Population-Level Evidence for an Autoimmune Etiology of Epilepsy

Mei-Sing Ong, PhD; Isaac S. Kohane, MD, PhD; Tianxi Cai, PhD; Mark P. Gorman, MD; Kenneth D. Mandl, MD, MPH

Epilepsy is a debilitating condition affecting 0.5% to 1.0% of the world’s population. Therapies address manifestations rather than the underlying etiology, which remains unknown in most patients, one-third of whom have a condition that is refractory to antiepileptic therapy. Surgical interventions in epilepsy are often ineffective, with seizures recurring in 50% of patients within 5 years of surgery, and the number of patients who remain seizure free decreases further over the years to 38%. A deeper understanding of the underlying etiologies is necessary to develop new therapeutic approaches.

Specific autoimmune causes, typically associated with autoantibodies, have been increasingly identified in a subset of previously idiopathic seizure disorders. In some of these situations, seizures are associated with other neurologic manifestations; in others, they are the only sign of neurologic autoimmunity. Small case studies and disease-specific investigations also report a high incidence of seizures in autoimmune diseases (ADs) such as systemic lupus erythematosus (SLE) and Hashimoto thyroiditis. Furthermore, published reports document success with immunotherapy in a substantial proportion of patients with presumed autoimmune mechanisms for their seizures.

Establishing an autoimmune basis in patients with idiopathic epilepsy is important because it highlights opportunities for developing new strategies for the treatment of medically refractory epilepsy. To date, evidence on the role of the autoimmune process in epileptogenesis is based mainly on animal studies and small-sample, disease-specific clinical observations. We conducted what we believe to be the largest population study to investigate the relationship between epilepsy and several common autoimmune diseases. Because clinical presentation of seizures, their etiology, and the presence of comorbidities in the elderly population differ considerably from those in younger patients, the present study focused on epilepsy in children (<18 years) and nonelderly adults (aged ≥65 years).
Methods

Study Population and Design
We conducted a population-based retrospective cohort study using claims data from a major nationwide employer-provided health insurance plan in the United States. The Boston Children's Hospital Institutional Review Board approved the study and granted a waiver of consent. Data included dates of enrollment in the insurance program, outpatient and inpatient visits, and prescription drugs dispensed. Demographic data included sex and age. All encounters were coded with 4 or fewer International Classification of Diseases, Ninth Edition (ICD-9), codes. Prescription drugs were reported using the National Drug Code.

Participants were beneficiaries between January 1, 1999, and December 31, 2006, excluding adults older than 65 years. To ensure adequate follow-up, we included only individuals continuously enrolled for 4 years or more, and we considered only those with epilepsy diagnosed 2 or more years after entry into our study and with at least 2 years’ follow-up after the first recorded epilepsy diagnosis.

Outcome Measures
We assessed the relationship between epilepsy and 12 ADs selected a priori: type 1 diabetes mellitus, psoriasis, rheumatoid arthritis, Graves disease, Hashimoto thyroiditis, Crohn disease, ulcerative colitis, SLE, antiphospholipid syndrome, Sjögren syndrome, myasthenia gravis, and celiac disease. Outcomes were stratified based on age groups: (1) children (<18 years) and (2) nonelderly adults (≤65 years).

Furthermore, we examined the potential effects of common therapies used for treating AD including aminosalicylates, disease-modifying antirheumatic drugs, systemic glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), anti-tumor necrosis factor agents, and other biologics (Supplement [eTable 1]). Only exposures that occurred before the first epileptic seizure were considered. Sex and age were included as covariates. Exposure to medications was expressed as a dichotomous variable.

Case Identification
Epilepsy was defined as 2 or more seizures occurring at least 24 hours apart within 2 years. Individuals with diagnoses of epilepsy and AD were identified using ICD-9 diagnostic codes (Supplement [eTable 2]) according to previously validated criteria: (1) at least 1 acute inpatient encounter with the relevant ICD-9 code as the primary diagnosis or (2) at least 2 health care encounters with the relevant ICD-9 code within 2 years. These criteria have been demonstrated to achieve high accuracy in identifying patients from administrative data (sensitivity, 92.9%; specificity, 91.2%). To further strengthen the specificity of epilepsy case identification, we considered only individuals prescribed at least 1 course of an antiepileptic medication.

Statistical Analysis
The risk of epilepsy in patients with AD was compared against the risk of epilepsy in individuals without AD using logistic regression, expressed as odds ratios (ORs) with 95% CIs. All analyses were performed using SPSS software, version 21 (IBM). All statistical tests were 2-sided.

Results

Prevalence of Epilepsy
A total of 2,518,034 individuals were included in our study; 0.4% of the study population developed epilepsy (Table 1). The risk of epilepsy was significantly heightened among patients with AD (OR, 3.8; 95% CI, 3.6-4.0; P < .001) (Figure 1). Collectively, individuals with AD accounted for 17.5% of patients with epilepsy in the study population. Elevated risk was consistent across different ADs. Patients with antiphospholipid syndrome and SLE had the highest risk, with a 9-fold and 7-fold increased risk of epilepsy, respectively.
respectively, followed by patients with type 1 diabetes and myasthenia gravis, eliciting a 5-fold increased risk of epilepsy. The risk of epilepsy was especially pronounced in children. Overall, children with AD had a 5-fold increased risk of epilepsy (Figure 2). In comparison, nonelderly adults with AD had a 4-fold increased risk of epilepsy (Figure 3).

Epilepsy susceptibility was consistently heightened in patients with autoimmune diseases (P < .001). Collectively, patients with any of the autoimmune diseases under study constituted 17.5% of the total epilepsy population. OR indicates odds ratio; SLE, systemic lupus erythematosus. Data markers indicate ORs and limit lines, 95% CIs.

Overall, children with an autoimmune disease had a 5-fold increased risk of epilepsy (P < .001 in all cases except otherwise indicated). OR indicates odds ratio; SLE, systemic lupus erythematosus. Data markers indicate ORs and limit lines, 95% CIs.

aP = .006.
bP = .008.
Timing of Epilepsy
The onset of epilepsy preceded the diagnosis of AD in 30% of cases. In 30% of the cases, the first epileptic seizure occurred within the first year after the AD diagnosis.

Effects of Medications
More than 70% of patients with AD and epilepsy were not exposed to antiepileptics for at least 2 years before the diagnosis of AD. The risk of epilepsy in patients with AD persisted after adjusting for medication use, including aminosalicylates, disease-modifying antirheumatic drugs, systemic glucocorticoids, NSAIDs, anti–tumor necrosis factor agents, and other biologics (OR, 4.1; 95% CI, 3.9-4.3; P < .001) (Table 2). There was no evidence that any of the medications led to an increased risk of epilepsy. Patients exposed to aminosalicylates, NSAIDs, anti–tumor necrosis factor agents, and other biologics appeared to have a reduced risk of epilepsy.

Discussion
Clinicians caring for patients with either AD or epilepsy should be aware of the strong association between them. Indeed, nearly 1 in 5 patients with epilepsy has a coexisting AD. Elevated epilepsy prevalence has been previously reported in ADs in which the disease directly involves the brain. Systemic lupus erythematosus is associated with a range of inflammatory mechanisms in the brain, and cerebral ischemia is a common manifestation of antiphospholipid syndrome. Rates of epilepsy in SLE vary between 4% and 51%, and in antiphospholipid syndrome from 3% to 8%. Our analysis is consistent with these published data. In addition, we established the association across a wide range of ADs, including those for which the primary biological mechanism is not known to directly affect the brain. Patients with myasthenia gravis had a 5-fold increased risk of epilepsy. Although our data do not elucidate the underlying causes of this relationship, they strongly support further effort to explore the potential role of autoimmunity in epileptogenesis. A focus on autoimmune mechanisms can guide translational approaches to new therapeutic options.

Seizures tend to occur within the first 1 to 2 years after the AD diagnosis. The risk of epilepsy is consistently higher in children with AD compared with adults with the same AD. Both clinical and biological features of AD may be influenced by the patient’s age at disease onset,20,21 with childhood-onset AD often more severe than adult-onset AD.22,23 Consistent with a previous study,11 our data showed that female sex is associated with a higher risk of epilepsy.

Effects of Medications
Prior studies on the effects of antiepileptics have produced inconsistent results. Antiepileptics have been reported to exert anti-inflammatory effects,24 but there also are reported cases of SLE-like symptoms caused by carbamazepine.25 However, evidence for causation remains largely anecdotal and inconsistent, with other studies26 failing to show a relationship between antiepileptic use and SLE. Our main findings are clearly not explained solely by immunologic adverse effects of antiepileptics, with 70% of patients with AD and epilepsy not exposed to antiepileptic medications for at least 2 years prior to the diagnosis of AD.

We also explored whether specific treatments for AD may cause or prevent seizures. Corticosteroids, certain immunologic agents, and NSAIDs have been found to induce seizures in some studies27-29 and to reduce the risk of seizures in others.30-32 We found the risk of epilepsy in patients with AD persisted, even after adjustment for these medications in regression models. Exposure to aminosalicylates, NSAIDs, and biologics appears to reduce the risk for epilepsy. However, because we did not study the duration and dose of exposure, whether these medications confer a protective effect against developing epilepsy is unknown and beyond the scope of the present study.

Nature of the Relationship
Among the growing list of neuronal autoantibodies identified in a subgroup of patients with epilepsy, some appear to play a pathogenic role while others may merely be markers of disease. For example, compelling clinical and laboratory evidence33-36 support the pathogenicity of antibodies against the NRI subunit of the N-methyl-D-aspartate receptor (NMDAR). Antibodies from patients with anti-NMDAR encephalitis cause a decrease in the density of NMDAR through antibody-mediated cross-linking and internalization, resulting in the impairment of NMDAR-mediated synaptic function.33-36 Clinical outcome of these patients has been found to correlate with antibody titers in cerebrospinal fluid, and in most cases, symptoms are reversible by immunotherapy. The pathogenic role of other autoantibodies, particularly those directed against intracellular antigens such as glutamic acid decarboxylase, is less clear.

The immune response in AD involves the adaptive immune system, for which the presence of autoimmune antibodies is just one manifestation, as well as the innate arm, as...
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Epilepsy and AD frequently co-occur, and patients with either condition should undergo surveillance for the other. Because ADs affect 8% of the population and for reasons unknown their prevalence is rising, the link between autoimmunity and epilepsy will underpin a rise in the global burden of neurologic disease. The potential role of autoimmunity must be given due consideration in refractory epilepsy so that we are not overlooking a treatable etiology.

Study Limitations

There are several limitations to our study. First, claims data have limited resolution and do not permit fine-grained classification of epilepsy type. However, the validity of using ICD codes in administrative data for identifying epilepsy cases has been demonstrated in several studies. To maximize the specificity of our case identification, we chose a stringent case definition for diagnosis of epilepsy that has been validated. In addition, we selected only patients with epilepsy who were given prescriptions for antiepileptic medications, thus minimizing the likelihood of misclassification of nonepileptic seizures, such as those induced by hypoglycemia, alcohol, or drugs. The consistency between our results and published data on the relationships between epilepsy and several ADs, including SLE and antiphospholipid syndrome, further validates our approach.

In reality, epilepsy is not a single disease entity but a variety of disorders reflecting the underlying brain dysfunction that may result from many different causes. Similarly, it is likely that multiple factors contribute to the risk of epilepsy in patients with AD. First, some patients with AD may have coincidental epilepsy that is unrelated to autoimmune mechanisms; we have accounted for this via comparison with the non-AD population. Second, some patients with AD may have noninflammatory brain abnormalities that give rise to epilepsy; although this is likely to be true, we do not think it fully explains the heightened risk as described above. Third, some patients with AD and epilepsy may have autoantibodies, such as NMDAR antibodies. Finally, we speculate that the largest subgroup consists of patients with as-yet-undefined autoimmune and inflammatory mechanisms that lead to epilepsy. Additional studies are needed to elucidate the pathogenesis of epilepsy in patients with ADs, especially in the latter subgroup. Identifying these mechanisms may also yield insights and novel treatment approaches for patients with epilepsy but without AD, particularly those without a known etiology and/or refractory epilepsy.

Conclusions

Epilepsy and AD frequently co-occur, and patients with either condition should undergo surveillance for the other. Because ADs affect 8% of the population and for reasons unknown their prevalence is rising, the link between autoimmunity and epilepsy will underpin a rise in the global burden of neurologic disease. The potential role of autoimmunity must be given due consideration in refractory epilepsy so that we are not overlooking a treatable etiology.

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