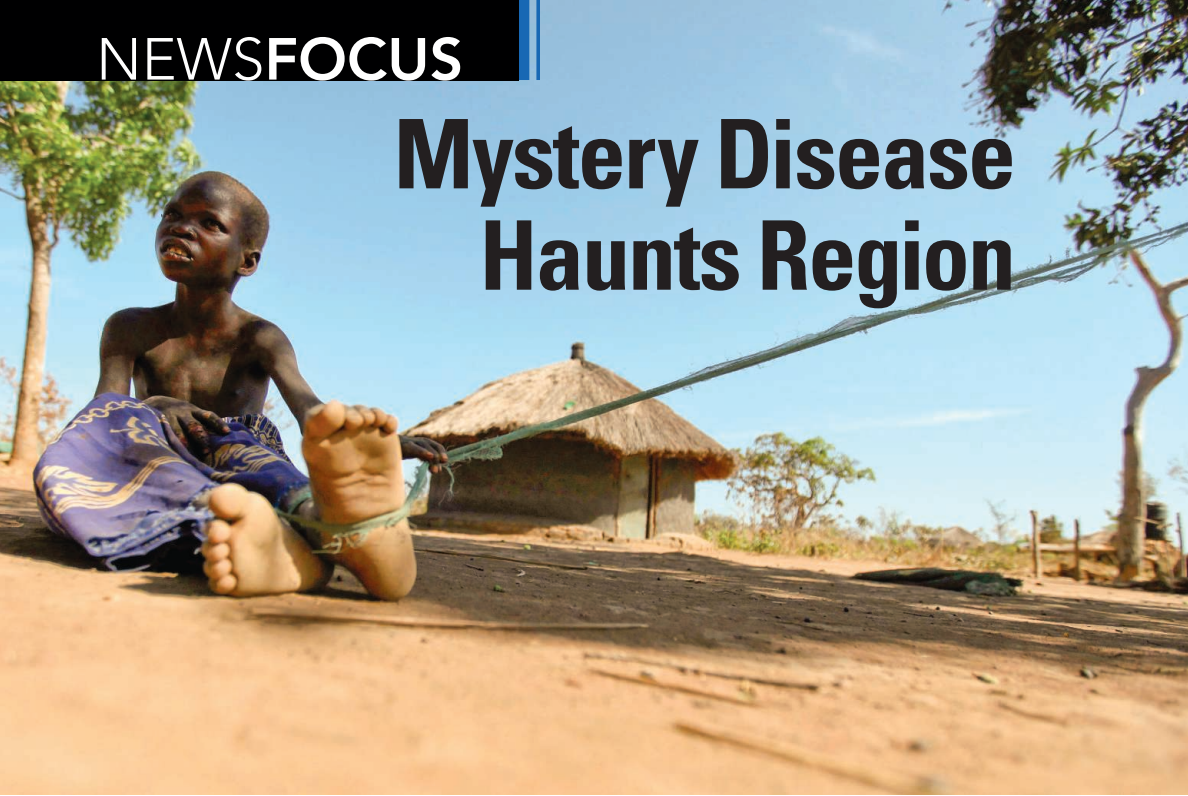


Mystery Disease Haunts Region



Could the parasite behind onchocerciasis, better known as river blindness, also explain the odd “nodding” seizures in a growing number of African children?

IN 1959, TROPICAL-DISEASE EXPERT Louise Jilek-Aall started working as a physician in Mahenge, a town in a mountainous and isolated area of southern Tanzania. She soon encountered an “astonishing” number of people suffering from epilepsy. As she investigated further, the mothers of some of the most severe cases told her their children were normal until they were around 4 or 5 years old, when they began to have seizures characterized by repeated downward movements of their heads. Jilek-Aall says the residents had a specific word for the condition, which translated literally as “nodding the head.”

Early on, children with the nodding seizures still led a somewhat typical life. They “were running around, playing with other children. They were not discriminated against at all,” recalls Jilek-Aall, who founded an epilepsy clinic in Mahenge in 1960. By the time they reached puberty, however, they grew sicker. “They became listless. They were not eating well,” and they suffered a noticeable decline in intelligence, she says. “Then one day, the usual grand mal seizures would start,” and the children would develop a form of full-blown epilepsy.

At that point, their prospects were grim. People with epilepsy were feared as possibly contagious, Jilek-Aall says: “They were shunned by the others. Some of them died of maltreatment.” The numbers were hard to determine, however. At the time, she says,

the people in Mahenge had very traditional beliefs, and it was taboo to discuss someone who had died.

Jilek-Aall, now a professor emerita at the University of British Columbia, Vancouver, in Canada first described the nodding seizures in a 1964 paper. For many years, Western colleagues doubted or dismissed her reports, but no more. An apparent outbreak of a similar nodding syndrome in Uganda and southern South Sudan over the past few years has attracted many more researchers, including teams from the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), to look for possible causes. They are chasing several suspects, including a parasitic worm, but so far there’s no proven culprit.

The world media has also become fascinated, showing videos of children nodding their heads uncontrollably or staring vacantly as if in a trance, a state that often follows the head-nodding attacks. Because food seems to trigger the attacks, many can’t eat properly and quickly lose weight. Gradually, they become more and more disabled. News accounts have described how families tie their children to trees so that they don’t wander off or fall into fires or rivers. Yet many do have deadly accidents; others die of malnutrition or secondary infections.

How many children are affected in Uganda and South Sudan, as well as the exact geographic scope of the problem, are unclear.

Desperate measures. Some children with nodding disease are restrained to prevent them from injuring themselves or wandering off.

The Ugandan ministry of health has said that at least 3000 children there have nodding disease. In South Sudan, cases have been reported in six counties. The pattern of reports suggests the syndrome may be spreading, but no one has systematically surveyed the entire area, and accurate counts are difficult to achieve.

The condition has become a prominent issue in Uganda’s volatile politics, exacerbated by long-standing tensions between the northern regions and the central government in Kampala. Legislators have

had heated debates over special funds to help nodding syndrome patients. And President Yoweri Museveni made two visits in March to health centers in the north that treat nodding syndrome patients. He pledged that he would defeat the disease just as he had defeated rebel warlord Joseph Kony and his Lord’s Resistance Army, which terrorized northern Uganda for more than a decade.

But without a clear explanation of the condition’s cause or effective treatments, that will be no easy task.

A new phenomenon

Northern Uganda and the southern tip of South Sudan are notoriously difficult places to live. Both regions have been torn by decades of civil war. In northern Uganda, tens of thousands of children were kidnapped and pressed into service in Kony’s army. A series of Sudanese civil wars, which culminated in South Sudan’s independence last July, displaced an estimated 5 million people and killed 2.5 million. Malnutrition and a host of endemic diseases are widespread. Health services are scarce.

A head-nodding syndrome similar to the one Jilek-Aall had described in Tanzania in the 1960s began showing up in South Sudan in the early 1990s. Then, in 2009, increasing numbers of children with head-nodding seizures began to draw the attention of health officials in northern Uganda. Residents in the area said they had never

before seen such behavior. Ugandan officials asked CDC for help.

CDC researchers were puzzled, says Scott Dowell, a pediatric infectious disease specialist who directs CDC's Division of Global Disease Detection and Emergency Response. When the call went out for qualified groups to help, "everyone said, 'This is really fascinating, but it's definitely not one of ours,'" he recalls. Dowell's usual job is to coordinate the logistics for the experts responding to various outbreaks, but since there weren't yet any experts on nodding disease, he says, "I had the chance to go myself."

Dowell helped assemble a team that included epidemiologists, toxicologists, nutrition experts, and neurologists from CDC, WHO, and the Ugandan ministry of health. The researchers conducted a variety of studies, including electroencephalography (EEG) and magnetic resonance imaging (MRI) of patients' brains, sometimes during seizures. The team went in "with an open mind" about whether the nodding might be a muscular disorder or even a behavioral syndrome, Dowell says. But patients' brain-wave activity on the EEGs "made it quite clear that [head nodding] was a seizure," and that most patients had ongoing seizure activity typical of epilepsy. The MRI scans added more evidence. "Something is badly wrong with the brains of these kids, and it's physiological," he says.

The researchers came together two more times in Uganda, and in May last year they visited South Sudan to investigate recent cases there. But they haven't yet figured out what is causing the condition. When WHO experts investigated a cluster of nodding disease cases in southern Sudan between 2001 and 2003, their early guesses for a cause included leftover munitions, measles, donated seeds treated with pesticides that were eaten instead of planted, donated food that might have been contaminated with toxic fungus, and even consumption of monkey meat. None of those turned out to be a clear culprit, says Abdinasir Abubakar, head of communicable disease surveillance and response for WHO in South Sudan. The region affected by nodding syndrome has actually received less food aid than other areas. "This is the bread basket of the country," he says. And comparisons of children with nodding syndrome and their healthy peers found no association with eating donated food, Dowell says.

Exposure to munitions doesn't seem to be the cause, either. There were other regions where fighting and bombardments were much heavier, Abubakar says, and "they have no sign of nodding disease." The South Sudan and Ugandan cases of the syndrome do seem



Geographic puzzle. Areas affected by nodding disease.

to have a geographic component, however. They are concentrated in a few relatively small areas. And previously healthy children who are forced to move to those areas by fighting suddenly become vulnerable to the syndrome. An influx of displaced families into affected locales is one likely reason the number of cases has gone up recently, Abubakar says.

The researchers have tested for a host of viruses, says CDC neuroepidemiologist James Sejvar, another team member. All tests have turned up negative. And although prion-triggered brain damage, perhaps due to eating monkey meat, has been floated as a possibility, the condition doesn't look like a typical prion disease, Sejvar says.

One environmental factor still on the table

is vitamin B-6 deficiency. A recently discovered genetic condition that prevents the body from processing B-6 causes a particularly severe form of epilepsy that doesn't respond to the usual antiepileptic drugs, Dowell says. The association with nodding syndrome isn't perfect: It isn't always children with the lowest levels of B-6 who have the symptoms, he says. But the clue is strong enough that the CDC team plans to distribute high-dose vitamin B-6 supplements as part of a proposed clinical trial to find a treatment. That trial still needs approval from ethical oversight committees in the United States and Uganda, Sejvar says, but the researchers aim to start recruiting participants this summer, ultimately enrolling 80 children. One group would receive the high-dose B-6 supplement; other participants would receive one of two antiseizure medications or a placebo.

Fear the worm

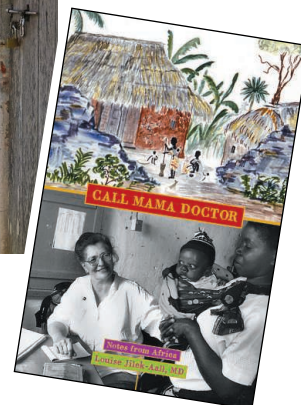
What that clinical trial won't address is the other leading hypothesis for the cause of nodding disease: an infection with the parasitic worm *Onchocerca volvulus*. The parasite is endemic in the regions that report nodding disease, and studies in Uganda and South Sudan have found that infection with the parasite is significantly more common in people with nodding syndrome than in their unaffected peers. Still, the *O. volvulus* connection isn't clear-cut. "The puzzling thing is that [the parasite] is widespread, but nodding is not," Dowell says. However, he says, the association "won't go away, even though people keep saying it doesn't make sense."

O. volvulus is no stranger to tropical-disease experts. It causes onchocerciasis, more commonly known as river blindness.

Black flies, which breed in fast-flowing rivers, transmit *O. volvulus*'s larval worms, which take up residence under the skin of black fly bite victims and grow to adulthood. The adult



Ray of hope. Louise Jilek-Aall and her colleagues have treated thousands of epilepsy patients at the clinic she founded in Mahenge, Tanzania. Her autobiography, *Call Mama Doctor*, describes her half-century of work in the region.



worms produce microfilariae, which reside mostly in the skin and connective tissue but are also sometimes found in blood, urine, and the eye. Microfilariae can damage eye tissue so severely that untreated infections can cause blindness. An international eradication campaign launched in 1974 has eliminated the parasite from large swaths of west Africa, but it persists in 27 countries in sub-Saharan Africa and six in Latin America.

Those who study river blindness have had a long-running debate over whether infection with the parasite might also cause epilepsy. Jilek-Aall says she suspected for years that the region's unusually high rate of epilepsy and onchocerciasis were connected, but it took 10 years before she and Erich Schmutzhard, a neurologist and tropical-medicine specialist at the University of Innsbruck, were able to address the question directly. Given the international efforts to eradicate river blindness, Schmutzhard says, many grant reviewers asked, "Why should we fund studies of a dying disease?"

Finally, in 2005, armed with funds from the Savoy Epilepsy Foundation in Canada and private donations, the researchers carefully categorized 62 Tanzanians with head-nodding seizures—the most thorough study to date of the disorder. Some had only head nodding; others had more severe epilepsy with other types of seizures. They analyzed blood and cerebrospinal fluid (CSF) from most of the patients. A subset traveled the 16-hour journey to Dar es Salaam, where they underwent MRI and EEG analysis.

The researchers reported in 2008 in *Epilepsia* that 43 of 51 patients tested either had microfilariae in their skin or tested positive for *O. volvulus* DNA using PCR. A positive PCR test was also weakly associated with brain lesions that showed up on the MRI scans. However, PCR tests on the CSF showed no traces of the parasite's DNA. The researchers concluded that the parasite could be involved in the head nodding but probably wasn't invading the central nervous system directly.

The hypothesis took a blow, however, when a follow-up study involving 300 individuals in Tanzania, published in 2010 in *Parasitology*, found no correlation between the intensity of *O. volvulus* infection and epilepsy. (About a third of the epilepsy patients in the study had head-nodding seizures.) That was enough to persuade Schmutzhard that nodding disease remains unexplained. Based on current evidence, he says, "onchocerciasis does not cause epilepsy."

But Jilek-Aall is not so sure. The studies failed to find a definitive link between onchocerciasis and nodding, but they don't rule it out either, she says: "I am convinced that somehow it is connected." Andrea Winkler, a neurologist at the Technical University of Munich in Germany who was corresponding author on both studies, agrees that the issue isn't settled. "We have not eliminated the possibility" that *O. volvulus* plays an indirect role, she says.

Other researchers who have seen similar cases of head nodding also suspect the worm. In 1998, pediatric neurologist Christoph Kaiser, now based in Baden-Baden, Germany, and his colleagues reported that at least 15 of the 91 epilepsy patients they studied in the Kabarole district in Western Uganda had head-nodding seizures. The evidence that



Inexplicable. James Sejvar (left) of CDC and Abdinasir Abubakar of WHO examine a child with nodding syndrome in South Sudan.

onchocerciasis can trigger epilepsy is persuasive, Kaiser says, but proving the connection has been difficult, in part because many studies simply check for microfilariae in the skin. Ivermectin, the drug distributed as part of the ongoing treatment campaigns, eliminates microfilariae, he says, but "the damage to the brain persists."

There are several ways that *O. volvulus* infections could damage the brain. In especially intense infections, the microfilariae reach the bloodstream, says parasitologist Michel Boussinesq, who studies onchocerciasis at the University of Montpellier in France, and in Cameroon. From the bloodstream, he says, they could enter the brain and cause damage directly. The lack of evidence for the parasite in the Tanzanian patients' spinal fluid argues against that, Boussinesq admits, but he says a definitive answer would come from autopsies of those who die with nodding disease. Although autopsies are difficult in

hot climates and many places in Africa have local taboos against disturbing the dead, such patient autopsies "are being attempted" in northern Uganda, Sejvar says.

Another possibility is that infection with *O. volvulus* triggers an autoimmune reaction. Antibodies produced to fight the parasite could also attack brain cells. There is evidence, Winkler notes, that antibodies for *O. volvulus* can cross-react with retinal cells. It is also possible that subtypes of the parasite could explain why head-nodding seizures seem to affect only certain regions. Winkler notes that it is widely accepted that the "savanna type" *O. volvulus* causes blindness more often than the "forest type," which primarily causes skin symptoms.

The most likely explanation for the disease, say several of the scientists chasing the disorder, is a combination of factors. Malnourished children deficient in vitamin B-6 might be particularly susceptible to neurological symptoms when they are infected with *O. volvulus*, for example. "Epilepsy is very often multifactorial," Boussinesq says. "Onchocerciasis could be a needed factor but not sufficient to provoke the condition."

New clues could come from blood and urine samples that the CDC team collected from patients in South Sudan and Uganda. They are almost done assessing vitamin levels, possible heavy-metal exposure, traces of thiocyanates (a sign of low-level cyanide poisoning due to eating improperly prepared cassava), and genetic markers among patients and healthy controls. More comprehensive surveys of

where and how many children have nodding syndrome are also planned in both Uganda and South Sudan. That should give a better picture of whether and how the syndrome is spreading.

One crucial problem, Abubakar says, is that nodding syndrome, as terrible as it is for the people and communities that are affected, is only one of many competing health emergencies in the region. In South Sudan, already overstretched health workers are also dealing with ongoing armed clashes and an acute outbreak of kala azar, or leishmaniasis, which has infected at least 22,000 people and killed nearly 1000 since late 2009. He says he hopes the recent publicity surrounding nodding syndrome will attract more researchers to the region. "I hope the advocacy and media might inspire some more institutions who might want to come and help figure out what is going on."

—GRETCHEN VOGEL