International Journal of Infectious Diseases 17 (2013) e149–e152

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Reviewing the evidence on nodding syndrome, a mysterious tropical disorder

Daniël Arnoldus Korevaar *, Benjamin Jelle Visser

Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 3 June 2012
Received in revised form 11 August 2012
Accepted 26 September 2012

Corresponding Editor: William Cameron, Ottawa, Canada

Keywords:
Head nodding disease
Nodding syndrome
Onchocerca volvulus
Onchocerciasis
River blindness

SUMMARY

Objectives: To review the literature on the prevalence, clinical manifestations, pathogenesis, treatment, and implications of nodding syndrome (NS).
Methods: This is a narrative review.
Results: NS is a mysterious tropical disorder that is emerging in South Sudan, southern Tanzania, and northern Uganda. Over the past decade, thousands of children have become affected, but the prevalence is unknown. NS is characterized by an occasional nodding of the head, which is considered as a form of epilepsy. After symptoms appear, the patient's health rapidly deteriorates. Seizures, stunted growth, and mental retardation may appear. In endemic areas, NS is increasingly becoming a public health problem with high morbidity and mortality, and severe social, psychological, and economic implications. However, the pathogenesis is unknown. Evidence suggests a role for *Onchocerca volvulus*, the parasitic filarial worm responsible for river blindness, which is highly endemic in these areas. There is no cure for NS, and treatment is symptomatic with common anticonvulsants to improve the quality of life.
Conclusions: NS seems to be a rapidly growing problem in several eastern African countries. Although it is starting to receive more and more attention in the scientific literature, little is known about NS. A better understanding of the pathogenesis may lead to prevention and treatment opportunities.
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1. Introduction

In 1962, Louise Jilek-Aall, a Norwegian physician, described a mysterious disorder characterized by head nodding in several children in southern Tanzania.[1] Some of these children eventually developed tonic–clonic seizures. In 1983, head nodding was also described among several patients in Liberia.[2] For years, the disorder remained isolated in these areas. However, around 1990, physicians began observing a similar disorder in distinct areas in southern Sudan (currently known as South Sudan).[3,4] After this, several cases of 'head nodding' were also observed in western Uganda.[5] The condition was officially reported to the World Health Organization (WHO) by Warren Cooper, a missionary doctor, from southern Sudan in 1997 and first described in the scientific literature as 'nodding disease' in 2003.[3,4]

Over the last decade, the disorder has appeared to be a rapidly growing problem in several eastern Sub-Saharan African countries. Increasing numbers of cases have been reported in geographically localized areas of southern Sudan, southern Tanzania, and northern Uganda. In 2003, an estimated 300 cases were reported in southern Sudan,[6] but currently, the disorder is affecting thousands of children in this area.[7] Northern Uganda, where the condition was first observed in 2003, seems to be the next most important epicenter.[8] In late 2009, the Ministry of Health of Uganda reported that more than 2000 children were affected in northern Uganda.[7] In 2011, the disorder started to receive more and more attention in journals and the scientific literature. Several reports stated that large areas of northern Uganda were experiencing an outbreak of the condition, with more than 1000 cases being diagnosed between August and mid-December of that year.[9] Further outbreaks were reported in early 2012, with the disease now spreading between districts in northern Uganda, leaving at least 170 patients dead and 3000 to 5000 others nodding continuously in these areas.[9–11] However, the exact prevalence and geographic distribution of the disease in the affected countries is unknown.[12] In August 2012, at the first International Scientific Meeting on Nodding Syndrome, a consensus was reached to refer to the combination of signs and symptoms as 'nodding syndrome'.[13]

2. Clinical features and classification

Nodding syndrome mainly affects children and adolescents. The WHO reported that 54% of patients are male.[8] Although it is uncertain whether there exists one defined clinical condition that can be applied in all reported areas, all current news reports and scientific publications more or less agree on the clinical course. The first stage of the disorder is characterized by an occasional,

* Corresponding author. Tel.: +31 64 2993008.
E-mail address: d.a.korevaar@amc.uva.nl (D.A. Korevaar).

1201-9712/$36.00 – see front matter © 2012 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijid.2012.09.015

momentary, involuntary nodding of the head.[14] The frequency of the nodding differs among patients. In a study group of 62 patients, more than half of them had daily episodes of head nodding.[15] It is suggested that the nodding is caused by a brief loss of neck muscle tone that may be due to abnormal brain activity.[7,14] Several publications have reported that the nodding is provoked by eating, and sometimes cold weather.[5,16] However, the significance of these signs is unclear.[14] Cases have been described where the nodding is associated with staring spells or a short loss of muscle tone of the upper extremities, and loss of consciousness may occur.[14] Before the nodding first appears, most children are considered normal.[3] However, once symptoms manifest, the patient's health seems to deteriorate rapidly. First the nodding becomes more frequent and longer-lasting. Later on, tonic–clonic or psychomotor seizure episodes may develop, often leading to collapse and injuries.[16] Documented natural history studies are lacking and little is known about the short- and long-term outcomes,[17] but over time, many children become severely weak and stunted growth sets in.[14] In addition, many decline cognitively, which eventually may lead to mental retardation.[3] In the same study, over 40% of the 62 patients seemed to have cognitive impairment, with half of them affected severely.[15] Children lose their attention span and their ability to interact normally.[9] Furthermore, many suffer from malnutrition because they are unable to feed themselves, partly because of the cognitive impairment and partly because the seizures inhibit eating.[7] Eventually, some patients die, often as a result of uncontrolled seizures that may lead to traumata, drowning, or burning.[3,7,9] No child is known to have recovered from the syndrome,[17] and it is unknown whether it is communicable.[9] However, the WHO reported recently that investigations have revealed the disorder not to be transmissible from person to person.[8]

Although nodding syndrome causes high morbidity and mortality in endemic areas, the disorder is still poorly understood and information on the syndrome is scarce. There is a wide variety of manifestations between patients and, therefore, it is sometimes uncertain whether people are describing the same phenomenon.[14,18] For example, it was reported that some patients initially presented with generalized seizures instead of nodding.[16] Currently, there is one clinical classification available, subdividing the symptoms into 'head nodding only' or 'head nodding plus', the latter consisting of additional partial or generalized non-head nodding epileptic seizures.[14]

3. Pathophysiology

The initial nodding that characterizes the syndrome is generally considered as a form of epilepsy. This is not unexpected since head nodding as a symptom has been associated with various epilepsy syndromes.[14] In 2002, electroencephalographs (EEGs) on 31 patients with nodding syndrome performed by a neurologist recruited by the WHO in southern Sudan were all abnormal and showed specific progressive epileptic encephalopathy.[3,16] EEGs between nodding episodes on 10 patients in southern Tanzania showed an abnormal background in six of them, of whom two had interictal epileptic activity.[14] However, the authors were unable to determine whether the seizures were focal or generalized in nature. The assumption that nodding syndrome may be a seizure disorder is strengthened by the fact that many patients who start treatment with anticonvulsants have a significant reduction in seizure frequency.[15,16]

The cause of nodding syndrome as observed in South Sudan, Tanzania, and Uganda is unclear. In the past decade, the WHO and the US Centers for Disease Control and Prevention (CDC) have sent several teams of experts to endemic areas to investigate the disorder. Many possible causes have been explored by these teams, but so far they have had little success in elucidating the pathogenesis. It was hypothesized that the disorder may be caused by toxic residues of the biological and chemical weapons left over from the civil war in southern Sudan. Or that it is linked to eating the donated seeds coated with toxic chemicals that were meant for planting,[16] or to eating monkey meat.[6] However, after investigation, the WHO teams ruled out involvement of an environmental pollutant, chemical agent, or food toxins.[3] Parasitological examinations established that the disorder is not caused by infection with *Trypanosoma brucei gambiense*, *Wuchereria bancrofti*, or *Loa loa*.[3] In addition, CDC teams have so far not been able to link any changes in dietary or cultural practices to the syndrome.[7] However, there might be a connection between nodding syndrome and infection with *Onchocerca volvulus*. This parasitic filarial nematode is transmitted by the black fly (*Simulium* species) and is responsible for river blindness, or onchocerciasis (see Appendix 1[19–21]). Interestingly, nearly all patients affected with nodding syndrome are thought to live near permanent fast-moving streams, the breeding habitat of the black fly.[9] In addition, in the latter half of 2009, an upsurge of onchocerciasis infection rates was recorded in parts of northern Uganda,[22] the same parts as where the sudden increase in nodding syndrome cases was described during that period. Furthermore, it was observed that 93% of surveyed patients in southern Sudan were infected with *O. volvulus*, compared to 63% among children without the disorder.[6,14] However, although these data have been reported in several reports, any further information on this study, for example the number of patients involved, is lacking. Nevertheless, more recent preliminary results of an investigation supported by the WHO in southern Sudan show that 75% of the 52 patients with nodding syndrome had a positive skin snip for *O. volvulus*, compared to 47% among 38 healthy children.[23] In a case–control study performed in 2011, CDC investigators found that in one South Sudanese community, 88% of 25 patients had positive skin samples for the parasitic infection, compared to 44% of 25 healthy controls.[17] However, they failed to find any difference in a second village, with around half of the 13 patients and half of the 13 controls being infected. Results from CDC investigators in Uganda have not been published, but it has been reported that these also found a positive association between the worm and the syndrome.[23]

These observations appear meaningful, since *O. volvulus* has been associated with epilepsy before. For example, in 1992, an unusually high number of patients with epilepsy were observed in a rural area of western Uganda, where infection with *O. volvulus* is hyperendemic.[24] In addition, onchocerciasis has been associated with the 'Nakalanga syndrome', which has many similarities with nodding syndrome. This syndrome consists of epilepsy, stunted growth, and mental retardation and has been reported from Uganda[25] and Burundi.[26] In 2004, a meta-analysis of all available epidemiological studies on the relationship between *O. volvulus* and epilepsy was only able to demonstrate a nearly significant association.[27] However, a more recent meta-analysis of epidemiological studies found that for every 10% increase in the prevalence of onchocerciasis, epilepsy rates go up by 0.4%.[28]

Several mechanisms have been proposed to explain the relationship between epilepsy and onchocerciasis.[29] *O. volvulus* may be present in the central nervous system. Microfilariae have in fact been demonstrated in the cerebrospinal fluid (CSF) of onchocerciasis patients.[30] Another possibility involves immunological mechanisms. Modulators and cytokines involved in the immunological response to the parasite may induce changes in cerebral activity. Finally, there might be a triggering role of insomnia due to itching. Several studies have shown a marked activation of epileptiform abnormalities and triggering of seizures following sleep deprivation.[31]

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