PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Nodding Syndrome in Ugandan Children - Clinical features, Brain imaging and Complications; an observational case series
AUTHORS	Idro, Richard; Opoka, Robert; Aanyu, Hellen; Kakooza, Angelina; Piloya, Theresa; Namusoke, Hanifa; Musoke, Sarah; Nalugya, Joyce; Mwaka, Amos; White, Steven; Chong, Kling; Atai-Omoruto, Anne; Mworozi, Edison; Nankunda, Jolly; Kiguli, Sarah; Aceng, Jane; Tumwine, James

VERSION 1 - REVIEW

REVIEWER	Andrea Winkler MD, PhD Consultant neurologist Department of Neurology Technical University of Munich Germany
REVIEW RETURNED	14-Jan-2013

GENERAL COMMENTS	Comments to authors: This is a well written paper which definitely adds to the almost non-existing scientific reports form children with devastating nodding syndrome of northern Uganda. The study is merely descriptive and reports on the finding of 22 children only. However, the authors at no point in the manuscript overstate the results and the ensuing messages and mention and discuss various times the short-comings of their observational study. The results are put into the context of results from other studies, especially those form southern Tanzania and clearly point out similarities and dissimilarities. Potential etiologies are discussed in the light of the latest state of various expert opinions and all the major areas of potential etiologies are mentioned. I have made many comments and suggestions of improvement into the manuscript pdf itself, most of them minor, and will summarize the major concerns below. 1. At various points in the manuscript the references are quoted wrongly. I have marked all of them in the manuscript mainly in the introduction, but also in the discussion and am asking the authors to correct them. *Kaiser et al. 2009* is just a reply to *Winkler et al. 2008* and does not describe head nodding cases or indicate etiology beyond a possible association with *Onchocerca volvulus*. In the context of a potential association of epilepsy and *O. volvulus*, the meta-analysis by *Pion et al. 2009 (PLoS NTD)* has to be quoted and the only CSF study form people with epilepsy form an onchocerciasis endemic area by *König et al. 2009 (Parasitology)* needs to be included. 2. The authors claim that the current manuscript is the first publication on a standardized observation of clinical details

	in children with nodding syndrome. This is wrong, as the first standardized interview and examination including EEG, CSF and MRI was performed by the group Schmutzhard/Winkler in 2005 in Mahenge, southern Tanzania, with the ensuing publications of *Winkler et al. 2008 (Epilepsia)* and *Winkler et al. 2010 (Tropical Doctor).* 3. Also, the term of “nodding syndrome plus” (page 6, line 26) is used which was coined by *Winkler et al.* in their publication of 2008 to denote those children who have additional seizure types to their head nodding seizures. Idro is using the same term but refers not only to additional seizures but to all possible mental and physical complications. This is confusing and it is the opinion of the reviewer that a different term should be chosen. 4. The methodology of cognitive testing has to be explained in the Methods section. 5. More details have to be given on how exactly the staging system was obtained. Was it through mere history taking form the parents, was there a group discussion etc?? 6. The hand depicted does not really show much of muscle wasting and therefore should either be taken out or be replaced by a better pictures. 7. The MRI does not show impressive cortical atrophy. I am almost certain that there are children with more pronounced results. If possible, the pictures should be exchanged with those demonstrating more obvious evidence of cortical atrophy.

REVIEWER	Dr. Helena Guerreiro International Clinical Research Center St Anne's University Hospital Brno Czech Republic I report no competing interests.
REVIEW RETURNED	25-Jan-2013

THE STUDY	The article should be revised by an english speaking or english translator.
GENERAL COMMENTS	In the section where the authors describe the result of the lab findings they do not include the result of the malaria parasite testing, as well as the CSF bacteriologic culture. The authors should correct the "gamma GGT" (gamma GT). The study is very interesting as it explores a yet unknown syndrome. However in the end i had a few topics I would have liked to see discussed. For instance, the vitamin B6 being a plausible ethiologic factor should have been tested in these cases; the birth conditions and maternal factors should have been considered in more detail. This syndrome seems a very promising field for research. As it was appropriately discussed in the paper, autoimmunity, genetic testing and brain as well as other tissue cultures/bipsies should be considered in the future. Nevertheless I would like to congratulate the authors for the excellent work documenting these interesting case reports.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
This is a well written paper which definitely adds to the almost non-existing scientific reports form children with devastating nodding syndrome of northern Uganda. The study is merely descriptive and reports on the finding of 22 children only. However, the authors at no point in the manuscript overstate the results and the ensuing messages and mention and discuss various times the short-comings of their observational study. The results are put into the context of results from other studies, especially those from southern Tanzania and clearly point out similarities and dissimilarities. Potential etiologies are discussed in the light of the latest state of various expert opinions and all the major areas of potential etiologies are mentioned. I have made many comments and suggestions of improvement into the manuscript pdf itself, most of them minor, and will summarize the major concerns below.

1. At various points in the manuscript the references are quoted wrongly. I have marked all of them in the manuscript mainly in the introduction, but also in the discussion and am asking the authors to correct them. Kaiser et al. 2009 is just a reply to Winkler et al. 2008 and does not describe head nodding cases or indicate etiology beyond a possible association with Onchocerca volvulus. In the context of a potential association of epilepsy and O. volvulus, the meta-analysis by Pion et al. 2009 (PLoS NTD) has to be quoted and the only CSF study form people with epilepsy form an onchocerciasis endemic area by König et al. 2009 (Parasitology) needs to be included.

We have made the corrections as indicated and replaced wrongly quoted references. The new references have also been added.

2. The authors claim that the current manuscript is the first publication on a standardized observation of clinical details in children with nodding syndrome. This is wrong, as the first standardized interview and examination including EEG, CSF and MRI was performed by the group Schmutzhard/Winkler in 2005 in Mahenge, southern Tanzania, with the ensuing publications of Winkler et al. 2008 (Epilepsia) and Winkler et al. 2010 (Tropical Doctor).

This misrepresentation in the summary has been corrected.

3. Also, the term of “nodding syndrome plus” (page 6, line 26) is used which was coined by Winkler et al. in their publication of 2008 to denote those children who have additional seizure types to their head nodding seizures. Idro is using the same term but refers not only to additional seizures but to all possible mental and physical complications. This is confusing and it is the opinion of the reviewer that a different term should be chosen.

Reference to this has been removed both from the above text and the table. We elected not to add an additional term but will allow accumulation of data from ongoing studies of the syndrome so that definitions based on a larger sample may in future be used.

4. Was there are correlation of wasting and stunting with age of onset of nodding or duration of nodding syndrome?

Yes. A summary of this is now included in the section on growth in results.
5. The methodology of cognitive testing has to be explained in the Methods section.

Detailed cognitive testing with the KABC was performed on 4 children. This is now reported in the

methods section.

6. More details have to be given on how exactly the staging system was obtained. Was it through mere history taking form the parents, was there a group discussion etc?

A new section on how the staging and proposed “natural history” was obtained has now been included in the methods section.

7. A drug history would be important as well. How were the children treated before admission to hospital? Which antiepileptic medication and in which dose?

Prior to the intervention of the Ministry of Health, there was no organized system for treatment. Some patients were receiving treatment (mostly low doses of any of phenobarbitone, phenytoin or carbamazepine). The

8. What do motor difficulties mean?

Spasticity with or without limb contractures with limitations in mobility

9. The hand depicted does not really show much of muscle wasting and therefore should either be taken out or be replaced by a better pictures.

We have taken out this picture.

10. The MRI does not show impressive cortical atrophy. I am almost certain that there are children with more pronounced results. If possible, the pictures should be exchanged with those demonstrating more obvious evidence of cortical atrophy.

A new set of images has been provided.

11. This reference is not clear. Please make clear how this can be accessed.

Unfortunately, this report is still not publically available on the WHO website. Hopefully, it will be soon.

Reviewer 2
12. The article should be revised by an English speaking or English translator.

Dr Steven White, a native English speaker and one of the co-authors has gone through and revised the manuscript.

13. In the section where the authors describe the result of the lab findings they do not include the result of the malaria parasite testing, as well as the CSF bacteriologic culture.

None tested positive for malaria on admission although one contracted malaria during the course of hospitalisation. There was no growth from all CSF bacteriologic cultures. These are now included.

14. The authors should correct the "gamma GGT" (gamma GT).

This has been corrected.

15. The study is very interesting as it explores a yet unknown syndrome. However in the end I had a few topics I would have liked to see discussed.

a. For instance, the vitamin B6 being a plausible etiologic factor should have been tested in these cases.

We acknowledge this weakness.

b. The birth conditions and maternal factors should have been considered in more detail.

All 22 cases were reported to have been carried through pregnancies with no major adverse events, had uneventful births, neonatal and early children periods. One child who was exposed to cerebral malaria as a toddler in the original group brought to Mulago was excluded.

We did not explore maternal factors in detail as we felt this will be prone to recall bias.

c. This syndrome seems a very promising field for research. As it was appropriately discussed in the paper, autoimmunity, genetic testing and brain as well as other tissue cultures/biopsies should be considered in the future.

We plan to assess these in future studies.

d. Nevertheless I would like to congratulate the authors for the excellent work documenting these interesting case reports.

Thank you.

Comments from the Editor
16. You state in the submission system that there are no identifiable features in the images submitted but this is clearly not the case. We require signed consent forms for the images with any identifiable children in to be used otherwise we will not publish them.

Please find attached scans of consent forms for the pictures.

17. Similarly I am very concerned by the table, where it seems clear to me that the children could be identified from the very detailed information that is presented about them. You will need to present consent forms for this information to remain, otherwise the information will need to be anonymised.

We have now taken out the personal and other identifiers including gender and weights. We hope the remaining information makes it less likely for an individual to be identifiable. We thought age and duration of symptoms should remain in the table as they appear to have a bearing on the development of complications.

VERSION 2 – REVIEW

REVIEWER	Dr. Dr. Andrea Winkler Associate Professor and consultant neurologist Department of Neurology Klinikum rechts der Isar Technical University of Munich Germany I have no conflict of interest
REVIEW RETURNED	02-Apr-2013

GENERAL COMMENTS	I spotted one small mistake "hippocampus sclerosis" instead of "hippocampus gliosis" and two of my queries did not get answered. Please see attached manuscript. Why was there no contrast given at MRI and was there are correlation between cerebellar atrophy and intake of phenytoin?

VERSION 2 – AUTHOR RESPONSE

Response to Reviewers queries 2
1. I spotted one small mistake "hippocampus sclerosis" instead of "hippocampus gliosis".

This is now corrected.

2. Two of my queries did not get answered. Why was there no contrast given at MRI?

This was not given because the appropriate contrast was unavailable.

Was there any correlation between cerebellar atrophy and intake of phenytoin?

It is difficult to assess this. Many of the patients had taken different anti epileptic medications at different times depending on what was available in the local health centre at the time and most in small doses.

3. Please note that we will not be able to publish the identifiable images without appropriate consent.

We have taken the figures out of the revised manuscript.