CHAPTER 1

Gender Difference in Epidemiology and Comorbidities of Epilepsy

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Case history: A 54-year-old woman with multiple sclerosis was first seen at an epilepsy center seeking expert advice after having received a diagnosis of post-traumatic epilepsy by her general practitioner. At age 16 years the patient was a victim of a car accident during which she was seriously injured in her head. A temporo-occipital subdural hematoma was evacuated with uneventful follow-up. At that time, the patient received prophylactic treatment with phenytoin for 6 months. At age 30, she had blurring of vision for 3 weeks and at age 35 she had numbness in her left leg associated with mild weakness and urinary urgency. A diagnosis of multiple sclerosis was made based on history, clinical findings, and MRI evidence of demyelinating disease. Neurological symptoms and signs disappeared 1 month after onset and recurred, but with lower severity and duration, at age 45. In the 3 months preceding the epilepsy consultation, the patient experienced episodes characterized by visual hallucinations, each lasting 1–2 min. A follow-up MRI showed multiple areas of increased intensity with periventricular distribution in the frontal and occipital areas. The following questions were posed by the patient to the epileptologist. (1) Is this epilepsy or simply a relapse of her multiple sclerosis? (2) Is head trauma the most plausible cause of her seizures? (3) Should antiepileptic treatment be taken for life?

Background and important detail

The frequency, etiology, and prognosis of epilepsy in men and women can be better outlined through population-based epidemiological studies. The diagnosis of epilepsy is made by epidemiologists when the patient experiences at least two unprovoked seizures 24 or more hours apart [1]. This definition has been revised by the International League Against
Epilepsy and the International Bureau for Epilepsy [2] which suggested that epilepsy can be predicted by a single seizure. However, the revision is not likely to affect gender-specific epidemiological indices, because there is no evidence that men and women have a different risk of relapse after a first unprovoked seizure.

Patients with epilepsy enrolled in epidemiological studies should represent the entire spectrum of the disease. Population-based surveys have been conducted in patients with epilepsy of all ages or in selected age groups (children, adults, elderly). In these studies, men and women were often compared. Several studies, especially those from developing countries, have been performed only in patients with major seizures. Others were limited to selected seizure types or epilepsy syndromes. Most surveys have been conducted in small urban or rural areas, with no nationally based reports and no international comparisons [3]. The sociocultural background of the underlying population (which has significant effects on the frequency and characteristics of the disease) may be a strong confounder when different populations are compared. This is particularly true when men and women are compared. Patients with mild or infrequent seizures may not receive medical care. Patients may also deny a history of epilepsy for fear of being stigmatized. This is particularly true in less developed countries where women are more likely than men to conceal the disease. In addition, in community surveys it may be difficult to exclude psychogenic nonepileptic seizures, which may occur in up to one-fourth of patients presenting to family physicians [4] and tend to prevail in women, who may account for about three-fourths of reported cases of such nonepileptic seizures [5]. Although community-based studies including all forms of epilepsy provide a better view of the whole spectrum of the disease, studies in patients with selected epileptogenic conditions may demonstrate different rates of occurrence in men and women because of differences in the gender distribution of the underlying disease.

Other methodological constraints and inconsistencies, in terms of case ascertainment and study conduct, may be present in studies performed in developing countries [6]. The quality and completeness of data collection is impaired by the use of standard screening instruments across populations with diverse social and cultural backgrounds (with different effects in men and women), the lack of specialized personnel, the virtual lack of diagnostic equipment, and the use of different terminologies to define seizures and epilepsy.

**Incidence of epilepsy**

With few exceptions [7–9], the incidence of epilepsy and unprovoked seizures is higher in men than in women in both industrialized and
developing countries, although the difference is not significant in the large majority of reports. In a recent Finnish survey, the incidence remained slightly higher [relative risk (RR) 1.21, 95% confidence interval (CI) 1.19–1.23] in men than women in all age groups and all regions and throughout the entire observation period [10]. However, the risk of developing epilepsy differs between men and women according to age. In a white population in the USA, the 50-year age-specific annual incidence of epilepsy was similar in the two sexes until about 50 years of age and was significantly higher in older men than in women [11]. In men, the cumulative incidence rate was 0.42% at age 65–69, 0.85% at age 70–74, 1.84% at age 75–79, 2.40% at age 80–84, 3.75% at age 85–89 and 4.26% at age 90 and older. The corresponding rates in women were 0.24, 0.52, 0.94, 1.53, 2.24, and 2.77%.

In the Icelandic population [12], the age-specific incidence was similar in male and female patients up to age 85 and older, when the incidence in women was half that in men. The results were similar in studies carried out in Switzerland and Estonia [3]. Studies done in children and adolescents reported incidences of 41–82 per 100 000 per year, with rates 30–60% higher in girls before the age of 5 years and 10–20% higher in boys in later childhood and adolescence [13]. These differences may be explained by the differing distribution of factors known to increase risk of epilepsy in children. These include congenital malformations of the central nervous system (CNS), moderate or severe head trauma, CNS infections, certain inherited metabolic conditions, and genetic factors. However, these differences can also be explained by factors intrinsic to the study populations and the methods of case ascertainment.

**Prevalence of epilepsy**

As with incidence, the prevalence of epilepsy is higher in men than in women. Among population-based studies in Europe [3], all but one [14] found higher prevalence ratios in males than females. However, the difference was only rarely statistically significant [15–18] and, in most studies, sex dominance shifted between age groups. In children, the prevalence was slightly higher in boys than in girls [13].

The distribution of epilepsy in men and women has been shown to vary across countries. This can be mostly explained by the same factors discussed with incidence. These include differences in genetic background, the prevalence of the commonest risk factors, the concealment of the disease by women for sociocultural reasons, and perhaps the structure of the study population and the methods of case ascertainment.
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Epilepsy syndromes and comorbidity

Epilepsy is a heterogeneous clinical condition characterized by differing syndromic patterns. Absence seizures are reported to be more common in girls than in boys, while both infantile spasms and Lennox–Gastaut syndrome are more common in males than in females [13]. Juvenile myoclonic epilepsy and other epilepsies of adolescence have an equal distribution between boys and girls [19]. Although in clinical series some epilepsy syndromes have been found to prevail in boys and others in girls, with few exceptions these observations have been rarely confirmed by community-based studies. In a white population in the USA, symptomatic partial epilepsies have been found to prevail in women and nonlocalized cryptogenic partial epilepsies in men, although gender-specific incidence rates were not available [20]. A community-based survey carried out in Croatia found that more males than females had generalized seizures, whereas more females than males had partial seizures [21].

The association between epilepsy and an epileptogenic condition (e.g., head trauma) does not necessarily establish a cause-and-effect relationship. In order for a given variable to be considered a risk factor for epilepsy, a number of conditions must be satisfied, including temporal relationship, strength, consistency, biological gradient, and biological plausibility of the association [22]. Cerebrovascular disorders, head trauma, developmental disorders, and CNS infection are the most common etiological factors in well-defined populations. However, using for reference the frequency of epilepsy in the general population, the clinical conditions carrying the highest risk of seizures and epilepsy are, in decreasing order, cerebral palsy (RR 17.9–34.4), mental retardation (RR 22.6–31), stroke (RR 22), CNS infections (RR 10.8), and multiple sclerosis (RR 3.6) [23]. Severe traumatic brain injury carries a 17-fold risk of seizures [24]. However, the risk decreases over time and overlaps that of the general population after 20 years. This is also true for other acute CNS insults while a high risk of seizures and epilepsy may persist with time in chronic or relapsing clinical conditions.

No gender differences were found between epilepsy and severe handicap in children with temporal lobe epilepsy followed up for 20 years [25]. In the general population, learning disorders are more common in boys than in girls (odds ratio, OR, 1.4–3.2) [26] and are present in up to one-fourth of patients with epilepsy [27] with no robust indication of a gender difference.

Migraine [28], attention-deficit hyperactivity disorder (ADHD) [29], and several psychiatric illnesses [30] have differing distribution in men and
women. In these clinical conditions the risk of seizures and epilepsy is higher than expected and may affect men and women to a differing extent. Although the results of published reports are inconsistent, comorbidity can be interpreted in light of a common genetic susceptibility and/or the presence of shared environmental factors. In a cross-sectional population-based study extracting data from the UK General Practice Research Database, psychiatric disorders occurred twice as often in people with epilepsy compared with the rest of the population, with significant differences between sexes (rate ratio 2.36 in men and 1.87 in women, with the largest differences for anxiety and depression) [30]. In this population, the risk of migraine was also increased, with a significant difference between men and women (rate ratio 2.22 vs. 1.44). In the Canadian Community Health Survey, a population-based prevalence study of several psychiatric conditions associated with epilepsy, major depressive disorder had a statistically significant age-by-sex interaction such that the sex difference (women > men) was seen to decline with age [31].

Clear-cut gender differences related to the etiology and comorbidity of epilepsy are difficult to find because the exact attribution of cause is often not possible and because a number of factors are likely to be involved in causation in a single individual.

A population-based study carried out in Norway showed that girls with epilepsy did not exhibit risk-taking behaviors (daily alcohol consumption, illegal drug use, criminal offences) more frequently than controls, but having epilepsy was a risk factor for such behavior in boys (OR 3.2) [32,33]; girls had more emotional problems, whereas boys had higher scores regarding peer relationship and hyperactivity/inattention problems. Male gender, low socioeconomic status (family income below poverty limit and living with a single parent), and other chronic diseases (asthma/diabetes) were independent risk factors for developing psychiatric symptoms, along with epilepsy. However, having or having had epilepsy was a much stronger risk factor for developing psychiatric symptoms in girls than in boys (OR 4.2 vs. 2.3). This finding is in line with other reports [34–36] but in contrast with others [37–40].

**Attitudes toward epilepsy and gender**

Sociocultural factors may play a major role in affecting differing public attitudes toward epilepsy in men and women. In India, a survey performed in a tertiary center in patients with juvenile myoclonic epilepsy and temporal lobe epilepsy indicated that comorbidities, lower employment, and higher anxiety state were more frequent for women than for men. Compared with men, women had more difficulty finding life partners,
were at increased risk of divorce, and had more problems with employment, even when the clinical profiles of their epilepsy syndromes were comparable [40]. However, these results were not confirmed in other studies [42–45] or could be verified only in selected patient subgroups (e.g., more unemployed women among those married) [46].

**Prognosis and mortality of epilepsy**

Population studies in western countries in patients with newly diagnosed epilepsy followed for several decades show that up to 80% of cases enter prolonged periods of seizure remission and up to 50% continue to be seizure-free after treatment discontinuation (terminal remission) [47,48]. The probability of long-term remission is similar in men and women and differences, where present, remain small when treatment is discontinued. These findings are confirmed by studies in developing countries where untreated patients present comparable long-term remission rates [8,49].

Long-term seizure remission is less frequent, but still possible, both in men and in women with symptomatic epilepsy (i.e., with seizures associated with a known epileptogenic condition).

Mortality from epilepsy has been found significantly higher in men than in women [50]. In the white population of the USA, the 30-year cumulative standardized mortality ratio was 2.1 (95% CI 1.5–2.8) in men and 1.6 (95% CI 1.1–2.2) in women [51]. Similar observations have been made in developing countries [52], although the data are sparse and flawed. Although the difference can be explained by the differing mortality of the underlying epileptogenic conditions among men and women, further studies are needed to address the reasons for the gender difference in mortality.

**Use of antiepileptic drugs**

There are only a few studies assessing the use of antiepileptic drugs (AEDs) in the two sexes separately. No major differences have been found between men and women in the total use of AEDs in epilepsy [53–55]. Lamotrigine, gabapentin, and topiramate are used to a greater extent in female than in male patients [53,56], while carbamazepine, valproate, phenytoin, and oxcarbazepine are mostly used in male patients, especially in combination [41,53,57]. No gender differences have been reported for levetiracetam, phenobarbital, and clonazepam [53]. The different tolerability profile (with special reference to weight gain, cosmetic effects, and teratogenicity) may explain the differential use of some AEDs in men and women.
Implications for management

Gender differences do not seem to play a major role in explaining incidence, prevalence, risk factors, and prognosis of epilepsy. Where present, differences between men and women can be found among patients with selected comorbidities (e.g., mood disorders, migraine, multiple sclerosis) and reflect differences in the attributable risk (i.e., the differing number of men and women with a given clinical condition and epilepsy reflect the differing distribution of the underlying disease in the two sexes). Although prevention of clinical conditions like stroke, head trauma and infection may affect the risk of seizures and epilepsy, this is unlikely to have a different impact in men and women.

Review of the case: Epidemiological studies provide evidence-based support to the causal association between epilepsy and multiple sclerosis rather than head trauma. Multiple sclerosis carries a threefold risk of seizures while a severe traumatic brain injury that occurred more than 20 years before is unlikely to be a risk factor. Even in patients with symptomatic epilepsy, long-term remission is not unlikely and treatment may be discontinued.

Key summary points

- The risk of seizures and epilepsy in women is only slightly lower than that of men.
- This slight (nonsignificant) difference may be attributed to the differing distribution of risk factors for epilepsy in men and women and to sociocultural attitudes.
- Some epilepsy syndromes prevail in women and others in men, but the differences tend to disappear in well-defined populations.
- Although the prognosis of epilepsy is similar in the two sexes, the higher mortality of the disease in men may reflect the higher severity of the underlying epileptogenic conditions in the male sex.
- With the aging of the world population and the older average age of women compared to men, an increasing number of women will experience seizures and epilepsy in the future.

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