

CRITICAL REVIEW AND INVITED COMMENTARY

Understanding the differences in prevalence of epilepsy in tropical regions

*†Luce-Perrine Yemadje, *†Dismand Houinato, *Fabrice Quet, *Michel Druet-Cabanac, and *Pierre-Marie Preux

*University of Limoges, IFR 145 GEIST, Institute of Tropical Neurology, EA 3174 Comparative and Tropical Neuroepidemiology, Limoges, France; and †Department of Neurology, School of Health Sciences, University of Abomey Calavi, Cotonou, Benin

SUMMARY

Epilepsy is a frequent chronic neurologic disorder that affects nearly 70 million people worldwide. The majority of people with epilepsy live in developing countries, where epilepsy remains a major public health problem. Wide prevalence differences exist among various populations across sub-Saharan Africa, Latin America, and Asia. In particular, prevalence is lower in Southeast Asia than in sub-Saharan Africa and Latin America. Methodologic problems alone do not seem to explain these differences shown in recent review papers. The distribution of numer-

ous risk or etiologic factors such as infectious diseases with neurologic sequel, head injuries, or genetic factors could explain these differences. Stigmatization of people with epilepsy could lead to underestimating the prevalence of epilepsy, even in well-conducted studies. It is important to standardize the process of epidemiologic monitoring of epilepsy in order to improve the reliability in data comparison. Understanding the reasons for these differences is a crucial issue for eventually raising new hypotheses or prevention strategies.

KEY WORDS: Prevalence, Epilepsy, Tropical regions, Epidemiology.

Epilepsy is a frequent chronic neurologic disorder that affects approximately 70 million people of all ages worldwide (Ngugi et al., 2010). Nearly 80% of people with epilepsy are found in developing countries, where epilepsy remains a major public health problem, not only because of its health implications but also for its social, cultural, psychological, and economic connotations (WHO, 2009a). The median prevalence of active epilepsy was 4.9/1,000 (2.3–10.3) for developed countries and, respectively, 12.7/1,000 (3.5–45.5) and 5.9/1,000 (3.4–10.2) in rural and urban studies in developing countries (Ngugi et al., 2010). It is known that wide prevalence differences exist among various populations across sub-Saharan Africa, Latin America, and Asia (Burneo et al., 2005; Preux & Druet-Cabanac, 2005; Mac et al., 2007). In contrast to Asia, the median prevalence of epilepsy remains high in sub-Saharan Africa and Latin America: respectively, 15.0 and 17.8/1,000 (Almu et al., 2006; Velez & Eslava-Cobos, 2006; Melcon

et al., 2007; Prischich et al., 2008). In Asia it is about 6/1,000, similar to the prevalence observed in Europe and North America, <8/1,000 (Wang et al., 2003; Forsgren et al., 2005; Theodore et al., 2006; Tran et al., 2006). It is necessary to better understand the factors that lead to these differences of prevalence. It will improve further our understanding of epilepsy in the world.

The aim of this paper was to examine the differences between the prevalence of epilepsy in tropical regions: Asia, Latin America, and sub-Saharan Africa. We discuss methodologic limitations and etiologic factors that may explain these differences.

SEARCH STRATEGY

We searched the PubMed database and the database of the Institute of Tropical Neurology (Neurology in sub-Saharan Africa, accessible through www.i-ent.unilim.fr) by using the keyword “epilepsy,” combined with each of the following: “epidemiology,” “prevalence,” and selected only references from the considered regions of the world (Asia, Latin America, and sub-Saharan Africa). We completed this search by hand searching references in the review papers on the prevalence of epilepsy in Asia (Mac et al., 2007), Latin America (Burneo et al., 2005), and Africa (Preux &

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Address correspondence to Pierre-Marie Preux, Institut de Neuro-Epidémiologie et Neurologie Tropicale (EA 3174), Faculté de Médecine, 2 rue du Docteur Marcland, 87025 Limoges Cedex, France.
E-mail: preux@unilim.fr

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Table 1. Relevant differences between Asia, Latin America, and sub-Saharan Africa concerning epilepsy and its prevalence

	Asia	Latin America	Sub-Saharan Africa
Median prevalence	6.0/1,000	17.8/1,000	15.0/1,000
Neurocysticercosis	Genetically different <i>T. solium</i> strain	Seroprevalence and severity of <i>T. solium</i>	Seroprevalence and severity of <i>T. solium</i>
Malaria	9% of worldwide cases	Uncommon	85% of worldwide cases
Bacterial meningitis	Uncommon	Small-scale endemic diseases	Large-scale epidemic diseases
HIV	5 million people living with AIDS	1.7 million people living with AIDS	22 million people living with AIDS
Onchocerciasis		Lesser extent in Latin America	Observed mainly in Africa
Toxocariasis		Bolivia (odds ratio 2.7, CI 95% 1.4–5.2)	Burundi (odds ratio 2.1, CI 95% 1.2–3.8)
Toxoplasmosis	Low seroprevalence of 10.2%	More prevalent in humid regions	Seroprevalence of 34.1%

Druet-Cabanac, 2005). Articles were included if they had at least an abstract in English or French.

METHODOLOGIC FACTORS

The wide variation in the frequency of epilepsy could arise from: (1) the use of different definitions of epilepsy (1993 and 2005 definitions), (2) the nature of epilepsy studied (lifetime epilepsy or active epilepsy), or (3) the difference in the samples of population studied (a general population or a more specially selected one) (ILAE, 1993; Jallon, 1997; Debrock et al., 2000; Mung'ala-Odera et al., 2008; Quet et al., 2008). In sub-Saharan Africa, a study on 903 persons in Nigeria reported a high prevalence of 37/1,000 [confidence interval (CI) 95% 24.2–49.8] (Osuntokun et al., 1982). Interestingly, and in contrast, Osuntokun et al. (1987b) did another study in a very near different town and showed a 10-fold difference in prevalence of epilepsy. A national study conducted in Rwanda on 8,400 people yielded a lower prevalence of 7/1,000 (CI 95% 5.0–9.0) (Simms et al., 2008). Working on a representative sample of the population is also critical. A small sample of the population may overestimate the prevalence. Inversely, on large populations it is possible to miss some epilepsy cases, since financial and human resources available for the study and/or organizational structures are often limited.

Most epidemiologic studies on epilepsy have relied on identification of potential cases by using a combination of a screening questionnaire and a clinical confirmation of cases by neurologists, general practitioners, or medical students. To this end, several epilepsy screening questionnaires have been developed, for example World Health Organisation (WHO) questionnaire or questionnaires derived from WHO questionnaire (Placencia et al., 1992) and Limoges Institute of Epidemiology and Tropical Neurology IENT questionnaire (Preux et al., 2000). The five-item IENT Limoges questionnaire was specifically designed for the tropical areas and has a sensitivity of 95.1% and a specificity of 65.6% (Diagana et al., 2006). Some authors have used a modified version of these questionnaires without validation; the true validity of the tool could then be questionable. The

screening methods using an individual examination, key informants, or heads of families could influence the outcome of prevalence studies (Debrock et al., 2000; Mung'ala-Odera et al., 2008). In addition, several studies have shown that the level of knowledge of the health staff performing may bring differences in the diagnosis or classification of epilepsy (Danesi, 1994). Partial seizures are less easily identified than generalized seizures, and that could explain probably an underestimation of the overall prevalence of epilepsy (Udani et al., 2009). Lastly there is a dramatic and wide range treatment gap estimate to 56% (CI 95% 31.1–100.0) in care of epilepsy in low-income countries with a high degree of heterogeneity between Asia, Latin America, and Africa (Mbuba et al., 2008; Meyer et al., 2010). The poor management of the patients and the huge epilepsy treatment gap in tropical areas may bring a selective survival bias because studies are conducted only on survivors.

The stigmatization of people with epilepsy, in addition to methodologic factors, could also explain the differences in prevalence of epilepsy. In fact people with epilepsy may not reveal their correct past history for fear of being stigmatized and marginalized (De Boer et al., 2008; Pal et al., 2008). This may underestimate the prevalence of epilepsy if there is no alternative system to identify these people. Population-specific risk factors and environmental factors could also help to explain the difference in prevalence of epilepsy. Standardization of the epidemiologic monitoring of epilepsy is, therefore, important to generate reliable estimates (Quet et al., 2008).

There are systematic differences in reported prevalence estimates, which are only partially explained by study characteristics (Ngugi et al., 2010). These methodologic issues could explain some of the differences in prevalence of epilepsy. However, recent review papers of the available literature show that most of the studies are now door-to-door surveys, using well-recognized and validated designs and reaching minimal quality criteria (Burneo et al., 2005; Preux & Druet-Cabanac, 2005; Mac et al., 2007). So other explanations of these prevalence differences have to be found.

RISK OR ETIOLOGIC FACTORS OF EPILEPSY

In tropical areas, the differences in prevalence of epilepsy could obviously be explained by the distribution of epilepsy-related environmental factors and etiologic factors such as infections with neurologic sequel, stroke, head injuries, or genetic factors.

Central nervous system infections

Neurocysticercosis, caused by *Taenia solium*, seems to be the most common parasitic infection of the human nervous system and the most frequent preventable cause of epilepsy in sub-Saharan Africa and Latin America (Nsenyiumva et al., 2003; Dongmo et al., 2004; Del Brutto et al., 2005). In Asia, epileptic sequels resulting in *T. solium* infection are observed in Indonesia, Vietnam, and India, and possibly in China, and in Nepal (Rajshekhkar et al., 2003). There is a genotype of *T. solium* in Asia different from those observed in Africa and in Latin America (Ito et al., 2003). *Taenia asiatica* was observed in Asia, but there is no evidence that this species has a preference for the brain or other predilection sites. Difference in severity of infection caused by *T. solium* could also explain the differences in prevalence of epilepsy. In addition, the extent of the presence of other environmental factors such as use of bad hygiene practices, availability of latrines, use of human excreta as fertilizers, proximity of humans and pigs, and consumption of undercooked pork may influence the differences in prevalence of epilepsy.

Malaria is a major parasitic disease, which has been geographically restricted, but remains entrenched in poor areas with suitable climates for transmission. According to the WHO world malaria report, 243 million malaria cases worldwide led to nearly 863,000 deaths in 2008. The majority of those cases arose from sub-Saharan Africa (86%), 9% in Southeast Asia, and 3% in Eastern Mediterranean regions (WHO, 2009b). In Africa, malaria was mainly due to *Plasmodium falciparum* and affects largely children younger than 5 years of age and pregnant women, whereas in Asia, it mainly affects adults. Sub-Saharan African studies show that epilepsy is more common in children with cerebral malaria than in those who have not had neurologic manifestations of malaria (Carter et al., 2004; Ngoungou et al., 2006; Ngoungou & Preux, 2008). No such study exists currently in Asia. Of four species of *Plasmodium* (*P. vivax*, *P. ovale*, *P. malariae*, and *P. falciparum*), only *P. falciparum* is responsible for cerebral nervous system infection. It is the most dangerous type and it is commonly observed in Africa. In Asia, a less dangerous type *P. vivax* is more common (Tjitra et al., 2008). This could be another explanation of the lower prevalence of epilepsy in Asia.

Onchocerciasis is a parasitic disease caused by *Onchocerca volvulus*. It is observed mainly in Africa and to a les-

ser extent in Latin America. A large meta-analysis searching for an association between onchocerciasis and epilepsy was at the limit of significance (Druet-Cabanac et al., 2004). There is no clear pathophysiologic mechanism that may support a causative relationship between onchocerciasis and epilepsy. However, a recent review has performed a meta-regression analysis and shows that prevalence of epilepsy increases on average by 0.4% for each 10% increase in onchocerciasis prevalence (Pion et al., 2009). Even if epilepsy prevalence in communities living in *O. volvulus* endemic areas is related to onchocerciasis prevalence, it seems unlikely that onchocerciasis could be a major cause of the difference in prevalence of epilepsy between continents.

Human toxocariasis is a zoonotic infection observed mainly in children and transmitted by *Toxocara canis* or *Toxocara cati*. The association between toxocariasis and epilepsy is well known. A significant association between toxocariasis and epilepsy was observed in Burundi (odds ratio 2.1, CI 95% 1.2–3.8) and in rural Bolivia (odds ratio 2.7, CI 95% 1.4–5.2) (Nicoletti et al., 2002, 2007). No specific study seems to exist in Asia. The tropical areas are characterized by high temperature and high humidity that allow conditions for development, survival, and transmission of toxocara eggs in the soil (Thompson et al., 1986; Bachli et al., 2004). There are different types of visceral larva migrans. A cosmopolitan form and a specific form are observed mainly in Japan and two other specific forms generally are observed in Asia (Chieffi et al., 1990). The difference in the visceral larva migrans types as well as the differences in diagnosis practices across tropical regions may further help explain the differences in prevalence of epilepsy resulting from toxocariasis.

Meningitis is an inflammation of the meninges with a high severity and risk of neurologic sequel. These sequel and global developmental delay may be seen in about one third of survivors of bacterial meningitis (Singhi et al., 2007). Despite a global distribution, epidemiology of meningococcal disease shows geographical diversity. Currently, large-scale epidemics are confined to the semiarid area of sub-Saharan Africa from Senegal in the West to Ethiopia in the East, while small-scale endemic disease occurred in South America; in major African epidemics, attack rates range from 100 to 800 per 100,000 people (World Health Organization, 2003). On the other hand, patients whose spleens have been removed, or are no longer functional (as patients with sickle cell disease, common in Africa) are more susceptible to meningococcal and pneumococcal meningitis infections. In Asia, bacterial meningitis is uncommon and its causes are heterogeneous. In Hong Kong, *Haemophilus influenzae* showed a very low annual incidence of 1.1 per 100,000 CI 95% (0.43–2.20) and 6 per 100,000 CI 95% (2.9–12.5) in South Korean children, even in the absence of an effective vaccination program (Sung et al., 1997; Kim et al., 2004). Different pathogens, serogroups, strain virulence, and population movements

predispose to meningitis epidemics and could help to explain the differences in epilepsy resulting from meningitis.

Epileptic seizures are often observed in human immunodeficiency virus (HIV)-positive patients without other epileptogenic risk factors. Therefore, the difference in prevalence of epilepsy can be explained partly by the differences in the prevalence of HIV in tropical areas. In 2007, WHO and the United Nations Programme on HIV/AIDS (UNAIDS) estimated that 22 million of the 33 million people living with HIV are in sub-Saharan Africa, whereas 5 million live in Asia and 1.7 million in Latin America (UNAIDS, 2009). Seizures result directly from neurologic complications of HIV or its associated infections such as tuberculosis, cryptococcosis, and mainly toxoplasmosis (Modi et al., 2002; Romanelli & Ryan, 2002). Other factors including difference in the care practices and treatment opportunities of HIV and its associated infections in tropical areas may further explain the differences. Infection from *Toxoplasma gondii* occurs worldwide, but is particularly more prevalent in humid regions of South America and Africa (Petersen, 2007). The seroprevalence is low in most Asian countries. A study of HIV-positive patients from Taiwan found a seroprevalence of 10.2%. Another study from Sudan found a seroprevalence in pregnant women from Khartoum of 34.1%. Of 1,828 HIV-positive patients from Bobo-Dioulasso (Burkina Faso), 25.4% had positive *T. gondii* serology (Palmer, 2007). More studies on HIV and epilepsy are needed to better explain the association between those two diseases. Relevant differences between regions are summarized in Table 1.

Stroke and its associated risk factors

Epilepsy may be an early or a late complication of stroke, which is a most common cause of epilepsy in elderly (Silverman et al., 2002). The prevalence of overall stroke varies considerably: The crude prevalence in Latin America and Asia is, respectively, 6.5 per 1,000 and 7.2 per 1,000. In Africa, these estimations are rather low at 0.58 per 1,000 in Nigeria but probably biased and old (Osuntokun et al., 1987b). Average systolic blood pressure in men is more than 140 mm Hg in Bolivia, and Senegal, and Gambia, whereas it is <120 mm Hg in Thailand and between 120 and 129 mm Hg in India and China (Mackay & Mensah, 2004). The prevalence of overweight population is much lower in some Asian countries such as India 0.70% and Indonesia 2.40% than in some Latin American countries such as Brazil 11.1% and Chile 21.9%. These proportions are much lower in sub-Saharan African countries but higher in some countries like South Africa 21.6% (WHO, 2006). Stroke and associated risk factors seem more common in Asia than in Africa. Hemorrhagic strokes are more epileptogenic than ischemic strokes (Camilo & Goldstein, 2004). It seems important to assess the frequency of stroke and stroke subtypes in tropical regions.

Traumatic brain injury

In Asia, posttraumatic epilepsy accounts for 20% of all symptomatic epilepsies (Mac et al., 2007). Although Southeast Asia has the highest proportion of global road fatalities—one-third of the 1.4 million occurring each year in the world—the road traffic injury mortality rate is highest in Africa at 28.3 per 100,000 population (Lagarde, 2007). The lack of road maintenance, the noncompliance with the wearing of seat belts or helmets, and the lack of organization of road traffic in developing countries can contribute to the increase of serious traumatic brain injuries potentiating for seizures and epilepsy. Unsafe working conditions, riots, or wars could also contribute to cranial injury in some specific zones. The risk of developing posttraumatic epilepsy depends upon the degree or the severity of the trauma and its resulting complications. The location of specialized trauma centers, the means of patient transportation, the time to hospitalization, the absence of a prehospital care, the lack of adequate equipment or trained personnel, or the unavailability of emergency road passages could decide the hospitalization patterns and, therefore, may help explain the differences in the prevalence of seizures and epilepsy in this case. These tendencies are expected to be potentially more common in Africa and Asia than Latin America; for example, road rage is higher in Africa than in some Asian and Latin American countries (Ryan et al., 2006).

Obstetric and perinatal factors

Perinatal and obstetric problems are important epilepsy-related risk factors in developing countries. Their overall outcome and neurologic consequences such as seizures and epilepsy depend heavily on the extent of good obstetric practices, maternal hygiene, maternal health and nutrition, availability of qualified personnel, and preference for childbirth at home. The practice and prevalence of these factors visibly vary across different tropical areas that may in effect lead to differences in the prevalence of epilepsy.

In many communities in Latin America, Southeast Asia, and sub-Saharan Africa, few women control their reproductive lives. They deliver at home and do not receive adequate prenatal care and supervision, especially when they live far from health care facilities. The number of antenatal consultations remains low in Latin America; for example, the median number of prenatal consultations is between 4.7 and 6.6 in Bolivia (Souza et al., 2007). In Africa these figures are unknown, but they may not be better, since the pregnancy-related complications remain high in this region; possible reasons include early marriage, early pregnancy, high pregnancy rate, and poor nutrition. In Latin America, 40–90% of births are supervised, whereas in Africa and Asia, only 34% and 38% of all pregnancies are attended at health facilities (Souza et al., 2007).

Genetic factors

Numerous studies have confirmed the family history and consanguinity as epilepsy-related risk factors. In sub-Saharan Africa, on average, a family history was noted in 25% of cases, and up to 60% (Preux & Druet-Cabanac, 2005). In Asia these rates are somewhat high, for example, 21–76% in Pakistan (Khatri et al., 2003). In a country-wide survey from Japan, consanguineous marriages constituted 4% of all marriages; in China, it is prevalent in some populations such as Tajik and Uzbek in Xinjiang (Mehndiratta et al., 2007). In some sub-Saharan Africa areas, the consanguinity is reported to be very high. For example in Mali in some specific settings, rates as high as 96% are reported (Kouassi, 2000). The stigmatization of patients with epilepsy potentially forces people with epilepsy to intermarry, especially in marginalized societies, thereby expanding the patient pool by promoting the genetic transmission of epilepsy. This practice of intermarrying is also often seen in some Latin American communities.

CONCLUSION

It is now clear that the prevalence of epilepsy varies across tropical areas. Southeast Asia shows a lower prevalence of epilepsy than sub-Saharan Africa and Latin America. Factors playing a role in explaining these differences include availability of diagnostic tools and human resources, limited economic conditions, and lack of access to antiepileptic drugs. However, the differences are probably due primarily to the higher prevalence of epilepsy-related risk factors in sub-Saharan Africa and Latin America compared to Asia. In particular, cerebral malaria, neurocysticercosis, meningitis, HIV infection, toxocarasis, and traumatic brain injuries are mostly seen or are more severe in sub-Saharan Africa. More thorough studies are needed to investigate these issues and to understand these differences. This could help to further understand the involved pathophysiologic mechanisms and to eventually propose some ways of prevention.

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DISCLOSURE

None of the authors has any conflict of interest to disclose. 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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