CHAPTER

51

Animal Model Development Based on the Human Epilepsies: Which Causes and Syndromes Should Be Modeled?

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INTRODUCTION

Animal models of epilepsy, whether *in vitro* or *in vivo*, genetic or acquired, whole animal or cell culture, have a fundamental and critical role in developing a scientific understanding of the physiology and anatomy of epilepsy (Sarkisian, 2001). *In vitro* slice and cell culture preparations provide the appropriate research environment to study properties of single cells and local synaptic networks, and *in vivo* whole animals models of genetic and acquired epilepsies are experimental systems for understanding mechanisms of epileptogenesis, therapy resistance, and the relationship between phenotype and genotype. Although all these experimental models and systems are important and useful, it is imperative to emphasize what is the purpose of animal models in the first place: Namely, to model elements of the human epilepsies with the goal of elucidating epileptic mechanisms so we can develop improved treatments for these disorders. With this central tenet in mind, the focus of this chapter is a critical assessment of our current understanding of the epidemiology of the human epilepsies, especially causes and syndromes that are therapy resistant, and to identify which of these conditions are not adequately modeled. To address this question, our approach is to survey the literature to generate a list of the most frequent human epilepsy causes and syndromes by age, gender, race, and geography; assess which syndromes are most likely to be therapy resistant; and then compare the human list with the available animal models. The final goal of this chapter is to recommend future clinical research studies to assist model development.

EPIDEMIOLOGY OF HUMAN EPILEPSIES: WHAT CAUSES AND SYNDROMES BY AGE, GENDER, RACE, AND GEOGRAPHY HAVE CHRONIC EPILEPSY?

Incidence and Prevalence of Epilepsy

Population-based epidemiology studies provide information regarding the incidence (number of new cases) of epilepsy, and, over the past 30 years, more than 40 studies have been published (Sander and Shorvon, 1987; Kotsopoulos et al., 2002). Although these studies differ in the populations surveyed and their study methods, collectively they show a consistent bimodal age distribution of epilepsy. The incidence of epilepsy is highest at the extremes of life, in earliest childhood and the most elderly. In children, the highest incidence rate is in the first year of life (80 to 150/100,000 people/year); the rate declines through the first decade and, in adults, varies from 20 to 60/100,000 people/year, and increases to more than 100/100,000 people/year in those over age 70 years (Hauser et al., 1993; Sidenvall et al., 1993; Ronen et al., 1999). Whether the incidence is higher in childhood or in older people depends on the geography of the studied population (Everitt and Sander, 1998). In general, life expectancy in developing countries is shorter than in industrialized societies. As a result, in the developing world fewer older people develop epilepsy (de Bittencourt et al., 1996a; de Bittencourt et al., 1996b). In addition, in developing countries, there is a higher incidence of children with epilepsy from central nervous system (CNS) infections, including malaria, onchocercosis, tuberculosis, and cysticercosis; infant CNS injuries from

inadequate obstetric care; and a higher rate of cerebral trauma (Gomez et al., 1978; Ogunniyi et al., 1987; Osuntokun et al., 1987; Wang et al., 2003). In developed countries, the incidence of epilepsy in children has gradually decreased over the past four decades, probably from better antenatal and prenatal care, and the number of elderly patients increased because of longer life expectancy (Hauser et al., 1993; Cockerell et al., 1995). Thus, in deciding which animal models to develop, consideration should be given to the age and populations with epilepsy to be studied. If a global view is taken of the human epilepsies for animal model development, then priority should be given to syndromes and causes at the extremes of age, and not just consider causes in industrialized countries (see Recommendation 1).

Epidemiologic studies report that the gender-specific incidence of epilepsy is slightly higher in males than females by 1 to 5/100,000 people/year. This is probably because of the higher risk factors in males for traumatic brain injury, stroke, and CNS infections, but this has not been adequately tested (Sander and Shorvon, 1996; Hauser, 1997). Even less is known about the incidence of epilepsy by race in population-based epidemiologic studies. Two studies from developed countries report no differences in the incidence of epilepsy among insured (vs. uninsured) black, white, and Hispanic ethnic groups (Shamansky and Glaser, 1979; Annegers et al., 1999). A question from these studies remains about a lower incidence of epilepsy in Asian—Americans and a higher incidence among Native Americans. No studies have examined incidence rates by race in the developing world. Knowing if there are differences in epilepsy incidence by gender or race would be an important consideration in the development of animal models for any identified syndrome or etiology, and should be a goal for future epidemiologic studies (see Recommendation 1).

The lifetime self-reported prevalence of epilepsy is from 2% to 5% in developed countries (Kobau et al., 2004). Population based studies indicate a general increase in the prevalence rate (number of people with epilepsy) with age (2 to 3/1000 by age 7 years to 8 to 10/1000 in adults) (Bharucha et al., 1988; Hauser, 1997). Knowing that incidence rates decline during the first decade of life, the increase in prevalence rate supports the concept that a significant proportion of adolescent and adult patients whose epilepsy is not controlled with medications (therapy resistant). If epilepsy abated, either through therapy or natural history, then the prevalence rate should decline with age. As with incident data, prevalence rates are generally much higher in developing countries (10 to 15/1000), indicating that the causes based on geography are frequently therapy resistant (Haerer et al., 1986; Hauser et al., 1991; Murphy et al., 1995; Kobau et al., 2004). Thus, prevalence data indicate that many adolescents and adults with uncontrolled epilepsy continue to have seizures throughout their life. Likewise, animal models of the human epilepsies should also show resistance to medical therapy, which is not routinely tested (see Recommendation 2).

Risk Factors, Etiology, and Syndromes of Chronic Epilepsy

Although incidence and prevalence rates provide general data about populations with epilepsy, this is only a beginning in determining what human conditions should be modeled. We also need to know what are the causes and syndromes responsible for the epilepsies? Here, epidemiology data become less clear because determining cause depends on when in time, the studies were performed because terminology and methods to classify etiology have changed. For example, in the era before modern neuroimaging (magnetic resonance imaging [MRI], computed tomography [CT], positron emission tomography [PET] and single-photon emission computed tomography [SPECT]), seizure classification was based mostly on clinical presentation and electroencephalography (EEG), and results found that seizure causes were classified as "unknown" in 55% to 75% of cases (Hauser et al., 1993). More recent studies, using MRI and better classification systems, currently categorize 25% to 30% of cases as idiopathic (probable genetic cause), and 15% to 20% as symptomatic (known structural cause). The remaining 30% to 50% of cases are classified as cryptogenic (no known genetic or pathologic cause), and this rate does not differ by age or geography (Berg et al., 1999a; Berg et al., 1999b; Jallon et al., 2001). In other words, using our best clinical tools and knowledge, we cannot appropriately determine a clear cause in 30% to 50% of those patients with epilepsy in 2005. This is a sobering fact that has an impact in deciding what epilepsy syndromes have highest priority in animal model development, and finding better tools to diagnosis epilepsy syndromes in patients should be an important clinical research endeavor (see Recommendation 3).

As might be expected based on incidence data, there are secular and geographic variation for the cause of the epilepsies based on age. For example, data from Rochester, Minnesota from 1935 to 1984 where the population was mostly of white Scandinavian descent identified causes in one third of the patients, with the most common being vascular (10.9%), childhood encephalopathies (8%), trauma (5.5%), tumors (4.1%), neurodegenerative disorders (3.5%), and intracranial infections (2.5%) (Hauser, 1997). Similar etiologic data have been obtained from a Texas HMO and large survey of the French population (Table 1) (Annegers et al., 1999; Jallon et al., 2001). In Jamaica, by comparison, the most common causes are trauma (19.5%), substance abuse (15%), and genetic (14.9%) (Hauser, 1997). In children, approximately 20% of cases have known causes, and the most common were intrauterine insults (7%), brain malformations (3%), neurocutaneous syndromes (e.g. tuberous

sclerosis; 2%), infection (1%), and tumor (1%) (Berg et al., 2000). In the elderly, cerebrovascular disease, which is the single most common cause, presents with status epilepticus in more than a third of affected patients (Stephen and Brodie, 2000; Camilo and Goldstein, 2004). Other common causes in the elderly include neurodegenerative disorders (e.g., Alzheimer's disease, Pick's disease) and tumors (e.g., gliomas, meningiomas, and metastases) (Dam et al., 1985; de la Court et al., 1996). Thus, cause by age plays an important role in deciding which animal models of epilepsy to develop and prioritize (see Recommendation 4 and Table 1).

MEDICAL INTRACTABILITY BY ETIOLOGY

It is equally relevant to know which of the human epilepsies, by cause and syndrome, are not controlled using current medical and surgical therapies in order to prioritize animal model development. Whereas this may seem easy to determine, reliable epidemiologic data are lacking. Persistent seizures on medication are not the same as being "medically refractory." Most studies have defined intractable epilepsy as failure of a certain number of drugs (usually more than two) with more than one seizure per month, for some specified time period (e.g., 12 or 18 months) (Berg et al., 2001; Cowan, 2002). Using this definition, the incidence of intractable epilepsy based on population studies ranges from 10% to 15%, and is highest in patients with symptomatic substrates (30% to 40%) compared with idiopathic (<10%) and cryptogenic causes (10% to 15%) (Chawla et al., 2002; Kwong et al., 2003). Seizure control, defined as no seizures on or off medical therapy, varies from 50% to 65% in population-based epidemiologic studies, and is higher in idiopathic and cryptogenic cases (60% to 70%) compared with symptomatic causes (30% to 35%) (Sillanpaa et al., 1998). The remaining 20% to 40% of patients with epilepsy have infrequent spontaneous or reactive seizures (≤12/year), and the incidence is nearly the same for idiopathic, cryptogenic, and symptomatic causes. This latter group is often referred to as "indeterminate," exist in a limbo between seizure control and medically refractory, and are infrequently the subject of detailed clinical studies. For animal model development, these data support the concept that priority should be given to modeling symptomatic causes because as these are the most likely cases to be medically refractory. That assessment, however, could change if we have better characterization of the indeterminate group,

TABLE 1 Most Common Cause or Syndromes (at least 1%) with Epilepsy Using Population-Based Epidemiology Data For All Ages and Geographic Locations

Cause or syndrome	Approximate incidence in patients with epilepsy	Likely to be therapy-resistant	Animal model of human condition
Stroke-related	17.4%	33% to 45%	Unclear
Trauma	15.7%	40% to 50%	Partial
MCD+	9.0%	≥70%	Partial
Perinatal insults	7.9%	30%	Partial
Tumors	6.2%	30% to 50%	Limited
Central nervous system infections[b]	3.9%	Unknown	No
Degenerative disease	3.9%	Unknown	No
Epileptic Encephalopathies	3.4%	>80%	No
Ethanol and substance Abuse	1.7% (higher certain countries)	Unknown	No
Hippocampal sclerosis	Unknown	≥70%	Partial
Syndrome defined Cryptogenic	30% to 50%	10% to 15%	No
Childhood absence (including atypical)	12.0%	>10%	Partial
Juvenile myoclonic Epilepsy	5.3%	>10%	Partial
Childhood epilepsy with central-temporal spikes	3.8%	>10%	No

Data Compiled from Jallon et al.; Berg et al.; Stephen et al.; Semah et al.; Berg et al.; and Sarkisian.

+MCD, Malformations of cortical development.

[a]Perinatal insults include hypoxia or ischemia; stroke, and intraventricular hemorrhage.

Epileptic encephalopathies include infantile spasms, Lennox-Gastaut Syndrome, and so forth that should be modeled separately.

[b]Special emphasis on childhood central nervous system infections in developing countries including malaria, onchocercosis, tuberculosis, and cysticercosis.

especially those with cryptogenic causes. These findings also indicate that seizure frequency (low vs. high) should be an element in designing animal models.

Current clinical studies are unclear about the percent of therapy-resistant cases in the population for specific epilepsy causes and syndromes. Population-based epidemiologic studies typically survey hundreds to thousands of patients. For example, the Rochester, Minnesota studies were based on a population of less the 70,000 (Hauser, 1997). Unless the sample size is increased into the millions, the number of patients sampled with specific causes of epilepsy will be very small, and most studies have not addressed what percentage of these patients by cause or syndrome are therapy resistant in the era of modern neuroimaging. Currently, population-based epidemiologic studies are of limited value in determining which human epilepsy causes and syndromes have the highest incidence of therapy resistance. Some information on therapy resistance is available from retrospective clinical surveys from centers that treat patients with epilepsy (Semah et al., 1998; Kwan and Brodie, 2000; Stephen et al., 2001). The limitation of these studies is that the study populations are those referred to tertiary centers and, by definition, have usually failed treatment in the community, so the sample is biased. Additional limitations are that the studies usually focus on specific age groups (children vs. adults), and are performed in developed countries with extensive resources devoted toward research. Less is known about the rate of intractable epilepsy by cause and syndrome in developing countries. Despite, these limitations, evidence is emerging that specific causes and syndromes have different rates of seizure control on medication as shown for adult patients in Table 2. In children, the risks of intractability are influenced by age at seizure onset and syndrome. For example, 20% to 30% of patients with neonatal onset seizures develop intractable epilepsy, and patients with epileptic encephalopathies are at high risk for developing refractory epilepsy (Ellenberg et al., 1984; Mizrahi, 1999).

The percentage of patients in the population with therapy-resistant epilepsy is even less clear for causes and syndromes familiar to epilepsy surgery centers but not captured in epidemiologic studies. Certain causes and syndromes (e.g., hemimegalencephaly, Sturge–Weber syndrome, tuberous sclerosis complex, Rasmussen syndrome, hypothalamic hamartoma, hippocampal sclerosis, Lennox–Gastaut syndrome, Landau–Kliefner syndrome and seizures from low-grade CNS tumors and vascular lesions) are relatively well-known conditions to epilepsy specialty centers and are often medically intractable. Patients with these syndromes, however, are often not clearly identified in population-based epidemiologic surveys. Thus, we need to improve our epidemiologic methods and increase the sample sizes to better capture these unique epilepsy syndromes well known to specialty centers (see Recommendation 5).

CONCLUSIONS AND RECOMMENDATIONS

From our literature review and analysis, one can identify limitations of our current knowledge of the epidemiology of the human epilepsies, begin to prioritize the human epilepsies that are most likely to be therapy resistant to compare with currently available animal models, and propose recommendations for future clinical and basic science research related to animal model development. Based on known epidemiologic data of the human epilepsies, it is recommended that model development should focus on age and geographic-specific causes and syndromes that are currently not adequately treated with medical or surgical therapies. Thus, by definition priority should be given to model the most common therapy-resistant, diffuse nonfocal causes and syndromes that have a high risk of inducing epilepsy-related cognitive and developmental disabilities or because of a "silent" period between insult to development of epilepsy might be stopped during the epileptogenic process. A proposed priority list of the common epilepsy causes and syndromes is shown in Table 1, along with the known chance of therapy resistance. This table could easily change with better epidemiologic data of patients with refractory epilepsy, especially in the cryptogenic group. Also included in Table 1 is an assessment of whether the human condition has been adequately modeled, and the reader should consult the appropriate chapters for greater detail and discussion of how the models relate to the human condition.

The recommended causes and syndromes to model in Table 1 were influenced by known epidemiologic data for age and geography. For infants, it is recommended that we model the syndromes associated with epileptic encephalopathy, injuries and malformations of cortical development, and

TABLE 2 Seizure-Free Control Rates Using Antiepileptic Drugs for Adults

Stroke	Vascular malformation	Tumor	Trauma	Cortical dysplasia	Hippocampal clerosis
54% to 67%	50% to 78%	46% to 63%	30% to 56%	24% to 54%	11% to 42%

Lower Rates for new onset cases; higher rates for cases referred to a tertiary referral center.
Data combined from Stephen, Kwan, and Brodie, 2001; and Semeh et al., 1998.

CNS infections important for developing countries (Gastaut et al., 1966; Senanayake and Roman, 1993; Kramer et al., 1998). In young children, genetic syndromes associated with atypical absence, juvenile myoclonic epilepsy, and childhood epilepsy with central-temporal spikes should be give priority because these are the most common and many are therapy resistant (Mattson, 2003). In adolescents and adults, priority should be given to model development for traumatic brain injury, tumors, multiple sclerosis, and alcohol and substance abuse (Bruns and Hauser, 2003; Frey, 2003; Kim, et al. 2004; Schauble, et al. 2004). In the elderly, models related to CNS cerebrovascular diseases and degenerative disorders (Alzheimer yndrome) are important (Stephen and Brodie, 2000).

In addition, listed below are several recommendations for future clinical studies needed to provide information to help animal model development. These include

1. We need better human epidemiologic studies that clarify if there are gender and race differences in the incidence and prevalence of epilepsy by syndrome and etiology. It may be important to model specific causes by gender (traumatic brain injury and stroke in males vs. females), or genetic syndromes may be more common in certain human populations, indicating that the phenotype of a condition should vary by mouse or rat strain.
2. A current limitation of *in vitro* and *in vivo* models of epilepsy is the question of whether the model or system is therapy resistant to current medical therapy. In theory, new compound development to treat epilepsy should be screened in simple high-throughput systems with reliable endpoints that model mechanisms that are currently "therapy resistant" in humans or have surrogate markers of the human condition. These model systems are in need of development and validation.
3. In 2005, we still classify 30% to 50% of patients with epilepsy as cryptogenic (without known cause). Knowing the specific genetic or symptomatic cause of the human epilepsies is important in prioritizing animal model development. Thus, we need better methods of diagnosing and classifying the human epilepsies. Consideration should be given to using the powerful tools of genetic screening and microarrays, along with improved neuroimaging, to identify human syndromes and significantly reduce the incidence of cryptogenic epilepsy classification.
4. Despite our inability to classify many patients with epilepsy, we can begin to prioritize the human epilepsies for model development based on the most frequent causes by age and geography (see Table 1). We know little, however, about the influence of other diseases and comorbidity on seizure control by cause and syndrome. Conditions such as arthritis, asthma, diabetes, alcohol use, obesity, and cigarette smoking have been linked to epilepsy (Kobau et al., 2004). Future studies, both clinical and in animal models, should assess if other chronic disease or comorbidity influences therapy resistance in epilepsy.
5. We need better epidemiologic studies using tools that identify causes and syndromes known to be medically refractory at epilepsy specialty centers to determine the incidence of these conditions and the probability of becoming therapy resistant. Every epilepsy surgery center is familiar with cases of refractory epilepsy associated with malformations of cortical development, including hemimegalencephaly, Sturge–Weber syndrome, tuberous sclerosis complex, and so forth, but these conditions are not clearly identified in population-based epidemiologic studies. Understanding the incidence of causes and syndromes commonly identified at specialty centers would assist in deciding which human epilepsy syndromes to develop animal models.

Finally, it should be re-emphasized that the recommendations and priority list provided are based on assessment of data in the beginning of 2005. It is hoped, as new epidemiologic information is published and new therapies developed, that the priority list would change accordingly. It would be wonderful to report, say in 2010, that progress in clinical and basic research has eliminated seizures from one of the larger epilepsy groups (e.g., stroke, trauma, or CNS infections) such that those categories were removed and we can focus on the next set of causes and syndromes to model and treat.

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