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Cassava, konzo, and neurotoxicity

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Cassava (*Manihot esculenta*) forms part of the staple diet for more than 600 million people across the world, particularly those that live in poverty and remote areas where food security is poor.[1] The plant grows in poor soil and is relatively drought resistant; the tubers are rich in carbohydrates and the leaves contain some protein.

Cassava contains cyanogenic glucosides (linamarin and lotaustralin) that are released as hydrogen cyanide, which are thought to protect the plants from insects and other animals. For human consumption, the plants need to be detoxified, usually by soaking, drying in the sun, boiling, fermentation, or grating with roasting.[2] These processes allow the cyanogenic glucosides to be released, but depend upon traditional practices, time taken, and the availability of water. Neurotoxicity is associated with incompletely detoxified cassava, although the exact mechanisms by which these compounds cause neurological damage is unclear. The toxicity of cyanide is reduced by its transformation to thiocyanate or cyanate, which requires sulphur donors, often limited in malnutrition.

Two neurological conditions are mainly associated with bitter cassava: a myeloneuropathy and konzo. The myeloneuropathy manifests as a slowly evolving bilateral sensory polyneuropathy, optic atrophy and sensorineural deafness, and sensory ataxia, is seen in adults (particularly elderly) who have a solely cassava diet.[3]

Konzo is a condition with selective upper motor neuron damage, manifesting as an acute or subacute onset of an irreversible, non-progressive, and symmetrical spastic paraparesis or quadriparesis.[4] It is found in remote poor regions, often occurring as epidemics in times of drought, famine, and war, when the usual detoxifying preparation of cassava are not followed.

Tshala-Katumbay and colleagues have been conducting seminal studies of konzo in the Congo, often in challenging circumstances of the remote areas in which this condition is found. They have clearly documented the neurophysiological impairment of the cortico-spinal tracts,[5] the hallmarks of konzo, and impaired sensation.[6] This group were the first to demonstrate cognitive impairment with konzo,[1,7] after earlier electroencephalographic studies suggested cortical involvement.[4,8]

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The study published in *The Lancet Global Health* by Michael J Boivin and colleagues[9] uses tools established by Boivin to extend these studies by showing the persistence of impaired motor proficiency as measured by the Bruininks-Oseretsky Test (BOT-2) of motor proficiency, in both girls and boys at least 4 years after the diagnosis. It is not surprising that motor proficiency would be affected, because it is a function of corticospinal tracts. However, the high urinary thiocyanate levels (a marker of recent exposure to incompletely processed cassava) in this study suggest continuing exposure to cyanogenic glucosides, and it is not clear whether the impaired motor proficiency is permanent or result of this continuing exposure. The fine manual motor proficiency was associated with wasting (a marker of recent malnutrition) in both sexes, suggesting nutrition is important.

What is perhaps more interesting and of greater concern globally, are the cognitive findings in this area that might be associated with poorly processed cassava. This study shows neurocognitive impairment in only boys with konzo, as measured by Kaufman Assessment Battery for Children (KABC)-II at 2 years, but not at 4 years; although the differences between the sexes remains unexplained. Furthermore, the KABC-II scores of children in areas affected by konzo were lower than areas that do not have konzo, suggesting that other factors might be important determinants or that even exposure to small amounts of poorly processed cassava (increased urinary thiocyanates in the children without konzo in the konzo areas) could affect cognition. Measuring the cognition in these areas is not easy, given the poor areas where konzo outbreaks occur, the cultural adaption of the tests and the presence of many confounding factors that are difficult to measure. The authors have examined some of these factors in depth, and show that the effect of konzo on cognition on boys is independent of nutritional status as measured by stunting. As the authors point out, other factors such as micronutrients (eg, selenium) and hormones (eg, thyroxine) might affect cognitive function.

Besides myeloneuropathy and konzo, cassava is associated with other neurological disorders. For example, cassava consumption is associated with epilepsy across Africa[10] and behavioural and emotional problems in Kenyan children;[11] but it is unclear whether this is a marker of poverty and thus associated with other risk factors, or a result of neurotoxicity. The results of these studies support Boivin and colleagues' suggestion that cassava consumption needs to be investigated more thoroughly. It is unclear whether small amounts of cyanogenic glycosides affect the central nervous system, and thus cause or aggravate neurological diseases and impair neurodevelopment in children.

Konzo can be prevented with appropriate preparation of cassava, but it remains unclear whether consumption of cassava has any subtle neurotoxic effects. In view of the reliance of many poor people in many parts of the world on cassava as a staple food, we need to determine the full extent of cassava's effect on the CNS.

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