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## International Journal of Infectious Diseases

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## Editorial

## Nodding syndrome—we can now prevent it



On Monday December 21, 2015, an information session was organized by the Ugandan Health minister Dr Elioda Tumwesigye in Pader district, northern Uganda, to explain the results of the investigations performed in Uganda to identify the cause of nodding syndrome (NS).<sup>1</sup>

NS was first reported in Uganda in the districts of Kitgum, Pader, and Lamwo in 2009. Retrospective studies would suggest cases as early as 1997. By May 2014, a total of 3320 cases of NS had been registered and treated, as well as 5185 cases of epilepsy in the affected districts. NS is a form of atonic epilepsy.<sup>2</sup> Patients with NS present with episodes of uncontrollable nodding of the head (the head drops forward), mental retardation, and stunted growth, and often develop generalized convulsions.<sup>3</sup> The Ugandan Health minister informed the local population that NS was caused by onchocerciasis, probably through an autoimmune response triggered by an *Onchocerca volvulus* infection, the nematode causing river blindness.<sup>1</sup>

Indeed many studies have now confirmed the association between NS, epilepsy, and onchocerciasis.<sup>3–5</sup> An autoimmune encephalitis caused by antibodies cross-reacting with *O. volvulus* or Wolbachia (a bacterial symbiont of *O. volvulus*) could be an explanation for this association. Johnson et al. reported that 11 (58%) of 19 patients with NS presented leiomodins 1 antibodies compared to five (26%) of 19 matched controls (matched odds ratio 7, confidence interval 0.9–11.1).<sup>6</sup> These antibodies were found to be neurotoxic in vitro and to cross-react with *O. volvulus* tropomyosin. However, because leiomodins 1 is an intracellular protein, it is possible that these antibodies are not causing the epilepsy but are rather the consequence of repeated seizures damaging the brain.<sup>6</sup> In a small pilot study in Tanzania, antibodies against N-methyl-D-aspartate receptor and voltage gated potassium channel complex (VGKC) (LG1 and Caspr2) were not detected in patients with NS.<sup>7</sup> In contrast, in Uganda, antibodies to the VGKC proteins were more often observed in patients with NS (15/31, 48.3%) than in controls (1/11, 9.1%) (R. Idro et al., unpublished). No patient or control subject had antibodies to the intracellular glutamic acid decarboxylase, which is also associated with complex epilepsy.

Despite the fact that *O. volvulus* DNA has not yet been detected in the cerebrospinal fluid (CSF) of patients with NS,<sup>8,9</sup> it is still possible that microfilariae occasionally penetrate the brain, particularly in highly infected individuals. In 1976 Duke et al. noted the presence of small numbers of *O. volvulus* microfilariae in the CSF (<2 mf/ml) in five of eight untreated heavily infected (>100 mf/mg skin) onchocerciasis patients; furthermore, the numbers of *O. volvulus* microfilariae in the CSF increased to 8–31 mf/ml during diethylcarbamazine treatment in 10 of 11 heavily

infected patients presenting with an ocular form of onchocerciasis.<sup>10</sup> Patients with *O. volvulus* infection receiving diethylcarbamazine have also been reported to develop optic atrophy, probably because of a Mazzotti reaction caused by the death of microfilariae present in the optic nerve.<sup>11</sup> *O. volvulus* microfilariae have been detected in the optic nerve and optic nerve sheaths,<sup>12</sup> but so far not in the brain. Recently, functional lymphatic vessels lining the dural sinuses were discovered;<sup>13</sup> could these vessels be an entry point for microfilariae?

Brain samples from NS patients who died in Uganda were flown to the US Centers for Disease Control and Prevention in the USA for analysis. A preliminary autopsy report showed that three of them had multiple polarizable deposits in the brain.<sup>1</sup> However, it remains unclear whether these lesions were artefacts (myelin altered by fixation) or real brain lesions. A new post-mortem study that includes controls and with appropriate processing of brain tissue shortly after the death of the patient is needed to elucidate the pathophysiological mechanism of NS and onchocerciasis-associated epilepsy.

Prior to the NS outbreak in Uganda, only one post-mortem examination had been performed on a child who had died of a condition with similar clinical features as observed during an NS epidemic—Nakalanga syndrome. During examination of the child's brain, histological changes were observed in the adenohypophysis, but no deep-seated microfilariae.<sup>14</sup>

Nakalanga syndrome was first described in 1950 among a population that had migrated to the Mabira Forest, close to the city of Jinja, on the east bank of the Nile in Uganda.<sup>15,16</sup> Nakalanga syndrome is characterized by extreme growth retardation and the absence of external signs of sexual development; it is often but not always associated with epilepsy.<sup>15,16</sup> Nakalanga features were later also reported from other onchocerciasis endemic foci, such as in West Uganda,<sup>17</sup> Burundi,<sup>18</sup> and Ethiopia.<sup>19</sup> In all these foci, the syndrome disappeared once onchocerciasis control was established.

The hypothesis that blackflies are the cause of NS was proposed in a publication in the *International Journal of Infectious Diseases* in 2014 and it was suggested that these blackflies could potentially transmit a neurotropic virus.<sup>20</sup> Today this hypothesis seems very unlikely because the NS epidemic in northern Uganda stopped following the mass distribution of ivermectin and the treatment of the main rivers in the region, the Ashwa and the Pager, with larvicides. A recent case-control study in Titule, Bas Uélé, an onchocerciasis endemic region in the Democratic Republic of the Congo (DRC), suggests that ivermectin has a protective effect on individuals for developing epilepsy.<sup>21</sup> In onchocerciasis hyper-endemic regions, where ivermectin has not been introduced, the

highest prevalence of NS and epilepsy is found among the 10–19 years age group.<sup>22</sup> In a study in Kyarusozzi sub-county in western Uganda performed in 1991, 91% of epilepsy cases were below the age of 19 years.<sup>22</sup> In contrast, in the Imo river basin in Nigeria, where ivermectin was distributed starting in 1994 but larviciding was never implemented, 67% of the patients with epilepsy were 20–29 years old in 2002.<sup>23</sup> This age shift in patients with epilepsy after the introduction of ivermectin suggests that ivermectin may reduce the incidence of epilepsy.

Therefore, the pathophysiological mechanism causing NS and other forms of epilepsy in onchocerciasis endemic regions is probably directly or indirectly related to the *O. volvulus* infection.

NS should be considered only the 'ears of the hippo', the hippo being onchocerciasis-associated epilepsy.<sup>4</sup> Indeed NS and other forms of epilepsy appear clustered in specific villages and also within households in onchocerciasis endemic regions.<sup>4,24</sup> Therefore they are likely to be caused by the same trigger: the *O. volvulus* infection. NS, and also Nakalanga syndrome, should be considered as different phenotypic presentations of onchocerciasis-associated epilepsy, or river epilepsy as proposed by Pion.<sup>25</sup> Nakalanga children are known to be very heavily infected with *O. volvulus*, and the first signs that a child will develop Nakalanga are already evident during the child's second or third year of life.<sup>15</sup> These children have become infected with *O. volvulus* at a very early age, when their brains were still developing. Nakalanga children may have been born from *O. volvulus*-infected mothers. Maternal infection with *O. volvulus* has been shown to increase the risk of children becoming infected with *O. volvulus* and developing higher infection levels.<sup>26</sup> An explanation for this may be that parasite antigen exposure during prenatal or neonatal life may depress the parasite-specific cellular immune responses in these children.<sup>26–28</sup> The in utero transmission of *O. volvulus* has also been described.<sup>29</sup> Other children, less exposed to *O. volvulus* and/or exposed later in life, may develop only tonic-clonic epilepsy with minimal or no mental retardation and no diminished growth or sexual development.

The reason for the epidemic of NS/epilepsy in northern Uganda and South Sudan is likely related to living conditions during the war. In northern Uganda, beginning in 1996, hundreds of thousands of people were put into internally displaced persons camps, some of them very close to large rapid flowing rivers infested with *O. volvulus*-infected blackflies. In such camps, people were living in households very close to each other. At that time there was no mass drug administration of ivermectin in northern Uganda in the Kitgum and Pader districts and this probably resulted in an increasing number of *O. volvulus* infestations in children with a weak immune system caused by malnutrition and co-infections. These *O. volvulus* infestations were followed by an epilepsy epidemic. The onchocerciasis hyper-endemicity in the region was shown in 2009, when in a case-control study microfilariae were observed in skin snips from 71% of patients with epilepsy and 54% of controls.<sup>5</sup>

Before the war, herds of cattle in Kitgum and Pader were stolen by the Karamajong (a tribe from north-east Uganda), and the remaining cattle were eaten by rebels roaming the areas during the start of the war (late 1980s). Blackflies of the species *Simulium bovis* normally bite cows and transmit *Onchocerca dukei* (a cattle parasite closely related to *O. volvulus*), but they also bite humans in this area, particularly those herding cattle. *Simulium damnosum* s.l. is the main vector transmitting *O. volvulus*, but this also bites cows and can transmit *Onchocerca ochengi* (another closely related cattle parasite). Humans are not known to develop any infection when exposed to the bites of blackflies infected with either *O. dukei* or *O. ochengi*, but they may develop antibodies against these cattle *Onchocerca* nematodes that may protect them against *O. volvulus*-related disease (or modulate the immune response in other ways).<sup>30</sup> It is

possible that during the war, the disappearance of the cows resulted in a decreased associated immunity against *O. volvulus*, which together with malnutrition led to very severe *O. volvulus* infections and the development of NS. *O. volvulus* and *O. ochengi* exhibit extensive antigenic cross-reactivity, as evidenced by the serological recognition of *O. volvulus* recombinant antigens by cattle infected with *O. ochengi*,<sup>31</sup> and can generate cross-protective responses both experimentally<sup>32</sup> and naturally.<sup>33</sup> The protective effect of *O. ochengi* antibodies against *O. volvulus* infection may explain why in Western Equatoria Province of South Sudan, an onchocerciasis endemic area with a high prevalence of NS, the Dinkas, who are cattle keepers, were reported to be less likely to develop NS.<sup>34</sup>

Action is urgently needed because onchocerciasis-associated epilepsy is catastrophic for entire villages. Many affected children not only suffer from epilepsy, but also dementia and psychiatric problems.<sup>35</sup> Caretakers are left desperate and living in fear of leaving their affected children alone, because some children simply wander away, disappear, and die a lonely and tragic death mostly due to burns or drowning. Many affected children drop out of school and lack access to quality patient care. Since the start of ivermectin distribution and larvicide treatment of rivers in Uganda, the NS epidemic has declined dramatically. In contrast, the situation continues to worsen in South Sudan because there is very little distribution of ivermectin and no larviciding of rivers in this country. Moreover, anti-epileptic treatment is generally not available in the affected villages.

The burden of disease caused by onchocerciasis-associated epilepsy remains to be determined. A high prevalence of epilepsy has been observed in most onchocerciasis endemic regions with low coverage of ivermectin.<sup>4,36,37</sup> If 1% of the 36 million people with *O. volvulus* infection (equivalent to the approximate excess prevalence of epilepsy over non-endemic areas<sup>38</sup>) were to develop epilepsy, the number of excess cases of epilepsy due to onchocerciasis would be in the order of 360 000.<sup>4</sup> This excess in prevalence of epilepsy may be preventable by increasing the coverage of ivermectin treatment. The fact that *O. volvulus* increases the risk of epilepsy should be used as an additional argument to strengthen onchocerciasis elimination plans and motivate individuals to take the ivermectin at least annually.

Uganda has shown that providing symptomatic care, mainly through timely consumption of anti-epilepsy drugs coupled with proper nutrition, can achieve big improvements in patient outcomes.<sup>39</sup> In Uganda, many children even manage to go back to school thanks to such treatment.

A lot of scientific progress has been made recently. We have learned that improved onchocerciasis control will stop onchocerciasis-associated epilepsy including NS. We have also learned from rehabilitation centres in Uganda that NS is a manageable disease.<sup>40</sup> The main challenge today is how to scale up and improve the treatment of patients suffering from onchocerciasis-associated epilepsy in all affected onchocerciasis regions of Africa. To deal with this challenge we should learn from the experience gained with the scaling up of HIV treatment in Africa. Similarly, for onchocerciasis-associated epilepsy, we will need to apply advocacy, fighting ignorance and misconceptions, provide uninterrupted free access to anti-epileptic treatment, including cheap and more effective anti-epileptic drugs, and provide decentralized services to diagnose and treat epilepsy early and to monitor treatment adherence, a public health approach that includes task shifting, training of primary and lower level health care workers, and working with communities. The problem is that onchocerciasis-associated epilepsy occurs in remote rural areas of Africa and involves very poor populations, often in zones where the health system is very weak and where there has been war or there is instability. Moreover, this is not an illness that threatens the industrialized world. Similar to the fight against AIDS, to reach the

goal of elimination of onchocerciasis-associated epilepsy will require partnerships between scientists, communities and advocacy groups, health care workers, ministries of health, non-governmental organizations, the pharmaceutical industry, and funding organizations.

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## References

- Report on nodding syndrome., New vision, December 18, 2015. Available at: <http://www.newvision.co.ug/news/676945-us-report-on-nodding-disease-due-on-monday.html> (accessed).
- Sejvar JJ, Kakooza AM, Foltz JL, Makumbi I, Atai-Omoruto AD, Malimbo M, et al. Clinical, neurological, and electrophysiological features of nodding syndrome in Kitgum, Uganda: an observational case series. *Lancet Neurol* 2013;**12**:166–74. [http://dx.doi.org/10.1016/S1474-4422\(12\)70321-6](http://dx.doi.org/10.1016/S1474-4422(12)70321-6)
- Dowell SF, Sejvar JJ, Riek L, Vandemaële KA, Lamunu M, Kuesel AC, et al. Nodding syndrome. *Emerg Infect Dis* 2013;**19**:1374–84. <http://dx.doi.org/10.3201/eid1909.130401>
- Wamala JF, Malimbo M, Tepage F, Lukwago L, Okot CL, Cannon RO, et al. Nodding syndrome may be only the ears of the hippo. *PLoS Negl Trop Dis* 2015;**9**:e0003880. <http://dx.doi.org/10.1371/journal.pntd.0003880>
- Foltz JL, Makumbi I, Sejvar JJ, Malimbo M, Ndyomugenyi R, Atai-Omoruto AD, et al. An epidemiologic investigation of potential risk factors for nodding syndrome in Kitgum District, Uganda. *PLoS One* 2013;**8**:e66419. <http://dx.doi.org/10.1371/journal.pone.0066419>
- Johnson T, Tyagi R, Lee PR, Lee M, Johnson KR, Kowalak J, et al. Proceedings of the XII International Congress on Neuroimmunology. *J Neuroim* 2014;**27**:5:103. <http://dx.doi.org/10.1016/j.jneuroim.2014.08.275>
- Dietmann A, Wallner B, König R, Friedrich K, Pfausler B, Deisenhammer F, et al. Nodding syndrome in Tanzania may not be associated with circulating anti-NMDA and anti-VGKC receptor antibodies or decreased pyridoxal phosphate serum levels—a pilot study. *Afr Health Sci* 2014;**14**:434–8. <http://dx.doi.org/10.4314/ahs.v14i2.20>
- König R, Nassri A, Meindl M, Matuja W, Kidunda AR, Siegmund V, et al. The role of *Onchocerca volvulus* in the development of epilepsy in a rural area of Tanzania. *Parasitology* 2010;**137**:1559–68. <http://dx.doi.org/10.1017/S0031182010000338>
- Winkler AS, Friedrich K, Velicheti S, Dharsee J, König R, Nassri A, et al. MRI findings in people with epilepsy and nodding syndrome in an area endemic for onchocerciasis: an observational study. *Afr Health Sci* 2013;**13**:529–40. <http://dx.doi.org/10.4314/ahs.v13i2.51>
- Duke BO, Vincelette J, Moore PJ. Microfilariae in the cerebrospinal fluid, and neurological complications, during treatment of onchocerciasis with diethylcarbamazine. *Tropenmed Parasitol* 1976;**27**:123–32.
- Taylor HR, Greene BM. Ocular changes with oral and transepidermal diethylcarbamazine therapy of onchocerciasis. *Br J Ophthalmol* 1981;**65**:494–502.
- Paul EV, Zimmerman LE. Some observations on the ocular pathology of onchocerciasis. *Hum Pathol* 1970;**1**:581–94.
- Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015;**523**:337–41. <http://dx.doi.org/10.1038/nature14432>
- Marshall AJ, Cherry JK. Endocrine dysfunction in a Nakalanga dwarf. *Trans R Soc Trop Med Hyg* 1961;**55**:188–91.
- Jeliffe DB, Jones PR, Stroud CE. Nakalanga notes on the endemic dwarfism of Uganda. *Trop Geogr Med* 1962;**14**:97–104.
- Rapert AB, Ladkin RG. Endemic dwarfism in Uganda. *East Afr Med J* 1950;**27**:339–59.
- Kipp W, Burnham G, Bamuhija J, Leichsenring M. The Nakalanga syndrome in Kabarole District, Western Uganda. *Am J Trop Med Hyg* 1996;**54**:80–3.
- Newell ED, Vyungimana F, Bradley JE. Epilepsy, retarded growth and onchocerciasis, in two areas of different endemicity of onchocerciasis in Burundi. *Trans R Soc Trop Med Hyg* 1997;**91**:525–7.
- Oomen AP. Onchocerciasis in Kaffa Province of Ethiopia. *Trop Geogr Med* 1967;**19**:231–46.
- Colebunders R, Hendy A, Nanyunja M, Wamala JF, van Oijen M. Nodding syndrome—a new hypothesis and new direction for research. *Int J Infect Dis* 2014;**27**:74–7. <http://dx.doi.org/10.1016/j.ijid.2014.08.001>
- Colebunders R, Tepage F, Mandro M, Musinya G, Mambandu G, Mokili J, et al. Why such a high prevalence of epilepsy in the Orientale Province in the Democratic Republic of the Congo (DRC)? Abstract O.LB1.003. European Conference on Tropical Medicine Basel. *Trop Med Int Health* 2015;**20**(Suppl 1):143.
- Ovuga E, Kipp W, Mungherera M, Kasoro S. Epilepsy and retarded growth in a hyperendemic focus of onchocerciasis in rural western Uganda. *East Afr Med J* 1992;**69**:554–6.
- Dozie IN, Onwuliri CO, Nwoke BE, Chukwuocha UM, Chikwendu CI, Okoro I, et al. Onchocerciasis and epilepsy in parts of the Imo river basin, Nigeria: a preliminary report. *Public Health* 2006;**120**:448–50. <http://dx.doi.org/10.1016/j.puhe.2005.10.010>
- Colebunders R, Post R, O'Neill S, Haesaert G, Opar B, Lakwo T, et al. Nodding syndrome since 2012: recent progress, challenges and recommendations for future research. *Trop Med Int Health* 2015;**20**:194–200. <http://dx.doi.org/10.1111/tmi.12421>
- Pion S. Contribution à la modélisation des filarioses à *Onchocerca volvulus* et à Loa loa en Afrique centrale, *Dissertation*, Université Paris XII-Val De Marne, 2004.
- Kirch AK, Duerr HP, Boatin B, Alley WS, Hoffmann WH, Schulz-Key H, et al. Impact of parental onchocerciasis and intensity of transmission on development and persistence of *Onchocerca volvulus* infection in offspring: an 18 year follow-up study. *Parasitology* 2003;**127**:327–35.
- Elson LH, Days A, Calvopina M, Paredes W, Araujo E, Guderian RH, et al. In utero exposure to *Onchocerca volvulus*: relationship to subsequent infection intensity and cellular immune responsiveness. *Infect Immun* 1996;**64**:5061–5.
- Petralanda I, Yarzabal L, Piessens WF. Parasite antigens are present in breast milk of women infected with *Onchocerca volvulus*. *Am J Trop Med Hyg* 1988;**38**:372–9.
- Brinkmann UK, Kramer P, Presthus GT, Sawadogo B. Transmission in utero of microfilariae of *Onchocerca volvulus*. *Bull World Health Organ* 1976;**54**:708–9.
- Wahl G, Enyong P, Ngosso A, Schibel JM, Moyou R, Tubbesing H, et al. *Onchocerca ochengi*: epidemiological evidence of cross-protection against *Onchocerca volvulus* in man. *Parasitology* 1998;**116**(Pt 4):349–62.
- Graham SP, Wu Y, Henkle-Duehrsen K, Lustigman S, Unnasch TR, Braun G, et al. Patterns of *Onchocerca volvulus* recombinant antigen recognition in a bovine model of onchocerciasis. *Parasitology* 1999;**119**(Pt 6):603–12.
- Achukwi MD, Harnett W, Enyong P, Renz A. Successful vaccination against *Onchocerca ochengi* infestation in cattle using live *Onchocerca volvulus* infective larvae. *Parasite Immunol* 2007;**29**:113–6. <http://dx.doi.org/10.1111/j.1365-3024.2006.00917.x>
- Renz A, Trees AJ, Achu-Kwi D, Edwards G, Wahl G. Evaluation of suramin, ivermectin and CGP 20376 in a new macrofilaricidal drug screen, *Onchocerca ochengi* in African cattle. *Trop Med Parasitol* 1995;**46**:31–7.
- Tumwine JK, Vandemaële K, Chungong S, Richer M, Anker M, Ayana Y, et al. Clinical and epidemiologic characteristics of nodding syndrome in Mundri County, southern Sudan. *Afr Health Sci* 2012;**12**:242–8.
- Idro R, Musubire KA, Byamah MB, Namusoke H, Muron J, Abbo C, et al. Proposed guidelines for the management of nodding syndrome. *Afr Health Sci* 2013;**13**:219–32. <http://dx.doi.org/10.4314/ahs.v13i2.4>
- Pion SD, Kaiser C, Boutros-Toni F, Courmil A, Taylor MM, Meredith SE, et al. Epilepsy in onchocerciasis endemic areas: systematic review and meta-analysis of population-based surveys. *PLoS Negl Trop Dis* 2009;**3**:e461. <http://dx.doi.org/10.1371/journal.pntd.0000461>
- Boussinesq M, Pion SD, Demanga N, Kamgno J. Relationship between onchocerciasis and epilepsy: a matched case-control study in the Mbam Valley, Republic of Cameroon. *Trans R Soc Trop Med Hyg* 2002;**96**:537–41.
- Zoure HG, Noma M, Tekle AH, Amazigo UV, Diggle PJ, Giorgi E, et al. The geographic distribution of onchocerciasis in the 20 participating countries of the African Programme for Onchocerciasis Control: (2) pre-control endemicity levels and estimated number infected. *Parasit Vectors* 2014;**7**:326. <http://dx.doi.org/10.1186/1756-3305-7-326>
- Idro R, Namusoke H, Abbo C, Mutamba BB, Kakooza-Mwesige A, Opoka RO, et al. Patients with nodding syndrome in Uganda improve with symptomatic treatment: a cross-sectional study. *BMJ Open* 2014;**4**:e006476. <http://dx.doi.org/10.1136/bmjopen-2014-006476>
- Burton A. Uganda: how goes the nodding syndrome war? *Lancet Neurol* 2016;**15**:30–1. [http://dx.doi.org/10.1016/S1474-4422\(15\)00350-6](http://dx.doi.org/10.1016/S1474-4422(15)00350-6)

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