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ORIGINAL RESEARCH

Yield of Brain MRI in Clinically Diagnosed Epilepsy in the Kingdom of Bhutan: A Prospective Study

Veronica Bruno, MD, MPH, Joshua P. Klein, MD, PhD, Dechen Nidup, MD, Damber K. Nirola, MD, Lhab Tshering, BA, Sonam Deki, BComm, Sarah J. Clark, BSc, Kristin A. Linn, PhD, Russell T. Shinohara, PhD, Chencho Dorji, MD, Dili Ram Pokhrel, Ugyen Dema, MD, Farrah J. Mateen, MD, PhD for the Bhutan Epilepsy Project

Boston, MA; Thimphu, Bhutan; and Philadelphia, PA

Abstract

BACKGROUND People with epilepsy (PWE) in low- and middle-income countries may not access the health resources that are considered optimal for epilepsy diagnosis. The diagnostic yield of magnetic resonance imaging (MRI) has not been well studied in these settings.

OBJECTIVES To report the diagnostic yield of brain MRI and identify clinical associations of abnormal MRI findings among PWE in a neurocysticercosis-endemic, resource-limited setting and to identify the proportion and putative structural brain causes of drug-resistant epilepsy.

METHODS PWE were prospectively enrolled at the Jigme Dorji Wangchuck National Referral Hospital in Bhutan (2014-2015). Each participant completed clinical questionnaires and a 1.5-Tesla brain MRI. Each MRI was reviewed by at least 1 radiologist and neurologist in Bhutan and the United States. A working definition of drug-resistant epilepsy for resource-limited settings was given as (a) seizures for >1 year, (b) at least 1 seizure in the prior year, and (c) presently taking 2 or more antiepileptic drugs (AEDs). Logistic regression models were constructed to test the cross-sectional association of an abnormal brain MRI with clinical variables.

FINDINGS A total of 217 participants (125 [57%] female; 54 [25%] < 18 years old; 199 [92%] taking AEDs; 154 [71%] with a seizure in the prior year) were enrolled. There was a high prevalence of abnormal brain MRIs (176/217, 81%). Mesial temporal sclerosis was the most common finding (n = 115, 53%, including 24 children), exceeding the number of PWE with neurocysticercosis (n = 26, 12%, including 1 child) and congenital/perinatal abnormalities (n = 29, 14%, including 14 children). The number of AEDs (odds ratio = .59, $P = .03$) and duration of epilepsy (odds ratio = 1.11, $P = .02$) were significantly associated with an abnormal MRI. Seizure in the prior month was associated with the presence of mesial temporal sclerosis (odds ratio = .47, $P = .01$). A total of 25 (12%) participants met our definition of drug-resistant epilepsy, with mesial temporal sclerosis (n = 10), congenital malformations (n = 5), and neurocysticercosis (n = 4) being the more common findings.

CONCLUSIONS The prevalence of abnormalities on brain MRI for PWE in resource-limited settings is high as a result of a diffuse range of etiologies, most commonly mesial temporal sclerosis. Drug-resistant epilepsy accounted for 12% of the referral population in a conservative estimation.

KEY WORDS diagnosis, drug resistant epilepsy, epilepsy, MRI, Asia

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From the Department of Neurology, Massachusetts General Hospital, Boston, MA (VB, SJC, FJM); Harvard Medical School, Boston, MA (JPK, FJM); Department of Neurology, Brigham & Women's Hospital, Boston, MA (JPK); Department of Radiology, Brigham & Women's Hospital, Boston, MA (JPK); Department of Radiology, Jigme Dorji Wangchuck National Referral Hospital, Thimphu, Bhutan (DN, DKN); Department of Psychiatry, Jigme Dorji Wangchuck National Referral Hospital, Thimphu, Bhutan (LT, SD, CD, DR, UD); University of Pennsylvania, Philadelphia, PA (KAL, RTS). Address correspondence to F.J.M. (fmateen@partners.org).

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INTRODUCTION

Of the 40 million or more people with epilepsy (PWE) in low- and middle-income countries (LMICs), many cannot access the health technologies and human resources that are considered optimal for epilepsy diagnosis.[1] The International League Against Epilepsy recommends brain magnetic resonance imaging (MRI) as the structural imaging modality of choice, especially in children.[2,3] The diagnostic yield of MRI has not been well studied in LMICs. A systematic study of community-dwelling PWE undergoing brain MRI in LMICs would help assess the prevalence of abnormalities of this test and identify patient subpopulations who are more likely to receive diagnostically useful results. Moreover, it is well recognized that a group of PWE are not able to become seizure-free on standard doses of antiepileptic drugs and continue to experience epilepsy despite appropriate therapy. These patients may be considered to have *drug-resistant epilepsy* (DRE) in high-income settings, some of whom may be surgically treatable, but a working definition for DRE in resource-limited settings has so far been absent.

Here, we identify and classify structural brain abnormalities on MRI among people with clinically diagnosed epilepsy in Bhutan, a neurocysticercosis-endemic, lower middle income country. We further consider how many operationally defined PWE would be classified as having DRE and potentially surgically treatable epilepsy, representing potentially missed opportunities for more advanced epilepsy care in resource-limited settings.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents. The Research Ethics Board of Bhutan, the Partners Institutional Review Board, and the University of Ottawa Ethics Board approved this study. Written informed consent was obtained from all participants or, in the case of children, their parent or guardian.

Study Design and Site. Participants of any age were recruited (July 2014—December 2015) from an existing epilepsy registry at the Jigme Dorji Wangchuck National Referral Hospital, the only tertiary care center, located in the country's capital city, Thimphu. Participants were referred through health care workers, traditional healers, and physicians or were self-referred. Advertisements were made through a local newspaper, *The Kuensel*, as well as radio. Details of our study recruitment and design have been reported previously.[4,5]

Participants. Participants were included if they resided in Bhutan and had a clinical diagnosis of epilepsy, defined as $\geq$2 unprovoked seizures, by their treating physician. A US-based neurologist and/or Bhutanese psychiatrist evaluated each participant and confirmed the clinical diagnosis. Participants were enrolled regardless of cause of epilepsy, type of seizure, type of treatment (ie, traditional versus allopathic), and neurologic status. People were excluded if they had exclusively (a) nonepileptic behavioral events, (b) febrile seizures, or (c) seizures provoked only in the setting of metabolic disorders or alcohol abuse or were (d) children <5 years old and did not need an MRI for clinical purposes. Each participant was reimbursed 500 Bhutanese Ngultrum (approximately 9 USD).

Data Collection. Each participant, or the next of kin proxy when required, underwent a detailed interview in Dzongkha or English by trained research assistants (L. Tshering, S. Deki). Survey instruments were developed by the Bhutanese and US investigators and refined to ensure interpretability and relevance to the study population through several iterations. Information about epilepsy history included questions on the number of antiepileptic drugs (AEDs) taken, timing of the most recent seizure, a family history of epilepsy in a primary relative, and seizure-related injury such as bone fracture, burn, or head trauma.

Drug-resistant epilepsy (DRE) cases were defined as failure of 2 or more appropriately selected and adequately tried anticonvulsant medications to achieve seizure freedom for a sustained period of either monotherapy or polytherapy,[6] with potential candidates for surgical treatment defined as people with DRE with seizures for >1 year and seizures in the prior year.[7] Our pragmatic definition was further defined as a history of having taken 2 or more antiepileptic drugs, a seizure in the prior year, and a long-term history of epilepsy.

Brain Magnetic Resonance Imaging. There is 1 MRI machine in Bhutan (1.5 Tesla, Siemens). Sequences included sagittal and axial T1, axial T2, axial T2-FLAIR, and thin-slice T1 and T2 images in orthogonal planes including oblique coronal perpendicular to the long axis of the hippocampi. T1 sequences after intravenous administration of gadolinium contrast were obtained if findings on the noncontrast images required further investigation. Any participant who had already undergone brain MRI (January 1, 2014 until study

enrollment) and did not need a repeat scan for clinical purposes was asked for permission to have the prior MRI included in this study. There were no refusals. MRI costs approximately 70 USD per person in Bhutan; however, MRIs were covered by the study funds so that participants incurred no out-of-pocket costs.

Images were saved as DICOM files and displayed by using the OsiriX Imaging Software (http://www.osirix-viewer.com). At least 1 neuroradiologist and neurologist in Boston as well as a radiologist in Bhutan interpreted the images. Prespecified categories of structural abnormalities that are probable causes of epilepsy included (1) mesial temporal sclerosis (MTS), (2) vascular lesions, (3) space-occupying lesions, (4) infections, (5) congenital malformations and perinatal insults, (6) head trauma, and (7) toxic-metabolic insults.[8] MTS was diagnosed based on the presence of abnormal T2 hyperintensity and hippocampal atrophy. Findings that were not specifically associated with the origin of the seizures, including the presence of cortical atrophy and microangiopathic subcortical and periventricular white matter changes, were also noted, and the severity was subjectively categorized. Finally, the underlying MRI brain finding was adjudicated as the probable cause of epilepsy by at least 1 neurologist.

Statistical Analysis. The cross-sectional prevalence of MRI abnormalities among PWE was reported as the proportion of participants with at least 1 abnormality divided by those who underwent the test. Stratification by age group (<18 years old versus >18 years old) was performed. To evaluate for potential associations with an abnormal test result, we constructed logistic regression models using current age, number of AEDs presently taken, duration of epilepsy, and the indicator of having at least 1 seizure in the previous month. Regression analyses were performed for (a) all MRI abnormalities, (b) MRI abnormalities deemed to be a probable cause of epilepsy, and (c) MTS as the outcome. A P value of $\leq$.05 was considered statistically significant with a 2-tailed probability.

RESULTS

Participant Enrollment and Demographic and Clinical Characteristics. The final analysis excluded 10 children <5 years old who had no additional indication for brain MRI and 44 adults who did not present for an MRI appointment before study closure. The final analytic sample included 217 participants (127 [57%] female; 54 [25%] <18 years old). Of these participants, 47 children (87%) and 107 adults (66%) reported a seizure in the last year, and 199 (92%) in total were currently being treated with AEDs (Table 1).

Brain MRI Findings. A total of 176 out of 217 participants (81%) had structural brain abnormalities, including 44 of 54 children (81%) and 132 of 163 adults (81%). Figure 1 illustrates the range of findings that occurred among PWE in Bhutan. MTS was the most common etiologic finding in both children and adults (115/217, 53%) and was most often unilateral (74/115, 64%). The degree of hippocampal atrophy was usually mild (67/115, 58%), although severe hippocampal atrophy was present in 7 (6%) adults. Neurocysticercosis was found in 25/163 (15%) adults but in only 1 child. A range of congenital and perinatal brain abnormalities was found in both children (14/54, 26%) and adults (15/163, 9%) (Table 2). The most common additional finding was the presence of nonspecific white matter lesions in 16 of 54 children (30%) and 69 of 164 adults (42%). Most of these changes were diffuse in location and mild in severity. Multiple abnormalities on a single MRI scan were noted in 7 of 54 children (13%) and 55 of 163 adults (34%).

There was a statistically significant association between duration of epilepsy (odds ratio [OR] = 1.11, P = .02) and number of current AEDs (OR = .59, P = .03) with any abnormality on MRI. When considering only participants whose abnormal brain MRI was deemed the probable cause of epilepsy, the association with the duration of epilepsy remained significant (OR = 1.10, P = .02). Using MTS as the outcome, there was a significant association between presence of seizures in the last month and abnormal brain MRI (OR = .47, P = .01) (Table 3).

Operationalized Definition of Drug-Resistant Epilepsy. Twenty-five participants (12%) met criteria for DRE, including 16 of 163 adults (10%) and 9 of 54 children (17%). Of these, 4 participants (16%) had focal spikes interictally on electroencephalogram (EEG) with region-concordant lesions (2 MTS, 1 congenital syndrome, and 1 neurocysticercosis). Seventeen (68%) had structural lesions with no evidence of epileptiform activity on the EEG. In this group, there were 8 cases of MTS, 2 vascular lesions, 1 tumor, 4 congenital malformations, and 2 neurocysticercosis. One participant (4%) had an epileptiform EEG without associated structural lesions in the MRI. The remaining 3 participants (12%) with DRE had age-appropriate results on both studies.

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Table 1. Demographic and Clinical Characteristics of People With Epilepsy by Age Group

	All People With Epilepsy		All Participants With Normal or Nonspecific MRI Changes	All Participants With Abnormal MRI (Including a Probable Etiology of Epilepsy)
	Children	Adults ≥18 y		
n	54	163	41	176
Female (%)	28 (52)	96 (59)	24 (59)	101 (57)
Mean age in y (SD)	11.7 (8)	30.2 (11)	25.9 (14)	24.8 (13)
Highest educational attainment level (n, %)				
None	23 (43)	48 (30)	17 (41)	54 (32)
Primary	23 (43)	41 (25)	15 (37)	49 (28)
Secondary	5 (9)	25 (15)	4 (10)	26 (15)
High school	3 (6)	30 (18)	2 (5)	31 (9)
College	N/A	19 (12)	3 (7)	16 (1)
Last seizure (n, %)				
Last wk	18 (33)	38 (24)	14 (34)	42 (24)
Last mo	19 (35)	45 (27)	12 (29)	51 (29)
Last y	10 (19)	24 (15)	4 (10)	30 (17)
>1 y ago	7 (13)	56 (35)	11 (29)	52 (30)
Seizure characterization				
Loss of consciousness	34 (63)	124 (76)	144 (74)	122 (72)
Tonic-clonic seizure	30 (56)	88 (54)	110 (57)	98 (58)
Atonic seizure	8 (15)	15 (9)	20 (10)	17 (10)
Focal clonic seizure	8 (15)	23 (14)	28 (14)	27 (16)
Staring spells	11 (20)	26 (16)	34 (17)	28 (17)
Unusual behavior	6 (11)	53 (33)	57 (29)	43 (26)
Feels spirits	1 (2)	15 (9)	7 (8)	10 (6)
Sensory events	10 (19)	31 (19)	36 (19)	30 (18)
Unknown	17 (31)	62 (38)	74 (18)	68 (40)
No. of current AEDs (n, %)				
Zero	8 (15)	10 (6)	4 (10)	14 (8)
One	27 (50)	97 (60)	24 (59)	100 (57)
Two	14 (26)	37 (23)	7 (17)	44 (25)
Three or more	5 (9)	18 (11)	6 (15)	17 (10)
Self-reported family history of epilepsy	10 (19)	18 (11)	4 (10)	24 (14)
History of a seizure-related injury	10 (19)	48 (30)	5 (12)	53 (30)

MRI, magnetic resonance imaging; N/A, not applicable; SD, standard deviation.

DISCUSSION

Our finding that brain MRI has a high diagnostic yield for etiologic brain abnormalities in this referral population of PWE has implications for other LMICs. Our results are particularly relevant to emerging economies where access to health technologies is improving but payors cannot afford all investigative tests.[9] In this case, MRI not only supports the diagnosis of epilepsy but also provides etiologic information in most PWE.

Our study reports, in a convenience referral-based cohort, an operational estimate of the prevalence of drug-resistant epilepsy cases in a lower income setting with neurocysticercosis. Most patients with drug-resistant epilepsy had brain lesions that were not neurocysticercosis but rather mesial temporal sclerosis. Given our pragmatic definition of drug-resistant epilepsy, with a lack of inclusion of a participant's historical AED usage and the inability to test drug levels, drug quality, and medication adherence, our definition is best considered an approximation. It is likely we have underestimated the prevalence here given the lack of inclusion of prior AED usage. In addition, patients with more severe drug-resistant epilepsy were likely unable to present to the referral hospital, too stigmatized to seek care, or may have even suffered early mortality given the high rate of unintentional injuries.

Our exploratory models indicated that longer duration of epilepsy could be a predictor of abnormal MRI. We also identified a higher number of AEDs as a predictor of a normal brain MRI.

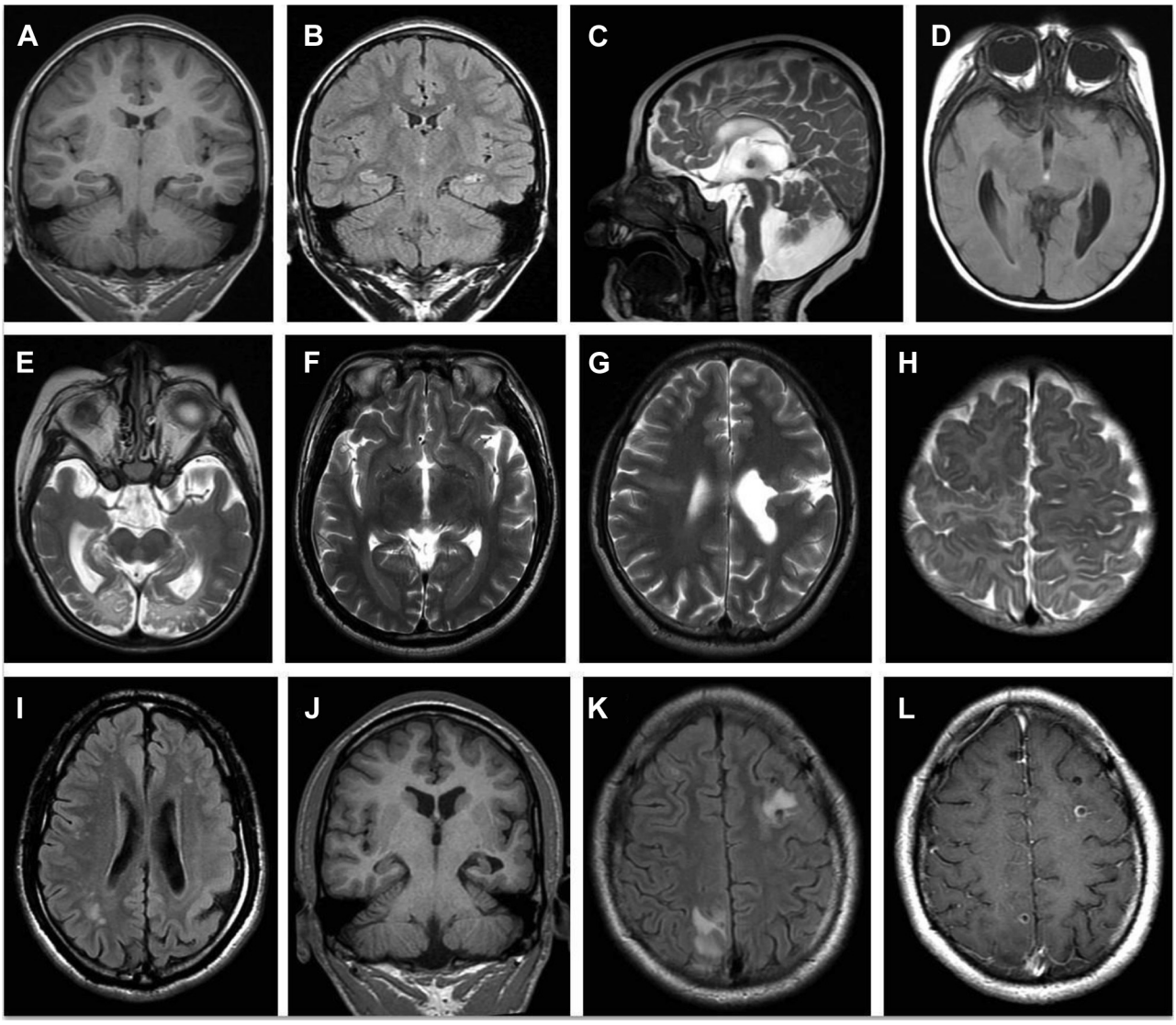

Figure 1. **MRI findings of epilepsy-related pathologies among people with epilepsy in Bhutan. (A, B) Coronal T1 and T2-FLAIR images of a girl with bilateral hippocampal sclerosis. (C, D) Sagittal T2 and axial T1 images of a boy with multiple midline malformations including corpus callosum, brainstem, and cerebellar vermis dysgenesis and hypotelorism. (E) Axial T2 image of a girl with bioccipital cortical dysplasia and polymicrogyria and bitemporal lissencephaly. (F) Axial T2 image of a woman with symmetric posterior periventricular gray matter band heterotopia. (G) Axial T2 image of a man with a left frontal open-lip schizencephalic cleft and less severe right frontal cortical dysplasia. (H) Axial T2 image of a girl with right perirolandic cortical dysplasia and polymicrogyria. (I, J) Axial and coronal T2-FLAIR image of a man with left parietal pachygyria and lissencephaly associated with diffuse hypoplasia of the left hemisphere. (K, L) Axial T2-FLAIR and T1-postcontrast images of a 24 year old man with multiple intracerebral viable and degenerating neurocysticercosis lesions. Several lesions show ring enhancement with gadolinium and are surrounded by vasogenic edema. A scolex is visible in the nonenhancing left frontal lesion.**

We hypothesize this is either a result of genetic causes of epilepsy in this population, which may be experiencing a "founder effect" because of its relatively remote location in the Himalayan Mountains, or to nonepileptic behavioral events. Mesial temporal sclerosis had fewer predictors but exploratory studies found a self-reported seizure in the prior month was statistically significantly associated with this neuroimaging outcome.

In spite of its likely utility, there is scarce information on the use of MRI in PWE in LMICs.[10,11] A prospective study of 366 patients from an epilepsy clinic in Pakistan reported brain abnormalities on head computed tomography or MRI in 21% of

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Table 2. Range and Prevalence of MRI Findings by Age Category and Etiologic Versus Incidental Findings

	Children (n)	Adults (n)
Abnormalities Etiologically Related to Epilepsy		
Mesial temporal sclerosis	24	91
Location		
Bilateral	8	34
Left	12	41
Right	4	16
Degree		
Mild	13	54
Moderate	11	30
Severe	0	7
Vascular lesions	6	9
Ischemic stroke	6	7
Intracranial hemorrhage	—	1
Cavernoma(s)	—	1
Space-occupying lesions	1	7
Tumors	—	4
Benign cyst (noninfectious)	1	3
Congenital/perinatal abnormalities	14	15
Malformations secondary to abnormal neuronal and glial proliferation or apoptosis		
Polymicrogyria	1	—
Malformations secondary to abnormal postmigrational development		
Focal cortical dysplasia	3	7
Non–syndromatically characterized congenital abnormalities		
Agenesis of the corpus callosum	2	—
Partial dysgenesis of the corpus callosum	2	—
Agenesis of septum pellucidum	2	2
Cavum septum pellucidum	1	3
Other congenital syndromes	3	3
Infections	1	25
Neurocysticercosis	1	25
Number		
Solitary cyst	1	14
Multiple cysts	—	11
Traumatic brain injury sequela	—	2
Toxic metabolic	—	1
Nonspecific Abnormalities		
Atrophy (in absence of other abnormalities)	2	3
Generalized	1	2
Cerebellar	—	1
Nonspecific white matter lesions	16	69
Location		
Focal	5	3
Diffuse	11	66
Degree		
Mild	12	58
Moderate	4	9
Severe	—	2
Other	2	3
Lipoma	—	1
Empty sella	—	1
Mega cisterna magna	1	1
Arnold-Chiari malformation	1	—

PWE.[10] Prospective comparison of brain MRI and electroencephalography (EEG) in Zambia to evaluate 81 HIV-infected adults with new-onset seizures found EEG abnormalities were common (68%), particularly in patients with neuroimaging abnormalities and advanced HIV.[11] However, it is difficult to extrapolate these results to community-dwelling populations with the full range of causes of epilepsy or to a non–HIV endemic setting. Additionally, prior study designs were limited because MRI was not available for all of the patients who had an EEG.

Our results are important because they may guide diagnostic testing decisions in other resource-limited settings. Prior data on epilepsy in LMICs may not reflect the epidemiologic transition. The high prevalence of perinatal and congenital injuries seen here may relate to Bhutan's low percentage of births in health facilities[12] or other treatable factors that are not yet recognized, such as micronutrient deficiencies like folate. Identifiable causes of epilepsy in LMICs without HIV endemicity appear analogous to those in high-income countries, suggesting that similar diagnostic approaches and treatments, especially for complex cases, should be planned.

Other LMICs have introduced surgical treatment for DRE with varying degrees of success.[13-15] Unfortunately, surgical treatment for epilepsy is not available in Bhutan. At least 25 of our participants met criteria for DRE, of whom brain MRI identified structural abnormalities in 21 (84%). In this way, Bhutan is typical of many LMICs and we calculate a rough estimate of "missed opportunities" for epilepsy surgery investigation of at least 10% of all epilepsy cases. Although seemingly expensive, it is likely that epilepsy surgery is a viable and cost-effective measure for a subset of PWE in LMICs given the substantial quality of life and economic

Table 3. Clinical Variables and Their Association With an Abnormal Brain MRI

	Any Structural Brain MRI Abnormalities		Abnormal MRIs Deemed Probable Cause of Epilepsy		Mesial Temporal Sclerosis	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Age	0.99 (0.95-1.03)	.68	0.98 (0.94-1.02)	.42	0.99 (0.96-1.01)	.69
No. of AEDs	0.59 (0.36-0.95)	.03	0.69 (0.42-1.15)	.15	1.15 (0.82-1.61)	.38
Duration of epilepsy	1.11 (1.02-1.22)	.02	1.10 (1.02-1.21)	.02	1.01 (0.97-1.05)	.45
Seizures in the last mo	1.07 (0.40-2.83)	.88	0.98 (0.36-2.65)	.98	0.47 (0.26-0.84)	.01

CI, confidence interval; MRI, magnetic resonance imaging.

gains that could be made for people with seizure freedom.

Our study had several limitations. The sample was referral based and does not provide population-based estimations of prevalence. Generalizability to other LMICs is uncertain but plausible for other neurocysticercosis-endemic, middle-income countries. Cases of epilepsy that were milder may not have been referred as often to our study. This may explain the overall high prevalence of abnormal findings here when compared with prior large case series elsewhere.[16] It is conversely possible that the most severe cases of epilepsy were not included in this study because of premature mortality, immobility, or economic hardship. Self-reported information is subject to recall bias. Participants had to present for testing on more than 1 occasion, one for first enrollment and another for the MRI. This may explain the noticeable number of participants who did not have a brain MRI in a timely way in this mountainous terrain. Our results do not generalize well to children <5 years old, who were often excluded because of lack of clinical indication for brain MRI and who may have a milder epilepsy presentation.

Our study strengths included the prospective and systematic data collection among participants in a resource-limited setting without routine epilepsy diagnostic services. Our study population is one of the largest in LMICs in whom brain MRI was completed. The MRI interpretations from different locations increase the quality of our interpretations and the precision and reliability of our results, minimizing bias from a single interpreter in any one setting. The population-based prevalence of brain MRI abnormalities, including white matter changes, in Bhutanese people without epilepsy is unknown. The very high prevalence of MRI white matter brain abnormalities in this cohort, although expected to be high, was still surprising.

In countries where there are no diagnostic tests available for PWE, a common first strategy is to recommend EEG or head computed tomography. From our perspective, however, improving access to brain MRI can provide a higher diagnostic yield and represents an important step toward closing the epilepsy treatment gap in LMICs. High-quality images through the introduction of new technologies like low magnetic field implementation of MRI could soon provide clinically relevant images via affordable and portable devices.[17] Additionally, current systems to exchange images and share files make the evaluation of the results and remote second opinions relatively easy for future patients.[18] Although MRI is not close to being universally available, its utility suggests it is a powerful clinical tool, and one whose value should be thoughtfully weighed when allocating resources for the diagnosis of epilepsy in LMIC settings.

REFERENCES

1. Dua T, de Boer HM, Prilipko LL, Saxena S. Epilepsy care in the world: results of an ILAE/IBE/WHO Global Campaign Against Epilepsy survey. Epilepsia 2006;47:1225–31.
2. Gaillard WD, Chiron C, Cross JH, et al. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia 2009;50:2147–53.
3. Recommendations for neuroimaging of patients with epilepsy. Commission on Neuroimaging of the International League Against Epilepsy. Epilepsia 1997;38:1255–6.
4. Brizzi K, Deki S, Tshering L, et al. Knowledge, attitudes and practice regarding epilepsy in the Kingdom of Bhutan. Int Health 2016;8:286–91.
5. McKenzie ED, Nirola DK, Deki S, et al. Medication prescribing and patient-reported outcome measures in

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May–August 2017: 415–422

people with epilepsy in Bhutan. Epilepsy Behav 2016;59:122–7.
6. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–9.
7. Kwon CS, Neal J, Telléz-Zenteno J, et al. Resective focal epilepsy surgery: has selection of candidates changed? A systematic review. Epilepsy Res 2016;122:37–43.
8. Connor SE, Jarosz JM. Magnetic resonance imaging of patients with epilepsy. Clin Radiol 2001;56:787–801.
9. McLane HC, Berkowitz AL, Patenaude BN, et al. Availability, accessibility, and affordability of neurodiagnostic tests in 37 countries. Neurology 2015;85:1614–22.
10. Bakhsh A. Value of neuroimaging in epilepsy: an experience from Pakistan. J Neurosci Rural Pract 2013;4(Suppl 1):S35–9.
11. Siddiqi OK, Elafros MA, Sikazwe I, et al. Acute EEG findings in HIV-infected Zambian adults with new-onset seizure. Neurology 2015;84:1317–22.
12. Tobgay T, Dorji T, Pelzom D, Gibbons RV. Progress and delivery of health care in Bhutan, the Land of the Thunder Dragon and Gross National Happiness. Trop Med Int Health 2011;16:731–6.
13. Campos MG. Epilepsy surgery in developing countries. Handb Clin Neurol 2012;108:943–53.
14. Kasradze S, Alkhidze M, Lomidze G, Japaridze G, Tsiskaridze A, Zangaladze A. Perspectives of epilepsy surgery in resource-poor countries: a study in Georgia. Acta Neurochir 2015;157:1533–40.
15. Mikati MA, Ataya N, El-Ferezli J, et al. Epilepsy surgery in a developing country (Lebanon): ten years experience and predictors of outcome. Epileptic Disord 2012;14:267–74.
16. Craven IJ, Griffiths PD, Bhattacharyya D, et al. 3.0 T MRI of 2000 consecutive patients with localisation-related epilepsy. Br J Radiol 2012;85:1236–42.
17. Sarracanie M, LaPierre CD, Salameh N, Waddington DE, Witzel T, Rosen MS. Low-cost high-performance MRI. Sci Rep 2015;5:15177.
18. Potchen MJ, Kampondeni SD, Ibrahim K, et al. NeuroInterp: a method for facilitating neuroimaging research on cerebral malaria. Neurology 2013;81:585–8.