Tropical Medicine and International Health doi:10.1111/tmi.12421

VOLUME 20 NO 2 PP 194–200 FEBRUARY 2015

Review

Nodding syndrome since 2012: recent progress, challenges and recommendations for future research

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Abstract We aim to review the current epidemiology of nodding syndrome (NS) and discuss relevant gaps in research. NS and convulsive epilepsy of unknown aetiology are clustered within the same villages and families in onchocerciasis-endemic areas. They are therefore potentially different clinical expressions of the same disease. It has been difficult to perform full autopsies on NS patients who die in remote villages. Adequate fixation of tissue immediately after death is critical for the examination of brain tissue. Therefore, post-mortem transsphenoidal brain biopsies, performed immediately after death by trained nurses, will provide the best option for obtaining tissue for analysis. We suspect that certain blackflies in onchocerciasis-endemic areas may transmit a novel pathogen that could cause NS and epilepsy. This is supported by a recent drop in the number of new NS cases coinciding with vector control activities aimed at reducing blackfly populations in northern Uganda. We propose that metagenomic studies of human samples, blackflies and microfilariae are conducted to screen for pathogens, and that a clinical trial is planned to evaluate the impact of larviciding against NS and epilepsy epidemics.

keywords nodding syndrome, epilepsy, onchocerciasis, vector control, metagenomics, transsphenoidal brain biopsies

Introduction

Nodding syndrome (NS) is a mysterious form of epilepsy known to occur in Western Equatoria State in South Sudan, in the districts of Gulu, Kitgum, Pader and Lamwo in northern Uganda, and in Mahenge in Tanzania (Dowell *et al.* 2013). Outbreaks of NS have contributed to epilepsy epidemics in South Sudan and northern Uganda, where it is considered to be a major public health problem. NS has severe socio-economic implications and, like other forms of epilepsy, is associated with social stigma (Mutamba *et al.* 2013; van Bemmel *et al.* 2014). The prevalence of NS is low, stable and endemic by contrast in Tanzania (Winkler *et al.* 2014).

The characteristic clinical feature of NS is a paroxysmal spell where the head nods forward repeatedly in a seemingly unresponsive affected child. These nodding episodes represent a form of epilepsy during which generalised electrodecrement is seen on electroencephalography and paraspinal dropout on electromyography (Sejvar *et al.* 2013). Children with NS present with varying degrees of mental retardation and in some there is a remarkable stunted growth and failure to develop secondary sexual characteristics (hyposexual dwarfism). Affected children are generally reported to be healthy until the nodding episodes begin and many die as a result of uncontrolled seizures that have led to drowning or burning (Dowell *et al.* 2013).

The cause of NS remains unknown but there appears to be an unexplained link with onchocerciasis infection (Kaiser *et al.* 2009; Vogel 2012; Foltz *et al.* 2013; Winkler *et al.* 2013). At a 2012 meeting in Kampala,

organised by WHO in collaboration with the Ugandan Ministry of Health and the US Centers for Disease Control & Prevention (CDC), case definitions for suspected, probable and confirmed cases of NS were proposed and recommendations for future research formulated (World Health Organisation 2012). It was also suggested that a follow-up scientific meeting on NS should be held in 2 years to assess progress and share newly acquired knowledge. During the Kampala meeting, the following potential aetiological/risk factors were identified as requiring further investigation: *Onchocerca volvulus* (*Ov*) infection, co-infection with different filarial worms such as *Mansonella streptocerca* and *Mansonella perstans*, early malnutrition, vitamin B6 deficiency, fungal contamination of local food, genetic pre-disposition, population displacement and psychogenic causes.

In this paper, we review the relevance of the 2012 research recommendations, taking into account the current epidemiology of NS and new research findings. We discuss the main research gaps and ways to address them.

Research progress since 2012

Onchocerca and *Mansonella*

A possible role for *Ov* in causing NS is still very relevant today and many questions remain to be answered (Table 1). One hypothesis being examined by Avindra Nath at the National Institutes of Health (NIH, Bethesda, USA) is whether the antibodies generated to fight *Ov* also recognise a protein in the brains of vulnerable children and trigger seizures (Collins 2014). Results of case-control studies in South Sudan and Uganda have also suggested possible associations between *Mansonella* spp. infection and NS cases (Tumwine *et al.* 2012; Dowell *et al.* 2013), although these have not been investigated further.

The African Program for Onchocerciasis Control (APOC) formally adopted the strategy of community directed treatment with ivermectin (CDTI) to control and eliminate onchocerciasis in 1997 (Amazigo 2008). However, CDTI has not always been possible to operate in areas affected by conflict such as northern Uganda and South Sudan (Amazigo *et al.* 2002). The emergence of northern Uganda from a civil war has enabled CDTI programmes to be established, and ivermectin has been distributed biannually in districts affected by both onchocerciasis and NS since 2012 (T. Lakwo, unpublished data). This coincided with a dramatic drop in the number of new NS cases, and no new cases were officially reported in 2013 (Ministry of Health 2014). Whether this was due to the improved ivermectin regimen is uncertain, and in November/December 2012 and 2013, the ivermectin programme was supplemented by control measures targeting vectors of *Onchocerca*. This included larviciding of the Achwa and Pager rivers (by both aerial application and from boats), and an ongoing programme to treat the larval breeding sites with an organophosphate (Temephos), which has continued in May/June 2014 (Colebunders *et al.* 2014).

Onchocerca volvulus is thought to be transmitted by blackflies of the *Simulium damnosum* complex in northern Uganda (Carter Center 2013). However, a new survey of biting blackflies has shown that a member of the *Simulium bovis* group represents approximately half of biting blackflies in the NS-affected areas in this region, and it has been found to be carrying larvae of an unknown *Onchocerca* species (not *O. volvulus*) (Post, unpublished). The larval ecology of the *S. bovis* group is similar to that of *S. damnosum* s.l. and they are often found together. The *S. bovis* group has been previously recorded breeding in the NS-*Ov* areas of both Tanzania (Hausermann 1966) and South Sudan (Baker *et al.* 1985).

This brief summary illustrates the difficulty in determining the possible role of therapeutic and vector control interventions in the reduction of NS cases in northern

Table 1 Key questions to explore the link between epilepsy and onchocerciasis

Does nodding syndrome only occur in children who are infected with *Onchocerca volvulus*?
Are there onchocerciasis-endemic areas without nodding syndrome, hyposexual dwarfism and an increased prevalence of epilepsy?
Does ivermectin treatment protect a child against nodding syndrome and epilepsy?
Is ivermectin treatment able to decrease the number of seizures?
Are nodding syndrome and high prevalence of epilepsy only present in hyper- and mesoendemic onchocerciasis areas and not in hypoendemic onchocerciasis areas?
Is there seasonal variation in the appearance of nodding syndrome and epilepsy in onchocerciasis-endemic areas?
Is *Onchocerca volvulus* genetically different in areas with high and low prevalence of nodding syndrome and epilepsy?
Are *Wolbachia* strains genetically different in areas with high and low prevalence of nodding syndrome and epilepsy?
Is there onchocerciasis in animals (cattle) in nodding syndrome-affected areas?
Does *Simulium bovis* group bite humans in all NS areas? Which species of the *S. bovis* group, and which species of *Onchocerca* is it carrying?

Uganda, and the complex nature of vector-parasite relationships in the NS-affected areas.

Early malnutrition, vitamin B6 deficiency

All populations known to have been affected by NS have experienced food shortages (Spencer *et al.* 2013a). In South Sudan, a case-control study suggested a possible association between food shortage in the first 2 years of life and NS (Spencer *et al.* 2013b). Today, however, Western Equatoria State, where most cases of NS have been reported, is considered to be one of the most stable and well-nourished areas of the country (World Food Programme 2014). This is in contrast to other onchocerciasis-endemic regions in South Sudan where NS is less frequently reported. Further nutritional studies from Uganda and South Sudan showed low levels of serum vitamin B6 (pyridoxine) among NS cases, but also among unaffected controls (Dowell *et al.* 2013). A clinical trial examining the effect of vitamin B6 was planned in Uganda by the CDC (Vogel 2012), but so far has not been initiated. Children with NS are often underweight and malnourished, (Idro *et al.* 2013) but this could also be a consequence of the condition rather than due to malnutrition.

Fungal contamination of local food

It has been proposed that mycotoxins may play a role in the pathogenesis of NS (Spencer *et al.* 2013b). Mycotoxins are secondary metabolites produced by toxigenic fungi that infect important food crops such as cereals and stored food products including maize and sorghum. However, it is unlikely that fungal contamination of local food plays a major role in causing NS. A wider geographical distribution of NS cases in regions with similar agricultural practices might be expected if this was the case. Moreover, during a visit to Mvolo village in Western Equatoria State, South Sudan, where one in six children presents with epilepsy, it was observed that families share food, eat from the same plate and store food in the same manner, yet only some of the children develop NS (R. Colebunders, unpublished report, Mvolo November 2013). A limited number of food samples (sorghum: 15, maize: 2, sesame: 4, peanut: 1 and soybean: 12) obtained from households and Mvolo marketplace were analysed using an enzyme-linked immunosorbent assay (Food & Agriculture Organization of the United Nations 2003). The following mycotoxins were identified: zearalenone; deoxynivalenol; T2; fumonisin B1, B2 and B3; aflatoxin B1, B2, G1 and G2; and orchratoxin A. However, all were below the internationally recommended maximum tolerated levels except for orchratoxin, where the level exceeded the maximum tolerated by 5 μg/kg in two samples of sorghum and maize. No mycotoxins were found in soya beans.

Genetic pre-disposition

Multiple cases of NS and/or other types of epilepsy often occur in the same family. However, this is more likely to be explained by common exposure rather than genetic pre-disposition. It is known that NS occurs in different ethnicities in the three affected countries, and a high prevalence of epilepsy has been reported among many ethnic groups in onchocerciasis-endemic regions elsewhere. A study in South Sudan previously suggested that NS does not occur in Dinka communities (Tumwine *et al.* 2012), but during a visit to an affected area in November 2013, R Colebunders also observed NS among Dinka families. Genetics may play a role in the aetiology of NS, but genetics alone cannot explain the pathogenicity of the disease.

Population displacement

If NS is caused by a pathogen to which people develop immunity, it is possible that population displacement plays a causal role in NS epidemics (Colebunders *et al.* 2014). In South Sudan and northern Uganda, the movement of non-immune populations who were previously displaced by civil conflicts may have resulted in contact with pathogens to which they had no prior exposure. The absence of recent population movement could explain the low and endemic prevalence of NS in Tanzania (Colebunders *et al.* 2014).

Psychogenic causes

Food shortages, war, displacement and associated repeated or chronic trauma can lead to post-traumatic stress disorder, depression, conversion disorder and developmental trauma disorders (Musisi *et al.* 2013). However, most of these stress factors are not present in NS-affected areas of Tanzania, and whereas psychogenic causes may play a role in the clinical presentation of NS, they cannot by themselves explain the syndrome.

Research challenges

Unfortunately, very little research progress has been made since the WHO-organised meeting took place in 2012. The difficulty in obtaining funding for NS research represents a major challenge to understanding the aetiology of a disease that burdens some of the poorest communities in affected countries. NS has only recently been added to

the WHO list of neglected tropical diseases under 'other neglected conditions' (WHO 2014). A greater effort is needed to raise awareness of the condition and bring it to the attention of major donors.

Further challenges include establishing projects in remote areas that are difficult to reach, where there is a lack of necessary infrastructure and expertise of local researchers to conduct sophisticated investigations involving MRI scanning and full autopsies. In South Sudan, political instability and insecurity are currently preventing active research, and political and administrative hurdles have delayed the start of research projects in other countries (e.g. projects involving autopsies in Uganda).

What type of research needs to be undertaken?

NS and convulsive epilepsy of unknown aetiology are spatially clustered in onchocerciasis-endemic foci (Colebunders *et al.* 2014). It is important to identify the cause of all forms of epilepsy within these areas, and to see whether NS and other forms of epilepsy represent different clinical expressions of the same disease. By comparing the epidemiology of onchocerciasis foci in different countries, we may be able to identify common factors that could play a role in the pathogenesis of NS. Ecological niche modelling could be used, integrating epidemiological data on epilepsy and onchocerciasis with environmental variables and spatial mapping of NS cases. This would allow for a better understanding of NS distribution at a local, regional and national scale. However, it can only be achieved if epilepsy is classified as a notifiable disease with compulsory reporting to health authorities.

Strengthening surveillance for epilepsy in onchocerciasis-endemic areas

A high prevalence of epilepsy has been reported in several onchocerciasis-endemic areas. Surveillance needs to be organised in all onchocerciasis-endemic countries and not just those in which NS has been reported. By geo-localising epilepsy cases, epilepsy and onchocerciasis cartography data could be compared and high-risk zones for epilepsy identified. This could be performed in collaboration with ministries of health, by using African Programme for Onchocerciasis Control (APOC) community workers and providing them mobile phones for cheap SMS reports. Epilepsy incidence data will enable the effect of interventions, such as increasing ivermectin coverage or treating rivers with larvicides, to be evaluated.

Case-control studies

Several case-control studies have been performed to identify possible causal factors of NS (Foltz *et al.* 2013; Tumwine *et al.* 2012). However, most of these studies have small sample sizes and address a very large number of possible risk factors.

The choice of controls is often problematic. Controls need to be representative of the general population without epilepsy. Controls therefore should not be excluded if they present with onchocerciasis symptoms such as itching or skin lesions. Another problem is with asking the right questions. Involving anthropologists, who specialise in understanding the daily habits and socio-behavioural patterns of local populations, can substantially improve the quality of designed questionnaires. Cases should be questioned about current activities that may be risk factors, but also about their behaviour before the onset of epilepsy. For example, individuals with epilepsy may avoid rivers because of an increased risk of drowning during a seizure, yet they may have frequented rivers prior to developing epilepsy, potentially exposing them to blackfly bites. Age-matched controls should also be asked about their activities and habits when they were the same age as the cases were, before they developed epilepsy. Recall bias will be minimised by preferentially including cases with a recent onset of epilepsy. Finally, the majority of the people in affected villages may be at risk and large sample sizes may therefore be needed to detect risk factors.

A house-to-house prevalence study targeting all individuals, combined with questionnaires aimed at identifying possible risk factors, may solve the problem of the control bias and small sample size. Making such a study feasible will, however, require that only a few key questions are asked and that those questions are relevant to the hypothesis being examined.

Post-mortem studies

Researchers from the CDC were only recently able to perform post-mortem exams of the brains of four dead Ugandan children who had suffered from NS. The results of these examinations are not yet known. It has been difficult to perform full autopsies on NS patients in Uganda, mainly because corpses had to be transferred from remote villages to Kampala. Adequate fixation of tissue immediately after death is critical for the examination of brain tissue. Therefore, performing post-mortem transsphenoidal brain biopsies may provide a better alternative to complete autopsies. This technique enabled the diagnosis of 92% of cryptococcal brain infections in a post-mortem

study performed at Mulago hospital in Kampala, Uganda (Cox *et al.* 2014), and trained nurses could perform such a procedure in a village shortly after a child dies.

Metagenomic studies of humans, blackflies, microfilariae and Wolbachia

Ten members of an Acholi family, including 3 teenage patients with NS (aged 13, 17 and 18) were recently transported to the National Institutes of Health Clinical Center in Bethesda, USA, where the exome of all three affected children and their unaffected parents is being analysed (Collins 2014).

We recently proposed the hypothesis that blackflies infected with microfilariae may also transmit an unknown pathogen, such as a neurotropic virus that is involved in the aetiology of NS (Colebunders *et al.* 2014). Laboratory studies have shown that arboviral transmission is enhanced in mosquitoes and other Diptera that concurrently ingest microfilariae (Turell *et al.* 1984, 1987) and the same could be true in blackflies. To detect such a pathogen, additional metagenomic studies of samples from human cases and controls, blackflies, microfilariae and *Wolbachia* should be carried out. The major pathologies associated with onchocerciasis are the consequence of the symbiotic bacteria (*Wolbachia pipientis*) carried by *O. volvulus*, rather than the parasite itself (Taylor *et al.* 2005). This bacterium is very variable and metagenomics will also indicate whether it occurs as a distinctive strain or co-occurring strains in the NS-affected areas.

Evaluating the effect of larviciding

From 1974 to 2002, the WHO Onchocerciasis Control Programme (OCP) implemented an extensive programme of treating rivers in West Africa with larvicides using light aircraft to control biting blackfly populations and successfully eliminated the parasite from large areas (Boatin 2008). Controlling blackfly populations to eliminate transmission may stop NS epidemics. It has already been mentioned that a drop in the number of NS cases coincided with aerial spraying of insecticides and the application of larvicides to rivers in northern Uganda (Colebunders *et al.* 2014).

However, there are both biological and logistical challenges associated with larviciding. Larvicides must be applied more frequently than the time it takes from an egg hatching to pupation to completely suppress biting blackfly populations (larvicides have no impact on adult flies present in the surrounding environment, which will oviposit and yield viable progeny in untreated waters). Reinvasion is known to be particularly problematic, and in the early years of the OCP blackfly cytospecies such as *Simulium damnosum* s.str. and *Simulium sirbanum* were found to be migrating long distances (<500 km wind-assisted) which seriously hampered control efforts (Baker *et al.* 1990). Such movement capacity has direct consequences on disease spread and would jeopardise the potential to contain the NS epidemics if related to blackflies.

It is therefore important to know precisely the vector species present in a study-area before treatments commence and their migratory tendencies. It must be certain that nearby rivers (other than those being treated) do not support the development of anthropophilic blackflies that are within host-seeking range of the human population being studied.

The choice of larvicides also needs to be carefully considered. Temephos is usually the insecticide of choice for use in Africa against the *S. damnosum* complex because it is efficacious, easy to handle, has good river-carry, low toxicity to non-target organisms and is value for money (Hougard *et al.* 1993). As an insecticide, its only major drawback has been the evolution of resistance by vectors during previous control operations (Kurtak *et al.* 1987; Palmer & Rivers-Moore 2008). However, this is unlikely to be an issue when used in a small and restricted geographical area, but it would still be important to have alternatives as a standby. *Bacillus thuringiensis israelensis* (Bti) is environmentally friendly but expensive, and Permethrin is also a possibility, but its impact against non-target organisms does not favour its routine use for vector control (Palmer & Rivers-Moore 2008).

Pre-control studies must include mapping of vector breeding sites, testing susceptibility to insecticides, river-carry of insecticides and determining the size of vector populations (by biting catches) (Traore *et al.* 2009). Routine monitoring of larval-susceptibility to insecticides and adult population activity should be conducted throughout any proposed intervention by regular larval prospection and vector collection. Finally, vector control of blackflies is costly (Hougard *et al.* 1993). The frequency and rate of application of insecticides to a river will need to be calculated in advance of activities commencing. If vector control is not sustained, there may be an increase of the vector-borne disease because of lower immunity during the vector control period, although this has never been reported for human onchocerciasis.

Given the advantages and challenges associated with implementing a larviciding programme, we propose studying the effect of treating rivers as one arm of a clinical trial aimed at reducing the incidence of epilepsy in onchocerciasis-endemic regions. In different onchocercia-

sis hyperendemic foci with high prevalence of epilepsy (>2%), we propose comparing the following three strategies: (i) annual ivermectin administration without larviciding rivers; (ii) annual ivermectin administration with larviciding rivers; and (iii) biannual ivermectin administration with larviciding rivers.

Conclusion

In conclusion, while conducting post-mortem and metagenomic studies to identify the cause of NS and the high prevalence of epilepsy in onchocerciasis-endemic areas, it is fundamental to start planning an intervention to control and prevent NS epidemics and to reduce the incidence of epilepsy. The preparation of such a trial requires the collaboration of epidemiologists, entomologists, ecologists, hydrologists, experts in onchocerciasis vector control, clinicians, anthropologists and public health experts, as well as the collaboration of national and local authorities and the local population. We need the support of WHO and APOC, and we need to convince major funding bodies of the importance of the project.

Acknowledgements

We thank the Uganda Ministry of Health and the Carter Center for their support for the entomological studies.

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