Epilepsy: the disorder

Prof Edward H. Reynolds

Introduction

Epilepsy is a common medical and social disorder or group of disorders with unique characteristics. Epilepsy is usually defined as a tendency to recurrent seizures. The word "epilepsy" is derived from Latin and Greek words for "seizure" or "to seize upon". This implies that epilepsy is an ancient disorder; indeed, in all civilizations it can be traced as far back as medical records exist. In fact, epilepsy is a disorder that can occur in all mammalian species, probably more frequently as brains have become more complex. Epilepsy is also remarkably uniformly distributed around the world. There are no racial, geographical or social class boundaries. It occurs in both sexes, at all ages, especially in childhood, adolescence and increasingly in ageing populations (*3*).

The periodic clinical features of seizures are often dramatic and alarming, and frequently elicit fear and misunderstanding. This in turn has led to profound social consequences for sufferers, which has greatly added to the burden of this disease. In ancient times, epileptic attacks were thought to be the result of invasion and possession of the body by supernatural forces, usually malign or evil influences, requiring exorcism, incantations or other religious or social approaches. Today, seizures are viewed as electromagnetic discharges in the brain in predisposed individuals, attributable in part to putative genetic factors, underlying neurological disorders, and largely unknown neurochemical mechanisms. A wide range of different seizure types and epilepsy syndromes have been identified. Patients are now treated with pharmacotherapy, occasionally with neurosurgical techniques, as well as with psychological and social support. How have we arrived at this transformation in our understanding of epilepsy? What have been the milestones along the way?

Ancient descriptions and concepts

The earliest detailed account of epilepsy is in the British Museum, London. It is part of a Babylonian text on medicine, Sakikku [All diseases], which was written over 3000 years ago, i.e. before 1000 BC. I have had the privilege of working with a Babylonian scholar, James Kinnier Wilson, on the translation of this text (Figure 1.1) (*7*). The Babylonians were keen observers of clinical phenomena and provide remarkable descriptions of many of the seizure types (miqtu) that we recognize today, including what we would call tonic clonic seizures, absences, drop attacks, simple and complex partial seizures and even focal motor (Jacksonian) or gelastic attacks. They also understood some aspects of prognosis, including death in status as well as post-ictal phenomena. The Babylonians had no concept of pathology, however, and each seizure type was associated with invasion of the body by a particular named evil spirit. Thus treatment was not medical but spiritual.

This supernatural view has dominated thinking about epilepsy until quite recently and even now remains a deeply rooted negative social influence in some parts of the world. It was, however, unsuccessfully challenged by the School of Hippocrates in 5th-century BC Greece, which first suggested that the brain was the seat of this disorder, as it was the mediator also of the intellect, behaviour and the emotions. In a famous text Hippocrates stated: "I do not believe that the Sacred Disease is any more divine than any other disease but, on the contrary, has specific characteristics and a definite cause. Nevertheless because it is completely different from other diseases it has been regarded as a divine visitation by those who, being only human, view it with ignorance and astonishment. ... The brain is the seat of this disease, as it is of other very violent diseases" (*8*). Interestingly, Hippocrates also had some notion that epilepsy could become chronic and intractable if not treated early and effectively, although it is not clear exactly what treatments he had in mind: "Moreover it can be cured no less than other diseases so long as it has not become inveterate and too powerful for the drugs which are given. When the malady becomes chronic, it becomes incurable."

Unfortunately the Hippocratic concept of a treatable brain disorder had little influence on the prevailing supernatural view, as is well described in the scholarly history of epilepsy from the Greeks to the late 19th century by Temkin (*9*).

Epilepsy as a brain disorder

It was not until the 17th and 18th centuries that the Hippocratic concept of epilepsy as a brain disorder began to take root in Europe – illustrated, for example, by an "Essay of the pathology of the brain and nervous stock: in which convulsive diseases are treated of" by Thomas Willis (*10*). During these two centuries epilepsy was one of several key areas of debate in the gradual identification and separation of "nervous disorders" from "mental disorders", which led to the beginnings of modern neurology in the 19th century. A major issue was what to include within the concept of epilepsy, i.e. all periodic "convulsive diseases" or only those with a rather restricted kind of motor convulsion with or without loss of consciousness. Thus many treatises on convulsive diseases appeared which included hysteria, tetanus, tremors, rigors and other paroxysmal movement disorders. The latter were gradually separated off from epilepsy in the 19th century, as illustrated in the distinguished Lumleian Lectures on convulsive diseases by Robert Bentley Todd in 1849 (*11*) and Jackson in 1890 (*12*).

With the development of neuropathology as a new discipline in the 19th century there also began a great debate, which is still with us to some extent, as to the distinction between pure primary idiopathic epilepsy, in which the brain is macroscopically normal, from secondary symptomatic epilepsy, associated with many different brain pathologies.

Also in the 19th century, with the development of the concept of functional localization in the brain (*13*) and the discovery, for example, of the motor cortex (*14*), the concept of "epileptiform" or "partial" seizures arose as models for the study of "generalized" seizures (*15, 16*). By meticulously studying the clinical features of unilateral epileptiform motor seizures, Jackson was able to conclude, as was later confirmed experimentally, that the motor cortex was concerned with movements rather than individual muscles (*16*). Paroxysmal episodes of an intellectual, emotional or behavioural kind, including hysteria or "hystero-epilepsy" (*17*), were more difficult to classify and localize; it was not until the discovery of human electroencephalography (EEG) in the 20th century (*18*) that the concepts of temporal lobe or frontal epilepsy were gradually clarified, and psychological concepts of hysteria evolved.

Electrical basis of epilepsy

As the concept of a brain disorder gradually took hold between the 17th and 19th centuries it was widely believed that epilepsy must have a vascular basis attributable to either acute anaemia or acute congestion of the brain. This view was challenged by Todd who was the first to develop an electrical theory of brain function and of epilepsy in his Lumleian Lectures of 1849 (*11*). Todd was an anatomist, physiologist and pathologist as well as an outstanding physician with an interest in disorders of the nervous system. He was aware of the great new discoveries in electromagnetism through his contact with his contemporary in London, Michael Faraday, the greatest electrical scientist of all time. Influenced by Faraday, Todd conceived of "nervous force" as a polar force, analogous to electricity but mediated by unknown molecular or nutritional mechanisms. He therefore preferred the term "nervous polarity". Applying Faraday's concept of "disruptive discharge" he viewed seizures as the result of electrical discharges in the brain, which he confirmed experimentally in the rabbit using Faraday's recently discovered magnetoelectric rotation machine.

It is often taught that Jackson was the first to develop an electrical theory of epilepsy with his famous statement that "Epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of grey matter" (*16*). It is difficult to understand why, in his Lumleian Lectures of 1890 (*12*), Jackson did not acknowledge Todd's lectures on the same subject 41 years earlier (*11*). However, it is apparent that the Jackson theory was not an electrical one. As Gowers makes clear (*17*), Jackson's concept of discharge was a vague one of a discharge of energy, as for example in a bent pin or spring. Jackson supposed the "liberation of energy during rapid decomposition (katabolism) of some matter in, or part of, those cells".

As a philosopher physician it is doubtful if Jackson had any significant grasp of electromagnetism in an era before the discovery of the human EEG. In fact, it was only about this time that Caton first discovered the EEG in rabbits, cats and monkeys (*18*). But it was not until 52 years later, in 1929, that Berger reported the discovery of the human EEG (*19*). This led rapidly to the confirmation that seizures were the result of electrical discharges in the brain, for example by Lennox at the 1935 Neurological Congress in London where he also finally laid to rest the still widely believed vascular theories of epilepsy (*20*).

In 1952 Hodgkin & Huxley (*21*) made the Nobel Prize-winning discoveries of the ionic basis of Todd's nervous polarity/force. Interestingly, it was Faraday's mentor at the Royal Institution in London, Sir Humphry Davy, who discovered sodium, potassium, chlorine, calcium and magnesium among other elements (*22*).

The modern era

It is premature to assess recent developments in historical terms, but in the second half of the 20th century remarkable progress was made in diagnostic facilities and possibilities through structural and functional neuroimaging, including CAT and MRI, as well as in video-telemetry and magnetoencephalography.

The modern era of pharmacotherapy probably began with bromides (1856), phenobarbital (1912) – still the most widely used drug in the world – and phenytoin (1938). In recent decades there has been a proliferation of new drugs in the developed world, for example nine in the United Kingdom in the last 15 years. To what extent newer drugs are more or less effective, selective or toxic than older drugs is still a matter of debate and evaluation, as is the role of polytherapy in the event of failure of carefully monitored monotherapy. The mechanisms of action of the drugs are largely unknown and it is uncertain whether the drugs merely suppress seizures or influence longer-term prognosis through "arresting" epilepsy (*17*) or other antiepileptic mechanisms.

The functional localization detected by studying focal or partial seizures played a key role in developing neurosurgery in the late 19th century, as did the development of the EEG in the first half of the 20th century. The modern interest in neurosurgery for epilepsy itself, especially intractable seizures associated with focal cortical lesions, including temporal lobe epilepsy, was pioneered by Horsley, Penfield and Falconer, among others (*23*).

The modern era is also marked by an expansion of interest in basic mechanisms underlying seizures and epilepsies, stimulated by developments in genetics, molecular biology, neurophysiology, functional imaging and numerous neurochemical techniques for exploring the concepts of excitation, inhibition, modulation, neurotransmission and synchronization. Every advance seems to add to the enor-

mous complexity of the nervous system and the probability that multiple elusive genetic–molecular–metabolic mechanisms contribute to the wide range of epilepsies.

Public health and social developments

Despite scientific advances in the 19th century, epilepsy remained a profound social problem compounded by deeply rooted historical concepts of a supernatural or sacred disorder. Widespread ignorance, fear, misunderstanding and stigma contributed to severe legal and social penalties.

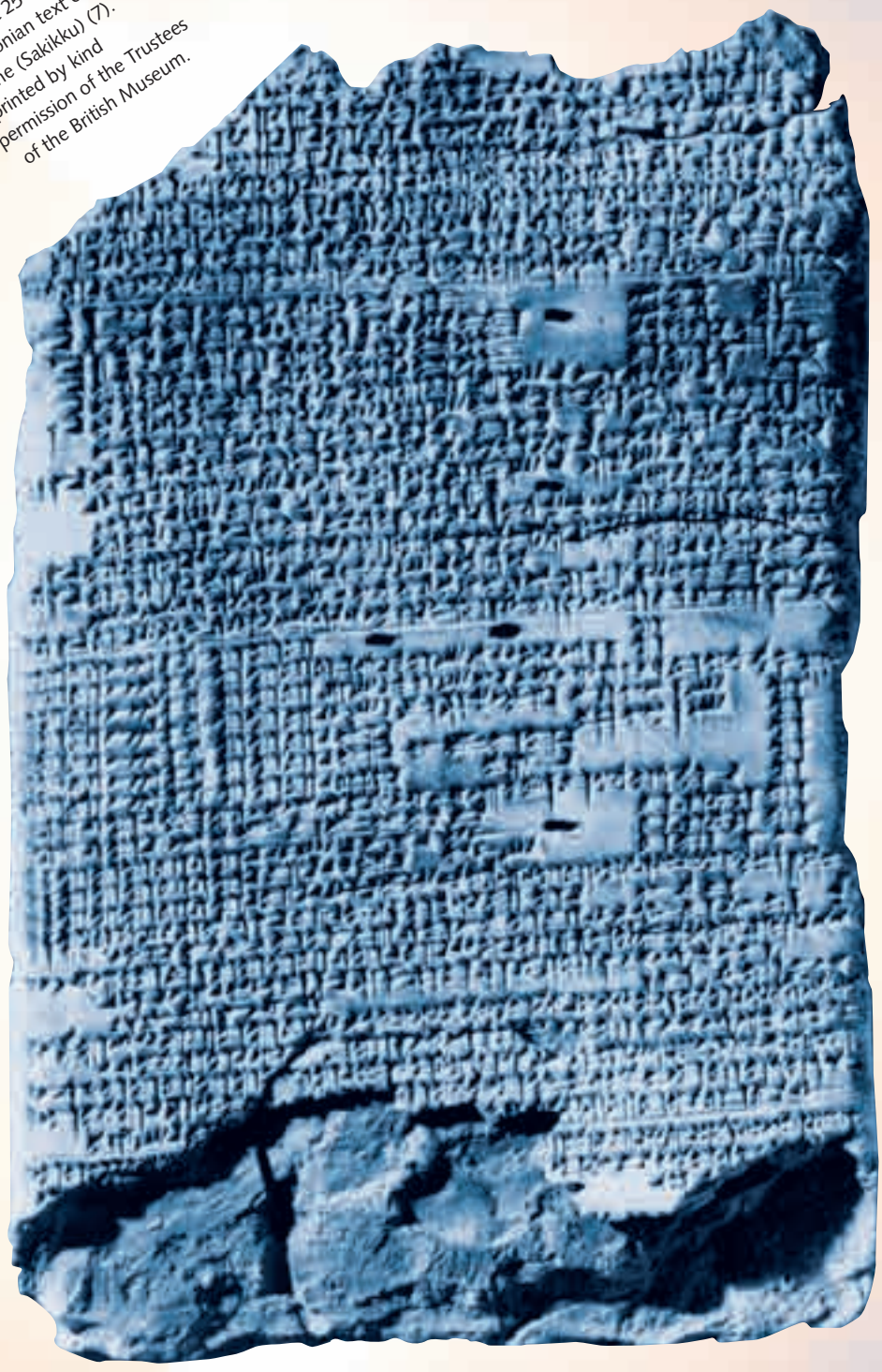
In Budapest in 1909 a group of European physicians founded the International League Against Epilepsy (ILAE) (*24*). From the beginning, ILAE was concerned with both the scientific and social aspects of epilepsy and with education, through international collaboration, congresses and its journal *Epilepsia*. Unfortunately the outbreak of the First World War led to the demise of ILAE for 20 years from 1915 to 1935, when it was reborn and reconstituted at the Second International Neurological Congress in London (*20, 24*). Apart from a brief interruption during the Second World War, the League has grown steadily into a truly international organization.

By 1966 it was felt that the social dimension of epilepsy required an organization of its own, involving patients and public, and the International Bureau for Epilepsy (IBE) was founded. By the end of the 20th century ILAE had over 90 Chapters and IBE over 80 full members and 30 associate members, covering every continent. Regional structures for both organizations are now evolving. In the last 25 years ILAE has played a key role in defining and classifying seizures and epilepsy syndromes through its International Commission on Terminology and Classification (*25, 26*).

After some initial tensions in the late 1970s and early 1980s, including a merger then separation, ILAE and IBE have worked very well together with interlocking executive committees. They are both nongovernmental organizations affiliated to WHO. During my presidency of ILAE (1993–1997) I proposed a major new initiative to address the public health aspects of epilepsy, including social aspects, involving a partnership between the League (professional), the Bureau (patients/public) and WHO (political). The ILAE/IBE/WHO Global Campaign Against Epilepsy was launched from Geneva and Dublin in the summer of 1997. Its objectives include raising political and public awareness of epilepsy, reducing stigma and misunderstanding, improving education, and especially the delivery of services, treatment and care to millions of people with epilepsy, mainly in developing countries, where studies have shown that between 60% and 90% of patients have no access to modern treatment, the so-called "treatment gap", despite the availability of relatively cheap medication (*27*).

Following the first phase of political and public awareness raising (1997–2001), the then Director-General of WHO, Dr Gro Harlem Brundtland, launched the second phase of the Campaign from Geneva and raised its status to the highest level within WHO, the first neurological disorder to be accorded this priority (*3*). Demonstration Projects are now under way in several developing countries including in Africa and China, and a third phase of the Campaign is being planned.

1.1 **The oldest detailed account of epilepsy**
Source: Tablet 25 or 26 in a Babylonian text on medicine (Sakikku) (7).
Reprinted by kind permission of the Trustees of the British Museum.



Introduction

- Knowledge about the number of people with epilepsy is essential for the identification of needs and the planning of appropriate services.

Salient findings

- A total of about 43 704 000 people with epilepsy are reported from 108 countries covering 85.4% of the world population.
- The mean number of people with epilepsy per 1000 population is 8.93 (SD 8.14, median 7.59) from 105 responding countries.
- The mean number of people with epilepsy per 1000 population varies across region. While it is 12.59 and 11.29 in the Americas and Africa, respectively, it is 9.97 in South-East Asia, 9.4 in the Eastern Mediterranean, 8.23 in Europe, and 3.66 in the Western Pacific.
- The mean number of people with epilepsy per 1000 population ranges from 7.99 in the high-income countries to 9.50 in the low-income countries.

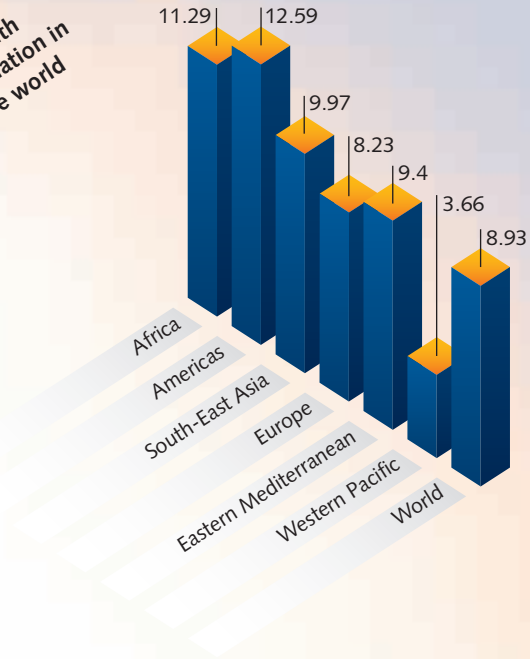
Limitations

- The data regarding the number of people with epilepsy were not collected using stringent research methods as for epidemiological studies; such methods are costly and are not easy to carry out.
- The sources of information vary across responding countries, limiting the interpretation of the data set. For example, some respondents provided figures based on generic prevalence or findings from one particular area of the country or on the number of people eligible for antiepileptic drugs. One of the reasons for low prevalence reported from the Western Pacific could be the lower prevalence rates reported from Pacific Islands; it also puts a bias on the global outcome, as the Western Pacific comprises 27% of the population in all WHO regions.
- Information regarding the number of people with active epilepsy was not obtained.
- Information regarding the number of people with epilepsy among special groups, e.g. children, was not obtained.

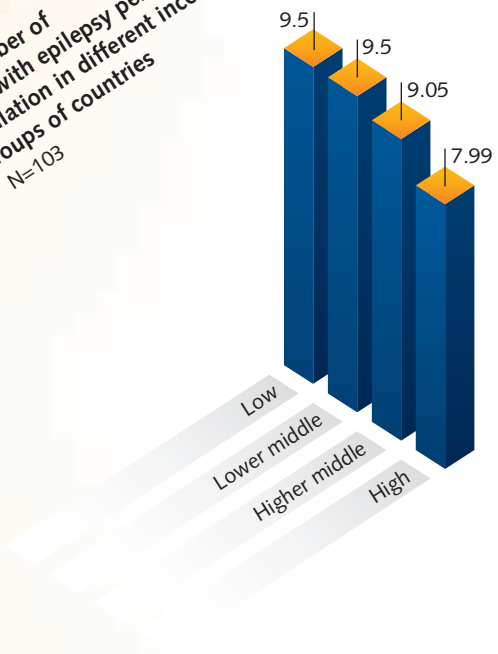
Conclusions

- The number of people with epilepsy is high in most regions of the world, thus constituting epilepsy as a major public health concern.
- There is a need to carry out multinational epidemiological studies using standardized definitions and case ascertainment methods.
- Studies of the burden of epilepsy should raise the awareness of authorities about the impact of epilepsy on the country.

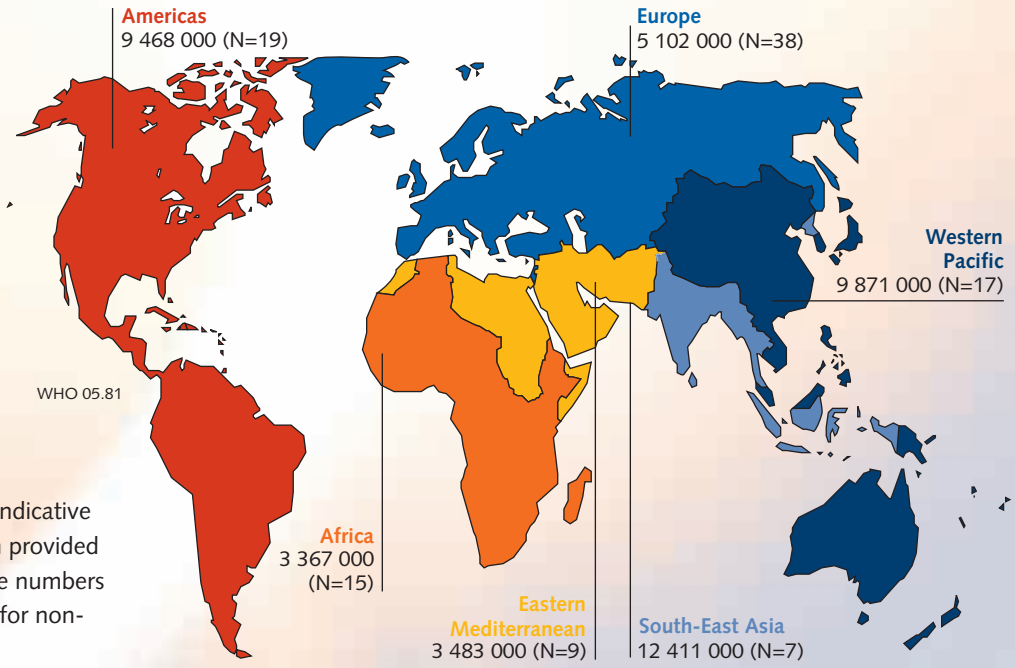
2.1 Mean number of people with epilepsy per 1000 population in WHO regions and the world
N=105



2.2 Mean number of people with epilepsy per 1000 population in different income groups of countries
N=103



2.3 Number of people with epilepsy in WHO regions
N=105*



* These numbers are only indicative based on the information provided by Atlas respondents. The numbers have not been corrected for non-responding countries.

Prof Nadir E. Bharucha

What is neuroepidemiology?

Neuroepidemiology is the study of the distribution and determinants of neurological diseases in human populations (*28*). While the clinician is concerned with disease in the individual patient, the epidemiologist is concerned with the occurrence of disease within a community. Epidemiological information benefits health policy-makers, public health officials, medical practitioners and patients, the pharmaceutical industry and other epidemiologists (*29*).

Diagnosis

Accuracy of medical diagnosis is fundamental. Diagnosis is clinical and should be confirmed by a professional with expertise in epilepsy. EEG may help diagnosis, but is certainly needed to classify seizure type and give a meaningful prognosis. Most epidemiological studies to date have lacked investigatory facilities in the field, especially in developing countries.

Studying epilepsy is beset with difficulties. Accurate diagnosis and case ascertainment remain major problems, because epilepsy is only a symptom of many disparate causative entities. Confident diagnosis or exclusion in all cases of seizures is difficult because seizure types vary, unusual behaviour and blank spells may not be recognized as seizures, there may be no accompanying neurological signs and if an eyewitness account is lacking, the diagnosis may not be made at all. Other conditions are readily confused with epileptic seizures. The most frequently occurring non-epileptic events requiring distinction and exclusion are pseudoseizures and syncope (*30*).

Definition of seizures and epilepsies

To ensure comparability of epidemiological studies, ILAE's guidelines for epidemiological studies on epilepsy (*31*) should be followed. The term epilepsy should be used only for recurrent, unprovoked seizures.

Seizures are categorized as partial or generalized. A partial seizure is presumed to start in a part of the brain and may or may not spread. The cause must always be sought, and epilepsies may be classified according to aetiology and type of seizure, as follows:

- Aetiology: remote symptomatic of known aetiology; cryptogenic probably symptomatic but unknown aetiology; idiopathic presumed genetic.
- Type of seizure: if partial, the epilepsy is localization-related, and if generalized, the epilepsy is either generalized or localization-related (generalized seizures can occur in both generalized and localization-related epilepsies).

Acute symptomatic seizures are those occurring in close temporal association with an acute systemic, metabolic, or toxic insult or in association with an acute central nervous system insult (*34*). Acute symptomatic seizures, though sometimes life-threatening and very common, are not considered epilepsy. They do, however increase the risk of future epilepsy. Febrile seizures are a type of acute symptomatic seizure and the commonest seizure disorder in children.

Progressive symptomatic seizures are unprovoked seizures owing to progressive central nervous system disorders (*34*). The prognosis is worse. The last group is the undetermined and unclassifiable epilepsies. Epidemiological studies often wrongly omit this group altogether.

Failure to separate active from inactive epilepsy causes differences in rates. A person with active epilepsy has had at least one epileptic seizure within the previous five years, regardless of antiepileptic drug (AED) treatment. In general, patients with inactive epilepsy do not need continuing treatment.

Incidence and prevalence

The incidence (the number of new cases per year) of epilepsy is 24–53 per 100 000 population in developed countries (*32*). There are few incidence studies in developing countries, none of which is prospective: they show rates from 49.3 to 190 per 100 000 population (*33*). Higher incidence rates in developing countries, thought to be attributable to parasitosis particularly neurocysticercosis, HIV, trauma, perinatal morbidity and consanguinity, are difficult to interpret because of methodological issues, particularly the lack of age adjustment, which is important because epilepsy has a bimodal peak with age. Incidence rates worldwide are greater in men than women. In developed countries, incidence among the elderly is rising and among children it is falling. This is relevant to developing countries as longevity rises and risk of cerebrovascular disease increases. Conversely, better obstetric care and infection control can diminish incidence in children.

The prevalence (the total number of cases at a particular point in time) of active epilepsy in a large number of studies has been shown to be fairly uniform at 4–10 per 1000 population (*34*). Higher prevalences in sub-Saharan Africa and Central and South America have been reported, possibly due to methodological differences, consanguinity or environmental factors and particularly so in rural areas (*35*). It is difficult to tease out racial and socioeconomic factors. Prevalence data are primarily used by health planners and for generating aetiological hypotheses.

Aetiology

Population-based prevalence and incidence surveys present percentage frequencies of presumed aetiologies of epilepsy. In most, no cause is found. Precise diagnosis remains difficult – even in the study in Rochester, MN, two thirds of cases were classified as idiopathic or cryptogenic (*36*). Aetiology of epilepsy is discussed in Section 5.

Seizure type and epilepsy syndrome

Generalized seizures are common in field studies, especially in developing countries, often because partial seizures are missed. In developed countries, over half the incidence cases are partial. Partial and generalized seizures vary with age, partial seizures being more common in the very young and in elderly people. Generalized tonic–clonic seizures occur uniformly throughout the life-course; absence seizures occur maximally between 5 and 10 years of age; and myoclonic seizures in the under-five-year-olds and around 15 years. Idiopathic epilepsy is usually seen in the young, and remote symptomatic epilepsy at the extremes. In developing countries, however, symptomatic epilepsy caused by infections should be considered at any age.

Diagnosis by syndrome is important for prognosis and treatment. For example, a cryptogenic/symptomatic localization syndrome, the commonest paediatric syndrome (*37*), is likely to be caused by a brain lesion which may be amenable to surgery if seizures are medically uncontrollable. Childhood absence epilepsy, the commonest idiopathic generalized epilepsy, whose prognosis is poor if untreated and excellent if treated, may be missed altogether in population screening.

Genetic studies

Genetic studies have identified rare epilepsy syndromes attributable to single gene mutations and simple Mendelian inheritance (*38*). Most idiopathic epilepsy syndromes have complex inheritance, probably because of interacting genetic and environmental factors. The category of cryptogenic epilepsies is diminishing as results of genetic and neuroimaging studies become available. There is scope for developing and developed countries to collaborate in properly designed incidence and genetic studies of different epilepsy syndromes. Genetic epidemiological studies will give information on individual prognosis and risk to other family members. When pathophysiological mechanisms are clearer, tailoring the drug to the gene will also become possible.

Prognosis

One in three people with a single unprovoked seizure will have a second seizure over the next five years (*39*). Treatment should be considered only to prevent recurrence, not to prevent epilepsy. Untreated, after a second seizure, 75% will have another seizure within the next one or two years (*40*). Whether "seizures beget seizures" is unclear. Numerous predictors for recurrence, control, remission and intractability have been developed at the onset and during treatment. Most important are diagnosis by syndrome and response to the first appropriately prescribed and taken AED. Persistence of seizures after two AEDs requires pre-surgical evaluation, as chances of remission are less than 5% with a third AED and 50–80% following successful surgery (*41*).

Mortality

In developed countries, mortality measured by the standardized mortality ratio (SMR) is 2–3 times that of the general population. Deaths may be attributable either to the cause of epilepsy, when death will occur soon after onset, or to the epilepsy itself, as in chronic epilepsy, or it may be unrelated. Comparison between studies is difficult because of different study designs and different populations studied. Symptomatic epilepsy has a higher mortality ratio than idiopathic epilepsy. The important epilepsy-related deaths are sudden unexpected, unexplained death in epilepsy (SUDEP) (2–18% of all deaths in epilepsy), death in status epilepticus (12.5%) and suicide (0–2%) (*42*). In status epilepticus, the mortality depends on the cause and is higher in elderly symptomatic patients. Risk of suicide is greatest when epilepsy starts in adolescents with a history of associated psychiatric disturbance. Both developing and developed countries need prospective incidence cohort studies with long-term follow-up.

Morbidity

Some psychiatric and physical conditions are more common in people with epilepsy (*43*). Cerebrovascular disease and brain tumours may be causally related to epilepsy. Head injury and psychiatric conditions may be caused by or result from epilepsy. AED teratogenic morbidity needs further study. Alert health providers must be aware of all these issues, in order to improve the quality of life of special groups such as women and children.

Interventional epidemiological studies

Up to 94% of patients with epilepsy in developing countries do not receive appropriate treatment and 80% of available AEDs are utilized by 20% of the world's sufferers. Phenobarbital is an AED that is effective, tolerable, cheap and easy to use, all essential considerations in developing countries (*44*). Surgery for refractory epilepsy could be cost beneficial. Cost-benefit and risk-benefit ratios of new AEDs should be assessed on a large scale in developed countries; such information would be of value for developing countries after appropriately designed clinical trials.

Conclusion

In developing countries with large rural populations, a few urban and semi-urban neurologists, substantial burden of disease and scantily allocated health-care resources, epidemiology provides information necessary for all involved in promoting health to optimize care in epilepsy. Neuroepidemiological studies provide more than indices of burden: they show the way forward.

Acknowledgement

Dr Roberta H. Raven for her help in preparing this manuscript.

Introduction

- The respondents were asked to provide the five most frequently encountered causes of epilepsy. Ignoring the order of the individual responses, the proportion of countries that mentioned each aetiology was calculated globally and for each of the regions.

Salient findings

- Globally, trauma was the most frequently reported aetiology of epilepsy by 92% of the responding countries.
- Central nervous system infections (including abscesses, encephalitis with all aetiologies, and bacterial meningitis but excluding parasitic infestations), antenatal and perinatal risk factors and cerebrovascular disorders were among the most frequently reported aetiology of epilepsy by 60.4%, 57.7% and 55% of the responding countries, respectively.
- Idiopathic epilepsy (including the genetic causes) was mentioned as one of the five most common aetiologies of epilepsy by 54.4% of the responding countries.
- Trauma, central nervous system infections and idiopathic epilepsy were mentioned among the five most frequently reported aetiologies of epilepsy by the responding countries across different income groups of countries.
- Among the five most common aetiologies, tumours were mentioned by 40.9% of the responding countries, congenital defects (27.5%), parasitic infestations (22.1%), exogenous chemicals including alcohol and drugs (13.4%), cryptogenic (9.4%), degenerative disorders (8.7%), febrile convulsions (7.4%), hippocampal sclerosis (7.4%) and cerebral palsy (2.7%).
- Cerebrovascular disorders were also among the five most frequently reported aetiologies of epilepsy by the responding countries in all income categories, except low-income countries where parasitic infestations were an important aetiology of epilepsy as mentioned by 44.2% of countries.
- Perinatal causes were reported among the five most important aetiologies of epilepsy by all income categories except high-income countries.

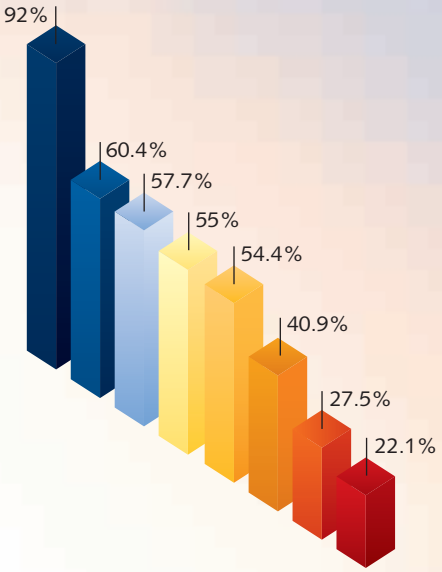
Limitations

- Aetiologies of epilepsy as reported by respondents are a rough estimate; data were not collected and calculated using stringent epidemiological research methods. The information is based on the experience and impression of a key person in a country working in the area of epilepsy and not necessarily on actual data from responding countries.
- In most cases a specific cause can only be determined using basic investigations including neuroradiological and electrophysiological services. There could be methodological differences among various countries because many low-income countries have poor accessibility to even basic investigations.
- In almost 30-60% of cases of epilepsy, the aetiology cannot be identified even with the most sophisticated methods. However, the cause being unknown was mentioned by only 8.4% of countries. One possible reason could be the way in which the question was framed. Another could be the use of term "idiopathic", which according to some refers to a genetic syndrome with strictly defined clinical and EEG findings while others may use it for any case in which aetiology has not been established.
- Some of the entities mentioned, such as cerebral palsy, are manifestations of cerebral damage where epilepsy coexists rather than being the cause of epilepsy.

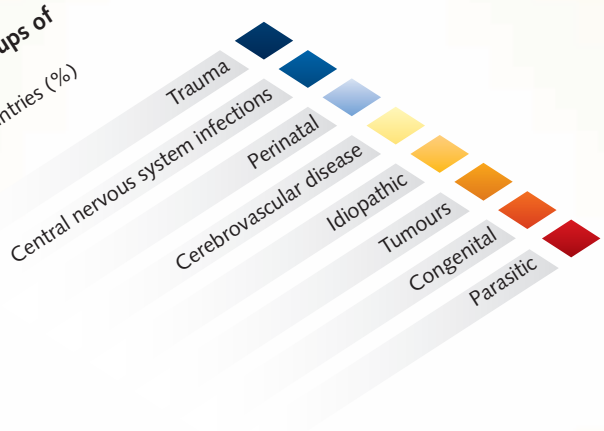
Conclusions

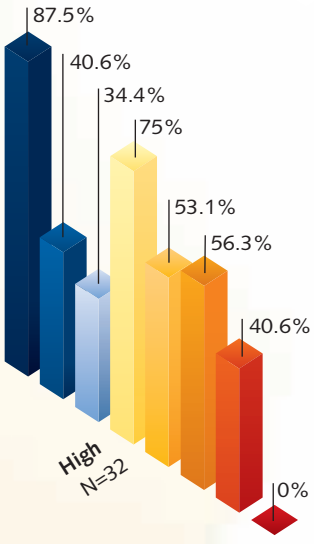
- Identifying the correct aetiology is essential in order to establish appropriate treatment and offer a prognosis to the patient and family.
- The information regarding the causes of epilepsy also has implications for making decisions about the development of locally relevant strategies for prevention and management, research goals, and education of primary healthcare workers and community physicians.
- The inequity in availability of diagnostic resources (including human resources) required for assessing the aetiology of epilepsy needs to be dealt with.
- The top four most frequently reported aetiologies of epilepsy (trauma, central nervous system infections, cerebrovascular disorders and perinatal risk factors) are preventable. Concerted multidisciplinary efforts focusing on the risk factors (e.g. enforcement of strict traffic regulations to prevent trauma) or providing specific protection (e.g. immunization against communicable diseases) for these preventable causes can help to decrease substantially the burden attributable to epilepsy.

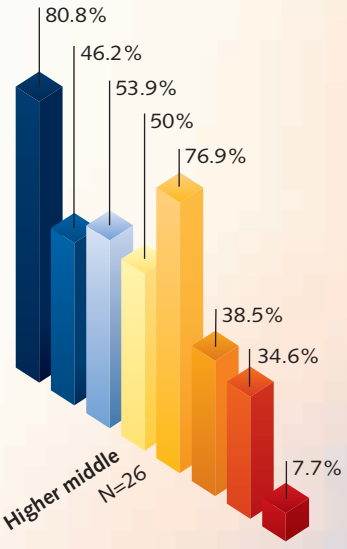
4.1 **Most frequently reported aetiology of epilepsy**
Reported by countries (%)
N=149

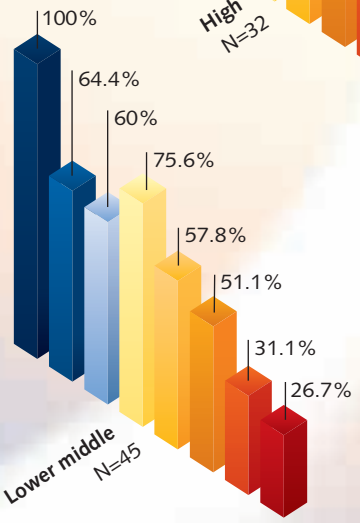


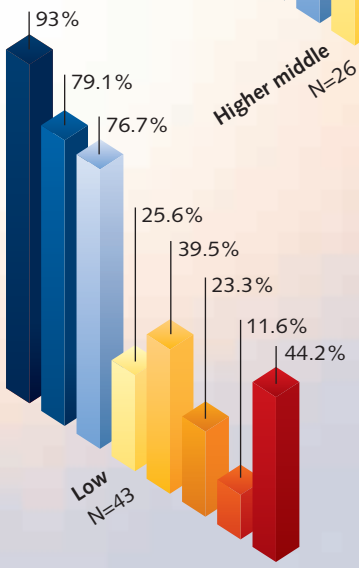
4.2 **Most frequently reported aetiology of epilepsy in different income groups of countries**
Reported by countries (%)











Prof Josemir W. Sander

Epilepsy is the propensity for an individual to have recurrent unprovoked epileptic seizures. These seizures are produced by abnormal discharges of neurons and may be a manifestation of many different conditions, which modify neuronal function or cause pathological changes in the brain. Many environmental, genetic, pathological and physiological factors may be involved in the development of seizures and epilepsy. The presence of a family history of epilepsy is known to enhance most risk factors for epilepsy (*45*). The susceptibility to epilepsy may, therefore, be partly genetically determined and this may vary according to the stage of brain maturation.

Epilepsy is associated with a variety of static or progressive pathological changes, either congenital or acquired (*46*). In addition, a number of inherited conditions may express themselves solely through epileptic seizures. It may therefore be more appropriate to describe epilepsy as a symptom complex rather than as a medical condition in its own right.

Aetiologically, the epilepsies are classified into four groups: idiopathic, symptomatic, cryptogenic and progressive (*26, 31*). The idiopathic epilepsies are thought to be genetically determined and are usually associated with particular clinical characteristic and specific electroencephalography (EEG) findings (*26*). Symptomatic epilepsies are acquired conditions and are usually associated with a structural abnormality of the brain. Epilepsy is classified as cryptogenic when no clear abnormality or putative risk factor is identified for what is presumed to be a symptomatic or acquired epileptic condition (*26, 31*). The term progressive epilepsy is used when epilepsy is associated with an evolving neurological condition (*31*).

The probable aetiology or risk factor for epilepsy depends on the age of the patient and the type of seizure (*47–52*). The most common acquired causes in young infants are perinatal hypoxia and trauma, metabolic disturbances, congenital malformations of the brain, and infection. In young children and adolescents, idiopathic epilepsies account for the majority of cases, although trauma and infection play a role. Febrile seizures, which are usually short convulsive attacks occurring during the early phase of a febrile disease, are common in children under the age of five years and need to be distinguished from seizures triggered by central nervous system infections causing fever, such as meningitis and encephalitis. Unless febrile seizures are prolonged, recurrent or occurring on a background of neurological handicap, the prognosis is excellent, and it is unlikely that the child will develop chronic epilepsy.

The causes of adult onset epilepsy are very varied (*47, 52*). Both idiopathic epilepsy and epilepsy attributable to birth trauma may begin in early adulthood. Other important causes of seizures in adulthood are head injury, alcohol abuse, brain tumours and cerebrovascular disease. In developing countries, parasitic disorders such as cysticercosis and malaria may be important causal agents for epilepsy.

Idiopathic and genetically determined epilepsies

The idiopathic (or primary) generalized epilepsies are the most common of the genetically determined epilepsies. The precise mode of inheritance for most of these conditions is currently unknown. Other inherited conditions in which seizures are the sole clinical manifestation include the idiopathic partial epilepsies (e.g. benign rolandic epilepsy). In addition to these conditions with seizures as the main clinical expression, there are many rare inherited disorders that present as neurological or systemic illnesses including seizures. The most common of these disorders are tuberous sclerosis and neurofibromatosis. Trisomy 21 (Down's syndrome) may be accompanied by seizures, particularly in later life.

Symptomatic epilepsies

Common causes of symptomatic epilepsies include head trauma, birth trauma, cerebrovascular disorders, cerebral anoxia, brain infections, cortical malformations and brain tumours. In resource-poor countries, parasitic infestations such as malaria, neurocysticercosis and paragonimiasis are important risk factors. Most epilepsies starting in adult life are symptomatic and investigations to detect any underlying aetiology are mandatory.

Head trauma is an important cause of symptomatic epilepsy and may account for up to 10% of all cases of epilepsy. The likelihood of developing epilepsy after head trauma depends on the severity of the injury and the presence of complicating factors, including prolonged loss of consciousness, post-traumatic amnesia, intracranial bleeding, missile penetration, or depressed skull fracture. It is unusual for epilepsy to develop unless one of these factors is present. Seizures occurring immediately after the injury do not usually presage the development of chronic epilepsy.

Thromboembolic events and cerebral haemorrhage are important causes of symptomatic epilepsy starting in later life, where they are responsible for up to 50% cases. It is estimated that approximately 15% of people with strokes will eventually develop epileptic seizures. Vascular malformations and cerebral aneurysms may also cause symptomatic epilepsy, whether or not haemorrhage has occurred.

Any intracranial infection, whether viral, bacterial or fungal, can cause seizures. The severity of the epileptic disorder usually depends on the nature of the infection and the extent of the damage. Meningitis, the most common intracranial infection, is common in young children but also affects older age groups. Epilepsy is an unusual complica-

tion of acute bacterial meningitis, occurring mainly in people given inadequate or late treatment.

Intracranial tuberculosis can cause cortical and meningeal tuberculomas that may present with seizures, sometimes developing years after the primary infection. Fungal infections of the central nervous system are a rare cause of epilepsy; the most common, cryptococcosis and blastomycosis, are often associated with immune deficiencies. Survivors of viral encephalitis, especially resulting from herpes, may develop epilepsy that is intractable to medical treatment. Intrauterine and perinatal infections caused by toxoplasmosis, rubella and syphilis may cause extensive cortical damage, and severe partial epilepsy may result if the child survives.

Brain abscesses are rare and often fatal. Epilepsy develops in about three quarters of survivors and is usually very severe and intractable.

Epilepsy may occur in the course of a number of parasitic disorders, including neurocysticercosis, falciparum malaria, schistosomiasis, and paragonimiasis. Such infections may be responsible for the higher incidence of epilepsy in some parts of the tropical world; those most frequently associated with epilepsy are neurocysticercosis and falciparum malaria. Neurocysticercosis is the most common acquired cause of epilepsy in resource-poor countries. This occurs when a human becomes the intermediate host for *Taenia solium* through the ingestion of eggs contained in human faeces. Cysts containing an embryo may emerge in any area of the cerebrum, ventricles or subarachnoid space of the infested patient, leading to a variety of neurological signs including epilepsy. Cerebral malaria, which is the most important complication of falciparum malaria, may first present as status epilepticus. It carries a high mortality and morbidity; survivors often have neurological disabilities and partial seizures that respond poorly to treatment.

An allergic reaction to vaccine components very occasionally leads to an acute encephalopathy that may result in chronic epilepsy. It is extremely rare, however, and is becoming even more uncommon as more purified and less antigenic vaccines are used. As the incidence of epilepsy is at its highest in early childhood, the age at which most vaccinations are carried out, some children will develop seizures in temporal association with vaccination by coincidence. Other children experience a febrile reaction to some vaccinations and may have a febrile seizure as a result, without long-term sequelae.

Errors in neuronal migration during embryogenesis may result in cortical malformations. These malformations were until recently considered to be rare; however, with the development of high-resolution neuroimaging they are being recognized with increasing frequency. The aetiology for these cortical malformations is unknown at this stage, but potential causes may include intrauterine infection, maternal illness or exposure to toxins at crucial phases of brain formation.

Hippocampal sclerosis is the most common lesion identified in pathological specimens of patients with temporal lobe epilepsy who have undergone temporal lobectomy. It consists of atrophic changes with a variable degree of cell loss and gliosis involving part or the whole of the hippocampus. It is usually unilateral and can be identified by brain imaging. Temporal lobe epilepsy with hippocampal sclerosis is strongly associated with a history of prolonged febrile convulsions in childhood. Resection of the atrophic area, when possible, is associated with a good surgical outcome, with complete seizure control in over 70% of cases.

Cryptogenic epilepsies

Currently up to 40% of patients have no identifiable cause for their seizures. This proportion is rapidly decreasing as advances in neuroimaging, particularly magnetic resonance imaging (MRI), are made. The term cryptogenic epilepsy is sometimes used interchangeably with idiopathic epilepsy. This should be avoided, and the term idiopathic epilepsy reserved for those inherited conditions in which seizures occur as the only manifestation of the disorder.

Progressive epilepsies

The progressive myoclonic epilepsies are a group of disorders characterized by the development of myoclonic and other seizures in association with other clinical inherited degenerative brain disorders and inborn errors of metabolism. These include adrenoleukodystrophy, Alpers' disease and Tay-Sachs disease. Phenylketonuria, porphyria and neuronal ceroid-lipofuscinosis may also cause seizures.

Epilepsy may sometimes complicate degenerative brain conditions such as Alzheimer's disease, Huntington's chorea, striatonigral degeneration and Creutzfeld-Jakob disease; as many as 20% of patients with Alzheimer's disease may develop seizures.

Involvement of the central nervous system eventually occurs in the majority of people developing AIDS. It may take the form of opportunistic infection or neoplastic lesions. An encephalopathy that seems to be caused by HIV itself has also been recognized.

Intracranial tumours, either primary or metastatic, may result in epilepsy. Tumours are responsible for about a fifth of seizures starting between the ages of 30 and 50 years, and about 10% of seizures starting after the age of 50 years.