Journal of the Neurological Sciences 405 (2019) 116434

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Tropical ataxic neuropathy: Findings of a neuroepidemiological survey of Odeda, southwest Nigeria

F.M. Otubogun[a,*], R.O. Akinyemi[b,c], |A.O. Ogunniyi[b,c]

[a] Department of Internal Medicine, Federal Medical Centre, Birnin Kebbi, Kebbi, Nigeria
[b] Department of Medicine, University College Hospital, Ibadan, Oyo, Nigeria
[c] Neuroscience and Ageing Research Unit, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, Ibadan, Nigeria

ARTICLE INFO

Keywords:
Tropical ataxic neuropathy
Toxiconutritional disorders
Nigeria
Africa

ABSTRACT

Background: Tropical ataxic neuropathy seems to have dwindled in public health importance in Nigeria despite the high consumption of cassava-based meals by a huge proportion of people in local Nigerian communities. Yet a recent report suggest its persistence in the same ethnogeographic setting where it was first reported in Nigeria. Our objective was to investigate the prevalence of tropical ataxic neuropathy in Odeda, Ogun state, southwest Nigeria inhabited by a different ethnic group compared to Epe where the disease was first described.

Methods: A two-stage, cross-sectional survey of Odeda local government area for the prevalence and profile of toxiconutritional neurological disorders was carried out between May and June 2015. A screening instrument was applied by trained non - medical interviewers with positive responders further evaluated by a neurologist.

Results: 2392 individuals aged 18 years or older were screened and had a mean age of 37.2 ± 16.1 years, were predominantly of Egba Yoruba ethnicity. Thirty nine cases of tropical ataxic neuropathy were diagnosed and crude prevalence rate was 16.3/1000 (95% CI 11.2–21.4/1000). Older age and rural residence were associated with higher prevalence. Distal sensory polyneuropathy was the most common feature whereas sensorineural deafness was the least common finding.

Conclusion: This report provides evidence that tropical ataxic neuropathy persists and in a wider geographic spread. Thus tropical ataxic neuropathy still remains a significant public health importance and concerted efforts are required to mitigate or eradicate tropical ataxic neuropathy in southwest Nigeria and other regions of Africa affected by cassava- related toxiconutritional disorders.

1. Introduction

The health of developing countries is often synonymous with endemic and epidemic infectious diseases such as Malaria, Tuberculosis, and Human immunodeficiency virus [1]. One less known class of non-infectious diseases is toxiconutritional disorder. Nutritional amblyopia, epidemic optic neuropathy and peripheral neuropathy of Cuba, Strachan's disease, prisoner of war neuropathy and tropical ataxic neuropathy(TAN) constitute a spectrum of toxiconutritional disorders with predominantly nervous system involvement which have been described over 100 years ago [2–6].

Are these diseases now medical rarities or curiosities which are no longer relevant or prevalent? A cross-sectional, community-based study conducted almost two decades ago in Ososa, southwest Nigeria suggests otherwise as it reported on the persistence of tropical ataxic neuropathy (TAN) [7]. TAN is a predominantly sensory neuropathy of subacute or chronic onset characterized by impaired light touch, vibration and proprioception, gait ataxia, sensorineural hearing loss, amblyopia, and infrequently muscle weakness and atrophy [8]. Its association with excessive consumption of cassava and in particular chronic cyanide intoxication has been well described in tropical regions of Africa and Americas where cassava products are an important source of calories for over half a billion people [9]. What is common to this study and many older reports on TAN in Nigeria is that they were carried out in predominantly Ijebu Yorubas [7,10]. It is however unclear if TAN persists or even exists in other ethnogeographic regions and its clinical and public health relevance in present times.

Persistence of TAN in endemic forms if confirmed especially in areas where previously unreported, is likely to be of public health importance considering the global production and consumption of cassava and cassava products. Hence, possible non-diagnosis, under-diagnosis and misdiagnosis of TAN is likely to translate into significant neurologic

* Corresponding author at: Department of Internal Medicine, Federal Medical Centre, Dukku Baracks Road, Birnin Kebbi, Kebbi State, Nigeria.
E-mail address: folabogun@gmail.com (F.M. Otubogun).

https://doi.org/10.1016/j.jns.2019.116434
Received 3 April 2019; Received in revised form 22 July 2019; Accepted 23 August 2019
Available online 27 August 2019
0022-510X/

morbidity, mortality and reduced quality of life for many in tropical regions of the world. As a result, TAN may be duly recognized or categorized as a neglected tropical disease [11].

1.1. Study objective

The objective of this study was to investigate the prevalence and profile of tropical ataxic neuropathy, a toxiconutritional neurological disorder, in adult residents of Odeda local government area (OLGA), southwest Nigeria.

2. Materials and methods

2.1. Study design

A cross-sectional survey of selected rural and urban communities of OLGA for the prevalence and profile of toxiconutritional neurological disorders was carried out between May and June 2015. This was part of a broader neuroepidemiological survey in that locality.

2.2. Study setting

This administrative unit is located between 7°13′00″-7°21′66″ North and 3°31′00″-3.5°16′67″ East. It has a land mass of 1560 km^2 and includes semi-urban and rural population.

2.3. Source population

The people are predominantly of the Yoruba tribe of the Egba dialect. The population is mainly agrarian with major food crops being cassava, yam, cocoyam, plantain, maize and vegetables and major cash crop, cocoa. Other economic activities are quarrying, trading and artisanship.

2.4. Participants

Consenting adults aged 18 years and above as at May 1st, 2015 and resident within the selected communities for most of the previous six months were invited to participate in the study.

2.5. Sampling

A two stage cluster sampling technique was employed. In the first stage, the 10 wards in OLGA were first sorted into predominantly urban/semi-urban and rural based on information provided by the local health authority, two urban and eight rural. Names of the all wards were written on paper rolled and ballots were picked from each pot, one urban and two rural wards based on population estimates to meet minimum sample size. Obantoko ward was drawn for urban/semi-urban while Odeda and Alabata wards were drawn from the rural wards.

At the second stage, the cluster units for urban and rural wards were different as they were organized differently. Obantoko ward is mainly organized as community development associations (CDA), this formed the cluster unit for Obantoko. A list of CDAs in Obantoko ward was obtained and this formed the sampling frame from names of CDA surveyed were picked from a ballot box. For the rural wards, villages and hamlets were used as a cluster unit. A list was also obtained from the local primary health centre. This formed the sampling frame from which villages were picked.

With a calculated minimum sample size of 964, 6 clusters of 161 each (two clusters from each ward) was proposed. However, the sample size was doubled in order to further strengthen the power of the study and to allow for a proportional representation of the population sizes of the different ward. However, because of the small population size of most villages and hamlets, some of them were merged to form a cluster while bigger communities (Apena CDA and Odeda town) provided 2 clusters units each.

2.6. Protocol

A two-stage evaluation was employed. The first stage entailed application of a screening instrument, developed to screen for neurological disorders in low resource settings [12], by trained nonmedical interviewers. The screening consisted of 22 history questions and performance of 16 tasks. Further assessment was performed on individuals who had positive response to questions on weakness and loss or odd sensation in arms and legs, loss of vision and difficulty hearing and difficulty with such as tactile discrimination between smooth and rough cloth samples, perception of vibration of a tuning fork on the ankle, visual field test and Romberg's test. The evaluation consisted of history taking, general and specific neurological examination (fundoscopy, vibratory perception, pain and fine touch perception, Rinne's test and tandem gait). A diagnosis of TAN was made based on previously established and reported diagnostic criteria [8].

2.7. Case ascertainment

All TAN diagnoses were made clinically and required the presence of at least two or more of optic atrophy, sensorineural deafness, distal sensory polyneuropathy and sensory ataxia and were defined as optic disc pallor, impairment of Rinne's test, impairment of pain, fine touch and vibratory perception above the malleoli and impaired tandem gait respectively.

2.8. Ethical approval

Ethical approval was sought and obtained the Health Research Ethical Committee of the Federal Medical Centre, Abeokuta. (FMCA/470/HREC/09/2014).

2.9. Statistical methods

Sociodemographic and clinical data were collated on designed proforma sheets and data analyzed with SPSS version 20. Background sociodemographic variables were presented as means ± S.D for continuous variables and frequencies and percentages for categorical variables. Crude prevalence rates were calculated and presented as period prevalence rates. The Pearson's chi square test was used to compare the prevalence rates of neurological disease categories between urban and rural communities. Fisher's exact test was used instead of Pearson's chi square test for two-by-two tables with cells < 5. For variables with normal distribution, comparison between groups was performed using independent *t*-test. A 5% significance level (*P*- value less than or equal to 0.05) was considered significant.

3. Results

3.1. Population characteristics

A total of 1891 households were enumerated with a base population of 3064 individuals aged 18 years and above (Fig. 1). The response rate was 78.0%. 2392 adults were screened, comprising 1470 women (61.5%) and 922 men (38.5%). The mean age of respondents was 37.2 ± 16.1 years (range 18–114 years). Majority of participants were younger than 50 years (Table 1).

Majority of the study population were Egba Yoruba ethnicity (86.4%), educated (77.4% had at least primary levels of education) and employed (80.9%). About a fifth of these individuals were either students or currently employed while artisanship, trading and farming were the most frequent occupations.

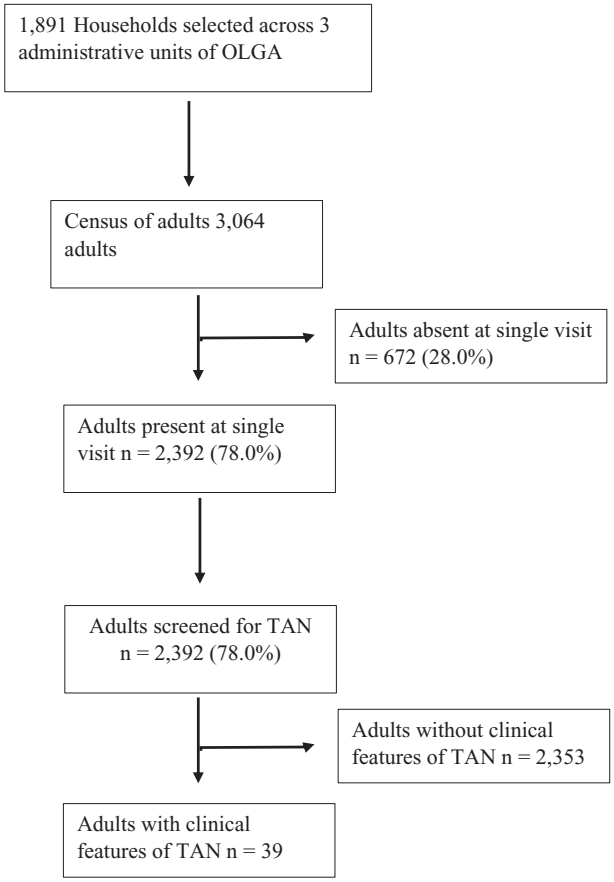

Fig. 1. Study flowchart.

Table 1
Sociodemographic profile of the Study Population (n = 2392).

	n (%)
Age (in years)	
18–29 years	947 (39.5)
30–39 years	574 (23.9)
40–49 years	351 (14.6)
50–59 years	203 (8.4)
60–69 years	173 (7.1)
70–79 years	94 (3.9)
80 years and above	50 (2.0)
Gender	
Females	1470(61.4)
Males	922(38.5)
Residence	
Rural	877(36.6)
Urban/semi-urban	1515(63.3)
Highest level of Education	
None	542 (22.6)
Primary	610 (25.5)
Secondary	800 (33.4)
Tertiary	440 (18.3)
Occupation	
Students	319 (13.3)
Artisans	559 (23.3)
Traders	751 (31.3)
Professionals	255 (10.6)
Farmers	369 (15.4)
Unemployed/retired	139 (5.8)

Table 2
Prevalence of TAN in OLGA.

		N (popn)	Prevalence per 1000(95%CI)	p value*
Age	18-29 yrs	0(947)	0	0.001
	30-39 yrs	0(574)	0	
	40-49 yrs	4(351)	11.3(4.4–28.9)	
	50-59 yrs	6(203)	29.5(13.6–63.0)	
	60-69 yrs	13(173)	75.1(44.4–124.3)	
	70-79 yrs	13(94)	138.2(82.6–222.4)	
	≥80 yrs	3(50)	60.0(20.6–162.2)	
Location	Urban	15 (1515)	9.9(6.0–16.3)	0.001
	rural	24 (877)	27.3(18.5–40.4)	
Gender	males	13 (922)	14.0(8.3–24.0)	0.73
	Females	26 (1470)	17.6(12.1–25.8)	
Ethnicity	Yorubas	38 (2067)	18.3(13.4–25.2)	0.023
	Others	1 (325)	3.0(0.6–17.3)	
Occupation	Students	0(319)	0	< 0.001
	Artisans	1(559)	1.8(0.3–10.1)	
	Traders	13(751)	17.3(10.1–29.4)	
	Professionals	0(255)	0	
	Farmers	15(369)	40.7(24.8–66.0)	
	Unemployed	10(139)	71.9(39.5–127.3)	

Key: * Pearson's chi square test.

3.2. Prevalence of TAN

Thirty nine cases of tropical ataxic neuropathy were diagnosed in the study population with a crude prevalence rate of 16.3 per 1000 (95% CI 11.2–21.4 per 1000).

No diagnosis of TAN was made in study participants younger than 40 years while the prevalence of TAN in individuals 40 years or older was 44.6 per 1000 (95% CI 32.8–60.4.4 per 1000). Furthermore, there was a significant difference in age-specific prevalence rates even in the ≥40 years subgroup (p = .001), which rose steadily from 40 to 49 years group (11.3/1000:95% CI 4.4–28.9/1000) to 70–79 years group the highest age specific prevalence (135.0/1000: (95% CI 82.6–222.4/1000).

Rural dwellers had significantly higher prevalence (rural 27.3/1000: 95% CI 18.5–40.4/1000: urban 9.9/1000: 95% CI 6.0–16.3/1000: p = .001) than people residing in urban communities (Table 2). Exclusion of the < 40 years group (68% urban, 55.6% rural) also showed a significant but smaller difference in the prevalence (31.1/1000 95% CI 18.9–50.7/1000 urban; 61.6/1000 95% CI 41.8–90.2/1000 rural; p = .03).

There was no significant difference in prevalence rate of TAN in women 17.6/1000 (95% CI 12.1–25.8/1000) compared to men (14.0/1000: 95% CI 8.3–24.0/1000).

3.3. Clinical profile of TAN in OLGA

Distal sensory polyneuropathy were present in all persons identified with TAN and was the only feature in four out of every five people diagnosed with TAN.

Optic neuropathy was the second most common feature and was detected in 5 individuals (12.8% TAN population). Old age and male sex were associated with optic neuropathy as a third of individuals with TAN aged 80 years or older had optic neuropathy while it was four times more common in men than in women.

Sensorineural deafness was the least common finding in this cohort, present in only 2 (5%) male subjects while only a male subject had all the features of TAN. (Table 3).

4. Discussion

The study population's age structure is typical of developing countries but with a marked female preponderance. This was likely due to the fact that women usually work at or near their homes and were more

Table 3
Clinical profile of TAN in OLGA.

Clinical findings			N (%)
DSP	Males	9	33(84.6)
	Females	24	
DSP and ON	Males	2	4 (10.2)
	females	3	
DSP and SND	Male	1	1 (2.5)
DSP, ON and SND	Male	1	1 (2.5)

Key: DSP- distal sensory polyneuropathy (impaired pain, fine touch, vibratory perception and tandem gait); ON- optic neuropathy; SND- sensorineural deafness.

available and accessible during the single visits to their homes by the research team. The ethnic composition of Egba Yorubas also provided an opportunity to evaluate the burden of TAN in a different ethnicity from the Ijebu Yorubas who have been exclusively reported in previous Nigerian studies [7,10]. Although both Egba and Ijebu Yorubas live within the same geopolitical region, differences exist in soil types, cassava cultivation, preparation and consumption- an important putative factor in the aetiopathogenesis of TAN [13–15].

The crude prevalence observed in this study was considerably lower (approximately a quarter) than reported in Ososa by Oluwole et al. with a crude prevalence of 6%. Various factors may account for this. Firstly, cassava species cultivation and processing methods with varying levels of cyanogenic residues vary within localities. Also a preponderance of urban dwellers in this study, who are more likely to consume more varied diets and in turn, less prone to toxiconutritional disorders, may lead to lower prevalence of TAN as observed in south India [16]. Moreover, a longer storage times have been demonstrated to reduce cyanide levels in cassava products and this is likely to be the case for urban dwellers in contrast to rural inhabitants who are more likely to begin consumption as soon as the products are made [15]. In fact, rural residents were observed to consume unprocessed cassava produce during this study.

Age has been consistently shown to be a determinant for the occurrence of TAN and this study corroborated this finding. This may be due to older subjects been exposed to dietary cyanogens and their metabolites for commutatively longer periods compared to younger individuals. A gradual phasing out of older inefficient processing methods may contribute to declining prevalence in younger subjects.

There was a slight but nonsignificant female sex predilection in contrast to the much clearer female to male ratio of 2:1 reported in Ososa. A smaller cohort of cases may account for this.

Certain parallels can be drawn from cassava-associated spastic paraparesis (CASP), which has been reported in a different geographic region predominantly in children and young women, which has distinct similarities with TAN [17]. Both conditions have been linked with cassava consumption and attributed to toxicity of cyanogens and their metabolites due to improper processing. However, CSP and TAN have different neurological presentations possibly because the former represents a high level and the latter a low level of cassava-cyanogen exposure [18]. This may explain why there is a subacute disease course at younger ages for CSP and a more insidious course in later life in TAN. Coexisting dietary deficiencies in sulphur-dependent amino acids such as L-cystine and L-methionine as well as in selenium, copper and zinc have been shown to play a role in CASP but are yet to be well established in TAN [19,20]. The excitatory neurotransmitter, glutamate toxicity is also implicated in the pathogenesis of CASP unlike for TAN [21].

Additionally, preventive community-level strategy has been identified, tested and found to efficacious and cost-effective in eradicating new cases of Konzo which possibly can be replicated in prevention of TAN [22].

4.1. Limitations

Non-utilisation of confirmatory electromyoneurogprahy and audiometry for polyneuropathy and sensorineural deafness respectively due to financial costs and technical difficulties of conducting these tests on large populations.

We also did not determine the levels of cyanogens and their metabolites in body fluids of the study population as well as dietary habits.

4.2. Further research

Considering that TAN remains a public health concern as it is still prevalent in endemic clusters, therefore further research is required to elucidate its cause(s) and risk-factors, understand its pathophysiology, identify biomarkers and subclinical correlates.

There is also a need to explore genetic variations among populations as this may explain the different phenotypic manifestations between TAN AND Konzo despite the similarity in aetiopathogenesis as TAN is seen predominantly among West Africans whereas Konzo is seen mainly among local tribes of East and Central Africa.

Clinical trials to identify potential effective therapies as well as community level interventions to prevent new cases are pivotal.

5. Conclusion

This study has provided some evidence that tropical ataxic neuropathy is still present in endemic forms and constitutes a public health concern in contemporary times as they were in the past. Cassava cultivation and processing methods may hold the key to mitigating and eradicating endemic forms of tropical ataxic neuropathy in southwest Nigeria.

Statement of ethics

Subjects (or their parents or guardians) have given their written informed consent.

The study protocol has been approved by the research institute's committee on human research.

Disclosure statement

The authors have no conflicts of interest to declare.

Funding source

The authors received no specific funding for this work.

Author contribution

FMO, ROA and AO contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

References

[1] M. Lemoine, P.M. Girard, M. Thursz, G. Raguin, In the shadow of HIV/AIDS: forgotten diseases in sub-Saharan Africa: global health issues and funding agency responsibilities, J. Public Health Policy 33 (4) (2012 Nov 1) 430–438.
[2] G.V. Gill, D.R. Bell, Persisting nutritional neuropathy amongst former war prisoners, J. Neurol. Neurosurg. Psychiatry 45 (10) (1982 Oct 1) 861–865.
[3] H. Strachan, On a form of multiple neuritis prevalent in the West Indies, Practitioner. 59 (59) (1897 Nov) 477.
[4] A.B. Netto, C.M. Netto, A. Mahadevan, A.B. Taly, J.B. Agadi, Tropical ataxic neuropathy–a century old enigma, Neurol. India 64 (6) (2016 Nov 1) 1151.
[5] G.C. Román, P.S. Spencer, B.S. Schoenberg, Tropical myeloneuropathies the hidden endemias, Neurology. 35 (8) (1985 Aug 1) 1158.
[6] J. Llorens, C. Soler-Martín, S. Saldaña-Ruíz, B. Cutillas, S. Ambrosio, P. Boadas-Vaello, A new unifying hypothesis for lathyrism, konzo and tropical ataxic neuropathy: nitriles are the causative agents, Food Chem. Toxicol. 49 (3) (2011 Mar 1)

563–570.
[7] O.S. Oluwole, A.O. Onabolu, H. Link, H. Rosling, Persistence of tropical ataxic neuropathy in a Nigerian community, J. Neurol. Neurosurg. Psychiatry 69 (1) (2000) 96–101 Jul 1.
[8] B.O. Osuntokun, An ataxic neuropathy in Nigeria. A clinical,biochemical and electrophysiological study, Brain 91 (1968) 215–248.
[9] D. Burles, Dimensions of Need: An Atlas of Food and Agriculture, Food & Agriculture Org, 1995.
[10] G. Money, Endemic neuropathies in the Epe district of southern Nigeria, West Afr. Med. J. 7 (1) (1958) 58–62.
[11] P.J. Hotez, A. Fenwick, L. Savioli, D.H. Molyneux, Rescuing the bottom billion through control of neglected tropical diseases, Lancet 373 (9674) (2009 May 2) 1570–1575.
[12] J.H. Bower, W. Howlett, V.P. Maro, H. Wangai, N. Sirima, H. Reyburn, A screening instrument to measure the prevalence of neurological disability in resource-poor settings, Neuroepidemiology. 32 (4) (2009) 313–320.
[13] A.O. Onabolu, O.S. Oluwole, M. Bokanga, H. Rosling, Ecological variation of intake of cassava food and dietary cyanide load in Nigerian communities, Public Health Nutr. 4 (4) (2001 Aug) 871–876.
[14] V.A. Aletor, Cyanide in garri. 1. Distribution of total, bound and free hydrocyanic acid in commercial garri, and the effect of fermentation time on residual cyanide content, Int. J. Food Sci. Nutr. 44 (4) (1993 Jan 1) 281–287.
[15] A.O. Onabolu, O.S. Oluwole, M. Bokanga, Loss of residual cyanogens in a cassava food during short-term storage, Int. J. Food Sci. Nutr. 53 (4) (2002 Jan 1) 343–349.
[16] M. Madhusudanan, M.K. Menon, K. Ummer, K. Radhakrishnanan, Clinical and etiological profile of tropical ataxic neuropathy in Kerala, South India, Eur. Neurol. 60 (1) (2008) 21–26.
[17] D. Tshala-Katumbay, K.E. Eeg-Olofsson, T. Kazadi-Kayembe, T. Tylleskär, P. Fällmar, Analysis of motor pathway involvement in konzo using transcranial electrical and magnetic stimulation, Muscle Nerve 25 (2) (2002 Feb) 230–235.
[18] P.S. Spencer, V.S. Palmer, Interrelationships of undernutrition; food for thought and research attention, Neurotoxicology. 33 (3) (2012 Jun 1) 605–616.
[19] J. Tor-Agbididye, V.S. Palmer, M.R. Lasarev, A.M. Craig, L.L. Blythe, M.I. Sabri, P.S. Spencer, Bioactivation of cyanide to cyanate in sulfur amino acid deficiency: relevance to neurological disease in humans subsisting on cassava, Toxicol. Sci. 50 (2) (1999 Aug 1) 228–235.
[20] G.M. Bumoko, N.H. Sadiki, A. Rwatambuga, K.P. Kayembe, D.L. Okitundu, D.M. Ngoyi, J.J. Muyembe, J.P. Banea, M.J. Boivin, D. Tshala-Katumbay, Lower serum levels of selenium, copper, and zinc are related to neuromotor impairments in children with konzo, J. Neurol. Sci. 349 (1–2) (2015 Feb 15) 149–153.
[21] P.S. Spencer, Food toxins, AMPA receptors and motor neuron diseases, Drug Metab. Rev. 31 (3) (1999 Jan 1) 561–587.
[22] J.P. Banea, J.H. Bradbury, C. Mandombi, D. Nahimana, I.C. Denton, M.P. Foster, N. Kuwa, D.T. Katumbay, Konzo prevention in six villages in the DRC and the dependence of konzo prevalence on cyanide intake and malnutrition, Toxicol. Rep. (2) (2015 Jan 1) 609–616.