# Unravelling the mysterious onchocerciasis—nodding syndrome link: new developments and future challenges

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Nodding syndrome (NS) is a chronic, progressive, epileptic encephalopathy of undetermined aetiology, affecting primarily children within the select age group of 5–15 years. Some cases having NS-like clinical features have been described in a number of onchocerciasis-endemic African countries (1), however it is in Northern Uganda (2) and Southern Sudan (3) were epidemic proportions have been noted. First described by Louise Jilek-Aall in Tanzania in the 1960s (4), NS core clinical features are the atonic seizures manifesting as repetitive head nodding episodes (5), often occurring in association with taking a meal or by cold weather, and may be trailed or heralded by other seizure types, behavioural difficulties and deteriorating cognitive function (5-7). In addition, patients may progressively develop other features such as growth decline, delayed sexual development, malnutrition, and psychiatric manifestations such as aggression, catatonia and/or disordered perception (7-9). The consensus case definitions include suspected, probable (further divided in major and minor criteria) and confirmed NS (10).

In 2013 in Uganda, a systematic assessment conducted in three northern districts using the probable case definition, reported approximately 2,000 cases (11). The current total burden in the two geographically distinct areas that have reported epidemics is unknown. However, over the past 15 years, several thousands of children have been affected with a reduction in the number of new cases lately following the introduction of mass treatment with Ivermectin (12) (a microfilaricide that paralyses and kills microfilariae, but does not kill the adult worms).

NS is very destructive to patients and communities because as it evolves, the victims may develop severe physical and functional deficits, making several children drop out of school and become solely dependent on their caregivers, due in part to the poorly controlled epileptic seizures, cognitive impairments and social stigma (13,14). Such a scenario has made NS a key public health problem in Africa, associated with a high burden of morbidity, as well as grave mental, societal and economic challenges to be reckoned with. NS is currently incurable, however symptomatic treatment including anti-epileptic drugs, reassurance, nutritional and physical rehabilitation—may improve the patient's quality of life (15).

Surprisingly, even after more than half a century following NS first description in the literature, its pathogenesis remains unknown despite previous extensive investigations. Whereas an epidemiological association has consistently been demonstrated between infections with the nematode parasite Onchocerca volvulus (OV), transmitted to humans by the black fly (Simulium sp.) (with a higher sero-positivity prevalence seen among NS cases as well as in those from the affected geographical areas) the evidence regarding its contribution as a cause of NS has been inconclusive (2,5,10). This has stemmed from the lack of proof of microfilariae and adult OV worms' capacity to invade the central nervous system, in spite of some reports of

**Table 1** Similarities in clinical characteristics between autoimmune epilepsy and nodding syndrome (18-22)

| Characteristic | Autoimmune epilepsy | Nodding syndrome |
|---|---|---|
| Presence of a preceding viral infection | ✓ | × |
| Acute to subacute onset of presentation | ✓ | ✓ |
| Associated cognitive or psychiatric symptoms | ✓ | ✓ |
| Unusually high seizure frequency, and multiple types, including pilomotor seizures | ✓ | ✓ |
| Poor response to anti-seizure medications | ✓ | ✓ |
| Status epilepticus of unknown cause | ✓ | ✓ |
| Personal or family history (1st degree relative) of autoimmune disease | ✓ | Not been investigated |
| Risk factors or personal history of cancer | ✓ | Not been investigated |
| Presence of neural autoimmune antibodies | ✓ | ✓ |
| Response to immune therapy | ✓ | Not been investigated |
| Evidence of cerebral spinal fluid inflammation-elevated protein, pleocytosis, oligoclonal bands | ✓ | × |
| Brain imaging findings of cerebellar/hippocampal atrophy | ✓ | ✓ |
| Electroencephalogram with epileptic or slow-wave activity involving the temporal lobe | ✓ | ✓ |

✓, present; ×, absent.

cerebral spinal fluid (CSF) infestation by microfilariae (16). Over the years, the perplexing relationship between OV infection and NS has continued to baffle scientists and question the role played it plays in the pathophysiology of NS development.

In an attempt to unravel this mystery and provide answers to explain the puzzle of the elusive "OV-NS link", Nath and his colleagues (17), employed state of the art protein chip methodology, to explore for the presence of potential autoantibodies in pooled sera from patients with nodding syndrome compared to that from unaffected village controls from the same village. They hypothesized that NS may be an autoimmune-mediated disease, and were able to demonstrate ample amounts of autoantibodies to a protein, leiomodin-1 (LMOD1) in patients with NS compared to unaffected controls. LMOD1 autoantibodies were localized to the sera and the CSF of patients with NS and *in vitro* experiments showed them to be expressed in many neuronal populations. Using a mouse model, they demonstrated LMOD1's predilection for the CA3 region of the hippocampus, Purkinje cells in the cerebellum and cortical neurons, areas which are coincidentally affected in patients with NS. Interestingly, the investigators in further *in vitro* experiments also showed that LMOD1 antibodies (Abs) were neurotoxic to cultured human neurons and cross reactive with OV antigens.

These research findings seem to suggest that NS could be an immune mediated, acquired epilepsy syndrome. Over the past decade it has been increasing recognized that autoimmune or inflammatory conditions can cause epilepsy (18-20), and in the literature three Abs have been well portrayed: voltage-gated potassium channels (VGKC), glutamic acid decarboxylase (GAD) and N-methyl-D-aspartate receptor (NMDA) Abs (21). It is estimated that 17.5% of patients with epilepsy suffer from a systemic autoimmune disorder (22).

Autoimmune epilepsies are associated with Abs that bind to membrane receptors and ion channel-associated CNS proteins on the surface of neurons. Taking a closer look at the clinical characteristics of the autoimmune epilepsies, in comparison to that of NS displays several similarities as shown in *Table 1*.

Notably, studies have shown a lack of evidence of CSF inflammation (5,10) in NS and it seems unrelated to a known viral infectious aetiology (2,5,10). A plausible explanation for a negative CSF inflammation finding however, could be related to the timing in which the children having NS are identified. The natural history of

 

NS is not well known (12), however it is likely that the symptoms of head nodding occur long after the acute phase of the CSF inflammation caused by the suspect organism has ceased. Large prospective cohort studies are needed to confirm these findings in a group of patients who later develop NS.

A history of autoimmune disease, or cancer has also never been formally studied in NS, and Nath and colleagues do not entertain this association as a possible pathophysiological pathway for NS development. In paraneoplastic neurological syndromes, the autoimmune reaction occurs as a result of the body's attempt to eliminate tumour cells via Abs or by T-cells that then affect normal neural tissues. The investigators postulate that for NS the autoimmune reaction is as a result of a molecular mimicking event arising from the sequence and structural resemblance between LMOD1 with OV proteins (17). What remains unsolved though is why the twelve unaffected village controls who were OV positive and LMOD1 positive did not develop NS. It is also baffling how the relatedness between these two proteins evolved and raises the concern of how many more newly emerging illnesses may have a similar basis, calling on future studies to investigate this mystery.

Further clarification is also needed regarding the finding of the neuronal LMOD1 auto Ab in the CSF. By nature, neuronal LMOD1 is an intracellular protein and by virtue of its intracellular location, is hardly within reach to enable receptor-antigen binding. This raises doubts whether its presence in the CSF is as a result of B cell receptors binding to a specific antigen and initiating an Ab response (23). It has been demonstrated in a number of studies that autoimmune illness associated with these intracellular proteins is mediated via cytotoxic T cells rather than through the production of Abs as is seen with cell surface proteins (20,23). Further study to determine the exact immune response at play in this scenario is warranted. In addition, this finding has implications regarding the possible management of NS patients, and the response to immune therapy. In T cell mediated immune response, any proposed immunomodulatory therapies may not be as successful because these Abs cause neuronal damages unlike what is seen with cell surface Abs (24).

The investigators are rather silent as to whether they were able to consistently measure the presence of these autoantibodies in the CSF, which would suggest a greater likelihood of pathogenicity.

In view of the finding of a >100-fold increase in four proteins from patients with NS compared to the controls, and with the two Abs namely, LMOD1 and DJ-1 showing differential immunoreactivity, it is also possible that these autoantibodies could be occurring secondary to structural damage or generalized immune activation following refractory seizures in these patients. Further studies should seek to preferentially include prospective cohorts of patients with new or recent-onset NS to further understand the contribution of autoantibodies to the pathophysiology of NS.

Another issue to bear in mind is that not all patients with autoimmune epilepsies will have positive results even following extensive conventional Ab testing (23) and NS is no exception (10,25). The investigators similarly noted that 20 NS cases were OV positive but LMOD1 negative (17). The possible reasons for this finding could be due to antigen denaturation during tissue fixation; false negative results arising from small amount of Ab or inadequately sensitive assays; probable presence of still undocumented Abs or the presence of a complex T-cell-dominant autoimmune response with no production of "marker Abs". It could also be related to genetic susceptibility. In a case series in Uganda, we observed that over 70% of families with children with NS reported multiple affected children (7). In view of these varied possibilities, further studies are of necessity to explain this discrepancy.

As is known, a positive Ab test does not always imply the presence of pathogenic Ab. Therefore, to concur with the investigators, follow-up *in vivo* studies should be carried out using animal models to determine whether the clinical manifestations of NS can be reproduced with these auto Abs. In the next steps they should also endeavour to obtain magnetic resonance imaging and consider CSF analysis testing in the unaffected village controls to corroborate their findings.

The investigators may also explore the possibility of setting up randomized controlled therapeutic trials in which immunomodulatory therapy is provided to the cases and unaffected village controls irrespective of OV or LMOD1 positivity status to determine their response as well as the ability to curtail complications like cognitive impairment. What is not clear though is whether this would cause more harm than good in case there is a neurotoxic immune response. If immunomodulatory therapy is to be instituted, it is also not clear what selection criteria to use for patients with NS most likely to benefit from this treatment; at what point in the clinical course of the disease to commence the immunotherapy and the optimal duration of long-term maintenance treatment. Another challenge would be

 

the institution and monitoring of this therapy in the rural locations where most of these children are situated and have limited health system support.

The investigators should be recommended for a meticulous job well done and for illustrating the benefits of international collaborations especially when the techniques and expertise for certain investigations in a low resource setting is lacking. However, while the discovery serves to provide an intriguing piece of the 'jigsaw puzzle' in the OV-NS link, the complete picture is yet to be assembled. Insight has been provided on some of the likely pathophysiological mechanisms that are involved in the development of NS and paved a way for a new direction of focus in investigating the OV-NS link, which still requires much more study. Their findings reiterate the importance of always being on the lookout for other autoimmune epilepsies, because these conditions are amenable to treatment and clinical symptoms may be reversed.

Several questions still remain unanswered. The full clinical spectrum of NS "autoimmune epilepsy" needs to be explored. It is conceivable that we may only be identifying patients with the obvious nodding which may be the severe manifestation in this heterogeneous group of patients, and the burden of this entity remains under appreciated in those with the milder, subtle presentations (12).

Nevertheless, the fundamental and most important factor in the management of NS is to institute an effective control and surveillance OV program by reinforcing regular mass treatment with Ivermectin, especially in the endemic areas. This calls for strengthening of local, regional and international partnerships between funding bodies, communities, healthcare and allied workers, the academic fraternity, advocacy groups, ministries of health, non-governmental organizations, and concerned stakeholders.

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## Footnote

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

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