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EC MICROBIOLOGY
Research Article

Onchocerciasis in Mozambique: An Unknown Condition for Health Professionals

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Received: January 01, 2019; **Published:** February 14, 2019

Abstract

Introduction: Onchocerciasis, remains an unfamiliar condition for health professionals in Mozambique leading to its misdiagnosis as leprosy or scabies as noted in previous studies. Meta-analyses conducted in some African countries, have concluded that onchocerciasis is associated with epilepsy and nodding syndrome. Epilepsy affects at least 3% of the Mozambican population.

Aim: We aim to discuss the possible misdiagnosis of scabies and/or leprosy in cases of onchocerciasis as well as insights into a putative role for onchocerciasis in the etiology of epilepsy. Based on these issues, we also highlight some priorities for future onchocerciasis research.

Methods: We carried out a literature review of the epidemiology of onchocerciasis in Mozambique and other parts of the world where the disease exists, its clinical features, and information on the prevalence of epilepsy, scabies and leprosy in Mozambique.

Results and Conclusions: A number of studies (1997 - 2007) revealed that onchocerciasis is present in at least five provinces of Mozambique, comprising 47% of the country's population, and at least three provinces of Mozambique where onchocerciasis has been reported are those where the incidence of leprosy is also high. This increases the possibility that onchocerciasis cases could be misdiagnosed as leprosy or scabies, as seen in previous studies by Noormahomed., et al. In addition, onchocerciasis may contribute to the development of epilepsy at an early age, as has been found in some other African countries such as Tanzania and the Democratic Republic of Congo.

Mozambique is not included in many epidemiological maps of onchocerciasis prevalence, while Tanzania and Malawi are listed as endemic countries and have well established community drug treatment with ivermectin, probably because the disease was considered hypoendemic in previous studies. Research should be carried out in focal areas to determine the burden and clinical features of onchocercal disease in Mozambique, as well as, the socio and economic impact of disease in the affected patients and communities. With these data in hand, it will also be possible to assess the possible association of onchocerciasis with epilepsy in Mozambique. It will be equally important to train health professionals in the diagnosis and management of this neglected and poverty-related disease.

Keywords: *Mozambique; Onchocerciasis; Simulium spp; Misdiagnosis; Leprosy; Scabies; Epilepsy*

Abbreviations

TDR: Training in Tropical Diseases; WHO: World Health Organization; REMO: Rapid Epidemiological Mapping of Onchocerciasis; NATOG: N-acetyltyramine-O,β-glucuronide; CDTI: Community Drug Treatment with Ivermectin; APOC: African Programme for Onchocerciasis Control; MDA: Mass Drug Administration; OAE: Onchocerciasis-associated Epilepsy

Research Highlights

1. It is probable that onchocerciasis has existed in Mozambique since time immemorial.
2. Because the disease is relatively unknown in the country, patients are often misdiagnosed with scabies or leprosy, given some common features like dermatitis and skin depigmentation.
3. Studies in some endemic countries in Africa and Latin America suggest that onchocerciasis infection might be an etiological cause of epilepsy at an early age.

4. There is an urgent need to know the burden of onchocerciasis in Mozambique and other countries endemic for onchocerciasis, as well as its relationship to epilepsy.
5. Health professionals in onchocerciasis endemic countries should be trained to recognize the signs and symptoms of onchocerciasis, as well as, the main differential diagnoses of leprosy, scabies and other skin diseases.

Introduction

Onchocerciasis, a parasitic and neglected tropical disease caused by *Onchocerca volvulus,* is the second leading infectious cause of blindness worldwide. It is commonly known as "river blindness", as it seems to affect mainly people living near rivers where the majority of its vectors breed, but it also exists in areas of savannah.

More than 99% of affected people live in 31 African countries with an estimated population at risk of about 118,285,000 and around 21,115,000 infected by the parasite. Among those infected, 690,000 people have visual impairment and 220,000 are blind [1].

The parasite is transmitted by vectors of the family *Simuliidae* (blackflies), which comprises more than 2,351 species, some of which (like *S. damnosum*) have a capacity to fly 200 - 400 km from their breeding site. Only eight species of *Simulium* spp. have been sighted in Mozambique, including *Simulium* (*Edwarsellum*) *damnosum*, a well-known onchocerciasis vector. In Malawi and Tanzania, there are at least 18 and 28 known species of *Simuliidae*, respectively, possibly because more extensive entomological studies have been conducted in those countries [2].

Onchocerciasis is characterized by complex symptoms and signs including subcutaneous nodules known as onchocercomas, severe itching, skin depigmentation (also known as leopard skin), and lymphatic system involvement. The subcutaneous onchocercomas are usually painless, hard, fibrous and mobile under the fingers. Some of the patients seen in Mozambique by Noormahomed., *et al*. have a history of suppuration from time to time, probably due to secondary infection or necrosis [3]. Onchocerciasis also can result in ocular lesions that can progress to partial or total blindness. The eye is a trap for the microfilaria, as it is for other parasites such as *Cysticercus cellulosae, Loa loa* and *Toxocara* spp.

The clinical and laboratory diagnosis of onchocerciasis is based on physical examination for signs and symptoms of the disease and the demonstration of microfilariae in skin biopsies. Onchocercomas are the more pathognomonic signs, but these are only detected by palpation when they occur over flat bones. However, many are in deep locations, only being detectable by diagnostic imaging techniques.

For community assessment, the Training in Tropical Diseases (TDR) programme from the World Health Organization (WHO) developed the Rapid Epidemiological Mapping of Onchocerciasis (REMO), which consists of nodule palpation in individuals up to 20 years to determine the geographical distribution of the disease, and to identify which communities could most profitably be treated with ivermectin. The administration of this drug must be done at least once yearly and for between 10 - 15 years, as ivermectin only kills the microfilariae. Alternative approaches to disease detection are based on amplification of parasitic DNA in skin biopsies to detect the O - 150 repeat sequence using PCR based techniques [4], or on the use of metabolome analysis of serum or urine samples from infected individuals, to identify urinary N-acetyltyramine-O,β-glucuronide (NATOG) as a unique biomarker for *O. volvulus* infection [5]. Immunological diagnosis of onchocerciasis can be based on the application to the skin of OCP-DEC or DEC (LTS-2 patch) patches that cause a small skin reaction in infected patients; both have similar safety, tolerability and capabilities [6]. Another approach for immune diagnosis is based on detection of IgG4 antibodies specific for parasite antigens (anti-Ov16 IgG4). As confirmed in other countries, immunological diagnosis with anti-Ov16 IgG4 is more sensitive than detection of nodules by palpation and it has been successfully used to evaluate the community drug treatment with ivermectin (CDTI) impact [7].

In this review, we aim to analyse and discuss existing data about onchocerciasis in Mozambique, and its possible misdiagnosis as either leprosy or scabies. We also aim to discuss the possible implications of onchocerciasis infection as an etiological agent of epilepsy in some rural and hard to reach communities in Mozambique.

Methods

We carried out a systematic literature review from the databases Google Scholar and MEDLINE/PubMed and also from the Mozambique Ministry of Health Documentation Centre to access existing data on onchocerciasis in Mozambique, as well as, its clinical features and disease control strategies.

We also reviewed and analysed historical, epidemiological and clinical data on onchocerciasis in Africa and Americas and other morbidities, namely leprosy, scabies and epilepsy.

The terms used were onchocerciasis or river blindness disease, epilepsy, leprosy and scabies written either in English or Portuguese. We preselected the potentially relevant articles based on the title and information on the abstract.

Papers with information that was not directly related to the searching words were excluded. We than screened other references from the relevant publications that were not initially retrieved from the databases and stored all references in an EndNote X8 database.

Results and Discussion

Historical notes about onchocerciasis with special emphasis on Mozambique

The first description of human onchocerciasis was made by O´Neill in 1875, who found its microfilariae in the skin of an African patient suffering from a disease traditionally named "craw craw". In 1893, Leuckart found adult worms in subcutaneous nodules extracted from two patients in Ghana. In the Americas, onchocerciasis was described in 1915 by Robles. In 1916 it was discovered that the vectors of this disease were the *Simuliidae* (*Simulium* spp.), traditionally called blackflies.

Ocular manifestations of onchocerciasis were first studied by an ophthalmologist (Pacheco-Luna) in Guatemala in 1918. In 1930, Hissette, a Belgian ophthalmologist, studied numerous patients in the ancient Belgian Congo, noticing the signs of interstitial keratitis, band keratopathy, iritis, posterior synechiae, and often a downward distortion of the pupil. He also described chorioretinal scarring of the fundus, in what became known as the Hissette-Ridley fundus [8].

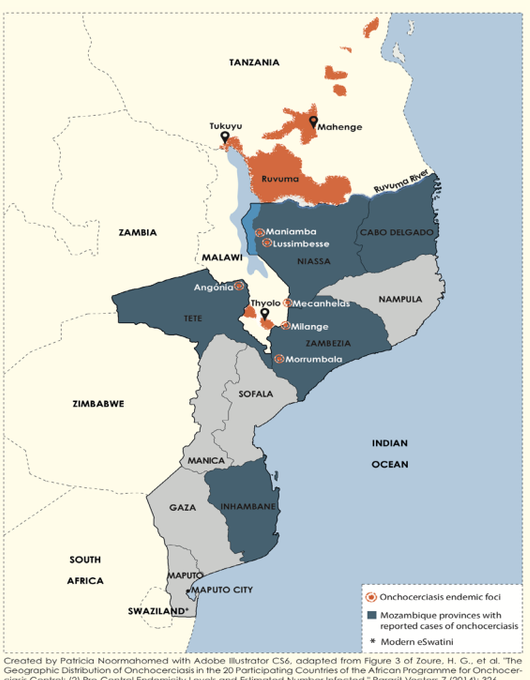
It is accepted that onchocerciasis existed in Africa since time immemorial, and further that it was brought to the Americas with the slave trade in the 16th century, transmitted by local blackflies and expanding via the migration of people to Ecuador, Colombia, Guatemala, Mexico and Northern Venezuela [9].

The American species of *Simulium* are not as effective at transmitting the disease as the African *S. damnosum* complex, thereby limiting expansion geographically. This could explain why onchocerciasis did not expand as fully on the American continent, and only became established endemically in restricted areas [9].

When Parasitology books began to be published for the first time at the beginning of the twentieth century, the limits of onchocerciasis were already drawn, placing the eastern limit in Nyasaland (modern-day Malawi). However, the borders of Mozambique have arbitrarily been modified over time. Moreover, with endemic foci in its neigbouring countries, Thyolo in Malawi and Ruvuma in Tanzania (See figure 1), it would be expected that Simuliidae could fly across borders and transmit onchocerciasis in Mozambique [10]. Thus, the first sampling to assess whether the disease exists in the country took place in 1997 and was sponsored by TDR-WHO.

Chronology

1997: The first study that sought to determine whether there were individuals affected by onchocerciasis in Mozambique was conducted in the Milange District, Zambezia province (See figure 1).



Created by Patricia Noormahomed with Adobe Illustrator CS6, adapted from Figure 3 of Zoure, H. G., et al. "The Geographic Distribution of Onchocerciasis in the 20 Participating Countries of the African Programme for Onchocerciasis Control: (2) Pre-Control Endemicity Levels and Estimated Number Infected." Parasit Vectors 7 (2014): 326.

The district borders Malawi along the Muloza River for 233 km, which was known to be a breeding site for *Simulium* spp. The overall prevalence of onchocerciasis, as assessed by examination of skin snips from 316 people, was 14%. Three of these individuals had never been in Malawi. Thus, the existence of infection by *O. volvulus* was confirmed, including autochthonous cases [3].

1998: A second study that aimed to clarify the variability in clinical presentations of onchocerciasis, and differences related to epidemiological and parasitological findings, took place in Milange and Mecanhelas districts (Niassa province) (see figure 1). In six villages, 370 persons were screened of whom 141 (38.1%) were not refugees. Nodule palpation showed that 120 (32.4%) of them had palpable onchocercomas, 196 (53%) were positive for *O. volvulus* microfilariae by skin biopsy, and 102 (27.5%) had visual alterations [3].

2001: REMO 1 was conducted in all provinces of Mozambique, other than Maputo and Gaza (See figure 1) located in south of the country, to assess the distribution and endemicity level of onchocerciasis in Mozambique. *O. volvulus* cases were found in Niassa, Cabo Delgado, Zambezia, Tete, and Inhambane provinces (see figure 1). Only 50 of the 7,270 persons examined showed nodules, and it was concluded that positive cases identified in Zambezia may have come from Malawi foci, whereas the Niassa focus could be independent and required further investigation [11].

2007: REMO 2 was conducted only in provinces where REMO 1 had found infected people except for Inhambane, namely Niassa, Cabo Delgado, Zambezia and Tete provinces. The aim of REMO 2 was to re-evaluate the status of the disease in relation to the findings of 2001. In REMO 2, 61 (1.6%) of 3,780 people showed nodules by palpation, leading to the conclusion that although onchocerciasis exists in Mozambique, it is hypoendemic [12]. However, the authors highlighted that "The nearest known foci of onchocerciasis in Mozambique are Thyolo and Ruvuma, in Malawi and Tanzania respectively [12] (See figure 1).

2015: The African Programme for Onchocerciasis Control (APOC) Record indicates: "The border between the two countries follows a river that probably contains breeding sites, as evidenced by the endemic villages on the right bank of the river in Malawi. The nodule prevalence contour just across the border in Mozambique is greater than 20% but there are no REMO villages in this area. The nearest REMO villages in Mozambique are located at > 30 km from the border but these had a very low or zero nodule prevalence. The available data suggest that just across the border in Mozambique there probably exists a small area with endemic onchocerciasis. Indeed, according to anecdotal reports, people from across the border in Mozambique cross the river every year to obtain ivermectin treatment in the villages in Malawi" [13].

In one of the maps of this report, one area of Mozambique near Malawi coincides with Milange where studies in 1997 and 1998 found a high rate of microfilaremia.

To date, onchocerciasis has not been re-examined in Mozambique since 2007, and the distribution and prevalence of the disease is still unknown, although the country has been considered hypoendemic for onchocerciasis.

The special circumstances of the country can partially explain this situation. After Mozambique gained independence from Portugal in 1975, the country went through 16 years of debilitating civil war (1976 - 1992) with destruction of the country's health services and leading to migration of about 1.5 million Mozambicans to neighbouring countries, including Tanzania and Malawi, where onchocerciasis foci exist [14]. The subsequent peace agreement in 1992 allowed 1,058,500 and 75,200 refugees from Malawi and Tanzania, respectively, to return. Furthermore, the country is home to refugees from the Democratic Republic of Congo, Burundi, Rwanda and Somalia, most of whom live in the Maratane Camp in Nampula Province [14-16]. So, this great mobility of the population within and outside the country, may have contributed to the spread of the disease given the existence of infected people as a source of disease, and the vectors that could potentially transmit it [2].

Furthermore, recommendations on the urgency of epidemiological studies of onchocerciasis in the country made by the REMO exercises [11,12], APOC Report 2015 [13] and also by United to Combat NTDS [17] and Envision [18] have been neglected. Potential investigations into, and implementation of, disease control in Niassa (between Maniamba and Lussimbesse), or the border of Zambezia with southern Malawi (Morrumbala villages located near the Shire river, and Milange district), are also needed, as these places could constitute foci of disease transmission. The non-compliance with previously mentioned recommendations could possibly be due to limited financial resources and lack of skilled human resources to carry out clinical, epidemiological, parasitological and entomological research [3]. The integrated mass drug administration (MDA) (ivermectin and albendazol for LF), initiated in Mozambique in 2009, covers 10.3% of the population that required treatment. In this remarkable effort, the population treated for LF has increased from 1.6 million in 2009 to 15.7 million in 2017 (See Table 1).

Year	Requiring PC for LF	Treated	Coverage
2009	15,538,610	1,607,688	10.3%
2010	17,118,460	3,739,881	21.8%
2011	17,114,949	8,496,428	49.6%
2013	17,726,780	11,467,739	64%
2014	18,218,250	13,976,842	76.7%
2016	28,180,229	14,915,255	73.9%
2017	19,762,613	15,799,350	79.9%

Table 1: *Preventive Chemotherapy (PC) against Lymphatic filariasis (LF) in Mozambique (data extracted from http://www.who.int/neglected_diseases/preventive_chemotherapy/lf/en/).*

In districts that are already under surveillance, both lymphatic filariasis and onchocerciasis should be assessed in order to measure the impact of MDA.

There are some regions (46 districts) located in the provinces of Niassa, Tete, Manica, Sofala, Gaza and Inhambane where there is non-coincidence of areas endemic for LF with those of onchocerciasis. This is the case for the endemic focus between Maniamba and Lussimbesse in Niassa Province (See figure 1) indicated in REMO 2 [12].

Although some countries report success in controlling onchocerciasis through CDTI, the effectiveness of the annual ivermectin treatment against onchocerciasis has been questioned in other countries, such as Tanzania. This, even after almost 20 years of annual CDTI, the infection rate of *S. damnosum* sl. in this country is now similar to that of the 1960s, and transmission is continuing in the southeast of Tanzania [19].

Onchocerciasis and other morbidities: leprosy and scabies

Onchocerciasis dermatitis can be severe in hypoendemic areas, leading to skin depigmentation that can mimic lepromatous leprosy, despite the fact that clinical characteristics of onchocerciasis, such as preserved skin sensitivity, may be at odds with findings of a loss of sensitivity in leprosy. Health professionals are unaware of onchocerciasis. Efforts to eliminate leprosy in Mozambique are hampered by the resurgence of the disease in Cabo Delgado, Nampula and Zambezia provinces, where more than 70 percent of new cases were found, ranking the country fourth amongst those most affected by leprosy on a global level [20]. We do not exclude the possibility of some of these cases of leprosy have been misdiagnosed, and are actually onchocerciasis.

A similar situation happens with the pruritic dermatitis of onchocerciasis that may be confused with scabies. In fact, some misdiagnosed cases of onchocerciasis did not improve for years, despite having been treated either for leprosy or for scabies. In the studies of Noormahomed [3] after skin biopsy was performed, some of these patients were found to be positive for *O. volvulus* microfilaria. Thus, a fraction of leprosy and scabies patients may in fact be unrecognized cases of onchocerciasis.

We have few data on the prevalence of scabies in Mozambique but in a study of dermatological conditions in a poor neighbourhood of Beira (in Sofala province located in the central region of Mozambique) scabies was so common (35%) that people consider it as something normal in life [21].

So, patients without well-defined signs and symptoms of leprosy and/or dermatitis, or not showing acceptable treatment responses for leprosy or scabies, should be subjected to a skin biopsy test for *O. volvulus* microfilariae, or screened using anti-Ov16 IgG4 to search for parasite antigens. This will in turn allow a better understanding of the possible role of onchocerciasis in this population.

Association between onchocerciasis, epilepsy and nodding (Nakalanga) syndrome (NS)

In the 1960s, L. Jilek-Aall working in Mahenge, Tanzania, an endemic focus for onchocerciasis but also with a high prevalence of epilepsy, identified an association of many cases of onchocerciasis with epilepsy and founded the Mahenge Epilepsy Clinic [22].

Later, an association of onchocerciasis with epilepsy was also suggested in other African countries. In 2009, a meta-analysis of data from seven countries, including 79,270 individuals from 91 communities, concluded that this association exists [23]. A study in Democratic Republic of the Congo also found that the prevalence of epilepsy in areas endemic for onchocerciasis was 2 - 10 times higher

than in non-endemic regions, and the peak incidence was at around the age of 12 years [24]. In fact, several recent epidemiological studies performed in *O. volvulus* endemic regions in Uganda, South Sudan and Tanzania suggested that nodding and Nakalanga syndromes, epidemic epileptic encephalopathies affecting thousands of children aged 5 to 15 years, should probably be considered as a subset of onchocerciasis-associated epilepsy (OAE) [25]. Although the exact pathophysiological mechanism of OAE remains unknown, there is increasing epidemiological evidence that by eliminating *O. volvulus* infection, these forms of epilepsy will disappear [26]. Mozambique is among the countries with the highest rates of epilepsy (3%) in the general population worldwide, with rural and poor regions having the highest prevalence. This condition constitutes one of the leading causes of demand for psychiatric services and neurological consultations throughout the country.

Data obtained from The Program to Reduce the Gap in the Treatment of Epilepsy in Mozambique, which began in 2014 [27], show that there is an overlap of epilepsy distribution in Mozambique with some of the provinces where onchocerciasis has been identified. Furthermore, about 64% of new cases of epilepsy in Mozambique are seen in individuals under the age of 18 years old, and only 2% of registered cases are in people over 60 years old [28]. This raises the concern of whether onchocerciasis infections are involved in the etiology of epileptic seizures and epilepsy, in addition to other parasitic diseases such as neurocysticercosis and toxocariasis that are also known to be endemic in the country [29,30]. It also can explain the differences in the age distribution of epilepsy prevalence between low income countries and developed countries, where epilepsy is more commons at the two extremes of life [31].

Data regarding other parasitic diseases that can cause epilepsy or epileptic seizures are also scarce. In a study in the Angónia district of Tete province (See figure 1), the prevalence of epilepsy in the community was 15% while the antigen Enzyme-Linked Immunosorbent Assay (Ag-ELISA) for cysticercosis was 14% [32].

Given that patients with onchocerciasis, leprosy, scabies and epilepsy are stigmatized and marginalized, it is likely that most of them remain within the community and do not seek health care. In addition to the stigma and marginalization, these patients suffer from sexual and labour rejection and have fewer opportunities for education, employment and marriage [33-35]. Studies on the societal, mental and economic effects of onchocerciasis, epilepsy, leprosy, and other poverty-related diseases such as neurocysticercosis, toxocariasis and scabies are greatly needed so that appropriate prevention, treatment and control measures can be taken. Educational measures to increase awareness in communities and amongst health professionals about these diseases and their manifestations also deserve special attention.

Conclusion

Although there are now enough data to conclude definitively that onchocerciasis exists in Mozambique, it's extent is unknown and it is often neither diagnosed nor treated. Assessment of the extent of disease in the country using anti-Ov16 IgG4 or skin biopsies (which may be less patient-friendly), should be done as soon as possible, especially in the regions mentioned in the last APOC report (Morrumbala, Milange), and in those villages where onchocerciasis has been reported.

In countries like Mozambique where onchocerciasis exists, it is also important to train health professionals to recognize the clinical and parasitological manifestations of the disease, emphasizing aspects that can lead to misdiagnosis as conditions such as scabies or leprosy.

It is equally important to carry out studies aimed at assessing the possible implication of *O. volvulus* in the etiology of epilepsy in regions suspected to have cases of onchocerciasis, as has been described in other countries endemic for onchocerciasis.

Given the existence in Mozambique of *Simuliidae* vectors, it is mandatory to perform entomological studies at least in the Cabo Delgado, Niassa, Zambezia Tete, Manica, Inhambane and even Nampula regions of Mozambique to assess the vectorial and transmission capacity of local blackflies, as well as their breeding sites.

In addition, multi- and transdisciplinary social studies should be carried out in order to access the real impact of onchocerciasis and the occurrence and impact of co-morbidities between this and other poverty-related diseases in affected patients.

Acknowledgement

The manuscript writing and publication was supported by Fogarty International Center, Office of the Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development and National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number D43TW010135. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Fogarty International Center or the National Institutes of Health. Furthermore, we are thankful to Professor Kim Barret distinguished Professor of Medicine from University of California San, USA for revising and editing this manuscript.

Conflict of Interest

Authors declare no conflict of interests.

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