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Epilepsy in Systemic Autoimmune Disorders

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Autoimmunity and inflammation have been implicated as causative factors of seizures and epilepsy. Autoimmune disorders can affect the central nervous system as an isolated syndrome or be part of a systemic disease. Examples of systemic autoimmune disorders include systemic lupus erythematosus, antiphospholipid syndrome, rheumatic arthritis, and Sjögren syndrome. Overall, there is a 5-fold increased risk of seizures and epilepsy in children with systemic autoimmune disorders. Various etiologic factors have been implicated in causing the seizures in these patients, including direct inflammation, effect on blood vessels (vasculitis), and production of autoantibodies. Potential treatments for this autoimmune injury include steroids, immunoglobulins, and other immune-modulatory therapies. A better understanding of the mechanisms of epileptogenesis in patients with systemic autoimmune diseases could lead to targeted treatments and better outcomes.
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Introduction

Autoimmunity and inflammation have gained recent popularity as either causative factors or bystanders in multiple neurologic disorders including epilepsy. There is evidence of inflammatory markers or presence of autoantibodies in several types of epilepsies, as detailed elsewhere in this issue.

This article focuses on the epilepsies that result from autoimmunity or inflammation secondary to systemic autoimmune or inflammatory disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Population-based studies have shown an increased incidence of epilepsy among patients with systemic autoimmune disorders. The onset of epilepsy can precede the diagnosis of autoimmune disease in approximately 30% of patients.[1]

The etiology of seizures and epilepsy in these disorders might involve the production of antibodies, the increased synthesis and release of cytokines and chemokines with increased inflammatory microglial response in the brain, or the results of vascular complications including stroke and hemorrhage.[2]

In a large, population-based, retrospective study including more than 400,000 children, Ong et al[1] found an overall epilepsy prevalence of 1.8% in children with autoimmune disease compared with 0.4% in children without it. Children with autoimmune diseases had a 5-fold increased risk of epilepsy compared with normal children, and they accounted for 17.5% of patients with epilepsy (Table).

This article reviews the epilepsies secondary to systemic autoimmune disorders.

Systemic Lupus Erythematosus

SLE is an autoimmune inflammatory disorder affecting multiple organs, including the brain and peripheral nervous system. Central nervous system manifestations are present in 25%-75% of SLE cases.[2] Seizures occur in approximately 20% of pediatric patients[3] with a range of 7%-40%.[2] In a multicenter study by Hanly et al[4] with a cohort of 1631 adult patients with SLE, 75 had 1 or more seizures (4.6%), which usually occurred close to diagnosis. Most patients presented with generalized seizures. In addition, 12%-43% of patients had recurrence of their seizure within a year. Therefore, 1%-20% of patients with SLE might develop epilepsy. Seizures may also occur during disease flare-ups.[5] Seizures might be the most common presentation of neuropsychiatric lupus in children, accounting for approximately 84% of initial symptoms in a group of 185 children with SLE.[6]

The mechanism of seizures in patients with SLE might be multifactorial. In a pathological study, Hanly et al[7] found that microinfarcts strongly correlated with seizures in 4 of 5 patients. In a pathology series of 57 patients with SLE, seizure history (present in 11 of them) also had a high incidence of microinfarcts and subarachnoid hemorrhage with meningeal hemosiderosis indicative of prior bleeding.[8]

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Table Epilepsy in Systemic Autoimmune Diseases

Autoimmune Disorder	Prevalence of Epilepsy in Children	OR (95% CI)[1]	Seizure Types
SLE	7%-40%	21.6 (11.0-42.7)	GTC, partial, and M
APS	3.2%-8.6%	9.0 (7.7-10.5)	Partial
RA	1%-1.7%	3.1 (1.4-7.0)	GTC and partial
SS	1%-10%	4.3 (3.2-5.6)	GTC, CP, and EPC
BD	2%-16%		GTC
IBD	3%-6%	8.4 (3.7-19.0)	GTC and CP
Celiac disease	1%-5.7%	16.7 (9.9-28.2)	Any type
WG	3%		GTC, CP, and M
Sarcoidosis	38% of pediatric neurosarcoidosis[49]		GTC, partial, and M
DM	1%-2%	3.9 (2.5-6.1)	
MG	1.7%	4.9	
HT	2.4% (66% in encephalopathy)	6.8 (3.5-13.3)	Any type, and EPC
GD	1.7%	4.7 (1.2-19.1)	GTC

Modified from Ong et al[1], Devinsky et al[2], and Baumann and Robertson[49]

APS, Antiphospholipid syndrome; BD, Behçet's Disease; CP, complex partial; EPC, epilepsia partialis continua; DM, Type 1 diabetes mellitus; GD, Graves disease; GTC, generalized tonic-clonic; HT, Hashimoto thyroiditis; IBD, inflammatory bowel disease; M, myoclonic; MG, myasthenia gravis; OR, odds ratio; RA, Rheumatoid arthritis; SLE, Systemic Lupus Erythematosus; SS, Sjögren's syndrome; WG, Wegener granulomatosis.

The presence of antiphospholipid antibodies doubles the risk of seizures in patients with SLE.[9] Antiphospholipid antibodies can be neurotoxic and cause vascular disease. Patients with neuropsychiatric SLE can have elevated levels of antineuronal antibodies in the cerebrospinal fluid.[10] Antiribosomal P protein levels are elevated in patients with neuropsychiatric SLE.[11] Using covariate-based linkage analysis, Bautista et al[12] analyzed 769 individuals with SLE, 106 of them with seizures identifying a potential seizure susceptibility locus on chromosome 15, near the region of the neuronal nicotinic acetylcholine receptor. Chloroquine has been blamed as a causative factor of seizures in patients with SLE.[13,14]

Besides using classical antiepileptic medications to control the seizures, these patients can benefit from immunomodulatory therapies to control their disease and epilepsy. These have included corticosteroids,[15] cyclophosphamide,[15] and rituximab.[16] Phenytoin should be avoided as it can cause and activate SLE.[17]

Antiphospholipid Syndrome

The antiphospholipid syndrome (APS) is defined as the presence of antibodies against phospholipids along with systemic clinical manifestations of a hypercoagulable state with venous or arterial thromboses or obstetric complications or both. The antiphospholipid antibodies include the lupus anticoagulant, anticardiolipin, and anti–β-2 glycoprotein. APS can be classified as primary, when there is no underlying disorder, or secondary, when a disorder is causing it, as is the case with SLE. Cerebral infarcts are the most common neurologic manifestation of APS. In a multicenter European study including 538 patients with APS (53% primary, 35% SLE-associated, and 12% associated with other autoimmune diseases), 46 of them (8.6%) had epilepsy,[18] which was more frequent in patients with secondary APS, especially SLE (13%). The incidence of epilepsy in primary APS was also elevated at 6%. As expected, patients with epilepsy and APS had a higher incidence of thromboembolic events (odds ratio of 4.05), which could be the cause of the epilepsy in these patients. Other etiologic factors for epilepsy in these patients include vasculitis, direct immune effect of autoantibodies, and cerebritis. In a neuropathological report, Leach et al[19] described widespread small cerebral thrombosis causing extensive microinfarcts within the cerebral cortex in a young man with epilepsy and transient ischemic attacks.

In a consecutive group of 50 children and 20 healthy subjects without any evidence of autoimmune disease, Eriksson et al[20] found a higher prevalence of antiphospholipid antibodies (44%) in seizure patients compared with the controls (10%). This suggests that there may be some autoimmune factors involved in epilepsy pathogenesis, even in patients with no history of autoimmune disease. Antiphospholipid antibodies may also inhibit γ-aminobutyric acid receptors, thus increasing neuronal excitability.[21]

Aspirin is strongly recommended in patients with APS who have additional stroke risk factors.[21] Patients with venous thrombosis and antiphospholipid antibodies should be treated with long-term anticoagulation therapy. The emergence of immunomodulatory drugs such as IVIg might provide the possibility of interfering with specific pathogenic pathways in APS.

Rheumatoid Arthritis

This autoimmune disease involving mostly the joints can produce vasculitis in the central nervous system in 1%-8% of cases.[22] Involvement of the brain in RA is rare and includes rheumatic meningeal nodules, choroid plexus infiltration,