Case Report: Nodding Syndrome, Western Uganda, 1994

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Abstract. Nodding syndrome (NS) is a poorly understood condition, which was delineated in 2008 as a new epilepsy syndrome. So far, confirmed cases of NS have been observed in three circumscribed African areas: southern Tanzania, southern Sudan, and northern Uganda. Case-control studies have provided evidence of an association between NS and infection with Onchocerca volvulus, but the causation of NS is still not fully clarified. We report a case of a 15-year-old boy with head nodding seizures and other characteristic features of NS from an onchocerciasis endemic area in western Uganda, with no contiguity to the hitherto known areas. We suggest that the existence of NS should be systematically investigated in other areas.

INTRODUCTION

Patients with head nodding movements as a feature of an epileptic disorder were observed as early as 1960 by Louise Jilek-Aall in a southern Tanzanian community with a highly elevated epilepsy prevalence.1 On the basis of comprehensive clinical, electroencephalographic and brain imaging investigations this condition was summarized as a distinct epileptic syndrome in 2005.2 During the past decade, increasing numbers of patients affected with the nodding syndrome (NS) were also reported from South Sudan3,4 and northern Uganda5–8 (Figure 1). It is accepted that patients with head nodding seizures combined with a number of other characteristic symptoms living in these three areas are affected by the same disease, NS. A case definition for NS was agreed upon at an international conference in Kampala, Uganda, 2012.9,10

With the help of the present case report we examine the question of whether NS also exists in western Uganda, an area with no contiguity to those mentioned above, and we give an overview on the present state of knowledge on the phenomenon of head nodding.

CASE REPORT

In May 1994, a 15-year-old boy was identified as suffering from epilepsy during a population wide survey in the Kabende parish, located in Kabarole District, western Uganda.11 This parish of 4,743 inhabitants is situated in the Itwara onchocerciasis focus, with a prevalence of microfilaria (mf) carriers ranging from 15% to 85% in the 10–20 years age group of its 13 villages in 1994.11 A detailed description of the epidemiology of onchocerciasis and epilepsy in Kabende parish can be found in our previous publications,11–14 and detailed maps of the entire Itwara focus are presented by Garms and others.15 All patients who were registered in the survey underwent a thorough clinical assessment.14 The information given in this article is based on the original records of the initial cross-sectional survey13,14 and of the subsequent follow-up of this cohort over a total period of 7 years.12,16–18

The patient was seen at his home because he was considered too weak to reach the central place of the parish on his own. He had been born in his residential village after an uncomplicated pregnancy and grew and developed normally up to the age of 7 years. At this age, he started experiencing episodes of about 10 minutes duration when he suddenly did not respond to his surroundings and his head moved repetitively forwards and backwards. Such episodes were known to the local community with the term “nateera omutwe” (head nodding). About 1 year later, these episodes were regularly followed by generalized tonic–clonic seizures (GTCS). After getting sick, the growth of the boy slowed down and his cognitive development changed for the worse to the point that he lost his ability to speak. When seen in 1994, he still could take food with his hands, but his parents said that, before a seizure was about to happen, he frequently refused to eat for about half an hour. Living in an onchocerciasis endemic area, he had received treatment with ivermectin 12 months before the present examination. In the patient’s village, Rwesenene, with 290 inhabitants, there were nine patients diagnosed with epilepsy in 1994,11 and three of these also gave an account of head nodding. During the cross-sectional epilepsy survey in 1994,11 a total of 10 patients with this seizure type were found in the villages of Kabende parish,14 and 5 additional patients were seen with a subsequent prospective study on epilepsy incidence.12,14 In accordance with the findings in the patient of this report, all these patients had been healthy at birth and had experienced the first seizure at a median age of 8 years (range: 3–14 years).

On examination, severe wasting and stunting was found (height 110 cm; z-score −7.3 of NCHS height-for-age standard).19 The boy was unable to understand what was said and his facial expression was generally reduced. He was weak and unable to stand upright without support. Muscle reflexes were normal and no focal neurologic deficit was noted. Genital development was at an infantile stage. Below the right iliac crest, a hard lump was palpable, consistent with an onchocercal nodule. A skin biopsy revealed the presence of microfilaria of Onchocerca volvulus.

Treatment with phenobarbitone (PHB) was started6,17 and over the following 2 years a slow but steady improvement was observed: seizures were less frequent and his physical and mental condition improved (Table 1). However, in October 1996, the seizures worsened and eventually went on without interruption until the patient died 1 month later. In a
Verbal autopsy in May 1998, his father said that, as long as he had been able to eat, he was given the PHB tablets daily as prescribed.

DISCUSSION

The 2012 Kampala case definition differentiates between suspected, probable, and confirmed cases of NS (Table 2). To classify a patient as a possible case, two major criteria are listed as mandatory: 1) Ages 3–18 at onset of head nodding, and 2) nodding frequency 5–20 times/min. With regard to the suggested criterion of nodding frequency, this appears difficult to be reliably ascertained because the symptom in question (head nodding seizures) only exceptionally can be observed at the time of examination. This constitutes a general problem in epileptology which in the more equipped facilities of the industrialized countries is overcome with examining the patient by use of long-term electroencephalography combined with synchronous video monitoring. In the areas where patients with NS are found, this technique is not available and it might be questioned if it is appropriate to include this criterion as mandatory in the 2012 Kampala definition. Despite this limitation, we consider it likely that the frequency of the head nodding movements in the presented patient, as well as in the other patients found in Kabende, were actually in the range given by the 2012 Kampala definition. This frequency is corresponding well with the descriptions that we obtained in our frequent caretaker interviews, and also with the direct observation of a head nodding seizure in one other patient, which was reported in our previous publication. This patient showed slow head movements, which were well compatible with the required frequency of 5–20 times/min.

Taking into account the mentioned considerations, we think that the patient presented in our report is consistent with a “probable” case of NS. Because his head nodding episodes were not observed by a trained health worker nor were

<table>
<thead>
<tr>
<th>Date</th>
<th>Observation/activity</th>
<th>Source of information</th>
<th>Relevant findings (patient history, clinical findings, therapy, follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979–1986</td>
<td>Birth, childhood</td>
<td>Parents report in May 1994</td>
<td>1979: normal pregnancy and birth in Rwesenene village, Kabende Parish, western Uganda, onchocerciasis endemic area, normal growth and development up to the age of 7 years</td>
</tr>
<tr>
<td>1986</td>
<td>Start of HN</td>
<td>Parents report in May 1994</td>
<td>No obvious external causation, accompanied with delayed growth, and progressive mental deterioration</td>
</tr>
<tr>
<td>1986</td>
<td>–</td>
<td>Parents report in May 1994</td>
<td>Received treatment with an antiepileptic drug over some weeks, probably PHB, with some improvement of his general condition but no effect on seizures. Stopped because of lacking supply</td>
</tr>
<tr>
<td>May 1994</td>
<td>Clinical assessment</td>
<td>Parents, G.A., C.K.</td>
<td>Stunting, wasting, weakness, scars from falling, cognitive impairment, onchocercal nodule, positive skin biopsy for Mf. Seizure frequency: 1–10/day. Start PHB at 60 mg/day</td>
</tr>
<tr>
<td>June 1994</td>
<td>Follow-up</td>
<td>Parents, G.A., C.K.</td>
<td>Reduced seizure frequency (none over several days). Improved strength, appetite and activity, slightly increased sleepiness. Dosage PHB increased to 90 mg/day, recommendation to reduce to 60 mg/day if the sleepiness increases</td>
</tr>
<tr>
<td>December 1994</td>
<td>Follow-up</td>
<td>Father, W.B., C.K.</td>
<td>Seizure frequency further decreased (none over 3 months, now again 1/week); seizure duration reduced (generalized tonic), no more HN seizures. Strength further improved, can walk some steps. Still not understanding, not talking. Dosage PHB unchanged 90 mg/day</td>
</tr>
<tr>
<td>June 1995</td>
<td>Follow-up</td>
<td>Father, W.B., C.K.</td>
<td>Seizure frequency increases (one seizure every 1–2 days), short duration, immediate recovery. Mental improvement: can make parents understand that he is hungry, is reacting to his name. Strength and appetite better. PHB unchanged 90 mg/day</td>
</tr>
<tr>
<td>February 1996</td>
<td>Follow-up</td>
<td>Father, W.B., C.K.</td>
<td>Seizures unchanged. Further mental improvement, still not able to speak. No tiredness. PHB increased to 120 mg/day. Recommendation to reduce again if sleepiness increases</td>
</tr>
<tr>
<td>August 1996</td>
<td>Follow-up</td>
<td>W.B.</td>
<td>Seen at home to receive drug provisions (W.B.). Noted: “Seen at home, he is well and comfortable,” no details on seizures or physical condition</td>
</tr>
<tr>
<td>October 1996</td>
<td>Death</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>May 1998</td>
<td>Death</td>
<td>Father, G.A., C.K.</td>
<td>Increase of seizures over several weeks without obvious cause. Death with continuing seizures. No fever or other sign of illness. PHB treatment not interrupted</td>
</tr>
<tr>
<td>August 2013</td>
<td>Consent for publication</td>
<td>Parents, D.K.</td>
<td>Home visit (D.K.) to parents of the patient. Explanation of intended publication. Parents’ consent obtained</td>
</tr>
</tbody>
</table>
the seizures documented by Video/EEG/EMG, in the strict sense of the Kampala case definition\(^1\) the diagnosis cannot be considered as confirmed. However, the overall constellation of the patient’s history, symptoms and signs appears typical of NS to such an extent that we consider this report as strong evidence that NS effectively existed in Kabende parish in 1994. This area in the Kabarole District of western Uganda has no contiguity with the known areas of NS, in particular with the focus in northern Uganda,\(^5\,7\) which is located several 100 km away (Figure 1). Kabende parish would thus be the fourth location where NS has been confirmed.

In 2003, the first report published from southern Sudan about children with head nodding mentioned that seizures were frequently precipitated when the patients were offered food.\(^3\) As a particularly striking example of this observation a patient was described who reliably started head nodding at the sight of a local maize dish but did not react when offered a western candy bar.\(^3,4\) The occurrence of this peculiar finding was confirmed in case series from northern Uganda\(^5,8\) and Tanzania.\(^2\) The study during which the patient of this report was examined was conducted 10 years before the publication of the mentioned report from northern Uganda\(^5,8\) and Tanzania.\(^2\) The authors explicitly pointed out the resemblance of these seizures with those described in western Uganda,\(^14\) the area of this report, and southern Tanzania.\(^1\) The high prevalence of epilepsy, the age distribution in the population, and the age of seizure onset in this Cameroonian village also show a striking similarity with the situation in Kabende,\(^11\) and with available data from other areas affected with NS.\(^5,6,23\)

Like all other patients found with head nodding seizures in Kabende parish, the patient presented in this report was also affected by another seizure type, in his case GTCS, with head nodding preceding the onset of GTCS. This was also found to be the typical sequence observed in series of clinical cases from the areas with confirmed cases of NS.\(^1,2,5,7,24\) A recently published follow-up study of those patients examined with the initial assessment leading to the conceptualization of NS in southern Tanzania\(^2\) found that 4 years later head nodding seizures had disappeared in half of those patients who initially had been suffering from head nodding in addition to other seizures, mainly GTCS, although in most cases GTCS had continued.\(^24\) This course was also observed with the patient in our report. We were also told by other patients interviewed in Kabende that head nodding had disappeared with the onset of a second seizure type or some time later, even if they had not received antiepileptic drug treatment (AED).

Following the start of therapy with PHB, we observed a marked reduction in the frequency of GTCS with seizure-free episodes of up to 3 months, and head nodding seizures stopped completely. To some extent the patient’s general condition and mental capacity also improved. However, lasting seizure control was not achieved and over time seizure frequency increased again. We think that this can be considered as a beneficial, though limited effect of therapy with PHB in this patient. A similar experience with treatment with PHB was reported from southern Tanzania where a significant reduction in seizure frequency has been observed in most patients but full control was achieved only in a few.\(^24\) In Tanzania, besides PHB patients also received treatment with other AEDs (phenytoine or carbamazepine) as monotherapy or in combination.
No clear difference was noted between the varying regimens, although this was not systematically studied. On the basis of some theoretical considerations, sodium valproate (VPA) was proposed as an AED that might be most appropriate for controlling the presumably myoclonic movements of head nodding seizures. However, only limited data on the use of VPA in NS are available, and these do not indicate the greater efficacy of VPA over the alternative AEDs already mentioned. In view of the possibly severe adverse effects of VPA, the high cost and its difficult availability in rural Africa, it might be reconsidered to abide by the general WHO recommendation to use PHB as the first-line drug, especially in patients with coexisting head nodding and convulsive seizures. Controlled comparative studies of different candidate AEDs should be undertaken to improve therapeutic efficiency.

The etiology and the pathogenesis of NS has not been fully clarified. A great number of possible causes were examined with case-control studies in South Sudan and northern Uganda including nutritional factors, possible environmental toxins, numerous infections (viral, bacterial, parasitic), and some genetic factors. As a common result of these studies, an association was found between onchocerciasis and NS whereas results on other possible factors were negative or inconsistent. Over the past two decades, numerous studies throughout endemic areas of sub-Saharan Africa have also demonstrated a strong relationship between onchocerciasis and epilepsy in general. A possible connection with onchocerciasis is also supported by the fact that NS so far has been found exclusively in onchocerciasis endemic areas. Clinical investigations including magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) studies could not demonstrate the presence of the parasite in the brain of patients with NS or patients with other seizure types. However, microfilaria (mf) of O. volvulus were found in the CSF of patients, particularly following antifilarial treatment. It may be conceived that mf are present at the time of seizure onset but, spontaneously or as a result of antiparasitic treatment, disappear from the intracerebral space whereas the epileptogenic lesion prevails. It also cannot be excluded that epilepsy in patients with O. volvulus infection can be induced by immunological mechanisms, or by a, so far unidentified, coexisting neurotropic factor found connected with O. volvulus transmission.

In summary, this report provides strong evidence that NS exists beyond the so far known endemic areas in Tanzania, South Sudan, and northern Uganda. Neurological investigations focusing on detecting cases of NS in other onchocerciasis endemic areas would be helpful in confirming this finding. This would further support existing evidence on the close, possibly causal, connection between onchocerciasis and NS, and epilepsy in general. We think that the many unclear questions of NS etiology would be best addressed with more longitudinal studies. These could provide a basis for allowing the adaptation and modification of research questions and programs with the affected communities. Under the difficult conditions for health-care provision in the NS affected areas, this could also help patients under study to receive continuing and long-term access to AEDs and to qualified health workers. Because children affected with NS constitute a particularly vulnerable group and their families are not able to cope with the disease on their own, connecting NS research with long-term epilepsy care is also an ethical necessity. Possibly, such projects could be realized by cooperation between research institutions and humanitarian programs. Should it turn out that NS is causally connected to infection with O. volvulus, the most effective measure to reduce its burden would probably be to intensify the approved and effective control measures against onchocerciasis in the affected communities.

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