Nodding Syndrome—South Sudan, 2011

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IN NOVEMBER 2010, THE MINISTRY OF Health of the proposed nation of South Sudan requested CDC assistance in investigating a recent increase and geographic clustering of an illness resulting in head nodding and seizures. The outbreak was suspected to be nodding syndrome, an unexplained neurologic condition characterized by episodes of repetitive dropping forward of the head, often accompanied by other seizure-like activity, such as convulsions or staring spells. The condition predominantly affects children aged 5-15 years and has been reported in South Sudan from the states of Western and Central Equatoria[1] and in Northern Uganda and southern Tanzania.[2,3] Because of visa and security concerns, CDC investigators did not travel to South Sudan until May 2011. On arrival, a case-control study was conducted that included collecting exposure information and biologic specimens to assess the association of nodding syndrome with suspected risk factors. A total of 38 matched case-control pairs were enrolled from two different communities: Maridi and Witto. Overall, current infection with *Onchocerca volvulus* diagnosed by skin snip was more prevalent among the 38 case-patients (76.3%) than the controls (47.4%) (matched odds ratio [mOR] = 3.2). This difference was driven by the 25 pairs in Maridi (88.0% among case-patients, 44.0% among controls, mOR=9.3); among the 13 pairs in Witto, no significant association with onchocerciasis (known as river blindness) was observed. Although onchocerciasis was more prevalent among case-patients, whether infection preceded or followed nodding syndrome onset was unknown. Priorities for nodding syndrome investigations include improving surveillance to monitor the number of cases and their geographic distribution and continued work to determine the etiology of the syndrome.

Investigation and Results

As part of the outbreak investigation, a descriptive case series and a case-control study to assess for risk factors were conducted in two locations (Witto village and Maridi town) in the state of Western Equatoria, in South Sudan, where cases of nodding syndrome had been reported. Witto village is a rural setting inhabited by internally displaced persons, and Maridi town has a large, semiurban population. To ascertain whether the clinical syndrome was the same as that observed in other East African countries, a clinical case series study, with complete physical and neurologic examinations, clinical and epidemiologic history, assessments of family history, and relevant laboratory investigations, was conducted. A case of nodding syndrome was defined as onset of repetitive dropping of the head within the preceding 3 years, as reported by a caregiver, in any previously developmentally normal child aged <18 years who had at least one other neurologic or cognitive abnormality or seizure type, based upon investigator observation or caregiver history.

Ten case-patients from the case-control study were included in the case series study by selecting every third case. Additionally, 14 case-patients were enrolled in the case series with the same criteria as the case-control study enrollment except for the age at head nodding onset. To gain an understanding of the natural history and progression of the illness, these 14 children were selected to represent affected children who displayed earlier onset of head nodding and therefore longer duration of illness.

The mean age of patients in the case series was 13.1 years, with 91.7% reporting onset of disease at ages 5-15 years. Clinical findings included reports by caregivers of typical nodding episodes, other seizure-like activity, and apparent cognitive defects, but a relative lack of focal neurologic deficits. In-depth analysis of these clinical features and comparison with other nodding syndrome reports is under way.

What is already known on this topic?

Nodding syndrome is an unexplained disorder characterized by stereotypic head nodding that affects primarily children aged 5-15 years. The condition has been reported from Tanzania and Uganda, but its cause and natural history are unclear.

What is added by this report?

Two clusters of nodding syndrome cases reported in South Sudan in 2010 were investigated. Multiple features of the disease (e.g., clinical presentation, neurologic findings, and patient age distribution) are consistent with those investigated previously in Uganda. As noted in previous cases, a positive association was observed between onchocerciasis and nodding syndrome, but whether the relationship is causative remains unknown.

What are the implications for public health practice?

Collaboration among investigators in South Sudan and other countries where nodding syndrome has been reported will be important for future investigations in identifying the cause of this debilitating condition.

To identify possible risk factors, a case-control study compared those who met the case definition to controls matched by age and location. Based on power calculations from previous investigations in Uganda, 38 matched pairs were enrolled in the case-control study from the two separate locations. Case finding was done through community mobilization. Persons with suspected cases of nodding syndrome were then brought to the study site by caregivers, along with potential neighbor controls, and after screening by investigators, the first 38 pairs that fulfilled the case definition were enrolled in the study. Eighteen (47.4%) of the 38 case-patients and 20 (52.6%) of the controls were female. The mean age of the case-patients was 11.1 years (range: 7-16 years), and the mean age of the controls was 10.6 years (range: 6-17 years).

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Overall, prevalence of current onchocerciasis as diagnosed by skin snip was found to be significantly greater among case-patients (76.3%) than among controls (47.4%). Onchocerciasis was more prevalent among case-patients for the 25 pairs in Maridi (88.0% among case-patients and 44.0% among controls); among the 13 pairs in Witto, no significant association with onchocerciasis was observed. In preliminary analyses, no association with nodding syndrome was found with other risk factors, including exposure to munitions, parents' occupations and demographic characteristics. Additional analyses of case-series data and additional exposures related to nutrition are under way. Results of laboratory testing (e.g., for vitamins A, B6, and B12; *Onchocerca* antibodies; heavy metals [urine analysis]; and genetic markers) are pending.

Public Health Response

Although the cause of nodding syndrome remains unknown, based on these preliminary findings, reinforcing mass ivermectin treatment for onchocerciasis and conducting seizure management using antiepileptic medications were recommended by CDC to the South Sudan Ministry of Health. Enhancing surveillance to identify new cases as they occur, their location, and the age of patients at onset will enable identification of epidemiologic patterns. Exploring the association of nodding syndrome with onchocerciasis and evaluating the role of malnutrition are important future priorities.

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CDC Editorial Note: The clinical presentation, neurologic findings, and patient age distribution of cases, along with other features of the South Sudan nodding syndrome outbreak described in this report are consistent with previous descriptions of the disease from neighboring Uganda. Nodding syndrome might be a new seizure disorder.[2] Often accompanied by other seizure-like activity such as convulsions or staring spells, the nodding is reported by some caregivers to be precipitated by food or cold weather. During the episodes, the child stops feeding and appears nonresponsive, with or without loss of consciousness.[2] Reports of nodding syndrome from Uganda and Tanzania, in addition to South Sudan, describe progressively worsening head nodding, along with cognitive decline and malnutrition[2,3]; however, documented natural history studies are lacking.

A published report on 12 nodding syndrome patients studied with magnetic resonance imaging of the brain found normal results or non-specific changes, and electroencephalography performed on 10 patients between nodding episodes showed abnormal background in six patients and electrographic seizures in two patients.[2] No child is known to have recovered from nodding syndrome, and the long-term outcomes of illness are not known. Reports from caregivers indicate that affected children sometimes suffer serious injuries or death resulting from falls during seizure episodes.

An illness descriptively similar to nodding syndrome has been reported from Tanzania for decades; however, nodding syndrome has only recently been reported from South Sudan and Uganda in geographically localized areas.[1,2,4] This temporal and geographic clustering of an unusual and unexplained syndrome, consistent with epilepsy but with a stereotypic presentation, has drawn attention of international public health agencies.[5,6] CDC is assisting the South Sudan Ministry of Health with its ongoing investigations.

Several etiologic factors have been proposed, including infectious, nutritional, environmental, and psychogenic causes. Specific exposures evaluated in previous studies include munitions, measles, monkey meat, relief seeds, or relief food (e.g., lentils and sorghum). However, despite previous investigations, the cause of the syndrome and the pathophysiology remain unknown.[1,2,4] Previous studies also have found an association with onchocerciasis, but the causal pathophysiologic mechanism by which infection with the nematode *O. volvulus* might lead to neurologic illness is not clear, and some have concluded that the association is spurious.[1,2,4] Additionally, onchocerciasis has been endemic in large parts of West and Central Africa, as well as parts of Central and South America; however, nodding syndrome has only been reported in three small localized regions.

A series of investigations by the World Health Organization and South Sudan Ministry of Health in 2001, 2002, and 2010 in Western Equatoria could not identify the cause for nodding syndrome.[1,4,7,8] Nodding syndrome in South Sudan appears to be the same clinical entity as described previously in other parts of East Africa, but the etiology remains unknown. Further collaborative investigations into nodding syndrome are needed to identify the cause, preventive measures, and treatments.

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