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Electroencephalographic features of convulsive epilepsy in Africa: A multicentre study of prevalence, pattern and associated factors

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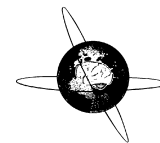
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Electroencephalographic features of convulsive epilepsy in Africa: A multicentre study of prevalence, pattern and associated factors

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HIGHLIGHTS

- Electroencephalographic abnormalities are common in Africans with epilepsy, with an adjusted prevalence of 2.7 (95% confidence interval, 2.5–2.9) per 1000 population.
- Electroencephalographic abnormalities are associated with preventable factors such as adverse perinatal events and frequent seizures.
- Electroencephalography is helpful in identifying focal epilepsy in Africa, where timing of focal aetiology is problematic and there is a lack of neuroimaging services.

ABSTRACT

Objective: We investigated the prevalence and pattern of electroencephalographic (EEG) features of epilepsy and the associated factors in Africans with active convulsive epilepsy (ACE).

Methods: We characterized electroencephalographic features and determined associated factors in a sample of people with ACE in five African sites. Mixed-effects modified Poisson regression model was used to determine factors associated with abnormal EEGs.

Results: Recordings were performed on 1426 people of whom 751 (53%) had abnormal EEGs, being an adjusted prevalence of 2.7 (95% confidence interval (95% CI), 2.5–2.9) per 1000. 52% of the abnormal EEG had focal features (75% with temporal lobe involvement). The frequency and pattern of changes differed with site. Abnormal EEGs were associated with adverse perinatal events (risk ratio (RR) = 1.19 (95% CI, 1.07–1.33)), cognitive impairments (RR = 1.50 (95% CI, 1.30–1.73)), use of anti-epileptic drugs (RR = 1.25 (95% CI, 1.05–1.49)), focal seizures (RR = 1.09 (95% CI, 1.00–1.19)) and seizure frequency (RR = 1.18 (95% CI, 1.10–1.26) for daily seizures; RR = 1.22 (95% CI, 1.10–1.35) for weekly seizures and

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RR = 1.15 (95% CI, 1.03–1.28) for monthly seizures)).

Conclusions: EEG abnormalities are common in Africans with epilepsy and are associated with preventable risk factors.

Significance: EEG is helpful in identifying focal epilepsy in Africa, where timing of focal aetiologies is problematic and there is a lack of neuroimaging services.

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1. Introduction

Epilepsy in Africa is associated with significant morbidity and mortality and a large treatment gap (Newton and Garcia, 2012). Focal features defined by seizure semiology and neurological deficits are common in people with epilepsy from Africa and may be related to perinatal complications, head injuries, and central nervous system infections (Kariuki et al., 2014). Active convulsive epilepsy (ACE) in Africa is associated with childhood onset in 60% of cases, convulsive status epilepticus in about 30%, non-adherence to treatment in 60% and psychosocial problems such as being single in over 60% (Mbuba et al., 2012; Kariuki et al., 2015b). The pattern of neurophysiological features and their association with clinical and psychosocial factors have not been fully ascertained in low and middle-income countries.

Electroencephalography (EEG) is a well-established investigation for evaluating epilepsy and is useful in confirming the diagnosis, classifying seizures, and identifying epilepsy syndromes and epileptogenic zones (Fish and Spencer, 1995). The proportion of abnormal EEGs varies between epilepsy syndromes and may differ between hospital- and community-based samples (Binnie and Stefan, 2003). In a broad sample of people with different types of epilepsy, the yield of interictal epileptiform activity in a single 30-min awake EEG recording is up to 50%, although there is substantial variability between individuals (Cockerell et al., 1996; Binnie and Stefan, 2003). The diagnostic yield of EEG can be improved through increased recording time, serial recordings, sleep and activation procedures such as hyperventilation and photic stimulation (Nuwer, 2012).

In Kenya, the EEG was abnormal in 41% of people with ACE (Munyoki et al., 2010), but this study did not relate the EEG findings to medical and psychosocial factors and cannot be extrapolated to other African settings, where clinical features and risk factors of epilepsy may differ (Ngugi et al., 2013; Kariuki et al., 2014). EEG services are becoming more readily available in Africa and are more common than neuroimaging (Wilmshurst et al., 2011). Studies characterizing the patterns of EEG abnormalities and their clinical and psychosocial correlates may contribute to improving the evaluation and management of epilepsy.

We performed EEGs on people with ACE in five African sites to determine prevalence and patterns of abnormality and to characterize the clinical and psychosocial correlates. We further determined whether these factors differed across these sites.

2. Methods

2.1. Population and sites

We performed EEG on people with ACE identified from a previous epidemiological survey conducted across five sites in Africa, (Agincourt in South Africa; Ifakara in Tanzania; Iganga in Uganda; Kilifi in Kenya and Kintampo in Ghana) (Ngugi et al., 2013). Specific details for the participating sites are available at: http://www.indepth-network.org/index.php?option=com_content&task=view&id=753&Itemid=635. The prevalence of ACE ranged from

7 to 15 per 1000 across the five sites and was associated with exposure to multiple parasites (Kamuyu et al., 2014).

2.2. Investigations and procedures

Electroencephalography was performed using a 16 channel digital recording system (Grass Technologies, Warwick, RI, USA) with electrode placement according to the international 10–20 system (Japer, 1958). All hyperventilated for 3 min and had photic stimulation (Binnie, 2003). EEGs were reported by one physician (EC), using a protocol developed under the guidance of an experienced neurophysiologist (SW). This protocol followed standard definitions of the EEG features commonly assessed in clinical practice (Binnie, 2003; Binnie and Stefan, 2003). Briefly, the report commented on the general background activity classified as normal or abnormal if there was a mild, moderate or severe excess of generalized slow activity. Significant background asymmetries between the hemispheres and non-epileptiform focal features (mainly focal theta and slow activity) were coded. Interictal epileptiform discharges (IEDs) were identified. These were defined as sharp waves, spike discharges, spike and wave complexes, polyspike and wave bursts. IEDs were classified as generalized (diffuse abnormal EEG pattern involving the entire brain), focal (localized abnormal EEG pattern involving a region of the brain) or multifocal (involving 3 or more discrete brain regions). Abnormalities during hyperventilation (focal or asymmetric slowing; focal or generalized epileptiform activity) and evidence of photosensitivity (photoparoxysmal responses) were noted. An EEG was categorized as abnormal if there was evidence of an abnormal background, focal changes, interictal epileptiform activity or an abnormal response to either of the activation procedures (hyperventilation and photic stimulation).

A sample of EEGs recordings and reports were checked for accuracy and consistency by SW. A clinician recorded use of anti-epileptic drugs (AEDs) and history of febrile or non-febrile seizures in the family.

2.3. Definition of terms

Epilepsy, defined as ≥ 2 unprovoked seizures (ILAE, 1993), was classified as active if seizures had occurred in the previous 12 months. Seizures were classified as focal, generalized, or other using a classification system devised for epidemiologic studies (Thurman et al., 2011). Seizure frequency was categorized into daily (at least one each day; coded 3), weekly (at least one a week; coded 2), monthly (at least one a month; coded 1), and yearly (at least one a year; coded 0). Status epilepticus was defined as a history of seizures lasting 30 min or more, while for those without watches, culturally appropriate events such as boiling a pot of maize were used to estimate time as defined previously (Kariuki et al., 2015b). Status epilepticus was considered febrile if it occurred with a febrile illness. Children were defined as those <18 years. A clinician assessed cognitive status by asking standardized questions about awareness of place, person and time. Determination of malnutrition was described previously (Kariuki et al., 2014). Acute encephalopathy was defined as a history of admission

to hospital with a febrile malarial, bacterial or viral illness. Adverse perinatal events were defined in those ≤ 18 years as a history of delays in crying, breathing and/or breastfeeding at birth.

2.4. Statistical analysis

We performed statistical analysis with STATA version 13.1 (Stata Corp, Texas, USA). Prevalence of EEG abnormalities was determined by dividing abnormalities over the surveyed population expressed per 1000 and accounted for the sensitivity of the three-stage screening methodology. The three-stage methodology involved asking of two seizure questions during a routine door-to-door census in the study area in stage-one, collection of detailed seizure information in those with a history of seizures in stage-two, diagnosis of epilepsy by clinicians in those whose seizure details suggested a possibility of repetitive unprovoked seizures in stage-three (Ngugi et al., 2013). Chi-square and Fisher exact (for infrequent measures) tests compared proportions between groups. Student's *t*-test and Mann–Whitney U-test (non-parametric) compared continuous variables such as age. We used modified Poisson regression to compute site-specific relative risks or risk ratios for the associations between EEG features and clinical features and/or psychosocial consequences, with associations reaching a *p*-value of ≤ 0.25 entered into a multivariable model adjusted for age and sex. For associations pooled across all five sites, mixed-effects modified Poisson regression model with a random intercept for site was used since the investigated variables and other unmeasured factors may differ across sites. The four categories of seizure frequency (1–4) were considered as non-linear in the fitted models and thus individual risk ratio (RR) for each category were provided compared with the baseline category. We reported RR since they are more easily interpreted in common conditions with a prevalence $> 10\%$ (Zou, 2004).

2.5. Ethical approval and data security

Ethical approval for this study was granted by the Kenyan Ethical Review Committee and all study participants provided a written-informed consent. Data were anonymised and secured at the research servers of the KEMRI-Wellcome Trust Research Programme.

3. Results

3.1. Description of participants

EEG was performed on 1426 (66%) of 2170 people with ACE whose clinical features were previously described (Fig. 1). Of the 1426 with an EEG, 746 (52%) were males and 679 (48%) were children. Most socio-demographic characteristics, medical history and seizure factors of the 1426 participants with EEG data differed across sites (Tables 1 and 2). There were no differences in features of severe epilepsy between those who provided an EEG sample and those who did not: convulsive status epilepticus (24% vs. 26%, $p = 0.577$), frequent seizures (20% vs. 19%, $p = 0.540$) and AED use (37% vs. 35%, $p = 0.372$).

3.2. Prevalence of EEG abnormalities

EEG abnormalities were present in 751/1426 (53%) in all sites, being highest in Kilifi (293/508 (58%)) and lowest in Iganga (61/147 (42%)) (Table 1–3). EEG abnormalities were similar in males and females (386/746 (52%) vs. 365/680 (54%); $p = 0.465$). EEG abnormalities were more frequent in children than adults (398/679 (59%) vs. 353/747 (47%); $p < 0.0001$).

The overall adjusted prevalence of EEG abnormalities per 1000 population was 2.7 (95% CI, 2.5–2.9), being highest in Agincourt and lowest in Iganga (Fig. 2). Focal features formed over half of the prevalence and were most common in Agincourt and lowest in Iganga (Fig. 2). The prevalence of EEG abnormalities differed with age group, increasing steadily with age and then declining after age 28 years. Prevalence of focal EEG features did not change with age ($p = 0.269$).

3.3. Pattern and distribution of EEG abnormalities

3.3.1. General pattern

Of the 751 subjects with EEG abnormalities, 390 (52%) had focal features, which were commonest in Agincourt (106/111 (96%)) and the occurrence differed with site (Table 3). Most of these focal features had temporal lobe involvement (292/390 (75%)). IEDs were present in 473/751 (63%) of those with abnormal EEG and temporal lobe involvement was common (375/473 (79%)). Multifocal IED were observed in 181/751 (24%) of those with abnormal EEGs,

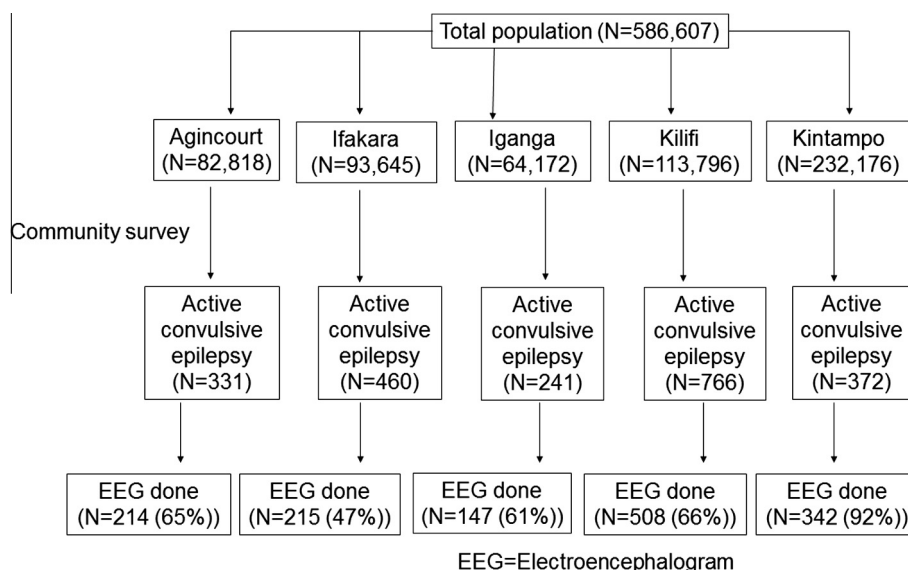


Fig. 1. Derivation of study sample across five sites in Africa. Electroencephalographic investigations were done in over half of those with active convulsive epilepsy across all the five sites in Africa.

Table 1
Sociodemographic characteristics, and medical comorbidities of active convulsive epilepsy in those with electroencephalograms.

Features	Agincourt		Ifakara		Iganga		Kilifi		Kintampo		All sites	
	Normal EEG (N = 103)	Abnormal EEG (N = 111)	Normal EEG (N = 95)	Abnormal EEG (N = 120)	Normal EEG (N = 86)	Abnormal EEG (N = 61)	Normal EEG (N = 215)	Abnormal EEG (N = 293)	Normal EEG (N = 176)	Abnormal EEG (N = 166)	Total normal (N = 675)	Total abnormal (N = 751)
Age in years: median (IQR)	36 (19–49)	27 (17–40)	25 (14–36)	16 (11–28)	11 (5–17)	13 (6–21)	19 (10–31)	16 (10–26)	23 (16–33)	18 (13–25)	21 (13–35)	18 (11–27)
Males	55 (53%)	58 (52%)	45 (47%)	50 (42%)	45 (52%)	31 (51%)	119 (55%)	153 (52%)	96 (55%)	94 (57%)	360 (53%)	386 (51%)
Perinatal complications	0/24 (0%)	5/33 (15%)	2/35 (6%)	7/68 (10%)	5/67 (8%)	0/41 (0%)	4/102 (4%)	14/171 (8%)	12/57 (21%)	30/88 (34%)	23/285 (8%)	56/401 (14%)
Abnormal pregnancy	1/15 (7%)	0/29 (0%)	5/34 (15%)	6/34 (9%)	9/66 (14%)	1/41 (2%)	18/100 (18%)	40/164 (24%)	11/48 (23%)	10/74 (14%)	44/263 (17%)	57/371 (15%)
Age at onset of seizures: median (IQR)	21 (6–36)	13 (4–30)	15 (3–25)	5 (2–13)	2 (1–5)	2 (1–7)	4 (1–18)	3 (1–10)	11 (4–21)	7 (2–13)	8 (2–21)	4 (1–12)
Family history of seizures	8 (8%)	10 (9%)	28 (29%)	38 (32%)	23 (27%)	17 (28%)	56 (26%)	84 (29%)	50 (28%)	53 (32%)	165 (24%)	202 (27%)
Family history of febrile seizures	1 (1%)	3 (3%)	2 (2%)	2 (2%)	15 (17%)	10 (16%)	26 (12%)	42 (14%)	12 (7%)	13 (8%)	56 (8%)	70 (9%)
Acute encephalopathy	2 (2%)	2 (2%)	0 (0%)	1 (1%)	17 (20%)	6 (10%)	28 (13%)	81 (28%)	2 (1%)	3 (2%)	49 (7%)	93 (12%)
<i>Comorbidities of active convulsive epilepsy</i>												
Malnutrition	11 (11%)	12 (11%)	9 (9%)	14 (12%)	17 (20%)	12 (20%)	34 (16%)	51 (17%)	15 (9%)	18 (11%)	86 (13%)	107 (14%)
Neurological deficits	14 (14%)	27 (24%)	2 (2%)	20 (17%)	4 (5%)	17 (28%)	21 (10%)	64 (22%)	7 (4%)	32 (19%)	48 (7%)	160 (21%)
Cognitive impairment	18 (17%)	39 (35%)	4 (4%)	23 (19%)	5 (6%)	16 (26%)	26 (12%)	102 (35%)	28 (16%)	62 (37%)	81 (12%)	242 (32%)
Head injuries	6 (6%)	11/110 (10%)	6/92 (7%)	3/119 (3%)	5/85 (6%)	3/60 (5%)	31/210 (15%)	35/288 (12%)	38 (22%)	49/163 (30%)	86/666 (13%)	101/740 (14%)
<i>Psychosocial factors and outcomes in active convulsive epilepsy</i>												
Burns	15 (15%)	15 (14%)	16 (17%)	17 (14%)	5 (6%)	5 (8%)	31 (14%)	61 (21%)	24 (14%)	29 (17%)	91 (14%)	127 (17%)
Unschooling	23 (22%)	32 (29%)	22 (23%)	65 (54%)	33 (38%)	29 (48%)	89 (41%)	145 (49%)	69 (39%)	67 (40%)	236 (35%)	338 (45%)
Unemployed adults	71/79 (90%)	75/80 (94%)	10/61 (16%)	24/52 (46%)	17/20 (85%)	15/20 (75%)	69/114 (61%)	74/122 (61%)	42/120 (35%)	46/79 (58%)	209/394 (53%)	234/353 (66%)
Unmarried adults	50/79 (63%)	64/80 (80%)	36/61 (59%)	37/52 (71%)	13/20 (65%)	17/20 (85%)	67/114 (59%)	90/122 (74%)	81/120 (68%)	63/79 (80%)	247/394 (63%)	271/353 (77%)

IQR = interquartile range; EEG = electroencephalography.

Table 2
Seizure types, status epilepticus and treatment of convulsive active epilepsy in those with electroencephalograms.

Features	Agincourt		Iganga		Ifakara		Kilifi		Kintampo		Total	Total
	Normal EEG (N = 103)	Abnormal EEG (N = 111)	Normal EEG (N = 95)	Abnormal EEG (N = 120)	Normal EEG (N = 86)	Abnormal EEG (N = 61)	Normal EEG (N = 215)	Abnormal EEG (N = 293)	Normal EEG (N = 176)	Abnormal EEG (N = 166)	Normal EEG (N = 675)	Abnormal EEG (N = 751)
All generalized seizures	55 (53%)	66 (59%)	54 (57%)	59 (49%)	57 (66%)	45 (74%)	60 (28%)	103 (35%)	118 (67%)	104 (63%)	344 (51%)	377 (50%)
Generalized tonic-clonic seizures	45 (44%)	60 (54%)	47 (50%)	51 (43%)	51 (59%)	43 (70%)	52 (24%)	85 (29%)	110 (63%)	97 (58%)	305 (45%)	336 (45%)
Generalized other convulsive seizures	5 (5%)	4 (4%)	0 (0%)	1 (1%)	2 (2%)	1 (2%)	8 (4%)	5 (2%)	5 (3%)	4 (2%)	20 (3%)	15 (2%)
Generalized absence seizures	8 (8%)	12 (11%)	2 (2%)	3 (3%)	2 (2%)	2 (3%)	2 (1%)	17 (6%)	5 (3%)	12 (7%)	19 (3%)	46 (6%)
Generalized unspecified seizures	2 (2%)	1 (1%)	7 (7%)	10 (8%)	3 (3%)	1 (2%)	0 (0%)	3 (1%)	2 (1%)	3 (2%)	14 (2%)	18 (2%)
<i>Focal seizures</i>												
All focal seizures	46 (45%)	46 (41%)	23 (24%)	42 (35%)	26 (30%)	19 (31%)	142 (66%)	201 (69%)	58 (33%)	66 (40%)	295 (44%)	374 (50%)
Focal with generalization	46 (45%)	42 (38%)	16 (17%)	33 (28%)	21 (24%)	13 (21%)	64 (30%)	101 (34%)	47 (27%)	57 (34%)	194 (29%)	246 (33%)
Focal convulsive seizures	1 (1%)	2 (2%)	2 (2%)	4 (3%)	1 (1%)	1 (2%)	48 (22%)	72 (25%)	2 (1%)	1 (1%)	54 (8%)	80 (11%)
Focal dyscognitive seizures	1 (1%)	7 (6%)	1 (1%)	6 (5%)	3 (3%)	6 (10%)	26 (12%)	39 (13%)	11 (6%)	11 (7%)	42 (6%)	69 (9%)
Focal sensory seizures	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	5 (2%)	2 (1%)	0 (0%)	1 (1%)	6 (1%)	4 (1%)
Focal unspecified seizures	0 (0%)	0 (0%)	3 (3%)	4 (3%)	2 (2%)	0 (0%)	9 (4%)	11 (4%)	0 (0%)	0 (0%)	14 (2%)	11 (2%)
Other unspecified seizures	1 (1%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	3 (1%)	1 (<1%)	0 (0%)	0 (0%)	4 (1%)	3 (<1%)
Other convulsive seizures	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	5 (2%)	6 (2%)	0 (0%)	4 (2%)	6 (1%)	10 (1%)
Impaired consciousness	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	2 (<1%)
<i>Status epilepticus and use of AEDs</i>												
Status epilepticus	29/85 (34%)	24/89 (27%)	2/70 (3%)	4/87 (5%)	37/79 (47%)	18/59 (31%)	60/200 (30%)	110/281 (39%)	14/169 (8%)	14/158 (9%)	142/603 (24%)	170/674 (25%)
Febrile status epilepticus	2/85 (2%)	6/89 (7%)	0/71 (0%)	1/88 (1%)	17/79 (22%)	7/59 (12%)	39/201 (19%)	88/283 (31%)	2/159 (1%)	3/147 (2%)	60/595 (10%)	105/666 (16%)
AEDs use	57 (55%)	69 (62%)	38 (40%)	68 (57%)	15 (17%)	18 (30%)	70 (33%)	146 (50%)	24 (14%)	21 (13%)	204 (30%)	322 (43%)

AEDs = anti-epileptic drugs; EEG = electroencephalography.

while other non-specific EEG features were observed in 435/751 (58%) of those with abnormal EEGs.

3.3.2. Distribution across epilepsy and medical factors

EEG abnormalities were more frequent in those with a history of adverse perinatal events (aged ≤ 18 years) (56/79 (71%) vs. 345/607 (57%); $p = 0.017$; Table 1) and acute encephalopathy (93/142 (65%) vs. 658/1284 (51%); $p = 0.001$) compared to those without such histories. Abnormalities were commoner in focal seizures than those without these seizures (374/669 (56%) vs. 377/757 (50%); $p = 0.021$) and in those with neurological deficits than in those without (160/208 (77%) vs. 591/1218 (49%); $p < 0.0001$).

Abnormalities were similar in those with convulsive status epilepticus compared to those without ($p = 0.487$) (Table 2), but were more common in those with a history of febrile convulsive status epilepticus compared to those without convulsive epilepticus status (105/165 (64%) vs. 561/1096 (51%); $p = 0.003$) and were associated with seizure frequency (univariate RR = 1.64 (95% CI,

1.46–1.83) for daily seizures; RR = 1.77 (95% CI, 1.47–2.14) for weekly seizures and RR = 1.44 (95% CI, 1.24–1.67) for monthly seizures). Abnormalities were observed more often in those with self-reported use of AED compared to those without (322/526 (61%) vs. 429/900 (48%); $p < 0.0001$) (Table 2).

3.3.3. Focal EEG features and epilepsy and medical factors

Focal features were associated with an earlier onset of seizures (univariate RR = 0.99 (95% CI, 0.98–0.99); $p < 0.0001$) and increased seizure frequency (univariate RR = 1.731 (95% CI, 1.43–2.10) for daily seizures; RR = 2.01 (95% CI, 1.54–2.62 for weekly seizures and RR = 1.61 (95% CI, 1.25–2.09) for monthly seizures), among those with abnormal EEG. Focal changes were similar in those with and without a history of adverse perinatal events (28/55 (51%) vs. 178/344 (52%); $p = 0.908$) and acute encephalopathy (40/93 (43%) vs. 350/658 (53%); $p = 0.076$). Focal features occurred in 196/375 (52%) of those with generalized seizure semiology and abnormal EEG.

Table 3

Distribution of abnormal electroencephalographic features across the five African sites.

Features	Agincourt (N = 111)	Ifakara (N = 120)	Iganga (N = 61)	Kilifi (N = 293)	Kintampo (N = 166)	All sites (N = 751)	p-value
Focal EEG features	106 (95%)	72 (60%)	23 (38%)	115 (39%)	74 (45%)	390 (52%)	<0.0001
Interictal epileptiform discharges	58 (52%)	79 (66%)	36 (59%)	170 (58%)	130 (78%)	473 (63%)	<0.0001
Multifocal epileptiform discharges	26 (23%)	36 (30%)	19 (31%)	65 (22%)	35 (21%)	181 (24%)	0.250
Generalized epileptiform discharges	5 (5%)	16 (13%)	9 (15%)	39 (13%)	46 (28%)	115 (15%)	<0.0001
Other EEG features	87 (78%)	83 (69%)	28 (46%)	190 (65%)	47 (28%)	435 (58%)	<0.0001
Hyperventilation	20/106 (19%)	25/98 (26%)	5/30 (17%)	30/235 (13%)	41/148 (28%)	12/617 (20%)	0.004
Photosensitivity	6/108 (6%)	15/115 (13%)	1/10 (10%)	20/280 (7%)	0/4 (0%)	42/517 (8%)	0.245

EEG = electroencephalography; The total population (N) is the abnormal EEG features in each site. The features are not mutually exclusive.

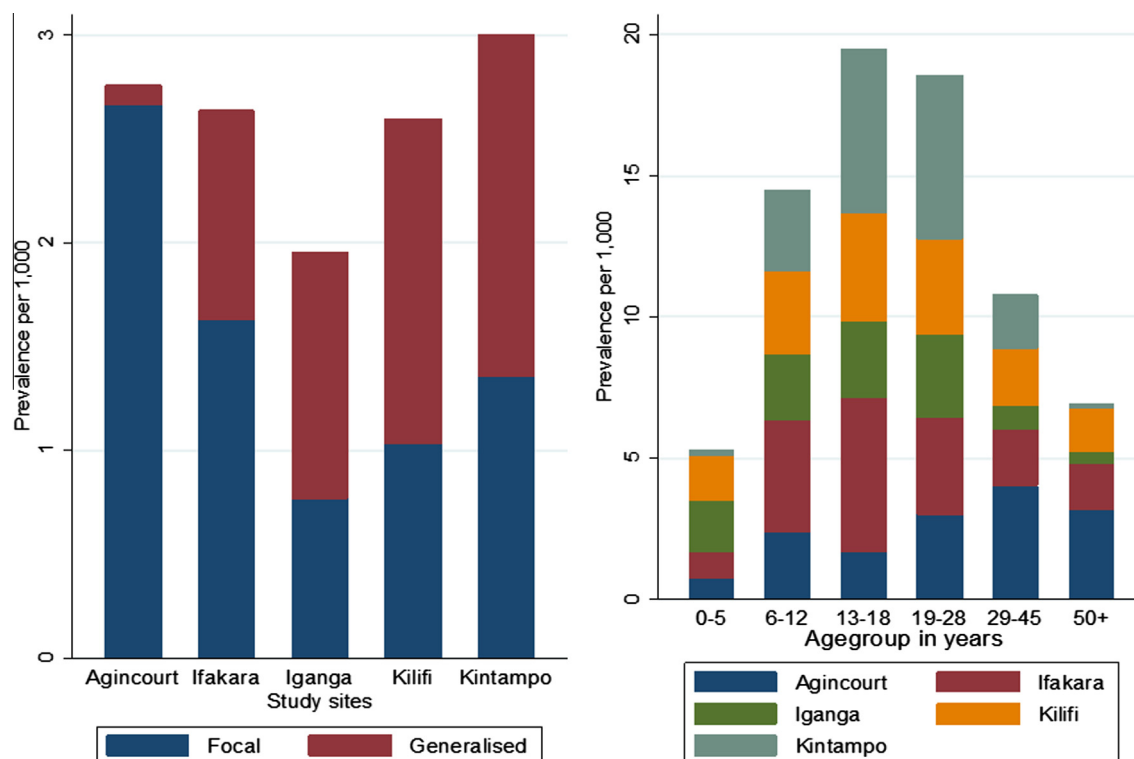


Fig. 2. Prevalence of electroencephalographic features in active convulsive epilepsy in Africa by focal features and site. The prevalence was heterogeneous across the five sites being highest in Kintampo; and increased with age up to 28 years then declined.

3.3.4. Activation procedures in EEG

Hyperventilation provoked abnormalities in 121/617 (20%) of abnormal EEGs, this being most common in Kintampo (41/148 (28%)), with significant differences across the five sites (Table 3). Abnormal hyperventilation responses were associated with the age (univariate RR = 0.0.97 (95% CI, 0.0.96–0.98); $p < 0.0001$) and were significantly greater in those with generalized IEDs than those without (47/79 (59%) vs. 80/538 (15%); $p < 0.0001$). Photosensitivity was seen in 42/517 (8%) with abnormal EEGs being most common in Ifakara (15/115 (13%)), and was similar across the sites. Photosensitivity was significantly commoner in children than adults (30/264 (11%) vs. 12/253 (5%); $p = 0.006$) and in those with multifocal IEDs compared to those without (31/120 (26%) vs. 11/397 (3%); $p < 0.0001$).

3.4. Factors associated with EEG abnormalities

Several factors were associated with abnormal EEG features in the univariate analysis (Table 4). After including variables with a p -value of ≤ 0.25 in a multivariable model, the following were independently associated with abnormal EEGs for all participants from the five sites combined: adverse perinatal events (RR = 1.19 (95% CI, 1.07–1.33)), cognitive impairments (1.50 (95% CI, 1.30–1.73)), use of AEDs (RR = 1.25 (95% CI, 1.05–1.49)), focal seizures (RR = 1.10 (95% CI = 1.00–1.19)) and seizure frequency (RR = 1.18 (95% CI, 1.10–1.26) for daily seizures; RR = 1.22 (95% CI, 1.10–1.35) for weekly seizures and RR = 1.15 (95% CI, 1.03–1.28) for monthly seizures). Factors independently associated with abnormal EEGs within the sites are shown in Table 5. None was significant in every one of the five sites.

4. Discussion

This study suggests that the prevalence of EEG abnormalities in Africans with ACE is high; particularly in children and that they dif-

fer significantly between sites. EEG abnormalities were associated with perinatal complications, neurocognitive impairments and epilepsy related factors such as AED use and seizure frequency. In the within site analysis, none of these factors was associated with abnormal EEG across all the five sites, with only AED use appearing significant in three sites.

4.1. Prevalence of EEG abnormalities

The prevalence of EEG abnormalities is higher than in a previous Kenyan study (Munyoki et al., 2010), suggesting that estimates from one site cannot be extrapolated across Africa. The estimates represent an absolute minimum since non-convulsive epilepsy was not assessed, which may increase the prevalence of observed EEG abnormalities (Zehtabchi et al., 2013). Only single routine EEG recordings were performed, which will be expected to have a lower yield of abnormalities than serial or sleep EEGs (Nuwer, 2012). It was observed that a few patients had EEG performed while drowsy or in light sleep which may have improved the yield (but this was not systematically documented during the study). The heterogeneity in prevalence across the sites may be related to differences in the aetiology, e.g. falciparum malaria in Kilifi and Iganga and head injuries in Agincourt, and epilepsy factors reported previously (Kariuki et al., 2014). All recordings from the five sites were rated by one individual with expertise in EEG and epilepsy, following a standardized protocol. Over half of people with abnormal EEG in ACE in this study may benefit from improved diagnosis and management, although EEG are not routinely performed in Africans hospitalized with epilepsy (Kariuki et al., 2015a).

4.2. Clinical utility of EEG

The EEG may help in classifying epilepsy as focal or generalized (King et al., 1998). In our sample about 50% of people with abnormal EEG for whom generalized seizure semiology was described in

Table 4

Univariate analysis of the association of abnormal electroencephalographic features with clinical features and psychosocial factors of epilepsy.

Features	Agincourt RR (95% CI)	Ifakara RR (95% CI)	Iganga RR (95%)	Kilifi RR (95%)	Kintampo RR (95%)	All sites RR (95% CI)
Age	0.99 (0.98–0.99)	0.99 (0.98–1.00)	1.00 (0.98–1.02)	0.99 (0.98–0.99)	0.97 (0.94–0.98)	0.99 (0.98–0.99)
Male sex	0.97 (0.75–1.27)	0.90 (0.70–1.16)	0.97 (0.67–1.42)	0.95 (0.82–1.10)	1.04 (0.84–1.30)	0.96 (0.92–1.01)
Family history of all seizures	1.08 (0.70–1.67)	1.05 (0.81–1.35)	1.03 (0.67–1.58)	1.06 (0.90–1.37)	1.09 (0.86–1.37)	1.06 (1.05–1.07)
Family history of febrile seizures	1.46 (0.81–2.61)	0.89 (0.33–2.41)	0.96 (0.57–1.62)	1.08 (0.88–1.33)	1.08 (0.73–1.60)	1.05 (0.95–1.17)
Perinatal abnormalities	1.86 (1.44–2.40)	1.20 (0.82–1.76)	–	1.26 (0.97–1.65)	1.27 (0.98–1.64)	1.25 (1.11–1.39)
Abnormal pregnancy	–	0.82 (0.47–1.44)	0.24 (0.04–1.59)	1.15 (0.93–1.40)	0.75 (0.47–1.21)	0.94 (0.68–1.30)
Head injuries	1.28 (0.88–1.87)	0.58 (0.23–1.48)	0.90 (0.36–2.26)	0.91 (0.71–1.15)	1.25 (0.99–1.57)	1.04 (0.86–1.26)
Age at onset of seizures	0.99 (0.98–1.00)	0.97 (0.95–0.99)	0.99 (0.97–1.02)	0.98 (0.98–0.99)	0.96 (0.95–0.98)	0.98 (0.97–0.99)
Focal seizures	0.94 (0.72–1.22)	1.24 (0.98–1.58)	1.03 (0.68–1.55)	1.05 (0.89–1.24)	1.16 (0.93–1.45)	1.11 (1.04–1.20)
Generalized seizures	1.13 (0.86–1.47)	0.87 (0.69–1.11)	1.24 (0.79–1.95)	1.15 (0.99–1.33)	0.91 (0.73–1.13)	1.01 (0.88–1.15)
Other convulsive seizures	–	–	–	0.95 (0.55–1.63)	2.09 (1.87–2.33)	1.12 (0.72–1.75)
Impaired consciousness	–	1.81 (1.60–2.05)	–	1.74 (1.61–1.88)	–	1.87 (1.73–2.01)
Seizure frequency: daily ^a	1.47 (0.93–2.31)	1.66 (1.14–2.42)	2.36 (1.35–4.12)	1.61 (1.30–1.99)	1.63 (1.09–2.44)	1.64 (1.46–1.83)
Seizure frequency: weekly ^a	1.83 (1.24–2.69)	1.03 (0.53–2.02)	2.51 (1.47–4.26)	1.65 (1.33–2.03)	2.36 (1.65–3.38)	1.77 (1.47–2.14)
Seizure frequency: monthly ^a	1.26 (0.94–1.69)	1.25 (0.87–1.79)	1.78 (1.04–3.06)	1.35 (1.12–1.63)	1.84 (1.33–2.56)	1.44 (1.24–1.67)
Status epilepticus	0.84 (0.60–1.18)	1.21 (0.68–2.18)	0.66 (0.43–1.03)	1.18 (1.01–1.37)	1.04 (0.70–1.53)	1.02 (0.80–1.32)
Febrile status epilepticus	1.05 (0.90–1.22)	1.82 (1.58–2.09)	0.64 (0.33–1.23)	1.27 (1.09–1.47)	1.25 (0.61–2.59)	1.10 (0.96–1.27)
Neurological deficits	1.36 (1.04–1.78)	1.75 (1.45–2.12)	2.32 (1.69–3.89)	1.39 (1.20–1.62)	1.86 (1.53–2.25)	1.58 (1.35–1.86)
Cognitive impairments	1.49 (1.17–1.91)	1.65 (1.34–2.04)	2.13 (1.52–2.98)	1.59 (1.39–1.81)	1.67 (1.36–2.04)	1.62 (1.52–1.74)
Malnutrition	1.01 (0.66–1.53)	1.10 (0.78–1.57)	0.99 (0.61–1.62)	1.05 (0.87–1.27)	1.14 (0.82–1.59)	1.06 (1.00–1.12)
AED use	1.15 (0.88–1.50)	1.34 (1.05–1.72)	1.45 (0.98–2.14)	1.34 (1.16–1.55)	0.96 (0.69–1.33)	1.28 (1.15–1.43)
Burns	0.96 (0.65–1.41)	0.91 (0.64–1.34)	1.22 (0.64–2.35)	1.19 (1.00–1.41)	1.15 (0.88–1.52)	1.12 (1.01–1.25)
Unmarried	1.23 (0.91–1.68)	1.09 (0.86–1.38)	1.33 (0.91–1.95)	1.07 (0.92–1.24)	0.98 (0.79–1.22)	1.09 (0.99–1.19)
Unemployed	0.88 (0.66–1.15)	1.33 (1.03–1.72)	1.17 (0.76–1.81)	0.88 (0.74–1.05)	1.15 (0.92–1.45)	1.00 (0.86–1.18)
Unschooling	1.17 (0.89–1.54)	1.74 (1.38–2.20)	1.24 (0.85–1.82)	1.15 (0.99–1.33)	1.03 (0.82–1.28)	1.21 (1.03–1.42)

RR = risk ratio; CI = confidence interval; AEDs = anti-epileptic drugs. Associations reaching a p -value cut-off ≤ 0.25 are highlighted in bold. AEDs = anti-epileptic drugs. Associations marked as a dash (–) represents variables that were too few to run the model.

^a The three categories of seizure frequency are compared with the baseline category of those who had yearly seizures.

Table 5
Multivariable analysis results for factors associated with abnormal electroencephalographic features in people with active convulsive epilepsy across five African sites.

Features	Agincourt RR (95% CI)	Ifakara RR (95% CI)	Iganga RR (95%)	Kilifi RR (95%)	Kintampo RR (95%)
Perinatal abnormalities	1.88 (0.77–4.59)	–	–	1.14 (0.86–1.50)	1.39 (1.02–1.90)
Head injuries	2.00 (1.22–3.29)	1.54 (0.31–7.73)	–	–	1.33 (0.96–1.85)
Febrile status epilepticus	–	3.52 (1.40–8.82)	0.88 (0.37–2.11)	1.14 (0.76–1.71)	–
Neurological deficits	0.83 (0.29–2.37)	1.92 (1.09–3.39)	2.36 (1.25–4.45)	1.09 (0.87–4.06)	0.93 (0.64–1.36)
Cognitive impairments	2.00 (0.98–4.06)	0.84 (0.48–1.45)	1.19 (0.70–2.11)	1.54 (1.24–1.91)	1.05 (0.75–1.46)
AED use	–	1.62 (1.08–2.42)	1.80 (1.06–3.05)	1.35 (1.13–1.61)	–

RR = risk ratio; CI = confidence interval; AEDs-anti-epileptic drugs. Significant associations (p -value < 0.05) in each site are highlighted in bold. The non-highlighted associations are not statistically significant and are provided where a risk factor was significant in at least one site to allow comparison across the five sites. Associations marked with a dash (–) are for those variables that did not reach a cut-off for multivariable analysis.

the clinical assessment had focal features, a comparable finding to previous studies in the United States and United Kingdom (Lomboroso, 1997; Kibuuka, 2011). In some people seizures may rapidly generalize after a focal onset (Gwer et al., 2012), particularly in focal symptomatic epilepsies, which are likely to be over-represented in this group from sub-Saharan Africa compared with unselected epilepsy populations with ACE from high-income countries. The correlation between focal features and focal neurological deficits would support this conclusion. Most focal abnormalities involved the temporal lobes. This may reflect the association between temporal lobe pathology and poorly controlled prolonged seizures particularly febrile status epilepticus, which is common in Africa (Sadarangani et al., 2008; Kariuki et al., 2015b).

4.3. Factors associated with EEG abnormalities across all sites

The frequency of abnormal EEGs in ACE was associated with several epilepsy-related and clinical factors in a pooled analysis of the five sites. Adverse perinatal events are a recognized cause of epilepsy in Africa and can lead to persistent brain damage (Ngugi et al., 2013), which may be associated with EEG changes (Pressler et al., 2005). This may account for the significantly higher frequency of EEG abnormalities in children, some of whom may die before reaching adulthood. Focal seizures could be a marker of localized brain damage by central nervous infections and injuries, which may be reflected in both acute and chronic EEG abnormalities (Crawley et al., 2001). AED use may be a surrogate marker of severe epilepsy, hence its association with EEG abnormalities, which are also related to seizure frequency (Kariuki et al., 2014). The association between an abnormal EEG and cognitive impairment confirms the negative impact which epilepsy may have on intellectual function and behavior (Aldenkamp, 2006).

4.4. Factors associated with EEG abnormalities within the sites

In the within site analysis, none of these factors was associated with abnormal EEG across all the five sites. This highlights the importance of site-specific preventative and management interventions for those with abnormal EEGs in ACE. For example, febrile status epilepticus was important in Ifakara, a malaria endemic area, where malaria may be the main cause for status epilepticus (Sadarangani et al., 2008). Head injuries were an important association in Agincourt, where most people with ACE were adults (Kariuki et al., 2014), and indulge in violent or risk behavior that can result in falls or accidents. These findings taken together suggest that EEG abnormalities in ACE may be related to head trauma, perinatal complications and infections, which could be preventable by site specific interventions. EEGs may help identify those at risk of cognitive impairments, which may be a consequence of ACE or use of AEDs.

4.5. Strengths and limitations

The large sample size, providing sufficient power to measure associations between clinical groups is the major strength of the study. Epilepsy cases were identified using a standard methodology and one experienced clinical researcher (experienced in reading EEGs) rated all EEGs following a standardized protocol. The pooled analysis of factors associated with EEG abnormalities is reliable since we accounted for clustering within the sites. A limitation is that we only performed a single routine EEG in each individual. For logistic reasons we did not do serial or sleep EEGs recording, which may have provided a higher diagnostic yield. The cognitive impairment in this study should be interpreted carefully since we assessed it by clinical evaluation of mental status rather than by standardized neuropsychological tests.

4.6. Conclusion

EEG abnormalities are common in Africans with ACE, but the prevalence and proportion of focal features vary according to site, probably related to specific aetiological and clinical features of epilepsy in these areas. The EEG features have clinical utility, particularly in helping to identify focal epilepsies that can be further evaluated with neuroimaging. EEG abnormalities are associated with perinatal complications and severe epilepsy, and may predict neurocognitive outcomes among those with ACE. Future studies should apply EEG findings along with other clinical and neuroimaging features to improve the understanding and management of epilepsy in Africa.

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