

53 countries. It has a population of 850 million people, who speak approximately 45 official languages. Striking is the diversity in economy and culture seen across the region, with 11 countries designated as low or low middle income by World Bank categories. This report examines the prevalence of epilepsy and its management across the region, highlighting some key areas that require action.

Within Europe there is a relatively large number of individuals with epilepsy. With a prevalence of 8.2 per 1,000, around 6 million individuals have epilepsy, and 15 million people will have had epilepsy at some time in their lives. Despite the fact that up to 70% of individuals can be treated effectively, the treatment gap between those requiring treatment and those receiving it is large. This may not be surprising in the low income countries, not helped by cultural perceptions of the condition, as well as the high cost of and availability of antiepileptic drugs (AEDs) and services, but it has been demonstrated that even the more “developed” countries are “developing” where epilepsy management is considered.

The provision of epilepsy treatment and care across Europe was investigated in a survey of the European International League Against Epilepsy (ILAE) chapters by the Commission for European Affairs. A questionnaire, the European Epilepsy Services Inventory, was sent to all 36 European chapters of the ILAE, with responses from 32. In addition to showing the regional variations in provision of epilepsy care, the results also demonstrated a wide range in the numbers of physicians and specialists involved in epilepsy care. Furthermore, although there was a high number of epilepsy specialists listed in many countries, the highest of all the World Health Organization (WHO) regions, access to comprehensive epilepsy care in many countries was limited, with a high rate of misdiagnosis, over investigation, as well as over treatment and under treatment. In addition, although epilepsy surgery is recognized as curative for selected individuals, the survey demonstrated such management to be underutilized in many countries in Europe.

Although there were large regional and national variations in the provision of epilepsy care, similar problems were reported. The most common problems were lack or underuse of epilepsy surgery; lack of comprehensive care; stigma and social problems; the high cost of AEDs (especially the newer drugs); lack of specialists and of specialized epilepsy care; lack of financing, equipment, and resource allocation; insufficient professional education and knowledge about epilepsy; and lack of epidemiologic data, violation of patients rights, and employment problems. Furthermore, the mortality rate among people with epilepsy is higher than that among the general population; it is estimated that there are 33,000 epilepsy deaths in Europe each year, 13,000 of which are preventable.

In response, several initiatives are already in process in an attempt to address the situation. These include commu-

nication with the European Medicines Agency (EMA) to contribute to the process of and guidelines for the approval of new AEDs, the development of European guidelines for the treatment of status epilepticus, and harmonizing the availability of and indications for AEDs across Europe. However, there is a need for further action to raise the profile of epilepsy within the European community, to reduce the stigma, enhance policy making and services for individuals with epilepsy, and improve access to care. This includes access to appropriate specialist care, medication, and surgery. The need for the promotion of existing and collaborative research across the region is also emphasized. The ILAE Commission for European Affairs has prepared a position paper on research priorities for use as a tool for communication with regard to further European support.

DISCLOSURE

I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

I am currently Co-Chair Global Outreach Task Force ILAE and IBE. I have no conflicts of interest to disclose.

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COMMENTARY

The following commentary on the Blumcke et al. Special Report was invited by the Editors-in-Chief

Revising the classification of focal cortical dysplasias

Scientific knowledge is dynamic and must be open to reexamination. This “tabula non-rasa”—the preexisting knowledge that serves as the basis for reexamination—is an inseparable part of the scientific enchantment and the necessary benchmark upon which reflections and reexaminations proceed. Progress is always progress over previous knowledge.

In the last 20 years, malformations of cortical development (MCDs) have taken a place as a major etiology of epilepsy. In the beginning, MCDs were grouped under the umbrella term “neuronal migration disorders” (Palmini et al., 1991), and later became synonymous with “cortical dysplasia” (Desbiens et al., 1993; Kuzniecky & Powers, 1993; Kuzniecky et al., 1995). It took years of clinical and basic research—particularly involving magnetic resonance

imaging (MRI)—for the emergence of correlations between mechanisms of interference with cortical development and associated anatomic subtypes of malformations (Barkovich et al., 1996). It is now understood that cortical development can be interfered with (1) at the level of neuronal–glial proliferation and differentiation, (2) during neuronal migration to the cortical plate, and (3) at the final stages of intracortical organization. Interference with each of these processes leads to different types of MCDs, identifiable through MRI, and displaying varying degrees of epileptogenicity.

Time and accumulated experience have taught a second key epileptologic lesson in this field: Although, as a group, MCDs are a major etiology of epilepsy, a specific subtype of MCDs—*focal cortical dysplasia (FCD)*—is responsible for the vast majority of medically refractory partial epilepsies in patients with MCDs. Once the various types of MCDs were distinguished, the next step was to disentangle the MCD subtype with the most practical relevance for those involved in the evaluation and treatment of patients with refractory partial epilepsies. Those efforts focused on FCD.

On the one hand, different lesions encompassed under the umbrella term “FCD” share histologic common denominators, such as abnormal cortical architecture. On the other hand, they differ in a number of features that are of practical relevance. Clinical–epileptologic scenarios are often different, and so are lesion localization, extent, and separation/distinction from surrounding cortex (Tassi et al., 2002; Sisodiya et al., 2009). Some lesions have distinct MRI features, such as localized increased cortical thickness, blurring of gray–white transition, and abnormal signal (Barkovich et al., 1997; Lerner et al., 2009; Sisodiya et al., 2009). Others have less compelling appearances and may present only with some atrophy or shrinkage of the subcortical white matter (Tassi et al., 2002; Krsek et al., 2008; Lerner et al., 2009). Still others may lie hidden within atrophic, partly destructive lesions (Krsek et al., 2008). Similar differences are often detected on neurophysiologic evaluations, particularly the occurrence of exquisitely epileptiform patterns upon direct recording of some types of FCD (Palmini et al., 1995; Chassoux et al., 2000). Because these features impact upon presurgical evaluation, surgical planning, and prognosis, a refined classification is needed.

Attempts at such classifications eventually led to a consensus reached in Cleveland and published in 2004 (Palmini et al., 2004), often referred to as the “Palmini classification system.” That classification scheme was histopathologic in nature, recognizing that FCD shared one major feature—intracortical laminar and columnar disorganization or “*dyslamination*”—but differed in the concomitant presence of abnormal neuronal–glial elements. Therefore, type I FCD was deemed as characterized by cortical dyslamination and type II FCD featured both dysl-

amination and grossly abnormal cellular elements, particularly dysplastic (dysmorphic) neurons (IIA) and balloon cells (IIB). After a timid start, this classification “took off” and has been an integral part of scientific reports in the vast epileptologic field of the FCD (Fauser et al., 2004; Krsek et al., 2008; Lerner et al., 2009; Sisodiya et al., 2009).

Six years later, the cycle repeats itself: Through usage, experience, and debate, a number of issues related to the current classification have been raised. Although no classification is flawless, it is also unwise to discard what has been a backbone of epileptologic reporting for many years. Therefore, building upon the widely used current classification scheme (Palmini et al., 2004), a new consensus for the histopathologic classification of FCD has been reached and appears in this issue of *Epilepsia* (Blümcke et al., 2010). Two major aspects of classification are revised in this new scheme. One refers to a better definition of what should be considered “*dyslamination*,” a cornerstone of the FCD lesion. The other aspect now implemented is the addition of a third category—FCD type III—to include those cases in which type I FCD (i.e., *dyslamination*) is associated with another epileptogenic lesion, particularly hippocampal sclerosis, tumors, vascular malformations, or gliotic scars. The major reason for this revision is our new understanding that FCD associated with these other lesions may prove to be pathogenically distinct from the isolated types, and thus treatment approaches may vary and be more specific. The jury is out for debate on this point. It is hoped that new knowledge proves to be improved knowledge. The likelihood is fortunately high.

DISCLOSURE

I have no conflicts of interest to disclose. I confirm that I 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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REFERENCES

Barkovich AJ, Kuzniecky RI, Dobyns WB, Jackson GD, Becker LE, Evrard P. (1996) A classification scheme for malformations of cortical development. *Neuropediatrics* 27:59–63.
 Barkovich AJ, Kuzniecky RI, Bollen AW, Grant PE. (1997) Focal transmantle dysplasia: a specific malformation of cortical development. *Neurology* 49:1148–1152.
 Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, Jacques TS, Avanzini G, Barkovich AJ, Battaglia G, Becker A, Cepeda C, Cendes F, Colombo N, Crino P, Cross JH, Delalande O, Dubeau F, Duncan J, Guerrini R, Kahane P, Mathern G, Najm I, Özkara Ç, Raybaud C, Represa A, Roper

- SN, Salamon N, Schulze-Bonhage A, Tassi L, Vezzani A, Spreafico R. (2010) The clinico-pathological spectrum of Focal Cortical Dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission'. *Epilepsia*, in press.
- Chassoux F, Devaux B, Landre E, Turak B, Nataf F, Varlet P, Chodkiewicz JP, Daumas-Duport C. (2000) Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. *Brain* 123(Pt 8):1733–1751.
- Desbiens R, Berkovic SF, Dubeau F, Andermann F, Laxer KD, Harvey S, Leproux F, Melanson D, Robitaille Y, Kalnins R et al. (1993) Life-threatening focal status epilepticus due to occult cortical dysplasia. *Arch Neurol* 50:695–700.
- Fausser S, Schulze-Bonhage A, Honegger J, Carmona H, Huppertz HJ, Pantazis G, Rona S, Bast T, Strobl K, Steinhoff BJ, Korinthenberg R, Rating D, Volk B, Zentner J. (2004) Focal cortical dysplasias: surgical outcome in 67 patients in relation to histological subtypes and dual pathology. *Brain* 127:2406–2418.
- Krsek P, Maton B, Korman B, Pacheco-Jacome E, Jayakar P, Dunoyer C, Rey G, Morrison G, Ragheb J, Vinters HV, Resnick T, Duchowny M. (2008) Different features of histopathological subtypes of pediatric focal cortical dysplasia. *Ann Neurol* 63:758–769.
- Kuzniecky R, Powers R. (1993) Epilepsia partialis continua due to cortical dysplasia. *J Child Neurol* 8:386–388.
- Kuzniecky R, Morawetz R, Faught E, Black L. (1995) Frontal and central lobe focal dysplasia: clinical, EEG and imaging features. *Dev Med Child Neurol* 37:159–166.
- Lerner JT, Salamon N, Hauptman JS, Velasco TR, Hemb M, Wu JY, Sankar R, Donald Shields W, Engel J Jr, Fried I, Cepeda C, Andre VM, Levine MS, Miyata H, Yong WH, Vinters HV, Mathern GW. (2009) Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: a critical review and the UCLA experience. *Epilepsia* 50:1310–1335.
- Palmini A, Andermann F, Olivier A, Tampieri D, Robitaille Y, Andermann E, Wright G. (1991) Focal neuronal migration disorders and intractable partial epilepsy: a study of 30 patients. *Ann Neurol* 30:741–749.
- Palmini A, Gambardella A, Andermann F, Dubeau F, da Costa JC, Olivier A, Tampieri D, Gloor P, Quesney F, Andermann E, Paglioli E. (1995) Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. *Ann Neurol* 37:476–487.
- Palmini A, Najm I, Avanzini G, Babb T, Guerrini R, Foldvary-Schaefer N, Jackson G, Luders HO, Prayson R, Spreafico R, Vinters HV. (2004) Terminology and classification of the cortical dysplasias. *Neurology* 62:S2–S8.
- Sisodiya SM, Fausser S, Cross JH, Thom M. (2009) Focal cortical dysplasia type II: biological features and clinical perspectives. *Lancet Neurol* 8:830–843.
- Tassi L, Colombo N, Garbelli R, Francione S, Lo Russo G, Mai R, Cardinale F, Cossu M, Ferrario A, Galli C, Bramerio M, Citterio A, Spreafico R. (2002) Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. *Brain* 125:1719–1732.

The following commentaries on the Greenberg and Subaran Critical Review, and the response by Greenberg and Subaran, were invited by the Editors-in-Chief

Comment on “Blinders, phenotype, and fashionable genetic analysis: A critical examination of the current state of epilepsy genetic studies”

Advances in our understanding of the molecular genetic bases of epilepsy with complex inheritance have failed to

match those of Mendelian epilepsy. Several new powerful genetic methods, including genome-wide sequencing and association analysis, are now “routinely” available to probe the genetic architecture of epilepsy, and the contribution from Greenberg and Subaran (2010) to the debate on how best to apply these methods is both timely and welcome.

Although some researchers in the field may disagree with their notion that progress has been retarded by a community psychology anchored in the premise that epilepsy is an ion-channelopathy, few would disagree that decisions regarding definition of phenotype will be key to the success of future research efforts. Epilepsy phenotype is not an absolute concept, but a device that can be flexibly adapted to fit the purpose at hand, be that presurgical assessment or an attempt to get “closer” to the molecular genetic origins. Therefore, Greenberg and Subaran (2010) and others have proposed that restricting the dimension of a phenotype is the best way to maximize the chances of detecting epilepsy genetic risk factors. However, others might point to the fact that the single most important epilepsy gene yet discovered, *SCN1A*, was identified precisely because it was recognized that heterogeneous forms of epilepsy might share a common genetic etiology (Scheffer & Berkovic, 1997).

Therefore, one might take a conceptually contrary approach, which explores the extent to which the epilepsies as a group of heterogeneous conditions might be related to each other at a higher level of functional organization. Because the expression of a disease at the level of the cell or organism often involves sets of genes acting together, a focus on individual genetic risk factors may mask their important combined effect on a common causal network. A failure to recognize a common pathway or biologic network for epilepsy seizures might itself impede the discovery of new therapeutic insights.

A key discovery from Mendelian epilepsy genetics is that mutations in many different genes can contribute risk for epilepsy. Because these different genetic conditions overlap at least by virtue of all having epilepsy seizures, the presence of locus heterogeneity in epilepsy supports the concept that different epilepsy genes may form part of an extended epilepsy-specific functional module. Epilepsy then becomes a disorder resulting from the perturbation of a specific functional module caused by genetic variation in one or more components of the module (as in Goh et al., 2007). In this way, “rare” variants such as copy number variants associated with heterogeneous forms of non-Mendelian epilepsy (Mefford et al., 2010) may yield critical contributions to the understanding of the overall disease mechanism, even though they account for only a few percent of all epilepsy. If all genetic epilepsy is the variable expression of a single functional module, the genetic signal from mechanisms fundamental to the expression of