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Title

ONCHOCERCIASIS IN TROPICAL NEUROLOGY: A SCOPING REVIEW

Authors

Jaime LUNA [a], Salvatore METANMO [a], Farid BOUMEDIENE [a,], Pascal MBELESSO [b], Emilie AUDITEAU [a], Daniel AJZENBERG [a], Pierre-Marie PREUX [a*]

Affiliation

a) INSERM, Univ. Limoges, CHU Limoges, IRD, U1094 Tropical Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges, France

b) Department of Neurology, Amitié Hospital, Bangui, Central African Republic

*** Corresponding author**

Professor Pierre-Marie PREUX

IENT, UMR Inserm 1094 NET

2 rue du Dr Marcland

Limoges, France, 78000

E-mail: pierre-marie.preux@unilim.fr

Phone: (33) 05 55 43 58 20

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Abstract

Background: Onchocerciasis is a serious problem in tropical areas. The role of the parasite as a factor associated with neurological diseases needs to be addressed because it might involve a reduction of the risk via elimination strategies. We performed a systematic scoping review to identify available studies on this association and put into perspective the different methodological approaches for interpreting the evidence.

Methodology: A literature search was conducted using MEDLINE (Pubmed) through October 1, 2020. We included all the studies evaluating the association between onchocerciasis and four neurological diseases (epilepsy, nodding syndrome, Nakalanga syndrome, and encephalitis) in tropical countries. A descriptive and critical summary of the results was conducted to provide an overview of the findings.

Results: Overall, 161 articles were identified in the literature search. After full-length examination, we included twelve articles for epilepsy and three for nodding syndrome. Two meta-analyses of case-control studies found a modest strength of the association between *O. volvulus* and epilepsy. Recent meta-analyses and original studies support a significant association. Epidemiological studies suggest an association between onchocerciasis and nodding syndrome, however, the level of evidence from case-control studies was relatively low. No measure of association was reported for Nakalanga syndrome. There was no specific study on the association between *O. volvulus* and encephalitis.

Conclusion: The association between onchocerciasis and epilepsy seems increasingly likely. However, there are still many unanswered questions about the different clinical presentations of this epilepsy. Strong international collaboration is essential to improve our understanding of risk factors and physiopathological mechanisms of these intriguing conditions.

Keywords: Epidemiology; association; onchocerciasis; epilepsy; nodding syndrome; Nakalanga syndrome; encephalitis; scoping review.

1. Introduction

Onchocerciasis is a neglected tropical disease caused by *Onchocerca volvulus* affecting millions of people in tropical areas. *O. volvulus* is a filarial nematode transmitted through the bites of infective blackflies of the genus *Simulium* (1). It is endemic in countries of West, East, and Central Africa, the Arabian Peninsula, and parts of South and Central America (2). The Global Burden of Disease Study reported around 20.9 million prevalent cases worldwide in 2017 (3). The highest proportion of cases occurred in sub-Saharan Africa (4).

O. volvulus infection leads to several clinical manifestations. The most frequent are skin lesions (e.g. pruritic dermatitis and nodules) and visual impairment (river blindness). In tropical neurology, onchocerciasis has been implicated as a potential risk factor in several disorders like epilepsy, nodding syndrome (NS), Nakalanga syndrome, and encephalitis (5). It has been particularly difficult to evaluate the evidence surrounding the association between *O. volvulus* and neurological tropical disorders due to different methods to assess onchocerciasis and define certain disorders (e.g. nodding syndrome, Nakalanga) along with heterogeneity in terms of study designs and the lack of understanding of related pathophysiological mechanisms. It is important to clearly establish this relation, as it could be a potentially modifiable component of risk.

In this context, we performed a scoping review of the existing literature regarding the association of *O. volvulus* and neurological disorders in tropical areas. The review aimed to identify the types of available epidemiological evidence, to examine how the research was conducted, and to analyze methodological advancement.

2. Methodology

The study was designed and conducted following the guidelines for scoping reviews (6,7) and the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews (8).

2.1 Search strategy and study selection

The search was conducted in MEDLINE (Pubmed). The following search strings and Boolean operators were entered to identify relevant studies: Onchocerciasis AND Epilepsy, Onchocerciasis AND Nodding syndrome, Onchocerciasis AND Nakalanga syndrome, Onchocerciasis AND Encephalitis. Systematic reviews and meta-analyses were also searched.

Rayyan QCRI (Qatar Computing Research Institute, Data Analytics Medical) (9) was used for managing and screening articles. Four authors (JL, SM, FB, DA) have independently performed an initial screening of title and abstract to select relevant studies. Full-length articles were examined to assess eligibility. We included publications evaluating the association between onchocerciasis and the previously mentioned neurological pathologies (epilepsy, nodding syndrome (NS), Nakalanga syndrome, and encephalitis) in tropical countries. Only studies that considered confirmed cases were included in the review. Case reports, editorials, and commentaries were excluded from the study selection. We also excluded opinion papers, reviews, and perspectives publications. There was no language restriction or restrictions on the publication date. The search was conducted through October 1, 2020.

2.2 Data extraction and synthesis of results

Data were extracted from included studies in an *ad hoc* document. The following standard information was collected: author, year of publication, country, study objective, study design, study population, numbers of cases, definition and confirmation methods (onchocerciasis and

neurological disorders), main results, and the measure of association together with the corresponding 95% confidence interval (CI). The data were summarized in tabular form. We presented a descriptive and critical summary of the results to provide an overview of the epidemiological evidence.

3. Results

3.1 Onchocerciasis and epilepsy

Epilepsy is a chronic neurological disorder characterized by an enduring tendency to have recurrent seizures. Epilepsy constitutes a major public health problem especially in tropical areas where etiologies such as parasitological infections are frequent (10). The association between onchocerciasis and epilepsy has been suggested in several studies (11,12).

3.1.1 Literature search

The search strategy yielded a total of 130 articles (more than half of these articles have been published in the last years, 2018 - 2020). After the initial screening of the title and abstract, 32 full-text articles were assessed for eligibility (28 original articles and 4 meta-analyses). Twenty studies were excluded for several reasons (Figure 1). Ten studies were previously reviewed in the meta-analyses (13–22). Four studies did not report a measure of association between onchocerciasis and epilepsy (relative risk, rate ratio, or odds ratio) (23–26). Two studies were randomized clinical trials (27,28). We excluded another study because the comparison of prevalence was conducted between neighbor villages at two time-periods (29). Three other studies were excluded because they included suspected cases of epilepsy rather than cases with a confirmed diagnosis of epilepsy: i) A study assessing the impact of repeated community-directed treatment with ivermectin (CDTI) campaigns on epilepsy prevalence after a 25-year interval (1991–1992 and 2017) (30), ii) Two cohort studies evaluating the

possibility of a temporal relationship between *O. volvulus* skin microfilarial density assessed during childhood and epilepsy incidence (31,32). Overall, twelve articles (4 meta-analyses and 8 new original studies) were included in the review (33–44)**.** The PRISMA flowchart of the literature research and selection process is shown in Figure 1. The localization of included studies is displayed in the map presented in Figure 2.

3.1.2 Evidence from meta-analyses

The first meta-analysis was published in 2004 (33). It included nine primary case-control studies using a cross-sectional approach. *O. volvulus* infection or exposure was determined using scarification, skin biopsies, or serological examination. A neurologist or a physician confirmed epilepsy diagnosis. An increased risk was reported with a common relative risk (RR) in the limit of significance. When the odds ratio (OR) was calculated using a random-effect analysis based on the method described by DerSimonian and Laird (45), the pooled OR was 1.70 (95% CI: 0.97 - 2.98, $p = 0.066$). The test of heterogeneity was significant ($p < 0.001$) and the I^2 was 76.7% (unpublished data). The data was then re-analyzed after excluding two publications: a study in a hypo-endemic area possibly resulting in a low prevalence of onchocerciasis-associated epilepsy (46) and another study where participants with growth retardation (Nakalanga like symptoms) were considered as non-epileptic controls (47). The meta-analysis found a relative risk of 1.30 (95% confidence interval: 1.04 - 1.62; p = 0.02). Significant heterogeneity was found (Cochran's Q test $p < 0.001$, $I^2 = 92\%$) (48).

In 2013, an updated meta-analysis was conducted (34). Primary case-control studies were included using qualitative skin biopsies to determine onchocerciasis. Epilepsy diagnosis was established with several methods like non-standardized or standardized interviews and neurologist or physician examination. The pooled OR was 2.49 (95% CI: 1.61–3.86, $p = 0.001$). Significant heterogeneity was found (Cochrane's Q test: $p = 0.001$; $I^2 = 65.7\%$). The analyses were restricted to studies achieving control for age, residence, and sex. The pooled

OR was 1.29 (95% CI: 0.93 – 1.79; $p = 0.139$) considering four studies using skin biopsies as an assessment method. No statistically significant heterogeneity between the studies was detected ($p = 0.59$; $I^2 = 0\%$). The pooled OR was 2.80 (95% CI: 1.57 – 5.00; $p = 0.001$) when two studies were considered using nodule palpation as a qualitative method of assessment.

In 2009, an interesting meta-analysis evaluated the relationship between onchocerciasis endemicity and epilepsy prevalence (35). Eight studies were included covering seven countries in Western Africa (Benin and Nigeria), Central Africa (Cameroon and Central African Republic), and Eastern Africa (Uganda, Tanzania, and Burundi). The prevalence of epilepsy was variable among those countries (ranging from zero to 8.7%). The logistic model found that the epilepsy prevalence was associated with the prevalence of onchocerciasis showing an odds-ratio of 1.044 (95% CI: 1.036 - 1.052) (35).

A recent meta-analysis estimated epilepsy prevalence and its relationship with onchocerciasis in West Africa (36). Epilepsy prevalence was obtained from population-based surveys and the pre-control onchocerciasis endemicity was estimated from historical data. However, onchocerciasis prevalence at the time of the epilepsy survey was available for few endemic study sites. The overall pooled epilepsy prevalence was 13.14 per 1000 (95% CI 11.28 – 15.00). A subgroup analysis was conducted based on endemicity and duration of onchocerciasis control. Epilepsy prevalence was 12.20 (95% CI 8.53 – 15.86) in non-endemic areas, 24.45 (95% CI 17.76 – 31.14) in endemic areas with no onchocerciasis control, 13.99 (95% CI 8.45 – 19.53) in endemic areas with 1 to 9 years of onchocerciasis control and 9.44 (95% CI 4.83 – 14.05) in endemic areas with more than 10 years of onchocerciasis control. Multiple linear regression showed a significant relationship between the prevalence of epilepsy and the prevalence of microfilariae and the duration of control. The prevalence of epilepsy increases with the prevalence of microfilariae ($p<0.001$) but decreases with the duration of control ($p<0.001$).

3.1.3 Updated evidence

There has been a large increase in the number of research publications on this subject mainly in the last years. The eight new studies included in this scoping review were classified as follows: i) Case-control studies, ii) Spatial analysis, iii) Prevalence of epilepsy after onchocerciasis control campaigns.

Three studies were carried out with a case-control design (37–39). In 2014, a case-control study was performed in three villages (endemic areas): Kifuma, Kalama, and Lalu Sefu of the District of Kasangulu, Bas-Congo Province, Democratic Republic of Congo (37). *O. volvulus* infection was determined via snip skin biopsies. The logistic regression showed a statistically significant association between epilepsy and onchocerciasis (OR = 4.5, 95% CI: 1.75 – 11.54, $p = 0.002$), with no change after adjusting for age and gender. Another study was performed in three villages (endemic areas) of the Democratic Republic of Congo: village of Salambongo (Tshopo Province), village of Rassia, and village of Draju (Ituri Province) (38). CDTI campaigns were carried out for several years in the two first villages. At the time of the study, the epilepsy prevalence ranged from 2.6% to 6.2%. Microfilariae were identified through skin snip biopsies to establish onchocerciasis, while exposure to *O. volvulus* was determined using the serological test. A significant association was observed between epilepsy and onchocerciasis (OR = 2.44, 95% CI: 1.56 – 3.84, $p = 0.0001$), and epilepsy and exposure to *O. volvulus* (OR = 1.98, 95% CI: 1.25 – 3.13, $p = 0.0037$). A large study was conducted to evaluate risk factors of active convulsive epilepsy in five African countries: Kenya (2007–2008), South Africa (2008–2009), Uganda (2009–2009), Tanzania (2009–2009) and Ghana (2010–2011) (39). Exposure to *O. volvulus* was established through serology. There was a statistically significant association for active convulsive epilepsy in children (aOR = 1.67, 95% CI: 1.09 – 2.57, $p = 0.019$) and active convulsive epilepsy in adults (aOR = 2.23, 95% CI: 1.56 – 3.19, $p < 0.0001$). To quantify the contribution of risk to disease burden,

the population attributable fraction was estimated at 0.06 (95% CI: 0.01 – 0.10) for children and 0.14 (95% CI: 0.08 – 0.20) for adults. Table 1 showed the description of updated case-control studies assessing the association between onchocerciasis and epilepsy.

A spatial analysis was performed in Ituri province (an onchocerciasis rural endemic area), Democratic Republic of Congo (40). The households were randomly sampled and located via Geographic Information Systems. A three-stage approach - screening survey, clinical examination by a general practitioner, and consultation with a neurologist - identified people with epilepsy. Epilepsy diagnosis was based on the 2014 International League Against Epilepsy (ILAE) definition (49). Exposure to *O. volvulus* was evaluated in participants older than 3 years old (OV16 test). A significant association between epilepsy and exposure to *O. volvulus* was observed in the spatial analysis (aOR = 3.19, 95% CI: 1.63 – 5.64, $p = 0.001$).

In recent years, it has been estimated the impact of CDTI in epilepsy prevalence. In Cameroon, epidemiological studies were performed to determine epilepsy prevalence in two villages (Bilomo, 1998 and Kelleng, 2004) followed by new surveys taken several years apart (Bilomo, 2017 and Kelleng, 2018) (41). These endemic areas have benefited from CDTI for more than a decade. The surveys were cross-sectional using a door-to-door approach. However, the methodology to identify people with epilepsy was heterogeneous. The crude prevalence of epilepsy remained stable in Bilomo (1998 (4.9%) and 2017 (4.6%), $p = 0.695$), and there was no statistically significant decrease in Kelleng (2004 (10.5%) and 2018 (7.8%), $p = 0.357$). The age- and sex-standardized epilepsy prevalence was only reported for Kelleng with a statistically significant decrease (2004 (13.5%) and 2018 (9.3%), $p < 0.001$). The median age of people with epilepsy shifted in Bilomo from 17 years (IQR: 12–22) to 24 years (IQR: 20–30) between the two survey periods. The highest epilepsy prevalence was found in the 10–19 years age group in 1998 (12.9%), while the 20–29 years age group reported the highest epilepsy prevalence in 2017 (17.1%). The age shift suggests a reduction of epilepsy

onset among young children after controlling onchocerciasis transmission using ivermectin. In Tanzania, another study compared epilepsy prevalence between two time periods (1989 (50) and 2017 (42)) in several villages in the Mahenge area (endemic area). The area was part of the annual CDTI since 1997. The authors reported no change in the epilepsy prevalence over time (Mdindo village 3.7% (1989) and 3.5% (2017); Vigoi and Matumbala 1.3% (1989) and 1.5% (2017)). It is important to note that the highest prevalence of epilepsy was observed in rural villages with the highest prevalence of OV16 prevalence among children, which suggests ongoing *O. volvulus* transmission. In Uganda, two publications compared the prevalence and incidence of epilepsy between two time periods in the same geographic endemic areas before and after the implementation of onchocerciasis control measures (43,44). The first publication concerns two cross-sectional studies performed in three villages of western Uganda (Kabende Centre, Masongora South, and Rwesenene) using a population-based approach in 1994 and later, in 2018. According to the publication, onchocerciasis transmission was interrupted in 2001, and the elimination of onchocerciasis was declared in 2016. Epilepsy crude prevalence had significantly decreased from 3.0% in 1994 to 1.2% in 2018 ($p = 0.0002$). An age-specific epilepsy prevalence decrease was observed in the 10 to 19 year age group between 1994 and 2018 ($p < 0.0001$). The overall incidence also decreased between the two periods, 418 per 100 000 person-years (95% CI: 265 – 626) in 1994 to 73 per 100 000 person-years (95% CI: 32 – 114; $p < 0.0001$). Interestingly, no new cases of nodding syndrome or Nakalanga had occurred since the interruption of onchocerciasis transmission (43). A similar study design was applied in selected villages of Kitgum and Pader districts (Northern Uganda). No significant decrease was observed in the epilepsy prevalence between 2012 and 2017. However, the cumulative incidence of epilepsy decreased from 675 to 87 per 100 000 persons per year ($p = 0.024$) and the number of new NS cases per year dropped from four in 2012 to zero in 2017 (44).

3.2 Onchocerciasis and nodding syndrome

NS is a term that first appeared in 2003 to describe an atypical form of epilepsy in African children with head nodding as a signature sign at an early stage of the disease (51). The disease can progress to other complications such as stunting, wasting, delayed sexual development, psychiatric illness, and eventually death (52–54).

The etiology of NS remains unknown and unclear. Because the disease occurs in settings with a high prevalence of epilepsy that are also endemic for onchocerciasis, NS could be part of a spectrum of onchocerciasis-associated epileptic (OAE) disorders that have in common to be triggered by a common factor, most likely *O. volvulus* (55).

3.2.1 Literature search

Our search strategy (Nodding syndrome AND Onchocerciasis) identified 61 articles. After reading titles and abstracts, eight articles were selected. After full reading, four of these articles did not study the association between NS and onchocerciasis and were therefore removed (44,56–58). One paper (59) used data already published in another article (60) and was therefore excluded. In total, three original articles were selected for our analysis (60–62). The PRISMA flowchart is shown in Figure 1. The localization of included studies is presented in Figure 2.

3.2.2 Evidence

Eight case-control studies were reported in these three articles: five in different locations of Southern Sudan between 2001 and 2011 and three in one place of Northern Uganda in 2009 (Table 2). The eight studies all took place before 2012, i.e. before the first international conference on NS organized by WHO (63), which explains why the definition of NS cases

may vary from one study to another. However, in all eight studies, the case definition included the occurrence of involuntary episodes of head nodding in a previously neurologically healthy resident of the study area who was less than 21 years of age at baseline.

Only two studies did not find a positive association between NS and onchocerciasis (61,62). When the US Centers for Disease Control and Prevention (CDC) investigated NS in Northern Uganda in 2009 (62), they selected only one location but used three different tests for assessing *O. volvulus* infection: the skin snip and two serologic assays based on different antigens and techniques (Table 2). A positive association between NS and onchocerciasis was found only when the serological tests were used. Because the positivity of a skin snip depends on the viability of the microfilariae in the sample, serological tests are more sensitive for detecting *O. volvulus* past infections, and this lack of sensitivity of the skin snip may explain the absence of association. The CDC investigated NS with the same methodology in two different locations of Southern Soudan in 2011: Maridi town and Witto village (61). A positive association between NS and onchocerciasis was found in Maridi but not in Witto. Since the number of case-control pairs was low in Witto (Table 2), one can reasonably expect that this lack of association in Witto be primarily due to a lack of statistical power rather than a true difference between settings.

3.3 Onchocerciasis and other neurological disorders: Nakalanga syndrome and encephalitis

Roscoe reported the first case of Nakalanga syndrome in Uganda at the beginning of the 20th Century (64). Recently, it has been defined as a combination of stunted growth without a clear cause, delayed or absence of signs of sexual development, intellectual disability, epilepsy, and

facial dysmorphia (65). The search strategy identified thirteen studies (Figure 1). We did not identify any study reporting measures of association (relative risk or odds ratio) between onchocerciasis and Nakalanga syndrome. The difficulty lies in the definition of the pathology, as a specific syndrome or a particular clinical expression of another disease. Reports of Nakalanga cases mainly concern with their proportion among people living with epilepsy: 8.2% in Burundi (21), 0.6% in Cameroon (66), and 10.9% in Tanzania (67). The majority of Nakalanga syndrome cases were located in hyper-endemic areas of onchocerciasis, notably where NS has been described in recent years. A specific study was conducted to identify Nakalanga syndrome in Kabarole district, Western Uganda (68). Thirty-one cases of Nakalanga syndrome were identified. Controls were matched to cases in terms of age and sex. Onchocerciasis was detected in all 31 cases of Nakalanga syndrome (100%) and 22 over 28 controls (79%), $p < 0.001$.

Parasites can also cause encephalitis. We identified thirteen articles in our search strategy (Figure 1). There was no specific study on the association between onchocerciasis and encephalitis.

4. Discussion

This scoping review describes the association between *O. volvulus* and neurological disorders in tropical areas. Studies of particular interest were analyzed to put into perspective the methodological approaches for interpreting evidence.

Most of the literature available in the tropical area focuses on epilepsy, with a sharp increase in the number of publications in recent years. The latter has resulted in a proposal to define onchocerciasis-associated epilepsy (OAE) (69) and the encouragement to carry out the First International Workshop on OAE (70). According to *Colebunders et al.*, the specific

characteristics distinguishing OAE from other forms of epilepsy are time at onset (between the ages of 3 and 18 years), geographical clustering (onchocerciasis-endemic region), and certain kind of family clustering (siblings often affected by epilepsy), along with a normal neurological development before the onset of epilepsy (69,70). Clinically, the most common presentation is generalized tonic-clonic seizures showing no difference from seizures of another etiology. NS and the Nakalanga syndrome are also included as clinical presentations of onchocerciasis-associated epilepsy. In the Democratic Republic of Congo, a cross-sectional study including 420 people with epilepsy reported 32 (7.6%) cases of Nodding syndrome (14 (43.7%) of them had a positive skin snip test) and 12 (3.1%) cases of Nakalanga syndrome (5 (41.7%) of them had a positive skin snip test) (71).

The exact pathophysiological processes of OAE remain unknown. Several mechanisms have been suggested (72) including the presence of the parasite in the central nervous system (however, microfilaria have been not detected in the CSF (73)), the pathogenicity of *O. volvulus* strains (74,75), immunological mechanisms involving cross-reactive immunization or cytokine production (58,76,77), the role of excretory-secretory products (secreted by *O. volvulus)* that may cross the blood-brain barrier and trigger CNS disease leading to OAE (78) and the triggering role of insomnia due to itching (79,80).

It is important to note that meta-analyses of case-control studies found a modest strength of the association between *O. volvulus* and epilepsy. Several methodological limitations were observed in the included studies. Additionally, the restricted analysis showed different results. Several considerations need to be taken into account for case-control studies. Epidemiological studies used a variety of methods for participant recruitment (population-based/health records), assessment of exposure (Skin snip/OV16), and matching (no individual matching/age/sex/area). This heterogeneity complicates the interpretation of the new evidence. We have to keep in mind the difficulty to recruit a sample of controls that provides

a representation of the subjects without the disease. Another crucial point is an adequate assessment of the exposure (*O. volvulus*) and outcome (epilepsy) using standard and well-determined criteria. The gold standard test for the diagnosis of onchocerciasis remains the skin snip biopsy (81), however, it depends on the viability of the microfilaria in the sample. Serological tests measure exposure to *O. volvulus* and therefore indirectly detect the transmission, but do not discriminate between past or active infections (82). To improve our understanding of the relationship between exposure and outcome, the temporal relation is mandatory, although not easy to achieve, notably due to the cross-sectional approach. In this scoping review, we excluded two cohort studies in Cameroon assessing the incidence of epilepsy relative to *O. volvulus* skin microfilarial density measured during childhood because suspected cases of epilepsy were considered for the analysis instead of confirmed cases of epilepsy (31,32). However, these two cohorts suggest a temporal relationship between onchocerciasis and epilepsy. The first cohort found that the risk of an individual being a suspected case of epilepsy increased rapidly with the increase in baseline microfilarial density (31). Similar results were found in the second cohort reporting a gradual increase of suspected cases incidence rate based on the initial microfilarial density with values ranging from 117.8 per 100 000 person-years for individuals without skin microfilarial to 952.8 per 100 000 persons-years for those with a microfilarial density >200 microfilarial/snip ($p < 0.0001$) (32). At this point, it is difficult to draw firm conclusions. It is equally important to say that the most reliable epidemiological evidence of association will not necessarily imply causation.

Another interesting issue is the relationship between seizure frequency and microfilarial density. A cross-sectional study was conducted to assess this relationship in two health zones (Logo and Aketi) in the Democratic Republic of Congo (71). No statistically significant association was found between seizure frequency and microfilarial density in the Logo health

zone (p = 0.148). However, the association was statistically significant in the Aketi health zone (p = 0.025).

Although there are innovative ways of approaching this topic, the potential limitations of these methods need to be accounted for. Many efforts have focused on directed treatment with ivermectin in onchocerciasis endemic countries (83,84). Ivermectin has been proposed as an adjuvant to anti-epileptic treatment, however, a randomized clinical trial carried out in the Democratic Republic of Congo found that ivermectin did not have an added beneficial effect over anti-epileptic treatment (phenobarbital) (28). Another clinical trial conducted by the same research team in the Democratic Republic of Congo showed that seizure reduction was more likely among those treated with multiple doses of ivermectin (27). Regarding the community-led treatment with ivermectin, it is difficult to estimate the impact of the program on epilepsy prevalence over time. The methodology used was heterogeneous across surveys to identify people with epilepsy and age- and sex-standardized epilepsy prevalence was not systematically reported for all the areas. Furthermore, it is extremely challenging to assess the impact of risk factors (family history of seizures, previous febrile seizures, perinatal trauma, head injury, and CNS infections (85)) and their relation with epidemiological indicators of epilepsy over time.

Endemicity is a key concept in onchocerciasis epidemiology (86). The severity of the disease and the public health importance in a given area are directly related to the local level of endemicity (87,88). This is also a key issue in tropical neurology. Publications support a high prevalence of epilepsy in onchocerciasis endemic areas (villages close to rivers or dams considered blackfly breeding sites). For instance, studies from Maridi County in South Sudan showed a significantly higher prevalence of epilepsy in villages <2 km from the Maridi River compared to those more distant from the river ($p < 0.001$) (89). A prevalence of 11.9% of epilepsy was observed in a village close to the Maridi dam, which is a hotspot for *O. volvulus*

transmission (26). The authors also reported a high percentage of people with epilepsy who met the diagnostic criteria for OAE in the area. Cysticercosis was considered unlikely given the absence of pigs in the Maridi area (90). Another study showed a high prevalence of epilepsy in areas with very high ongoing *O. volvulus* transmission in the Democratic Republic of the Congo (villages of Wela (6.8%) and Makoko (8.4%) and the town of Aketi (5.7%)) (23). The relationship of neurological diseases with endemicity level (hypo, meso-and hyper-endemic) according to geographic areas is intriguing.

To improve our understanding of the association between onchocerciasis and epilepsy, it could be interesting to analyze the relationship according to seizure types. There is a lack of information on the type of seizure in these studies. However, we recognize the challenging context to perform epidemiological research in tropical areas for a variety of reasons (methodological, logistic, political, economic, ethical, and often the low perceived value of such works (91)).

Regarding NS, it seems quite clear that there is an association with onchocerciasis. However, association does not imply causation and it is still unknown whether NS is directly or indirectly caused by *O. volvulus* or not. The level of evidence from case-control studies is relatively low because it is often impossible to prove that exposure to a factor was anterior to the occurrence of the disease. Thus, even if studies reported an association between *O. volvulus* and NS, it is impossible to know whether *O. volvulus* infection preceded or followed NS onset (60–62). Another limitation of case-control studies is the adjustment variables used in the different models, especially for the variable age since the disease develops in children aged 3 to 18 years with previously normal development. In the Ugandan study, the authors stated that the results were unchanged when three models were used, including an age-adjusted one and two models adjusted for exposure factors (62). However, in the Sudanese

studies, cases and controls were matched by age and area but the authors did not specify either the model used or not the adjustment variables (60,61).

NS is still a challenging condition to understand. The pathogenesis is still unclear. One hypothesis suggests that NS is an autoimmune disorder triggered by cross-reacting antibodies between neuronal proteins and *O. volvulus* antigens (58,92). Postmortem examinations showed pathological changes in the brain characterized by neuronal loss especially in the cerebellum at the top of the folia, with associated hyperplasia of Bergmann glia and foci of gliosis (93).

The specific geographic distribution of NS is another intriguing aspect. Onchocerciasis is endemic in many areas of Africa and Latin America for centuries but NS has the pattern of an epidemic strictly limited in children and a few areas of Africa.

The Nakalanga syndrome is another clinical condition observed in onchocerciasis-endemic regions of Africa and is considered a form of onchocerciasis-associated epilepsy by several authors (69). The causes and physiopathological mechanisms of the disease are not yet known. There is still a knowledge gap in understanding this syndrome.

The major strength of this work relies on the critical review of key studies focusing on methodological aspects to establish a link with the findings for their interpretation. The major limitation of this study is the use of only one major database (Medline/Pubmed), which could lead to a lack of inclusion of certain studies, mainly in the grey literature. We only included studies providing evidence from confirmed cases and we have placed particular emphasis on the measure of association to quantify the relationship. However, relevant data from studies that did not meet the inclusion criteria were also described and discussed. Another limitation is the lack of formal assessment of the risk of bias. Scoping reviews aim to provide an overview of the evidence. Due to this, an assessment of the risk of bias of the evidence

included within a scoping review is generally not performed (unless there is a specific requirement due to the nature of the scoping review aim) (6,7). Further reviews need to perform a careful assessment of biases using standard tools (e.g. the Newcastle-Ottawa Scale). The Bradford Hill criteria need to be considered to evaluate the likelihood of a causal association.

5. Conclusion

Given that the incidence and mortality of epilepsy are highest in tropical countries, it is of fundamental importance to understand specific risk factors in these areas as a crucial milestone to reduce disease burden. The association between onchocerciasis and epilepsy is more and more likely based on recent epidemiological studies. However, there are still many unanswered questions about the different clinical presentations of this epilepsy. Multidisciplinary research teams are now taking a step forward to further understand these conditions in tropical neurology.

Tables and Figures

Table 1. Description of updated case-control studies assessing the association between onchocerciasis and epilepsy

Table 2. Description of case-control studies assessing the association between onchocerciasis and Nodding syndrome

Figure 1. Flow diagram for the scoping review process

Figure 2. Countries of the studies included on the association between of *O. volvulus* and neurological disorders in tropical areas

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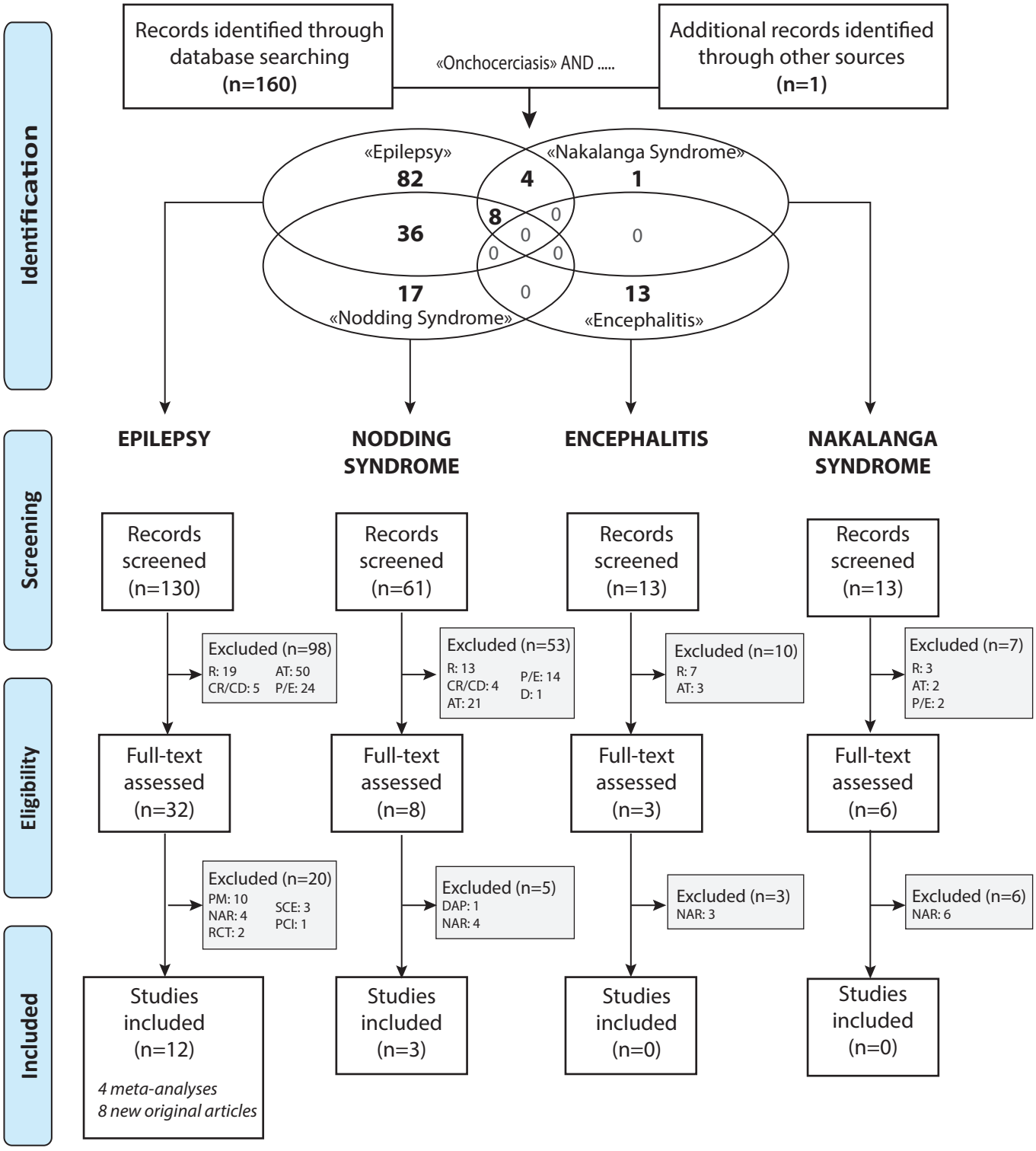
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(PRISMA) flow diagram for the scoping review process



R: Review ; CR/CD: Case Report/Clinical Description ; AT: Another Topic ; P/E: Protocol/Editorial ; D: duplicate
PM: Previous Meta-analysis ; NAR: No Association Reported ; RCT: Randomized Controlled Trial ; SCE: Suspected Cases of Epilepsy ; PCI: Prevalence Comparison Issues; DAP: Data Already Published

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta *A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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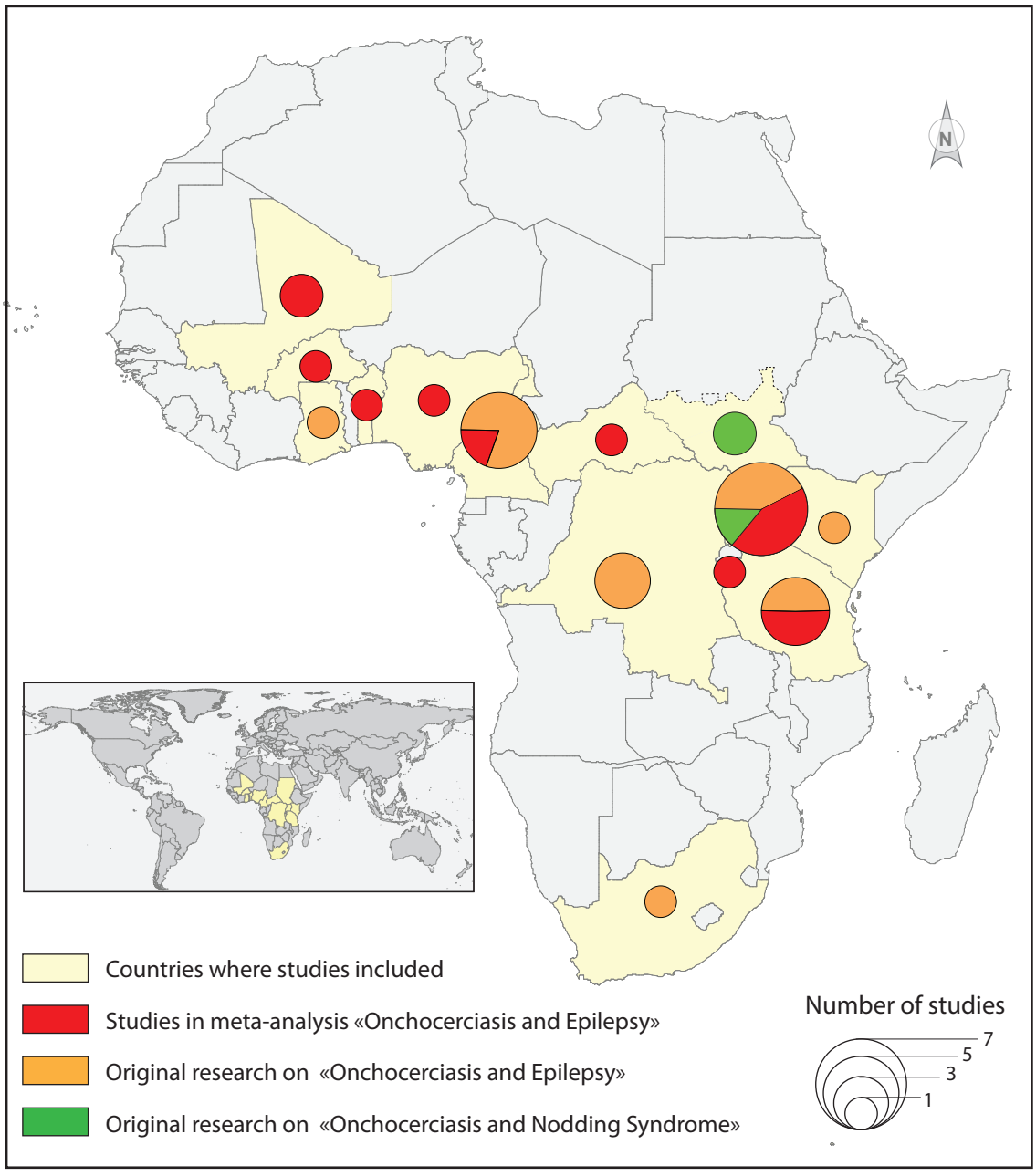

N
Countries where studies included
Studies in meta-analysis «Onchocerciasis and Epilepsy»
Original research on «Onchocerciasis and Epilepsy»
Original research on «Onchocerciasis and Nodding Syndrome»
Number of studies
7
5
3
1

Table 1. Description of updated case-control studies assessing the association between onchocerciasis and epilepsy

Author, year of publication	Country	Place, year	Study population	Participants recruitment	Diagnosis of onchocerciasis	Epilepsy definition	Epilepsy diagnosis	Numbers of cases PWE	PWE OV + (%)	Number of controls PWOE	PWOE OV + (%)	Matching Criteria	Measure of association (95% CI)
Burfeind et al., 2019	Democratic Republic of Congo	District of Kasangulu, Bas, Congo Province, 2014	All ages	Active search of health records from the local rural clinics and public announcements	Skin snip	ILAE 2014	Neurologist	82	68 (83%)	27	14 (52%)	Age, sex and area	OR = 4.51 (1.75 – 11.54)
Mandro et al., 2018	Democratic Republic of Congo	Cillage of Salambongo, Draju, and Rassia, 2015	All ages	Door-to-door survey	Skin snip	Active epilepsy definition	Neurologist	175	103 (59%)	164	62 (38%)	No individual matching	OR = 2.44 (1.56 – 3.84)
					OV16			175	79 (45%)	169	49 (29%)		OR = 1.98 (1.25 – 3.13)
Ngugi et al., 2013	Kenya, South Africa, Uganda, Tanzania, Ghana	Kilifi, Kenya, 2008; Agincourt, South Africa, 2008-2009; Iganga-Mayuge, Uganda, 2009; Ifakara, Tanzania, 2009; Kintampo, Ghana, 2010-2011.	Children¶	Door-to-door survey	OV16	Active epilepsy definition	Clinician	244	55 (22.5%)	414	61 (14.7%)	Age	aOR§ = 1.67 (1.09 – 2.57)
			Adults¶¶					291	147 (50.5%)	422	128 (30.3%)		aOR§§ = 2.23 (1.56 – 3.19)

aOR, adjusted odds ratio; ILAE, International League Against Epilepsy, OV: *Onchocerca volvulus*; PWE, people with epilepsy; PWOE, people without epilepsy.
§ Odds ratio adjusted for age, sex, mother's education, mother's marital status, employment of mother or father, and country
§§Odds ratio adjusted for age, sex, education, marital status, employment, and country
¶ Children: aged < 18 years
¶¶ Adults: aged ≥18 years

Table 2. Description of case-control studies assessing the association between onchocerciasis and Nodding syndrome

Author, year of publication	Country	Place, year	Study population	Diagnosis of OV	Number of NS cases	Cases OV + (%)	Number of controls	Controls OV + (%)	Matching criteria	Measure of association (95% CI)
CDC, 2012	Southern Sudan	Maridi, 2011	Cases <18 years	Skin snip	25	22 (88)	25	11 (44)	Age and area	OR = 9.3 (1.9–52.3)
CDC, 2012	Southern Sudan	Witto, 2011	Cases < 18 years	Skin snip	13	7 (53.8)	13	7 (53.8)	Age and area	OR = 1.0 (0.2–6.2)
Tumwine et al., 2012	Southern Sudan	Lui, 2001	Cases ranged 5–21 years	Skin snip	39	35 (89.7)	31	15 (48.4)	Age and area	OR = 9.3 (2.7–32.6)
Tumwine et al., 2012	Southern Sudan	Amadi, 2001	Cases ranged 5–21 years	Skin snip	30	29 (96.7)	34	17 (50)	Age and area	OR = 29.0 (3.5–237.7)
Tumwine et al., 2012	Southern Sudan	Lui, 2002	Cases ranged 5–21 years	Skin snip	13	12 (92.3)	16	7 (43.8)	Age and area	OR = 15.4 (1.6–148.8)
Foltz et al., 2013	Northern Uganda	Western Kitgum District, 2009	Cases ranged 5–15 years	Skin snip	45	32 (71.1)	39	21 (53.9)	Area	aOR = 1.11 (0.37–3.27)
Foltz et al., 2013	Northern Uganda	Western Kitgum District, 2009	Cases ranged 5–15 years	OV16 by Elisa	39	26 (66.7)	44	14 (31.8)	Area	aOR = 3.14 (1.08–9.13)
Foltz et al., 2013	Northern Uganda	Western Kitgum District, 2009	Cases ranged 5–15 years	OVFAR/MSA by LIPS	39	37 (94.9)	41	20 (48.8)	Area	aOR = 14.40 (2.65–78.31)

CDC: Centers for Disease Control and Prevention
OV: *Onchocerca volvulus* infection
OR: Odds ratio
aOR: Odds ratio adjusted for age
LIPS: Luciferase immunoprecipitation system