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Review

Does gender influence susceptibility and consequences of acquired epilepsies?

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ABSTRACT

Gender differences in the incidence and clinical course of acquired and "cryptogenic" epilepsy are reviewed based on a literature search. We emphasized incidence and population-based studies because they are best suited to assess the effect of gender on susceptibility and clinical evolution of these epilepsies and may control for potential confounding factors. However, such studies were only available for a few acquired etiologies. These included tumor, prenatal and perinatal brain insults, cerebrovascular disease, infection, trauma, neurodegenerative disease, and autoimmune disorders. None of these acquired causes has been consistently shown to affect women or men to a greater or lesser degree, although some of the literature is contradictory or inadequate. There is almost no literature that addresses the effect of gender on the clinical course of epilepsy associated with these acquired causes. In addition, most studies of acquired causes do not take into account the incidence of the cause in the population with or without associated epilepsy. In children, "cryptogenic" epilepsy (non-syndromic and without causative MRI lesion) does not appear to have a gender preference and gender does not seem to affect the likelihood of remission. As further population-based studies of the etiology and clinical course of epilepsy are undertaken, it may be worthwhile to more specifically define the role of gender.

Contents

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Introduction

Epidemiological data suggest that gender may affect susceptibility to epilepsy and its prognosis. Most studies found that the overall incidence of epilepsy is slightly higher in men than women, both in developing and industrialized countries (Benn et al., 2008; Christensen et al., 2007; Hauser et al., 1993; Lavados et al., 1992; Tekle-Haimanot et al., 1997), although this difference rarely reaches statistical significance (Joensen, 1986). In a systematic review and meta-analysis of incidence studies, the median annual incidence of epilepsy was 50.7/100 000 for men and 46.2/100 000 for women (p value not significant) (Kotsopoulos et al., 2002). Pediatric population-based studies find the ratio of males and females essentially equal (Arts et al., 2004; Berg et al., 2001; Camfield et al., 1996; Ross et al., 1980; Sidenvall et al., 1993; Wirrell et al., 2011b). The likelihood of seizure remission does not differ significantly between men and women (Cockerell et al., 1997), but male gender is associated with a greater risk of premature death (Forsgren et al., 2005), including sudden unexpected death in epilepsy (SUDEP) (Hesdorffer et al., 2011). In a pooled analysis of case–control studies (Hesdorffer et al., 2011), male gender carried a 1.42-fold increased risk for SUDEP (95% C.I.: 1.07–1.88). In pediatric populations, gender may not exert an effect on mortality. In a recent combined analysis of four population-based pediatric cohorts including 2239 children with newly diagnosed epilepsy followed >30 000 person-years, 69 deaths occurred (37 males and 32 females) (Berg et al., 2013). Male and female subjects were approximately equally represented across cause of death categories (SUDEP; seizure-related, not SUDEP; other natural; non-natural). However, given the small numbers involved, formal statistical tests were not conducted.

Gender differences are also identifiable at the level of specific forms of epilepsy, particularly those in which genetic predisposition has a central role in the development of the disease (genetic epilepsies) (Christensen et al., 2005; Dibbens et al., 2008; Kleveland and Engelsen, 1998; Scheffer et al., 2008). Despite the wide range of environmental factors leading to the development of epilepsy, limited research has investigated the influence of gender in acquired epilepsies (Berg et al., 2010; Christensen et al., 2005; Hauser et al., 1993). Some etiologies of acquired epilepsies, such as traumatic brain injury (TBI), are more common in one gender. As a group, symptomatic epilepsies, which according to the 1989 International League Against Epilepsy (ILAE) terminology also included acquired epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), are slightly more common in men (Christensen et al., 2005; Hauser et al., 1993; Manford et al., 1992). Symptomatic epilepsies are associated *per se* with excess mortality (Hauser and Beghi, 2008), but no significant differences have been observed between sexes (Sillanpaa and Shinnar, 2010; Strauss et al., 2003). The combined analysis of four large population-based pediatric cohorts of newly diagnosed patients demonstrated an excess mortality among the symptomatic epilepsies, but no differences in gender (Berg et al., 2013).

In this article, we will review available evidence on the impact of gender in different types of acquired epilepsies, highlight limitations of the current literature, and provide recommendations for future studies. For the purposes of this review, "acquired epilepsies" are defined as epilepsies due to external or environmental causes (e.g. traumatic brain injury) as well as internal pathological processes (e.g. autoimmune disorders), in which no clear genetic component is involved. In addition, we will focus on population-based and incidence studies, as prevalence estimates can be misleading if used for etiologic studies or to provide information on prognosis (Hauser et al., 1993). This is not a systematic review and reflects our own assessment of the literature available in this area. We searched PubMed up to January 31st, 2014, using the terms "epilepsy", "seizures", "incidence", and "population-based". These were combined with specific causes of acquired epilepsy, such as "hippocampal sclerosis", "febrile status epilepticus", "tumor", "glioma", "meningioma", "prenatal brain insults", "perinatal brain insults", "birth asphyxia", "birth ischemia", "birth infection", "cerebrovascular disease", "stroke", "hemorrrhage", "infection", "meningitis", encephalitis", "trauma", "traumatic brain injury", "neurodegenerative disease", "dementia", "Alzheimer's disease", and "autoimmune disorders". A separate search was done for "cryptogenic epilepsy". Additional studies were sought in reference lists of retrieved articles and in our personal files. Of note, the term *cryptogenic epilepsy* is used here to reflect the inclusion criteria of studies performed prior to the most recent ILAE classification of epilepsies (Berg et al., 2010).

Causes of acquired epilepsies and gender differences

Hippocampal sclerosis/febrile status epilepticus

Hippocampal sclerosis is the most common histopathological finding in adults with drug-resistant temporal lobe epilepsy (Blumcke et al., 2013). Febrile status epilepticus has been associated with hippocampal injury and subsequent hippocampal sclerosis and temporal lobe epilepsy (Lewis et al., 2002; Provenzale et al., 2008). In a U.K. population-based study of convulsive status epilepticus in childhood, the incidence of first ever episodes of febrile status epilepticus was comparable in boys and girls (5.5/100 000/year vs 4/100 000/year) (Chin et al., 2006). In a prospective, multicenter, case–control study comparing children with a first febrile status epilepticus ($n = 169$) and those with a first simple febrile seizure ($n = 102$), female gender was found to be a risk factor for febrile status epilepticus (multivariate OR [95% C.I.] = 2.2 [1.14–4.43]) (Hesdorffer et al., 2013). The development of epilepsy in these cohorts, as well as any associated gender differences, has yet to be assessed.

To our knowledge, no incidence study has explored gender differences in patients with epilepsy and hippocampal sclerosis. Retrospective studies mostly from tertiary epilepsy care centers suggest that hippocampal sclerosis occurs with equal frequency in men and women with epilepsy (Blumcke et al., 2002; Briellmann et al., 1999). In another retrospective study, female gender was found to be a predictor of poorer outcome following surgery for temporal lobe epilepsy associated with hippocampal sclerosis (Burneo et al., 2006); this was not confirmed in a subsequent investigation by the same group (Burneo et al., 2008). In an MRI study including 60 patients with drug-resistant temporal lobe epilepsy (70% of whom had hippocampal sclerosis), men were found to have more brain atrophy than women (Briellmann et al., 2000). Seizure frequency was a factor contributing to reduced brain volumes in men but not in women, suggesting that male gender may be associated with greater vulnerability to seizure-related brain damage. Overall, these findings should be interpreted with caution, as they were obtained retrospectively in highly selected patient samples.

Tumor

Brain tumors account for 4–8% of cases with newly diagnosed epilepsy (Hauser et al., 1993; Olafsson et al., 2005). In patients with brain tumors, epileptic seizures occur in 10–100% depending on tumor type (van Breemen et al., 2007). A Swedish study assessing the incidence of unprovoked seizures in a catchment area of >100 000 people found that tumor-related seizures were five times as common in men compared to women (10/100 000/year vs 2/100 000/year, calculated from study results) (Forsgren et al., 1996). However, in the few other studies exploring gender differences in tumor-related epilepsy, similar rates were found in men and women (Adelow et al., 2009; Beilmann et al., 1999; Forsgren, 1990). It should be noted that none of the studies controlled for gender differences in the incidence of tumors in the investigated populations. To our knowledge, there are no other data from incidence studies on the effect of gender in tumor-related epilepsies.

Small, retrospective, single-center, cohort studies of patients with tumors have found no significant differences in the male-to-female ratio between patients developing unprovoked seizures and those who did not (Alajbegovic et al., 2009; Lieu and Howng, 2000). Gender