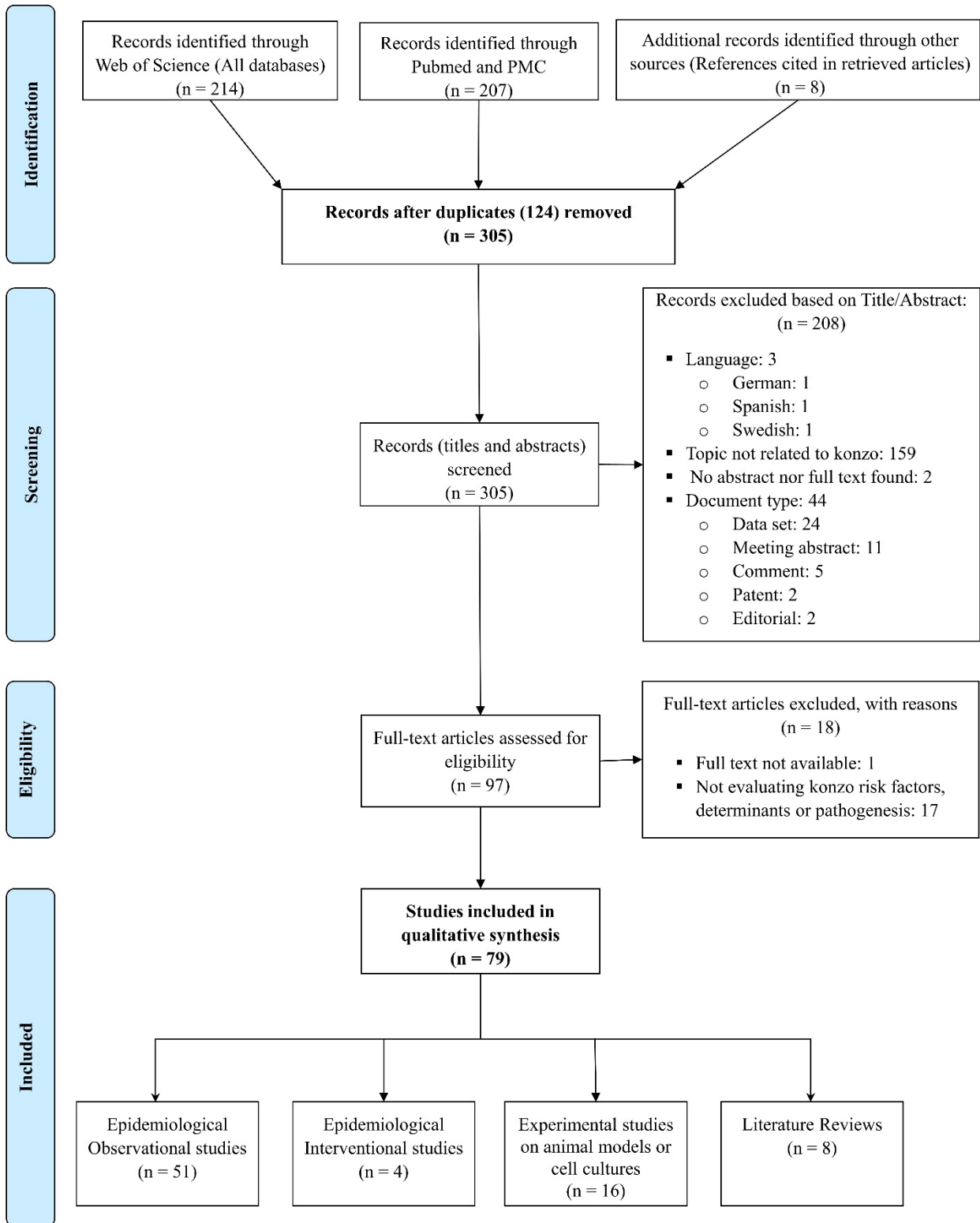
1054 Weyns, Y., Hoex, L., Matthysen, K., 2016. Analysis of the interactive map of artisanal mining
1055 areas in eastern DR Congo: 2015 update. Antwerp.

1056 Woldeamanuel, Y.W., Hassan, A., Zenebe, G., 2012. Neurolathyrism: two Ethiopian case reports
1057 and review of the literature. *J. Neurol.* 259, 1263–1268. [https://doi.org/10.1007/s00415-011-](https://doi.org/10.1007/s00415-011-6306-4)
1058 6306-4

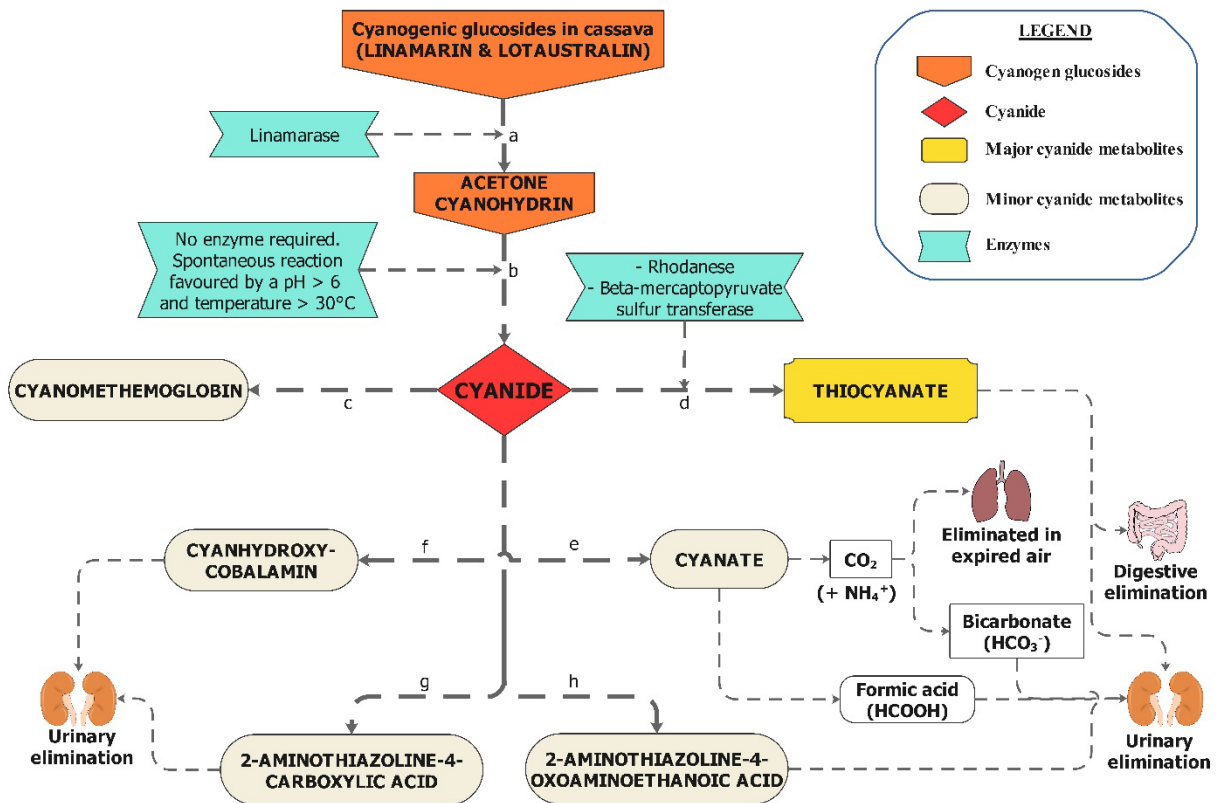
1059 World Health Organization, 2010. First WHO report on neglected tropical diseases: working to
1060 overcome the global impact of neglected tropical diseases, World Health Organization.
1061 <https://doi.org/10.1177/1757913912449575>

1062 World Health Organization, 1996. Konzo - a distinct type of upper motoneuron disease. *Wkly.*
1063 *Epidemiol. Rec.* 71, 225–228.

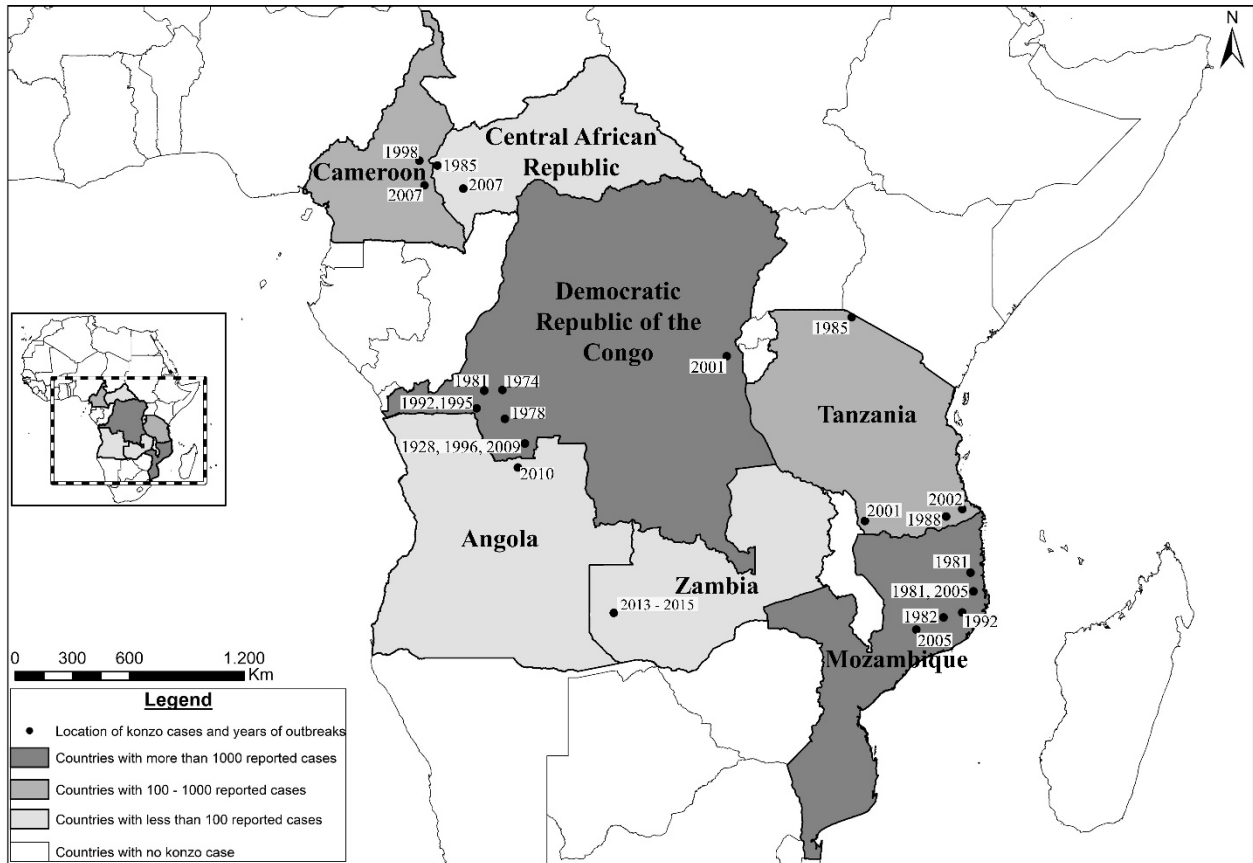
1064 Zaninovic, V., 1999. On the etiology of tropical spastic paraparesis and human T-cell
1065 lymphotropic virus I - Associated myelopathy. *Int. J. Infect. Dis.* 3, 168–177.
1066
1067



1071 **Figure 1. Flowchart summary of the search and selection of the studies.**



1076 **Figure 2. Cyanide detoxification pathways.** During the processing of cassava, its cyanogenic
 1077 glucosides are hydrolyzed by linamarase into acetone cyanohydrin (a). The latter can spontaneously
 1078 break down into cyanide in the small intestine due to the hot (>30°C) and humid environment, with
 1079 a pH>6 (b). Once released in the blood stream, cyanide is rapidly trapped by methemoglobin to
 1080 form cyanmethemoglobin, a stable non-toxic compound (c). But this rapid pathway is quickly
 1081 saturated, a larger amount of cyanide (approximately 80 %) is transformed into thiocyanate, the
 1082 major cyanide metabolite, via trans-sulfuration reactions catalyzed by the rhodanese and beta-
 1083 mercaptopyruvate sulfur transferase (d). This pathway requires the availability of a sulfate donor
 1084 (thiosulfate). In absence of sufficient available thiosulfate, cyanide is detoxified via other (minor)
 1085 pathways including oxidation of cyanide to cyanate, occurring especially in nutritionally
 1086 compromised subjects (e), or its combination with hydroxycobalamin to form
 1087 cyanhydroxycobalamin(f). Cyanide may also react non-enzymatically with cystine to form 2-
 1088 aminothiazoline-4-Carboxylic acid (g), or with glutathione to form 2-aminothiazoline-4-
 1089 oxoaminoethanoic acid (h).



1092 **Figure 3. Locations of (sporadic and epidemic) konzo cases.** This map was generated by ArcGIS
 1093 version 10.3. For more information, see the Supplementary material 1.

1094

Table 1. List of locations where konzo outbreaks have been reported

Country	Province	District	Years	References
The Democratic Republic of the Congo	Bandundu	Kwango	1928; 1978; 1981; 1992; 1995	(Banea et al., 1997; Carton et al., 1986; Lucasse, 1952)
		Kwilu	1974; 1996; 2009	(Banea et al., 2015, 1992; Okitundu et al., 2014; Tylleskar et al., 1991)
	South-Kivu	Mwenga	2001	(Chabwine et al., 2011)
Mozambique	Cabo Delgado	Chiure	1981	(Cliff et al., 2011)
	Nampula	Memba	1981; 2005	(Cliff et al., 2011; Ministry of health Mozambique, 1984; Nhassico et al., 2016)
		Murrupula	1982	(Essers et al., 1992)
		Mogincual	1992	(Cliff et al., 2011, 1997; Ernesto et al., 2002; Nhassico et al., 2016)
	Zambezia	Ile	2005	(Cliff et al., 2011)
Tanzania	Mara	Tarime	1985	(Howlett et al., 1990; Mlingi et al., 2011)
	Mtwara	Masasi	1988	(Mlingi et al., 1991, 2011)
		Mtwara rural	2002	(Mlingi et al., 2011)
		Newala	2002	(Mlingi et al., 2011)
	Ruvuma	Mbinga	2001	(Mlingi et al., 2011)
Central African Republic	Nana-Mambéré	Baboua area	1985	(Tylleskar et al., 1994)
	Nana-Mambéré	Health Region No. 2	2007	(Mbelesso et al., 2009)
Cameroon	East-Province	Garoua boulai	1998	(Lantum, 1998)
		Kadei	2007	(Ciglencéki et al., 2011)
		Lom-et-djerem	2007	(Ciglencéki et al., 2011)
Angola	Lunda-Norte	Caungula	2010	(Allen, 2010)
Zambia	Western Province	Mongu	2013 - 2015	(Kasonde, 2015; Siddiqi 2020)

Table 2 Summary of investigations for infections performed in konzo patients

District/Area, Province (Country)	Year	Investigated Infections	Nb of tested patients	Results	References
Murrupula district, Nampula (Mozambique)	1982	HTLV-1	7	All tests were negative.	(Essers et al., 1992)
Kwango, Bandundu, (D.R.C.*)	1985	HTLV-1 HIV-1	10	All tests (10 serum and 10 CSF samples) were negative.	(Carton et al., 1986; De-The et al., 1989)
Tarime district, Mara Region (Tanzania)	1985	HTLV-1 Syphilis Schistosomiasis	39	All HTLV-1 and Syphilis (VDRL) tests were negative. Schistosoma serology: positive in 8/18 patients (and 3/8 controls).	(Howlett et al., 1990)
Tarime District Mara Region (Tanzania)	1985	HTLV-1 HIV-1&2	61**	All tests were negative.	(De-The et al., 1989)
Masi-Manimba, Bandundu (D.R.C.*)	1987	HTLV-1 HIV-1&2	15	100 % negative for HTLV-1 & HIV.	(De-The et al., 1989; Rosling et al., 1988)
Masi-Manimba, Bandundu (D.R.C.*)	1990	HTLV-1 HIV-1 & 2	3	All tests were negative.	(Tylleskär et al., 1992)
Pay-Kongila, Bandundu (D.R.C.*)	1990	HTLV-1 HIV-1 & 2	3	All tests performed on patients' sera were negative for HTLV-1 & HIV (but 3 out of 15 tested konzo-free controls were positive for HTLV).	(Banea et al., 1992)
Tarime district, Mara Region (Tanzania)	1985 & 1991	HTLV-1 HIV-1 & 2 Syphilis Hepatitis A, B & C	2	All tests (on sera and CSF) were negative.	(Tylleskar et al., 1993)
Masasi district, Mtwara Region (Tanzania)	1991	HTLV-1 HIV-1 & 2	1	All tests were negative.	(Mlingi et al., 1991)
Baboua area, Nana-Mambéré (Central African Republic)	1994	HIV-1/2 HTLV-1/2	13	All tests were negative for HTLV-1/2. 10/13 were negative for HIV-1/2. 3/13 presented an unspecific reactivity for HIV-1/2.	(Tylleskar et al., 1994)
Popokabaka, Bandundu (D.R.C.*)	1996	HIV-1/2 HTLV-1/2	38	All tests were negative.	(Tshala-Katumbay et al., 2001)
Unspecified village, Bandundu (D.R.C.*)	1996	HIV-1 HTLV-1	33	100 % of sera were negative for HIV-1 antibodies on ELISA and none fulfilled the criteria for a positive HIV-1 Western blot reaction.	(Tylleskar et al., 1996)
Burhinyi, South-Kivu (D.R.C.*)	2005	HIV-1/2	29	1 positive test [using ELISA (Biorad) and Determine (Abott) kits].	(Chabwine et al., 2011)
Health-Region N°2 (Central African Republic)	2007	HIV-1/2	81	All tests were negative.	(Mbelesso et al., 2009)
Kahemba, Bandundu (D.R.C.*)	2011	HIV-1/2 HTLV-1/2	123**	All tests were negative.	(Boivin et al., 2013; Bumoko et al., 2015; Kambale et al., 2017; Okitundu et al., 2014)

Nb: Number; HIV: Human Immunodeficiency Virus; HTLV: Human T-lymphotropic virus; D.R.C.*: The Democratic Republic of the Congo. From 1971 to 1997, D.R.C. was called Zaïre;

** Including the 39 patients from Howlett et al., 1990

Appendix A. Detailed data for Figure 3

This figure shows all locations where konzo cases (both epidemic and sporadic) have been reported. This information was collected from articles retrieved from the literature search.

Following data were recorded from articles reporting konzo cases:

- the country, province(s), district(s), and when available, the health area(s) where the cases were recorded,
- the number of reported cases,
- the year of appearance of konzo (if available) or the year when cases were recorded.

Subsequently, geographic coordinates of corresponding health-areas or districts were extracted from Google maps (<https://maps.google.com/>).

Collected data (see Table S1 below) was compiled in an excel spreadsheet and saved in CSV format. The CSV file was imported in ArcGIS 10.3, and converted to a shapefile format.

The African administrative boundaries shapefile was downloaded from the GADM database (www.gadm.org), version 2.5, July 2015.

Both shapefiles were used as vector layers in ArcGIS 10.3 to plot konzo locations (years of appearance) on the map.

Table S1. Geographic coordinates of locations where konzo cases have been reported.

Country	Province	District	Health area	Years	Latitude	Longitude
Angola	Lunda-Norte	Caungula		2010	-8.4270	18.6306
Cameroon	East-Province	Garoua Boulai		1998	6.0290	13.9842
Cameroon	East-Province	Kadei		2007	4.8675	14.2260
Central African Republic	Nana-Mambéré	Baboua area	Baboua area	1985	5.8033	14.8306
Central African Republic	Nana-Mambéré	Health Region No2		2007	4.7136	16.0544
D.R.C.	Bandundu	Kwango	Kahemba	1928, 1996, 2009	-7.2958	18.9621
D.R.C.	Bandundu	Kwango	Popokabaka	1992, 1995	-5.6338	16.6837
D.R.C.	Bandundu	Kwango		1978	-6.1332	18.0155
D.R.C.	Bandundu	Kwango		1981	-4.8089	17.0429
D.R.C.	Bandundu	Kwilu	Masi-Manimba	1974	-4.7714	17.8989
D.R.C.	South-Kivu	Mwenga	Burhinyi	2001	-3.1805	28.4734
Mozambique	Cabo Delgado	Chiure		1981	-13.3760	39.9589
Mozambique	Nampula	Memba	Cava	1981, 2005	-14.2584	40.0981
Mozambique	Nampula	Mogincual	Mujocojo	1992	-15.2552	39.5702
Mozambique	Nampula	Murupula		1982	-15.4884	38.6874
Mozambique	Zambezia	Ile		2005	-16.0627	37.4067
Tanzania	Mara	Tarime		1985	-1.3433	34.3629
Tanzania	Mtwara	Masasi		1988	-10.7323	38.8089
Tanzania	Mtwara	Mtwara Rural		2002	-10.3860	39.5704
Tanzania	Ruvuma	Mbinga		2001	-10.9428	34.9836
Zambia	Western Province	Mongu	Lwatembu area	2013-2015	-15.2737	23.1503

D.R.C.: The Democratic Republic of the Congo