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Association Between Onchocerciasis and Epilepsy in the Itwara Hyperendemic Focus, West Uganda: Controlling for Time and Intensity of Exposure

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Abstract. In 38 pairs of epilepsy patients and controls matched for time and intensity of exposure to transmission of onchocerciasis, the presence of microfilariae in the skin of epilepsy patients was found insignificantly elevated compared with controls (odds ratio = 1.68; 95% confidence interval [CI] = 0.60–4.57; $P = 0.31$). This difference was more pronounced when detection of subcutaneous nodules was used as indication of infection with *Onchocerca volvulus* (odds ratio = 2.77; 95% CI = 0.92–8.33; $P = 0.065$). These findings from a patient group of limited size suggest that intensity of infection may play a substantial role in the development of onchocerciasis-associated epilepsy. Our results are in contrast to the results of two other independent studies from the identical endemic area; one case concluded a significant positive correlation between onchocerciasis and epilepsy, and the other case concluded a clearly negative correlation. Studies with a greater sample size are needed to confirm this possible relationship.

INTRODUCTION

Over the last two decades, numerous studies have confirmed an association between the prevalence of onchocerciasis and epilepsy in various endemic areas throughout West, Central, and East Africa.[1] Although some reports using a case-controlled approach seem to corroborate the results of prevalence studies,[2–4] a more comprehensive review on controlled studies searching for a relationship between onchocerciasis and epilepsy concluded that the link between the two entities still remains controversial.[5]

Ovuga and others[6] reported on the frequent occurrence of epilepsy in the Kyarusozi subcounty close to the Itwara forest, West Uganda, an area known to be highly endemic for onchocerciasis.[7] Two years later, a second study conducted in the same area found an elevated prevalence of epilepsy of 8% in a village hyperendemic for onchocerciasis compared with a low prevalence of epilepsy of 0.2% in a nearby hypoendemic village.[8] When data of both these studies were included in the cited review by Druet-Cabanac and others,[5] a contradictory result was observed. Although Kipp and others[8] found a high risk ratio of 6.5 (95% confidence interval [CI] = 3.0–15.0), suggesting a significant positive association between epilepsy and onchocerciasis, the risk ratio of 0.84 (95% CI = 0.74–0.95) derived from the data of Ovuga and others[6] indicated a clearly negative association (Table 1).

The present article presents unpublished case-controlled data of a third study originating from the Itwara onchocerciasis focus and relates the data to the conflicting results of the previous investigations.

METHODS

Study area and study population. Epilepsy patients and controls were identified during a survey on the prevalence of epilepsy and onchocerciasis in Kabende Parish, West Uganda, during the period from March to June 1994.[9] The study area is bordering on the Sogohi river, a known breeding site for *Simulium neavei* flies at the northwestern edge of the Itwara onchocerciasis focus.

In this survey, epilepsy was defined as two or more unprovoked seizures during the previous 2 years.[10] Onchocerciasis endemicity was determined with a skin snip survey from a random sample of apparently healthy inhabitants aged 10–23 years without a history of epileptic seizures and residing in their village for 10–19 years. All patients and controls had been palpated for subcutaneous onchocerciasis nodules by two of the authors (C.K. and G.A.), and two skin snips from both iliac crests had been examined for detection of microfilariae (mf) of *O. volvulus* after 24 hours incubation.[7,9]

Community treatment with ivermectin in Kabende Parish started in 1991, and at the time of the survey, the latest treatment round had taken place in June 1993. At the occasion of the examination, patients and controls were asked about their history of antifilarial treatment.

A full description of the study area and its epidemiological background can be found in our previous publications,[9,11] and detailed maps of the Itwara focus are presented by Garms and others.[12]

Pair-matching procedure and statistical analysis. Because control data were available only for individuals with a time of residence in the area of 10–19 years,[9] epilepsy patients with a residential time of less than 10 years or more than 19 years were excluded from this analysis. For each epilepsy patient, eligible persons living in the same village with a corresponding residential time were identified from the list of the above-mentioned skin snip survey compiled in 1994. If two or more possible controls of the same gender as the epilepsy patient were found, supernumerary controls were excluded by use of a list of random numbers.[13] If no control of the same gender was available for a given epilepsy case, a control person of the opposite gender was selected. A matched-pairs analysis was then carried out to compare the results of nodule palpation and skin biopsies by use of EPI Info software, Windows version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, GA).

Ethical considerations. The data presented within this article were entirely collected at the occasion of the community study on the relationship between onchocerciasis and epilepsy in 1994.[9] Unlike the previous publication, we now focus on a case-controlled analysis of these data, but no additional

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TABLE 1
Case-controlled data on epilepsy and onchocerciasis from the Itwara hyperendemic focus as published by Druet-Cabanac and others[5]

Study	Onchocerciasis	Cases (people with epilepsy)	Controls (people without epilepsy)	Risk ratio (95% CI)
Ovuga and others[6]	Positive	112	72	0.84 (0.74–0.95)
	Negative	38	9	
Kipp and others[8]	Positive	32	364	6.80 (3.00–15.20)
	Negative	7	582	

investigations on humans were needed for this purpose. The protocol of the study by Kaiser and others[9] was approved by the ethical committee of the University of Heidelberg.

RESULTS

From the 61 patients diagnosed as suffering from epilepsy in 1994, 38 (20 females and 18 males) were found to have lived in their residential village for a time span of 10–19 years (median = 15 years). For all epilepsy cases with this time of residence, at least one control was found matching for village and time of residency. In 33 pairs, case and control were the same gender, whereas gender was different in five epilepsy patients (three males and two females) and their controls. All control persons and 34 epilepsy patients declared to have taken ivermectin at the occasion of the latest drug distribution in June 1993, which was 10–12 months before the present survey. For three epilepsy patients, they had missed the latest drug distribution but had received the drug at least one time during the previous campaigns. Only one epilepsy patient gave an account of never having been treated with ivermectin.

The skin biopsy was found positive for mf of *O. volvulus* in 29 of 38 epilepsy patients (76%) and 25 controls (66%; difference not significant). This difference was even smaller when pairs without ivermectin intake during the latest treatment round were excluded from the analysis (Table 2). Subcutaneous nodules were detected in 13 epilepsy patients (6 females and 7 males) and 6 controls (1 female and 5 males; $P = 0.065$, Mantel–Haenszel χ^2 test). In two epilepsy patients, nodule palpation revealed two onchocerciasis nodules, and in one patient, three nodules were found, whereas only one control person had two nodules. This corresponds to a total count of 17 nodules in 38 epilepsy patients versus 7 nodules in the respective controls ($P = 0.061$, Kruskal–Wallis test).

TABLE 2
Infection rates of *O. volvulus* according to skin biopsies and nodule palpation from 38 epilepsy patients and pair-matched controls (residential village and time of exposure; Kabende parish, Itwara hyperendemic focus, 1994)

	Cases (people with epilepsy)	Controls (people without epilepsy)	Odds ratio (95% CI)
Skin biopsy			
Complete sample*			
Positive	29	25	1.68 (0.60–4.57)
Negative	9	13	
Reduced sample†			
Positive	26	23	1.55 (0.53–4.53)
Negative	8	11	
Nodule palpation			
Complete sample*			
Positive	13	6	2.77 (0.92–8.33)
Negative	25	32	
Reduced sample†			
Positive	11	5	2.77 (0.84–9.12)
Negative	23	29	

*Complete sample (38 pairs).
†Patients without recent ivermectin treatment and respective controls excluded (34 pairs).

DISCUSSION

In this study from an area endemic for onchocerciasis, we found a slightly elevated rate of mf in the skin of epilepsy patients compared with the control group of healthy persons matched for intensity and time of exposure to infection. This difference was more pronounced when detection of subcutaneous nodules was used as indication of infection with *O. volvulus*.

Kipp and others,[8] in their study performed in two villages at a distance of only 10 km from Kabende parish, found a clearly elevated risk of epilepsy for inhabitants with a positive skin snip compared with those without evidence of infection with *O. volvulus* (risk ratio = 6.5; 95% CI = 3–15). This study combined the results found in one hyperendemic village of 475 inhabitants (onchocerciasis prevalence = 63%; 38 epilepsy patients were identified and 32 of 38 had mf found in skin biopsy) with the results of a hypoendemic village of 510 inhabitants (onchocerciasis prevalence = 19%; one epilepsy patient identified and no reported result of the respective skin biopsy). Consequently, in this analysis, one epilepsy patient from the hyperendemic village with a high intensity of transmission was compared with 11.5 inhabitants without epilepsy (38 patients to 437 controls), whereas in the hypoendemic village, only one epilepsy patient was related to 509 controls. The resulting more than 40-fold overrepresentation of control subjects from the village of low transmission intensity may have been one factor explaining the strongly positive correlation reported by Kipp and others.[8] When applying a more rigorous case-controlled procedure, we were not able to reproduce this result in the present analysis.

In the same onchocerciasis-endemic area where the study of Kipp and others[8] and our study were done, a study on clinical features of epilepsy had been performed 1 year before those studies. In that study, Ovuga and others,[6] for the first time, brought to notice the clustering of epilepsy in the Itwara focus. Moreover, this article reported on the frequent occurrence of a circumscribed condition of growth failure more than 40 years after it had been described as Nakalanga syndrome in another Ugandan area endemic for *O. volvulus*.[14] As appropriate in a descriptive study, patients were purposefully identified through community key persons and then, were subdivided into groups of epilepsy alone ($N = 126$), growth arrest alone ($N = 67$), epilepsy and growth arrest ($N = 24$), and presented as patients but did not fit with the two conditions of interest ($N = 14$). These subgroups were further characterized in describing relevant clinical features and their infection status with *O. volvulus* as assessed by skin biopsy. Because the rate of infection with *O. volvulus* in a representative sample of the general population was not assessed with this study, Ovuga and others[6] consistently did not subject their results to additional statistical analysis. Despite these limitations, the review of the study by Druet-Cabanac and others[5] constructed a risk ratio from the data of Ovuga and others[6] by relating the rate of infection with *O. volvulus* of epilepsy patients to the rate found

in the non-epilepsy patients reported in the article. However, the majority of these people without epilepsy was affected by the mentioned Nakalanga syndrome, which again, has been found to be associated with onchocerciasis.[2,3,11,14,15] The use of these highly selected patients as a comparison group has to be considered inappropriate for the determination of a risk ratio, and the study by Ovuga and others[6] did not qualify for inclusion in the meta-analysis of Druet-Cabanac and others.[5]

So far, only two studies have been published on the relationship between onchocerciasis and epilepsy using a clearly matched case-control design. Both of these studies, Druet-Cabanac and others[4] in a meso-endemic area in the Central African Republic and Boussinesq and others[3] in a hyperendemic area in Cameroon, found a slightly higher rate of microfilaridermia in epilepsy patients compared with matched controls, although this was not statistically significant. This is not surprising, because in highly endemic areas, prevalence rates for onchocerciasis are approaching 100% and virtually all cases and controls will have mf of *O. volvulus* detected in their skin. In areas of lower endemicity the potential effect of the parasite on the development of epilepsy is expected to be weak,[1] and comparatively, more patients will be found having epilepsy from other possible causes.

We found a more distinct difference between cases and controls when nodule palpation was used as the discriminating variable. Nodule palpation for both groups, epilepsy patients and controls, was performed in a comparable setting by the same examiners (C.K. and G.A.). The validity of nodule palpation for the demonstration of infection with *O. volvulus* in the Itwara focus has been confirmed by nodulectomy,[7] with only 4 of 312 extirpated nodules found to not be onchocercomata. It has been shown that the load of onchocercal nodules correlates with prevalence and intensity of infection in a population,[16–18] and our observation may indicate that intensity of onchocerciasis infection is playing a decisive role in inducing epilepsy. It would be of interest to know the quantitative mf count in the skin of the 38 patients and controls of our present analysis. This would have allowed us to (1) reconfirm the known relationship between nodule load and infection intensity in our study and (2) immediately investigate the relationship between infection intensity and the development of epilepsy. However, an assessment of quantitative mf counts in our study population of Kabende parish was prevented by the preceding antimicrofilarial treatment. So far, only one study has been published that investigated intensity of infection with *O. volvulus* in epilepsy patients[3] who at the time of examination, had not yet received microfilaricidal treatment. In this study, a highly significant elevation of mf loads was found in patients with epilepsy. Unfortunately, Boussinesq and others[3] provided no results of nodule palpation of their patients. We would be curious to know if such an analysis would corroborate the still unconfirmed observation of an elevated nodule count in epilepsy patients found in our study.

A number of epidemiological observations support the hypothesis that onchocerciasis is involved in the etiology of epilepsy. (1) The age distribution of epilepsy prevalence and incidence is very similar between the various onchocerciasis foci where this was investigated, but it is very unusual if compared with other areas in developing as well as industrialized countries.[3,9,19,20] This age distribution would also be consistent with the buildup of onchocerciasis infection in the population. (2) When known alternative etiologies for epilepsy were investigated, such as neurocysticercosis,[21] arbovirus infection,[22] or hereditary factors,[9,23] no explanation for the unusual clustering of epilepsy in onchocerciasis-endemic areas was found. (3) A specific type of epilepsy, which has been delineated as head-nodding syndrome, is found exclusively in areas known to be endemic of *O. volvulus*.[24–28] (4) The association between the above-mentioned Nakalanga syndrome and epilepsy has also been reported only from onchocerciasis-endemic areas.

Complex clinical studies searching for a pathological substrate inducing epilepsy are made difficult by the scarcity of neurological expertise and investigational facilities available in the endemic areas. Electroencephalography tracings in a series of epilepsy patients of the Itwara focus found a clear predominance of focal or multifocal changes.[25] This finding is compatible with a localized brain lesion, which could be produced by a parasitic infection such as onchocerciasis, but also by other post-infectious or post-traumatic conditions. Two recent reports from the Mahenge focus in Tanzania presented detailed clinical findings of patients living in an onchocerciasis-endemic area, including magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis.[27,29] Although these investigations failed to show the presence of the parasite in the central nervous system, in the subset of patients with head-nodding syndrome, a correlation was found between the pattern of non-specific MRI findings and skin snip results. The endemic area of Mahenge had been subject to annual mass treatment with ivermectin for several years before these studies were done, and microfilaricidal treatment may have interfered with the results of the parasitological investigations. It cannot be excluded that mf had been present in the CSF before treatment, because mf was previously seen in the CSF of untreated patients.[30,31] At present, the possible pathomechanism explaining the involvement of *O. volvulus* in the development of epilepsy is still unclear.

The main limitation of our data is the small sample size. It would be of great interest to test the hypothesis that intensity of infection with *O. volvulus* is reliably associated with epilepsy in a greater context. Because the transmission of onchocerciasis in the Itwara-endemic area has been fully interrupted since 2003,[12] this focus is no longer eligible for such an investigation. Areas where control measures are still at their start and patients can be examined before receiving microfilaricidal treatment would be particularly suitable for such studies. In those areas already subject to ivermectin mass therapy, the prevalence of palpable nodules and nodule load may be used as indicators for intensity of infection at least during the first years after the start of control campaigns when only minor changes of nodule counts are expected.[32] More rigorous case-controlled studies using the example of those studies carried out on cysticercosis[33] are needed to enhance our understanding of the enigmatic phenomenon of river epilepsy.[1]

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