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Incidence of convulsive epilepsy in a rural area in Kenya

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SUMMARY

Purpose: There are only a few studies of incidence of epilepsy in low and middle income countries (LMICs). These are often small and conducted in specific age groups or areas where the prevalence of risk factors is high; therefore, these studies are not representative of the wider populations. We determined the incidence of convulsive epilepsy (CE) in a large rural population in Kenya.

Methods: We conducted two cross-sectional surveys 5 years apart within a health and demographic surveillance system. Initially we identified residents without epilepsy who were then reexamined in the follow-up survey to determine incidence. We estimated the overall incidence of CE and incidence by age-group, sex, and by administrative location. Estimates were adjusted for attrition during case identification and for the sensitivity of the screening method.

Key Findings: In a cohort of 151,408 people, 194 developed CE over 5 years. The minimum crude incidence rate was 37.6/100,000 persons per year (95% confidence interval (CI) 32.7–43.3) and adjusted for loss to follow-up, and the sensitivity of the survey methodology was 77.0/100,000 persons per year (95% CI 67.7–87.4). Incidence was highest in children 6–12 years (96.1/100,000 persons per year; 95% CI 78.4–117.9), and was lowest in the 29–49 year age group (37.4/100,000 persons per year; 95% CI 25.7–54.7).

Significance: We estimated a high incidence of convulsive epilepsy in this population. Incidence was highest early and late in life, suggesting that preventive interventions should target exposures that occur in these age groups. Incidence of focal epilepsy was more than twice that of generalized epilepsy, suggesting that etiologies that are amenable to intervention were most important in this population. It is likely that incidence is underestimated because of the early mortality of incident cases.

KEY WORDS: Epilepsy, Convulsive epilepsy, Incidence, Kenya.

Epilepsy is a common neurologic condition and an important cause of disability and mortality (Carpio et al., 2005; Forsgren et al., 2005; Kaiser et al., 2007), accounting for 1% of days lost to illness globally (Leonardi & Ustan, 2002). It is estimated to affect around 70 million people in the world (Ngugi et al., 2010), of whom 80% live in the poorer regions of the world (Newton & Garcia, 2012).

These estimates are based on life-time prevalence data, which may underestimate the burden, since epilepsy is associated with considerable mortality early after the onset of seizures and it may spontaneously remit (Sander, 1993; Kwan & Sander, 2004; Carpio et al., 2005; Diop et al., 2005), leading to poor recall of seizure events (Sillanpaa et al., 2008). Incidence is not affected by either mortality or remission and may provide a more accurate assessment of the burden of epilepsy.

There are, however, only a few estimates of incidence in low and middle income countries (LMICs) (Ngugi et al., 2011). This is due mainly to lack of health facility data to identify incident cases and the high cost of continuous surveillance of population-based cohorts required for accurate incidence estimates.
We estimated the incidence of convulsive epilepsy (CE) in a large population-based cohort in a rural area of Kenya over a 5-year period. We targeted CE, as opposed to all epilepsies, because convulsive epilepsies are easier to identify in cross-sectional settings and thus do not require specialists, thereby reducing cost and enabling us to survey a large population efficiently. Furthermore, we compared the prevalence of CE 5 years apart to determine if the reduction in infectious diseases such as malaria and meningitis had changed the prevalence.

**Methods**

The study consisted of two cross-sectional surveys, conducted 5 years apart, nested in a demographic surveillance system. In the first survey we determined the active convulsive epilepsy (ACE) status of residents to identify a cohort of individuals without epilepsy; in the second survey we reexamined this cohort to determine the number who had developed ACE during the intervening period. The incidence of epilepsy was then calculated by dividing the number of incident cases by the person years of observation.

**Study setting and study population**

We conducted the study within the Kilifi Health and Demographic Surveillance System (KHDSS – http://www.kemri-wellcome.org/khdss/), which covers an area of 891 km², in Kilifi District, one of the poorest districts in Kenya comprising a population of 233,881 persons in 2008 living in 25,526 homesteads (Scott et al., 2012). The KHDSS area was mapped using global positioning system (GPS) receivers, and digital maps derived from these data were used to locate homesteads and follow study participants. Community-based field workers conduct reenumeration and vital status registration to update the population registers by visiting every homestead two or three times per year. The population is served by the Kilifi District Hospital (KDH), which is located at the center of the KHDSS area.

Residents of the study area are predominantly Mijikenda, a Bantu grouping of nine tribes with Girima (45%), Chonyi (33%), and Kauma (11%) being the most common. About 55% of the population is considered absolutely poor with per capita monthly income of about 10 USD.

The majority (80%) depend on subsistence farming, which is constrained by the low agricultural potential of the land (only 19% is arable). Only 45% of people are literate. Crude birth and death rates for this area are approximately 35/1,000 and 6/1,000 per year, respectively, and migration rates are approximately 100/1,000 per year, most of which is within the study area (Scott et al., 2012).

**Cohort identification and follow-up**

We identified cohorts of people with and without ACE in a baseline cross-sectional survey (Edwards et al., 2008). The survey was undertaken by door-to-door visits of all residences within the KHDSS between August and November 2003.

The three-stage method used to identify cases has been described elsewhere in detail (Edwards et al., 2008; Ngugi et al., 2012, 2013). Briefly, the first stage (stage I, SI) involved asking the head of each household two screening questions to identify members of the household with a history of convulsions (Appendix S1). Those that were positive were followed in stage II (SII) and were interviewed by a team of field personnel trained to administer a more detailed and specific screening tool for epilepsy (Appendix S2) (Placencia et al., 1992). Respondents positive in SII were then evaluated in stage III (SIII), where a diagnosis of ACE was made using detailed clinical history taken by a clinician trained in epilepsy and fluent in the local languages. The International League Against Epilepsy (ILAE) definitions of active epilepsy were used (Commission on Epidemiology & Prognosis: International League Against Epilepsy, 1993; Meinardi et al., 2001; Thurman et al., 2011), but a cutoff of at least one seizure in the preceding 12 months was used for active epilepsy (Meinardi et al., 2001; Ministry of Health, Kenya, 2002; Thurman et al., 2011). We excluded children younger than 6 years of age because of difficulties in differentiating between neonatal seizures, febrile seizures, and epilepsy in this age group.

Deaths and migration were identified in the routine reenumeration within the KHDSS during the follow-up period. In the second cross-sectional survey, conducted between December 2007 and June 2008, we attempted to interview every subject in the cohort who had not died and was still a resident in the KHDSS (Ngugi et al., 2013). Due to logistical and cost implications, no attempt was made to find subjects from the first survey who had migrated out of the study area. The second cross-sectional survey used the same methodology as the first cross-sectional survey to identify new cases of ACE.

In both surveys, we defined ACE as at least two unprovoked convulsions (tonic and/or clonic seizures) of which one occurred in the 12 months preceding the survey (Edwards et al., 2008; Ngugi et al., 2013). An incident case of CE was a participant who was found not to have ACE in the first survey but was subsequently detected as a case in the follow-up survey. For an incident case, the first seizure may have occurred days or years before the second survey (Jallon et al., 2001). These cases were included in the analysis because there had been no other diagnosis of epilepsy before the presentation in the current study (Hauser et al., 1996; Olafsson et al., 2005). We thus defined an incident case on the basis of the date of diagnosis of epilepsy rather than on the date of the second unprovoked seizure (Commission on Epidemiology & Prognosis: International League Against Epilepsy, 1993), since the recall of dates by the patients and their caretakers is often poor. Seizure types for all cases were classified by the study neurologist (CRN) using the recommendations of the Commission of the
Classification and Terminology of the ILAE (Berg et al., 2010; Thurman et al., 2011).

Analysis

We estimated incidence of CE as the number of new diagnoses of ACE among the subjects that did not have ACE in the baseline cross-sectional survey, divided by the total person years of observation (pyo). All person-observation time for those lost due to out-migration or death was excluded from the denominator. We estimated an overall incidence together with 95% confidence intervals (95% CI) assuming a Poisson model for the number of incident cases. Given that some people may have developed epilepsy during the follow-up but were inactive at the second survey, we assumed that the incidence estimated in this study was a minimum rate. Incidence rates were estimated by seizure type, age-group, sex, and administrative location.

We used the technique of multiple imputations (MIs) with five imputations to reduce bias due to loss to follow-up between stages of the two surveys (Rubin, 1987; van Buuren, 2007; Ngugi et al., 2013). The imputation model used the outcome from SI to impute SII where this was missing, and the outcome from SII to impute SIII. All incidence estimates were adjusted for the low sensitivity (48.6%) of the screening methodology (Ngugi et al., 2012). This was done for both the baseline and follow-up prevalence surveys to preclude the inclusion of cases missed in the baseline as incident cases (thereby increasing the incidence) and to include new-onset cases of ACE identified at baseline that were lost to follow-up but were inactive at the second survey, we assumed that the incidence estimated in this study was a minimum rate. Incidence rates were estimated by seizure type, age-group, sex, and administrative location.

We identified 194 incident cases of CE. The median (interquartile range, IQR) age of incident cases was 19.5 (14–31) years, and 49% were male. We estimated that there would be 233 incident cases (after adjustment for loss to follow-up) and 479 incident cases (after adjustment for both loss to follow-up and sensitivity of the screening methodology). The total person-years of observation (pyo) for this cohort was 623,004, after MIs with five rounds. The minimum crude incidence rate was 37.6/100,000 pyo (95% CI 32.7–33.3) and was 77.0/100,000 pyo (95% CI 67.7–87.4) after adjusting for loss to follow-up and the sensitivity of the three-stage survey methodology. At an adjusted rate of 51.6/100,000 pyo (95% CI 42.5–62.2), incidence of focal seizures was more than two times that of generalized seizures in this population, although a large proportion of convulsive seizures could not be classified according to onset due to lack of adequate information (Table 3).

There was strong evidence of variation of incidence of CE with age, with the highest incidence in the 6–17 year olds, lowest in 28–49 year olds, and an increase in the ≥50 year olds (Table 4). Incidence did not vary according to sex, administrative area of residence, or ethnicity (Table 4).

Of the 194 incident cases detected in the 2008 prevalence survey, 130 experienced the first nonepileptic seizure prior to the baseline epilepsy survey of 2003, 64 had seizure onset during the follow-up period (i.e., between 2003 and 2007), and in 10 the date of onset was not available. During follow-up, the highest proportion of incident cases (31.3%) occurred in the year preceding the reevaluation survey (2007), whereas the lowest (12.5%) was in the base-
line year (2003), and these proportions were significantly different \((p = 0.008)\). However, there was no significant trend in the number of incident cases over the years \((p\text{-value for trend } = 0.18)\).

**Discussion**

We used two cross-sectional surveys 5 years apart within an existing HDSS of a rural population in Kenya to identify...
incident cases of ACE, and we estimated a minimum inci-
dent rate of convulsive epilepsy at 77.0/100,000 persons per
year, which varied with age. Cases were identified in three-
stage cross-sectional surveys at the beginning and at the end
of the follow-up period. ILAE definitions with modified
timelines (Commission on Epidemiology & Prognosis:
International League Against Epilepsy, 1993; Thurman
et al., 2011) were used to define cases and noncases
(Edwards et al., 2008; Ngugi et al., 2013).

Within the KHDSS framework, the study benefitted from
continuous follow-up for migration and death, but we were
able to determine the cumulative incidence of new cases
from the cross-sectional study that was conducted at the end
of the study. As such, we have reported a minimum incident
rate, since we were not able to detect newly developed epi-
lepsy cases that may have died shortly after the onset of sei-
zures or been inactive during the reevaluation survey of
2008. For example, of the 448 people with ACE identified
at the baseline survey of 2003, 61 had died as at 31 Decem-
ber 2011. About 10% died within the first 3 years and 23%
within the first 5 years of onset of seizures (data not shown).
In addition, it was not possible to determine the epilepsy sta-
tus of residents who migrated out of the KHDSS or died,
although the demographic profiles of the incidence cohort
(as well as for the cases of ACE) identified at baseline were
similar to those of the cohort members who were found at the
second cross-sectional survey. In particular, the propor-
tions of people with histories of convulsions at baseline
(i.e., positive in the first stage of the baseline survey and
therefore more likely to develop epilepsy) were similar
among those lost and those who remained in the cohort. We
also used the MIs to determine and incorporate the propor-
tion of incident cases among participants lost to follow-up
into the overall estimate of incidence, thereby minimizing
selection bias. Because mortality is typically highest in the
first 1–2 years following the onset of seizures (Cockerell
et al., 1994; Forsgen et al., 2005), incidence may have been
underestimated as we evaluated the cohort 5 years apart.
This is supported by the timing of the first seizure, which
showed a significantly higher proportion of new-onset epi-
lepsy nearer to the reevaluation survey compared to that
immediately after the baseline survey.

We estimated the incidence rate of CE at 77/100,000 pyo.
Prevalence studies in LMICs that have included nonconvul-
sive epilepsies (Kaamugisha & Feksi, 1988; Birbeck &
Kalichi, 2004) have reported prevalence estimates that were
3 times higher than those that studied convulsive epilep-
ties only (Rwiza et al., 1992; Tekle-Haimanot et al., 1997).
Assuming similar rates for mortality and remission across
studies, these findings would suggest that the incidence of
all epilepsies in our population could be in the range of 154–
231/100,000 persons per year, which is higher than rates
reported for all epilepsies from other studies in LMICs.
These estimates have varied widely, from 49/100,000 in
The age-incidence relationship in our study showed a U-shaped curve, with highest incidence in the children and adolescents and old aged adults, and lowest in 28–49 year olds, as has been observed in the high income countries (HICs) (Jallon et al., 1997; Olafsson et al., 2005). In the 6–28 year age group, onset of recurrent seizures could be related to perinatal insults and infections of the central nervous system, particularly in the younger children (Preux & Druet-Cabanc, 2005; Ngugi et al., 2013). Many genetically determined epilepsies may also manifest during this age (Goudsmit & van der Waals, 1983; Edwards et al., 2008). In the adolescents and young adults, recurrent seizures may develop as a consequence of temporally remote etiologies that result in static encephalopathies, for example, infectious brain insults earlier in life, cerebral palsy, and head injuries (Ogunniyi et al., 1987; Edwards et al., 2008). However, there was no change in the prevalence between the surveys in 2003 and 2008, particularly in the 6–12 year age group, despite the introduction of Haemophilus influenzae type B (Hib) vaccine in 2001 (Cowgill et al., 2006), and a reduction of the incidence of severe malaria (O’Meara et al., 2008) and acute seizures (Karuki et al., 2011) admitted to Kilifi District Hospital since 2004. These potential causes may not be responsible for a significant population-attributable fraction of ACE, but could cause other forms on nonconvulsive epilepsies (Pomeroy et al., 1990), or there may not have been sufficient time for the reduction in the incidence of these conditions to reflect in the decrease in the prevalence. The incidence rate was not different between males and females in our study population.

The higher incidence rate in the elderly (50+ years) compared to younger adults has also been observed in industrialized countries (Sander et al., 1990) and in one study in an LMIC (Rwiza et al., 1992) but not in another LMIC (Teklehaimanot et al., 1997). Although it has not been documented in LMICs, elderly people may experience higher risk of developing epilepsy associated with progressive brain conditions that include tumors, cerebrovascular accidents and neurodegenerative conditions such as Alzheimer’s disease (Commission on Epidemiology & Prognosis: International League Against Epilepsy, 1993).

In view of the high incidence of CE in this population, etiologic studies are necessary, preferably in incident cases in order to elucidate causes, particularly among children, adolescents, and the elderly who are at highest risk. Neuroimaging may also help elucidate the causes. Furthermore, these age groups should be targeted for preventive public health interventions.

**Limitations of the Study**

We utilized a three-stage survey methodology that had low sensitivity (48.6%) to detect cases of ACE. We were able to adjust estimates for the low sensitivity, but it is possible that some cases were missed during the baseline survey and counted as incident cases in the follow-up survey resulting in an overestimation of the incidence rate. Furthermore, poor recall of seizures, particularly those that occurred long ago, could have led to underestimation of incidence.

Premature mortality due to epilepsy, remission, as well as lack of identification of newly onset epilepsy cases that may have been inactive during the reevaluation survey (2008) may have led to an underestimate of the number of incident cases. Future studies would benefit from a more frequent reevaluation (e.g., every 6 months) of the cohort to increase the detection of incident cases. We also excluded children ≤5 years of age from this study, which may imply that the incidence of epilepsy in the study area could be considerably higher given that most of the epilepsy starts during early childhood.
CONCLUSION

We estimated the incidence of CE in a large population-based prospective cohort study that was twice as high as that in HICs and within range of estimates reported for LMICs. Incidence of epilepsy was highest in children, adolescents, and the elderly; the causes should be investigated to prevent the development of epilepsy in these age groups. The incidence of focal epilepsy was more than twice that of generalized epilepsy, suggesting that etiologies that can be prevented could be most important in this area.

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DISCLOSURE

All authors confirm that they have no financial or personal interest, including advisory board affiliation, in any company or organization sponsoring the research. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Main characteristics of epilepsy cases that completed the study and those lost to follow-up.

**Appendix S1.** Stage I (SI) of the cross-sectional survey: (Census screen for convulsions).

**Appendix S2.** Stage II (SII) screening questions.