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# The Pathogenesis of Nodding Syndrome

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## Keywords

nodding syndrome, epilepsy, *Onchocerca volvulus*, tau, autoantibody, immune mediated

## Abstract

Nodding syndrome is a rare, enigmatic form of pediatric epilepsy that has occurred in an epidemic fashion beginning in the early 2000s in geographically distinct regions of Africa. Despite extensive investigation, the etiology of nodding syndrome remains unclear, although much progress has been made in understanding the pathogenesis of the disease, as well as in treatment and prevention. Nodding syndrome is recognized as a defined disease entity, but it is likely one manifestation along a continuum of *Onchocerca volvulus*–associated neurological complications. This review examines the epidemiology of nodding syndrome and its association with environmental factors. It provides a critical analysis of the data that support or contradict the leading hypotheses of the etiologies underlying the pathogenesis of the syndrome. It also highlights the important progress made in treating and preventing this devastating neurological disease and prioritizes important areas for future research.

## INTRODUCTION

Nodding syndrome, a form of pediatric epilepsy, emerged as an epidemic in the early 2000s in distinct regions of South Sudan and northern Uganda. Rigorous efforts on the part of local governments, including requesting assistance from international health organizations, resulted in resources and expertise converging in 2012 to define nodding syndrome and provide a consensus case definition. This important step allowed for epidemiological studies into the etiology and risk factors for nodding syndrome and the recognition of a weak but consistent association with the parasite *Onchocerca volvulus*. Nodding syndrome is recognized as an independent diagnosis, but it is likely one manifestation along a continuum of *O. volvulus*–associated neurological complications. Much work has been undertaken since 2000 to understand the pathogenesis of the syndrome. To date, no clear etiology has been elucidated, but several hypotheses have emerged. In this review, we explore the evidence for each line of inquiry as well as postulate potential pathogenic mechanisms and suggest areas for future research. Importantly, advancements in understanding nodding syndrome have led to treatment protocols that have reduced disability and improved patients' quality of life. A carefully planned campaign against *O. volvulus* in Uganda appears to have reduced the incidence of the syndrome and certainly has reduced the burden of this parasite within affected communities. Continuing research into nodding syndrome may help inform the response to and treatment and management plans for future epidemics of neurological diseases. Additionally, insights into the pathogenesis of nodding syndrome may shed light on the etiology and mechanisms of disease for other forms of pediatric epilepsy.

## CLINICAL DESCRIPTION OF NODDING SYNDROME

Nodding syndrome is a rare and distinct form of pediatric epilepsy. The name of the syndrome is derived from the atonic seizures that are the hallmark of the disease. While there may be several causes of atonic seizures in childhood—including Dravet syndrome, myoclonic-atonic seizures, Lennox–Gastaut syndrome, and focal atonic seizures due to an underlying structural abnormality—nodding syndrome is a unique clinical syndrome. Unlike most pediatric seizure disorders that usually start in infancy, the age of onset for nodding syndrome is generally between 5 and 15 years (1, 2). During a nodding episode, atonic seizures cause a sudden loss of muscle tone in the neck and the head drops forward toward the chest, with approximately 5–10 head drops per minute (1, 3, 4). Atonic seizures can begin as focal or generalized seizures, and signs of both have been documented in patients with nodding syndrome (5). While atonic seizures are characteristic of this syndrome, patients often progress to other forms of seizures, including generalized tonic-clonic and absence seizures (3, 6). Without antiepileptic treatment, nodding episodes occur frequently in patients, with more than half of patients reporting daily seizures and only 25% of patients having less than one seizure a week (7). The majority (59.7%) of patients with nodding syndrome also experience a loss of muscle tone in the upper extremities during atonic seizures, and a minority of patients (17.7%) lose consciousness (8). Patients may also drool or experience incontinence during head-nodding episodes (6, 8). Excitatory stimuli, such as food or cold weather, may precipitate the head-nodding episodes, although they may also occur spontaneously.

Due to difficulties in accessing magnetic resonance imaging (MRI) and electroencephalogram (EEG) equipment in the rural areas where nodding syndrome occurs, few comprehensive studies have been completed. However, the studies that have been undertaken are quite informative, with interictal epileptic activity having been recorded (3, 8). Variable EEG patterns were noted, including intermittent generalized slowing with and without sharp wave activity, unilateral slowing, and generalized slowing (5, 8). MRI studies have demonstrated cerebral and cerebellar atrophy (3, 5), as well as hippocampal sclerosis and gliosis (8). Despite the marked atrophy observed in

the cerebellum of patients with nodding syndrome, only a few cases of ataxia or gait disturbances have been described (3). Examinations of cerebrospinal fluid (CSF) are largely unremarkable, with normal protein, glucose and immunoglobulin G indices (3, 8). Only a few patients have had CSF pleocytosis (3, 8).

In addition to seizures, patients with nodding syndrome also develop cognitive impairment (3, 6, 7). This is a common feature of the syndrome (1, 3, 6, 7), as well as other forms of epilepsy (9–12). In a recent study of 210 patients from the Pader district in Uganda, patients demonstrated learning impairment, poor attention, reductions in comprehension, and memory difficulties (6). Hearing impairments were fairly rare in these patients (5.7%) as were visual impairments (16.7%), which suggests that a lack of auditory or visual stimulation is not the cause of cognitive impairment. Psychiatric and behavioral disorders are also observed in patients with nodding syndrome (1, 6, 13). These manifest as hallucinations, both auditory and visual, as well as aggressive behaviors, depressive behaviors, and hyperactivity (5, 13). A lack of maturation and development has also been documented (1), as well as deformities of the torso and, more rarely, of the limbs (14). Many patients have delayed sexual development, although they do not have other signs of hypothalamic dysfunction or systemic manifestations.

The case definition for nodding syndrome was established in 2012 (1). Nodding syndrome is currently classified into three categories: (*a*) suspected, (*b*) probable, and (*c*) confirmed, based on a well-defined set of major and minor characteristics (**Figure 1**). There is concern that this case definition is too restrictive to accurately capture all patients with the syndrome due to the heterogeneity of disease presentation and the lack of diagnostic and imaging resources. In 2015, it was suggested that the clinical case definition of nodding syndrome be updated (14) to reflect the highly diverse presentation of the syndrome. A more refined case definition will likely be proposed as more data emerge about clinical presentation and manifestations, and as diagnostic

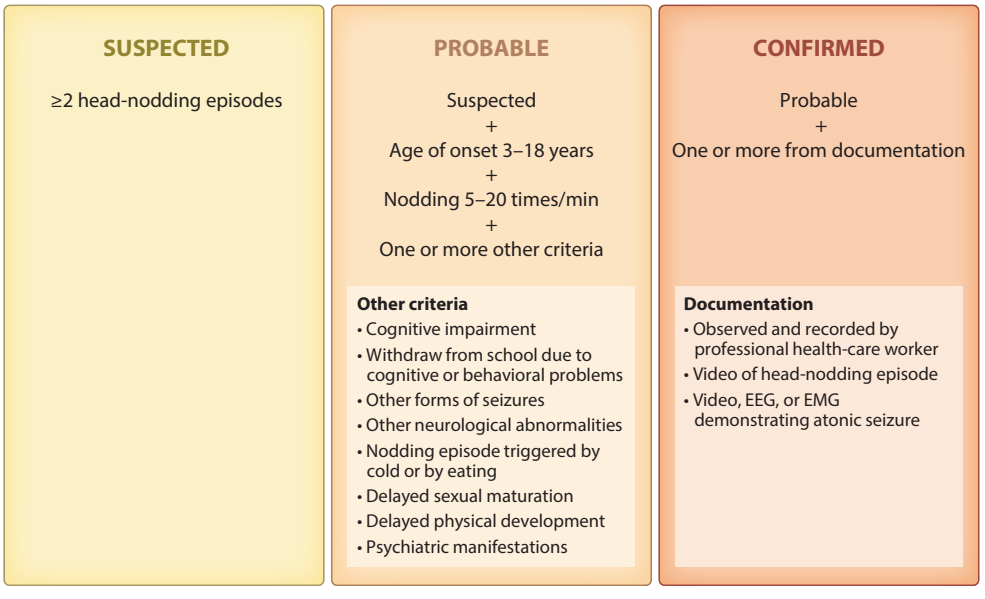


**Figure 1**

Clinical case definitions for nodding syndrome. Nodding syndrome cases are currently classified as suspected, probable, or confirmed, according to the characteristics included in the figure. Abbreviations: EEG, electroencephalogram; EMG, electromyogram. Figure adapted with permission from Reference 1.

tools are developed. This would include a better characterization of the seizures and associated neurodevelopmental and behavioral abnormalities and the development of biomarkers.

Although nodding syndrome is not diagnosed until after seizures start, there appears to be a prodromal period of variable length prior to the onset of atonic seizures (1, 6, 13). During this prodromal period, patients may experience a decrease in attentiveness, social withdrawal, bouts of dizziness, weakness, lethargy, and excessive sleepiness (6). Not all patients have obvious signs or symptoms of a prodromal period, but the majority of patients have at least one symptom prior to developing nodding syndrome (6). This is an absolutely critical area for future investigations, as interventions aimed at preventing the development of the syndrome are likely to have a greater impact on both the individual patient and the community compared with managing epilepsy once seizures have started. Prospective longitudinal studies that include careful observation of children at risk for nodding syndrome and annual or semiannual surveys of caregivers of these children may help elucidate other prodromal symptoms that could be useful for identifying children at risk for developing other neurological diseases. Studies that incorporate the biobanking of serum samples, urine, and other biological fluids prior to the development of disease would provide excellent resources for investigations into biomarkers or diagnostic discovery during the prodromal period.

## THE EPIDEMIOLOGY OF NODDING SYNDROME

Previously healthy children are the main victims of nodding syndrome, making this disease particularly devastating for families and communities. Nodding syndrome impacts both males and females, and the age of onset is typically between 5 and 15 years (1, 2, 6). Although historical descriptions of similar syndromes in Africa can be found from the 1960s (15), nodding syndrome was only recognized and investigated as an independent clinical entity beginning in the 1990s (1). Therefore, nodding syndrome, at least in regions of Africa, is likely not a new disease, but rather a reemergence of a phenotype not observed, or not recognized, for some time.

However, starting in 2000, there was an increase in the number of reported cases of nodding syndrome (2), leading to a strong interest in characterizing and understanding this disease and providing necessary information to halt the epidemic. In 2001, local governments in Sudan invited the World Health Organization to investigate nodding syndrome and attempt to determine the cause of the disease. In 2011, the United States Centers for Disease Control and Prevention also participated in investigations into the epidemiology and etiology of the syndrome. The geographical foci of these investigations were in South Sudan and northern Uganda. Overall, the incidence of nodding syndrome in Uganda was reported to continue to increase until 2013, but since then no new cases have been reported by the Ugandan Ministry of Health (16). The reason for the rapid decline in incident cases in northern Uganda in 2013 is unclear, but it has been attributed to the delivery of mass treatment for onchocerciasis with ivermectin and controlling blackflies, the vectors responsible for transmission of *O. volvulus*. The reasons for the ongoing new incidence and burden of nodding syndrome in other regions remain less clear.

Nodding syndrome is thought to occur in distinct geographical regions in northern Uganda (3), South Sudan (4, 17), and the United Republic of Tanzania (18). However, pediatric illnesses with head-nodding episodes have also been reported from other regions in Uganda (19), Cameroon (20), and the Democratic Republic of the Congo (21). It may be that other regions also experience nodding syndrome, but that the resources needed to confirm it are not available, such as video recording devices, professional health-care workers, or EEG equipment (**Figure 1**).

## THE ETIOLOGY OF NODDING SYNDROME

Many hypotheses have been put forth to explain the pathobiology of nodding syndrome, and extensive investigations into its etiology have been undertaken. Epidemiological investigations have

not revealed an association with a history of measles or meningitis, sex, or the consumption of sorghum, baboon meat or brain, mycotoxin-contaminated food products, or traditional medicines (1, 2, 4, 22). Nutritional deficiencies have been detected in patients, especially of vitamin $B_6$ (23), but these deficiencies were also detected in unaffected members from the same communities (2). Nodding syndrome was found to be associated with exposure to ammunition (2), although no specific toxic substance is thought to contribute to the development of this neurological disease. The association with ammunition exposure may be an autocorrelation, as the regions in Uganda and South Sudan most impacted by nodding syndrome and civil war—which disrupted food supplies and medical services—overlap considerably (24). Several studies have found an association between nodding syndrome and *O. volvulus* infection (1, 2, 19).

An epidemiological association between epilepsy and infection with *O. volvulus* was established as early as 1938 by Guillermo Casis Sacre (25, 26). In the Chiapas and Oaxaca regions of Mexico, Casis Sacre described a high prevalence of epilepsy in patients with *O. volvulus* infection. In addition, he described seizures, cognitive impairment, sexual dysfunction, and stunting. In 1965, Louise Jilek-Aall carefully documented an unusually high incidence of epilepsy in the Mahenge region of Tanzania, an area with a heavy *O. volvulus* burden. In some of her clinical descriptions of the seizures, the term head nodding appears, as do stunted growth, lack of sexual maturation, and atrophy (15). In the 1990s, further reports of increases in the prevalence of epilepsy and stunted growth and development emerged from Uganda (27), and these reports showed positive correlations between epilepsy rates and *O. volvulus* burden (28, 29) as well as elevated mortality (30). Case–control studies have also revealed an association between *O. volvulus* infection and epilepsy in Cameroon (31). In sub-Saharan Africa, a large population-based case–control study examined factors associated with the prevalence of epilepsy in Kenya, Uganda, South Africa, Tanzania, and Ghana (32). The incidence of epilepsy in this study varied across the five centers, ranging from 7 to 14.8 cases per 1,000 people. Several factors were found to be significantly associated with pediatric epilepsy, including a family history of seizure and brain injury, both of which are known risk factors for epilepsy. In addition, this study showed that severe malaria requiring hospitalization is also associated with epilepsy, but no association was shown between seropositivity for malaria and epilepsy. Cerebral malaria is also a known risk factor for the development of epilepsy (33), demonstrating that this work is consistent with previous findings. A strong association was established between *O. volvulus* infection and the development of pediatric epilepsy, but not adult-onset epilepsy (32). The same association was not observed for infections with *Toxoplasma gondii*, *Toxocara canis*, or *Taenia solium*. Additional meta-analyses also revealed a correlation between *O. volvulus* infection and epilepsy (34, 35). A recent cohort study that measured microfilarial density by skin snip in children aged 5–10 years and assessed whether they had developed epilepsy 25 years later revealed that epilepsy occurred after *O. volvulus* infection and that the risk of developing epilepsy increased with higher microfilarial density (36). A causal inference is supported by the molecular, pathological, and epidemiological observations of microfilarial load and a time- and dose-dependent development of epilepsy. Yet other studies in Tanzania (37) and Uganda (38) have demonstrated no association between *O. volvulus* infection and epilepsy, and direct evidence showing that *O. volvulus* infection causes epilepsy is lacking.

That nodding syndrome is caused by *O. volvulus* is unclear. Many of the epidemiological studies that revealed an association between the parasite and the syndrome do not account for confounders, such as other infections, trauma, or toxins (39). However, other investigations that looked for an association between nodding syndrome and known infections, heavy metals, nutrient deficiencies, or birth trauma have not found any such associations. Anecdotally, vector control of blackflies, which transmit *O. volvulus*, and administration of ivermectin have been related to a decline and eventual end to the epidemic of nodding syndrome in northern Uganda, and similar

efforts seem to have resulted in a decrease in seizure incidence in other areas of sub-Saharan Africa. Together, these studies suggest an association between *O. volvulus* infection and nodding syndrome. Yet in the discussion of *O. volvulus* infection and epilepsy it is important to remember that causality cannot be established through temporal association. Only through mechanistic studies and well-controlled studies using animal models can causality be established. No human studies are feasible that would clearly indicate that *O. volvulus* infection causes nodding syndrome or epilepsy. However, the accumulation of indirect evidence, such as epidemiological studies and intervention studies, in addition to in vitro and in vivo models will ensure that the appropriate causal factors are pursued. These studies are critical, for only by addressing the causal factors of nodding syndrome will the burden of disease be reduced. While this is true for every disease, it is especially true for pediatric neurological diseases, such as epilepsy, for which treatment can be challenging and ongoing morbidity is substantial.

## THE PATHOGENESIS OF NODDING SYNDROME

Although many epidemiological investigations into the etiology of nodding syndrome have been completed (1–4), only a few have focused on its pathogenesis. Nevertheless, the relationship between nodding syndrome and infection with *O. volvulus* appears strong, given that no cases of nodding syndrome have been found in areas not endemic for *O. volvulus*. Because only limited neuropathology data are available—as few postmortem or central nervous system (CNS) biopsy–based investigations have been completed on the brains of those with nodding syndrome—most studies of pathogenesis have focused on proving or disproving the leading hypotheses. These hypotheses are that nodding syndrome is (*a*) caused by direct infection of the CNS by *O. volvulus*, (*b*) caused by *O. volvulus*–induced immune responses, or (*c*) a tauopathy, manifesting as aggregates of tau protein in the brain. Multiple studies are ongoing to test, or corroborate, each of these three leading hypotheses, including case–control postmortem studies in Uganda, natural history studies, observational cross-sectional studies, and a variety of intervention studies. Additional investigations using cell culture models and establishing relevant animal models are also underway. Here, we review evidence related to the pathogenesis of nodding syndrome and attempt to provide a mechanistic framework for understanding the underlying disease pathogenesis.

What little is known about the pathology of nodding syndrome comes largely from inferences from imaging studies of patients with the syndrome and from the few autopsies performed. These findings are summarized below.

- EEG: Diffuse background slowing, epileptiform discharges, and polyspike activity are seen on EEGs. Nodding episodes demonstrate a drop out on cervical paraspinal electromyography. EEG findings are consistent with atonic seizure activity (3, 8).
- MRI: Generalized cortical and cerebellar atrophy are seen, most notably impacting the parieto-occipital and anterior temporal areas and the cerebellum. Also observed in some patients are hippocampal atrophy and unilateral or bilateral hippocampal sclerosis. No focal inflammatory changes are observed, and there are no white matter lesions. Gliosis was observed in the frontal subcortical regions in some patients (3, 8).
- Postmortem findings: On postmortem examination, there are generalized frontotemporal cortical atrophy and mild microvacuolation of the cerebral cortex. There is no immunohistochemical detection of α-synuclein, TDP-43, or β-amyloid accumulation. No Lewy bodies or Pick bodies were observed in any patients. Phosphorylated tau tangles, pretangles, neuropil threads, and dot-like lesions were observed in the prefrontal cortex and in the superior and middle-frontal gyri. Lower levels of hyperphosphorylated tau were observed in the occipital lobe and amygdala, and no tau accumulation was observed in the hippocampus (40).

## Direct Invasion of the Brain by *Onchocerca volvulus*

Imaging studies do not suggest that *O. volvulus* induces CNS lesions or vesicular or colloidal cysts in the brain (41), as are observed in neurocysticercosis (NCC). Instead, imaging studies in patients with nodding syndrome and *O. volvulus* infection demonstrate diffuse cortical or cerebellar atrophy that differs from the findings in other forms of epilepsy in patients in the same geographical region (41). Although postmortem studies performed on patients with onchocerciasis found parasites in the kidneys, liver, lungs, and pancreas (42), demonstrating that *O. volvulus* is capable of infecting deeper organs, there is a paucity of postmortem studies that specifically investigated the presence of *O. volvulus* in the CNS. A case series of five patients with nodding syndrome did not reveal any evidence of parasites in the brain (40). *O. lupi*, a related parasite of wolves (and, more recently, dogs), has caused spinal infections in two humans (43, 44), suggesting CNS penetration is possible by some *Onchocerca* species. To date, there is no documented incidence of *O. volvulus* in brain tissue. It remains unclear whether *O. volvulus* is even capable of entering the CNS.

## Nodding Syndrome as a Neurological Complication of *Onchocerca volvulus* Infection

*O. volvulus* is transmitted to humans by bites from an infected blackfly carrying third stage larvae. The larvae develop into mature adult worms in the subcutaneous tissue, where they are found encased in host tissue as nodules (termed onchocercomata). Female worms can live for up to 15 years, and they continuously produce microfilariae (mf) (the life cycle of *O. volvulus* is reviewed in Reference 45). It is the mf that are believed to be responsible for most of the pathology seen in onchcocerciasis, as they can drive inflammatory responses in the skin (onchocerdermatitis) and in the anterior chamber of the eye (keratitis). If *O. volvulus* is a causal factor in the development of nodding syndrome, it may be because there is direct parasite damage through CNS invasion or secreted factors or the induction of host responses that ultimately damages the CNS.

One important reason for the controversy (46–48) over whether *O. volvulus* has a role in causing nodding syndrome, as well as other forms of onchocerciasis-associated epilepsy (OAE), is that the parasite is not typically found in the CNS. Despite the original clinical description of OAE in 1938, in which mf were detected in the CSF (26), and two additional reports in 1959 and in 1976 (49, 50), the preponderance of evidence suggests that mf in the CNS are exceedingly rare and they are most commonly found in the CNS following diethylcarbamazine treatment, known to mobilize mf from the skin and the anterior chamber of the eye. Moreover, subsequent studies and current investigations utilizing polymerase chain reaction techniques have not detected *O. volvulus* DNA in the CSF of patients with epilepsy and onchocerciasis (37) or in patients with nodding syndrome (1, 8).

Many of the patients tested in recent studies (7, 8, 37) have been treated with ivermectin, which is distributed through annual or semiannual mass drug administration programs to populations at risk for onchocerciasis (51). Because the previous reports in which *O. volvulus* was detected in the CSF were from patients with heavy burdens of infection or from patients just initiating antiparasite treatment, it is possible that the longer-term use of these therapies reduces the occurrence of parasites entering the CNS or decreases the ability to detect parasites or parasite DNA in the CSF. Moreover, since the widespread use of ivermectin began in areas known to be at risk of nodding syndrome, no incident cases of nodding syndrome have been seen (16).

## Direct Effect of *Onchocerca volvulus* on the Central Nervous System

Although there is no evidence that *O. volvulus* enters the brain, other parasitic infections of the brain are associated with increased risks of epilepsy (52). Therefore, if *O. volvulus* is capable of

**Table 1 Examples of parasitic diseases associated with epilepsy**

| Organism | Disease | Evidence of direct central nervous system infection? | Type of seizures | Mechanism or suspected mechanism of neurological disease | References |
|---|---|---|---|---|---|
| *Taenia* species | Cysticercosis | Yes | Generalized tonic-clonic, partial (simple and complex) | Immune response to degenerating cysts, axonal damage, substance P–induced signaling cascades, increased cranial pressure | 57–60, 63, 149, 150 |
| *Plasmodium* species | Malaria | No | Partial, generalized, status epilepticus, subclinical | Fever; sequestration, vasoconstriction, hypoxia; inflammatory responses; loss of blood–brain barrier integrity, edema, hemorrhage | 33, 66, 67, 70, 151, 152 |
| *Toxoplasma gondii* | Toxoplasmosis | Yes | Myoclonic, hypsarrhythmic | Infection of astrocytes and neurons, alterations in neuronal activity, cyst formation, altered GABA signaling | 72, 153 |
| *Schistosoma* species | Schistosomiasis | Yes | Generalized tonic-clonic, focal deficits | Granulomatous reaction to eggs, fibrotic scar formation | 73, 74, 154 |
| *Onchocerca volvulus* | Onchocerciasis | No | Atonic, myoclonic, absence, generalized tonic-clonic | Unknown, but hypotheses include direct infection of the central nervous system, secreted products from the parasite driving neurological toxicity, inflammatory responses, autoimmunity | 36, 85, 155 |

penetrating the CNS, seizure development might be possible, albeit unlikely. Many different seizure types are associated with other parasitic infections, and parasites are thought to cause epilepsy through a variety of mechanisms (33, 53) (**Table 1**). However, much of the damage to the CNS is thought to be due to the large size of the parasites and tissue destruction arising from parasite migration. Additionally, parasitic infections of the CNS drive neuroinflammation, resulting in edema and further tissue damage. This is particularly true of eosinophilic meningitis, which has been linked to multiple parasitic infections and is thought to contribute to the development of seizures in conjunction with parasite-driven encephalitis (54, 55). *O. volvulus* has been linked to low-level eosinophilia in the CSF (55), but this is not a consistent finding among infected patients, and the data are limited. These parasite-induced traumas are suspected to disrupt neural networks, resulting in the development of epilepsy, a mechanism similar to that in traumatic brain injury (56). In addition to research exploring physical damage to the CNS, much research has been undertaken to understand the molecular pathogenesis of parasite-driven changes in the CNS that may result in epileptogenesis. If *O. volvulus* is capable of infecting the CNS, then findings from other investigations may have direct correlates with the development of nodding syndrome in response to parasitic infection.

## Lessons Learned from Other Parasites and Their Relevance to Onchocerciasis-Associated Epilepsy and Nodding Syndrome

In NCC, degenerating cysts may drive the development of epileptic foci (57, 58). Animal models of NCC demonstrate not only inflammatory changes in the brain but also the formation of spheroids and axonal swelling distal from the cysts (59). The loss of axonal integrity may contribute to the hippocampal atrophy observed in patients with NCC and result in seizure development (59). Degenerating cysts also trigger the production of substance P, a tachykinin produced by neurons in the host brain (60), which activates its receptor, neurokinin-1 (61). Once activated, this G protein–coupled receptor can cause calcium flux and activate the nuclear factor kappa–light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways, which promote neuroinflammation (reviewed in Reference 62). Substance P appears to mediate the development of epilepsy, as animals deficient in substance P are resistant to seizures induced by degenerating cysts (60), and blocking the receptor for substance P prevents the development of epilepsy (63). Substance P activates eosinophils (64), and these cells have been shown to be degranulated when in proximity to substance P–expressing peripheral nerves (65). The role of substance P in nodding syndrome or in *O. volvulus* infection has not yet been established.

Cerebral malaria is a leading cause of epilepsy (33), although the exact mechanisms by which *Plasmodium* causes seizures to develop is unknown and is likely multifactorial. For example, the parasite can cause sequestration of infected red blood cells in the endothelium of the CNS, a process that is mediated by parasitic proteins and host intercellular adhesion molecule-1 (ICAM1) binding (66), resulting in reduced cerebral blood flow and hypoxia (67). Malaria parasites also initiate inflammatory cascades and trigger the release of cytokines and chemokines, disrupt the blood–brain barrier, activate *N*-methyl-D-aspartate (NMDA) receptors, prompt metabolic changes in the CNS, and induce high fever (reviewed in Reference 67), all of which could contribute to the development of epilepsy. These features are not typically observed in patients with nodding syndrome, although there may be a role for NMDA receptor activation leading to excitotoxicity and seizure development (68, 69). Additionally, metabolites of the kynurenine pathway are increased in patients with cerebral malaria (70), and these are known to activate the NMDA receptor. Metabolomic profiling of CSF from patients with nodding syndrome has not been completed, although such studies may be revealing.

Other parasites, including *T. gondii*, *Echinococcus granulosus*, and *Schistosoma* species, are also found in the CNS. *T. gondii* can directly infect neurons and astrocytes (71, 72). *Schistosoma* species cause the formation of granulomas within the CNS around their ectopically migrating eggs (73, 74). The subsequent disruption of neuronal function caused by all of these parasitic infections is thought to induce epilepsy. Although it is theoretically possible that a few *O. volvulus* mf could be found in the CNS, it is unlikely that these would be capable of disrupting neuronal networks to allow for the establishment of an epileptic focus.

## *Onchocerca volvulus*–Specific Immune Responses and Their Effect on the Central Nervous System

*O. volvulus* can also have indirect effects on host tissues through eliciting particular immune responses (**Figure 2**). Indeed, host immune and inflammatory responses are thought to be major contributors to the development of pathologies associated with *O. volvulus* infection, albeit there are a range of human immune responses to infection. Strong immune responses that eliminate the parasite result in what has been termed a putatively immune state, whereas inappropriate or overzealous (hyperresponsive) immune responses result in immune-mediated pathologies (75).

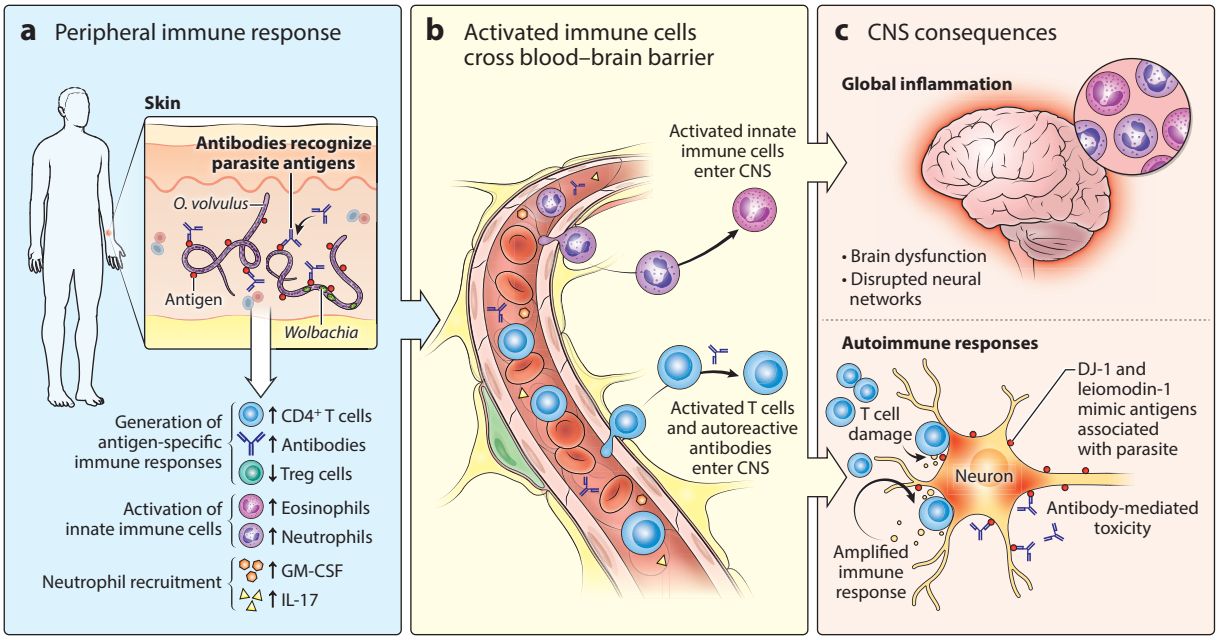


**Figure 2**

The immune-mediated hypotheses of the pathogenesis of nodding syndrome. (*a*) *Onchocerca volvulus* induces both innate and adaptive immune responses, including the activation of eosinophils, neutrophils, and T cells; the production of antibodies; and a reduction in regulatory T cell responses. Increased levels of several cytokines, including GM-CSF and IL-17, are produced during immune responses to *O. volvulus* infection. As the immune responses trigger parasite death, the commensal bacterium *Wolbachia* is released from the dying parasite, which may elicit additional immune responses. (*b*) Activated immune cells can traffic from the periphery into the CNS. (*c*) These cells promote global neuroinflammation, which may result in neurotoxicity and the disruption of neural networks. Antigen-specific immune responses to parasite proteins can also cross-react with antigens present in the CNS. This may trigger neurotoxicity that is mediated by either cytotoxic T cell responses or antibody-mediated cell death. Antigen recognition within the CNS by cross-reactive immune responses can induce further immune responses to CNS antigens, resulting in a feedforward loop of immune-mediated injury and inflammation. Abbreviations: CNS, central nervous system; DJ-1, protein/nucleic acid deglycase DJ-1; GM-CSF, granulocyte–macrophage–colony stimulating factor; IL, interleukin; Treg, T regulatory cell.

For example, the localized hyperreactive onchodermatitis (known as sowda) has severe pathological manifestations, yet patients have few mf or undetectable levels of skin mf (76). In these patients, there is a robust host response involving eosinophils, macrophages, and perivascular infiltrates of the few onchocercomata (45). Further, these patients have robust *Onchocerca*-specific $CD4^+$ T cell responses, but diminished T regulatory cell (Treg) responses (77).

Classic examples of inflammation-mediated manifestations due to *O. volvulus* infection are the blinding forms of onchocerciasis, most commonly those associated with anterior chamber scarring and inflammation (sclerosing keratitis) and posterior eye disease (chorioretinitis and optic neuritis) that lead to the eponymous "river blindness" (78). In some patients with onchocerciasis, mf can be found in the anterior chamber of the eye. As the mf die, they elicit potent inflammatory responses that may be a result of *Wolbachia* released from their intracellular location within the cells of the *O. volvulus* parasite that, in turn, recruit and activate neutrophils and eosinophils. Immune-mediated pathology can also result in optic neuritis and chorioretinitis (79), although the mechanism by which this occurs is less clear. Data suggest that posterior eye disease occurs as a result of the induction by *O. volvulus* of antibodies that cross-react with retinal antigens (80, 81).

Autoimmune responses have been detected in patients with *O. volvulus* infection and are thought to contribute to pathologies, in particular, to posterior eye disease (80–84). Patients with nodding syndrome also have autoantibodies that may contribute to pathogenesis (69, 85). Antineuronal antibodies, including those targeting the voltage-gated potassium channel (VGKC) complex proteins (69) leiomodin-1 and DJ-1 (85), have been described in subsets of patients.

Autoantibodies targeting VGKC proteins are associated with epilepsy, limbic encephalitis, and encephalopathies (86). In one case series, anti-VGKC responses were found more frequently in patients with nodding syndrome than in their unaffected siblings (69), but this was not found in a smaller series that utilized a different VGKC detection method (68). A prospective study of 178 patients with pediatric epilepsy found low occurrence rates of antineuronal antibodies in patients and also that these antibodies did not persist in some patients even in the absence of immune-suppressive therapies (87). Furthermore, in some patients these antibodies developed after the onset of seizure, suggesting that they may not be directly contributing to pathogenesis. Yet cognitive impairment was associated with the detection of antineuronal antibodies in pediatric epilepsy (87). Animal models have also found that anti-VGKC immunotherapy reduces the number of seizures and protects against neuronal loss and cognitive impairment in epilepsy (88).

Antibodies against leiomodin-1 were increased in patients with nodding syndrome compared with levels in unaffected controls in the same village, and the antibodies were present in both serum and CSF (85). Importantly, these antibodies cross-reacted strongly with *O. volvulus* antigens, suggesting that they were in fact *O. volvulus* antibodies that weakly cross-reacted with leiomodin-1. Autoantibodies to leiomodin-1 from patients with nodding syndrome were shown to be directly neurotoxic in vitro (85), and studies investigating their in vivo toxicity and ability to induce seizures are ongoing. Leiomodin-1 is an actin-nucleating protein that is expressed in the human CNS and in neurons in regions of the brain affected by nodding syndrome (85). However, some unaffected controls in the same village also had detectable levels of leiomodin-1 antibodies; therefore, the presence of the antibody in serum per se is not enough to cause disease (85). It may be that in order for nodding syndrome to develop, these antibodies must enter the CNS or be produced in the CNS (local antibody production). Because of the inability to collect CSF from children without neurological diseases, it is unclear whether unaffected control children with leiomodin-1 antibodies in serum also have detectable antibodies in their CSF. It may also be that certain leiomodin-1 autoantibodies that are associated with nodding syndrome recognize unique epitopes. To date, no epitope mapping antibodies to leiomodin-1 from patients and unaffected village controls has been completed. Further studies will be important to increase understanding of the consequences of leiomodin-1 autoantibodies in vivo as well as understanding of the mechanism of antibody-mediated toxicity.

Patients with *O. volvulus* infection have multiple detectable autoantibodies (69, 80, 82–85). Patients with nodding syndrome also have enrichment of autoantibodies against DJ-1 (85), a protein encoded by *PARK7*, which functions as a protein and nucleotide deglycase (89). DJ-1 is expressed in the brain, serves a neuroprotective role, contributes to proper mitochondrial function (90), protects against damage from oxidative stress (91), and is involved in a nucleotide repair system (92). Mutations in *PARK7* are associated with Parkinson's disease (93), and some patients with Parkinson's disease were recently shown to have cryptogenic epilepsy (94, 95), including absence seizures (96). A homolog to DJ-1 found in *O. volvulus* (DJ, accession number A0A044RAJ4) has strong structural similarity to human DJ-1 (85), and, therefore, it is possible that antibodies generated against *O. volvulus* DJ-1 may cross-react with human DJ-1. However, these experiments have not been completed, and DJ-1 autoantibodies were not preferentially detected in the CSF from patients with nodding syndrome. The relevance of DJ-1 autoantibodies in nodding syndrome remains to be investigated further.

Some patients with onchocerciasis have a parasite-permissive immune response. Interestingly, a relatively suppressed immune response can lead to high levels of mf in the host, although the actual cause may be that the mf are themselves driving the immune-tolerant state. Similar to other parasites, *O. volvulus* can suppress immune responses from the host to prevent immune-mediated destruction (reviewed in Reference 97). In patients with long-term parasitic infections, Tregs may lead to $CD4^+$ T cell hyporesponsiveness to the parasite. This occurs both through an increase in the number of Tregs (98, 99) as well as an increase in their activity (100, 101).

Most notably, in patients with high mf loads there is an increase in interleukin (IL)-10 production and a decrease in IL-6 production (102), responses generally characteristic of an anti-inflammatory state. In contrast, epilepsy is often associated with proinflammatory states (103) and autoimmune diseases (104). IL-6 is typically elevated in patients with epilepsy, whereas increasing levels of IL-10 are neuroprotective (103). However, a delicate balance exists between the CNS and the immune system, and a functional immune system is important for proper neurocognition and neurodevelopment (105–107). Therefore, while immune suppression by *O. volvulus* is unlikely to contribute to the development of epilepsy, understanding the role of parasite-induced immune suppression on cognition may be of interest.

However, when treatment is initiated in patients with high mf loads, patients are more likely to develop significant posttreatment adverse events, largely due to inflammatory responses induced by the dying and degenerating mf (108, 109). Importantly, the risk of developing epilepsy increases with increasing mf load prior to treatment (36). Therefore, robust immune responses and decreasing numbers of Tregs may also allow for greater neuroinflammation and could contribute to the development of epilepsy. Increases in IL-17 and in granulocyte–macrophage–colony stimulating factor, as observed in patients with robust immune responses to *O. volvulus* infection (77), are associated with an increased frequency of seizures in pediatric patients with epilepsy (110). However, in almost all patients with nodding syndrome, epilepsy was established prior to the initiation of antiparasite treatment.

## Nodding Syndrome as a Tauopathy

The only published postmortem case series demonstrated the presence of phosphorylated tau in the CNS of five patients with nodding syndrome (40). It remains unclear whether this represents a small subpopulation of patients or has broader implications. Hyperphosphorylated tau has also been observed in up to 94% of patients with temporal lobe epilepsy (111–113). The pathological findings of neuropil threads, neurofibrillary tangles, and pretangles are comparable between patients with nodding syndrome and patients with temporal lobe epilepsy; however, patients with nodding syndrome had extensive tau tangles in their cortical and subcortical regions, distinguishing them from patients with temporal lobe epilepsy (40, 111–113). In patients with temporal lobe epilepsy, the pattern of tau deposition was different from that in aged-matched patients with Alzheimer's disease and from that seen in chronic traumatic encephalopathy (111), suggesting that the underlying processes leading to tau accumulation in patients with epilepsy may be different than they are in tauopathies.

In temporal lobe epilepsy, the burden of tau pathology was not associated with seizure type, frequency, age of epilepsy onset, or duration of epilepsy (111–113). The presence of phosphorylated tau in patients with epilepsy is thought to arise from a combination of neuronal network rearrangements, seizure activity, axonal damage, and neuronal loss (114, 115). Alternatively, the accumulation of phosphorylated tau may directly contribute to the development of epilepsy, although the molecular mechanisms by which it drives epileptogenesis are unclear. Yet tau certainly plays a role in epilepsy. The deletion of *Mapt*, the gene that encodes tau, is protective in some, but

not all, animal models of epilepsy (116–118), and inhibiting the phosphorylation of tau decreases seizures in animal models (119). The phosphorylation of tau may be due to overactive NMDA receptor signaling, which mediates glycogen synthase kinase-3β (GSK-3β) phosphorylation of tau, resulting in tau tangles (115, 120). There is conflicting evidence about whether there is abnormal activation of NMDA receptors in patients with nodding syndrome (68, 69).

It remains to be determined whether the accumulation of tau contributes to cognitive impairment in patients with nodding syndrome. While a cross-sectional study of patients with temporal lobe epilepsy found that tau deposition was not associated with cognitive decline (113), a longitudinal case series indicated that the burden of tau at the time of resection surgery was correlated with future cognitive decline (111). Severe neurocognitive decline is observed in patients with nodding syndrome (3, 13) and in those with other forms of epilepsy (9–12). Serial measurements of tau in the serum or CSF may be useful for correlating the burden of tau accumulation with cognitive impairment or seizure activity. Serum levels of tau have been established as a potential predictor of cognitive impairment in patients with Alzheimer's disease and in those with mild cognitive impairment (121).

Importantly, these studies suggest that if tau accumulation could be prevented, perhaps through adequate seizure control, cognitive decline may also be slowed. Antiepileptic drugs (122), the ketogenic diet (123), and other adjunctive therapies (124) have been shown to improve cognition in other forms of epilepsy. Children with nodding syndrome whose seizures have been adequately controlled by antiepileptic drugs have returned to school and improved clinically (125).

## GENETIC CONTRIBUTION AND OTHER POTENTIAL FACTORS

As many individuals with *O. volvulus* infection do not develop neurological complications, it is important to consider what other factors may contribute to the development of OAE and nodding syndrome. Within the context of the three leading hypotheses regarding the pathogenesis of nodding syndrome, several important factors may play a role in disease development.

If nodding syndrome is caused by infection with *O. volvulus*, it will be important to consider whether there are underlying differences in either parasite or commensal bacterial phenotypes between patients with nodding syndrome and unaffected controls from the same village. Differences in the ability of distinct types of *O. volvulus* (i.e., savanna versus forest) to cause blindness have been reported (126) as have differences in *Wolbachia* densities (127). However, to date there has not been a comprehensive analysis of the genetic differences between *O. volvulus* isolated from patients with nodding syndrome and *O. volvulus* from unaffected village controls. In addition to parasite differences, an individual's parasite burden, malnutrition, or the presence of other underlying infections could all potentially influence the pathogenesis of nodding syndrome.

If nodding syndrome is caused by *O. volvulus*–induced immune responses, it will be important to consider the genetic contribution of patients to the development of neurological disease. For example, narcolepsy is an uncommon neurological disease associated with influenza infection. However, narcolepsy primarily impacts people with both influenza and a particular human leukocyte antigen (HLA) haplotype (128), indicating that an immune response to a particular antigen may be important for disease etiology. This disease association with a particular HLA phenotype is observed in several autoimmune diseases. However, genetic contributions other than HLA haplotype, such as neuroprotective or neuronal survival genes, may also play a role in the development of nodding syndrome and OAE. Large genome-wide association studies will be needed to address these issues.

If nodding syndrome is a tauopathy, it will be important to understand why this particular pathology occurred in an epidemic fashion. Genetic variability in tau is associated with

frontotemporal dementia and progressive supranuclear palsy (reviewed in Reference 129); however, its role in epilepsy has not been demonstrated.

## TREATMENT FOR NODDING SYNDROME

Patients with nodding syndrome benefit from comprehensive therapeutic regimens that aim to reduce seizures and help them regain or accommodate lost functions; patients also benefit from supportive therapies to improve their overall health. Importantly, with early, adequate, and sustained treatment, patients can demonstrably improve (130).

### Antiseizure Medications

The initiation and continual use of antiepileptic drugs is critical for seizure control. Patients with nodding syndrome are typically treated with either sodium valproate monotherapy (10–40 mg/kg per day) (131) or sodium valproate plus carbamazepine (0.1–0.2 mg/kg per day) (130, 131). An overall reduction in seizure burden has been reported with appropriate antiepileptic therapy regimens, and up to 25% of patients achieve seizure freedom, with concurrent improvements documented via EEG monitoring (125). Despite the ability to control seizures with antiepileptic medicines, there is a substantial treatment gap for patients with epilepsy living in low- and middle-income countries (132). Children with nodding syndrome often face periods during which drugs and resources are limited and, therefore, they are not able to achieve or maintain freedom from seizure activity (130). They also do not have access to the newer antiepileptic medications. This problem could be addressed through ensuring the availability of additional resources. Other barriers to treatment include cultural beliefs and superstitions surrounding epilepsy, which can be addressed through education (132, 133). It is less clear whether some patients have nodding syndrome that is refractory to current therapeutic approaches. Alternative therapies, including the ketogenic diet, have been successful in controlling refractory epilepsy in pediatric patients with other forms of epilepsy (134), but these have not been tested in patients with nodding syndrome. Very little data are available on proper weaning from antiepileptic medicines in this population, although abruptly stopping medications due to a lack of availability has been demonstrated to increase in seizure incidence (130). It is likely that these patients will require lifelong therapy.

### Nutritional Supplements

Supportive therapies aimed at correcting micronutrient deficiencies and improving overall nutrition are an important component of managing the syndrome. More than 50% of patients with nodding syndrome are malnourished (131). Nutritional supplementation should be considered for patients with documented malnutrition, and daily supplementation with vitamin B complex and vitamin A is recommended as needed (131).

### Rehabilitation

Rehabilitation strategies are also important for children with nodding syndrome to ensure they regain functions and independence. Some therapeutic approaches include providing occupational, speech, and cognitive therapies (131). The majority of therapeutic approaches are based on an individual patient's needs and goals, with customized interventions aimed at improving each patient's ability to perform daily activities, such as feeding, dressing, and participating in family life.

### Social Interventions

Patients with nodding syndrome represent a vulnerable population. There have been increasing reports of abuse, including sexual abuse, of patients with nodding syndrome, likely due to their

cognitive impairment (as detailed in the section, Clinical Description of Nodding Syndrome). This abuse has resulted in young girls and women on antiepileptic medicines becoming pregnant through rape. Additional treatment programs and centers are urgently needed that aim at protecting patients with epilepsy and aiding families in protecting relatives from abuse and rape (135).

## Antiparasite Therapy

Patients with nodding syndrome are treated for underlying infections, including other parasitic infections, depending on the patient's clinical needs (131). Treatments include those for intestinal parasites as well as ivermectin for *O. volvulus* infection. Currently, the majority of the population in regions with a high prevalence of nodding syndrome is receiving semiannual ivermectin as part of a community-based mass drug administration program.

Limited evidence suggests that treating patients who have epilepsy with ivermectin reduces seizure burden. In 1992, it was reported that there was a decrease in seizure burden and frequency in patients with epilepsy after an initial dose of ivermectin given as part of a mass drug administration campaign (136). Patients were asked about seizure improvement approximately 4 months after receiving ivermectin. A subset of patients with epilepsy self-reported an improvement in seizure burden and frequency (37% of patients), and 14% reported they were seizure free for 3–7 months after ivermectin treatment. However, the majority of patients reported either no change in seizure frequency or a worsening of seizures (136). Despite these interesting observations, this study is limited by the recall bias of patients and a lack of accurate documentation of seizure frequency prior to and after drug administration. Further, information regarding patients' microfilarial burden before and after treatment with ivermectin was not included. A study in the Democratic Republic of the Congo is underway to assess whether there is a reduction in seizure burden in patients with epilepsy and onchocerciasis who are treated with ivermectin in addition to antiepileptic drugs compared with those receiving only antiepileptic medicine (137). Preliminary findings from this study show that patients who received both ivermectin and antiepileptic drugs were more likely to be seizure free within 4 months compared with those patients who were treated only with antiepileptic drugs (138). In addition, another trial is underway to determine whether the addition of doxycycline (100 mg/day for 6 weeks), a drug shown to deplete *Wolbachia*, to the treatment regimen will further reduce immune responses either to neuronal proteins, including leiomodin-1, or to parasite and seizure burdens (139).

The hypotheses surrounding these studies are not only that *O. volvulus* is driving the incidence of epilepsy in areas where it is endemic but also that higher microfilarial burdens are driving higher numbers of seizures. However, because ivermectin does not typically enter the CNS (140), any reduction in seizure burden in patients treated with ivermectin is likely attributable to a systemic reduction in parasite burden. If these studies demonstrate that a further reduction of seizure burden is correlated with a reduction in microfilarial burden, this would further strengthen the association between *O. volvulus* infection and nodding syndrome. However, the off-target effects of ivermectin, including a direct antiepileptic effect, cannot be excluded through this method (136, 141).

## Immunotherapy

Because antibodies to leiomodin-1 and other neuronal autoantibodies have been associated with patients with nodding syndrome (13, 85), it is tempting to consider immune modulatory therapies as a potential treatment avenue. No trials have compared patients with nodding syndrome treated with and without immune suppression. However, it is plausible that immune-mediated damage

may initiate an epileptic focus; once the focus is formed, the epileptic process that is already established would be self-sustained. In this case, immune modulation after the establishment of an epileptic focus may not have an impact on seizure frequency or burden in patients with nodding syndrome. However, it is also possible that early immunotherapy may prevent the focus from spreading and subsequent neurodegeneration. Studies are underway to understand the mechanisms of the immune-mediated toxicity of leiomodin-1 antibodies, and these will likely provide information about the utility of using immune suppression to target these antibodies.

Overall, the proper management of patients with nodding syndrome was found to reduce seizure frequency and improve many outcomes, including behavioral and psychiatric. In a further indication of the benefits of treatment, the ability of patients to manage self-care increased from 36% prior to treatment to 83.1% at 1 year posttreatment (125).

## PREVENTING NODDING SYNDROME

Mass drug administration programs, community-directed ivermectin treatment programs (51, 142, 143), and strategies to reduce the vectors that transmit *O. volvulus* (144, 145) have substantially reduced the *O. volvulus* burden in many endemic areas (51). It is notable that in regions with a reduced burden of the parasite, the incidence of new cases of epilepsy appears to be decreasing (146, 147), and there is a reduction in the number of young children with epilepsy. However, epilepsy rates remain high in regions with ongoing parasite transmission and a continuing high burden of *O. volvulus* (21, 148). A rigorous campaign initiated in 2014 by the Ugandan Ministry of Health against *O. volvulus*—that includes applying larvicide to rivers, aerial spraying against blackfly, and delivering semiannual ivermectin therapy—has resulted in a rapid and massive decrease of the vector and a decrease in the transmission and prevalence of the parasite in northern Uganda (16). Concomitantly, there has also been near-elimination of new cases of nodding syndrome in this same region (16), thus establishing a strong association between the presence of *O. volvulus* infection and nodding syndrome. However, association alone does not prove etiology. Yet independent of the parallel reduction in the incidence of nodding syndrome, the government's efforts should be heralded as a success for diminishing the impact of this parasite on the populations inhabiting this region. The successes of the Ugandan government may encourage other areas with high burdens of *O. volvulus* to replicate these efforts. It may be that a reduction in parasite burden is enough to diminish both nodding syndrome and other forms of OAE.

## CONCLUSIONS

While the epidemic of nodding syndrome appears to be abating, the incidence of *O. volvulus* infection and the burden of epilepsy in regions where the parasite is endemic remain high. It is important to increase and sustain efforts to eliminate the parasite through vector control measures and continued delivery of mass administration of antiparasite drugs. Despite efforts to understand the etiology and pathogenesis of nodding syndrome, absolute answers to why and how this disease occurs remain enigmatic, although the process of molecular mimicry between *O. volvulus* and brain antigens has been implicated as has the involvement of tau accumulation. However, prevention and treatment are possible, and future studies are likely to be informative for nodding syndrome and other forms of pediatric epilepsy and *O. volvulus*–associated neurological diseases.

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