EPILEPSY CARE IN DEVELOPING COUNTRIES: PART II OF II

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Although 80% of people with epilepsy reside in resource poor, developing countries, epilepsy care in these regions remains limited and the majority of epilepsy patients go untreated. Cost-effective, sustainable epilepsy care services, delivering first-line antiepileptic drugs through established primary health care facilities, are needed to decrease these treatment gaps. Neurologists with local experience and knowledge of the culture, who are willing to serve as educators, policy advisors, and advocates, can make a difference. This is Part II of a two-part article. Part I reviewed the burden of epilepsy and the current state of resources for treatment in developing countries, while Part II will now discuss various aspects of care in these countries.

Overview of Care

"*In developing countries there is no place for 'demarcation disputes' about who should do what*" (1).

Epilepsy is a common, largely untreated disorder in many resource poor regions. The basic medical principles of epilepsy care are the same in developed and developing regions, but there are unique challenges to providing good care in developing country settings and equally unique solutions may be considered. As with optimal epilepsy care anywhere, it is critical to consider the person with epilepsy in the context of their home, family, community, and broader environment.

AED Selection

The approach to determining when to use AED selection in developing country setting does not differ appreciably from guidelines or recommendations in developed countries. What does differ is the range of options of AED type and the ability to monitor drug levels. The goal should be monotherapy with the lowest effective dose of a tolerated AED, and when diagnostic accuracy allows it, the AED selection may be determined by seizure type or epilepsy syndrome. Much debate has occurred about the relative pros and cons of using older AEDs, specifically phenobarbitone, in a developing country setting (2). When studied in developed settings, phenobarbitone has an efficacy profile similar to newer AEDs but is associated with more adverse side effect, particularly behavioral and cognitive problems. Paradoxically, the frequency and severity of adverse side effects related to phenobarbitone use does not consistently bear out in studies conducted in resource poor, developing regions. Reports from Tanzania (3), Mali (4), India (5), and China (6) all found phenobarbitone to be effective and well tolerated. While it is certainly possible that biomedical differences explain these findings, it seems more likely that study design and investigator biases impact studies at both ends of the spectrum. For locations where no other immediately feasible options to phenobarbitone exist, both patient and care providers may be more inclined to accept side effects than patients and providers in settings with relatively easy access to second- and third-line AEDs. The influence of pharmaceutical industries vested in marketing newer AEDs must also be considered as a potential source of bias in studies from developed regions.

All debate aside, unless the neurologist in the developing country setting is practicing in a well-funded private sector or is able to influence centralized drug purchasing practices, only first-line AEDs are likely to be available. Historically, phenobarbitone was by far the least expensive agent, followed by phenytoin, carbamazepine, and valproate. This profile may be changing as increased regulatory activities in developing countries are decreasing the availability of scheduled drugs, including phenobarbitone. Phenobarbitone has several advantages in terms of easy dosing (important not only for patients but also when nonphysician health care workers are prescribing and dispensing medications) and spectrum of activity.

Medical Comorbidities

When delivered as part of a primary health care package, epilepsy care includes assessments for other basic health needs. For example, among children, vaccination status and routine nutritional and developmental assessments can be undertaken at the same time that seizure management is provided. Whether in the primary or specialized care setting, people with epilepsy may benefit from screening for anxiety and depression, as these

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are common comorbid conditions amenable to inexpensive treatments, and the failure to address them has a significant impact on the overall well-being of the individual (7). Rapidly administered, culturally appropriate screening tools for mood disorders have been developed and validated for many regions of the world (8).

Women's Issues

Women with epilepsy face some additional issues that may require special attention and that largely, but not entirely, involve issues of child bearing and rearing. Epilepsy-associated stigma may lead to concealment of epilepsy from the spouse until after marriage, and subsequently these women are vulnerable to abandonment, with corresponding loss of any children from the union. Optimizing epilepsy care prior to marriage or pregnancy may not be possible, but provision of folate supplements to all women of childbearing age and advice regarding the possible interaction of enzyme-inducing AEDs and hormonal contraceptive agents is warranted. In resource-poor settings, where most obstetrical care occurs late in the pregnancy and home births are the norm, women with epilepsy, especially those with poorly controlled seizures, are likely at high risk for obstetrical complications and should be encouraged to deliver at the hospital. Vitamin K supplementation in the last month of pregnancy to decrease bleeding risks in both mother and infant are needed. During antenatal visits, breast-feeding infants can be assessed for sedation. It is important to reassure these women that their condition is not a contagious to be one passed onto their fetus/infant. Breast-feeding, usually the only sustainable, safe food source for infants in the first few months of life in developing countries, can be encouraged and supported. Rational precautions regarding bathing and carrying of infants (bundling infants on the back) can be made based upon seizure risks.

Pediatric Issues

Most epidemiologic studies suggest that age of onset for epilepsy in developing countries is younger than in more resource rich regions (9). This finding may reflect the relatively young age of populations in developing countries or a lack of age-adjusted epidemiologic data for epilepsy from these countries. Alternatively, younger age of onset may also be due to birth injury, poor postnatal or antenatal care, and pediatric CNS infections that simply represent a greater overall attributable risk for epilepsy in developing countries compared to developed countries.

Neonatal seizures are common in developing countries, and health care providers engaged in maternal and child health care services need to have the knowledge and resources to initiate treatment (10). Neonatal seizures may be related to hypoxic ischemic encephalopathy, infections, and metabolic disorders as well as to other less common conditions. Phenobarbitone is the agent of choice for neonatal seizures in resource poor settings—an initial loading dose of 20 mg/kg IV or IM are cited in most textbooks, but doses may need to be decreased in settings without recourse to ventilators. Maintenance doses of 3–5 mg/kg/24 hours, divided into two daily doses, may also need reduction if respiratory status declines. The balance between the need for the AED and the risk of compromised respiration may be especially precarious in the premature infant, and referral to a tertiary care center offering ventilatory support is warranted, if such a center is available.

Ongoing outpatient management of neonatal and pediatric seizures may be complicated by the lack of pediatric syrups or other formulations of AEDs appropriate for children. The shortage of pediatric AED formulations is due to higher cost and shorter shelf life of these agents compared to adult formations and may be further exacerbated by the scarcity of trained pharmacists to prepare and dispense pediatric formulations. Unfortunately, despite 2007 recommendations by the Expert Committee on Essential Drugs that pediatric formulations of essential drugs need to be a priority, they remain largely unavailable in the public sector of low-income settings (11).

Epilepsy Surgery in Developing Countries

As with other resources for epilepsy care, epilepsy surgery is limited or unavailable in most of the developing world, but successful surgery programs nonetheless have been developed (12,13). Determining whether the development of an epilepsy surgery program is appropriate for a specific country depends upon several factors. If public funds are to be used, then it is critical that a careful cost effectiveness analysis be conducted to establish if a surgery program is the optimal use of limited funds. Public resources spent on the development of an epilepsy surgery program presumably translates into the loss of funds for the maintenance or expansion of epilepsy care services at the primary care level—which can provide relatively inexpensive agents and successfully manage most people with epilepsy. If the epilepsy treatment gap (i.e., the number of individuals with epilepsy who remain untreated with AEDs) is high, then an investment in basic medications, public health education, and retraining of health care workers at the primary health care level may be a better investment. When considering the cost of epilepsy surgery in locations where no such program exists, the cost of the human and physical infrastructure for the development of the program must also be included in cost estimates, rather than the marginal cost of one additional surgery. Centralization of epilepsy services at a tertiary surgery-based care center may also contribute to "brain drain" (i.e., loss) of epilepsy care providers from rural to urban regions or from the public to the private sectors. A successful epilepsy surgery program in Columbia reported being able to provide successful callosotomy surgery for $2,864 to $3,722 per patient. This amount is a small fraction of the dollars required for epilepsy surgery in the United States, but might provide up to 1,000 person-years of AED treatment with phenobarbitone in a resource poor setting.

Nonmedical Consequences of Epilepsy

The social and economic problems faced as a consequence of having epilepsy are far-reaching for people in developing countries. Within urban Zimbabwe, people with epilepsy noted difficulty with speed of thinking and problem solving (14). The most common antiepileptic drug (AED) used was phenobarbitone, well known to slow cognition; however, it was not possible in this study to distinguish primary epilepsy issues with problems secondary to medication side effects. Other common problems reported included limitations on travel (resulting from fears both of using public transportation and of having a seizure in public, while vulnerable and alone), and difficulties with personal relationships, which the people with epilepsy directly attributed to epilepsy. These issues were also common concerns among people in rural Zambia (15). Fears of exploitation may be well founded. Stigma associated with epilepsy can result in greater vulnerability to physical violence, including rape. Even within the family unit, physical neglect and spousal abandonment are common (16). Although the clinician cannot be expected to ameliorate most of these grim realities, understanding the life situation of patients under one's care is essential to understanding barriers to adherence and care-seeking and will contribute to potential approaches to optimizing care. For example, employment problems are extremely common and advice from clinicians to employers (or potential employers) may be helpful (17).

Safety Issues and Role Assignments

Epidemiologic studies have suggested that relative to developed countries the incidence of epilepsy in developing countries is out of proportion to prevalence, indicating that people with epilepsy in these nations either have a higher mortality rate or a greater rate of spontaneous remission (18). Anecdotal evidence and some limited systematic data argue that higher mortality rates are the explanation (3,19). Standardized mortality ratios, albeit ones that may not include a representative sample, are increased for people with epilepsy in China (SMR 3.7–3.9), Ecuador (SMR 6.3), and Uganda (SMR 7.2).

Many of the identified causes of death among people with epilepsy are seizure related and potentially preventable. Therefore, the importance of addressing physical safety issues among people with epilepsy in developing countries cannot be overstated. These educational and counseling duties need not be undertaken by a physician and, in fact, may be best addressed by trained peer educators. Table 1 delineates some of the potential safety hazards that may warrant discussion. An exhaustive list cannot be generated, as risks tend to have a very local or regional distribution. Part of the management of epilepsy can routinely include educational sessions for the patients and their families that assist them in evaluating safety risks and establishing approaches to decrease the risk of seizure-related injuries. Ideally, this discussion will include the head of household and, under some circumstances, communications with community leaders may be needed. One critical element is to try to dispel contagion beliefs and fears that can contribute to seizure-related injuries, such as burns, since people fearful of "catching" epilepsy may be very reluctant and slow to lend assistance when someone having a seizure falls into a fire. Family members should also receive clear instructions on the safe positioning and handling of a person during an acute seizure, including explicit information against using forceful restraints or any type of oral manipulation, both of which frequently result in trauma.

Role of Indigenous Healers and Medicines

Indigenous or traditional healers provide a substantial proportion of the care delivered to people with epilepsy in developing countries. Such healers are more numerous and equitably distributed than physicians and often are more affordable. For example, in India, the cost of a single physician visit for an individual with epilepsy was 9–13% of the family monthly household income and required 5–12 person hours of dedicated time to access, compared to negligible costs of visiting a traditional practitioner (20). While the biomedical efficacy of indigenous care is uncertain and substantial adverse effects of traditional medicines have been reported, this cadre of health care providers fills an important niche in regions with limited access to any other options. It is key to recognize that the simple acts of caring and care-seeking likely form an important part of the therapeutic support provided to people with a chronic condition, such as epilepsy. When a family member or spouse is concerned enough about a person with epilepsy to seek care with or for them, this is an act of caring, in and of itself.

In some circumstances, indigenous healers may also play a role in dispelling contagion fears (21) or assisting in the identification of stressors resulting in nonepileptic psychogenic seizures (22). Furthermore, given the greater accessibility of indigenous healers to people with epilepsy in regions with the greatest treatment gap, they may provide the most effective means of decreasing this gap either by training them to provide basic epilepsy care or by developing productive collaborative working relationships that encourage the referral of people with

TABLE 1. *Injury Risks that Warrant Discussion and Counseling*

Activity	Risk	Potential Amelioration
Driving any vehicle, including bicycle or tractor	Injury to person with epilepsy as well as to others	Avoid driving until seizure free; use helmet with bicycling and no passengers*
Carrying infant on back	May result in infant injury or even death if mother has generalized tonic–clonic seizure	Provide counseling on safer methods of transporting child; older sibling may be able to assist. Key is to assure mother that this activity can be relinquished without loss of her role and that the activity may be resumed when seizures come under better control.
Cooking/exposure to open flames	Burns	Another family member may need to take on the cooking responsibilities. It is important to try to identify roles the person with epilepsy can accept in return, if at all possible, to avoid loss of role fulfillment.
Swimming, bathing, boating, fishing, collecting water from rivers/streams	Drowning, crocodile attacks	No exposure to bodies of water when alone; accompanying person must be willing to assist, if needed.†
Travel into bush/wilderness/waterside	Animal attacks, generally getting lost	Avoid these activities when alone; accompanying person must be willing to assist, if needed.†,‡
Pedestrian injury on roadway	Road traffic accidents	Avoid walking on busy roadsides, especially if alone.
Roof thatching or otherwise working from high areas (e.g., agricultural and construction employment)	Falls	Counsel to seeking alternative activities.§

*It is important that health care providers for people with epilepsy familiarize themselves with the local legislation regarding driving laws.

†Note that contagion fears are substantial enough that an accompanying person willing to assist if the person has a seizure may need to be explicitly sought. Contagion fears are substantive enough in some environments to result in drowning, severe burns, and/or death while fearful relatives and friends only watch, being too afraid to assist.

‡For people with epilepsy who have spells of "wandering," special measures (e.g., placement in an enclosed dwelling) may be warranted. Family should be explicitly asked if they use other restraint measures (e.g., ropes, chains, etc.), as restraint of patients who are in a supine position could prove fatal, and the use of restraints undoubtedly contributes to the demoralization of people with epilepsy.

§ In some cultures, duties such as annual thatching represent an important aspect of manhood.

active epilepsy. The potential for such collaborative physician–healer relationships is likely to be regional and dependent upon the practice patterns of each.

The initial evaluation and subsequent follow-up of people with epilepsy in developing countries includes determining what types of complementary or alternative care they are receiving, with special attention paid to treatments that might potentially interact with AEDs. This information can only be acquired accurately if the questions are posed in a nonjudgmental, open fashion. Periodic review of the active use of traditional medicines at subsequent follow-up visits is needed since pluralistic care involving both allopathic and indigenous systems is common. Dogmatic recommendations against the dual usage of the allopathic and indigenous systems are likely to be met with half-truths and may even discourage the use of allopathic services. A more effective approach may be to reserve recommendations against indigenous methods to circumstances in which the treatment seems to interfere or interact with AEDs or the practice is obviously harmful (23).

In addition, drug interactions between other commonly prescribed medications for chronic conditions must also be considered—treatments for tuberculosis and HIV/AIDS may be especially problematic in terms of their interactions with enzyme-inducing AEDs (24). When AED failure occurs, particularly if a cohort of previously well-controlled patients experience seizures, the neurologist in a developing country setting must also consider the possibility of counterfeit drugs. Finally, during times of famine, adults with epilepsy are susceptible to extreme weight loss, which may be associated with AED toxicity in previously well-controlled patients (25).

Clinician Biases When Providing Care Services

For clinicians, understanding one's own subtle biases in regard to epilepsy is an important aspect of being able to provide more ideal care. Knowledge, attitude, and practice (KAP) surveys of health care workers in developing countries generally indicate that even though they are more knowledgeable about epilepsy than the lay public, health care workers still inadvertently contribute to epilepsy-associated stigma (26). In Zambia, health care workers, who otherwise seem to hold relatively positive views of people with epilepsy, still recommend significant restrictions on important functions, such as those related to child bearing and parenting (27). Sometimes subtle biases become evident serendipitously. For example, during the initial gathering to organize peer support groups for people with epilepsy in Zambia, physician investigators assumed that the less well-groomed and articulate individuals were the participants and the more well-coifed and well-spoken individuals were accompanying family members. The investigators were humbled and surprised to subsequently discover the opposite was true (personal verbal communication, March 13, 2009, Professor Alan Haworth, MB)!

Perhaps some humility on the part of physicians is also warranted. When confronting a Zambian *ng'anga* (traditional healer) about the adverse reaction one person with epilepsy had in response to a traditional bush tea, the healer reminded this neurologist about a fatal case of carbamazepine-induced Stevens–Johnson syndrome in a patient who had been prescribed this agent during the prior year. It is encouraging to note that formal studies of the potential value of botanical treatments for epilepsy are being conducted at Harvard's Epilepsy Botanical Program (28). Such investigations may lead to locally available sources of AEDs in resource poor settings.

Conclusion

In resource poor settings, people with epilepsy reside in social, economic, and physical environments that present challenges to care seeking on the patient's part and care delivery on the health care provider's part. The limited medication and diagnostic options for epilepsy care in some sense simplifies the medical aspects of epilepsy management in developing countries, but optimal care requires recognizing unique barriers to treatment delivery and adherence as well as to additional epilepsy-associated health risks. Addressing these unique challenges and working with the patients, their family, their community, and the country's overall health system to try to develop effective approaches to overcoming such barriers adds complexity and potential rewards to serving this otherwise underserved population.

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