Review article

Nodding syndrome: A key role for sources of nutrition?

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ABSTRACT

Nodding Syndrome (NS) has occurred among severely food-stressed communities in northern Uganda and several other East African populations that, with their forced physical displacement, have resorted to nutritional support from available wild plants and fungi, some of which have neurotoxic potential. Among the latter is an agaric mushroom with an unknown content of hydrazine-generating agaritine, namely Agaricus bingensis, the unusually wide consumption of which may relate to the low serum levels of vitamin B6 in Ugandan NS subjects relative to controls. Hydrazine-related compounds induce patterns of DNA damage that promote neuropathological changes (tauopathy) reminiscent of those associated with established NS. While the cause of this childhood brain disease is unknown, we encourage increased attention to the role of malnutrition and B6 hypovitaminosis in the etiology of this devastating brain disease.

1. Introduction

Nodding syndrome (NS) is a pediatric epileptic and apparently progressive encephalopathy of unknown etiology that has been present in several east African countries, including first-case reports in impoverished communities in Tanzania (1934), South Sudan (1991), Uganda (1994), Democratic Republic of Congo (2016), Cameroon (2018) and Central African Republic (2019), with possible cases in Liberia (1983). Currently estimated prevalence rates include 0.3% in Uganda, 0.4% in Democratic Republic of Congo, 0.7% in Tanzania and 4.6% in South Sudan [1]. Onset of head nodding, which precedes or accompanies convulsive seizures, occurs in 2-18-year-old children [2-5], more of whom than healthy controls were born pre-term and were infected with the nematodes Onchocerca volvulus and Mansonella spp. [4,6,7]. Five overlapping clinical stages have been described among Ugandan children with NS: prodromal (staring, inattention, dizziness, etc.), head nodding, convulsive seizures, multiple impairments, and severe disability [8]. NS is often accompanied by severe malnutrition and avitaminoses with skin changes, wasted muscles, stunted growth and marasmic-kwashiokor stigmata accompanied by neuropsychiatric complaints, including slowed mentation, mental retardation and convulsions [9]. [8]. Developmental delay, tardy sexual development and seizures in NS [6] overlap with the clinical picture of Nakalanga dwarfism [10]. Some longstanding Tanzanian subjects developed signs consistent with parkinsonism [11]. The neuropathology of mid-stage NS is dominated by tau-associated neuronal degeneration, notably in the pre-frontal cortex [12].

Nodding syndrome has been the subject of two recent systematic reviews that surveyed reports relating to NS etiology, including infections, malnutrition, toxins, autoimmunity, hormonal, metabolic, genetic and psychiatric factors [1,13]. One hypothesis is that NS is a form of onchocerciasis-associated epilepsy [7] secondary to autoimmunity driven by molecular mimicry between tropomyosin in O. volvulus (OV) and leiomodin-1 in brain tissue [14,15]. Autoimmune antibodies to three extracellular peptides of glutamate receptors have been reported in NS; patients’ purified IgG antibodies induced seizure activity when released continuously in the brain of mice [16]. Specific amino acids in HLA-B have been proposed to convey disease susceptibility [17]. NS has shown both positive and negative associations with reported infection with measles virus (Paramyxoviridae) [6,18], and no association with several other virus families [19]. A small number of NS cases was found to have low levels of luteinizing hormone, follicle-stimulating hormone, testosterone and estrogen [20]. Metabolic changes reported in NS include low biotinidase and acetyl carnitine levels, normal urate levels [20,23] and leiomodin-1 in brain tissue [14,15]. Autoimmune antibodies to three extracellular peptides of glutamate receptors have been reported in NS; patients’ purified IgG antibodies induced seizure activity when released continuously in the brain of mice [16]. Specific amino acids in HLA-B have been proposed to convey disease susceptibility [17]. NS has shown both positive and negative associations with reported infection with measles virus (Paramyxoviridae) [6,18], and no association with several other virus families [19]. A small number of NS cases was found to have low levels of luteinizing hormone, follicle-stimulating hormone, testosterone and estrogen [20]. Metabolic changes reported in NS include low biotinidase and acetyl carnitine levels, normal urine levels [22] and a high-anion-gap metabolic acidosis [21]. Nodding Syndrome has been compared with wartime-induced Developmental Trauma.
Disorder [9].

Common to at least three foci of NS were population displacement and periodic food insecurity during which people resorted to food collected in the wild. Seasonal food shortages impacted the Wagakoro people of Tanzania, among whom NS was evident as far back as 1934 [11]. In NS-affected Moru communities of South Sudan, wild vegetables, fruit, mushrooms, grass, fish and bush meat were used to supplement emergency relief food, while the largely NS-free Dinka cattle herders had access to cows’ milk [4]. Even in normal times, mushrooms and African winged termites (“white ants”) were collected and sold for income by very poor households in parts of Uganda [23]. During the civil war (1991–2006) between the Ugandan government and the Lord’s Resistance Army, 1.84 million Acholi people of northern Uganda were moved to 251 Internal Displacement Camps (IDP) [24] where emergency food (maize, sorghum, beans or yellow split peas, vegetable oil and Corn Soya for children) was provided, but supplies were often of extremely poor quality and even rotten [25]. Red sorghum (serena) provided by the World Food Program was weakly associated with NS in Sudan [4] but not in Uganda [26]. In Kitgum, a high-incidence NS region in northern Uganda [27], ratios were reduced to 60% for Non-Extremely Vulnerable Individuals [24]. Although being born in an IDP camp was not a risk factor for NS in Kitgum [7], many developed NS in that setting [28], peaking 5–7 years after their arrival [29]. In addition to significantly lower body weight, food dependence on moldy maize showed the peaking 5 factor for NS in Kitgum [7], many developed NS in that setting [28]. Importantly, perturbations of the kyneurine pathway have been noted in pyridoxine-deficient animal hosts may have reduced PLP uptake linked to epilepsy and progressive neurodegenerative disease [33,34], although none of the NS cases reportedly was consuming the aforementioned mushrooms at the time of a 2016 Ugandan study of this disorder [28]. However, A. bingensis Heinem., a species known only from Africa (Bénin, Democratic Republic of the Congo, Togo, Uganda) [46,47], is gregarious around termite mounds in Western and Northern Uganda, where in particular it is used as a source of food by the Acholi people [48]. Known in Kitgum, Uganda, by the local name Ayaa kum Got, the fungus is collected in the rainy season (from March onward) and mainly harvested in August and September; the mushroom is considered by local people to be non-poisonous, and a similar species lacked acute and subchronic toxicity at levels tested in laboratory rats [43]. Other species, such as T. robustus and T. striatus, reportedly harbor an unknown heat-labile substance that does not support growth and may be toxic to rats [44].

Ingestion of certain mushrooms (specifically Agaricus bisporus, Gyromitra esculenta) can depress vitamin B6 levels, and that depletion can result in abnormal EEG patterns and intractable seizures [45], although none of the NS cases reportedly was consuming the aforementioned mushrooms at the time of a 2016 Ugandan study of this disorder [28]. Among Acholi people in the disease epicenter of northern Uganda, onset of head nodding was most frequent between March and September, when crop production was low and feeding families was challenging [18]. Wild mushrooms are of special interest because they may harbor natural compounds with toxic potential. The Acholi people normally collect mushrooms (obwool) from anthills, forests, gardens, from decomposing tree trunks, and from fresh-growing grass; they are named depending on the season of the year in which they commonly grow. Wild mushrooms consumed by the Acholi include a species of Termitomyces that grows symbiotically on termite nests (“anthills”) and is mainly harvested in August and September; the mushroom is considered by local people to be non-poisonous, and a similar species lacked acute and subchronic toxicity at levels tested in laboratory rats [43]. Other species, such as T. robustus and T. striatus, reportedly harbor an unknown heat-labile substance that does not support growth and may be toxic to rats [44].

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4. Hydrazinic fungi

All species of Agaricus mushrooms harbor the water-soluble phenylhydrazine, Agaricus bisporus (N\(^2\)-4-hydroxymethylphosphoryl)-4-hydroxymethylphosphorylhydrazine), levels of which in wild agarics range from 100 to 10,000 mg kg\(^{-1}\) fresh weight compared to 200–500 mg agaritine kg\(^{-1}\) in cultivated A. bisporus samples that are sold for use as food worldwide [51,52]. Some agaric species in Africa are considered poisonous [44]. While levels of agaritine in A. bingensis are unknown, it is noteworthy that mushroom soup prepared from an unknown fungal species is recorded as...
a pre-lacteal liquid given to Ugandan children in a nationwide survey with oversampling of IDP camps, where people were found to be most disadvantaged and children underweight for age [53]. No reference has been found to intoxication by *Gyromitra spp.*, other than isolated poisoning incidents in South Africa [44].

Arginine is catalyzed in rat and mouse kidney homogenates by removal of the glutamate group to yield reactive free hydrazine [54,55] which, after formylation to its corresponding hydrazone, may be activated both *in vitro* and *in vivo* to a methylyating intermediate resulting in the formation of O^2^-methyl-(O^2^-mG) and N7-methylguanines (N7-mG) in DNA [56-58]. Additionally, 4-hydroxymethyl benzenediazonium salt, a carcinogen in *A. bispora*, generates a carbon-centered radical, the 4-(hydroxymethyl)phenyl radical, which causes DNA strand breaks [59]. Similarly, melamethoxyxanthanol (MAM), the free-radical-generating aglycone of cycasin, increases DNA adducts (O^2^-mG, N7-mG) and elevates tau mRNA expression in rat neuronal cultures treated with glutamate [60] and, in mice, modulates brain cellular pathways involved in neurodegenerative disease and cancer in a DNA damage-linked manner [61,62]. MAM-D-glucoside (cycasin) is the principal toxin in cycad seed, the traditional food use of which by the Chamorro people of Guam is etiologically associated with the Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Complex, a tau-dominated polyproteinopathy that can begin early in life [63] and has a neuropathologic profile with some overlap with that of Nodding syndrome [12]. While there is some evidence that dietary B vitamin (B12, B6) supplementation can slow the advance of Mild Cognitive Impairment and AD [64,65], controlled studies with mouse models of human tauopathy show that chronic administration of a diet low in folate and B vitamins increases CNS homocysteine levels, which directly up-regulates the 5-lipoxygenase enzymatic pathway, thereby promoting tau phosphorylation, synaptic pathology, neuroinflammation, and behavioral deficits [66,67]. Taken together, therefore, there is a theoretical link between ingestion of hydrazinic compounds, depression of serum vitamin B6, and genesis of tauopathy. This may be of special relevance in the context of populations subject to protein-calorie malnutrition that by itself results in low vitamin B6 levels.

Several other features of NS [3,27,68,69] overlap with those associated with vitamin B6/PLP deficiency, namely: decreased ability to resist infection (nematodes? measles virus?) [70], reduced bone formation [71], cardiac dysrhythmia [72], sleep difficulties [73], swollen lips [74], anemia [75], peripheral muscle wasting [76], aggressive behavior [77], and hallucinations [78]. Vitamin B6 deficiency reduces the secretion of pituitary growth hormone [79] and mediators thereof (e.g., Insulin-like Growth Factor and/or IGF binding protein-3) associated with the stunted growth, delayed bone age and delayed onset of puberty of children with NS [20]. Significantly, NS children diagnosed with Severe or Moderate Acute Malnutrition improved markedly when treated with multivitamins, local food supplements, anticonvulsants and psychosocial support; they gained weight and height, their seizure frequency and cognitive impairment were reduced, and their health condition and mental health status improved [80].

5. Conclusion

While the etiology of NS is unknown, the disease has affected infants and children of impoverished populations in which nematode infestation and food stress are significant factors, and in whom vitamin B6 levels are low. An autoimmune disorder is posited, but studies of cross-reactivity of OV and neuroproteins have yielded contradictory results [14,15,51], and OV antibody-negative NS cases are reported [52]. Displaced and food-insecure families used wild plants and mushrooms as emergency food. Eaten during periods of near-famine are mushroom species that would be rejected as food in normal times [44] or, in the case of *A. bingensis*, reserved for older people to consume. Considered inedible in NS-affected Tanzania [83], *A. bingensis* has an unknown content of the potentially genotoxic phenylhydrazine agartine. Hydrazinic compounds have the potential to lower vitamin B6 levels, generate DNA-damaging free radicals, and modulate neuronal tau expression, and one such compound (MAM) is linked with tau-related neuronal degeneration, the dominant neuropathology of mid-stage NS. Studies are needed to determine the agartine content of wild *A. bingensis* in NS-affected areas (which include the Kabarole District of Western Uganda [84] where the mushroom is also consumed [48]), to establish the food-use patterns of this hydrazinic fungus in disease foci, to determine its acute and chronic neurotoxic potential (with respect to PLP and 3-HK), and assess whether it has a role in the etiology of NS and NS-related Nakalanga syndrome (NLS) [5,10,85]. This principle extends beyond NS in Uganda; for example, the brain disease has been recently reported in a poverty-stricken, food-insecure region of the Central African Republic [86], the location of the poisonous agaric mushroom *A. aurantioviolaceus* R. Helm [44]. Whether toxic or not, it is noteworthy that the NS/NLS-free Zulu people of South Africa claim that all edible mushrooms contain a poisonous principle when uncooked [44].

Credit

PSS conceived and drafted the paper. CO and VSP contributed information on NS electroencephalography. All authors conducted field studies of Nodding syndrome in Sudan (PSS), Tanzania (PSS, VSP) and Uganda (CO, RM, RVA, PSS, VSP).

Declaration of Competing Interest

The authors declare no competing interests.

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