Neuroimaging abnormalities and seizure recurrence in a prospective cohort study of Zambians with human immunodeficiency virus and first seizure

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Abstract

In HIV-positive individuals with first seizure, we describe neuroimaging findings, detail clinical and demographic risk factors for imaging abnormalities, and evaluate the relationship between imaging abnormalities and seizure recurrence to determine if imaging abnormalities predict recurrent seizures. Among 43 participants (mean 37.4 years, 56% were male), 16 (37%) were on antiretroviral drugs, 32 (79%) had advanced HIV disease, and (28) 66% had multiple seizures and/or *status epilepticus* at enrollment. Among those with cerebrospinal fluid studies, 14/31 (44%) had opportunistic infections (OIs). During follow-up, 9 (21%) died and 15 (35%) experienced recurrent seizures. Edema was associated with OIs (odds ratio: 8.79; confidence interval: 1.03-236) and subcortical atrophy with poorer scores on the International HIV Dementia Scale) (5.2 *vs*. 9.3; P=0.002). Imaging abnormalities were not associated with seizure recurrence or death (P>0.05). Seizure recurrence occurred in at least a third and over 20% died during follow-up. Imaging was not predictive of recurrent seizure or death, but imaging abnormalities may offer additional diagnostic insights in terms of OI risk and cognitive impairment.

Introduction

In patients presenting with their first seizure, identifiable structural brain abnormalities are a risk factor for recurrent seizure and imaging helps guide clinicians in determining whether or not to recommend the initiation of chronic treatment with antiepileptic drugs (AEDs) after an initial seizure.[1] The epidemiologic data that informs this decision-making process was obtained in studies of HIV negative individuals. Whether structural brain lesions in people with HIV, a significant proportion of which may represent transient, infectious phenomena, are predictive of recurrent seizures and indicate the need for chronic therapy is unknown. In resource-limited settings, where enzyme-inducing AEDs may be the only available medications, initiating long-term epilepsy treatment carries the additional concern of adverse AED-antiretroviral (ARV) interactions and warrants especially careful consideration.[2]

In the US, neuroimaging is indicated in HIV+ patients with new onset seizure for diagnostic purposes and to assure that lumbar puncture is not contraindicated.[3] In sub-Saharan African (SSA) countries, HIV remains the number one cause of disease and disability, despite the availability of ARVs.[4] Although neuroimaging was not routinely available in most African settings in 2004,[5] there is some evidence that, at least in tertiary care centers, access to imaging technology is improving.[6]

There are few studies of HIV-related neuroimaging findings in Africa,[7] and viral clade differences may make extrapolations from the United States and European studies inappropriate.[8] In African children with HIV, brain atrophy with dilatation of the lateral ventricles, calcification of the basal ganglia, and periventricular white matter involvement are the most common neuroimaging findings.[7] We report the neuroimaging findings in a Cohort study of HIV-Associated Seizures and Epilepsy (CHASE study) which was conducted in Zambia. Acute clinical and demographic risk factors for imaging abnormalities and the prognostic value of imaging for seizure recurrence and death are also described.

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Materials and Methods

HIV+ adults who presented to the University Teaching Hospital in Lusaka, Zambia with new onset seizure between August 1, 2011 and June 19, 2013 were enrolled in CHASE. Additional inclusion criteria included age ≥18 years and no prior history of seizures except for childhood febrile seizures. Written consent from the patient or their proxy was required. At enrollment, clinical and demographic characteristics were obtained as well as an electroencephalograph and, for patients who consented to lumbar puncture, cerebrospinal fluid (CSF) analysis which included extensive studies using PCR technology to identify opportunistic infections (OIs). After discharge, neuropsychiatric assessments with instruments previously used in Zambia to detect HIV-associated neurocognitive disorders (HAND) and psychiatric morbidity[9,10] were conducted by a neuropsychologist (LK) including the Shona Symptom Questionnaire (SSQ),[11] the International HIV Dementia Scale (IHDS) and the Zambian Mini-mental State Exam (zMMSE).[12-14] CHASE participants were followed prospectively with explicit assessments made during their HIV clinic visits to identify recurrent seizures. Death outcomes were obtained through clinic and hospital records and contact with family members through December 21, 2013. When family members were interviewed after the death of a participant, specific questions were asked regarding recurrent seizures including seizures around the time of death.

A head computed tomography (CT) with contrast was performed as part of the study for CHASE participants in whom no seizure etiology was established based upon other diagnostic assessments, including CSF analyses. CT imaging was acquired on a Siemens CT2007YS CT scanner and magnetic resonance (MR) imaging on a Siemen's Magnetom Essenza 1.5T MRI scanner Siemens, Munich, Germany). CT protocols included: 1.5 mm contiguous axial imaging from the foramen magnum through the vertex for 3D reconstruction with 4 mm oblique axial imaging pre- and post-contrast. CT contrast using Ultravist 300 was administered. MRI protocols included sagittal T1, Axial T2, FLAIR, Diffusion weighted imaging with apparent diffusion coefficients, and T1 pre and post contrast, as well as Coronal T2 images. MRI contrast using Magnevist was administered by hand injection. Several participants had neuroimaging studies, including 2 MRIs, obtained as part of their routine clinical care. In these patients, there were no predetermined criteria for contrast administration and not all of them received contrast, possibly due to medical contraindications or cost incurred directly by the patient. Both CT and MRI findings were interpreted and coded using an early version of NeuroInterp which codes dichotomous or ordinal values for specific anatomical findings.[15] These included the presence of cortical abnormalities, the presence of white matter abnormalities, the extent of white matter involvement, deep structural abnormalities, and posterior fossa abnormalities. Other radiographic findings captured included the presence of: abnormal masses or mass effect, abnormal fluid collections, intracranial bleeds, and calcifications. The extent of ventricular size (decreased, normal or increased), and brain volume (on a scale of 1-5 with 3 being normal) were determined as well as contrast enhancement, if contrast was administered. The study radiologist (MJP) interpreted both the clinical and research images. He was provided with age and gender and was aware of the patients' HIV status and presenting symptoms, but was blinded to other clinical findings and outcome. Data were analyzed using Epi Info version 7.0.

We used chi-square, t-test analysis or the Kruskal-Wallis test where population variances were non-homogenous to i) identify clinical and demographic risk factors for imaging findings, and ii) determine if imaging findings were predictive of death or recurrent seizure. The small sample size precluded multivariate analyses. A P-value <0.05 was considered statistically significant.

Prior to study initiation, the Michigan State University Biomedical Institutional Review Board (MSU BIRB) and the University of Zambia, School of Medicine Biomedical Research Ethics Committee (UNZA BREC) provided ethical approval of the study. Written consent for participation was obtained from the participant or their proxy, if the participant was incapacitated.

Results

A total of 43 CHASE participants were imaged: 41 with CT and 2 using MRI. The mean age of participants was 37 years; 24 were male. Almost two-thirds had never received treatment with ARVs. Approximately 80% had advanced HIV infection (WHO Stage III or IV; mean CD4 count 186 cells/mm^3) and 44% had an OI identified. The neuropsychiatric symptom burden was high, with over half of participants endorsing symptoms of anxiety and depression severe enough to warrant further clinical evaluation based upon WHO recommendations using the SSQ.[11] Over half also scored below normal values on the IHDS and on the less specific zMMSE suggesting a substantial burden of cognitive impairment in this cohort (Table 1).

Imaging abnormalities were identified in 70% of participants, with white matter abnor-

Table 1. Clinical characteristics and outcomes (n=43).

Characteristics	Values
Age, mean years (SD)	37.4 (11.0)
Gender, male n (%)	24 (56)
CD4 count, mean (SD) >200 n (%) <50 n (%) 50-200 n (%)	186 (215) 14 (33) 12 (28) 17 (40)
WHO clinical stage, n=40, n (%)	I: 6 (14) II: 2 (5) III: 14 (36) IV: 18 (43)
Antiretroviral use, n (%)	Never: 24 (56) Active: 16 (37) Defaulted: 3 (7)
Psychiatric Symptom Burden n=59 mean Shona Symptom Score (SD)	4.6 (3.0): 56% requiring additional evaluation*
International HIV Dementia Scale, n=59 (mean, SD, % impaired)	8.7 (2.8): 54% impaired
Zambian Mini-Mental State Exam n=59 (mean, SD, % impaired)	20.7 (3.9): 51% impaired
Seizure severity at first seizure, n (%)	Single, brief seizure 15 (35); Multiple seizures, not status epilepticus 20 (47); Status epilepticus 8 (19)
CNS opportunistic infection n=31, n (%)	14 (44)
Outcomes, n (%)	Recurrent seizures 15 (35) Died 9 (21)

*Based upon score and recommendations during Zimbabwe-based validation studies.

malities being the most common finding (56%), primarily from vasogenic edema. Deep gray (19%), posterior fossa (21%), and cortical abnormalities (28%) were also common. Contrast enhancement was seen in 29% of the 37 subjects who received contrast. Brain volumes were increased in 17% of subjects usually associated with CNS infections, while other participants showed evidence of generalized atrophy. Isolated enlarged ventricles, indicative of subcortical atrophy, were seen in 16% (Table 2). Given the prevalence of imaging abnormalities in this cohort, our analyses had ~90% power to detect an effect size difference of 22% or more in the primary outcomes of interest (death and recurrent seizure). During follow-up, 15 (35%) had recurrent seizures and 9 (21%) died.

Patients with entirely normal brain images had a lower burden of depression and anxiety symptoms based upon the SSQ (3.0 *vs*. 5.3, P=0.04) and patients with subcortical atrophy had a lower mean IHDS score (5.2 *vs*. 9.3, P=0.002). Although edema was associated with OIs (36 *vs*. 6%, OR 8.79 (95%CI: 1.03-236, P=0.04), none of the imaging findings, including cortical lesions, were predictive of seizure recurrence or death (Table 3).

Discussion and Conclusions

In this cohort of HIV-positive patients with their first seizure, most had advanced HIV disease and *status epilepticus* was common. Imaging abnormalities were evident in 70%. The imaging findings were diverse and included evidence of acute OIs as well chronic atrophic changes. *Recurrent seizures and death occurred in over half during follow-up. Structural brain lesions, evident primarily using CT, were not predictive of recurrent seizure or death in this cohort.*

This patient population was evaluated at Zambia's only tertiary care referral center and as such they may not be representative of all adults with HIV in Zambia. Attempts to recruit from a community-based HIV clinic for more than 6 months failed to identify anyone with HIV presenting in the outpatient settings within 2 weeks of a new onset seizure. CT was the imaging modality used in 41/43 patients. MRI imaging may have identified lesions not evident on CT. However, CT is more readily available and less expensive in most African tertiary care centers and therefore this data may be particularly useful in such resource limited settings. Imaging was preferentially obtained on CHASE patients who had no evident etiology for their seizure after a thorough work up including extensive CSF studies. Recurrent seizures in participants who died may not have been adequately identified, but there was also no association between imaging abnormalities and death.

Participants with any abnormality on their brain image had a higher burden of psychiatric symptoms. This is particularly interesting since psychiatric morbidity, as measured by the SSQ, has previously been shown to predict early mortality in rural Zambians with HIV, even after controlling for HIV stage and socioeconomic status.[12] Subcortical atrophy was associated with clinical evidence of cognitive impairment based upon lower IHDS scores. Previous research in South Africa using MRI technology identified brain atrophy in several brain regions (white matter, thalamus, gray matter, subcortical regions) in HIV+ *vs*. HIV– individuals.[8] Using CT technology, we found that subcortical atrophy was specifically associated with the evidence of lower mean scores on the IHDS but not zMMSE. Neuropsychiatric morbidity, including cognitive impairment, depression and anxiety, are likely underdiagnosed and undertreated in most resource limited settings. The association between psychiatric symptoms and structural brain lesions provides further support for the need to institute basic neuropsychiatric screening in HIV clinics.[12,13] Epilepsy is a common non-communicable disease in SSA, where most people with HIV reside and the inevitable co-occurrence of two common conditions is further compounded by the high risk of provoked seizure in people with HIV due to OIs, metabolic derangements, ARVs which reduce the seizure threshold, and other challenges. Further studies are needed to determine neurologic vulnerabilities and outcomes in people with HIV, particularly in rural and pediatric populations. As HIV continues to evolve from a fatal to a chronic condition and neuroimaging becomes increasingly available, clinicians and researchers need additional epidemiologic and natural history data relevant to this population to direct care and set research priorities.

Table 2. Imaging abnormalities identified in HIV+ patients with new onset seizure (n=43).

Location of abnormality	Prevalence, n. (%)	Description (n)*
Entirely normal	13 (30)	-
Cortical	12 (28)	Decreased attenuation on CT/increased T2 on MRI (4); diffuse cortical thickening (1); focal cortical thickening (2); focal cortical atrophy (1); multifocal enhancing lesions (1); old CVA (1); small cortical defect (1); calcification (2)
White matter	24 (56)	Decreased attenuation on CT/Increased T2 on MRI: mild (3); markedly diffuse (5); markedly multifocal (6). Gliosis (1);° focal vasogenic edema (8); focal deep infarct (old) (1)
Deep gray matter	8 (19)	Decreased attenuation on CT/Increased T2 on MRI with mass effect (3); decreased attenuation on CT/Increased T2 on MRI without mass effect (2); focal encephalomalacia (1); multifocal cystic (2)
Posterior fossa	9 (21)	Decreased attenuation on CT/Increased T2 on MRI (6); edema (1); multifocal cystic (2)
Contrast enhancement (n=34)	10 (29)	Discrete cortical lesions (3); leptomeninges (4); vague peripheral (1); ring enhancing (1); subcortical white matter and basil cisterns (1)
Brain volume	Atrophy 7 (16); normal 29 (67); mild swelling 5 (12); gross swelling 2 (5)	2=atrophy; 3=normal; 4=mild swelling; 5=gross swelling. Decreased brain volume associated with generalized atrophy
Ventricular size	Normal 31 (72); small 5 (12); large 7 (16)	Increased ventricular size associated with subcortical atrophy

MRI, magnetic resonance imaging; CT, computed tomography. *Not mutually exclusive categories; °Meaning white matter T2 changes without mass effect.

Table 3. Association between neuroimaging findings in HIV+ patients with new onset seizure, acute clinical characteristics, recurrent seizure and death.

	CD4+ T-cell count (mean)	WHO clinical stage (early I/II vs. late III/IV)	On ARVs at enrollment	SSQ (mean)	IHDS (mean)	MMSE (mean)	Seizure severity (single brief vs. multiple/ prolonged)	CNS OI	Recurrent seizure	Death
Normal image	172 *vs.* 193 P=0.77	44 *vs.* 26%; OR 2.22 (0.43-10.6); P=0.26	21 *vs.* 34%; OR 0.53 (0.10-2.28); P=0.31	3.0 *vs.* 5.3 P=0.04	9.0 *vs.* 8.6 P=0.69	22.4 *vs.* 20.0 P=0.18	33 *vs.* 29%; OR 1.24 (0.3-4.93); P=0.38	29 *vs.* 33%; OR 0.81 (0.16-3.81); P=0.54	23% *vs.* 40%; RR 0.58 (0.20-1.71); P=0.24	23% *vs.* 20%; RR 1.15 (0.34-3.92); P=0.56
Cortical abnormality	278 *vs.* 151 P=0.60	11 *vs.* 32%; OR 0.27 (0.01-1.99); P=0.20	28 *vs.* 29%; OR 1.05 (0.23-4.40); P=0.61	5.9 *vs.* 4.0 P=0.09	8.7 *vs.* 8.7 P=0.95	20.8 *vs.* 20.7 P=0.92	27 *vs.* 29%; OR 0.91 (0.20-3.77); P=0.59	21 *vs.* 44%; OR 0.35 (0.06-1.69); P=0.16	42 *vs.* 32%; OR 1.29 (0.56-3.00); P=0.29	8 *vs.* 26%; RR 0.32 (0.05-2.31); P=0.21
White matter abnormality	187 *vs.* 185 P=0.98	33 *vs.* 62%; OR 0.32 (0.06-1.51); P=0.13	57 *vs.* 55%; OR 1.08 (0.29-414); P=0.46	5.0 *vs.* 4.0 P=0.32	8.1 *vs.* 9.5 P=0.17	20.0 *vs.* 21.8 P=0.18	60 *vs.* 53%; OR 1.29 (0.36-4.89); P=0.35	64 *vs.* 56%;OR 1.40 (0.33-6.46); P=0.32	46 *vs.* 27%; RR2.18 (0.82-5.76); P=0.08	17 *vs.* 26%; RR 0.63 (0.20-2.04); P=0.34
Deep gray matter abnormality	140 *vs.* 197 P=0.37	0 *vs.* 24%; OR undefined; P=0.13	14 *vs.* 21%; OR 0.65 (0.08-3.59); P=0.28	5.8 *vs.* 4.4 P=0.48	8.3 *vs.* 8.8 P=0.74	20.7 *vs.* 20.7 P=0.97	27 *vs.* 14%; OR 2.14 (0.41-11.19); P=0.18	36 *vs.* 16%; OR 2.69 (0.50-16.66); P=0.21	50 *vs.* 31%; RR 1.59 (0.68-3.72); P=0.27	25 *vs.* 20%; RR1.25 (0.32-4.92); P=0.37
Posterior fossa abnormality	135 *vs.* 200 P=0.77	11 *vs.* 24%; OR 1.04 (0.02-3.20); P=0.39	22 *vs.* 21%; OR 1.04 (0.18-5.06); P=0.62	3.9 *vs.* 4.8 P=0.46	9.1 *vs.* 8.6 P=0.64	21.0 *vs.* 20.6 P=0.83	33 *vs.* 14%; OR 2.92 (0.62-14.65); P=0.14	29 *vs.* 17%; OR 1.96 (0.33-12.56); P=0.35	33 *vs.* 35%; RR 0.94 (0.34-2.65); P=0.62	22 *vs.* 21%; RR 1.10 (0.27-4.33); P=0.91
Contrast enhancement	311 *vs.* 154 P=0.78	29 *vs.* 27%; OR 1.10 (0.13-6.87); P=0.63	18 *vs.* 31%; OR 0.51 (0.06-2.79); P=0.36	3.8 *vs.* 4.7 P=0.46	8.4 *vs.* 8.8 P=0.77	20.0 *vs.* 21.4 P=0.29	36 *vs.* 33%; OR 1.96 (0.42-9.21); P=0.19	42 *vs.* 27%; OR 1.91 (0.36-10.8); P=0.34	20 *vs.* 41%; RR 0.49 (0.13-1.84);P=0.22	20 *vs.* 19%; RR 1.08 (0.25-4.70); P=0.63
Subcortical atrophy	257 *vs.* 173 P=0.58	11 *vs.* 86%; OR 0.59 (0.03-4.85); P=0.54	29 *vs.* 10%; OR 3.35 (0.59-20.93); P=0.14	4.2 *vs.* 4.7 P=0.73	5.2 *vs.* 9.3 P=0.002	17.0 *vs.* 21.3 P=0.72	13 *vs.* 18%; OR 0.71 (0.86-4.18); P=0.53	*vs.* 17%; OR 0.84 14 (0.09-6.50); P=0.62	*vs.* 33%; RR 1.29 43 (0.49-3.40); P=0.47)	43 *vs.* 17%; RR 2.57 (0.83-7.92); P=0.23
Edema	197 *vs.* 184 P=0.89	0 *vs.* 21%; OR undefined; P=0.17	17 *vs.* 14%; OR 1.24 (0.21-10.43); P=0.59	5.3 *vs.* 4.5 P=0.53	9.3 *vs.* 8.6 P=0.54	21.2 *vs.* 20.6 P=0.76	13 *vs.* 18;OR 0.71 (0.09-4.18); P=0.53	36 *vs.* 6%; OR 8.79 (1.03-236); P=0.04	43 *vs.* 33%; RR 1.29 (0.49-3.40); P=0.47	14 *vs.* 22%; RR 0.64 (0.09-4.36); P=0.54
Atrophy	225 *vs.*179 P=0.47	22 *vs.* 71%; OR 1.64 (0.19-10.37); P=0.46	21 *vs.* 14%; OR 1.68 (0.27-9.51); P=0.41	4.8 *vs.* 4.6 P=0.89	6.4 *vs.* 9.1 P=0.05	17.6 *vs.* 21.2 P=0.72	14*vs.* 86%; OR 0.27 (0.01-2.08);P=0.21	7 *vs.* 17%; OR 0.40 (0.01-4.18); P=0.40	4.3*v* s. 33%; RR 1.29 (0.49-3.40); P=0.47	43 *vs.* 17%; RR 2.57 (0.83-7.92); P=0.15

ARV, adverse antiepileptic drugs-antiretroviral; SSQ, Shona Symptom Questionnaire; IHDS, International HIV Dementia Scale; zMMSE, Zambian Mini Mental State Examination; OI, Opportunistic infection.

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