Headaches More Common among Epilepsy Sufferers with Neurocysticercosis than Other Structural Brain Lesions

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Abstract

Neurocysticercosis is a leading cause of seizures and epilepsy in the developing world. Cysticercosis is endemic in many regions of Central and South America, sub-Saharan Africa, India, and Asia. Neurocysticercosis is of emerging importance because globalization has increased travel between Hawai'i and disease-endemic areas. Headache and epilepsy are two of the most common complications of neurocysticercosis infection. Currently, it is not known if epilepsy patients with neurocysticercosis are more likely to have headaches than those with other structural brain lesions or those with no structural brain abnormalities. This study was designed to investigate whether epilepsy patients with neurocysticercosis report co-morbid headaches more frequently than those with other or with no structural brain lesions. A retrospective cross-sectional study of all patients treated at a community based neurology clinic for epilepsy during a three-month period was performed. One-hundred sixty patients were included in the analytical study. Co-morbid headaches were more commonly present among those with neurocysticercosis (40%) than those with other structural lesions and those with no structural brain abnormalities (19% and 22%, respectively; P = .031). Headache frequency among those reporting co-morbid headaches did not differ significantly between the groups. Prevalence of co-morbid headaches is greater among epilepsy patients with neurocysticercosis than those with other structural brain lesions or no structural brain abnormality. Epilepsy patients with neurocysticercosis may be especially vulnerable to development of headaches and a thorough headache history should be obtained to help screen for affected individuals.

Keywords

Neurocysticercosis, headaches, epilepsy, seizure

Introduction

Neurocysticercosis is a parasitic worm infection acquired by humans through the ingestion of *Taenia solium* eggs that are shed in the feces of humans carrying the intestinal parasite.[1] Neurocysticercosis is especially common in Latin America, India, Africa, and China.[1] Poor hygiene practices are the main factor contributing to transmission of the disease through the fecal-oral route.[2,3] Over the last several decades cysticercosis infections have become more common in the United States, with 221 deaths due to cysticercosis occurring between 1990 and 2002, including 33 among individuals born in the United States.[4] The economic costs of neurocysticercosis in the United States are significant, with treatment and hospitalization costs, lost working days, and losses of jobs estimated to approach $8.8 million in the year 2000 alone.[5] One economic study completed in Los Angeles County showed that the economic costs associated with neurocysticercosis infection are especially great, with the average hospitalization charge for patients with neurocysticercosis approaching $66,000, compared to $29,000 for those without the infection.[6] Neurocysticercosis is of emerging importance in Hawai'i because of immigration and tourism from disease-endemic areas.[7] According to the Hawai'i Tourism Authority, visitors from Asia to Hawai'i increased from approximately 225,000 visitors in 2006 to 778,000 in 2015.[7] Visitors from Latin America to Hawai'i increased from approximately 19,000 visitors in 2006 to 27,000 visitors in 2015.[7] The John A. Burns School of Medicine (JABSOM) at the University of Hawai'i at Manoa is also committed to training competent healthcare professionals with the skills to address critical global health problems. To that end, JABSOM has pursued alliances with medical schools and programs unique to the Asia-Pacific region, including Asia and Philippines.[8] Neurocysticercosis is a leading cause of seizures and epilepsy in the developing world, is a growing health concern throughout the United States, and is relevant to healthcare providers in Hawai'i.

The most common presenting symptoms for patients with neurocysticercosis are seizures (78.8%), headaches (37.9%), focal neurologic deficits (16.0%), and signs of intracranial hypertension (11.7%).[9] Additionally, common long-term complications associated with parenchymal calcified neurocysticercosis lesions include seizures (38.0%) and headaches (34.0%).[10] The cause of headaches linked to neurocysticercosis is theorized to be due to inactive calcified parenchymal brain cysticerci which undergo structural changes and cause exposure of parasitic antigenic material to the host. The exposure of foreign material in the brain leads to transient inflammatory changes in the parenchyma producing painful sensations.[3,11]

Others have reported an increased prevalence of primary headache disorders among those with calcified parenchymal brain cysticercosis, similar in magnitude to what is observed among patients with primary brain tumors.[12] The hypothesis for this study was that the presence of calcified parenchymal neurocysticercosis was associated with an increased prevalence of co-morbid headaches in epilepsy patients, compared to those with no structural brain abnormalities, and similar to those with other types of structural brain lesions such as primary brain tumors. An increased risk for headaches among epilepsy patients with calcified parenchymal neurocysticercosis would suggest that these patients may be more vulnerable to development of headaches, possibly related to factors specific to the parasitic infection, such as inflammation and ongoing immune system activation.

Methods

Participants

Participants were adults over the age of 18 years, who presented sequentially to a community-based neurology clinic located in

Los Angeles, CA, USA during a three-month period from October 1, 2013 to December 30, 2013 for evaluation or treatment of epilepsy. De-identified data were obtained and analyzed in a retrospective fashion for all participants. Institutional Review Board approval from the Los Angeles BioMedical Research Institute was obtained for retrospective analysis of already acquired and de-identified clinical data. All work was conducted in accordance with the Declaration of Helsinki (1964). Demographic information and clinical factors were determined by review of chart notes and ICD-9 codes.

Diagnosis of Neurocysticercosis

Diagnosis of brain parenchymal neurocysticercosis infection was made according to published guidelines.[1] In summary, all of the patients included in this study met clinical diagnostic criteria for probable neurocysticercosis, based on the combination of neuroimaging findings of one or more punctate calcifications located in the brain parenchyma without alternative etiologic explanation, presence of neurologic complications such as headache or epilepsy, and membership in a population in which neurocysticercosis is endemic.[1]

Headache Frequency Determination

Headache frequency was determined by self-report or caregiver report from chart notes. Headache frequency was calculated by dividing the number of headaches reported by the patient or caregiver during a three to six-month time interval (depending on the duration of time between scheduled clinic visits) by the number of months comprising the time interval to produce a rate consisting of number of headaches per month.

Statistical Analysis

Participants were divided into three groups: those with structural neuroimaging findings consistent with parenchymal calcified neurocysticercosis; those with other structural brain lesions such as brain tumors, old ischemic strokes, vascular malformations, structural lesions due to prior traumatic brain injury, and developmental abnormalities; and those with no structural abnormalities identified on neuroimaging studies. Presence or absence of headaches and other non-parametric data was then compared between groups using the chi-square test. Mean values for continuous demographic factors and other continuous variables, including headache frequencies, were compared between groups using an analysis of variance (ANOVA). A *P*-value of .05 or less indicated statistical significance and no correction for multiple comparisons was made. All statistical calculations were performed using SPSS version 22 (IBM corporation, New York, NY, USA).

Results

One-hundred sixty patients with epilepsy and neuroimaging results were evaluated in the clinic during the study period. These patients were approximately evenly distributed between the three groups, with 63 (39%) having neuroimaging findings consistent with parenchymal neurocysticercosis, 42 (26%) with other structural lesions (8 with brain tumors, 8 with old ischemic strokes, 4 with vascular malformations, 14 with structural lesions due to prior traumatic brain injury, and 8 with developmental abnormalities), and 55 (34%) with no structural brain abnormalities identified on neuroimaging studies.

No significant difference in mean age was detected between the groups. The groups also did not differ significantly in use of tobacco, alcohol, or illicit substances, which could potentially trigger headaches. However, the groups did differ significantly in gender distribution, with more females present in the group with neurocysticercosis compared to the other two groups (Table 1).

For the main clinical outcome being evaluated, co-morbid headache disorders were reported more frequently among epilepsy patients with neurocysticercosis than those with either other structural brain lesions or no structural abnormalities (40%, 19%, 22%, respectively; $P = .031$). However, mean headache frequency did not differ significantly between the groups (Table 1).

Discussion

This retrospective cross-sectional study found increased prevalence of headaches among epilepsy patients with co-morbid calcified parenchymal neurocysticercosis compared to those with other types of structural brain lesions or those without structural brain abnormalities. The results of this study suggest that the presence of calcified parenchymal neurocysticercosis may be associated with increased likelihood for headaches among epilepsy sufferers. However, because this was a retrospective study, further research is needed to determine if a causal relationship exists between the calcified parenchymal lesions and the headaches.

Previous reports indicate that around 37% of patients with neurocysticercosis will report experiencing headaches.[9] The percentage of epileptic patients with calcified parenchymal neurocysticercosis who reported headaches in this study was 40%, which is similar to the value reported in the literature.

Table 1. Demographic and Clinical Outcomes for Epilepsy Patients with Parenchymal Neurocysticercosis, Other Structural Brain Lesions, and no Structural Brain Abnormality.

	Neurocysticercosis (n = 63)	Other Lesions (n = 42)	Structurally Normal (n = 55)	*P*-Value
Mean Age in Years (SD*)	42 (13)	42 (13)	40 (13)	.588
Female (%)	42 (67%)	15 (36%)	28 (51%)	.017
Tobacco, alcohol, or substance use (%)	7 (11%)	3 (7%)	5 (9%)	.735
Headaches present (%)	25 (40%)	8 (19%)	12 (22%)	.031
Headache frequency per month (SD*)	17 (16)	12 (12)	19 (14)	.683

*SD = Standard Deviation

Additionally, the percentage of patients in our study with non-cysticercosis related brain lesions and those with no structural abnormalities both reported comorbid headaches at rates that are essentially equivalent to what has been reported previously in the literature.[13] The increased frequency of headaches among those with neurocysticercosis compared to epileptic patients with other types of structural brain lesions may suggest that there is a mechanism specific to neurocysticercosis that is triggering headache generation in these patients.

Possibly, the headaches generated by calcified parenchymal neurocysticercosis may be triggered by a different mechanism than headaches caused by other types of structural brain lesions. Secondary headaches are often described as being similar to specific primary headache disorders based on the constellation of symptoms experienced by the patient, such as "migraine-like" or "tension-like" headaches. This terminology suggests that the secondary headache is occurring through a mechanism or pathway that is in some way similar to the mechanism or pathway that is implicated in generation of the primary headache disorder. One theory on how calcified parenchymal brain cysticerci may cause headaches is that an inflammatory response to the foreign parasitic material in the brain tissue is generated episodically due to remodeling of the calcified lesion.[14] The inflammation then leads to an increase in intracranial pressure and disruption of the blood brain barrier.[14] As a result, rates of synaptic transmission are affected and the primary manifestation is one of increased excitatory synaptic signaling.[15] This may then facilitate triggering of the trigemino-vascular pathway which is implicated in the generation of migraine headaches.[15] The increased synaptic transmission may also aid the spread of epileptic activity and contribute to seizure generation.

This study supports the proposed mechanism that focal areas of brain inflammation occurring episodically as a response to calcified cyst remodeling may be an important mechanism for headache generation in patients with neurocysticercosis.[14] Consequently, presence of calcified parenchymal neurocysticercosis may episodically trigger hyperexcitability of the neocortex and thereby contribute to development of both headaches and epilepsy.[14]

There are limitations to the study. First, there was a greater proportion of women among the group with calcified parenchymal neurocysticercosis than in the other two groups. Because female gender is known to be associated with a greater lifetime risk for developing headaches, this is a potential confounding factor that could not be excluded and, because of the relatively small sample size of this study, we were not able to control for this factor in the statistical analysis. A larger prospective study with equal gender representations would be useful in separating out the effects of gender on headache development in patients with calcified parenchymal neurocysticercosis. Second, because this was a retrospective cross-sectional study we were not able to obtain comprehensive information related to the temporal relationship between development of headaches and calcified parenchymal neurocysticercosis lesions, which would be necessary to determine causation. Third, patients with multiple types of intracranial pathology were combined due to a limited sample size. Fourth, the cross-sectional nature of this study prevented collection of data regarding MRI findings such as the severity of cerebral edema and contrast-enhancement in the acute and chronic setting and the associated headache characteristics, severity, and responsiveness to therapies. Future studies could take into account headache specific factors such as headache type, family history of headaches, localization of headache pain, responsiveness to medications, adding a homogeneous comparison group with other structural lesions, and prospective collection of MRI characteristics such as the severity of cerebral edema and contrast-enhancement. This type of information would be interesting to know since it would help to clarify additional patient specific risk factors related to headache development and treatment efficacy. Another potential research direction could be to obtain pain scale information for all patients to include pain severity ratings of headaches of those with different types of structural lesions. It would be interesting to learn if characteristics such as the total number and/or location of calcified parenchymal neurocysticercosis lesions affect variables such as pain severity or other characteristics such as headache frequency or type.

Conclusions

The results of this study support the hypothesis that parenchymal calcified neurocysticercosis lesions may contribute to the development of headaches in epilepsy patients through episodic increases in inflammation related to ongoing cyst remodeling. Further research is needed to better understand the mechanisms by which calcified parenchymal neurocysticercosis lesions contribute to headache development. In particular, if episodic antigen release with resulting focal areas of inflammation is a causative mechanism, it would suggest the possibility of directed therapy targeting this mechanism through treatment with anti-inflammatory medications. As the frequency of neurocysticercosis cases in the United States continues to increase, the number of individuals suffering from chronic problems related to calcified parenchymal neurocysticercosis lesions such as epilepsy and headaches will likely increase as well.[4] Consequently, more research on this disorder and treatment of common problems associated with these lesions could lead to better diagnostic methods and treatment options for future patients.

Conflict of Interest

None of the authors identify any conflict of interest.

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