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Global Perspectives

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CASSAVA FOOD TOXINS, KONZO DISEASE, AND NEURODEGENERATION IN SUB-SAHARA AFRICANS

Endemoepidemic neurodegenerative diseases putatively caused by food toxins have been reported around the globe with no clear understanding of their pathogenetic mechanisms. These diseases include the amyotrophic lateral sclerosis/parkinsonism dementia complex among the Guamanians; neurolathyrism among Europeans, Indians, and populations of the Horn of Africa; and tropical ataxic neuropathy or konzo among sub-Sahara Africans.[1,2] We focus on the molecular determinants of susceptibility to konzo, a poorly known self-limited and irreversible upper motor neuron disease (spastic paraparesis) highly prevalent in Congo-Kinshasa, Mozambique, Tanzania, Central African Republic, Angola, and Cameroon. The main clinical picture consists of a symmetrical, permanent, and irreversible spastic paraparesis with no signs of sensory or genitourinary impairments.[2,3] Severely affected individuals may present with a tetraparesis and pseudobulbar signs. The disease konzo was named after a fetish used by the "Yaka" population of Congo-Kinshasa. The World Health Organization has adopted the following epidemiologic criteria for the disease: 1) an abrupt onset (<1 week) of weakness in legs and a nonprogressive course of the disease in a formerly healthy person, 2) a symmetrical spastic abnormality when walking and/or running, and 3) bilaterally exaggerated knee and/or ankle jerks without signs of disease of the spine.

A recent neuropsychological profiling indicates that cognition may be affected in konzo or cassava-associated human disease. Both subjects with konzo disease and age- and sex-matched controls show a very low performance in the global cognitive domain of planning/reasoning (figure). A secondary weakness in sequential cognitive processing is possible.

The exact pathogenetic mechanisms of konzo remain unknown. So far, serologic studies have ruled out retroviral infections by HIV types I and II or human T-lymphotropic viruses types I and II. A study of motor-evoked potentials in affected subjects clearly indicates a prominent dysfunction of the corticopyramidal tract suggesting a transsynaptic failure within the motor cortex.[4] Epidemiologic studies consistently show an association between outbreaks of konzo and chronic dietary reliance on foodstuffs derived from insufficiently processed toxic and cyanogenic cassava (also known as manioc or tapioca). Most outbreaks arise when adherence to traditional methods of cassava processing become difficult, e.g., in times of famine, drought, or armed conflicts. The disease mainly affects children and women of childbearing age for reasons that have yet to be elucidated. Biochemical and toxicologic studies suggest that the metabolites of linamarin (α-hydroxyisobutyronitrile β-D-glucopyranoside, the main cassava cyanogen), notably cyanide (mitochondrial toxin), thiocyanate (AMPA [α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid] chaotropic agent), and cyanate (motor system toxin) may be important players in the pathogenesis of konzo. The risk for the disease is thought to be determined by poor dietary intake of sulfur amino acids needed for the conversion of cyanide into urinary excretable thiocyanate (water-soluble and presumably less toxic) through a sulfur-dependent rhodanese-mediated detoxification pathway.[2,3] Experimental data suggest that thiol redox and protein folding mechanisms may be perturbed.[5] As a consequence of the complexity of the proposed pathogenetic mechanisms, levels of exposure to cassava cyanogens, deficiency in essential nutrients, serum markers of protein modifications, and (meta)genomic variations are under research scrutiny among human populations affected by the disease.

The global health significance of the research work on konzo and cassava neurotoxicity is several-fold: research on konzo, particularly in a highly prevalent region (up to 5% in select areas), will help elucidate

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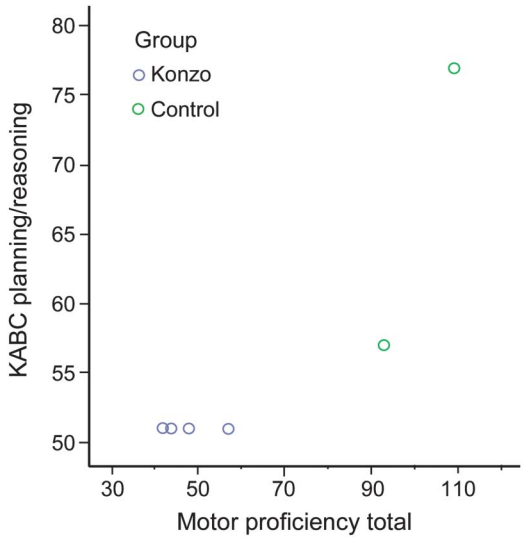
Figure Neuropsychological profile of konzo in rural Africa



Illustrative neuropsychological profiles of 2 pairs of twins with konzo disease (blue circles) and their respective age- and sex-matched controls in Congo-Kinshasa. All 4 children with konzo disease were severely impaired in all 4 major domains of motor proficiency tested using the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition, or all major cognitive ability domains (memory, visual-spatial analysis, learning, planning/reasoning) tested using the Kaufman Assessment Battery for Children, Second Edition (KABC-II). Control children (green circles) were in the "normal" range for motor proficiency scores. An apparently healthy control, with cognitive impairment at the KABC-II testing, resembled the children with konzo disease in a differential weakness in fine-motor manual dexterity.

the role of food toxicant exposure, (meta)genomic variations, dietary deficiencies, or their combination in modulating the risk for neurodegenerative diseases. Risk modulation by the gut flora (functional microbiome) and the host genome, including the cross-talk between the nuclear and mitochondrial genomes, should be of critical relevance to the pathogenesis of konzo and is a significant aspect of the research work in place. Of particular interest are the putative roles of bioenergetic failure (possibly related to mitochondrial toxicity), imbalance in thiol-redox mechanisms, and protein misfolding in relation to motor neuron degeneration. The prominent dysfunction of the corticopyramidal tract, along with the putative konzo-associated cognitive impairment, make konzo a suitable model to study glutamatergic and transsynaptic modalities in neurodegenerative diseases. This approach will probably bring new paradigms to the field of risk assessment in environmental exposures and risk for human neurodegeneration.

Cassava is a staple food for more than 600 million people around the globe. Cyanogenic crop varieties are resistant to drought, plant diseases, insects, and animal predators and, hence, represent an extremely valuable crop for subsistence (food security) of the millions of those dwelling under the tropics. Cassava-derived food products are increasingly exported for snack production, animal feed, and used as thickening agents in food industries. It is therefore critical to understand the potential neurotoxic properties and the extent of neurodevelopmental risk associated with this staple. Findings from ongoing research will also help regulatory agencies to set up safety standards for the international trade of cassava and other cyanogenic crops such as sorghum, almond, and lima bean, and determine exposure limits for cyanogenic compounds used in gold mining, painting industries, or theatres of warfare. Similarly, the scientific community will be informed on the neurotoxicity risk associated with linamarin, the main cassava cyanogenic compound, which is increasingly promoted for use as an anticancer agent.

The disease konzo has no cure. Prevention measures such as proper cassava processing, i.e., detoxification of cassava roots before their consumption, and promotion of genetically engineered low-toxin strains of the plant are of paramount importance as they may help eradicate the disease. Local efforts in affected areas include mass education, promotion of safe cassava processing methods, and distribution of low-toxin strains among farmers. Although physical therapy is often performed to reduce spasticity and/or joint contractures and help increase mobility, strategies need to be diligently in place to address any cognitive burden associated with the disease outbreaks (*vide supra*). The existence of cognitive impairment in apparently healthy children raises serious concern over a cassava-dominant diet. The potential threats to child development and human health, possibly associated with heavy dietary reliance on toxic cassava, need to be further elucidated.

The Congo-Kinshasa research work on konzo and cassava neurotoxicity is embedded in a plan to enhance neuroscience research capacity for local physicians and scientists. We have established an institutional review board for human research, a cryobank for human specimens, and have initiated the creation of a research unit to address molecular determinants of complex neurologic disease. A graduate-level, research-based training plan has been established. These efforts are built on existing and newly developed transdisciplinary, multicultural, and multi-institutional grounds, ingredients for a sustainable capacity-building enterprise in resource-limited settings.

AUTHOR CONTRIBUTIONS

D. Tshala-Katumbay, N. Mumba, and L. Okitundu: design of the study, analysis of the data, drafting the manuscript. K. Kazadi and M. Banea: design of the study, analysis of the data. T. Tylleskär: design of the study. M. Boivin and J.J. Muyembe-Tamfum: design of the study, analysis of the data, drafting the manuscript.

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DISCLOSURE

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