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Conceptual Modeling of Nodding Syndrome: A System Dynamics and Sequence Approaches

Kizito Ongaya[1] Paul Ssemaluulu[2] Benedict Oyo[3] Pido Bongomin[4]

Abstract

Conceptual modelling of nodding syndrome (NS) has hardly been considered in most scientific literature although symptoms of the disease has been widely studied. A conceptual model is a representation of hypothesis about a system under investigation and enables a comparison between hypothesis and data. Since nodding syndrome is an unexplained neurological illness that mainly affects children aged between 5 to 15 years, without specific diagnosis and treatment, the aetiology remains unknown and under investigation, conceptual modelling may be a crucial ingredient in understanding the disease.

Purpose of the Study: The purpose of the study is therefore, to represent nodding syndrome occurrence and immune-pathogenic pathways in the causation of nodding syndrome using system dynamics approaches.

Methodology: We have used systematic review method to filter literature on nodding syndrome from the year. We also used Systems Dynamic Approach and we emphasized confirmed scientific investigation to enable the relationships conform to reality. Vensim software was preferred for implementation of the casual-loop diagrams. Microsoft Office Visio 2007 was identified as suitable for implementation of the sequence conceptual model of nodding syndrome for its ability to show interactions between electrolytes and other actors.

Findings: Our findings were that system dynamics approach has not been used research of nodding syndrome. More so, conceptual modeling were not considered by most articles.

Key words: Nodding syndrome, Epilepsy, System dynamics, Conceptual model

1.0 Introduction

Conceptual modelling of nodding syndrome (NS) has hardly been considered in most scientific literature although symptoms of the disease has been widely studied. A conceptual model is a representation of hypothesis about a system under investigation and enables a comparison between hypothesis and data (Zawedde, 2016). Nodding syndrome is a disease that has numerous hypotheses; in the case of Uganda, communities think it is a result of heavy artillery used during the two decades of war in Northern Uganda, while others attached the spirits of the dead people as the cause (Bemmel, 2014), scientific community however, believe that nodding syndrome is a disease transmitted by black flies infested with nematode onchocercas volvulus and its intra-cellular bacteria wolbachia (Idro *et al.*, 2016; Colebunders *et al*., 2014). Due to lack of proper scientific evidences, conceptual modelling of nodding syndrome has apparently been left out of scholarly literature resulting to unconstructive hypotheses flooding both social and scientific communities.

Nodding syndrome is a devastating neurological disorder (Idro *et al.*, 2013) that makes an individual experience seizures, developmental retardation and growth stunting (Dowell, 2013). The atonic seizures causes characteristic rhythmic dorso-ventral "nodding" of the head and comorbidities include but are not limited to: psychological and behavioral abnormalities, malnutrition, cognitive decline and other seizure types (Gazda, S. *et al*, 2015; Kitara, 2015). It is a form of epilepsy which the cause (aetiology) has not been properly established affecting many

children at epidemic level in East Africa (Buchmann, 2015). Because parents are caught up to take care of the children throughout the day, reducing their productivity resulting to severe socioeconomic implications. Just like other forms of epilepsy, it is associated with social stigma. Many children have died as a result of uncontrolled seizures that have led to drowning or burning (Idro *et al*., 2013).

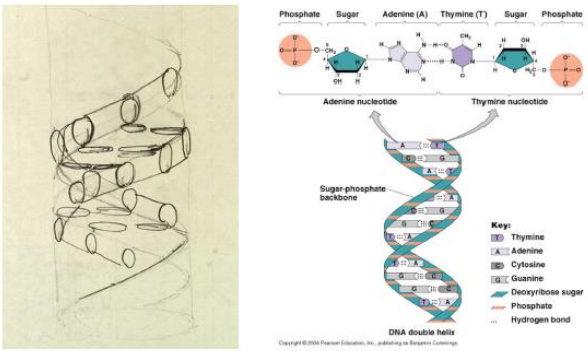
The condition was officially reported to the World Health Organization (WHO) by Warren Cooper, a missionary doctor, from southern Sudan in 1997 and first described in the scientific literature as 'nodding disease' in 2003 (Richer & Kolaczinski, 2012). It is characterized by episodes of head nodding, a form of atonic epileptic like seizure (Sejvar, 2013). In 1962, Louise Jilek-Aall, a Norwegian physician, described a mysterious disorder characterized by head nodding in several children in southern Tanzania. Some of these children eventually developed tonic–clonic seizures. In 1983, head nodding was also described among several patients in Liberia and for years, the disorder remained isolated in these areas. However, around 1990, physicians began observing a similar disorder in distinct areas in southern Sudan (currently known as South Sudan). After this, several cases of 'head nodding' were also observed in western Uganda (Korevaar & Visser, 2013). The disease affects massive number of people, and current epicenter are located in the Northern part of Uganda.

The Ministry of Health of Uganda and partner organizations identified the gaps in knowledge of nodding syndrome that "the actual geographic coverage and distribution of NS is not known and that there is need for surveillance in other areas outside the current foci and the overlap of areas of distribution of NS, etiological, potential risk factors and other information of interest (Ministry of Health Uganda, 2012). Also, the burden of NS in the currently reported three foci and surrounding areas are also not known. There is need to conduct systematic surveys and surveillance in areas of known foci for an accurate estimation of the burden of illness (prevalence, incidence). Furthermore, the overlap of areas of distribution of NS and etiological/ potential risk factors and other information of interest needs to be identified. There is need to Generate overlap maps for: Onchocerciasis (including ivemectin mass treatment history), Soil transmitted helminths, Human African Trypanosomiasis (HAT), epilepsy and other filarial infections. The overlap of areas of distribution of NS and etiological/ potential risk factors and other information of interest Overlap of areas of distribution of NS and etiological/ potential risk factors and other information of interest (World Health Organization, 2012). Because the disease is relatively a new development, not many studies have exhaustively been done about it. In this paper, we would like to bring out some modelling techniques in the fields of information systems that can aid describing the basic bionomics of the disease.

How Modelling May Aid Understanding Nodding Syndrome

Since the aetiology, risk factors, climatic and socio-demographic effects of nodding syndrome is/are not well established, it is important to model the attributes to bring out more understanding of the ailment affecting children at epidemic scale. Modelling has always been an important part of understanding systems (Krogstie, 2007). It has emerged as a means to capture the relevant aspects of the world on which it is necessary to provide information (Rolland, 2007). It promotes the scientific understanding and guides data collection in the sense that, scientifically, a model is a representation of hypothesis about a system under investigation and enables a comparison between hypothesis and data (Zawedde, 2016). Conceptual models are used to create a representation that aids in the understanding of the problem domain (Bera et al. 2010). Conceptual

models describes phenomena within the target domain which are created using a well-defined grammar (Parsons, 2011; Soffer and Hadar, 2007). Conceptual schemas (i.e., maps of concepts and their relationships describing the semantics of the domain) and ontology languages (i.e., a representation of the concepts within a domain and relationships defined through a shared vocabulary and taxonomy) serve as a means by which conceptual models are constructed (Patel, 2015).



Original drawing of DNA by Francis Crick and conceptual model today

There are many theories proposed for modelling especially if we observe the field of information system design theory explains how to design appropriate conceptual models. The models should focus on representation and processing of ontological data and information about the problem domain. Ontological problem domains of Information systems in many cases are abstraction deducible from structure that has a name, attribute and operation (Patel, 2015). There are many modelling theories and approaches postulated in the field of information systems that can be applied in other fields as well. A representative example is found in the unified modeling language (UML), which suggests modeling the structural as well as dynamics behavioral modelling using system dynamics approach (Forrester, 2009). A survey by Wieringa (1998) categories and deliberates on these techniques in detail. Numerous other techniques have been proposed over the years including the so called traditional techniques such as the data flow diagram (Gane and Sarson, 1979), entity-relationship modeling (Chen, 1976) and numerous extensions thereof, as well as newer modeling techniques for object-oriented modeling such as UML and OML (Opdahl *et al.*, 2000). Reviews and classifications of these techniques appear in (Rossi and Kemper, 1996; Siau *et al.* 1997). In addition, considerable work has been carried out in understanding appropriateness of modeling notations (Kim *et al.*, 2000), modeling the modeling notations (Rossi *et al*., 1992), and evaluation of modeling notations (Wand and Weber 1993). Out of these varieties of modelling approaches, some are effective methods for behavior modelling not only machine based systems ontologies, but biological systems too.

The behavioral modelling using system dynamics approach is of special interest in this research because of its suitability for biological ontologies since biological entities has strong behavioral attributes. Luckily knowledge advancement in biological sciences including specialized clinical sciences are well revolutionized by humans, and technologies are available to support in identification of attributes of biological ontologies with precision. Even with the contemporary ontological challenges of nodding syndrome, scientist have been able to identify attributes that suggest an ontological reality of an abstraction as nodding syndrome. By gathering systematically

these confirmed nodding syndrome attributes, we can be sure that given appropriate modelling techniques we would be moving closer to the precise ontological reality of the disease.

1.1 Towards Developing Conceptual Models of Nodding Syndrome

In developing conceptual models, Patel's ***theory of deferred action*** succinctly explains that;

> "the factors or constructs, variables and concepts that explaining a phenomenon should be clear and concise. They should be comprehensive but parsimonious, meaning that no more than the essential factors should be included and that naming relationships between the variables is the defining feature of a theory. How are these factors related? A theory should be internally consistent. Its logic should reflect the domain of the theory (Patel, 2012)"

Models may assume abstractions that may not be physical and yet come up with clear characteristics as pointed by Patel's theory of differed action. For such abstractions they are considered objects of ontological reality. And it is therefore, interestingly, modelling is even possible for poorly understood systems such as nodding syndrome aetiological abstraction. The cause of nodding syndrome though not yet known, can therefore, be possible to represented as ontological reality. An ontology is a formal way of representing knowledge in which concepts are described both by their meaning and their relationship (Bard & Rhee, 2016).

Nodding syndrome presents a very unique case due to unestablished biological cause (Korevaar *et al., 2013;* Idro *et al., 2016)* and yet ontological realities has been sufficiently established by clinical investigations due to ailments in infected individuals (Colebunders *et al.,* 2014). Clinical sciences has further established properties of this aetiology. They have even proposed behavioral relationship of the aetiology and clinical attributes (Idro *et al.,* 2016) which are requirements for almost complete modelling to be possible.

The purpose of this research is to develop conceptual models using influence diagrams (system dynamics approach) to bring visualization of relationship of scientific understanding of nodding syndrome as so far established by clinical scientists. The *Objectives* of the Study were firstly to examine current scientific knowledge about nodding syndrome with emphasis on established facts about aetiological characteristics in peer reviewed journals. Secondly, to identify conceptual models and actors in nodding syndrome infection with intention to establish relationships, and thirdly to improve on conceptual model identified in 2) above, using system dynamics approach. While the research questions were; What is the current scientific knowledge about nodding syndrome with emphasis on established facts about aetiological characteristics? What are the current conceptual models in NS infection? Is there any conceptual model designed using system dynamics approach to represent nodding syndrome occurrence?

1.2 Methodology

Systematic Review Process

A huge amount of research literature on nodding syndrome are produced each year, some of the finding have conflicting findings and reporting. The challenge between-study differences may be due to, flaws or chance (sampling variation) (Siddaway, 2016). In this situations, it is not clear what the overall picture of nodding syndrome is, or which results are most reliable and should be

used as the basis for practice and policy decisions. We have used systematic reviews for two reasons;

1) We are not sure how much of the literature has considered conceptual modelling nodding syndrome.
2) We are also not sure whether system dynamics has ever been used for investigation of immune-pathogenic pathways of nodding syndrome.

In the systematic review method we filtered literature on nodding syndrome from the year 2000-2016. We used Boolean logic in our retrieval.Out of three Boolean logics (AND, OR and NOT), we chose to use "AND" and "NOT" only to for the reason that we would likely to retrieve relevant publication about nodding syndrome. "NOT" was not considered for it overwhelming results of inclusion.

Search Engine Inclusion Exclusion Criteria

The researcher used libhub.kiox aggregator of Makerere University Library to optimize the search results from the queries. Libhub redirected querries to science direct as the preferable search engine with most results on nodding syndrome. When the researcher used keywords; "Nodding syndrome" the retrieval results were 10,343 journals articles. The use of "Nodding syndrome AND Epilepsy" resulted to 1st Exclusion of 9,277 & journals articles and retrieved only 1,066 articles. Further filtering was executed by use of "Nodding syndrome AND Epilepsy AND system dynamics" (spatial analysis) as 2nd Exclusion 866 journal articles and retrieved 200 only. The 3rd Exclusion was executed by reading abstracts of the 200 articles and the researcher was left with 19 very relevant articles.

Sn	Article Details	Has Conceptual Model	Use System Dynamics in the Model	Has other Models
1	Nodding syndrome, other forms of epilepsy, and the Nakalanga syndrome most likely directly or indirectly caused by Onchocerca volvulus	-	-	-
2	Environmental, dietary and case-control study of Nodding Syndrome in Uganda: A post-measles brain disorder triggered by malnutrition? Peter S. Spencer et al	-	-	Map & Graph
3	Nodding syndrome: 2015 International Conference Report and Gulu Accord P.S. Spencer, D.L. Kitara b, S.K. Gazda c, A.S.Winkler	-	-	-
4	Is nodding syndrome an Onchocerca volvulus-induced neuroinflammatory disorder? Uganda's story of research in understanding the disease Richard Idro et al.	Yes	-	Maps
5	Neurophysiological and clinical findings on Nodding Syndrome in 21 South Sudanese children and a review of the literature Gianni de Polo et al.	-	-	Table & EEG
6	These nodding people': Experiences of having a child with nodding syndrome in postconflict Northern Uganda Kristine Buchmann	-	-	-
7	Nodding syndrome—a new hypothesis and new direction for research Robert Colebunders et al.	-	-	Graph
8	Nodding Syndrome in Onchocerciasis Endemic Areas R. Colebunders,1,* A. Hendy,2 and M. van Oijen1,3	-	-	Graph

9	Nodding syndrome in northern Uganda: Overview and community perspectives Katrina B. Mitchell et al.	-	-	-
10	Reviewing the evidence on nodding syndrome, a mysterious tropical disorder Danie¨ l Arnoldus Korevaar	-	-	-
11	Editorial Nodding syndrome—we can now prevent it	-	-	-
12	Uganda: how goes the nodding syndrome war?	-	-	-
13	The nodding syndrome: A new form of epilepsy? R. Idro	-	-	-
14	Clinical, neurological, and electrophysiological features of nodding syndrome in Kitgum, Uganda: an observational case series James J Sejvar, et al.	-	-	EEG
15	Nodding syndrome—a challenge for African public health	-	-	-
16	WFN15-1813 Environmental Neurology T 20.1Nodding Syndrome: an epileptic disorder restricted to Africa? P. Spencer.	-	-	-
17	CDC planning trial for mysterious nodding syndrome, world report	-	-	-
18	Detection of auto-antibodies to leiomodin-1 in patients with nodding syndrome Tory Johnsona,	-	-	-
19	Nodding syndrome; a new (infectious?) disease entity of the CNSin Eastern Africa R. Idro.	-	-	-

Table 1: Showing lack of system dynamic modelling approach used in research articles on nodding syndrome.

Software Consideration for System Dynamics Modelling

The researcher considered two soft wares (Vensim and Stella) for possible execution of the models. Because nodding syndrome researches are still ongoing and quantification of variables are not yet possible, it was prudent that vensim would be more suitable than stella in this research. The research has not considered simulating variables to arrive are decision support system model due to lack of statistical data of articles considered for the systematic review. Microsoft Office Visio 2007 was identified as suitable for implementation of the sequence conceptual model of nodding syndrome for its ability to show interactions between electrolytes and other actors.

1.3 Review of Scientific Knowledge of Nodding Syndrome with Emphasis on Conceptual Modelling

Nodding Syndrome (NS) is an idiopathic brain disorder of children and adolescents in parts of east Africa (Spencer *et al.,* 2015). Its clusters are known from East Africa, with initial clinical description in the 1960s by Louise Jilek-Aall among the Wapagoro people of Mahenge, Tanzania (Winkler *et al.,* 2008), Southern Sudan (Tumwine *et al.,* 2013) and Northern Uganda (Sejvar *et al.,* 2013). Nodding Syndrome is a largely age-bound (onset mainly between 5 and 15 years) (Spencer *et al., 2015*). It is probably for the following: (1) protection of very young children by the antibodies of their mothers; (2) the fact that very young children are less likely to spend a lot

of time near rivers; (3) the incubation time of the disease; (4) treatment with ivermectin is only started after the age of 5 years. If the pathogen is a microfilarial endosymbiont, then young children may be at particular risk of developing the disease. It is also possible that, similar to other viral childhood infections, the 'NS pathogen' could lead to immunity for life, explaining why adults rarely develop the disease (Colebunders *et al.,* 2014).

There is currently no specific treatment for nodding syndrome. With careful observations of small numbers of patients hospitalized for a few weeks, symptoms and signs amenable to symptomatic relief have been identified and a package of symptomatic therapies for care has been developed by the present researchers. Treatment aims at symptom relief and includes the use of sodium valproate for seizures and nutritional, behavioural, and physical therapy. It would appear that patients receiving appropriate antiepileptic treatment may not go through all five clinical stages of nodding syndrome and cognitive function may improve with seizure control (Idro *et al.,* 2016).

The Preliminary studies of natural history of nodding syndrome suggest that the symptoms and complications of nodding syndrome develop through five distinct but overlapping clinical stages over several years (Idro *et al.,* 2016).

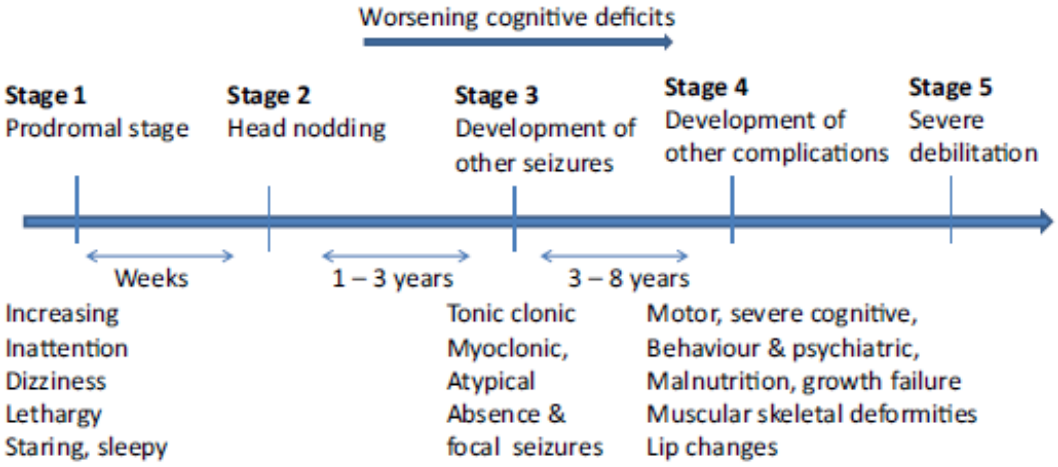


Figure 1: Adopted from (Idro et al, 2015). Five distinct but overlapping clinical stages over several years (Idro et al., 2016).

Idro's model can be re-represented in system dynamics approach with three causual-loops of dynamic activities as the sickness progresses as in figure 2. Carbomizapine (active), phinobabitone, phenetoin,

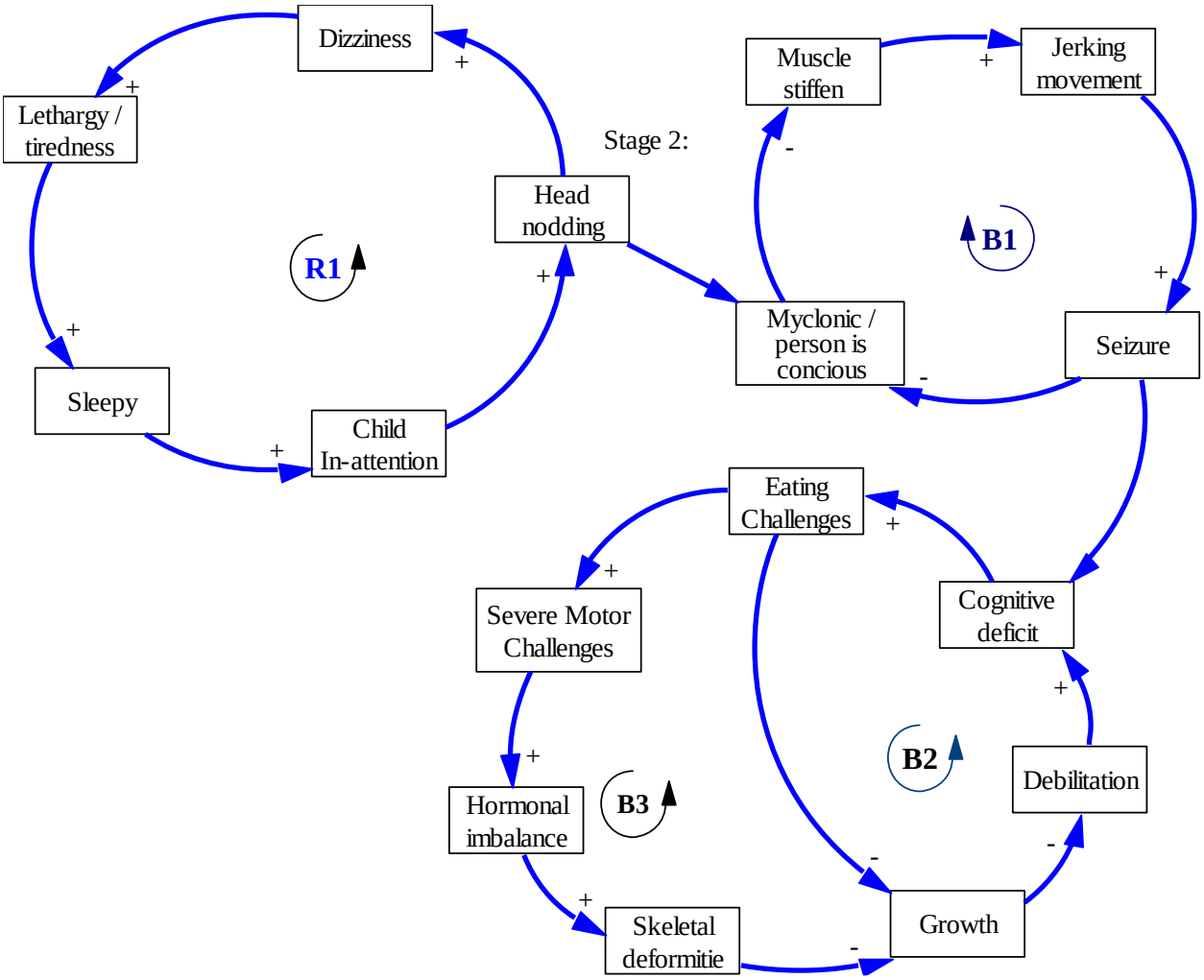


Figure 2: System dynamics complexities of nodding syndrome progression in an infected person Redesigning Idro's model in system dynamics, clearly brings three loops as the infection progresses.

Reinforcing Loop 1 (R1)
The first loop with symptoms "diziness", "lethargy", "sleepy", "inattention" resulting to "head nodding". This will point to some physiological activity that needs to be investigated.

Balancing Loop 1 (B1)
The second loop when the patient is conscious "Myclonic" and yet can not control muscle movement "jerkin", "stiffening" and then later epileptic seizure is a sign of inability of immune system to defeat the pathogen in the blood stream.

Balancing Loop 2&3 (B2 & B3)
As the sickness progresses, other more complications come in sending the patient to the third loop. These Idro's characteristics are consistent with psychiatric and psychological features also identified by other scholars (Gumisiriza et al., 2015). It seems that severity causes hormonal imbalance therefore, resulting to numerous chains of negative reinforcement.

Furthermore, dwarfism could be caused by an infection with the 'NS pathogen' at an early age, when the child's brain is still developing. Hypothalamic-pituitary dysfunction has been described post-encephalitis (Schaefer *et al.,* 2008) and a similar stunted growth and lack of secondary sexual characteristics has also been observed in perinatally HIV-infected children who survived up to 18 years without antiretro-viral therapy,28 and in perinatally human T-cell lymphotropic virus type 1 (HTLV-1)-infected children (K. Verdonck; personal com-munication). It is unlikely that the pronounced dwarfism is only caused by malnourishment because not all these children are particularly malnourished (Colebunders *et al.,* 2014).

Ecological analyses were performed on information drawn from publicly available electronic records. These data included region-specific annual rainfall; ambient temperature; crop planting and harvesting patterns; measures of food security, and emergency food supplies provided by the World Food Programme (World Food Programmme, 2016). A series of studies of potential toxins was undertaken by investigators from the Ministry of Health, the US CDC, and local universities. Body fluids and tissue samples were obtained from cases and unaffected controls. None of the studies identified a specific toxin, however a vitamin B6 deficiency was present in the majority of cases (84%) and controls (75%) (Foltz *et al.,* 2013; Korevaar, *et al.,* 2013). David Lagoro Kitara described 10 northern Uganda (Pader District) NS children referred for seizures, injuries and nutritional rehabilitation. Findings of low serum calcium and bicarbonate levels, coupled with a high anion gap supported his published hypothesis that NS is a mitochondrial disorder associated with metabolic acidosis. He also reported a deficiency of biotinidase in urine and blood samples of NS children at the Odek rehabilitation center. More studies are needed to determine if this could be a biomarker of the disease. Thyroid and vitamin D levels were largely normal. Another child with NS had abdominal wall pyomyositis, a relatively common disease in northern Uganda. (Noteworthy is that inclusion body myositis has been linked with paramyxovirus infection, vide supra) (Spencer *et al.,* 2015). Similar findings of toxicity were observed by other scientist and importantly, antibodies to leiomodin-1 were also present in the CSF of patients with NS, and these antibodies were found to be neurotoxic in vitro. Neurons treated with anti-leiomodin-1 showed increased toxicity compared to isotype control (Johnson *et al*, 2014). The acidosis (blood toxicity) seems the only explanation for seizure, however, how this happens needs to be investigated.

A lot of literature reveal strong association between NS and OV infection was reported from case–control studies in South Sudan and Uganda but studies of cerebrospinal fluid in patients with NS from South Sudan and Tanzania, and in DRC epilepsy cases (reported at the Conference by Robert Colebunders and colleagues), proved negative for OV DNA (Tumwine *et al.,* 2013; Dowell *et al.,* 2013). However, despite the consistent association, it is unclear how O. volvulus may cause nodding syndrome and several questions have been asked. First, this parasite is endemic in many parts of Africa, Latin America, and Asia where it causes river blindness, yet nodding syndrome has only been reported in a few areas of Africa. Secondly, only children are affected. Third, it is unclear how the parasites can cause brain injury as there is hardly any evidence of breach of the blood–brain barrier and none has ever been demonstrated in brain tissue or in cerebrospinal fluid. Alternative mechanisms other than direct parenchymal (the functional parts of an organ) injury are likely (Idro *et al.,* 2015). The action of nodding and deformities may be due to some alteration of hormonal balance due to certain physiological processes caused by presence of OV wolbachia in the body.

Furthermore, other scientist points out that OV infection is not uniformly present in Ugandan cases, suggesting that OV is not primarily causal of NS. Adam Hendy and colleagues described planned research to clarify this issue by plotting the blackfly-OV relationship in NS affected and NS-unaffected regions of northern Uganda (Kitara *et al.*, 2015). Indeed, no evidence of prior disease has been observed on histology. However, a strong epidemiological association has been documented between nodding syndrome and infection with Onchocerca volvulus (Dowell *et al*., 2013). Although yet to be investigated, the team of scientist from Uganda Ministry of Health, the US Centers for Disease Control and Prevention, and the University of Oxford proposed potential pathological host inflammatory responses in O. volvulus-infected individuals may also be against Wolbachia. Wolbachia are intracytoplasmic symbiotic bacteria found in filarial worms. They are essential for the survival, reproduction, and probably for the pathogenesis of O. volvulus. O. volvulus extracts depleted of Wolbachia with doxycycline do not induce the inflammation seen in O. volvulus-associated corneal keratitis (Kluxen *et al.*, 2007) Variant species may increase the pathogenicity, and treatment with tetra-cycline could eliminate the tissue injury (Min *et al.*, 1997).

The identification of any such variants could be crucial in elucidating other targets for intervention. Furthermore, Wolbachia exist in up to 11 serogroups or super-groups (A–K). Super-groups A, B, E, H, I, and K are commonly found in arthropods, while groups C, D, and J are limited to filariae. It is unknown whether unique super-groups exist in regions with nodding syndrome and in patients with nodding syndrome, or whether new and virulent super-groups have evolved. An investigation of this hypothesis is part of the proposed studies for 2016 to 2019 (Idro *et al.*, 2015). This position is also agreed by other scientist; blackflies can transmit vesicular stomatitis New Jersey virus to cattle, horses, and swine (Mead *et al.*, 2004). There are no reports of blackflies transmitting arboviruses to humans. However with over 1700 Simulium species described worldwide, it is plausible that blackflies may transmit unidentified viruses from human and zoonotic origin (Colebunders *et al.*, 2014), at the same time complicating realistic findings of exact aetiological factors.

Rehabilitation services include; Symptom treatment with ivermectin, sodium valproate, (Spencer *et al*., 2016, carbamazepine, phenobarbitone or phenytoin) (Polo et al., 2015). Recent data provide strong evidence that symptomatic treatment, including nutrition (Idro *et al*., 2014). Special-needs education program, music and dance therapy are also vital components of the treatment protocol (Spencer *et al*., 2015) due to cognitive impairment. It has been proved that these activities help improve a child's perception and reduces mood-swing.

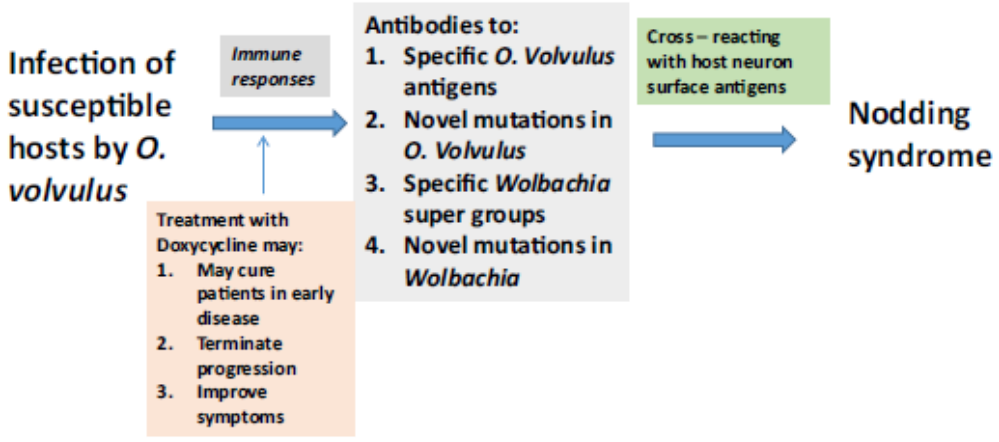


Figure 2: Adopted from (Idro et al, 2015).Potential immune-pathogenic pathways in the causation of nodding syndrome.

3.0 Sequence Approach to Conceptual Model of Nodding Syndrome

We build sequence approach to modelling nodding syndrome based on research findings from multiple scientists. Finds shows that parasitic worm often found in the children might trigger the body's own defenses to attack neurons (Vogel *et al.,* 2017). This theory is supported by Obol and colleagues that the children with nodding syndrome have low vitamin B6 concentration which leads to a buildup of 3-hydroxykynurenine concentration in cases as a main risk factor. Therefore, cases should be treated with vitamin B6 and community members should be sensitized to ensure adequate dietary intake of vitamin B6 so that the risk of nodding syndrome among children is averted (Obol *et al*., 2016). Other theories such nodding syndrome might be caused by malfunctioned mitochondria further explains similar self-acidosis accumulation (Spencer *et al.,* 2013*).* The High-anion gap acidosis theory (Kitara, 2015) fits in-line with such scientific findings. In his paper at Gulu University Dr. Kitara notes that normal serum potassium level was found to be statistically significant between the cases and controls (X2 =7.846, p=0.005; **OR** 11.361 95%CI 1.401, 92.137). This means that, it was more likely to find a normal serum potassium level in controls than in NS cases. Low serum sodium level were found to be statistically and significantly different between the NS cases and their controls (X2 =5.127, p<0.001; **OR** 0.049 95%CI 0.023, 0.102). This indicated that most NS were in a state of hyponatraemia (<135mEq/L) compared to their controls. Over 80% of the cases had a serum concentration of between 130–133 mEq/L. Hyponatraemia alone could in part explain some of the symptoms and signs found in NS children such as seizures, deformed bones and floppy muscles (Gazda *et al.*, 2015; Kitara, 2015). Similarly, it was observed that it was more likely to find a normal serum sodium level (135-145mEq/L) in the controls than the cases and this was statistically significant (X2 =75.093, p<0.001; **OR** 19.225 95%CI 9.177, 40.275)

Further, Dr. Kitara noted that as regards the other electrolytes; serum bicarbonate and chloride levels had a similar pattern of statistically significant difference between NS cases and controls. The serum bicarbonate was specifically noted to be very low, a point below the critical clinical limits. Because of these observed differences between the concentration of cations and anions among cases and controls, the Anion Gap (AG) was calculated in order to determine any clinically detectable anion difference. It was found that there was a high AG which was statistically and significantly different between cases and control (X2=146.752, p=0.000; **OR** 6.313 95%CI 4.027, 9.895). A high AG was defined as the difference between the measured cations and anions in the cases compared to the controls and any value more than 28mEq/L was considered significantly high *(Kitara, 2015).* With these passages, we propose a conceptual design of nodding syndrome using the suspected aetiological factors OV, wolbachia as in the figure 3 below. The actors being environment, human body, blood serum, immune system, central nervous system (brain).

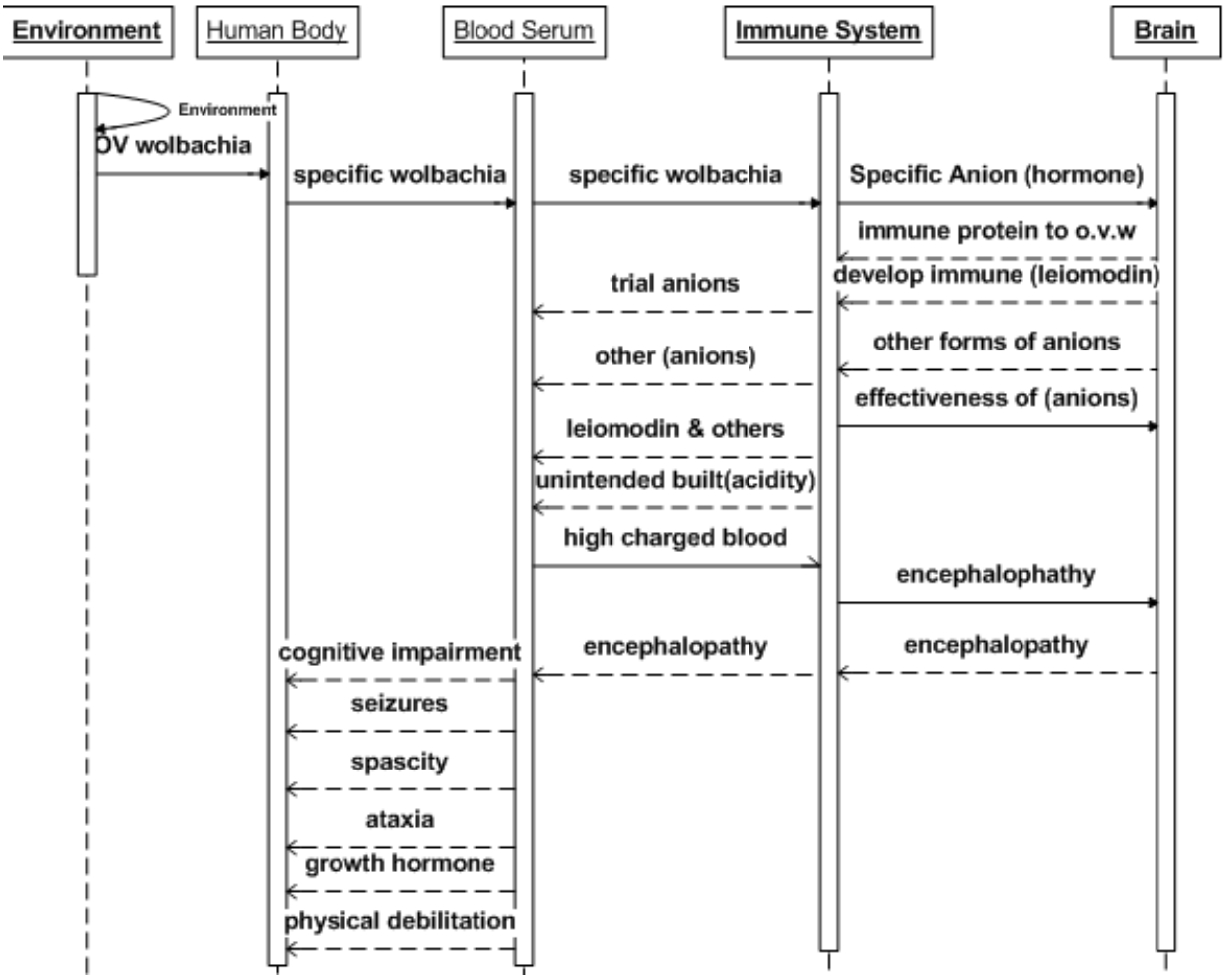


Figure 3: Sequence Conceptual Model of Nodding Syndrome, based on Onchocerca aetiological theory (Idro et al., 2016; Colebunders et al., 2015) and High-anion-gap acidosis theory (Kitara, 2015)

The sequence model based on onchocerca volvulus aetiological theory of nodding syndrome and High-anion gap acidosis theory (Kitara, 2015) supported by other studies of protein anion such as leiomodin (Johnson, et al., 2014; Spencer et al., 2015), deficiency of Vitamin B6 (Obol et al., 2015) and mitochondrial malfunction (Idro et al., 2015) brings out the roles of the different actors in nodding syndrome ailment. It starts with the terrestrial ecological (bionomics) environmental suitability for vector reproduction which is thought to carry onchocercas volvulus, wolbachia (OV) (Hendy et al., 2015). It is assumed that the vector (black flies) bites humans, then the pathogen is introduced in the blood serum triggering immune systems to seek for help from the brain, however, this association is not yet clear. The brain will direct the immune system to produce protective immune protein. But because the host has never been immunized against the pathogen, a series of immune proteins are produce in the blood stream resulting to toxicity of the serum. One of this immune proteins is leiomodin which is prevalent in the patients' blood streams. Since the blood serum and the brain has been found to host no pathogen, then, the only current theory that can explain for now is that the toxic blood due to pathogen activities coupled with unusual immune

proteins are transported back to the brain creating electrical imbalance. The brain thus behave like its sending signals to organs and muscles of the body further worsening situations with hormonal balances resulting to deformities.

Conclusion

There are a number of studies that are going on to understand nodding syndrome and there are increasing literature in peer reviewed journals as evident. Few journal articles have considered conceptual modelling of nodding syndrome, however, none have considered system dynamics approach in modelling of nodding syndrome. Idro's models of nodding syndrome has been a good attempt, however, there is need to explore more actors and physiology of nodding syndrome.

Areas for Further Research

There is need to explore climatic conditions in influencing nodding syndrome prevalence. The dynamics of environment and mechanism by which the pathogen wolbochia enters the blood serum. Relationship in the serum with other organic matters including immune system. The dynamics of other anions provided by dietary changes that results to improvements of patients. The anions / proteins that may be use for diagnosis of nodding syndrome and its dynamics in the system serum.

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