Revising and refining the epilepsy classification system: Priorities from a developing world perspective

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SUMMARY

Although the technical and human resources for epilepsy care and classification are located largely in high income countries, most people with epilepsy reside in developing regions of the world. Advances over the past two decades in the clinical and basic neurosciences have transformed epilepsy care and largely drive the present need for a revised epilepsy classification. These advances have been mirrored by new knowledge about epilepsy in tropical, resource limited settings. A nonhierarchical, multidimensional approach to classification that includes dimensions that can be ascertained in, and are relevant to, resource-limited settings is needed. Such a classification system could be designed for relevance at tertiary care settings in developed regions as well as primary health care settings in developing regions. Insights from the global use of such a classification approach would also offer opportunities to gain complementary information regarding epilepsy across a broad range of settings and could provide new insights into epilepsy and epileptogenesis. Failure to develop a classification inclusive of the developing world would exclude 80% of the epilepsies globally.

KEY WORDS: Global burden of disease, Risk factors, Health services, Multidimensional.

WHY CONSIDER THE DEVELOPING WORLD’S PERSPECTIVE?

Approximately 80% of the 50 million people with epilepsy worldwide reside in developing countries (WHO, 2006). Epilepsy is the most common chronic neurologic disorder in sub-Saharan Africa (Eisenberg, 1997; Leonardi & Ustun, 2002) and contributes substantially to the global burden of noncommunicable diseases, representing 0.49% of the overall global burden of disease as measured in disability-adjusted life years (DALY). World Health Organization (WHO) estimates indicate that 41% of all DALYs lost to epilepsy could be regained if antiepileptic drugs (AEDs) were universally available, and the World Bank ranks epilepsy in the top five of all non-communicable diseases for cost-effectiveness in treatment (World Bank, 2006). Recent mortality data from rural China indicate that mortality rates among people with epilepsy are substantially higher than previously appreciated. Among people with epilepsy who are younger than 35 years of age, mortality rates were 50 times that of people without epilepsy, with most deaths related to seizures or seizure-associated injuries (Mu et al., 2012).

Epilepsy is a global problem. Most people with epilepsy reside in developing regions. Gargantuan efforts are required to revise the ILAE epilepsy classification and thus facilitate rationale inclusion of clinically relevant information from more than two decades of advances in neuroimaging, neurogenetics, and other disciplines. But if this revision offers value to only 20% of people with epilepsy who reside in wealthy countries, can the international epilepsy community and/or the International League Against Epilepsy (ILAE) consider that an acceptable outcome? Moreover, almost a decade of enthusiastic investment in international research and capacity-building by the U.S. National Institutes of Health through the Fogarty International Center, the National Institute of Neurologic Disorders and Stroke, and the National Institute of Child Health, among others, has led to advances in our understanding of the epidemiology, etiology, natural

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history, and critical comorbidities of epilepsy in low-income tropical settings (Fogarty International Center, 2011). These advances mirror the rapid advances seen in other neuroscience-related disciplines over the same period. Developing an epilepsy classification approach that can be inclusive of all people with epilepsy will offer opportunities to “bridge” what we know about epilepsy and epileptogenesis across the geographic, environmental, and economic divides that delineate the “developed” versus “developing” worlds. If we build it, this bridge could offer critical insights into the pathophysiology of epilepsy and epileptogenesis that would benefit everyone.

**KEY ISSUES FOR A CLASSIFICATION SYSTEM THAT CAN CONTRIBUTE TO OUR GLOBAL KNOWLEDGE**

For an epilepsy classification system to be used and useful in resource limited, tropical settings, it needs to be clinically relevant locally. This requirement is challenging, as diagnostic and treatment options in low income countries are extremely limited. Only one AED might be routinely available in the public sector, and diagnostic options do not routinely include electroencephalography (EEG) or neuroimaging. But many basic characteristics of epilepsy can be ascertained without advanced technology; these include age of onset, seizure semiology, family history, predisposing factors for seizures such as sleep deprivation, risk factors, response to first-line treatments, associated disabilities such as cerebral palsy, and critical comorbidities such as HIV. An epilepsy classification system for use in the developing world also needs to capture the critical information required for public health and health policy planning. For example, “response to treatment” has been proposed as a relevant dimension in a revised classification system (Kwan et al., 2010). Including this concept—but expanding it to include treatment exposure—would provide insights into the treatment gap. There are several established potentially modifiable risk factors for epilepsy development—for example late-term prematurity (Petrini et al., 2009) and cerebral malaria (Birbeck et al., 2010). Capturing risk factor information would offer insights into attributable risks and might further delineate the natural history of epilepsy resulting from specific injuries or exposures.

The resources, both human and technological, available for applying the classification system in a developing country will differ substantially from the resources routinely available in wealthier, more developed settings. Figure 1 depicts the global distribution of neurologists. Note that these levels are optimistic estimates, since no adjustments were made for the many regions of the developing world for which no neurologist survey respondent could even be identified. Figure 2 shows territory size in proportion to the number of all physicians that work in that territory, and further illustrates that the problem is not a lack of neurologists but a dearth of physicians in general. Health care providers in resource-limited settings have limited neurologic expertise and training, so it is especially important to be as clear, simple, and direct as possible in classification terminology. Our idiosyncratic use in neurology of some terms—for example “idiopathic” when we actually mean “genetic”—is unfortunate and contributes much to confusion among the nonspecialist health care providers who are the de facto health care providers for most people with epilepsy in the world. Can an epilepsy classification system be developed that could be used not only by nonspecialist physicians but by the nonphysician health care workers who routinely provide care in developing regions? If we want a system that works for >20% of people with epilepsy, this is what we must strive for.

**A MULTIDIMENSIONAL, NONHIERARCHICAL SYSTEM IS NEEDED**

Hauptman et al. (2012) urge the ILAE to “acknowledge that both MRI [magnetic resonance imaging] and EEG are necessary diagnostic tools in the classification of epilepsy syndromes and etiologies in the modern era.” The 1989 Commission on Classification made recommendations that required EEG capability, forcing most epidemiologic studies from low income regions without recourse to EEG to resort to using older classification systems (ILAE 1981, 1989). A more inclusive approach to epilepsy classification is needed.

As is evident from the articles in this supplement, there are many potential users of any revised ILAE classification system, and each seeks revisions that will produce a
A multidimensional approach for classifying epilepsy has been used by the Cleveland Clinic (Onsurbe et al., 1999). Only a multidimensional, nonhierarchical approach can offer the depth, breadth, and flexibility needed to develop a classification system that can address the needs of tertiary care clinicians offering epilepsy surgery, as well as neuroepidemiologists and public health officials in low-income regions. In a multidimensional classification system, the clinicians could rank order dimensions based upon their perspective of relevance for a specific patient care setting. The researcher could assign “null” values to dimensions that could not be adequately assessed in a specific environment. And the clinicians’ rank order of relevant clinical dimensions might actually be a “meta” dimension of interest to researchers. Table 1 offers a list of potential dimensions for inclusion, and comments on their relevance and considerations from the developing world perspective.

### Table 1. Potential dimensions for inclusion in a revised classification

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Considerations from the developing world perspective</th>
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<tbody>
<tr>
<td>Seizure semiology</td>
<td>Continuing to characterize seizure semiology across all studies would facilitate comparisons on this aspect of epilepsy across high and low income settings</td>
</tr>
<tr>
<td>Seizure frequency</td>
<td>Might need to include indicator of frequency on and off treatment given epilepsy treatment gap, limited AED access and the inevitable lapses in AED use</td>
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<td>Etiology</td>
<td>This may be a dimension that cannot often be applied where advanced diagnostics are almost nonexistent. “Cause depends on degree of investigations” (Shorvon, 2011). Nonetheless, recently described syndromes such as FIRES might deserve inclusion (Kramer et al., 2011)</td>
</tr>
<tr>
<td>Key comorbidities</td>
<td>Comorbidities may be associated with the underlying epilepsy etiology or coincidental but relevant. For example, AED and antiretroviral interactions make this an important consideration for patients in HIV endemic settings (Birbeck et al., 2012a,b)</td>
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<tr>
<td>Physical disability (e.g., cerebral palsy)</td>
<td></td>
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<tr>
<td>HIV</td>
<td></td>
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<tr>
<td>Risk factors</td>
<td>Risk factors might be approached on a categorical basis (e.g., CNS infection) or based upon specific entities (e.g., Japanese encephalitis). Availability of such data may offer insights into the attributable risks for epilepsy in different environments</td>
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<tr>
<td>Therapeutic response</td>
<td>Consideration would need to be given to including some indicator of treatment access and options. For example, would a patient with epilepsy who has failed one drug be considered refractory if only one drug is available to that patient (Kwan et al., 2010)? This might be a characteristic of value where diagnostic options are limited</td>
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<tr>
<td>Medical</td>
<td></td>
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<tr>
<td>Surgical</td>
<td></td>
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<tr>
<td>Epilepsy associated with progressive, focal neurologic symptoms</td>
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CNS, central nervous system; FIRES, febrile infection-related epilepsy syndrome.
applicability in the developing world. One critical aspect of such an approach would be the need to carefully delineate when sufficient information on a dimension was ascertained for its inclusion as one of the dimensions.

**Conclusions**

The epilepsy classification undoubtedly needs revisions. Using a novel approach, such as the multidimensional, nonhierarchical one described here, would allow for the development of a flexible classification tool that could be used everywhere epilepsy exists. Any classification system lacking utility or applicability in the developing world will ultimately be useful to only a small subset of people with epilepsy and may fail to describe epileptic conditions unique to tropical, resource-limited setting.

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**References**


