1

Introduction and Epidemiology

Joseph I. Sirven[1] and Gregory D. Cascino[2]

[1] *Department of Neurology, Mayo Clinic, Jacksonville, FL, USA*
[2] *Department of Neurology, Division of Epilepsy, Mayo Clinic, Rochester, MN, USA*

Incidence and Prevalence of Epilepsy

Epilepsy is one of the most common and chronic neurologic disorders that may affect individuals in any age group [1, 2]. The evaluation and management of people with seizures is a frequent occurrence for all global healthcare providers. There were approximately 50 million people with epilepsy worldwide in 2016 [1]. The WHO's 2010 Global Burden of Disease study ranks epilepsy as the second most burdensome neurologic disorder in terms of disability-adjusted life years [2]. Epilepsy may adversely affect the individual's quality of life because of the presence of physical trauma related to seizures, long duration of a seizure disorder, inability to work or attend school, treatment-emergent adverse effects, comorbid conditions, psychosocial debilitation, development of drug-resistant seizures, and premature mortality [1–5]. The goals of treatment include rendering the patient seizure-free, minimizing treatment-related side effects and allowing the patient to become a participating and productive member of society. The following remarks will be restricted to a discussion on the epidemiology of epilepsy.

Active epilepsy, i.e. doctor-diagnosed epilepsy, taking antiseizure medication, or having at least one seizure per year, affects approximately 3 million Americans, with a lifetime risk estimated at 3% [5]. A Morbidity and Mortality Weekly Report (April 20, 2018) indicated that the number of people with epilepsy in the U.S. increased from 2.3 million in 2010 to 3 million in 2015 [5]. The annual prevalence of active epilepsy was approximately 1.1% [5]. Over 90% of patients in the U.S. were receiving an antiseizure medication [5]. Only 44% of patients were seizure-free and had a seizure disorder in remission [5]. Individuals with drug-resistant epilepsy have poorer employment status, significantly limited activities, impaired quality of life, and increased mortality rates compared to the general population [1–8]. Studies indicate that continued trials of antiseizure drugs are unlikely to produce seizure remission in this group of participants [1–8]. Even people with well-controlled seizures or whose seizures completely remit have relatively poor educational and social outcomes years after their seizures have resolved.

Epilepsy, Second Edition. Edited by Gregory D. Cascino, Joseph I. Sirven and William O. Tatum.

The annual economic cost of epilepsy has been estimated at ~$12.5 billion, of which $1.7 billion (14%) are direct medical costs and $10.8 billion (86%) are related to loss of employment and earning potential [1–3, 5]. Approximately 25% of people with epilepsy are unemployed because of their medical condition [9]. The tremendous burden of epilepsy on society is fundamentally related to our limited understanding of the biological processes underlying seizures and *epileptogenesis*, despite intense research using a wide range of approaches. The failure to understand the fundamental pathophysiology of epilepsy is a critical barrier to progress because existing treatments address the symptoms rather than the causes of epilepsy and, consequently, have serious shortcomings. No preventive strategies, i.e. *anti-epileptogenic drugs*, are currently available.

A ***seizure*** is characterized by an abnormal discharge of synchronized neurons in a discrete or generalized portion of the brain. ***Acute provoked seizures*** [6] are those that occur in the context of an acute brain insult or systemic disorder such as head trauma, stroke, or metabolic condition. Conversely, a seizure that occurs in the absence of an acute provoked event is considered an ***unprovoked*** [6] event. ***Epilepsy*** or a ***seizure disorder*** is the occurrence of at least two unprovoked seizures separated by a minimum of 24 hours. Individuals with a single seizure, who are at an increased risk of recurrent seizures, e.g. seizure related to primary brain tumor, may be evaluated and treated as if they have epilepsy. Typically, the condition of having recurrent, repeated events underlies the definition of epilepsy. Because the diagnosis of epilepsy is a clinical diagnosis and there is not a fixed test or biomarker that conclusively designates an individual as having epilepsy, studies that address the epidemiology of seizures or epilepsy can be fraught with error. This is due to the fact that multiple lines of converging data, that is, history and diagnostic tests are the basis to make a diagnosis and there is not one single point that is utilized to confirm the disorder. Therefore, it is essential to know the population on which an epidemiologic study is conducted in order to extrapolate accurate incidence and prevalence data.

Table 1.1 [7] provides results displaying the incidence and prevalence of epilepsy as reported in several population-based studies throughout the world. Clearly, the incidence rates for epilepsy are estimated to be typically between 30 and 50 per 100 000 population though some studies have reported higher approximations between 60 and 80 per 100 000 per year [7].

A systematic review and meta-analysis of worldwide epilepsy published in 2017 examined 222 studies (197 on prevalence, 48 on incidence) that included 655 000 people with epilepsy [4]. Studies were included from 1985 to 2013. The point prevalence of active epilepsy was 6.38 per 1000 persons, and the lifetime prevalence was 7.60 per 1000 persons [4]. The pooled annual cumulative incidence of epilepsy was 67.77 per 100 000 persons and the incidence rate was 61.44 per 100 000 person-years [4]. The prevalence of epilepsy did not differ by age group or sex. The active annual period prevalence, lifetime prevalence, and incidence rate of epilepsy were higher in low- to middle-income countries [4].

To provide context comparing epilepsy incidence rates versus other neurologic disorders, the American Academy of Neurology systematically analyzed the incidence and prevalence of common neurologic maladies [8]. Their results showed that epilepsy ranks among the top disorders in children, adults, and older adults. In four Class I studies [9, 21–23] and six Class II studies [13, 24–27] of incidence, the median estimate was 46 per 100 000 per year, (range 32–71). The incidence of epilepsy is related to age. Analyzing studies restricted to children

Table 1.1 Incidence and prevalence of epilepsy as reported in various population-based studies around the world.

Author	Year	Country	Age groups	Incidence 100 000/year	Prevalence/1000
Annegers et al.	1999 [10]	USA	All	35.5	–
Beilmann et al.	1999 [4]	Estonia	0–19	–	3.6
Karaagac et al.	1999 [11]	Turkey	All	–	10.2
Jallon	1997 [12]	Switzerland	All	45.6	–
Camfield et al.	1996 [8]	Canada	<16	41	–
de la Court et al.	1996 [13]	Netherlands	55–95	–	9
Mendizabal and Salguero	1996 [14]	Guatemala	All	–	5.8
Olafsson et al.	1996 [7]	Iceland	All	47	–
Aziz et al.	1994 [15]	Pakistan	All	–	10.1
Snow et al.	1994 [16]	Kenya	All	–	4
Loiseau et al.	1990 [17]	France	All	24–42	–
Li et al.	1985 [18]	China	All	–	4.4
Bharucha et al.	1988 [19]	India	All	–	4.7
Hauser and Kurland	1975 [20]	USA	All	–	5.4

Source: Modified from Epidemiologic aspects of epilepsy, in The Treatment of Epilepsy, 4th edn (eds. E. Wyllie, A. Gupta and D. Lachhwani), Lippincott, Wilkins Philadelphia, PA, p. 113 [7].

and adolescents alone led to a higher median estimate of 57 per 100 000 per year, (range 41–65) [8]. Even higher incidence rates occurred among infants younger than one year and people older than 60 years [8]. Most studies do not show any gender differences.

Six Class I [9, 28–32] and seven Class II studies [10, 13, 22, 27, 33–35] have addressed the prevalence of epilepsy. Three Class I studies in children and adolescents up to age 19 [9, 29, 31] found the median prevalence value was 3.9 per 1000 and among the Class II studies that included all age groups [22, 23, 27, 34, 35] the median estimate was 7.1 per 1000 population. Observably, seizures and epilepsy have a fairly high incidence and prevalence globally.

Incidence and Prevalence of Acute Symptomatic Seizures

Acute symptomatic seizures differ from epilepsy in that each seizure has a clear, identifiable, proximal cause. Potential etiologies can include metabolic causes such as medications or electrolyte derangements, trauma, stroke, neoplasms, and many other possibilities. The incidence of acute seizures has been provided by several studies. Two often-cited studies based on the population of Rochester, Minnesota reported age-adjusted incidence rates of 39 per 100 000 person years in 1970 [36, 37]. This represents about 40% of all cases of a febrile seizure identified in the community. This result has been replicated in European studies.

The incidence of acute symptomatic seizures tends to be higher in men than women [36]. Just like epilepsy, the age-specific incidence of acute symptomatic seizures is highest during the first year of life. This is attributed to the high incidence of acute symptomatic seizures associated with metabolic, infectious, and encephalopathic causes during the neonatal and perinatal periods. Incidence declines in childhood and early adult years and reaches a nadir among those between the ages of 25–34 years of age [36]. After 35 years of age, the incidence increases progressively, reaching 123 per 100 000 among those more than 75 years of age [36]. Therefore, acute symptomatic seizures have a bimodal age distribution.

The most commonly reported cause of acute symptomatic seizures arises from metabolic conditions. Several conditions can be underlying etiologies or causes for seizure disorders. Common conditions that need to be considered when evaluating a patient presenting with a seizure include hypoglycemia and hyperglycemia which are often reported in patients with diabetes. Hyponatremia, uremia, and hypocalcemia are also well represented in the literature. Abrupt discontinuation of antiepileptic drugs, sedative, and anxiolytic agents is also a prominent cause of seizures. All barbiturates and benzodiazepines present a risk of withdrawal seizures. The use of medications that lower the seizure threshold is an important cause of acute seizures. Drugs, such as phenothiazines, tricyclic antidepressants, theophylline, bupropion, antibiotics such as new generation quinolones and certain pain medications such as meperidine can also cause seizures. Recently stimulant agents, such as ephedra, often found in over-the-counter herbal/botanicals and weight loss preparations, have been causally implicated in seizures [11].

Central nervous system (CNS) and systemic infections such as meningitis, pneumonia, and urosepsis can promote seizures. Acute trauma, embolic, and hemorrhagic strokes are also common causes of seizures. It is important to consider all of these risk factors when assessing a patient with an acute symptomatic seizure as this is a relatively common occurrence in any age group.

Looking Beyond Epidemiology: The State of Epilepsy Care in the United States

The Institute of Medicine of the National Academies March 2012 report indicated that 1 in 26 Americans will develop a seizure disorder during their lifetime [3]. Nearly one-third of people with epilepsy who continue to experience seizures have not seen a specialist in the previous year [5]. In 2005, the US Centers for Disease Control and Prevention (CDC) conducted surveillance work to assess the state of epilepsy and seizure care in the US based on 19 reporting states [12]. The US CDC worked with the Behavioral Risk Factor Surveillance System (BRFSS) and assessed a number of epilepsy and seizure-related variables to better characterize how well the US healthcare structure was handling epilepsy care. The BRFSS is an ongoing, state-based, random digit dial telephone survey of non-institutionalized US adults over the age of 18. This system collects information on health risk, behaviors, and preventative health services that relate to the leading causes of death and morbidity.

The surveillance system included a total of 2207 adults from 19 states or 1.65% with a reported history of epilepsy [12]. Moreover, 0.84% had active epilepsy defined as either a

history of epilepsy and currently taking medications, or reporting one or more seizures during the past three months. 0.75% was classified as having inactive epilepsy or a history of epilepsy or seizure disorder but not currently taking medicine to control epilepsy and no seizures in the three months preceding the survey [12]. There were no differences among the states with regards to prevalence of lifetime, active, or inactive epilepsy. Prevalence estimates for active and inactive epilepsy revealed no significant difference by sex, race, or ethnicity.

However, American adults with a history of epilepsy and active epilepsy were much more likely to report fair or poor health by being unemployed or unable to work [12]. These individuals also lived in households with the lowest annual incomes and had a history of concomitant disorders such as stroke or arthritis. Adults with a history of epilepsy and active epilepsy also reported significantly worse health-related quality of life. Individuals with epilepsy were more likely to be obese, physically inactive, and smoking. In adults with active epilepsy with recent seizures, 16.1% reported not taking their epilepsy medications and 65.1% reported having had more than one seizure in the previous month [12]. Among adults with a history of epilepsy, almost 24% reported cost as a barrier to seeking care from a physician over the previous year [12]. A total of 35% of adults with active epilepsy with seizures reported not having seen a neurologist or an epilepsy specialist in the previous year [12].

This study showed that the incidence and prevalence rates reported by population-based studies as previously outlined are relatively accurate. Seizures and epilepsy are a frequent occurrence among the American population. Yet, the CDC analysis also demonstrated the significant burden of disease that cannot be assessed from epidemiologic studies. A number of public health interventions are necessary in order to better educate the public, understand the barriers to care, financing of the care and how to improve quality of life for patients with epilepsy.

Risk Factors for Epilepsy

The risk factors for epilepsy in adults are somewhat established and are further discussed in the chapter on etiologies for seizures. There are several known risk factors for epilepsy in adults including head trauma, CNS infections, strokes, both embolic and hemorrhagic, CNS malignancies, particularly cortically-based tumors such as gliomas and metastatic lesions, Alzheimer's disease and other neurodegenerative conditions. However, the relationship between epilepsy and other conditions such as subcortical white matter diseases, demyelinating conditions, and certain psychiatric conditions (i.e. depression and schizophrenia) have not been sufficiently characterized.

Of all the various potential risk factors toward epilepsy, there are three that merit further review: Alzheimer's disease, head trauma, and neurocysticercosis. The underlying pathology of Alzheimer's disease appears to be associated with a potential increased susceptibility toward seizures. Given that the diagnosis of Alzheimer's disease is confirmed only by autopsy, it is difficult to establish whether some patients may have concurrent epilepsy because of the overlapping similar presentations. One study found a 10-fold increased risk for unprovoked seizures in Alzheimer's disease [36]. Another reported new onset seizures

developed in 16% of patients with probable Alzheimer's disease after they became severely demented [37]. Moreover, a Class I study of geriatric epilepsy in a veteran's population found that neurodegenerative conditions accounted for almost 11% of epilepsy disorders in this group [14]. Clearly, more investigations are needed to understand this relationship.

Because trauma is a relatively preventable but common condition, its role in epileptogenesis has been evaluated. There are three major categories of traumatic head injury loosely divided as mild, moderate, and severe [15]. Severe head injuries have a significant relative risk (RR) of development of epilepsy over the course of one's life with a commonly reported RR of 29 compared to a normal population of 1 [15]. Moderate head injury has a RR of 4 and a mild head injury is equivocal with regards to seizure risk as compared to a normal-aged population [15].

Neurocysticercosis deserves special mention due to its frequent nature in developing countries. This infection is caused by the Taenia solium tapeworm by ingestion of uncooked pork. The tapeworms have a predilection for brain tissue and the ensuing inflammatory response often results in epilepsy. Neurocysticercosis is one of the most common causes of epilepsy in the third world and one that is completely preventable by adequately cooking pork and simple hygiene [16]. Given recent immigration patterns and globalization with easy transport to and from various parts of the world, this condition has become endemic in areas with no previous history of this problem. It is important to understand the highly preventable aspect of this condition and be aware of the increasing regularity of this epilepsy cause.

Conclusion

This chapter has served to outline the incidence and prevalence of epilepsy in the world. Epilepsy and acute symptomatic seizures are common disorders which can present as an independent condition or can often be associated with other comorbidities such as cerebrovascular disease, neurodegenerative disorders, and traumatic brain injuries. The disorder is seen in the extremes of age, but can afflict anyone. The potential concerns of individuals with epilepsy in the US, based on current public health estimates suggests that there is a significant psychosocial, economic, and quality-of-life burden for patients who have seizures and epilepsy.

References

1. GBD 2016 Epilepsy Collaborators (2019). Global, regional and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study. *Lancet Neurol.* 18: 357–375.

2. Murray, C.J., Vos, T., Lozano, R. et al. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380: 2197–2223.

3. England, M.J., Liverman, C.T., Schultz, A.M., and Strawbridge, L.M. (2012). Epilepsy across the spectrum: promoting health and understanding. *Epilepsy Behav.* 25 (2): 266–276.

4. Fiest, K.M., Sauro, K.M., Wiebe, S. et al. (2017). Prevalence and incidence of epilepsy a systematic review and meta-analysis of international studies. *Neurology* 88: 296–303.
5. Tian, N., Boring, M., Kobau, R. et al. Active epilepsy and seizure control in adults in United States-2013 and 2015. *Morb. Mortal. Wkly. Rep.* 67 (15): 437–442.
6. Commission on Epidemiology and Prognosis, International League against Epilepsy (1993). Guidelines for epidemiologic studies on epilepsy. *Epilepsia* 34 (4): 592–596.
7. Berg, A. (2006). Epidemiologic aspects of epilepsy. In: *The Treatment of Epilepsy*, 4e (eds. E. Wyllie, A. Gupta and D. Lachhwani), 113. Philadelphia, PA: Lippincott, Williams & Wilkins.
8. Hirtz, D., Thurman, D.J., Gwinn-Hardy, K. et al. (2007). How common are the "common" neurologic disorders? *Neurology* 68 (5): 326–337.
9. Beilmann, A., Napa, A., Hämarik, M. et al. (1999). Prevalence of childhood epilepsy in Estonia. *Brain Dev.* 21 (3): 166–174.
10. Verity, C.M., Ross, E.M., and Golding, J. (1992). Epilepsy in the first 10 years of life: findings of the child health and education study. *Br. Med. J.* 305 (6858): 857–861.
11. Sirven, J., Drazkowski, J., Zimmerman, R. et al. (2003). CAM for epilepsy in Arizona. *Neurology* 61: 576–577.
12. Kobau, R., Zahran, H., Thurman, D. et al. (2005) Epilepsy Surveillance Among Adults—19 states. Behavioral Risk Factors Surveillance Risk System. http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5706a1.htm (accessed 1 July 2020).
13. Kurtz, Z., Tookey, P., and Ross, E. (1998). Epilepsy in young people: 23 year follow up of the British national child development study. *Br. Med. J.* 316 (7128): 339–342.
14. Rowan, A., Ramsay, R.E., Collins, J.F. et al. (2005). New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine and carbamazepine. *Neurology* 64: 1868–1873.
15. Salazar, A.M., Jabbari, B., and Vance, S.C. (1985). Epilepsy after penetrating head injury. I. Clinical correlates; a report of the Vietnam head injury study. *Neurology* 35: 1406–1414.
16. Nash, T., Del Brutto, O., Butman, J., and Corona, T. (2004). Calcific neurocysticercosis and epileptogenesis. *Neurology* 62: 1934–1938.
17. Loiseau, J., Loiseau, P., Duché, B. et al. (1990). A survey of epileptic disorders in Southwest France: seizures in elderly patients. *Ann. Neurol.* 27 (3): 232–237.
18. Li, S.C., Schoenberg, B.S., Wang, C.C. et al. (1985). Epidemiology of epilepsy in urban areas of the people's Republic of China. *Epilepsia* 26 (5): 391–394.
19. Bharucha, N.E., Bharucha, E.P., Bharucha, A.E. et al. (1988). Prevalence of epilepsy in the Parsi community of Bombay. *Epilepsia* 29 (2): 111–115.
20. Hauser, W.A. and Kurland, L.T. (1975). The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. *Epilepsia* 16 (1): 1–66.
21. Freitag, C.M., May, T.W., Pfäfflin, M. et al. (2001). Incidence of epilepsies and epileptic syndromes in children and adolescents: a population-based prospective study in Germany. *Epilepsia* 42 (8): 979–985.
22. MacDonald, B.K., Cockerell, O.C., Sander, J.W., and Shorvon, S.D. (2000). The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 123 (Pt 4): 665–676.
23. Olafsson, E., Hauser, W.A., Ludvigsson, P., and Gudmundsson, G. (1996). Incidence of epilepsy in rural Iceland: a population-based study. *Epilepsia* 37 (10): 951–955.

24. Camfield, C.S., Camfield, P.R., Gordon, K. et al. (1996). Incidence of epilepsy in childhood and adolescence: a population-based study in Nova Scotia from 1977 to 1985. *Epilepsia* 37 (1): 19–23.
25. Rantala, H. and Ingalsuo, H. (1999). Occurrence and outcome of epilepsy in children younger than 2 years. *J. Pediatr.* 135 (6): 761–764.
26. Hauser, W.A., Annegers, J.F., and Kurland, L.T. (1993). Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 34 (3): 453–468.
27. Holden, E.W., Thanh Nguyen, H., Grossman, E. et al. (2005). Estimating prevalence, incidence, and disease-related mortality for patients with epilepsy in managed care organizations. *Epilepsia* 46 (2): 311–319.
28. Oun, A., Haldre, S., and Mägi, M. (2003). Prevalence of adult epilepsy in Estonia. *Epilepsy Res.* 52 (3): 233–242.
29. Eriksson, K.J. and Koivikko, M.J. (1997). Prevalence, classification, and severity of epilepsy and epileptic syndromes in children. *Epilepsia* 38 (12): 1275–1282.
30. de la Court, A., Breteler, M.M., Meinardi, H. et al. (1996). Prevalence of epilepsy in the elderly: the Rotterdam study. *Epilepsia* 37 (2): 141–147.
31. Waaler, P.E., Blom, B.H., Skeidsvoll, H., and Mykletun, A. (2000). Prevalence, classification, and severity of epilepsy in children in western Norway. *Epilepsia* 41 (7): 802–810.
32. Luengo, A., Parra, J., Colás, J. et al. (2001). Prevalence of epilepsy in northeast Madrid. *J. Neurol.* 248 (9): 762–767.
33. Olafsson, E. and Hauser, W.A. (1999). Prevalence of epilepsy in rural Iceland: a population-based study. *Epilepsia* 40 (11): 1529–1534.
34. Begley, C.E., Famulari, M., Annegers, J.F. et al. (2000). The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. *Epilepsia* 41 (3): 342–351.
35. Hauser, W.A., Annegers, J.F., and Kurland, L.T. (1991). Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. *Epilepsia* 32 (4): 429–445.
36. Annegers, J.F., Hauser, W.A., and Lee, J.R. (1995). Incidence of acute symptomatic seizures in Rochester, Minnesota: 1935–1994. *Epilepsia* 36: 327–333.
37. Annegers, J.F., Dubinsky, S., Coan, S.P. et al. (1999). The incidence of epilepsy and unprovoked seizures in multiethnic, urban health maintenance organizations. *Epilepsia* 40 (4): 502–506.