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Nodding Syndrome and Autism Spectrum Disorder

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Abstract

Nodding syndrome (NS) is a devastating childhood neurological disorder seen in clusters in Eastern Africa but of uncertain nosology. It is characterized by repetitive head nodding, atonic seizures, cognitive decline, and school dropout, wasting and stunted growth and it occurs in children subject to internal displacement, food insecurity, and exposure to infectious diseases, contaminated environment and with a number of repetitive behavioral abnormalities. On the other hand autism spectrum disorders (ASD) is a group of behaviorally defined neurodevelopmental disorders with lifelong consequences. They are defined by impairments in communication and social interaction along with restrictive and repetitive behaviors. It is a complex disorder associated with a wide range of disparate and seemingly unrelated factors such as; maternal exposure to various chemical substances, maternal exposure to child abuse, maternal evidence of Diabetes, autoimmune diseases, age of either parents at conception, exposure of infants to various chemical substances, low vitamin D levels of the infant at birth, gender of the infant and a large number of genetic factors. There are a number of similarities in the clinical, biochemical and behavioral findings in children with NS and ASD.

Keywords: nodding syndrome, autism spectrum disorder, Gulu, Uganda

1. Introduction

Nodding syndrome (NS) is a devastating childhood neurological disorder of uncertain nosology [1]. The syndrome is characterized by atonic seizures, head nodding, cognitive decline, muscle weakness, school dropout, thermal dysfunction, internal displacement, food insecurity, wasting, stunted growth, exposures to infectious diseases, contaminated environment and with a number of repetitive behavioral abnormalities [1, 2]. It occurs in clusters in three Eastern African countries (Uganda, Tanzania and South Sudan) and has spatial temporality and clustered in time (during IDP period), space (clustered on either sides of the two main rivers of Aswa and Pager) and person (mainly at 5–15 years of age at onset) particularly in Northern Uganda [3]. The syndrome was first described in 1st scientific meeting organized by the Ugandan Ministry of Health (MOH) and World Health Organization (WHO) in Sheraton, Kampala, Uganda in 2012 [4]. The outcome of the meeting was the agreed WHO epidemiological and surveillance case definition of probable nodding syndrome [5, 6]. It states, “Probable NS cases should meet the following criteria:

- Reported head nodding in a previously normal person who have been observed and recorded by a trained healthcare worker.
- Head nodding is defined as repetitive, involuntary drops of the head to the chest on two or more occasions.
- Age at onset of nodding between 3 and 18 years old.
- Frequency of nodding 5 to 20 per minute.
- Plus at least one of the following criteria:
 - Other neurological abnormalities (cognitive decline, school dropout due to cognitive/behavioral problems, other seizures or neurological abnormalities).
 - Clustering in space or time with similar cases.
 - Triggered by food and/or cold weather.
 - Stunting or wasting.
 - Delayed sexual or physical development.
 - Psychiatric symptoms.”

In addition, it has been observed that nodding episodes were stimulated by sights of local food, starvation, exposure to cold weather/temperatures, cold water, stress, physical exercises and there was an association with high anion gap and that most NS began in the internally Displaced Peoples camps (IDPs) or immediately after resettlement into the satellite camps and eventually to their original villages [1–5]. Researchers propose that NS is an emerging neurological disorder in Eastern Africa likely due to factors that were experienced during the IDPs [1, 3–5] and that no new NS cases have been reported since 2012 by the Ugandan Ministry of Health (MOH) and WHO after the IDP camps were disbanded and the affected communities resettled in their villages [1, 3, 5].

Some authors have suggested that nodding syndrome may perhaps be similar to a psychogenic disease (psychogenic illness) in which physical illnesses that are believed to arise from emotional or mental stressors or from psychological or psychiatric disorders may have resulted from the 20 year old civil war that occurred in Northern Uganda. Psychogenic diseases are most commonly applied to illnesses where there is a physical abnormality and other biomarker has not yet been identified as observed in children with NS. Interestingly, the onset of NS perhaps has some similarities to a mass psychogenic illness which involves rapid spread of illness, signs and symptoms affecting a cohesive group originating from a nervous system disturbance involving seizures, loss/reduction of cognitive function with emotional and behavioral abnormalities.

However, findings in NS children contrasts greatly from epidemic hysteria, psychogenic contagion, imitation as perhaps observed among some NS families where two or more children in the same family were affected with the syndrome. Important to note was that all the children that developed NS in the same family did not show evidence of hysterical behavior but physical signs and symptoms that seems to arise from a common experience during the IDPs. Each NS child’s

presentation vary from each other and perhaps reflecting the spectrum nature of NS occurrence from the most severe to mild form. It was also noted that the course of the NS illness was greatly altered and improved by early initiation of medical intervention on the affected NS child.

The most recent findings through an extensive histoimmunochemistry of brains of deceased nodding syndrome children have revealed that Nodding Syndrome is a tauopathy [7]. This draws more attention to the possibility of diet and environmental exposures of NS children as the likely source of the pathology [3].

Interestingly, all communities where NS occur at epidemic proportion experienced some degree of internal displacement before the onset of NS [2, 3, 5]. In addition, there is a widely held belief among the affected communities in Northern Uganda that NS had possibly originated from contaminated relief food provided during IDPs or exposure to war munitions/chemicals during the protracted 20 year old war in Northern Uganda between the rebel, Lord's Resistance Army (LRA) and the Government of Uganda where 90% of the population in Acholi were displaced into IDPs [8, 9]. Some studies have reported consumption of spoiled relief foods by NS children while in IDPs but there are no mentions of the proportions of NS children that ate it [10–14]. Furthermore, Researchers have extensively investigated cause(s) of NS due to infectious agents but with no single cause that have so far been confirmed [1, 10]. In particular, studies from Northern Uganda have identified high Anion gap metabolic acidosis among NS children compared to their sex and age matched controls [1, 6, 10, 15]. These findings suggested perhaps that NS could be secondary to a metabolic disorder and perhaps a mitochondrial disorder [1, 6, 10, 15]. In addition, researchers observed that nodding episodes were precipitated by sights of local food, starvation, exposure to cold weather/temperatures or cold water, stress, excess physical exercises and there was a statistically significant association with high anion gap [1, 6, 10, 15]. Other researchers suggested that since the IDPs were disbanded, no new NS cases were reported when the affected communities resettled in their villages and feed on their home grown foods [2, 6, 8, 15] an indication that perhaps the factors that led to the onset of the syndrome were removed by moving the communities from the agents that may have been involved in its etiology.

In a recent case control study, researchers found a statistically significant association between NS and biotinidase and acetyl carnitine deficiencies [16]. In addition, other studies had previously observed a deficiency in Vitamin B6 [15] and Vitamin D in NS children [17, 18]. All these findings may suggest perhaps that NS could be secondary to a metabolic disorder and perhaps a mitochondrial disorder may be one of the factors [1, 3–6, 10, 16]. Interestingly, recent data on NS children in a study conducted by a team of researchers from the US funded by National Institute of Health (NIH) suggested an association between NS with cerebrospinal fluid (CSF) VGKC antibodies [19] and serum leiomidin-1 antibody, suggesting a neuroinflammatory cause [20]. All these findings give credence to an emerging neurological disorder which is devastating the lives of many young people in Eastern Africa and that there is no single identifiable marker and that management and prevention strategies have remained elusive.

On the other hand, autism spectrum disorders (ASD) is a group of behaviorally defined neurodevelopmental disorders with lifelong consequences [21]. They are defined by impairments in communication and social interaction along with restrictive and repetitive behaviors [21]. Autism spectrum disorder is now estimated to affect 1 out of 68 individuals in the United States with approximately four times more males than females being affected [22]. Although ASD is behaviorally defined, children with ASD also have many co-occurring medical conditions such as gastrointestinal abnormalities [23], seizures and epilepsy [24], attention

deficits [25], anxiety disorders [26] and allergies [27]. It is reported that one of the most significant co morbidities associated with ASD that causes significant disability is epilepsy [28] and a number of studies have suggested that epilepsy affects a high proportion of individuals with ASD [28]. In addition, a number of risk factors for autism can be categorized as risk factors for inflammation or indicators of inflammation [28] which seems to be similar to the factors suggested in the etiology of nodding syndrome.

2. Nodding syndrome and displacement into IDP camps

Several epidemiological studies in Uganda show NS clustered in time (IDP camp period); space (Geographically located on either side of two major rivers (Aswa & Pager) and in person (NS onset is mainly between ages of 5–15 years) [2, 3, 29]. There is an association between life in the IDP camps and onset of NS [2–4, 29]. Historically from 1986 to 2007/2008, Northern Uganda experienced a civil war between the Ugandan Army and rebel groups [2, 30]. Starting in mid-1990s, IDP camps were established in some parts of Northern Uganda with the goal of protecting the population and with an estimated 285,000 people from Kitgum District displaced into IDPs [2, 31, 32]. In the period before displacement into IDPs, there were no reported cases of NS [2]. Similarly in 2001, another community of Aromwanglobo in Awere sub county, Gulu District were moved into IDPs where many of them became dependent on food rations supplied by the relief agencies [3, 33]. IDP camps became associated with malnutrition, social norm breakdown, rising incidence of alcoholism, mental health disorders, suicidal tendencies, increasing prevalence of HIV, Cholera, Hepatitis B & E and other infectious diseases, neglect and waste of the youths [2–4, 29]. The IDPs began to be disbanded in late 2006 when the LRA retreated to South Sudan but during the height of the insurgency in 2002 over 1.5 million people were displaced in the Acholi sub region and thus accounting for over 90% of the population [31, 32]. After 2007, the Government began returning the displaced people into their homes in a phase-wise approach from the main IDPs to satellite camps near their villages [2, 31, 32]. Eventually by 2010, the communities were returned to their original homes in their farmland where the returnees were to settle and rebuild their lives [2–4, 31, 32].

In 2009, the Ugandan Ministry of Health (MOH) identified NS in communities in Northern Uganda and later on established NS screening and rehabilitation centers in 2012 where NS children were treated with anticonvulsants, multivitamins and nutritional supplements [3, 5, 6, 10, 19, 29]. The consistency of supplies and rehabilitation processes faced challenges including irregular supply of anticonvulsants and food for NS children and the vulnerable families [2, 8, 9, 31, 32]. In the same period, there was an apparent relationship between the peaks of NS cases in Kitgum District and earlier peak influxes of households into IDPs [2] which was similarly observed in Awere Sub County in Gulu district [3]. Important to note was that the 1997 peak influx of IDPs in Kitgum District was followed 7 years later by an elevated number of new NS cases in 2004 (2003–2005) and similarly in the 2003 large influx of households had a larger peak in new NS cases 5 years later in 2008 [2]. This was similarly observed in Awere in Gulu where the 2001–2002 influxes were followed with increased incidences of NS, 7 years later in 2008–2009 [3]. The peaks of reported NS onset correlated with peaks of household displacement and food insecurity, where residents were heavily dependent on food aid from relief agencies [2, 3, 29, 31–34]. The IDP camps were exceptionally poor, insecure, unsanitary, with overcrowding, violence, food insecurity and squalid, and morbidity and mortality rates were high [2, 35].

In 2005, a Government survey of Kitgum district estimated an IDP population of 310,111 persons; 21% of whom were children under 5 years [2]. At the time of the survey, over 66% of children were reported to have been ill sometime in the previous 2 weeks and the crude mortality rates were reported to be 2 deaths per 10,000 per day and double that rate for children under the age of 5 years [2, 29, 35]. In addition, the top self-reported causes of death in IDPs were malaria/fever (34.7%), AIDS (15.1%) and violence (10.5%) [2] and water was obtained from protected sources but water intake was low and the waiting time was high and the infant feeding practices were poor [2]. It is reported that for children under the age of 5 years, the traditional disease concept of “Two Lango” or “Gin pa Omiru” which was a combination of oral thrush, malnutrition and diarrhea was the second most commonly reported causes of death [2, 34]. These findings were thorough analysis of the events in all IDPs across the Acholi and Lango sub regions where NS occurred at epidemic proportions.

3. Epidemiological, environmental and dietary findings on nodding syndrome children

Studies show that NS in Awere, Gulu district, Northern Uganda was first noted in 2002 which corresponded with 1 year stay in IDPs [3]. The month of peak incidence of NS onset was April and October [3]. These peaks corresponded fairly with the peaks of monthly average rainfall for 1st and 2nd rainy seasons [3] and related to scarcity of food as observed by Landis et al. [2]. The factors around the syndrome onset could have perhaps been in IDPs since all NS children were in IDPs before onset of nodding [2, 3, 29]. The other reason could perhaps be that NS children who were born before IDPs, had developed NS earlier except, the condition was not detected or overtly manifested but that the IDP camp conditions precipitated its overt manifestation perhaps coupled with other stressor factors such as *Onchocerca Volvulus* (OV) infection; malnutrition, war trauma and febrile illnesses [1–5, 29]. In addition, most NS children were in 1st, 2nd and 3rd birth orders in descending orders respectively [3, 5] and all of them experienced IDP life which peaked at 5 years of IDP stay [3]. Additionally, most NS children have other siblings with NS and its occurrence in siblings mirrored NS children’s birth orders [3]. This finding, perhaps point towards a possibility of an acquired disease which was overtly manifested possibly as a result of family/household factors such as; poor storage of food leading to contamination and/or infection with OV or stress which made the syndrome perhaps manifestly overt on exposure to these factors [3, 5]. Perhaps the perfect examples of such could be seen in deficiencies of metabolites in acquired diseases whose disease occurrence becomes overtly expressed in circumstances of stress [36]. That could perhaps explain why there are no new NS cases since 2012 when the communities were resettled in their villages and feed on their own home grown foods [3, 19, 29, 37].

In general, the information provided by parents of NS children show that NS children were all reported to have been born normal and that the developmental milestones were normal until NS began [1, 3, 5, 29, 37, 38]. Before onset of nodding, food listed in [3, 5] were the supplementary and weaning foods that were supplied by relief agencies and eaten by the IDPs residents including NS children [31]. The quantity and duration of these food ration eaten by each NS child could however, not be determined but report on it was provided by the World Food Program (WFP) [31, 32].

Interestingly in 2012 when some NS children were examined before admission to the Hope for HumanNs (HfH) centre for NS rehabilitation, they were diagnosed

mostly with Severe Acute Malnutrition (SAM) and a few with Moderate Acute Malnutrition (MAM) respectively on the basis of their z-scores [38]. Upon enrolment for a multidisciplinary and syndromic treatment with anticonvulsants, multivitamins, local food supplements, and psychosocial support; their health conditions greatly improved, seizure frequency reduced, mental health status improved, cognitive impairment improved, they gained weight and height and by 2014 when the author re-assessed these NS children in a longitudinal study, most of them had improved and categorized as MAM and healthy nutritionally [5, 29, 38, 39]. This observation was perhaps due to good feeding program at the HfH centre and adequate rehabilitation processes accorded to NS children. However, much as they had improved and some had returned to school, none of them could be declared cured because they still experienced sporadic episodes of nodding, emotional and perceptual disturbances and some cognitive impairment [5, 10, 29, 38, 39].

4. Biotinidase and acetyl carnitine deficiency, nodding syndrome and metabolic disorder

In one of the pilot studies conducted on NS children in Northern Uganda, it was observed that most NS children demonstrated a deficiency of biotinidase enzyme activity ranging from 0 to 100% [16]. The average percentage deficiency was 78% (78 SD \pm 13.362), an indication that this enzymatic deficiency was a spectrum which varied considerably from one NS child to another depending on the percentage deficiency of biotinidase activity [40–43] just like the severity and clinical presentations of NS varied from one child to another [5]. Biotinidase deficiency has commonly been classified as partial or profound deficiency whereby the clinical presentations and occurrence depended on the percentage deficiency and the presence of stressor factors [40–43]. It is reported that partial biotinidase deficiency is a milder form of this condition in which without treatment with biotin, the affected child may experience hypotonia, skin rashes and hair loss, but these problems may appear only during illness, infections, or other times of stress [40–43]. These authors suggest that NS occurs as a spectrum similarly to biotinidase deficiency and that for NS children that had partial biotinidase deficiency, they experienced severe stress (Malnutrition, psychological stress and *OV* infection) that resulted into the overt presentation of NS [16]. The stressors in this case could have perhaps been the IDP camp life, where there was inadequate food for consumption (with resultant malnutrition) [31, 32, 35] or infection with *Onchocerca volvulus* which afflicted nearly 80% of NS children or psychological stress [1, 4, 17]. Other stressors could have been severe illnesses such as malaria, meningitis, cholera and others which were common in the IDP camps and affected a large number of IDP residents [2, 35, 44]. On the other hand profound biotinidase deficiency is a more severe and can cause seizures, weak muscle tone (hypotonia), breathing problems, hearing and vision loss, problems with movement and balance (ataxia), skin rashes, hair loss (alopecia) and fungal infection particularly candidiasis [40–43]. The affected children with biotinidase deficiency also have delayed development milestones [40–43]. Most of these symptoms and signs were similarly observed in NS children in Northern Uganda.

The clinical presentations of NS children examined in 2012 and repeated in 2014 as part of a longitudinal study are similar to the clinical presentations of biotinidase deficiency [39]. However, hearing and vision loss which are typically seen in profound biotinidase deficiency were not observed in 2014 perhaps due to 2 years of rehabilitation where it is suspected that the symptoms and signs which were akin to profound biotinidase activity deficiency could not all be observed [39]. It is

important to note that biotinidase functions by recycling the vitamin biotin which is also known as vitamin B7 and it is bound to amino groups of lysine residues of apoenzymes [41–43, 45]. If levels of serum biotinidase are low then biotin cannot be broken down and released from proteins into the diet [41–43, 45]. In addition, biotin serves as a coenzyme for four carboxylases enzymes; propionyl-CoA carboxylases & β -methyl crotonyl-CoA carboxylases, which are important in protein catabolism; pyruvate carboxylases, which are essential for gluconeogenesis and acetyl CoA carboxylases, which are involved in the first step in fatty acid synthesis [42, 45]. Similarly, the majority of the NS children had deficiency of the acetyl carnitine, a metabolite responsible for the transfer of short chain fatty acids into the mitochondrium for metabolism and this perhaps represented the view that at the time of stress, NS children were unable to utilize the short chain fatty acids and perhaps with the resultant observed clinical features. Similarly, a previous study had noted a near significant association between NS and pyridoxine deficiency (Bunga's study ($p = 0.06$)) [11]. This finding was very important as seizures are normally associated with abnormal pyridoxine metabolism [11].

In the same study, the levels of serum urate were overall unremarkable, demonstrating that NS wasn't perhaps associated with abnormalities involving purine or pyrimidine metabolism [16]. The urate/creatinine ratio levels were lower than normal range, suggesting that NS was not probably associated with rhabdomyolysis [16]. In addition, it was previously observed by another author that NS was associated with vitamin D deficiency in which 7 out of 8 NS cases had reported vitamin D deficiency [17]. Furthermore, findings from other studies indicate that the levels of organic acid in urine were generally high and this was consistent with other findings of high anion gap metabolic acidosis seen in NS patients in a case control study [1]; case series [17]; case reports [10, 15] and clinical studies [39].

Therefore, NS in South Sudan & Northern Uganda represents an emerging neurological disorder where investigations searching for potential environmental toxins have not yet been fully conducted [4, 29, 46]. It is reported that thousands of pesticides, solvents and other industrial chemicals have not been tested for neurodevelopmental toxicity in the community where NS occurs at epidemic proportions [46]. Historically, it has taken several decades of scrutiny to confirm developmental neurotoxicity secondary to industrial chemicals following initial clinical diagnosis of poisoning [47]. In South Sudan in 2011, CDC study collected urine and blood and did analysis for heavy metals; however the preliminary analysis of blood and urine results remains unpublished [48]. Bunga's (2011) Sudanese unpublished study mentioned in Dowell et al.'s study, found no abnormality detected in the urine for mercury, thiocyanate and arsenic [11]. Foltz et al., tested serum for copper and urine for homocysteine & thiocyanate levels [49]; Sevjar et al. reported to have had an unremarkable toxin analysis (data not shown) [50]. The vast majority of investigations into possible neurotoxic causes to NS children came from information regarding diet, collected via questionnaires from NS caregivers [14, 18, 46, 51–54]. There have been associations that have been demonstrated between eating red sorghum and NS in a South Sudan study [46]. It has also been further reported that there is an unidentified associated with mycotoxins which was suggested as a likely putative agent [4, 29, 46]. Interestingly to date, there is no published laboratory microbiological or neurotoxicological analysis of food that was eaten in the IDPs camps to confirm these hypotheses. Further to this, NS in South Sudan and Northern Uganda is suspected to be caused by a chemical neurotoxin from war munitions used during the civil wars [8, 9, 46]. However, there are no published studies investigating quantifiable war munitions and/or chemicals as possible cause(s), despite several case control studies demonstrating a positive association with exposure to war munitions and gun raids [11, 46, 49]. However, a

recent case series in Northern Uganda found that all NS children had been exposed to either severe war-related psychological and physical trauma and that most of those interviewed in an observational study laid blame on war munitions/chemicals [8, 55]. These findings showed that the environmental exposures of the affected communities were reported although not proven but still forms a basis for hypothesis that it could be a factor that could not be ignored in the epidemiology of NS in Northern and South Sudan.

5. Experience of treatment and rehabilitation of children with nodding syndrome

The treatment and rehabilitation responses of NS children in Northern Uganda by Hope for HumaNs (HfH) has registered positive outcome with improved mid upper arm circumference (MUAC), height, weight and hematological indices [39]. The comprehensive rehabilitation approach (correcting protein-energy using MAMA nutritional food supplements and vitamin-related malnutrition, deworming, oral fungicide, anti-seizure medications (sodium valproate with/without Carbamazepine); close monitoring; tailored dosing and adjustments; special needs education program; counseling) pioneered by HfH at Odek rehabilitation centre has proven clinically transformative (steady growth, improved emotional and marked seizure reduction status—though greater among males than females for unknown reasons) [3, 4, 38]. It was still noted though that cognitive, behavioral problems and social difficulties still confronted these NS children even 9 months after rehabilitation at the HfH centre [39].

6. Nodding syndrome (NS), biotinidase and acetyl carnitine deficiency and autism spectrum disorder (ASD)

Although autism spectrum disorder (ASD) was originally thought to be a static, inheritable neurodevelopmental disorder, its understanding is currently undergoing a major shift [45]. It is now emerging as a dynamic system of metabolic and immune anomalies involving many organ systems, including the brain and environmental exposures [45, 56]. The initial detailed observation and inquiry on patients with ASD and related conditions, the histories of their caregivers and families have been providing important information [45]. To date, it is not yet clear how gastrointestinal (GI) factors are related to ASD [45, 56] however, many patients with ASD have a history of previous antibiotic exposure or hospitalization, GI symptoms, abnormal food cravings and unique intestinal bacterial populations, which have been proposed to relate to variable symptom severity [45, 57]. An author recently recommended that new approaches would be required to examine the diverse symptoms and co morbidities of this growing family of neurodevelopmental disorders known as autism spectrum disorder [45]. It is reported that neurochemical changes which is consistent and predictive with findings in ASD patients, including neuroinflammation, increased oxidative stress, mitochondrial dysfunction, glutathione depletion and altered phospholipids/acylcarnitine profiles, have been observed [45, 57]. In addition, propionic acid have been reported to have bioactive effects on; neurotransmitter systems; intracellular acidification and calcium release; fatty acid metabolism; gap junction gating; immune function and alteration of gene expression that warrant further exploration [45]. Furthermore, other authors have proposed that traditional scientific experimentation was required to verify the hypothesis that enteric short-chain fatty acids may be a

potential environmental trigger in some forms of ASD [45, 56, 58]. Interestingly, the collaborative developments in systems biology particularly examining the role of microbiome and its effects on host metabolism, immune and mitochondrial function and gene expression, is reported to hold a great promise in investigation on ASD [23, 45, 58–61]. It is further suggested that the microbiome produces an array of bioactive metabolic products capable of entering systemic circulation [23, 45, 61]. Other authors have suggested that enteric microbiome and its metabolic products were dynamic and could be altered throughout an individual's life cycle, particularly during the first 18 months of life [57–60, 62]. In addition, it was reported that the metabolic products from the GI tract microbiome could have profound and dynamic effects on host metabolism, immune functions and gene expressions which happens in many organ systems including the CNS [58]. Furthermore, other authors recommended that it was important to consider the effects of infant formula versus breastfeeding, a high-calorie Western diet and exposure to antibiotics and disinfectants in human beings, animals and plants on the alteration of the human microbiome and its metabolites [45, 54, 56, 63, 64]. These should be considered a possible source of environmental triggers of many diseases of increasing incidence including ASD [45]. This was particularly evident from human populations who migrated to Western societies, such as the Somalis in the diaspora, who appeared to have a much higher incidence of ASD than it existed in their country of origin [45, 65].

Furthermore, there are examples of this experience in biology to show that it may be possible that GI biome could alter the behaviors of animals [45, 66–68]. Examples; Rabies and *Bornavirus* infect the CNS in animals and induce aggression that spreads the virus in the saliva from one animal to another through biting behaviors [45]; *Cordyceps* (*Ophiocordyceps unilateralis*) is a fungal infection that affects the behavior of ants, causing them to climb to the top of plants before they die [45]. The resulting fruiting bodies of the fungus then sprout out of the dead insect to spread spores [45]; in addition, *Toxoplasmosis* causes rodents to act without an appropriate fear response, leading to transmission of the infectious agent through cats via predation and ultimately on to humans [45]; Furthermore, Mundane acts such as sneezing with a common cold or increased gastric motility leading to nausea and vomiting in viral gastroenteritis are said to be in the best interest of spreading the infectious agent [45]. The researcher then ponders whether similar things that happen such as carbohydrate craving, diarrhea and fecal smearing in ASD helps to feed and spread bacteria? [45]. It was observed that families of ASD children just like NS children often become more alienated when they are told about their children's regression condition and that there was not much that could be done [45] and they were often encouraged to use medications to partially reduce aggressive behavior and to wait for their turn for the under-funded behavioral intervention programs that take years to begin and years to complete [45, 56]. The strain and stress of dealing with these children can destroy families and end productive careers, leading desperate and vulnerable parents to turn to unproven controversial treatments that can be costly, potentially dangerous and without confirmed effectiveness [45]. This has been observed in parents of children with NS who have in their helplessness resorted to the use of traditional medicines including and not limited to the use of crashed roots, traditional medicines, witchcrafts, prayers, visits to shrines and animal sacrifices as remedies for the treatment of this syndrome [10, 15, 46, 50]. In addition, there are new interesting issues to learn about some observations of bizarre food cravings, GI symptoms, epilepsy, infectious processes and metabolic disturbances in children affected with ASD [45, 68–70] just like for the NS children. However, there were reports that some ASD children appeared to improve, either spontaneously, after certain broad spectrum antibiotics, or possibly

by altering their diet [45]. This particular scenario has been observed in NS children at the HfH rehabilitation centre in which NS children whose feeding pattern (using a locally prepare MAMA food supplement) and symptomatic treatment have made them improve physically but still confronted with cognitive, emotional and perceptual difficulties [3, 4, 38, 39]. A researcher wonders whether there might be a common digestive system link to these findings even if current understanding in conventional western medicine could do little for these ASD and NS children. The mitochondrial disorders observed in ASD—studied extensively by Dan Rossignol, Rossignol Medical Center, Irvine, California, and Richard Frye, University of Arkansas, appeared to occur largely through environmental and not inherited means [45, 71, 72]. It is reported that these disorders observed might be caused by or at least worsened by enteric short-chain fatty acids including propionic acid from GI tract bacteria [45, 57, 71, 72]. This is similarly a suggestion being advanced on NS children seen in Northern Uganda and South Sudan because first, they were made to feed on food provided by the relief agencies which were not their usual diet during IDPs period (plumpy nuts, powdered milk, soya beans, red sorghum, cooking oil which were sometimes of uncertain composition, rice, yellow posho and other food substances that were made available to them) [3]. Secondly, there have been consistent observation in case control studies, case series, case reports and clinical and biochemical studies that NS children do have high anion gap metabolic acidosis with depleted bicarbonate levels and one author proposed that the cause of this syndrome may perhaps be due to mitochondrial disorders, a factor which may be common to ASD and NS [1, 2, 10, 15, 50]. The cooking oil supplied and consumed by the IDP residents provided by the relief agencies were not common to their GI microbiome but may have perhaps been those of short chain fatty acids [1–3, 5].

Furthermore, the reported collaborative work of Dr. Frye, who reviewed his ASD patient population and found a large subset with the lipid (acylcarnitine) and biochemical (citric acid, glutathione) findings predicted by the propionic rodent model was another breakthrough in the advancement of science of ASD [45, 71–74]. His finding in June 2012, that there was an absence of genetic abnormalities to explain these changes in ASD, suggesting that the biochemical findings stemmed from environmental factors and were not inherited [45, 73, 74]. These similar findings were observed in NS children in Northern Uganda where there have been observed acetyl carnitine and biotinidase deficiency in a pilot study conducted on NS children undergoing rehabilitation at the HfH centre [5].

In addition, a recently work with Bistra Nankova, from New York Medical College, found that short chain fatty acids, including propionic acid are histone deacetylase inhibitors and thus were switchers for genes particularly those involved in the metabolism of catecholamines and was important in anxiety, arousal, movement disorders, aggression and cravings [45]. This brings to mind a thought that potentially bacteria can control and tinker with our metabolisms and even human genes [45]. Additionally, some researchers now argue that these bacteria, through natural selection, may be controlling or modulating our behavior and they may serve the host well until environmental factors such as the Western diet or overuse of antibiotics reset the microbiome to produce alterations of this behavior—the obsessions, perseverations, food fixations and tics but also at times enhanced memory associated with ASD [45, 75–80].

The author argued that it was important to note that propionic acid affects multiple systems at different developmental periods in a complex manner and that the evidence of increased propionic acid or other short-chain enteric fatty acids involved in the pathophysiology of ASD, although compelling, was still circumstantial [45, 77–79]. These researchers further reported that propionic and related

short-chain fatty acids could elicit behaviors that are anxiety-like, perseverative, repetitive, ritualistic and antisocial [80–84]. These behaviors were reported to be common to many other neuropsychiatric conditions (obsessive compulsive, mood, anxiety, attention deficit/hyperactive and eating disorders, irritable bowel syndrome, and schizophrenia) where infectious agents have been proposed [45, 81, 84]. In addition, the researchers argued that there was a growing incidence of ASD and ASD-related conditions, coupled with the observed alterations in the human microbiome secondary to dietary, medical and agricultural factors and their potential effects on human and animal behavior should be examined further [45, 58, 60, 81, 85, 86]. Professor Jared Diamond contended in his book *Guns, Germs, and Steel* that the impact of human migration and urbanization, domestication of plants and animals and resultant human diseases shaping cultures was not trivial [87]. He further stated that, it was not so far-fetched to say that Western society has altered human microbial populations, which in turn may be altering human behavior and culture [87]. The similarities in the clinical presentations and the biochemical findings in children with NS and ASD draws the attention of these researchers to perhaps an understanding that NS may perhaps be a condition akin to autism spectrum disorder (ASD); a disease spectrum that is not well understood but continues to ravage the lives of many young people and families in developing and developed world akin to the experience of NS in the East Africa. Nodding syndrome were seen only in children who were born normal, lived in the IDP camps, were from poor families, all ate food ration from relief agencies foreign to their GIT and that all the children who developed NS were IDP resident at some stage in their lives [2–5]. The relief agencies distributed various forms of cereals (Plumpy nuts, Beans, soya, red sorghum, yellow posho, and maize) and cooking oil which were perhaps foreign to their GI microbiome of the affected communities and the communities ate them, they provided cooking oil whose constituents were foreign to the population and they consumed them [2, 3, 33, 34]. In addition, NS children have been found to have deficiency of Vitamin B6, Vitamin D, Acetyl carnitine and biotinidase [5]. These factors point to the changes in the diet of the children and adults in these communities where NS occurs at epidemic proportions during and after the war and/or IDPs camp life which may have perhaps been partly responsible for the syndrome that we have been investigating without finding the cause [2, 3, 5]. Important to note was that the Ugandan Ministry of Health and World Health organization have since 2012 reported no new cases of NS in Northern Uganda since the IDP camps were disbanded and communities returned to their farmland and feed on their locally grown foods [2–5]. Therefore autism spectrum disorder, nodding syndrome, biotinidase and acetyl carnitine deficiency [1–3, 5, 88] may be conditions that share many things in common and this may be the right moment to think of considering them as similar/common entities.

7. Conclusion

Nodding syndrome (NS) is a childhood neurological disorder that occurs in clusters in Eastern Africa and of uncertain nosology. However, studies have demonstrated biotinidase and acetyl carnitine deficiency, Vitamin B6 deficiency, high anion gap metabolic acidosis and Vitamin D deficiency. In addition, NS children experienced internal displacement, fed on IDP diets which were mainly foreign to their GI microbiome and other environmental exposures, exposure to wartime situations and infectious diseases at childhood. Rehabilitated of NS children using home grown food supplement (MAMA supplement plus other symptomatic remedies), their conditions improved tremendously and some have returned to school

although there is no clear evidence that they have been completely cured. Furthermore, there are no new cases of NS as reported by the Ugandan Ministry of Health (MOH) and World Health Organization (WHO) since 2012 when the IDP camps were disbanded and communities resettled in their own communities and feed on their own home grown foods. Although these findings are inconclusive at this stage, perhaps NS observed in this region may be akin to autism spectrum disorder (ASD).

Acknowledgements

The authors acknowledge the support of Hope for HumaNs (HfH), an NGO which contributed tremendously towards the rehabilitation of NS children for over 5 years. Gulu University, an academic institution which has provided logistical and administrative support to the authors for this book chapter.

Conflict of interest

All authors declare no conflict of interest.

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