New evidence for nodding disease as an autoimmune reaction to *Onchocerca volvulus*

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Over the past decade, we have seen the emergence of an enigmatic condition called nodding syndrome (1). This condition is characterized by episodes of repetitive nodding forward of head that may be the result of atonic seizure. The etiology of this seizure is unknown, although associations with other developmental conditions have been established (2,3). This syndrome is also characterized by significant brain atrophy near the hippocampal and glia matter along with cerebellar signs. The brain injury leads to life-long severe neurodisability and accompanying behavior problems, and high mortality (4).

This disease is considered to be a progressive epilepsy encephalopathy syndrome of poorly understood etiology, seen predominantly in East Africa (5). Onset is sudden and is usually at 5 to 15 years of age (6). Outbreaks have been documented during the past decade in the countries of Uganda, Liberia, Tanzania, the Democratic Republic of Congo, and southern Sudan. The overall prevalence in affected regions is estimated to be 6.8 per 1,000 children, with over 2,000 cases in northern Uganda alone during one epidemic (6). Some reports suggest an association between nodding syndrome outbreaks and increased malnutrition from drought and/or crop failure in this region (7).

Nodding syndrome is most prevalent in areas with high infection rates of the nematode *Onchocerca volvulus* (*O. volvulus*) carried by the black fly. This nematode can cause Onchocerciasis, which is a leading cause of blindness in adults in sub-Sahara Africa. It has been difficult for medical researchers and public health scientists to understand the epidemiology and etiology of the possible relationship between Onchocerciasis and nodding disease in children. Therefore, there is an urgent need to develop scientific models that allow for the integration of, for example, satellite imagery geographic ecological and climate mapping, maps of parasitology dispersion, population-based geographic genotypic mapping, and geographic mapping of epidemiological prevalence and risk of such diseases as onchocerciasis. Only with such integrated multi-disciplinary modeling can we better understand the complex epidemiology of such emerging diseases such as nodding syndrome. This understanding can enable scientists to better establish the neuropathogenic mechanism for this disease, which can lead to sensitive and specific brain inflammatory markers as well as the corresponding neuropsychological sequelae of such central nervous system (CNS) inflammatory markers. These are critical in the diagnosis of this disease, as well as in the surveillance of emerging outbreaks in at-risk populations.

Nodding syndrome is characterized by stunted brain growth that includes significant brain atrophy near the hippocampal and glia matter of the brain and significant cerebellar involvement (8). Cerebral spinal fluid (CSF) analysis is usually negative, while the magnetic resonance imaging (MRI) shows cerebral and cerebellar atrophy. A MRI study of Tanzanian nodding disease patients revealed that the most frequent abnormality was generalized atrophy, followed by intra-parenchymal pathologies such as changes

in the hippocampus, gliotic lesions, and subcortical signal abnormalities (5,8). There was an overall trend towards an association of intra-parenchymal cerebral pathologies and skin infection with *O. volvulus*, although polymerase chain reaction (PCR) of CSF was negative in all patients.

As previously noted, this disease is characterized by daily, rapid, paroxysmal forward head bobbing spells lasting several minutes. During this time, patients are typically unresponsive or may respond to commands. These spells may be indicative of atonic seizures, although there may also be associated definable generalized tonic-clonic, petit mal, or absence seizures or absence seizures (9). The EEG demonstrates a disorganized slow background and inter-ictal generalized 2.5–3.0 Hz spike and slow waves, with generalized diffuse slow wave abnormality and para-spinal electromyography dropout suggestive of an atonic seizure (5). Interestingly, nodding episodes may be triggered during meals while eating hot foods or drinking cold liquids; cold environmental temperature may also trigger a nodding episode, indicating other areas of brain involvement. Treatment of seizures is indicated; however, the response to treatment is poor.

Since there is limited evidence that the parasite itself is neuroinvasive, it has been hypothesized that nodding syndrome may be an autoimmune-mediated disease. Recent preliminary studies in Uganda of its pathogenesis support the suggestion that nodding syndrome may be a neuroinflammatory disorder, possibly induced by antibodies to *O. volvulus* cross-reacting with neuron proteins (9). Although histological examination of post-mortem brains revealed polarizable material in the majority of specimens, these initially proved difficult to characterize or identify (9).

More recently, a breakthrough has come about in terms of evidence in support of the autoimmune hypothesis in the etiology of nodding disease. An NIH intramural research team led by Tory P. Johnson and Avindra Nath (National Institute of Neurological Disorders and Stroke) published in *Science Translational Medicine* in February 2017, a study which provided new and important evidence for a reactive autoimmune component to nodding syndrome. The investigators discovered autoantibodies to leiomodin-1 in both serum and cerebrospinal fluid in Ugandan patients with nodding syndrome (6).

Using a protein chip technology to detect antibodies to the CNS neuroinflammatory biomarker leiomodin-1, they found that this biomarker was in greater abundance in Ugandan patients compared to unaffected controls from the same village. The leiomodin-1 antibody was detected in both the serum and CSF of about half of the patients, and provided the first conclusive evidence that the mature parasite had entered the brain in affected children. In this study, Leiomodin-1 was expressed in mature and developing human neurons *in vitro*, which was then localized in mouse brain to the CA3 region of the hippocampus, Purkinje cells in the cerebellum, and cortical neurons. This is highly significant, because these are the very brain structures documented to be most affected in nodding syndrome patients.

Since Leimodin-1 antibodies cross-react with the Onchocerciasis parasite *O. volvulus* proteins, the authors provide the first compelling evidence in their study that nodding syndrome may likely be autoimmune epilepsy initiated by this parasitic infection. The translational medical implications of their findings are important, because they suggest that this disease may be prevented in the early stages by treatment with anti-parasitic strategies such as the drug ivermectin. This disease may also perhaps be treated in the early stages with immunomodulatory therapies.

The authors note, however, that not all their patients with nodding syndrome had detectable antibodies to leiomodin-1. Most of the patients had multiple autoantibodies, as demonstrated by proteomics. The Leimodin-1 antibodies which Johnson *et al.* [2017] characterized, simply had the highest titer that best distinguished the patients with nodding syndrome from unaffected village controls. Therefore, nodding syndrome may not be a single antibody syndrome. Furthermore, other investigations have suggested that patients with nodding syndrome may have antibodies to other neuronal proteins (9), further suggesting that nodding syndrome may not be mediated by a single specific patho-immune process.

Irrespective, the implications from the Johnson *et al.* [2017] findings have very significant implications in terms of future therapeutic strategies for this disease, and therefore have direct clinical translational value. Patients with nodding syndrome are presently treated with antiepileptic medications so as to control their seizures (10). The Johnson *et al.* findings, however, suggest that patients may also benefit from immunomodulatory therapies, especially early in the course of disease before serious brain injury takes hold. On the other hand, if the immune responses in nodding syndrome cause monophasic neurotoxicity, then immunotherapy may not be helpful. Therefore, an urgent priority in further research on nodding syndrome is to deepen our understanding of the neuropathophysiological basis of the brain injury, as it relates to an autoimmune reaction to *O. volvulus*, of the sort that Johnson *et al.* have documented.

The public health impact of such advances in our understanding of nodding syndrome would be tremendous. Given the extent of brain pathogenesis in nodding disease, it is not surprising that it is accompanied by life-long profound cognitive neurodisability, severe behavior problems, and high mortality (5). These seizures typically arise in previously healthy children, although there may be a family history of seizures. One constant feature, however, is an epidemiological association between nodding syndrome and areas with high infection rates of the parasitic worm *O. volvulus*. Onchocerciasis tends to have the highest prevalence in rural east and central African areas with poorly developed health care and social service infrastructure.

Because of this, families with children affected by nodding disease, already often existing in the margins of their resources in impoverished areas, have little in the way of caregiving resources needed to cope with the profound disability that results from this disease (1). Also, some patients also have delayed sexual development, suggesting pituitary-hypothalamic dysfunction (11). Johnson and colleagues did not investigate whether leiomodin-1 is expressed in these regions of the brain. Therefore, further epidemiological work on this disease is also very much needed, given the geographical restriction of nodding syndrome relative to the presence of *O. volvulus*. The spike in the prevalence of this disease over the past decade in affected regions may be due to interruption of parasite control in these regions, suggesting that unidentified co-factors may also contribute to the pathobiology of nodding syndrome, leading to outbreaks among children especially (12).

In conclusion, ongoing research must continue to focus on understanding the immune-reactive neuropathophysiological etiology. Only with this foundational understanding can we make an early diagnosis for more effective treatment, and develop effective strategies for prevention. As such, this work provides an important opportunity for developing diagnostic, management, and intervention techniques adapted to low and middle income countries (LMICs) for a host of other present and future outbreaks (1,13). Presently, such advances can especially be used for prevention worldwide outbreaks of other infectious parasitic diseases that can lead to severe disability in children (e.g., CNS invasive trypanosomiasis, trypanosomiasis, schistosomiasis, neurocysticercosis, zika, dengue, malaria).

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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