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Research Article

Multiple Parasitic Infections as Risk Factors of Active Convulsive Epilepsy

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Abstract: The main objective of the study was to investigate the prevalence of parasitic infections and the association between these parasitic infections and the development of active convulsive epilepsy (ACE) in Ifakara district of Tanzania. Results from the tests for detection of the parasitic infections were analysed statistically by logistic regression to determine statistical odds ratio with a P value of ≤ 0.05 being considered significant. Logistic regression was also used to model the association between parasitic infections' antibody titres and ACE as well as the relative risk of interaction on multiple parasitic infections. Out of the 528 participants the prevalence of the parasitic infections under investigation was; Cysticercosis (17.1/1000), Toxoplasmosis (687.5/1000), Toxocariasis (341/1000), Onchocerciasis (316.3/1000) and *Plasmodium falciparum* infection (969.7/1000). The findings showed an increase in antibody levels with age in both cases and controls for *O. volvulus*, *T. canis*, *T. gondii* and *P. falciparum*. It was established that significant associations with ACE included exposure to *O. volvulus*, exposure to either larval or adult stages of *T. solium* in Ifakara, exposure to *T. canis*in Ifakara, *T. gondii* in Ifakara. ACE was associated with high antibody levels to *O. volvulus*, *T. canis* and *T. gondii* whereby high antibody levels were significantly associated with increased prevalence of ACE for *O. volvulus*, *T. canis* and *T. gondii*. For *T. canis, O. volvulus* and *T. gondii* the OR were greater than estimated for the seropositivity outcome.
Keywords: epilepsy, *Plasmodium falciparum* , Toxocariasis , Cysticercosis

INTRODUCTION

Epilepsy is a medical condition characterized by recurrent seizures unprovoked by any immediate identifiable cause [1]. The condition is more prevalent in Africa especially in sub-Saharan Africa (SSA) than in the Western countries with a proportion of 5-74/1000 in sub-Saharan Africa compared to 4-7/1000 in the west [2]. In SSA, high prevalence of epilepsy is recorded in children under the age of 15 years but is much lower in people above 45 years [3] [4]. Specific parasitic infections contribute notably to increased prevalence of epilepsy with diseases like neurocysticercosis being one of the major risk factors of epilepsy in South America [5].

Many preventable epileptogenic factors exist in SSA with causes of newly diagnosed epilepsy in these developing countries being often preventable [6]. Countries like South Africa have recorded high prevalence of epilepsy, which has been associated with an over 20% prevalence of *Taeniasolium* [7]. *Taeniasolium* infection is occasioned by a complex life cycle, which involves pigs as the intermediate host and man as the only definitive host [8]. Humans acquire infection through ingestion of taenid eggs, which migrate through the intestinal mucosa in form of larvae. Eventually the larvae encyst in various visceral organs especially the muscle tissues in form of cysticerci, which on manifestation in the brain causes neurocysticercosis [9].

Other parasitic infections commonly associated with epilepsy include; onchocerciasis, toxocariasis, toxoplasmosis and cerebral malaria. Onchocerciasis is a parasitic infection found across Africa and Latin America where it causes dermatological problems and in severe cases can result in blindness [10]. The plausibility of onchocerciasis causing seizures has always been in questions with previous surveys, but not all, suggested causal relationship existed between onchocerciasis infection and epilepsy. A study from southwestern Burundi carried out on 103 patientscompared with controls with high sero-prevalence for cysticercal antibodies with onchocerciasis-associated epilepsy indicated a possible association between onchocercosis and epilepsy (11.7%

versus 2.8%; p=0.06) [11]. Toxocariasis and toxoplasmosis protozoan parasitic infections have also shown weak to strong association with epilepsy [12-14].

Although not fully elucidated, severe *falciparum* malaria has been linked with epilepsy especially in children under the age of five [15]. The burden of HIV in SSA is enormous with the HIV virus predisposing its victim to opportunistic parasitic infections due to depletion of CD4 cells, which are responsible for pathogen clearance. With recent studies indicating HIV as a possible cause of epilepsy, the disease also plays a major role as a compounding factor on parasitic infections associated with epilepsy [16].

Epilepsy is a treatable condition [17], but in SSA the treatment has not been achieved due to lack of identification of the condition, cost of getting to the clinics and the beliefs about the causes of epilepsy. This is despite the fact that anti-epileptic drugs, with the drug of choice "Phenobarbital" the first line drug costing about $10 US dollars for a year's treatment [18]. In East Africa, treatment is not sustainable because of the ineffective drugs used, reliance on community health workers as well as lack of engagement between the healthcare providers and the community [19]. The treatment gap has been widened especially in resource-poor countries by factors like; failure of diagnosis, beliefs and attitudes, lack of access to anti-epileptic drugs, poor adherence and stigmatization of people with epilepsy [20].

METHODOLOGY

A case-control design in which the cases were matched on age and sex was used. The blinded serum samples were tested for antibodies to malaria, onchocercosis, toxopasmosis, toxocariasis and cysticercosis by enzyme linked immunosorbent assay (ELISA) and western blotting. An ELISA reader at 450 nm determined optical densities on antibody titres to various parasitic diseases in the serum samples while immunoblotting strips were used to test for *Taeniasolium* and cysticercosis antibodies. Serum samples were drawn from identified individuals through a case controlled design within the human demographic surveillance system in which a total sample size of 600 individuals (cases and controls)within Ifakara district were targeted. The matching was planned on the basis of 1:1 for the cases and controls. A sample size of 300 cases and 228 controls were eventually chosen to give 80% power to detect an odds ratio (OR) > 2.8 (5% significance level) given a frequency of the risk factor at least 5% in the controls. For each case, an age-matched control was selected at random from a database of individuals in the human demographic surveillance system (HDSS). The controls were frequency matched using the age bands 0-5, 6-12, 13-18, 19-28, 29-49 and 50+ years, to account for increasing exposure with age. These were individuals within the INDEPTH network active demographic surveillance system.

RESULTS

All 528 participants were successfully included in the study. The social demographic information was as tabulated below;

Table 1: Demographic characteristics of cases and controls

	Age category	Ifakara, Tanzania	
		Control (%) (N= 251)	Case (%) (N= 277)
Age categories in years	0-5	25	27
	6-12	36	41
	13-18	62	63
	19-28	37	39
	29-49	64	66
	50+	27	41
Sex	Male	123	136
	Female	128	141

Out of the 528 participants, 277 were diagnosed as having active convulsive epilepsy with 251 being community controls. This set of individuals in the study had consistency in key parameters at an accuracy of $P < 0.05$.

In Ifakara, positive cases for the various parasitic infections within the exposure groups were; Neurocysticercosis 9 cases, Toxoplasmosishad 363 cases, Toxocariosis 180 cases, Onchocerciasis 167 cases while *Plasmodium falciparum* positive cases were 512 respectively.

The number of cases to the various parasitic infections under investigation is shown in figure 1 below;

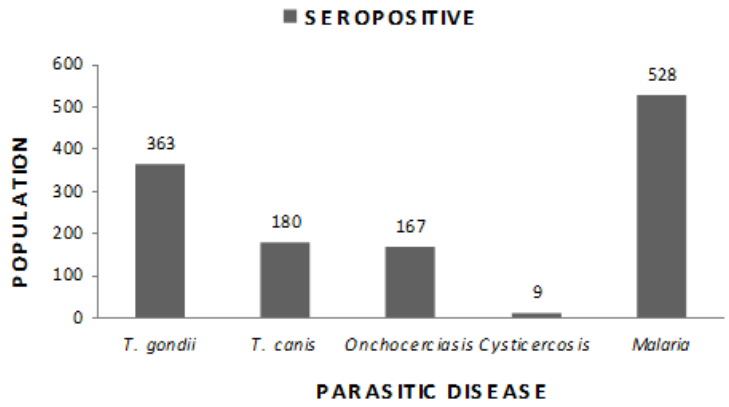

Fig. 1: Number of positive cases for the parasitic infections in Ifakara

On the prevalence of the parasitic infections under investigation, highest prevalence was observed in malaria cases while the least population were positive for cysticercosis.

Table 2: Prevalence of parasitic infections and epilepsy

	Ifakara		
	No. of cases	**Prevalence**	**Proportion of cases with epilepsy who have infection**
Epilepsy	277	0.52	-
T. gondii	363	0.69	0.42
T. canis	180	0.34	0.68
Onchocerciasis	167	0.31	0.69
Cysticercosis	9	0.02	0.78
Malaria	528	0.97	0.51

Cysticercosis

From the deductions of the Ifakara samples, 9 cases positive for cysticercosis were obtained, giving a prevalence of 17.1/1000. Out of the nine, only two were negative for epilepsy therefore 7 of the cysticercosis positive cases had epilepsy as opposed to the two who had not had cysticerca infections.

Onchocercosis

The prevalence of onchocercosis in Ifakara on the sample assayed for onchocerca antibodies in serum was 167 individuals hence a prevalence of 316.3/1000. The prevalence showed high antibody titres in older people compared to children with individuals aged between 19 and 49 years showing highest prevalence in both epileptic and non-epileptic groups (Fig. 2).

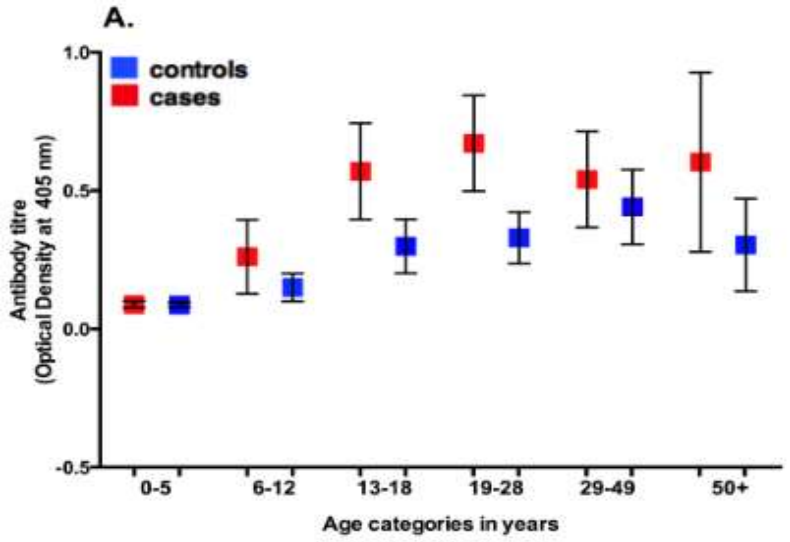

Fig. 2: Highest prevalence in both epileptic and non-epileptic groups

Exposure to multiple infections and prevalence of ACE

A total of 76.1% of cases and 61.4% of controls tested for exposure to all five infections had evidence of exposure to two or more infections. A high proportion of individuals were exposed to both *O. volvulus* and *P. Falciparum* (36%), *T. canis* and *P. Falciparum* (31%) and exposure to *T. gondii* and *P. falciparum* occurred in 41% of the study population. The remaining combinations occurred in less than 10 % of individuals. Multiple infections have an additive or negative value towards development of ACE.

Interactions between exposures to multiple parasites

From the findings there was evidence of interaction which was additive to exposing individuals to various parasitic infections with positive relative excessive risk due to interaction of the parasitic infections. A Positive RERI adjusted for age, sex, indicates that the combined effect of the two parasites is greater than the sum of the individual effects with a negative RERI indicating lower effect of the combined parasites infections.

With the exception of exposure to *T. solium* (OR=0.85; 95%CI: 0.16-4.51, p=0.845), exposure to multiple infectious agents was associated with an increased prevalence of ACE after adjusting for age with the majority remaining statistically significant. There was evidence of interaction on an additive scale in individuals exposed to *T. canis* and *T. gondii* (RERI=0.57 95% CI: 0.05-1.17, p=0.041) and to *T. gondii* and *O. volvulus* (RERI=1.22; 95% CI: 0.36-2.07, p=0.005) which implies that the combined effect of these parasites is greater than the sum of the individual effects. Interaction could not be determined for *O. volvulus* and *P. falciparum* co-infection and *T. solium* and *P. falciparum* co-infections as all cases of ACE with exposure to either *O. volvulus* or *T. solium* were exposed to *P. falciparum.*

Table 4: Analysis of the association between exposure to multiple infections and risk of ACE determined by logistic regress

Exposure to multiple infections	Relative excess risk due to interaction (RERI)	p-value
Toxocaracanis + Toxoplasma gondii	0.57 (0.05-1.17)	0.041
Toxocaracanis + Onchocerca volvulus	-0.13 (-1.16-0.89)	0.800
Toxocaracanis + Plasmodium falciparum	0.20 (-0.62-1.02)	0.638
Toxoplasma gondii + Onchocerca volvulus	1.22 (0.36-2.07)	0.005
Toxoplasma gondii + Plasmodium falciparum	0.23 (-0.49-0.96)	0.53
Onchocerca volvulus + Taeniasolium	1.52 (-2.27-5.32)	0.432

DISCUSSION

People living in SSA are exposed to multiple parasites, some of which are associated with epilepsy [21]. There is limited data on the prevalence of the various parasitic infections in SSA emanating from neglect and the rural setting in this place. In Ifakara there is a high prevalence in most of the parasitic infections under investigation given the duplicity of lifestyle, consistency of prevailing environmental conditions and the disregard for general hygiene within the general population.

The results indicate a high prevalence of all the parasitic infections with *falciparum* malaria in particular being the most prevalent given the tropical climate which favours vector breeding with a prevalence of 970/1000. Despite previous association between individuals admitted with cerebral malaria and their seizure frequencies being established [22], it was not clear from the findings on the outcome of the relationship given that the experimental set up did not include admission with cerebral malaria, which determines the relationship between seizure and cerebral malaria.

In this site the population has a close relationship with animals with some families sleeping under the same roof with pigs and thereby predisposition to cysticerci. Cysticercosis has shown significant association with epilepsy thereby showing that cysticercosis does raise the risk towards development of active convulsive epilepsy especially in endemic areas. The prevalence of antibodies increased with age in both cases and controls for *O. volvulus, T. gondii* and *P. falciparum, T. canis* (Fig. 1-4). Antibody prevalence to *T. solium* was low in the samples analysed. It showed a prevalence of 17.04/1000 and showed no trend with age.

With the close association of epilepsy with infections of the central nervous infection, there is limited data associating the various parasitic infections with the condition. Previous studies though have showed strong association between cysticercosis and ACE [23]. The point of infection is critical in predicting the epilepsy dynamics across all age sets. Despite the strong association, there can also be people who have anticysticercal antibodies but test negative for ACE, the same has been depicted in previous studies [24].

A total of 363 individuals were confirmed to have anti-toxoplasmosis antibodies presenting a prevalence of 687.5/1000. The odds ratio predicted a strong association between *Toxoplasma gondii* and active convulsive epilepsy. High contact with contaminated soil could be a major contributing factor

towards the high *Toxoplasma gondii* infections in this area [25].

Among the earliest studies, showing relationship between toxocariasis and epilepsy was that documented in 1951 by Beautyman and Woolf [26]. With embryonated eggs hatching into larvae, the larvae are believed to migrate through the circulatory system into various body organs including the thalamus accompanied with excretion of toxins associated with toxocara symptomatology [27]. In this study, it was found that toxocara prevalence was high and this was majorly attributed to the close association between the people in this area and their pets. With 34.1% of the total population screened positive for toxocariasis, this was in line with previous projections within sub-Saharan Africa. In relation to epilepsy a statistical odds ratio of 2.15 at $p<0.001$ shows a significant relationship between epilepsy and Toxocariasis. Previous studies have been in agreement with these findings [28]. By 2003, 50 patients had been documented as indeed showing toxocara species involvement in CNS activity with experimental animals depicting larval migration to the brain [29].

High antibody titres against individual parasites were associated with an increased prevalence of ACE as opposed to seropositivity alone. There was a clear trend of increased prevalence of ACE with higher levels of antibodies and the association was stronger compared to estimates based on seropositivity for *O. volvulus, T. Canis* and *T. gondii.* Elevated antibody responses could reflect recent or current infection or could serve as a proxy for estimating the level or degree of exposure as antibody levels would be elevated due to repeated infections. The association between high antibody levels against these parasites and an increased prevalence of ACE, in the study site, could be due to higher levels of exposure/repeated exposure.

Previous studies reporting the association between parasitic infection and epilepsy is based on evidence of exposure defined as seropositivity with none taking into account the degree of exposure as a predictor for risk of ACE [30]. This may explain previously conflicting results, such as the increased prevalence of epilepsy with exposure to *T. canis* in Burundi [31].

With the exception of cysticercosis, the epileptogenesis of parasitic infections is often not clear [32]. Neurocysticercosis is a well-known risk factor for epilepsy in South America and has been identified as a risk factor in few studies in Africa [33]. In this study, the prevalence of antibodies to *T. solium* was low. In Ifakara Tanzania, the main agricultural activities include subsistence farming of maize, rice and cassava and fishing is their main source of income [34]. The main inhabitants of Ifakara are both Christians and Muslims and it is likely that pork consumption is low among the Muslim inhabitants. In addition, the low sensitivity of the detection assay in identifying single viable cysts, calcified cysts or degenerating cysts that could be epileptogenic and possibly the lack of the statistical power to detect an association due to a low prevalence of *T. solium* antibodies.

In addition, exposure to multiple infectious agents was associated with an increased prevalence of ACE and the combined effect is often greater than the sum of the individual effects. Although studies have analysed exposure to two parasites such as cysticercosis and toxocariasis or three parasites, there is no report on the risk of epilepsy associated with exposure to multiple infections. The findings depicted conflicting findings whereby some parasitic infections which otherwise show strong association with epilepsy on interaction were found not to be having any relationship with the condition [35, 36]. This study on the other hand provides evidence of interaction for an additive model on co-infection as illustrated in Table 4.

The evidence of interaction on an additive scale in individuals exposed to *T. canis* and *T. gondii* and to *T. gondii* and *O. volvulus* may be explained by the predominant immune responses induced by the different infections. Cysts containing *T. Gondii*bradyzoites rupture in immuno-compromised individuals, which may result in focal lesions in the brain resulting in inflammation of the surrounding tissue leading to epilepsy. Interferon gamma (IFNy), a Th1 response is pro-inflammatory, thought to result in parasite destruction, and has been shown to be essential for controlling *T. Gondii*tachyzoite proliferation as well as maintenance of latency in chronic infections [37]. The Th2 responses that have been shown to dominate in chronic filarial infections such as *Brugiamalayi*(in a murine model) and *O. volvulus* tends to suppress the Th1 responses [38].

In addition, *Toxocara* larvae secrete and excrete products that are highly immunogenic and promote a Th2 type cellular immune responses characterised by interleukin 4 and 5 in humans. As such, a possible scenario would be that individuals with chronic *O. volvulus* infection and co-infected with *T. gondii* or chronic *T. canis* infection and co-infected with *T. gondii*, may be unable to mount an adequate protective response resulting in increased severity of disease such as the rupture of cysts containing *T. gondii* that are then epileptogenic [39].

CONCLUSION

In conclusion, the study shows that the degree of exposure and multiple parasitic infections are associated with increased prevalence of ACE. The limited data on epilepsy prevalence and its implication on overall wellbeing in society have far-reaching ramifications**.** Apart from research by WHO and ILAE, research towards this end has been limited especially in

developing economies. In this study, there is relatively high prevalence of parasitic infections in Ifakara, Tanzania. These findings can be attributed to consistence in risk factors which include; cultural orientation, interaction with domestic animals and high poverty levels. The strong association between some of these parasitic infections under investigation and active convulsive epilepsy therefore calls for constitution of programmes aimed at controlling parasitic infections hence subsequent reduction in the prevalence of ACE.

These results will advise policy implementation on the role of parasitic infections as causes of epilepsy in sub-Saharan Africa and more so in Tanzania since efforts to control these infections are likely to reduce the burden of epilepsy in SSA. Efforts to control parasitic infections to reduce the burden of epilepsy in sub-Saharan Africa should target as many of the putative parasites as possible. These control measures should be explored and their contribution to the burden of ACE evaluated. If there are proper measures against predisposing parasitic infections, there could be a significant drop in epilepsy cases in affected individuals through reduction in the population attributable fraction.

In Ifakara if multiple parasitic infections can be eliminated then a population attributable fraction of 20% could be achieved. Other causes of epilepsy including poor obstetric practices, head injury accounts for significant cases especially in developed countries hence researchers should explore these causes for significant reduction or elimination of epilepsy. Efforts to control these infections are likely to reduce the burden of epilepsy in SSA. Control is possible with ivermectin for individual and mass-treatment of onchocerciasis, niclosamide for treatment of taeniasis as well as albendazole or praziquantel for treatment of parasitic cysts such as in *T. solium* and *T. canis* infection.

In addition, efforts to improve sanitation and personal hygiene practices that include safe food consumption practices will reduce transmission of *T. canis*, *T. gondii* and *T. Solium* infections. Safe pig rearing practices will reduce the impact on *T. Solium* transmission. Vector control measures as well as bed net usage, intermittent preventative treatment and effective chemotherapy are available for controlling *P. falciparum* infection [40]. These control measures should be explored and their contribution to the burden of ACE evaluated [41].

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