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EC MICROBIOLOGY
Case Series

Neurocysticercosis in Epileptic Children: An Overlooked Condition in Mozambique, Challenges in Diagnosis, Management and Research Priorities

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Received: February 18, 2021; **Published:** May 29, 2021

Abstract

Previous studies suggest that neurocysticercosis (NCC), the most common cause of acute symptomatic seizures (ASS), epilepsy and other neuropsychiatric disorders, typically presents with a solitary lesion and focal seizures in children from places where cysticercosis is endemic.

We report a series of 3 patients, aged 7 to 11 years, with a history of epilepsy and or recurrent headache referred from Mocuba to the Quaternary Central Hospital in Quelimane, Zambeze Province, Mozambique, an area endemic for cysticercosis. Clinical history and examination, blood chemistry and hemogram screening, serological testing for Cysticercus antigens and antibodies detection, and a computerized tomography (CT) scan, were performed. NCC was confirmed in all 3 patients, based on criteria defined by Del Bruto. Two confirmed cases tested positive for antigen (Ag) by enzyme-linked immunosorbent assay (ELISA) with CT lesions in different stages of parasite evolution. Headache/encephalopathy was present in all patients. This case series of children with epilepsy confirms for the first time the presence of NCC in children from Zambezia province, an east-central region of Mozambique. Further, NCC should be included in the differential diagnosis of children with ASS, epilepsy and other neuropsychiatric disorders. Future studies should be targeted to the identification of biomarkers to support the diagnosis of NCC, given the limited availability of imaging tools and limited value of serological assays for the diagnosis and management of NCC.

Keywords: *Cysticercosis; Epileptic Seizures, Neuropsychiatric Disorders; Neurological Disorders; Cysticercus Encephalopathy; Central Nervous System Parasites*

Abbreviations

Ag: Antigen; ASS: Acute Symptomatic Seizures; CNS: Central Nervous System; CT: Computerized Tomography; ELISA: Enzyme-Linked Immunosorbent Assay; GTCS: Generalized Tonic Clonic Seizures; HIV: Human Immunodeficiency Virus; NCC: Neurocysticercosis; MRI: Magnetic Resonance Imaging

Introduction

Neurocysticercosis (NCC), a poverty related disease of the central nervous system (CNS) caused by the larvae of *Taenia solium*, is considered the main preventable cause of acute symptomatic seizures (ASS) in children and late onset epilepsy in young adults from countries where cysticercosis is endemic [1-9]. In the last decades it is emerging in eastern and southern African countries especially in rural smallholder communities, primarily due to the increase in pig production and consumption of infected meat [10]. However, with increased globalization and migration from endemic countries to developed countries, NCC is also becoming an emerging health problem that sometimes is underdiagnosed even in places like the United States, United Kingdom and Australia [4,8,9,11,12]. According to the International League Against Epilepsy (ILAE) ASS are seizures that occur within one week after a systemic insult or in close temporal association with a documented brain insult, while epilepsy is a chronic brain disorder where the individual experiences at least two unprovoked (or reflex) seizures occurring > 24 hours apart [13].

NCC can be asymptomatic for years, and when symptomatic, epileptic seizures are the most common presentation in 80% to 90% of infected patients [2,4,5,7,12]. Other symptoms include headache, intracranial hypertension, dementia, and other neuropsychiatric disorders [4,7,12,14]. Like in adults, the clinical manifestations of NCC in children are pleomorphic depending on the number of cysts in the brain, their location, the size and the immune response of the host [7]. Thus, NCC should be suspected in a child with sudden-onset seizures, headache, vomiting, focal motor deficits, strokes, communicating hydrocephalus, neurocognitive deficits, and other neuropsychiatric conditions, where there is no other evidence of an underlying neuropsychiatric disorders [1,6,9,14].

Studies conducted in South Africa, Tanzania, Uganda, Kenya and Ghana, found that half of patients presenting with ASS were under 18 years old [15,16]. The prevalence of epilepsy in Mozambique is estimated to be between 3 to 4%. The most common reason for outpatient psychiatric consultations in Mozambique, comprising 54%, are children less than 18 years old with epilepsy [16-18]. However, the underlying causes of epilepsy are not well defined in this setting. On the other hand, in Mozambique the seroprevalence of cysticercosis varies from 13% to 54% [1,2,4]. Computerized tomography (CT) scan based studies in adults with epilepsy from endemic countries reported the prevalence of NCC brain lesions in 18.8% to 47.3% [1,2,4,9,14,19]. These data indicate that ASS, epilepsy, and NCC are public health problems in endemic countries, both in children and adults [2,4,19,20], although studies of the local burden of these conditions or the fraction of patients with ASS or epilepsy due to NCC or other CNS parasitic diseases such as toxocariasis, onchocerciasis, toxoplasmosis, and schistosomiasis are limited [2,4,18,20-24].

In this case series, we highlight the contribution of NCC as a cause of epilepsy and other neurological disorders such as headache in children from Mocuba district, Zambeze province, Mozambique, discuss challenges in the diagnosis and management, and recommend future research.

Case Series

From August to November 2018, we identified 3 consecutive children with a history of epilepsy and or recurrent headache referred for evaluation from Mocuba District Hospital to Quelimane Central Hospital in Zambeze province, an area endemic for cysticercosis in the central eastern region of Mozambique [18,25].

We obtained informed consent from the patient's guardians. The Mozambique National Bioethics Committee approved the study.

We collected sociodemographic and clinical data, including funduscopic eye examination, age, gender, symptoms, and signs such as headaches, type of epileptic seizure, and frequency. For the diagnosis of NCC, we used the criteria proposed by Del Bruto [26,27] the presence of one absolute criteria (visualization of the vesicular cyst with scolex on imaging, or in the brain biopsy samples or visualization of the cysticercus larva in the retina), or two major criteria (positive cysticercosis serology or the presence of brain lesions highly sugges-

tive of NCC on CT-scan) combined with one minor criteria (the presence of brain lesions compatible with NCC on neuroimaging, clinical manifestations suggestive of NCC and cysticercosis antigens or antibodies detected in cerebro spinal fluid and epidemiological suggesting exposure, defined as evidence of household contact with infection by *T. solium*, individuals coming from or living in areas where cysticercosis is endemic or history of frequent travel to disease-endemic areas) were considered definitive cases of NCC. Probable cases of NCC include the presence of one major criterium combined with two minor criteria, or one major criterium combined with one minor criterium and epidemiological data or three minor criteria combined with epidemiological data [26,27].

A 3 ml sample of venous blood and serum was processed and aliquoted. One aliquot was submitted for complete blood chemistry and hemogram screening at Quelimane Central Hospital, and the second aliquot was frozen at -20ºC and sent to the Parasitology Laboratory at Faculty of Medicine, Eduardo Mondlane University in Maputo for *Cysticercus* antigens and antibodies detection.

Sera were screened for *Cysticercus* antigens and antibodies using the HP10 Ag-ELISA assay (http://www.apdiagroup.com) and Western Blot IgG kits from LDBIO® Diagnostics (www.ldbiodiagnostics.com), respectively. A plain CT-scan was offered to all patients to detect brain lesions consistent with NCC.

Demographic, clinical, serological, imaging findings and diagnostic interpretation are summarized in table 1. CT-scan findings included multiple lesions in different stages of evolution (vesicular, colloidal, granular and calcified) [26,27] (Figure 1). All three patients reported generalized tonic clonic seizures (GTCS) and one with partial complex seizures, each with a frequency for one to three per week. All patients reported encephalopathic symptoms or headaches. Blood chemistry and hemogram tests were all normal. Neurological examination (including fundoscopy) was also normal for all three patients.

Case number	Age	Gender	Case Presentation	Age of Symptom's On-set	Head-ache	Fre-quency of GTCS	Focal Seizures	Ag- ELISA assay	Western Blot assay	CT-Scan findings
Case 1	11	M	GTCS	8 years	Yes	One epi-sode per week	No	Positive	Negative	Multiple calcified lesions
Case 2	10	F	GTCS	2 years	Yes	One epi-sode per week	No	Positive	Negative	Vesicular cyst and multiple calcified lesions
Case 3	7	M	GTCS and dys-arthria	3 years	Yes	One epi-sode per month	Yes	Negative	Negative	Multiple Calcified lesions

Table 1: *Demographic, clinical, serological and imaging findings of all studied children.*

On CT-scan, all three patients had multiple calcified brain lesions consistent with NCC (patient 2 also had vesicular and nodular granular lesions) (Table 1 and figure 1). Ag-ELISA tests for cysticercosis were positive in the two children with multiple calcified and vesicular lesions (case 1-2), while a Western Blot assay was negative in all children. All but one patient (case1) had a family history of epilepsy.

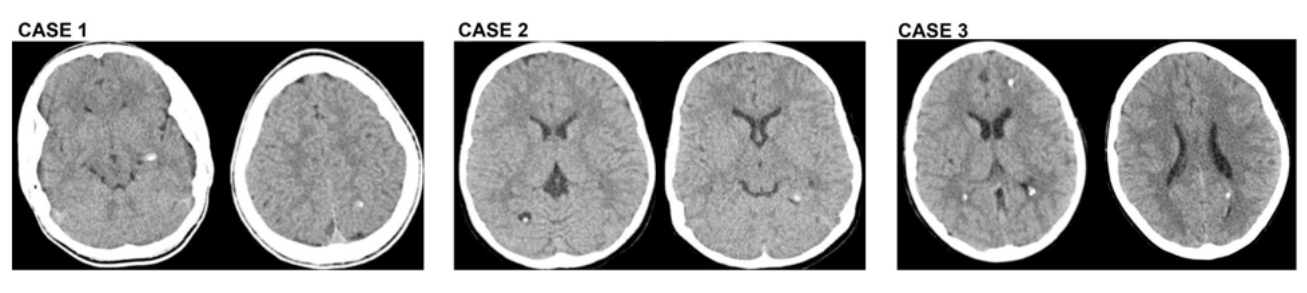

Figure 1: *Non-Contrast Computed Tomography of the brain in three children presenting with seizures, headaches, and neurological signs. Case 1: Calcified lesions in the left insular region and left occipital lobes. Case 2: cystic lesion in the right occipital region with eccentric scolex at the granular stage, other calcified lesion in the left occipital lobes with surrounding edema, plus another cystic lesion anteriorly. Case 3: Calcifications of the choroid plexus, several calcified NCC, and active cystic lesions in the left parietal lobe one of them with mild perilesional edema.*

None of the patients had ever received anti-epileptic drugs, but their guardians indicated that local traditional medicines were used without any improvement in their seizures.

All patients were prescribed anti-epileptic therapy and followed accordingly. All patients demonstrated improvement, defined by a decrease in seizures frequency or absence after one week of treatment.

Discussion

Worldwide, there are relatively few studies in children to assess NCC's burden or its clinical and imaging features mainly due to the lack of systematic population-based studies, community surveillance programs, lack of gold standard serological tools to help in diagnosis and surveillance, limited access to imaging tools [9].

Previous studies suggest that NCC in children presents typically with a solitary lesion and focal seizures [1,5,9,28]. In a study done in Nepal, they enrolled 1355 children aged 0-17 years with seizures disorders, out of which 229 (16.9%) were NCC. Of those 78.16% had a single lesion and 21.83% had multiple lesions on CT-scan. Further, seizures were the most common presenting symptom in 88.65% of children with NCC. Other symptoms included neuropsychiatric illness (16.59%), raised intracranial pressure (9.6%) and encephalitis (3.49%) [14]. In our prior experience, the solitary calcified lesion is usually due to calcified tuberculoma. While multiple calcified lesions measuring between 1 to 10 mm are pathognomonic of calcified NCC [29]. This was not the case for our children, who had multiple calcified lesions associated or not with vesicular or nodular granular lesions. We think that the high number of brain lesions is probably due to the burden of disease in this particular region were the rate of reinfection can be higher and to the patient's individual immunological status (Table 1).

Our children were likely infected at a very early age, given the natural history of NCC and early onset of symptoms, as shown by the CT-scan findings coupled with the onset of seizures beginning at 2 years of age [2,5-7].

We also noted that two cases of NCC had a positive Ag-ELISA but were negative to Western Blot assays. These results can be attributed to limited sensitivity and specificity of the Western Blot assays, which is related to the evolutionary stage of the parasite or to the number and location of possible cysts at the time the assay was performed [2,7].

For case 3, despite the presence of multiple calcified lesions, the serological assays were negative. This may be related to the absence of live parasites or to an inactive immune response due to a past infection. These findings should be viewed in the context of other studies, suggesting that serology alone for antibody detection is not accurate for the diagnosis of NCC in endemic countries [2,7,30,31]. For children with active lesions due to NCC (case 2) in our study, we decided to administer only antiepileptic therapy and defer anti-parasitic drug treatment, because of the inflammatory reaction side effects [1,3,6,8,30,32] that may be exacerbated in those of younger age.

Our study had some limitations. First, we only did a non-contrast CT-scan of the brain due to the unavailability of contrast, so we may have missed patients that could have presented with ring-enhancing lesions due to intraparenchymal NCC. Therefore, we did not include on this report those patients without clear images of vesicular, colloidal, granular, or calcified lesions on CT-scan. We do not have access to magnetic resonance imaging (MRI) facilities in this setting. However, this problem does not modify our results because a CT-scan is better than an MRI to confirm NCC worldwide. It is also true that MRI is the investigation of choice to diagnose intraventricular or subarachnoid NCC (or racemose) [26,27,32,33]. However, none of our patients had signs of ventricular dilatation on CT-scan. While an MRI is necessary to exclude intraventricular NCC, clinically we determined the diagnosis of NCC based on the clinical picture of the patients plus NCC positive serology as previously described [26,27,33]. Second, this are the first three case series of NCC in children diagnosed at the Quelimane Central Hospital, Zambeze Province. Therefore, future studies in this particular group should be done so that firm conclusions about the epidemiology and clinical pattern of NCC in children from this region can be drawn. Risk maps for cysticercosis in Mozambique indicate that the countries central, north and northeast areas might carry a higher risk for porcine and human cysticercosis [18,25,34]. Coincidentally, these are the country poorest regions and have higher epilepsy rates and school dropout rates than other areas of the country [35]. Some of these may represent ASS and epilepsy, whether or not associated with NCC [3,15].

The WHO considers epilepsy a primary health problem and, therefore, treatment should be made available at primary care levels in remote rural areas [36]. However, the Mozambique Ministry of Health has made a significant stride to fill the gap in mental health. By creating a cadre of psychiatric technicians, whose number rose from 66 in 2010 to 241 in 2014 [17] there is an urgent need to expand training of these and other health professionals to diagnose and manage epilepsy as well as other neurological symptoms that may be due to NCC and thus to ensure the achievement of sustainable development goals.

Our findings suggest that NCC could be one of the leading causes of epilepsy in children as reported in other endemic countries where at least 30% of epileptic cases in the general population are due to NCC [1,3,14,15,19]. NCC in children is not well characterized in other endemic countries, such as Brazil, Uganda, Zambia, Tanzania, Zimbabwe, nor in Mozambique [10,23]. Health professionals in all endemic countries should be aware that NCC is a potential cause of ASS, epilepsy, and other CNS disorders in these settings [3,21,22,34].

Further studies to determine the burden of ASS, epilepsy, headache, and other neurological syndromes and their relationship with NCC and other CNS parasitic diseases will bring more clarification to this matter [18,22,24].

We suggest performing investigations on other zoonotic disease like toxocariasis, onchocerciasis, toxoplasmosis. Other perinatal events and co-infection with cysticercosis and human immunodeficiency virus (HIV) need to be studied.

Given the limited availability of CT-scan and MRI and limited value of serology for the diagnosis and management of NCC, future studies should be directed at identifying a biomarker or diagnostic studies to support the diagnosis of NCC.

The socioeconomic impact of these disorders on affected communities, should be a goal for future research in Mozambique and other endemic countries [3,18,20,34,37]. Awareness about the causes of epilepsy and its management should reduce stigma and the negative socioeconomic impact of seizure disorders in affected people and their families.

Conclusion

NCC should be suspected in all cases of ASS, epilepsy and neuropsychiatric disorders in children from countries where cysticercosis is endemic, including Mozambique, given the growing evidence that this infection is a significant emerging infectious disease. As serology alone is not accurate for diagnosis and managing NCC in the absence of imaging, which is expensive and limited in endemic countries, future studies should be targeted to the identification of biomarkers to support the diagnosis of NCC. Primary care providers should be educated and in turn should educate their patient's population. Health systems should be strengthened in endemic countries to ensure appropriate evaluation for seizures and other neuropsychiatric disorders and the possible roles of cysticercosis infection and other parasitic diseases in their etiology.

Ethics Approval and Informed Consent

The study was approved by the Mozambique Bioethics Committee. National Written informed consent was obtained from the patient's guardian for publication of these cases report and any accompanying images. Further, the patient's guardian provided written informed consent for study and publication of the findings.

Acknowledgements

We express our gratitude to the patients and their guardians who contributed and consented to participate in this study. This research work 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 authors' responsibility and does not necessarily represent the Fogarty International Center's official views or the National Institutes of Health.

Conflict of Interest

The authors declare that they do not have conflicts of interests in this work.

Authors' Contributions

EVN, RTS, HFS and CAB conceptualized, analyzed and interpreted the patient's data and were the major contributors in manuscript writing. JM and NN - Contributed to the recruitment, serological testing and interpretation, and wrote the manuscript. All authors read and approved the final manuscript.

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