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Nodding Syndrome in the Spotlight –placing recent findings in perspective

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Abstract

Nodding syndrome (NS) is a debated scientific topic. A recently published study suggests that NS is an autoimmune disorder based on findings of cross-reacting antibodies between neuronal structures and a protein present in *Onchocerca volvulus* (OV). In our opinion, the proposed causal relationship between OV infection and NS has yet to be demonstrated and, instead, OV infection in NS may be opportunistic.

Nodding syndrome (NS) is an epileptic encephalopathy that manifests in previously healthy children and adolescents in eastern Africa, with confirmed cases in southern Tanzania, South Sudan, and northern Uganda. In Uganda, the NS epidemic began in 2000 and ended in 2013; around 1700 children were estimated to have been affected [1]. Official numbers from South Sudan and southern Tanzania are not available.

The core features of NS are nodding attacks with repetitive forward bobbing of the head, frequently associated with other types of epileptic seizures [2]. In addition to these neurological signs, children may be stunted and underweight, with delayed sexual development and signs of psychiatric illness. Without symptomatic treatment, NS is frequently described as a progressive encephalopathy leading to death. NS was initially defined as a ‘syndrome’ rather than a ‘disease’. However, a suggestion for refinement of the current definition was put forward during the 2015 Nodding Syndrome Conference in Gulu based on new findings [3].

The etiology of NS is unknown. Infectious, toxic, environmental, nutritional and genetic causes of NS have been considered [4]. An epidemiologic association between NS and

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infection with *Onchocerca volvulus* (OV), a filarial nematode transmitted by the black fly (*Simulium* spp.) and the etiological agent of onchocerciasis, has been demonstrated but its significance is unclear [4]. A recent study [5] proposes that NS may be an autoimmune-mediated disease associated with OV infection. Johnson and colleagues [5] collected serum samples from 55 patients with NS from northern Uganda and South Sudan and matched village controls, as well as cerebrospinal fluid (CSF) from a subset of Ugandan NS patients. Based on results using protein chip methodology, leiomodins-1, an actin-binding protein, was one of two proteins with autoantibodies found biochemically to have increased reactivity in NS patients compared to village controls. Half of 16 NS subjects showed antibodies to leiomodins-1 in CSF, compared to zero of 8 North American patients with epilepsy serving as controls. In further steps using different methods, leiomodins-1 was found in vitro in developing and mature human neurons and in different types of neurons in mouse brain. Antibodies targeting leiomodins-1 decreased human neuronal viability in vitro (described as neurotoxicity), and leiomodins-1 antibodies from patients with NS cross-reacted with OV antigen.

While these results are consistent with prior evidence that non-central nervous system but otherwise systemic infection with OV contributes to the clinical picture of NS, evidence is lacking for a causal relationship. Key questions remain. For instance, since OV has a wide distribution across central Africa, northern South America, and southern Central America, why is NS confined to three countries in eastern Africa? Ivermectin is an effective drug treatment for systemic OV microfilarial infection but, in our experience in Tanzania, has not stopped new cases of NS [6].

Although there was a higher percentage of OV-positive status in Ugandan NS patients than in unaffected controls [5], the difference was small (in NS patients, 54.5% were positive for both OV infection and leiomodins-1 antibodies, whereas in village controls this was as high as 41.4%). While Johnson and colleagues suggest that OV-infected leiomodins-1-positive control subjects had yet to develop clinical NS, the outbreak in Uganda had a well-defined beginning and ending, suggesting the 19 ‘pre-NS’ Ugandan controls included in the study may not have developed NS. Whether these controls have developed NS is thus of pivotal importance and should be addressed.

Leiomodins-1 transcripts are expressed in many tissues, with the highest levels in thyroid, eye muscle, ovary and, notably, skeletal and cardiac muscle. Since leiomodins-1 is an intrinsic component of the actin-myosin muscle fiber complex, leiomodins-1 autoantibodies, which were higher in blood than CSF, would be expected to induce a myopathy and/or cardiomyopathy, neither of which has been reported in NS. Since leiomodins-1 is also present in neurons [5], one may argue that in individuals with NS, the majority of whom also suffers from generalized tonic-clonic seizures, neuronal and muscular damage during the actual seizures may result in leiomodins-1 exposure, triggering antibody production. In this case, leiomodins-1 autoantibodies would be the result, rather than the cause, of the seizures. The inclusion of a control group of matched individuals with generalized tonic-clonic seizures but without NS from the same villages as patients with NS (instead of North American patients with epilepsy) would help elucidate this point.

NS often shows a progressive course, but some cases arrest, relapse or, rarely, even return to apparent clinical normality [7]. If leiomodrin-1 autoantibodies are neurotoxic, as implied [5], one might expect a relentlessly progressive neurological disease and an improvement with immunomodulatory therapy. However, in a separate study, three OV-negative children with NS who were given immunomodulatory treatment by plasmapheresis or intravenous injection of immunoglobulin, showed no short-term clinical improvement [8]. Moreover, when König and colleagues [9] examined the CSF of over 50 children with NS, the inflammatory signs to be expected in some children with autoimmune-mediated encephalopathy were mainly absent, as were antibodies against OV. These two studies question whether autoimmune mechanisms have etiological significance in NS.

An alternative recent etiologic hypothesis for NS, not considered by Johnson and colleagues, is based on the case association with prior measles infection shown in Ugandan NS cases, and the striking clinical overlap between NS and some cases of the post-measles disorder subacute sclerosing panencephalitis (SSPE) [7]. In SSPE, masses of mutant measles nucleocapsids form intranuclear crystalline inclusions in neurons and glial cells known as Cowdry bodies. Preliminary neuropathological findings from the U.S. Centers for Disease Control and Prevention in three Ugandan cases of NS revealed intracellular crystalline-like structures in the brainstem by polarized light microscopy. (<http://www.monitor.co.ug/News/National/Nodding-disease--Crystals-found-in-victims--brains/688334-2403276-k6t33jz/index.html>). While formal publication of these data is awaited, and preparation artifact should be excluded, it is noteworthy that inclusion bodies are not seen in CNS disorders of autoimmune etiology but are reminiscent of the Cowdry bodies seen in SSPE. Infantile measles infection and ongoing malnutrition seen in children with NS – both well-known causes of immunosuppression – would open the door for heavier OV infection in NS subjects, which in turn would be consistent with higher OV-derived leiomodrin-1 antibody titers in individuals with NS compared to village controls. Importantly, comparable opportunistic infections with nematodes other than OV, including *Mansonella* spp., which like OV is also significantly associated with South Sudan and Ugandan NS cases compared to village controls [4], are seen in untreated HIV-immunocompromised patients [10].

In summary, the findings of Johnson and colleagues [5] contribute to the neurobiology and clinical picture of NS as they demonstrate that a) leiomodrin-1 is present in human neurons, b) leiomodrin-1 auto-antibodies cross-react with OV protein, and c) leiomodrin-1 autoantibodies are more frequently found in cases of NS than in village controls without NS. Although these results extend the previously established association between OV infection and NS, they do not in our opinion support the authors' statement that “*This syndrome can now be added to a growing list of autoimmune epilepsies*”. Further studies, including detailed neuropathological examination of well-fixed brain tissue, are warranted to determine the definitive cause of NS.

References

1. Iyengar PJ, et al. Prevalence of Nodding Syndrome – Uganda, 2012–2013. *Morb Mortal Wkly Rep*. 2014; 63:603–606.
2. Winkler AS, et al. The head nodding syndrome – clinical classification and possible causes. *Epilepsia*. 2008; 49:2008–2015. [PubMed: 18503562]

3. Spencer PS, et al. Nodding Syndrome: 2015 International Conference Report and Gulu Accord. *eNeurologicalSci*. 2016; 3:80–83.
4. Dowell SF, et al. Nodding syndrome. *Emerg Infect Dis*. 2013; 19:1374–1373. [PubMed: 23965548]
5. Johnson TP, et al. Nodding syndrome may be an autoimmune reaction to the parasitic worm *Onchocerca volvulus*. *Sci Transl Med*. 2017; 9:eaaf6953. [PubMed: 28202777]
6. Winkler AS, et al. A longitudinal study on nodding syndrome—a new African epilepsy disorder. *Epilepsia*. 2014; 55:86–93. [PubMed: 24359274]
7. Spencer PS, et al. Environmental, dietary and case-control study of Nodding Syndrome in Uganda: A post-measles brain disorder triggered by malnutrition? *J Neurol Sci*. 2016; 369:191–203. [PubMed: 27653888]
8. Soldatos A, et al. Evaluation and immunomodulatory treatment at the NIH of children with Nodding Syndrome from Northern Uganda. *Neurology*. 2015; 84(Suppl):S37.005.
9. König R, et al. The role of *Onchocerca volvulus* in the development of epilepsy in a rural area of Tanzania. *Parasitology*. 2010; 137:1559–1568. [PubMed: 20388236]
10. Brown M, et al. Helminth infection is not associated with faster progression of HIV disease in coinfecting adults in Uganda. *J Infect Dis*. 2004; 190:1869–1879. [PubMed: 15499545]