Nodding syndrome leaves baffled scientists shaking their heads

Louise Jilek-Aall was a young Norwegian physician working in the Mahenge mountains of Tanzania in the 1960s, when she noticed that an unusual number of people there suffered from a debilitating convulsive disorder preceded by a peculiar symptom: in childhood, their heads would bob back and forth for minutes at a time. The head nodding usually stopped before the general seizures set in. But when the epilepsy started, the children were typically weaker and of lesser intelligence than other children of the same age, often with neurological symptoms not seen in people with general epilepsy. The disease was "unexplainable to me," recalls Jilek-Aall, now a professor emerita at the University of British Columbia in Vancouver.

For years, the disease remained an isolated oddity. But over the past decade, physicians began observing this 'nodding syndrome' in several African countries, where it continues to perplex researchers to this day. "Nobody has yet been able to find an explanation," says Jilek-Aall, "and we are not sure that we are always describing the same phenomenon."

The latest attempt to find an explanation came last year when an emergency-response team from the US Centers for Disease Control and Prevention (CDC) visited South Sudan to investigate two recent clusters of the disease. Previous epidemiological studies had suggested a possible link between the neurologic condition and infections with *Onchocerca volvulus*, the nematode worm responsible for river blindness, also known as onchocerciasis. So the CDC scientists analyzed skin samples taken from children with and without nodding syndrome for signs of the infection.

Reporting in the 27 January issue of the *Morbidity and Mortality Weekly Report* (**61, 52–54, 2012**), the researchers found that 22 of 25 children with nodding syndrome in one South Sudanese community had the parasitic infection compared to 11 of 25 healthy controls. But the CDC team failed to find any such difference in the second village they visited, with around half of all individuals there infected with the worm whether or not they suffered from nodding syndrome.

"It is still a significant finding that there is some association with onchocerciasis and tells us this is one direction we should continue to pursue," says Sudhir Bunga, the CDC epidemiologist who led the latest study. However, Bunga is quick to point out that the observed association does not necessarily imply a causative relationship. "We do not know whether the infection with onchocerciasis occurred before or after the onset of nodding syndrome," he says. "The skin snip only tells us that they are currently positive."

The findings are largely consistent with what researchers have observed elsewhere in Africa. A previous study in Tanzania led by Andrea Winkler, a neurologist at the Ludwig-Maximilians-University in Munich, found the parasite affecting 43 of 51 people with nodding syndrome. But when Winkler's team tested their cerebrospinal fluid for signs of infection, which would suggest direct invasion of the brain by the parasite, only 3 of 48 had elevated levels of anti-worm immune cells (*Epilepsia* **50**, 2008–2015, 2008). Last autumn, the CDC also sent scientists to Uganda to investigate more than 1,000 cases of nodding syndrome there. Although the results have yet to be published, agency insiders say the association with the river blindness parasite is similar to that reported from the first South Sudanese community, with a positive association between the worm and the syndrome.

As *Nature Medicine* went to press, data from other candidate drivers of disease—including vitamin deficiencies, genetic markers and worm-specific antibodies—were still being analyzed from the Sudanese and Ugandan cohorts but had not been reported publically. "We have managed to rule out some potential associations," Bunga says of his team's unpublished findings. "But at the same time we still have multiple routes of investigation to pursue."

Heading off nodding

Even without definitive evidence of nodding syndrome's root cause, the CDC intends to move ahead with interventional drug trials. "We plan to assess the effectiveness of standard antiseizure drugs as well as high doses of pyridoxine," otherwise known as vitamin B6, says Scott Dowell, director of the CDC's Division of Global Disease Detection and Emergency Response. Last month, Dowell and his colleagues met with local doctors in Uganda to lay the groundwork for these trials.

Dowell says the latest report by Bunga's team provides enough data to conclude that the nodding syndrome clusters in South Sudan and Uganda have the same clinical presentations. "And that's important, because if we find [a drug] that works in one place, it should work in the other," he says.

But Winkler argues that more work is needed to compare the cohorts in different countries. Together with Jilek-Aall, Winkler has just completed a four-year follow-up of the people she studied previously in Tanzania—the first prospective study done to date. The long-term effects she sees in Tanzania, she says, are milder that what she's heard anecdotally reported out of South Sudan and Uganda.

"A longitudinal comparative study across all three sites would be the ideal next step," she says. "We would like to compare the three cohorts in terms of clinical presentation, genetics, vitamins and parasites." Collaboration between the researchers and international teams working on each site may be the key to uncovering the syndrome's cause, she says.

Sarah C P Williams

Centers for Disease Control and Prevention

Nod big deal: The disease affecting these Ugandans continues to puzzle scientists.