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IS THERE A LINE BETWEEN INTERNAL DISPLACEMENT; ENVIRONMENTAL AND DIETARY FACTORS IN THE ONSET OF NODDING SYNDROME IN NORTHERN UGANDA? A CLINICAL OBSERVATIONAL STUDY DESIGN

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ABSTRACT

Background: Nodding Syndrome (NS) is a childhood neurological disorder characterised by atonic seizures, cognitive decline, school dropout, muscle weakness, thermal dysfunction, wasting and stunted growth. The objective of this study was to describe the epidemiological, clinical, dietary and environmental factors associated with NS children who were undergoing treatment at the Hope for HumaNs (HfH) rehabilitation centre in Northern Uganda. **Methods:** We conducted a study on 47 NS children in 2014 as part of a pilot project. This was one of prospective studies conducted at HfH centre to find the cause of NS. Ethical approval for the study was obtained from Lacor Hospital IRB (LHIREC No. 065/10/14) and STATA version 12 (Stata Corp LP, Texas, USA) was used for data analysis. **Results:** We found Low BMI for age (z-scores) mean 16.92 95% CI(16.09, 17.74); Current age 14.08 95% CI(0.78, 4.66); Duration of IDP camp stay 4.82 95% CI(4.48, 5.21); Age of nodding onset 8.02 95% CI(7.03, 9.01); Nodding associated with loss of consciousness 1.98 95% CI(1.61, 2.35); multiple nodding episodes (χ^2)=22.15, p=0.005; Birth oders (χ^2)=9.68, p=0.38; Caretakers were their mothers (χ^2)=6.39; p=0.041; Mothers gave better social support (χ^2)=10.59; p=0.005; NS child had other siblings with NS (χ^2)=9.68, p=0.004; and NS child was in the IDP camps (χ^2)=22.15, p=0.005. **Conclusion:** Nodding Syndrome is a childhood neurological disorder identified by World Health Organization (WHO) in three sites in East Africa but the cause is not known. The epidemiological, clinical, dietary and environmental analysis of NS children's history and physical assessments show that we may perhaps be dealing with environmental and dietary factors that have not yet been identified but perhaps experienced in the IDP camps. There are no new NS cases reported by the Ugandan Ministry of Health (MOH) or WHO since 2012 when all the IDP camps had been disbanded and communities resettled in their villages and feed on their own home grown foods.

KEYWORDS: Nodding Syndrome, IDPs, environmental and dietary factors, Uganda, Hope for HumaNs (HfH).

1.0 INTRODUCTION

Nodding Syndrome (NS) is a childhood neurological disorder characterised by atonic seizures, cognitive decline, school dropout, muscle weakness, thermal dysfunction, wasting and stunted growth.[1,2] Disparities in epidemiology, presentations and investigations between NS described in Tanzania and in South Sudan/Northern Uganda point towards a disease of perhaps differing aetiology.[1,3,4] All these communities where NS occur at epidemic proportions experienced some degree of internal displacement before the onset of the syndrome.[2] There is a widely held belief among the communities in Northern Uganda that NS had possibly originated from contaminated relief food provided during the internal displacement into IDP camps 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 when the population were displaced into the Internally Displaced Peoples camps (IDPs).[5,6] Several studies have reported consumption of spoiled relief foods by NS children while in the IDP camps but with no mention of the proportions of NS children that ate it.[7,8,9,10,11,12] In addition, several researchers have extensively investigated cause(s) of NS due to infectious or nutritional deficiencies with no cause that have so far been identified.[1,7] A series of studies from Gulu University in Northern Uganda have identified High

Anion Gap metabolic acidosis among NS children compared to their sex and age matched controls.[1,7,13,14] These suggested that NS could be secondary to a metabolic disorder and perhaps a mitochondrial disorder.[1,7,13,14] In addition, they have observed that nodding episodes were precipitated by sights of local food, starvation, exposure to cold weather/temperatures or cold water, stress, physical exercises and there was a statistically significant association with High Anion Gap[1,13,14] and these began in the IDP camps or immediately after resettlement into the satellite camps and then their villages. This researcher suggests that NS is an emerging neurological disorder in East Africa likely due to factors that were experienced during the internal displacement into IDPs[1,5,7,15] and that no new NS cases have been reported in the area by the Ugandan Ministry of Health (MOH) and WHO since 2012 after the IDP camps were disbanded and the affected communities resettled in their villages and feed on their own home grown foods.[1,2,15] It is important to note that in late 2012, the Ugandan Government conducted an extensive aerial spray of the two rivers (Aswa and Agago) to eliminate the black flies in support for the control of *Onchocerca Volvulus*.[15] The effects of these interventions await a formal evaluation research.

We aimed in this study to describe the epidemiological, clinical, dietary and environmental factors associated with this disorder that affects NS children in Northern Uganda as a result perhaps of displacement, food eaten in IDPs and other related environment factors.

2.0 MATERIALS AND METHODS

2.1 Study Design

This study was a prospective observational study conducted on 47 Nodding Syndrome children admitted to Hope for HumaNs (HfH) Nodding Syndrome rehabilitation centre in 2012 and were studied in 2014.

2.2 Study site

This study was conducted at a Non-Governmental Organisation (NGO)-Hope for HumaNs (HfH) centre at Aromowang lobo. The site is situated in Odek Sub County, Gulu district; an area in the epicentre of Nodding Syndrome epidemic in Northern Uganda.[1,2,7,15,16] It is an area which is largely a rural community with one of the highest levels of poverty, inadequate water and sanitation and with significant disease burden.[15,16,17] The centre was built in 2012 as a private initiative of two American founders from Texas, USA solely for the treatment and rehabilitation of NS children on an outpatient basis. It is a well built facility with classrooms for teaching basic education; a medical clinic run by qualified medical staff; a refectory and cooking place for the food rehabilitation, a play field for soccer; a piggery for livelihood project and a medical staff quarter. There was a daily schedule of activities for the NS children undergoing rehabilitation beginning with travel from home, registration, administration of medication, physical exercises, feeding, bathing, hygiene, toiletry, psychotherapy, music, dance and physiotherapy. This was a comprehensive rehabilitation centre which was effectively run by the administrators of this Organization.[1,2,16] The NS children were undergoing a multidisciplinary management with anticonvulsants; multivitamins; folic acid (5mg/day); high energy food for nutritional rehabilitation; social care; hygiene and basic educational skills. Before enrolment of NS children into the HfH rehabilitation centre they were assessed by a multidisciplinary team from Ugandan Ministry of Health (MOH), Gulu District Health Department, Gulu University and other research institutions in Uganda.

2.3 Study population

We recruited forty seven (47) Nodding Syndrome children from the area of study in 2014. Each child was individually screened and examined by the research team to confirm conformity to the inclusion criteria (probable Nodding Syndrome) as defined by the WHO surveillance and epidemiological case definition agreed in Kampala in 2012.[1,2,13,14,16] Forty (40) NS children were undergoing comprehensive daily outpatients' rehabilitation and seven (7) were NS children in the community who were being served by the medical outreach programs.

2.4 Recruitment methods

We recruited NS children consecutive into the study.

2.5 Inclusion criteria

We recruited NS children as participants into the study after diagnosis, in accordance with the WHO epidemiological and surveillance case definition of probable Nodding Syndrome.[1,2,16,18] Informed consent from parents/Guardians and assent for children 14 years and above were required.

2.6 Exclusion criteria

We excluded those children aged 2 years and below with reported history of abnormal physical, cognitive and social development prior to onset of nodding and lack of consent from their parents/guardians.

2.7 The study instruments

We used a questionnaire designed to investigate the current and past physiological, psychosocial and mental health conditions of NS children and their mothers. These questions were directed towards the parents/guardians. The questions included information on the socio-demographic characteristics; age, sex, weight (Kg), height (cm), Mid-Upper-Arm-Circumference (MUAC), level of education, address, the head of household, the caregiver, school attendance, when nodding episodes were first observed, the birth order, history of onset of Nodding Syndrome; where NS started from; the year of onset; the month; the relationship between the onset of nodding with IDPs, the nodding trigger factors, the number of nodding episodes that occurred per day, the observed time when it most

frequently occurred; Other symptoms such as epileptic fits, uncoordination of limb movements, disorientation, drooling of saliva, tongue biting, urinary and stool incontinence among others were the vital symptoms explored in the history of each NS child covered under this study. In addition, a whole section of the questionnaire explored the psychological and social assessment of a wide range of inquiry into the sleep pattern, changes in appetite, emotions, predominant thoughts/worries, perceptual disturbances before and after nodding, history of mental illness in the family, the number of other siblings in the family with NS and extent to which social support was being offered to the NS child in the family.

Further to that, each NS child underwent a neurological assessment using a 5 criteria methods to determine whether there is any mental impairment, visual impairment, Gait ataxia, inability to walk and features of Parkinsonism (resting tremours, bradykinesia and rigidity). In addition, each NS child underwent disability assessment using a four scale criteria; motor disability using Gross Motor Function Classification System (GMFCS) which was Graded as; I, II, III, IV and V; feeling and swallowing difficulties, behavioural difficulties, cognitive and learning difficulties, emotional problems, malnutrition and growth failure, speech difficulties, personal care and daily activities and injuries and/or burns that may have been experienced over the period.

We further conducted a mental state examination of each NS child using a nine step assessment methods including awareness of the environment; concentration and attention; ability to recall (memory) for recent and past events; general appearance; interaction with caregivers and others; Speech and language ability whether appropriate or not; the mood and affect whether normal, low or elated; the thought process whether appropriate or inappropriate with emphasis on obtaining whether they had suicide ideation or persistent fears/worries; and finally assessment of the patient's perceptions including knowing whether the patient had hallucinations or any illusions.

The questionnaire explored further the suspected risk factors of the syndrome among the children suffering with NS including IDP camp life, maternal factors during pregnancy; maternal vaccination, maternal illnesses during pregnancy; maternal medications with adverse effects during pregnancy; mode of delivery of the affected NS child and postnatal care. It further looked into the breastfeeding habits of the NS child, its duration, when the supplementary food was introduced, what were the weaning foods and the weaning age. In addition, the types of illnesses suffered by the NS child before NS onset were explored including diseases which could present similarly such as cerebral malaria, meningitis, measles, head trauma and others that were required to be specified by the parents/Guardians. Furthermore, the pattern of growth and development of the affected NS child was probed to obtain information on family history of epilepsy and Nodding Syndrome and the number of family members affected by the two conditions.

Finally, the last part of the questionnaire described the treatment history after the onset of the Nodding Syndrome symptoms. The questions explored the treatment being received for the condition; whether modern or traditional medicine and to establish whether each of them was providing improvement to the condition of NS child.

2.7.1 Anthropometric measurements

Each Nodding Syndrome child participant was measured clothed and barefoot for height (cm) and body weight (kg). Weight was measured using a calibrated digital weighing scale which was standardised before use while height was measured in centimetres using a stadiometer. The mid upper arm circumference of the left arm was measured using a MUAC tape approved by the WHO for the assessment of nutritional status and recorded in centimetres (cm).

2.8 Ethical Considerations

This study was approved by the Local IRB; Lacor Hospital Institutional Review and Ethics Committee (LHIREC LHIREC No. 065/10/14). The research team worked in close collaboration with the administration of HfH centre, Gulu District Health Department, the local councillors and the village health teams (VHTs). Parents/Guardians of the NS children gave informed consent on behalf of the NS child participants but for those that were above 14 years but below 18 years, assent was also obtained. Two medical students from Gulu University Medical School were the research assistants (Dr. Akite Sarah and Dr. Lucy Akello Emma) together with a senior clinician DLK (author) supervised the data collection. The majority of the parents/Guardian of the study participants could not read and write and so we used the placement of inked thumbprints on the position for signature in the questionnaires. In addition, the patients' identity was anonymized and only accessible to the main investigator of this research. We obtained informed consent from parents/guardians for this information to be published to the wider scientific community.

2.9 Data analysis

The data analysis for this study was performed using STATA version 12 (Stata Corp LP, Texas, USA) where parametric data was presented as mean ± Standard Deviation (SD), median, maximum and minimum values. We used two Gulu University medical students to extract information from the questionnaires independently and we compared the data consistency and resolved any inconsistencies with mutual agreement and in consultation with the Principal Investigator. Logistic regression was used to screen 74 potential explanatory variables (5 continuous, 45 ordinal and 24 dichotomous)

for the associations with Nodding Syndrome. Formal adjustments for the multiple testing were done because the investigation sought to identify the associations and the correlations of specific interest with pre-specified lists of targets. We used Chi Square (χ^2) and Fisher's tests for bivariate analysis to identify differences between variables by age, sex, birth order, length of IDPs stay, trigger factors, presence of *Onchocerca Volvulus*, use of herbal medicines and treatment with modern medicines in the NS patients. We fitted ordinary least squares (OLS) regression models to identify trends in factors in relation to Nodding Syndrome during the time period. Stepwise regression was used as an exploratory tool to guide the introduction of covariates in our modeling approach. Finally, a multivariable logistic regression was conducted to identify the variables that correlated with the occurrence of Nodding Syndrome among the study participants. A p-value that was less than 0.05 was considered statistically significant.

3.0 RESULTS

The descriptive statistics showed the mean age of NS participants was 14.1SD^{+}2.8 years with a minimum of 6 years and maximum of 19 years **(Table 1)**. The male to female ratio was 1.5:1. The mean Body Mass Index (BMI) was 16.9SD^{+}2.7 with a minimum of 11.4 and maximum of 23.2; meanwhile the Mid Upper Arm Circumference (MUAC) was 19.9SD^{+}2.8cm with a minimum of 13.1 and maximum of 25.4cm **(Table 1; 2; 3 & 4)**. The anthropometric findings showed that in spite of the good feeding program at HfH centre, NS children were still generally malnourished; an indication that perhaps there is/are a factor(s) that prevents them from fully utilizing the food nutrients being provided at the HfH centre **(Figure 1)**. The years of NS onset corresponded with the period of internal displacement into IDPs **(Figure 2; 3; 4; 7)**. The majority of NS children 33/45(73.3%) had dropped out of school; 9/45(20%) never attended school while 3/45(6.7%) were still in primary school **(Table 1)**. The head of the households for NS children were exclusively peasant farmers and the majority of NS children were 1st born 10/45(22.2%); 2nd born 9/45(20.0%) and 3rd born 6/45(13.3%) respectively **(Figure 3)**. The number of siblings with NS was notably higher in families where a NS child was first, second and third born in that descending orders respectively **(Figure 3)**. All NS children were in the IDPs of Northern Uganda and were fed on food ration provided by the relief agencies **(Figure 4) (Table 4).** Additionally, the majority of NS children experienced nodding episodes in the morning (48.8%), followed by evening (22.73%); night (15.15%); lunchtime (10.61%) and least in the afternoon (3.03%) **(Figure 5)**. In addition, most NS children had supplementary and weaning food from rations that were supplied by the relief agencies including; Yellow posho, maize, beans, soya beans, red sorghum, powdered milk, millet, rice, Plumpy'nuts and cooking oil **(Table 4)**. The quantity and duration of food ration eaten by each NS child was however not determined.

Figure 1: The study site, Aromowang lobo, Odek Sub County, Gulu District, Uganda.

Figure 1: Shows the geographical location of the site of the study, Hope for HumaNs (HfH) Nodding Syndrome rehabilitation centre situated at Aromowang lobo, Odek sub county, Gulu District, Northern Uganda. Nodding Syndrome children in Northern Uganda are found among the Acholi and Lango tribes and found in the districts of Oyam, Lira, Gulu, Pader, Kitgum, Lamwo and Amuru.

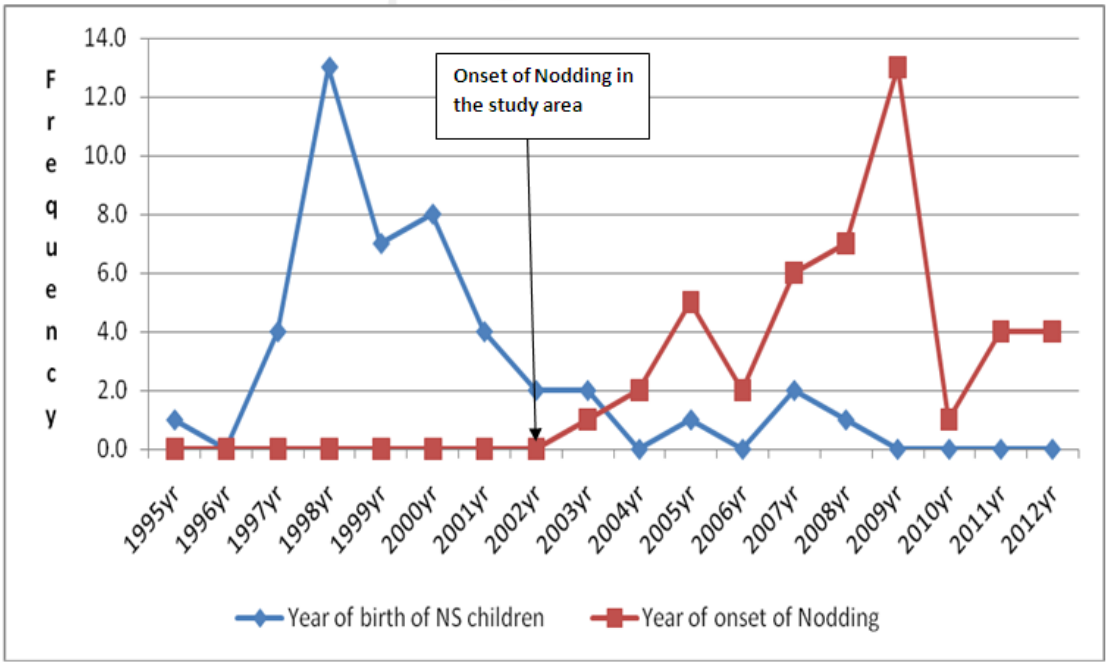

Figure 2: The years of birth and onset of nodding episodes in NS children.

Figure 2: Blue line graph shows the year of birth for NS children. The first NS child studied in this cohort was born in 1995 and this was followed by a peak year in 1998 and descended down until one and zero seen in 2012. No new incidence of Nodding Syndrome were reported after 2012. All these NS children experienced IDP camp life which was reported to have been from 2001 to 2006. We observed that the NS child who was born in 1995 and developed Nodding Syndrome in IDP camp is alive and his condition have greatly improved. Most NS children began to develop Nodding Syndrome during the IDP camp (2001–2006) (χ^2)=22.15, p=0.005 or immediately after IDP camps. The **Red line graph** shows the incidence of nodding onset which were seen in two semi-binomial peaks in year 2005 (5/45) and year 2009 (13/45) (Most NS children have had more than 50 attacks of nodding episodes since onset of the syndrome (χ^2)=22.15, p=0.005). The graph shows the relationship between nodding onset and date of birth of NS children. It showed that eight years later (in 2002) was the year when cases of Nodding Syndrome were first observed in the NS child and this corresponded with the period of internal displacement into the IDP camps (2001-2006). This figure is consistent with long- latent disorder in which an acute illness around birthtime gives rise to a long-latent disorder expressed years later.

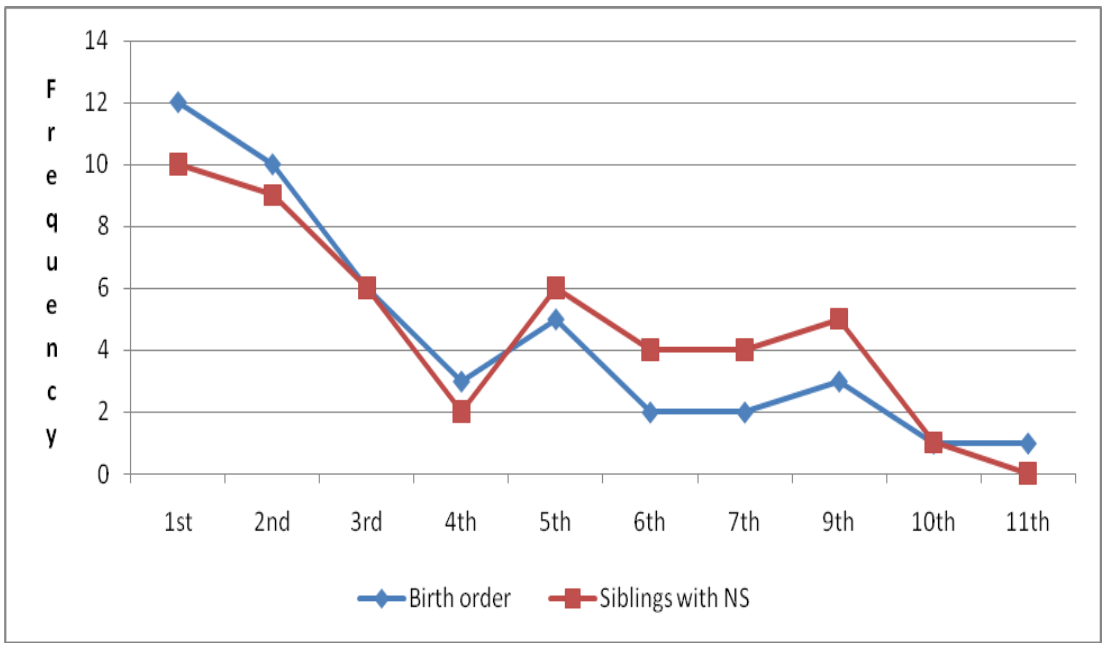

Figure 3: The pattern of NS occurrence and birth orders and other NS siblings in the family.

Figure 3.The line graph **(blue line)** shows the birth order of NS children which was highest at 1st birth and sloped down to the minimum at 4th birth order and then two semi binomial peaks were observed at 5th and 9th birth orders. Therefore, birth order for these NS children indicates that they were more commonly found in the 1st, 2nd and 3rd birth order of the family (χ^2)=9.68; p=0.377. The second graph **(Red lines)** shows a near mirror image-like pattern of occurrence of NS among the other siblings in the family, following closely with the birth orders. There were more siblings who had NS in a family where there is the 1st born having Nodding Syndrome and this association was observed to be statistically significant (χ^2)=9.68, p=0.004. In addition, one head of the household (we studied) had married 5 wives in the area and all the five wives produced a child that developed NS. This perhaps points towards a disease which is probably acquired and based in particular households. We suggest that this was an acquired disease because none of the parents of NS children have clinical evidence of NS and neither do the offsprings of some NS patients have been diagnosed with NS. Furthermore, no new cases of NS have been reported by the Ugandan Ministry of Health and World Health Organization since 2012 when all the IDP camps were already disbanded and the communities resettled in their homes.

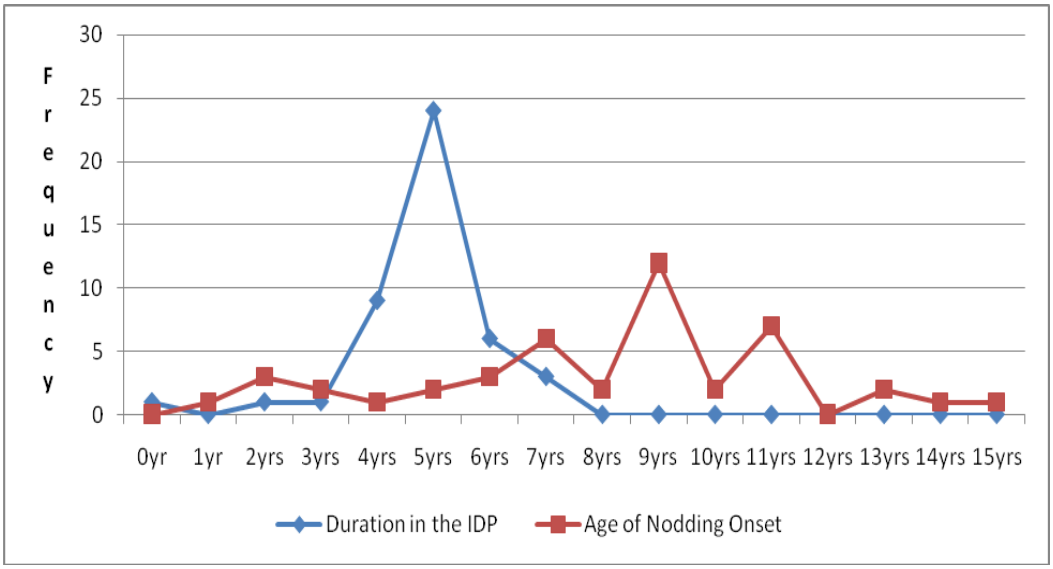

Figure 4: The length of stay in IDPs in relation to the age of nodding onset in NS Children.

Figure 4. The **(blue line graph)** for the duration of IDP camp stay shows a peak at 5 years (24/45) and slopes to zero by the 8th– 9th year when the IDP camp had been disbanded while **(Red line graph)** shows the age of nodding onset which has three semi-peaks at 7 years (6/45), 9 years (12/45) and 11 years(7/45) respectively. All NS children were in IDP camps and that the majority (25/45) had spent 5 years in the IDP camps before onset of nodding. This perhaps indicates that the exposure factor of NS was in the IDPs camps (χ^2)=22.146, p=0.005.

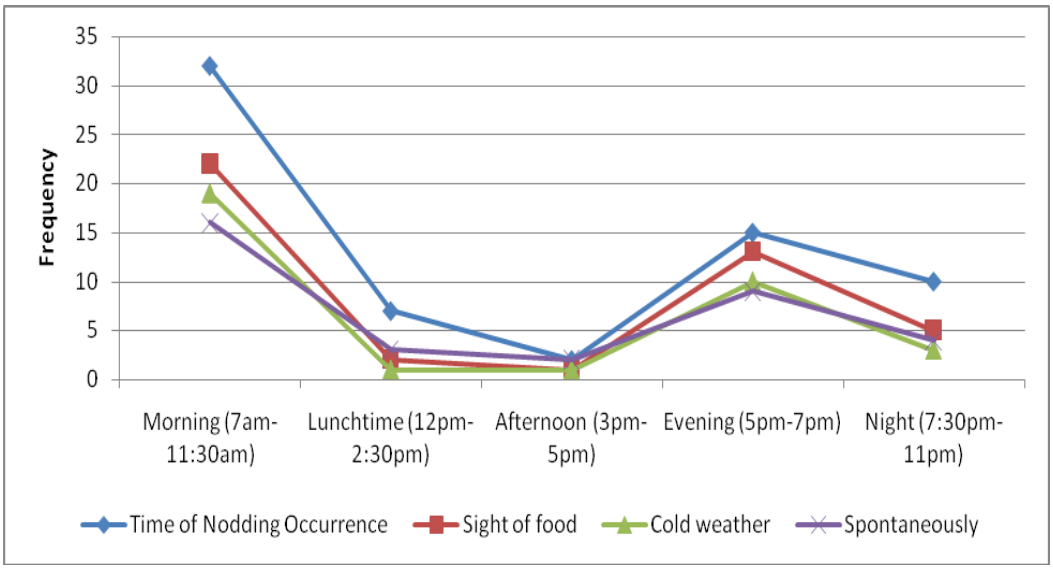

Figure 5: The time of occurrence of nodding and associated trigger factors

Figure 5. The line graph shows a uniform pattern of nodding episodes plot against the trigger factors with respect to the time of the day. Most nodding episodes occurred in the morning 57/111 (51.35%), decreased to a minimum in the afternoon 4/111 (3.60%) and rose to a semi-peak in the evening 32/111 (28.83%) and declined to 12/111 (10.81%) at night (χ^2)=5.102; p=0.825. The observed trigger factors mirrored each other across the day and night. Most NS children nod because of sight of local food 43/111(38.74%); cold temperature/weather 34/111(30.63%) (It was usually colder in the mornings and evenings in this region) and spontaneously 34/111(30.63%). The main trigger factor for nodding was the sight of local food which were commonly served in the morning and evening in communities of Northern Uganda 43/111 (38.74%). The sight of local food and cold temperatures/weather were two trigger factors that accounted for most nodding episodes majorly occuring in the morning and evening and contributed 77/111 (63.36%) incidences of nodding experienced and additionally morning and evening contributed 89/111(80.18%) of all episodes of nodding in the NS children studied.

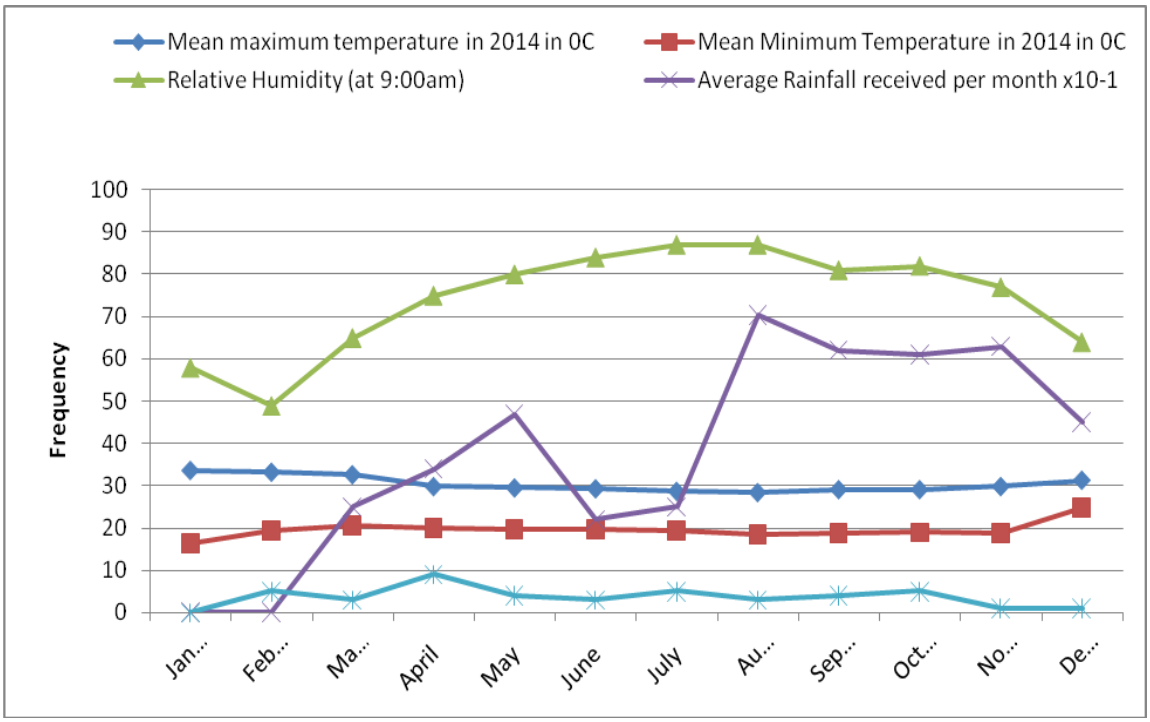

Figure 6: The average rainfall, humidity and temperatures in relation to onset of nodding in NS children.

Figure 6. Light blue line graph shows the reported month of onset of Nodding Syndrome among the 47 NS children studied. The reported month of nodding onset has a peak incidence in April 9/45(20.0%) while there were three semi-peaks in February 5/45 (11.11%); July 5/45(11.11%) and October 5/45 (11.11%) and the least in January 0/45 (0.0%). Therefore the reported month of onset of nodding was non-uniform, with all year round peaking in April but with semi peaks in February, August and october which was closely related to the monthly average rainfall pattern of Gulu District (2006-2016) which peaks in May in the first half of the year and August in the second part of the year. This finding has also been seen in Spencer *et al* (2016) paper in which he found there was a reported seasonal difference in NS onset but a close relationship with rainfall and food availability. The **(violete line graph)** shows the average rainfall received in Gulu district per month in 2014 ($x10^{-1}$mm). The first half of the year shows its peaks in May and decreases upto June. The second part of the year has its peak in August and maintained up to November and decreases gradually up to December each year. The Relative Humidity of Gulu district **(Green line graph)** taken at 9:00am every day decreased slightly from January to February but gently rose and curved downward after reaching the maximum humidity in July. From July onwards it gently sloped down to December of 2014. The temperature ranges over the year 2014 was near uniform across the months with an average maximum 30.5^0C **(Red line graph)** and minimum 19.6^0C **(Blue line graph)**. For the onset of nodding **(light blue line graph)** showed a non-uniform distribution throughout the year. The month when head nodding onset was obseved was recorded in 2014 during the clinical and biochemical study of 47 Nodding Syndrome children at Hope for HumaNs (HfH) rehabilitation centre.The rainfall pattern data was collected from the meterological Department at the weather station in Gulu district over a 10 year period (2006-2016).

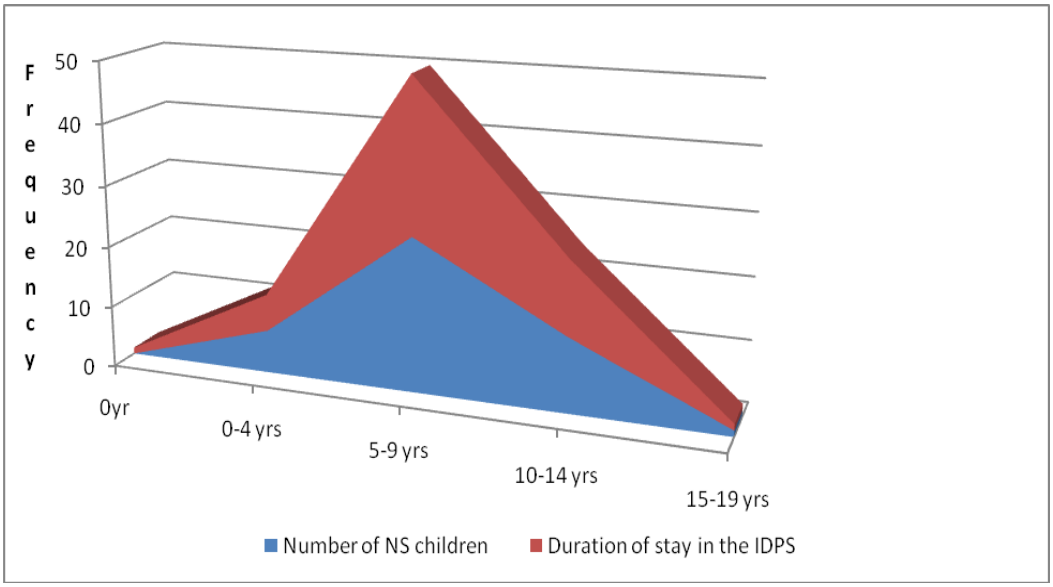

Figure 7: The relationship between the duration of IDP camp stay and number of NS children.

Figure 7. Area under curve which shows that all NS children experienced IDP camp life before the symptoms and signs of nodding were exhibited (χ^2)=22.146, p=0.005).

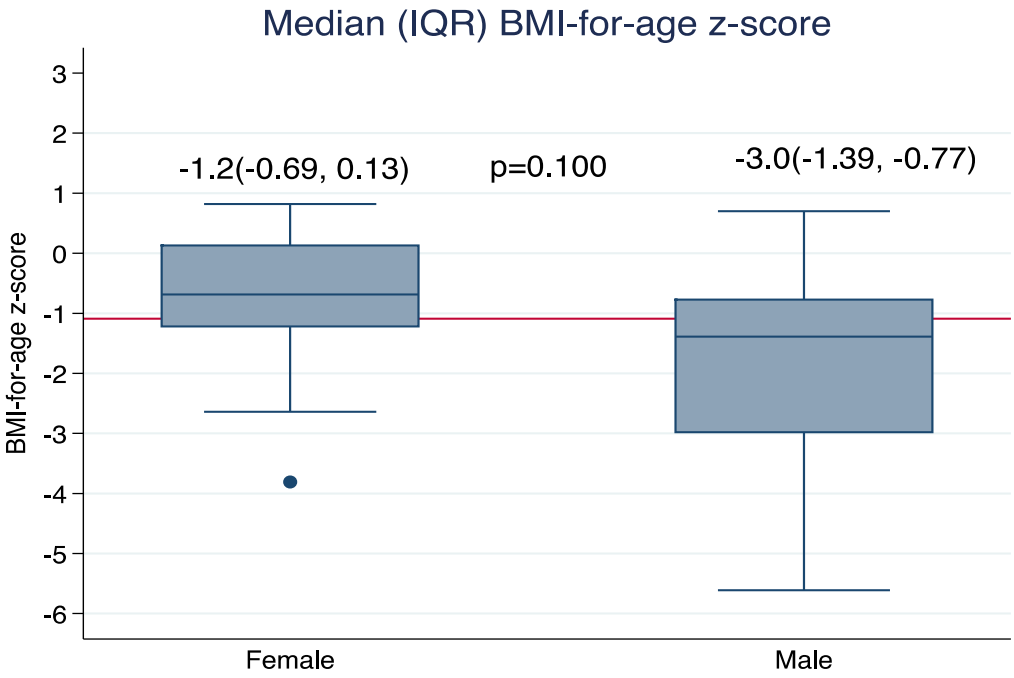

Figure 8: The Median BMI for age (z-scores) for the NS children studied.

Figure 8 shows the Median (IQR) BMI for age (z-scores) for the NS children where there was low median BMI for age (z-scores) and that there was no statistically significant difference between the female and male NS patients.

Table 1: Shows the clinical features and anthropometry measurements of NS children.

Variables	Female (SD)	Male (SD)	Total	Mean (SD)	Range
Number of NS children	18	27	45		
Age (yrs)	13.4(3.3)	14.5 (2.4)	45	14.1(2.8)	6,19
Weight (Kg)	38.4(12.1)	35.7(10.8)	45	36.8(11.3)	17,58
Height(cm)	145.6(14.9)	145.6(16.9)	45	145.6(15.9)	110.5,177.6
MUAC(cm)	20.6 (2.8)	19.4(2.9)	45	19.9(2.9)	13.1,25.4
Age of onset (yrs)	8.1(3.5)	7.9(3.3)	45	8.0(3.3)	1,15
Duration with NS (yrs)	5.3(1.9)	7.9(3.3)	45	6.1(3.3)	1,15
Duration in the IDP camps (yrs)	4.7(1.4)	4.9(1.1)	45	4.8(1.2)	0,7
% of family members with Epilepsy	33.3	29.6	45	31.1	
% of family members with NS	72.2	48.1	45	57.8	
Number of other siblings with NS	22	26	48		
NS started before the IDP camps	0	0	0		
NS started during the IDP camps	6	16	22		
NS started after the IDP camps	12	11	23		
School Enrolment					
Never attended School	4	5	9		
Dropped out of School	14	19	33		
Now still enrolled in School	0	3	3		

MUAC: Mid Upper Arm Circumference; NS: Nodding Syndrome; IDPs: Internally Displaced Peoples camps; SD: Standard Deviation

Table 2: The bivariate analysis of factors observed in the Nodding Syndrome children.

Variables	Chi square (χ^2)	p-value	Fisher's test
Sex	1.13	0.287	0.245
Year of nodding onset	10.22	0.511	0.477
Length of IDP camp stay	7.50	0.277	0.277
Birth order of NS child	9.68	0.377	0.270
School Attendance	0.76	0.683	1.000
Caretaker is the mother	**6.39**	**0.041**	**0.140**
NS child was in IDP camps	**22.15**	**0.005**	**0.156**
NS child had other siblings with NS	**9.68**	**0.004**	**0.267**
>50 nodding attacks since the onset of NS	**22.15**	**0.005**	**0.296**
Number of nodding episodes per day	5.10	0.825	0.664
Epileptic fits experienced by NS child	**4.64**	**0.099**	**0.180**
Fixed Gaze/Staring of NS child	3.14	0.208	0.199
Uncoordinated movement of the limbs	0.01	0.923	0.721
Drooling of Saliva (open mouth)	0.68	0.411	0.567
Disorientation	1.91	0.385	0.327
Loss of consciousness	**5.76**	**0.056**	**0.155**
Localized Tonic clonic seizures	0.60	0.742	1.000
Generalized Tonic-clonic convulsions	4.19	0.123	0.151
Urinary incontinence	3.14	0.208	0.367
Stool incontinence	1.16	0.561	1.000
Tongue biting	0.95	0.331	0.471
Sleeping after nodding episodes	3.22	0.200	0.252
Confusion after fits/Nodding	4.43	0.107	0.327
Rhythmic jerking during nodding episodes	2.62	0.270	0.236
Recent injuries, burns and scars on NS patients	0.01	0.923	0.721
Good sleep pattern	1.53	0.675	1.000
Aggressive behaviour after fits/nodding	2.19	0.139	0.233
Foaming in the mouth	**3.45**	**0.063**	**0.137**
Perceptual disturbances before/after nodding	1.16	0.283	0.410
Presence of visual hallucinations	3.45	0.486	0.384
History of mental illness in the family	**3.21**	**0.073**	**0.212**
Good family social support to NS child	**10.59**	**0.005**	**0.088**

Table 2 shows that NS was a statistically and significantly associated with the following variables; IDP camp life (χ^2)=22.15, p=0.005; NS child had other NS siblings (χ^2)=9.86, p=0.004; NS child received good social support from the mother (χ^2)=10.59, p=0.005; Caretaker of NS child was the mother (χ^2)=6.392, p=0.041; NS child had more than 50 nodding episodes since onset (χ^2)=22.15, p=0.005; In addition, some variables had near statistically significant associations with NS: NS child experienced epileptic fits (χ^2)=4.64, p=0.099; NS child had an episodes of loss of consciousness (χ^2)=5.76, p=0.056; NS child experienced foaming in the mouth during nodding episodes (χ^2)=3.447, p=0.063; and NS child had history of mental illness in the family (χ^2)=3.205, p=0.073.

Table 3: Shows the findings by sex in NS Children.

Variables	Female (n=18)	Male (n-27)	p-value
Mean current age (yrs)	13.4	14.5	0.77
Mean age at onset (yrs)	8.1	7.9	0.64
Mean duration with NS (yrs)	5.3	7.9	0.58
Mean duration in the IDP camps (yrs)	4.8	4.9	0.92
NS child was in IDPs	17	27	0.64
Anthropometric measurements			
Weight (kg)	38.4	35.7	0.42
Height (cm)	145.6	145.6	0.43
MUAC (cm)	20.6	19.4	0.38

NS: Nodding Syndrome; IDPs: Internally Displaced Peoples' camps; MUAC: Mid Upper Arm circumference. From the comparative analysis of the variables between the two sexes, there is no evident statistically significant difference between male and female NS patients.

Table 4: Mean frequency of food types eaten in the week in the IDPs.

Food Type	Average Frequency of consumption (Number of days per week)			
	Gulu	Kitgum	Pader	Total (All)
Vegetable oil	3.6	5.0	4.2	4.2
Beans	3.8	4.1	3.7	3.9
Maize	3.6	4.3	3.0	3.6
Other vegetables	3.0	3.8	2.6	3.1
CSB	2.1	3.7	1.0	2.2
Other cereals	1.8	2.3	2.3	2.1
G/nuts/Simsim	1.0	1.9	2.4	1.8
Roots & Tubers	2.1	1.1	1.7	1.7
Sugar	1.2	0.7	0.9	1.0
Meat	0.7	0.4	0.4	0.5
Fish	0.5	0.3	0.5	0.5

4.0 DISCUSSIONS

4.1 Nodding Syndrome and displacement into IDP camps

Several epidemiological studies in Northern Uganda show that NS is clustered in time (IDP camp period); space (geographically located on either side of the two major rivers (Aswa & Pager) and in person (NS onset is mainly at the age of 5-15 years).[1,2,4,7,15,16] There is an association between life in the IDP camps and onset of Nodding Syndrome **(Table 2); (Figure 4 & 7)**. Spencer *et al*, (2016) also alluded to the spatial temporarity of NS occurrence in the Acholi and Lango sub regions[2,4,15,16] **(Figure 1)**. From 1986 to 2007/2008, this study area experienced a civil war between the Ugandan Army and the rebel Lord's Resistance Army (LRA).[15,19] Starting in the mid-1990s, IDP camps were established in some parts of Northern Uganda by the Government with the goal of protecting people from the LRA, with an estimated 285,000 people from the nearby Kitgum District displaced into IDPs.[15,20,21] In the period before the population were displaced into IDPs, there were no reported cases of Nodding Syndrome. In 2001, the community of Aromowang lobo (site of the study) were moved into the IDPs where many of them became dependent on food ration supplied by relief agencies.[1,7,14,19] IDP camp life 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.[2,15,16,19] The IDPs began to be disbanded in 2006 when the LRA retreated to South Sudan but during the height of the insurgency over 1.5 million people were displaced into the IDPs and thus accounting for over 90% of the population in the Acholi sub region.[20,21] After 2007 when the LRA rebels retreated to South Sudan, the Government of Uganda began returning the displaced people into their homes in a phase-wise

approach from the main IDP camps to the satellite camps near their villages.[15,20,21] Eventually the communities were returned to their original homes after the Government undertook an extensive demining process in the farmland where the returnees were to settle and rebuild their communities and lives.[2,15,16,20,21] In 2009, the Ugandan Ministry of Health identified NS in communities in Northern Uganda and it established NS screening and rehabilitation centres starting in 2012 where the children were supplied with anticonvulsant medicines, multivitamins and nutritional supplements.[2,7,13,14,16,18] The consistency of the supplies and rehabilitation processes faced many challenges including irregular supply of anticonvulsant medicines and food supply for the NS children and the vulnerable families.[5,6,15] In the same period, there was also an apparent relationship between the peaks of NS cases in the nearby Kitgum District and earlier peak influxes of households into IDPs[15] which was similarly observed in this study area. The 1997 peak influx of IDPs in a nearby Kitgum District was followed 7 years later by an elevated number of new NS cases in 2004 (2003–2005) and the 2003 large influx of households anticipated a larger peak in new NS cases 5 years later in 2008.[15] This was similarly observed in this case study area where the influx of communities into IDPs in 2001-2002 was followed by peak incidences of Nodding Syndrome 7 years later in 2008-2009 **(Figure 2).** The peaks of reported NS onset also correlated with peaks of household displacement and prolonged residence in camps for internally displaced people (IDP) for the study community, where residents were heavily dependent on food aid provided by the relief agencies[2,15,20,21,23] **(Figure 2, 4,7)**. The IDP camps were insecure, unsanitary and squalid, and morbidity and mortality rates were high.[15,24] The conditions in the IDP camps were exceptionally poor, with overcrowding, violence, food insecurity and high potential for disease transmission.[15,24] Again in 2005, a Ugandan Government survey of Kitgum district estimated an IDP population of 310,111 persons; 21% of whom were children under 5 years of age.[15] At the time of the survey, over 66% of children were reported to have been ill sometime in the previous 2 weeks[15] 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.[2,15,17] In addition, the top self-reported causes of death in IDP camps were malaria/fever (34.7%), AIDS (15.1%) and violence (10.5%).[15]

Furthermore, an estimated 1,216 persons were killed and 304 (mostly children) abducted during the first half of 2005.[15] In addition, water was obtained from protected sources but water intake was low and the waiting time was high[15] and the infant feeding practices were poor and 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 diarrhoea, was the second most commonly reported causes of death.[15,23] These findings were thorough analysis of the events in the IDP camps which cut across all IDPs in the Acholi and Lango sub regions where Nodding Syndrome occurred. The site where we conducted this epidemiological, clinical, dietary and environmental study was similar to those described in a nearby Kitgum district by Landis *et al*, (2014).[15]

4.1 Epidemiological, environmental and dietary findings on Nodding Syndrome children

The result shows that between the year 2002 and 2012, the community of Aromowang lobo in Odek Sub County, Gulu district, Northern Uganda experienced semi-trinomial epidemic of onset of Nodding Syndrome and these were peaked at years 2005, 2009 and 2011 **(Figure 2)**. NS was first noticed in this area in 2002 which corresponded with one year stay in IDP camps by the population **(Figure 2)**. In addition, the prevalence of NS was notably higher in families according to birth orders **(Figure 3)** and all the NS children experienced IDP camp life **(Figure 4 & 7)** and the commonest nodding trigger stimuli were cold weather, local food and most nodding occurred in the morning **(Figure 5).** The observed month of peak incidence of onset of NS among the children was April and October **(Figure 6)**. These peaks corresponded fairly with the peaks of the monthly average rainfall received for the 1st and 2nd rainy seasons **(Figure 6)** and perhaps related with the availability of food as postulated by Landis *et al*., (2014).[15] The factors around the syndrome onset could have perhaps been in the IDP camps because all the NS children were in the IDPs before the onset of the nodding (p=0.005) **(Figure 4 & 7)** and the median BMI for age (z-scores) for NS by sexes were not statistically significant **(Figure 8)**. The other reason could perhaps be that NS children born were born before IDP camps had developed the condition prior to IDP except, the condition was not detected or overtly manifested but that the IDP camp conditions precipitated the overt manifestation of the Syndrome. The IDP camps may have stimulated the overt manifestation of the syndrome perhaps coupled with other stress factors such as infection with *Onchocerca volvulus;* malnutrition and febrile illnesses.[1,15,16] In addition, most NS children were in the 1st, 2nd and 3rd birth order **(Figure 3)** and all of them experienced IDP camp life which peaked at 5 years of IDP camp stay **(Figure 4)**. Additionally, most NS children have other siblings in the family with Nodding Syndrome and the occurrence of NS in other siblings mirrored the number of NS children's birth orders **(Figure 3)**. This finding, perhaps point towards a possibility of an acquired disease condition which was overtly manifested possibly as a result of family/household factors e.g. stressors such as malnutrition which was experienced in IDP camps **(Figure 7);** poor storage of food leading to its contamination and/or infection with *Onchocerca Volvulus* which made the syndrome manifestly overt on exposure to these factors. Perhaps the perfect examples can be seen in deficiencies of metabolites in acquired/inherited diseases whose disease occurrence becomes overtly expressed in circumstances similar to

what we present that could have happened with NS.[25] That could perhaps explain why there are no new NS cases reported by the Ugandan Ministry of Health (MOH) or World Health Organization (WHO) since 2012 when the IDPs camps had been disbanded and the communities returned to their villages. It is important to note that in late 2012, the Ugandan government did extensive aerial spraying/treating rivers especially Aswa and its major tributary Agago river to clear the black flies for the *OV* control. A formal study is awaited to determine the outcome of this intervention.

Furthermore, most NS children experienced nodding episodes during morning and evening hours or on sight of local food and during colder temperatures/weather **(Figure 5)**. In the Acholi and Lango communities of Northern Uganda, two meals are mainly served in the day; breakfast and supper are provided at the mornings and evenings respectively **(Figure 5)**. The communities of NS sufferers at Aromowang lobo, Gulu district were mainly of Acholi and Lango tribes **(Figure 1)**. In general, the information provided by the parents of NS children show that these NS children were all reported to have been born normal and that the developmental milestones were normal until nodding began.[1,7,13,14] Before the development of nodding, yellow posho, maize, beans, soya beans, red sorghum, powdered milk, millet, rice, Plumpy'nuts and cooking oil were the supplementary and weaning food rations that were supplied to IDPs by the relief agencies and eaten by all NS children **(Table 4)**. The quantity and duration of these food ration eaten by each NS child could however, not be determined.[1,2,16,20,21] It is further important to note that when these NS children were examined in 2012 before undertaking the rehabilitation process at the HfH centre by one of the authors, they were mostly classified to have Severe Acute Malnutrition (SAM) and a few as Moderate Acute Malnutrition (MAM) respectively on the basis of their BMI for age (z-scores).[1] Upon enrolment into the HfH rehabilitation centre for multidisciplinary treatment, their health conditions greatly improved, seizure frequency declined, mental health status improved, cognitive impairment improved, they gained weight and height and by 2014 when the author reassessed the NS children, most of them were categorized as MAM and healthy, nutritionally[2,15,16] **(Figure 8)**. This observation was perhaps due to good feeding program at the HfH centre and adequate rehabilitation process accorded to these NS children by HfH **(Figure 8)**. However, much as the NS children 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 impairments.[2,14,16]

4.3 Treatment and Rehabilitation experience of NS children in Northern Uganda

Experience with the treatment and response of NS children in northern Uganda by Hope for HumaNs (HfH) is tremendous because of the positive outcome registered recently.[1,2,15,16] The comprehensive rehabilitation approach (correcting protein-energy and vitamin-related malnutrition, de-worming, oral fungicide, anti-seizure medications (sodium valproate with/or without carbamazepine), close monitoring, tailored dosing and adjustments, special needs education program, and counseling) pioneered by Hope For HumaNs (HfH) at their Odek care center has proven clinically transformative (steady growth) **(Figure 8)**, improved emotional and marked seizure reduction status - though greater among males than females for unknown reasons).[1,2,16] However, cognitive and behavioral problems and social difficulties (both requiring formal evaluation) still confronted them after discharge from the HfH rehabilitation centre.[2,16]

4.4 Measles and Nodding Syndrome

Most case control studies, case series, case reports and clinical studies on NS that have been published have demonstrated no association between NS and Measles infection.[1,5,10,14] In this study, none of the parents/guardians reported any of the NS children suffering from any forms of measles before the onset of nodding episodes. A review of the Gulu District health reports where NS occurs at epidemic proportion shows that the immunization coverage for the seven killer diseases (Tuberculosis, Polio, Tetanus, Measles, Diphtheria, Pertussis and Influenza) was near 100% for nearly 10 years of follow-up beginning in the year 2000 (DHO, Gulu report).[30] The suggestion of subclinical measles infection as a cause of NS perhaps suffers from the inadequate data to corroborate this hypothesis. More so there have been laboratory investigations that were conducted by CDC and WHO on NS in nearby Kitgum district, Northern Uganda and South Sudan and none have confirmed the occurrence of subclinical measles in NS children and none of the laboratory studies have so far yielded any positive results in blood or cerebrospinal Fluid (CSF).[31,32] We suggest that in the event that measles may be found in some NS cases; it could perhaps be a stressor factor to the existing acquired metabolic condition in NS children such as biotinidase and acetyl carnitine deficiency as we observed in the other metabolic studies under review for publication **(Kitara DL, personal communication)**.

Limitations of this study

1. This study was an epidemiological, clinical, dietary and environmental study which was conducted on a limited number of NS patients (47) but with no matched controls.
2. Recall bias. The study depended heavily on the accurate information of the recall of the caregivers; the parents and guardians of NS children.

Strengths of this study

1. This is one of the few studies to evaluate the epidemiological, clinical, dietary and environmental factors of this neglected epidemic brain disorder (Nodding Syndrome) that places the lives of

hundreds and probably thousands of individuals in the Sub Saharan Africa at great risk for life and future.

2. This study was conducted in a well organized NS rehabilitation centre (HfH) fully supported by an individual, Dr. Suzanne Gazda (founder of the Hope for HumaNs centre for rehabilitation of Nodding Syndrome) and who sponsored the rehabilitation of these NS children since 2012 and the majority of the NS children have improved and discharged from the centre but were still being confronted with emotional, cognitive and perceptual disturbances.
3. The study was conducted in this community of Aromowang lobo, Odek Sub County, Gulu District, Northern Uganda with a very high burden of Nodding Syndrome.
4. For the outreaches, the research team travelled to the homes of the affected NS children and therefore reduced the chances of bias associated with differential participation of individuals with increased disabilities due to prolonged effects of Nodding Syndrome.
5. All the caregivers were living with NS children at the onset of Nodding Syndrome and to avoid recall bias we crossed checked the records of information given at different times by these caregivers which were recorded at the HfH centre and the Government Health centres and we found that the information given were consistently the same, an indication perhaps that their recall could be relied on as true.

CONCLUSION

Nodding Syndrome is a childhood neurological disorder found in Northern Uganda, South Sudan and Southern Tanzania and the cause is not yet known. However, our epidemiological, clinical, dietary and environmental analysis of NS children history and physical assessments show that we could be dealing with environmental and/or dietary factors that have not yet been well identified but which may have perhaps been experienced in the IDP camps. All the NS children were in IDP camps, fed on food ration provided by the relief agencies and there are no new NS cases reported by the Ugandan Ministry of Health and World Health Organization since 2012 when all the IDP camps had been disbanded and communities resettled in their villages. Additionally, the parents of NS children, the offspring of NS patients are reportedly normal without NS, this perhaps eliminates hereditary factor as the possible aetiology of NS. This finding may perhaps point to a disease with a long latent period but with a self limiting course. In addition, all Nodding Syndrome children were born normal and fed on food ration provided in IDPs as supplementary and weaning foods prior to developing Nodding Syndrome.

We therefore recommend that in the future we need to conduct case control studies on large enough sample size (adequately powered) to reliably infer associations. We hope this small pilot study serves as an impetus to publish and undertake more studies exploring possible environmental, dietary/toxicological aetiologies of Nodding Syndrome in the region.

Abbreviations

HfH: Hope for HumaNs – A Non-Governmental organization that has been rehabilitating children with NS for the last five years with positive results (from June 2012 to 2017); NS: Nodding Syndrome; IDPs: Internally Displaced Peoples camps; BMI: Body Mass Index; MUAC: Mid-Upper-Arm Circumference; CDC: Centre for Disease Control and Prevention; WHO: World Health Organization; OV: *Onchocerca Volvulus;* CSF: Cerebrospinal fluid; DHO: District Health Officer.

Ethical Approval and Consent to participate

All authors hereby declare that the study was approved by the Local Ethical and Review Committee (LHIREC No. 065/10/14) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. We obtained informed consent from the participants and parents/Guardians of the Nodding Syndrome children. Where it was appropriately required, assent was obtained from the NS child participant.

COMPETING INTEREST

All authors declare that they have no conflict of interests.

AUTHORS' CONTRIBUTIONS

Anywar Arony Denis contributed in protocol design, sample processing and literature review; Collines Angwech contributed in the management of NS children, literature review and supported the research team; Dr. Makumbi Fred conducted literature review and analyzed the data; Dr. Suzanne Gazda contributed in protocol design, literature review and management of the NS children; Professor David Kitara Lagoro designed the study, obtained ethical approval, developed the protocol, conducted literature review, collected and analysed the data. All authors reviewed the manuscript for intellectual contents.

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