Konzo outbreak in the Western Province of Zambia

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Abstract

Objective

To identify the etiology of an outbreak of spastic paraparesis among women and children in the Western Province of Zambia suspected to be konzo.

Methods

We conducted an outbreak investigation of individuals from Mongu District, Western Province, Zambia, who previously developed lower extremity weakness. Cases were classified with the World Health Organization definition of konzo. Active case finding was conducted through door-to-door evaluation in affected villages and sensitization at local health clinics. Demographic, medical, and dietary history was used to identify common exposures in all cases. Urine and blood specimens were taken to evaluate for konzo and alternative etiologies.

Results

We identified 32 cases of konzo exclusively affecting children 6 to 14 years of age and predominantly females >14 years of age. Fourteen of 15 (93%) cases ≥15 years of age were female, 11 (73%) of whom were breastfeeding at the time of symptom onset. Cassava was the most commonly consumed food (median [range] 14 [4–21] times per week), while protein-rich foods were consumed <1 time per week for all cases. Of the 30 patients providing urine specimens, median thiocyanate level was 281 (interquartile range 149–522) $\mu\text{mol/L}$, and 73% of urine samples had thiocyanate levels >136 $\mu\text{mol/L}$, the 95th percentile of the US population in 2013 to 2014.

Conclusion

This investigation revealed the first documented cases of konzo in Zambia, occurring in poor communities with diets high in cassava and low in protein, consistent with previous descriptions from neighboring countries.

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Glossary

CDC = Centers for Disease Control and Prevention; HCN = hydrogen cyanogen; IQR = interquartile range; MOH = Ministry of Health; WHO = World Health Organization.

The World Health Organization (WHO) defines konzo as a distinct upper motor neuron disease characterized by the abrupt onset of a symmetric, nonprogressive, but permanent paraparesis.¹ The condition is believed to result from an interplay between chronic cyanide intoxication arising from consumption of inadequately processed varieties of bitter cassava and a dietary deficiency of sulfur amino acids such as cysteine and methionine.^{2–6} The first cases of konzo were described in 1939⁷ with outbreaks in Tanzania, Mozambique, and the Democratic Republic of Congo in the 1980s and 1990s.^{8–10} Konzo has been reported exclusively among poor rural African communities subsisting on cassava and simultaneously consuming a protein-deficient diet.¹¹ However, the specific pathogenesis of konzo has not been elucidated.

In Zambia, cassava is the second most consumed food crop after maize.¹² It is produced predominantly for domestic consumption and is the staple food for 30% of the population. Cassava is grown mostly by subsistence farmers in all the provinces of Zambia, with Luapula, Northern, North-Western, and Western being the major producers. International, government, and nongovernmental organizations have increasingly promoted cassava as a sustainable alternative staple to maize due to its resistance to drought, tolerance to pests, and potential to give higher yields per unit of land than maize.^{12,13}

Although cassava-dependent communities in countries bordering Zambia have documented konzo cases, konzo has never been reported in Zambia.¹⁴ In June 2015, 29 cases of spastic paraparesis were detected through intensified acute flaccid paralysis surveillance conducted during the biannual Child Health Week in the Mongu district of the Western Province. Because of the clinical presentations, environmental setting, and nutritional practices of the affected communities, Zambia's Ministry of Health (MOH) was notified that these cases could represent konzo. We investigated this illness cluster to characterize the clinical features, to identify the etiology, and to determine the factors that led to this disease outbreak.

Methods

Given that this was an outbreak investigation with public health implications commissioned by the Zambia MOH, it was deemed to be exempt from ethics approval.

Setting

The Mongu District lies in the central part of the Western Province, approximately 620 km from the capital city of

Lusaka (figure 1). The district had an estimated population of 180,000 during the 2010 census.¹⁵ The climate and landscape are dry, and subsistence farmers rely on rains in the flood plains for farming. We visited the Mongu District from September 29 to October 3, 2015, and focused our investigation within the Luatembo Health Centre catchment area, which appeared to have the highest concentration of reported cases. The Luatembo Health Centre is located ≈90 km southeast of Mongu city, the provincial headquarters. This health center sits 22 km off the tarred road, and it serves a catchment area of predominantly rural villages.

Case identification

During June to September 2015, the Mongu District Health Management Team conducted active case finding through a combination of door-to-door evaluation in affected villages and sensitization at health clinics in the affected catchment areas to identify potential konzo cases. The team compiled a list of 80 people with lower extremity weakness, regardless of symptom onset, in the catchment areas of the Luatembo, Nasange, Luandui, Litawa, and Limulunga health facilities. This list included persons with weakness onset dating back to 2007. In addition, staff from the Luatembo Health Centre sent messages through community health workers requesting all persons with lower limb weakness to present to designated areas on specified days for evaluation by the investigative team. The team comprising a neurologist, an infectious diseases physician, a physiotherapist, a field epidemiologist, and laboratory staff from the MOH and WHO traveled to the Western Province.

We used the WHO case definition of konzo: a visible symmetric spastic abnormality of gait while walking or running, a history of onset of <1 week followed by a nonprogressive course in a formerly healthy person, and bilaterally exaggerated knee or ankle jerks without signs of disease of the spine.¹ We graded disease severity according to the following WHO classification: mild disease was defined as walking without aid, moderate disease as walking with the use of 1 to 2 sticks or crutches, and severe disease as bedridden or inability to walk without living assistance.¹

Patients convened for assessment at the Luatembo and Nasange health posts, Nasange and Mulwa schools, and Kaoti, Namandindi, and Siyaka villages. Clinicians observed all children during a mass walk to identify any previously unrecognized persons with spastic gait.

Data and specimen collection

We obtained a medical and dietary history and conducted a neurologic examination and physiotherapy assessment for each person identified with lower limb weakness. We

Figure 1 Konzo outbreak investigation area in the Mongu District, Zambia, 2016

documented demographic, medical, and exposure history using a structured questionnaire. Neurologic examination findings were documented with a structured data collection tool provided by the US Centers for Disease Control and Prevention (CDC) (J. Sejvar, CDC, Atlanta, personal communication, April 2017). Physiotherapy assessments used a tool adapted from the University Teaching Hospital (Lusaka, Zambia) Physiotherapy Assessment Form.

We conducted focus groups with 10 to 12 people in each location to identify any changes in farming practices and food consumption that may have preceded the outbreak. Whenever possible, we collected urine and blood samples from patients who met the konzo case definition. Blood and serum were collected in evacuated tubes stored on ice for 1 to 3 days until transfer to -45°C at the University Teaching Hospital in Lusaka. We collected 1 mL urine per sterile container from each patient, which was stored at -45°C . Some patients provided >1 container of urine, depending on the volume of the voided sample. Serum samples were tested for HIV and rapid plasma reagin. Additional serum and plasma samples were shipped to the US CDC in Atlanta, GA, for viral testing by PCR. In addition to the specific viral assays, a generic PCR was done for all human herpes viruses, enteroviruses, and

parechoviruses. Testing for human T-lymphocytic virus was done by enzyme immunoassay. Serum copper and urine thiocyanate testing was also performed at the US CDC.

Rainfall data

Because drought conditions have been associated with numerous konzo outbreaks in sub-Saharan Africa,¹⁴ we obtained the Mongu District rainfall data for 2005 to 2015 from the Meteorological Department of Zambia. We fitted a zero-inflated negative binomial regression to measure the association between the counts of konzo cases for each month and average monthly rainfall. We report the incidence rate ratios and their associated 95% confidence intervals.

Determination of cassava cyanide concentration

On December 20, 2015, a team from the Zambia Agricultural Institute assessed the 5 most commonly grown cassava varieties (Nalumino, Mutembo, Benford, Lingoma, and Litale) from Luatemo for hydrogen cyanogen (HCN) concentration. Three samples of each species of cassava were collected from 3 different locations covering a 300-km² area. Total HCN concentration in the leaves and roots was determined with a previously described procedure.¹⁶

Data availability

The data collected during this investigation are the property of the Zambian MOH. Anonymized data may be shared by request from any qualified investigator on the basis of approval of the Zambian MOH authorities.

Results

The investigation team evaluated 53 (66%) of the 80 patients with lower limb weakness who were identified by the Mongu District Health Management Team. Of these 53 patients, 28 (62%) met the case definition of konzo, while 25 (38%) were deemed to have other medical conditions, including cerebral palsy, stroke, bone disease, and HIV-associated malnutrition. We observed a total of ≈ 100 children from the communities through mass walks. An additional 4 konzo cases were identified in children via observation of mass walks, medical history, and neurologic examinations, leading to 32 total cases. None of these cases had HIV infection.

The median age of cases was 14.5 (interquartile range [IQR] 8.8–25.3) years, and no cases occurred in children <6 years of age (table). Of the 16 cases 6 to 14 years of age, 13 (81%) were male, 13 (81%) were mild, and none were severe. Of the 16 cases ≥ 15 years of age, 13 (81%) were categorized as mild or moderate, and 3 (19%) were severe. All but 1 of the 16 cases ≥ 15 years of age were females, 11 (73%) of whom were breastfeeding at the time of symptom onset. The year of symptom onset among identified cases ranged from 2007 to 2015 (figure 2). Three families had 2 members affected. No individuals reported more than a single attack.

Cassava was the most commonly consumed food among cases (median [range] 14 [4–21] times per week), while protein-rich foods (eggs, chicken, legumes, fish, beef) were consumed <1

Table Konzo cases categorized by age, sex, and severity: Mongu District, Zambia

Age, y ^a	Cases, n	Severity, n		
		Mild	Moderate	Severe
<6	0	—	—	—
6–14				
Male	13	10	3	0
Female	3	3	0	0
≥ 15				
Male	1	1	0	0
Female	15	5	7	3
Total	32	19	10	3

Median age for females ≥ 15 was 26.0 (interquartile range 22.5–33.5) years.
^a Median age was 14.5 (interquartile range 8.8–25.3) years.

Figure 2 Konzo cases by year of onset in the Mongu District, Zambia, 2008 to 2015 (n = 32)

*Low rainfall in preceding growing season (November to February), defined as less than the median rainfall during the growing season, 2005 to 2015.

time per week. The most common methods for processing cassava were by sun drying and, less commonly, soaking. Soaking was used less frequently due to lack of access to water particularly in communities located far from rivers or lakes. We were unable to determine whether there were shortened processing times during periods of low rainfall because we did not have the rainfall data available when the information was collected.

Of the 30 patients providing urine specimens, median thiocyanate level was 281 (IQR 149–522) $\mu\text{mol/L}$, and 73% of urine samples had thiocyanate levels $>136 \mu\text{mol/L}$, the 95th percentile of the US population in 2013 to 2014.¹⁷ PCR testing was negative in all 32 samples for pan-herpes, pan-enterovirus, and pan-parechoviruses, and human T-lymphocytic virus enzyme immunoassay was negative in all samples. Serum copper levels were low in 4 cases, ranging from 22 to 51 $\mu\text{g/dL}$ (adult reference range 70–155 $\mu\text{g/dL}$).

Rainfall

Median rainfall during the growing season (November to February) from 2005 to 2015 ranged from 723 to 1,061 mm. The rainfall was lower than the median of 806 mm during the growing periods in 2005 to 2006 (723 mm), 2010 to 2011 (756 mm), 2011 to 2012 (785 mm), 2013 to 2014 (711 mm), and 2014 to 2015 (590 mm). Figure 2 demonstrates the occurrence of konzo cases in relation to periods of low rainfall. We found no evidence of an association between average konzo and monthly rainfall (incidence rate ratio 0.99, 95% confidence interval 0.99–1.00, $p = 0.14$).

Cassava cyanide concentration

The HCN levels of all of cassava samples tested fell into the expected range for roots and leaves (1–2,000 ppm) with

a median of 400 (IQR 200–400) ppm.¹⁸ All the varieties tested were locally cultivated.

Discussion

This investigation revealed the first recognized cases of konzo in Zambia. Cases were found among school-aged children and women of childbearing age and clustered in families, which is characteristic of previously documented konzo outbreaks.^{11,19–21} The most severe cases in this cohort occurred in females of childbearing age. Prior outbreaks have documented females developing the onset of symptoms within the first year of childbirth.²² We have not seen prior documentation in the literature that this group developed the greatest severity of symptoms.

We did not find a correlation between rainfall and konzo cases. The relatively low number of confirmed cases limits any meaningful inferences related to rainfall. Poor rainfall increases food insecurity, which can lead at-risk populations to skip important but time-consuming cassava processing steps, which reduce the concentration of cyanogenic compounds.¹⁴

Our findings suggest the possibility of increasing konzo cases in this region of Zambia. Although our data and cross-sectional design do not allow full examination of potential causes, this increase could have resulted from changes in cassava processing practices that led to higher cyanide concentrations, decreases in protein-rich foods, or relative increases in cassava consumption. However, temporal trends must be interpreted cautiously on the basis of our case identification methods. District health officials sought to identify anyone with lower extremity weakness living in the targeted catchment areas, but we did not actively seek potential cases by visiting households. Our case finding approach was likely biased toward cases with more recent symptom onset because patients with earlier onset would likely have been older and may have been less likely to present for examination or may have died. For similar reasons, we cannot conclude that the first case occurred in 2007.

This report likely underestimates the true number of konzo cases in the Western Province because we did not conduct active case finding in all districts. Because konzo affects predominantly rural dwellers with poor access to health services, it can take years for cases to come to the attention of public health specialists through passive surveillance, particularly in areas where the disease has not previously been documented and in cases with mild disease. Indeed, the first Zambian patients with konzo developed symptoms in 2007 but were only recently identified by the Zambian MOH.

The median urine thiocyanate levels in the cases were higher than the reference range based on US norms. We hypothesize that the elevated urine thiocyanate levels may have been related to dietary cyanogen exposure through consumption of

improperly prepared cassava in a setting of a low-protein diet.⁵ However, in the absence of a control group, this inference should be interpreted with caution. In addition, a cross-sectional measurement of urine thiocyanate does not reflect past dietary cyanide exposure. Many of the cases from this investigation experienced symptom onset several years before providing biological samples. Serum copper was low in 4 cases of konzo, likely indicating general malnutrition in this population. There are case reports of copper deficiency causing myelopathy but in the setting of nearly undetectable copper levels and not in the low range seen here.²³ The negative virologic screening also supports numerous prior studies that the etiology of konzo is a toxic rather than an infectious exposure.

Additional limitations of this investigation include the lack of a well-defined catchment area to help estimate konzo prevalence. Four previously unrecognized cases in children were identified through a mass gait assessment, suggesting that clinically subtle cases remain unidentified, especially because we did not assess each village in this manner. We were unable to evaluate potential risk factors for konzo due to lack of a control group. In addition, the majority of cases experienced symptom onset years before we took detailed histories, raising the possibility of poor recall related to clinical and dietary histories.

Lastly, the cyanogen testing of cassava varieties was not comprehensive. The HCN levels in roots and leaves of 5 commonly planted cassava varieties in 1 health center catchment area of the outbreak district were within the expected range. It would have been most informative to sample these varieties from a representative geographic area over multiple time points that included periods of low rainfall. However, this information was not readily available and was beyond the scope of this investigation. Future studies should identify whether subsequent konzo outbreaks are associated with a particular species of bitter cassava.

Since the recognition of this konzo outbreak in 2015, the government of Zambia has taken several steps to improve disease detection and to prevent further cases. Konzo has been added to Integrated Disease Surveillance and Response reporting through the Zambian MOH. The MOH provided emergency food supplies that included maize and protein-rich foods to the villages that had documented cases. Given that cassava is a valuable food source in communities that have food insecurity, it is not realistic to transition away from it as a staple crop. Efforts to address food insecurity, specifically access to protein sources, are needed to reduce further cases. Food insecurity was identified as a root cause of a 2011 anthrax outbreak in Zambia associated with consumption of infected hippopotamus meat,²⁴ highlighting that food insecurity poses risks for acute infectious diseases and non-communicable diseases like konzo.

The public health system needs to raise awareness of konzo among at-risk communities in the Western Province and

other regions of Zambia and to strengthen systems to communicate new cases to relevant health authorities. This should include training of district medical officers on the case definition of konzo, along with screening of at-risk populations in health facilities of cassava growing regions. The government and agricultural entities should educate at-risk communities about proper cassava processing techniques²⁵ that decrease cyanogen content and reduce the risk of developing konzo. Finally, konzo-affected communities should be encouraged to cultivate protein-rich foods such as ground nuts to diversify the local diet and to mitigate food insecurity.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC, Department of Health and Human Services, or the US government.

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Appendix (continued)

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