

Current Review

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Epilepsy Associated with Systemic Autoimmune Disorders

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Systemic autoimmune disorders affect multiple organ systems. Brain involvement commonly causes seizures, which may be the presenting symptom. Systemic lupus erythematosus, Sjogren's syndrome, Wegener's granulomatosis, sarcoidosis, celiac disease, Crohn's disease, Behcet's, and Hashimoto's encephalopathy are reviewed. Mechanisms underlying CNS pathology in systemic autoimmune disorders—and specifically factors predisposing these patients—are discussed, including vascular disease (e.g., prothrombotic state, antinuclear antibody, emboli, vasculitis), antineuronal antibodies, immune complexes, cytokines, metabolic disorders, infection, and therapy. Diagnostic and therapeutic strategies must be individualized for both the disorder and the patient. Systemic autoimmune disorders affect multiple organ systems and frequently involve the central and peripheral nervous systems. Seizures are among the most common neurological manifestation and occasionally can be the presenting symptom. There are many causes of seizures in systemic autoimmune disorders (Table 1), and the first clinical challenge is to determine not only the cause but also the significance of seizures. In some cases, they are clues to metabolic or infectious disorders or medication toxicity; in other cases, seizures herald a life-threatening progression of the underlying illness.

Systemic Lupus Erythematosus (SLE)

SLE involves central nervous system in 25% to 75% of cases (1). Seizure or psychosis is one of the 11 primary diagnostic criteria for SLE; they can occur around the time of disease onset (2). Seizures occur in 7% to 40% of SLE patients, with an average of ~15% (2–5). In SLE patients, generalized tonic-clonic seizures are most common (~75%), but simple and complex partial seizures can occur (6, 7). The first acute symptomatic seizure can occur either at (32%) or after (68%) SLE onset (2). After the initial seizure, 12% to 43% recur (2, 7), with most recurrences in the first year. Seizures are associated with increased morbidity and mortality in adults and children (3, 4). Status epilepticus may herald death (5); it should be aggressively treated and, if possible, the underlying cause identified. Seizures often occur during disease flares; the onset or worsening of seizure activity may reflect uremia, hypertension, CNS infection, stroke, or antiphospholipid antibodies (2).

Hypertension may be associated with a posterior reversible encephalopathy syndrome characterized by altered mental status, headache, visual changes, seizures, and posterior leukoencephalopathy on imaging studies (8).

Antiphospholipid antibodies are elevated in most studies of lupus patients with seizures or epilepsy, as well as those with stroke and headache (1, 9). Antiphospholipid antibodies are prothrombotic and can cause vascular disease, which can secondarily cause seizures. However, antiphospholipid

antibodies are neuropathogenic in vitro, potentially causing seizures through direct neurotoxic effects (10). Other autoantibodies are also elevated in lupus patients with epilepsy (1, 11). To further complicate interpretation of antibody titers, some antiepileptic drugs can induce the lupus anticoagulant.

To examine the role of IgG class antinuclear antibody antibodies in an epilepsy (non-SLE) population, the frequencies of these antibodies were determined in a cohort of 960 epilepsy patients and 580 reference subjects; 4.5% of the epilepsy patients had elevated titers, similar to a control group (11). However,

Table 1. Mechanisms of Seizures in Systemic Autoimmune Disorders

Vascular disease
Platelet-fibrin thrombi (e.g., TTP)
Prothrombotic state
Antinuclear antibody
Emboli
Vasculitis
Antineuronal antibodies
Immune complexes
Cytokines
Metabolic disorders
Infection
Therapy
Coincidence

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patients with chronic epilepsy and high seizure frequencies had elevated anticardiolipin titers relative to controls (11, 12). The question of cause and effect remains unanswered.

Among SLE patients, CSF antineuronal antibodies are increased in 90% with psychosis, encephalopathy, or seizures as compared to 11% without CNS disease and 25% of patients with stroke or movement disorder (13). CSF but not serum NMDA receptor subunit NR2 antibody levels correlate with neuropsychiatric symptoms, including seizures (14, 15). Antiribosomal P proteins elevated with CNS disease, including psychosis and seizures (1, 16). Notably, a lower risk of seizures correlates with higher anti-La Ab and the use of antimalarials (3, 17).

Lupus patients who develop epilepsy often have higher disease activity at onset, a higher frequency of neuropsychiatric disorders (especially psychosis) (1, 7), as well as anticardiolipin and anti-Smith antibodies (7). One group found that a locus on chromosome 15 was linked with the development of seizures in SLE (18).

Neuropsychiatric features are common in pediatric SLE, with diverse manifestations and a high mortality (19). Seizures occur in 20% of pediatric lupus cases (20), with neuropsychiatric disorders in 35% (19). In a series of 185 pediatric SLE cases, 14 (7.5%) had neuropsychiatric features at presentation. Seizures were the most common neuropsychiatric manifestation, occurring in 84% of cases, stroke in 28%, psychosis in 22%. Seizures were generalized in 80% and recurred in 63%. Compared to patients without neuropsychiatric features, affected patients had higher mean C3/C4 and anticardiolipin antibodies, and a lower percentage of elevated anti-dsDNA antibodies. In one large cohort of children with neuropsychiatric SLE, mortality decreased from 52% between 1985 and 1994 to 28% between 1995 and 2005.

The neuropathology of SLE sheds light on the pathogenesis of seizures and other neurologic symptoms. In a consecutive series of 50 autopsies, there were no cases of active vasculitis and only two with evidence of healed vasculitis. However, more than a third were clinically—and incorrectly—diagnosed with CNS vasculitis (21). Mitral valvulitis was identified in 23 (46%), 9 with cerebral emboli. During the terminal illness, TTP was present in 14 (28%). Since four features of TTP—thrombocytopenic purpura, renal dysfunction, neurologic disorder, and fever—are common in SLE, only microangiopathic hemolytic anemia provided specific value in making the diagnosis. It is critical to review the blood smear in sick SLE patients.

Sjögren's Syndrome

Sjögren's syndrome (SS) is characterized by inflammation and destruction of lacrimal and salivary glands and may be associated with visceral involvement and vasculitis. Approximately 50% of SS patients have an isolated syndrome (primary SS) and another 50% of cases are often associated with other autoimmune disorder in a mixed connective tissue disorder (e.g., SLE, rheumatoid arthritis, scleroderma). Neurologic disorders occur in ~20% to 25%, with equal involvement of the peripheral and central nervous systems. Headache, polyneuropathy, cognitive dysfunction and mood disorder are common (22). Early nervous system involvement as primary presentation might precede the diagnosis of SS

(23). Seizures, partial or generalized, occur in 3% of all SS patients (22), and ~8.5% of those with neurologic involvement (23). The clinical and neuroimaging findings in SS can mimic stroke and multiple sclerosis.

Wegener's Granulomatosis

Wegener's granulomatosis is a necrotizing, granulomatous vasculitis primarily involving the lungs and kidneys. The vasculitis affects medium and small arteries. The classical antineutrophil cytoplasmic antibody (c-ANCA) is often positive in necrotizing vasculitides, including Wegener's. Peripheral and central neurologic involvement occurs in one third of patients (24). Peripheral nervous system disease is much more common than central involvement and is often a result of vasculitis, while CNS disease is often a result of granulomatous involvement. Many patients with CNS disease have granulomas in the ear, nose, or throat and have a refractory course. The reversible posterior leukoencephalopathy syndrome due to hypertension can complicate Wegener's.

As a primary presenting manifestation of Wegener's granulomatosis, seizures are rare (25), occurring in ~10% of patients with the neurological involvement (24). Seizures can be tonic-clonic, partial, or myoclonic.

Sarcoidosis

Sarcoidosis is a multiorgan noncaseating granulomatous disorder associated with oligoclonal CD4(+) T cell infiltrates and immune complexes. Neuropathological involvement is identified in 10% to 15% but is often asymptomatic (26). Neurological symptoms occur in ~5% (27), often within 2 years of presentation. Isolated neurologic manifestations are the primary presentation in approximately 50% of neurosarcoidosis (28). Blood and CSF ACE levels are variable in neurosarcoid and cannot be used to exclude the disorder (29). Two percent of all sarcoid cases have isolated nervous system disease involvement.

The differential diagnosis of neurosarcoidosis includes multiple sclerosis, Sjögren's syndrome, acute disseminated encephalomyelitis, infection, tumor (e.g., lymphoma), and vasculitis. Cranial neuropathy, often reflecting basal leptomeningeal involvement, occurs in 80% and is a presenting feature in 50% of patients with neurosarcoidosis. Spread to the parenchyma may be via Virchow–Robin spaces (29). Brain T2-hyperintense lesions that enhance respond better to steroids than enhancing T2-hypointense and nonenhancing lesions (30). Tonic-clonic seizures are most common, but complex partial and myoclonic seizures are also described (27). Seizures occur more frequently in children (35%) than in adults (10%) with neurosarcoidosis (31–33). Seizures often mark severe, relapsing, and progressing disease (34). Seizures are more likely to respond when diagnosed early. However, if the granulomatous inflammation is not controlled, seizures may be refractory to AEDs (34). Although the inflammation is often controlled with corticosteroids, refractory cases often require other immunomodulatory therapies (e.g., anti-TNF-alpha antibodies). Epilepsy surgery can be effective in selected cases (36).

Celiac Disease

Celiac disease is an increasingly recognized autoimmune disorder of the small intestine provoked by exposure to gliadin, a

**Table 2. Seizures, Epilepsy and Other Neurological Disorders Associated with Systemic Autoimmune Disorders**

Systemic Autoimmune Disorder	Frequency of Seizures	Common Seizure Types	Other Neurological and Neuropsychiatric Disorders	Frequency of Neurological Involvement
Systemic Lupus Erythematosus (SLE)	7–40%	Generalized tonic–clonic (most common); complex partial; simple partial; myoclonic	Depression and psychosis; encephalopathy; cognitive dysfunction; headaches; stroke; posterior reversible encephalopathy syndrome; papilledema; pseudotumor cerebri; movement disorder (chorea); myelitis; peripheral neuropathy	30–50%
Sjögren's Syndrome (SS)	3% of all SS cases; 8.5% of cases with neurological involvement	Generalized tonic–clonic; complex partial	Headache; cognitive dysfunction; mood disorder; peripheral polyneuropathy	25%
Wegener's Granulomatosis	3% of all cases; 10% of cases with neurological involvement	Generalized tonic–clonic; complex partial; myoclonic	Peripheral neuropathy (mononeuropathy multiplex, distal symmetric polyneuropathy); cranial neuropathy; external ophthalmoparesis; strokes; cerebritis; posterior reversible encephalopathy syndrome	33%
Sarcoidosis	10% (adult neurosarcoidosis) 35% (pediatric neurosarcoidosis)	Generalized tonic–clonic (most common); complex or simple partial myoclonic	Cranial neuropathy; leptomeningeal disease; headache; hydrocephalus; pituitary dysfunction; intraparenchymal lesions; white matter disease; myelopathy; polyneuropathy	5% (clinical studies); 10–15% (neuropathological studies)
Celiac Disease	1–5%?	Generalized tonic–clonic (most common); complex partial; absence	Ataxia; headache; cognitive dysfunction and dementia; mood disorder; vestibular dysfunction; cerebral calcification; peripheral neuropathy	10%?
Crohn's Disease	3.5–5.9%	Generalized tonic–clonic (most common); complex partial	Central demyelination; stroke; peripheral neuropathy; myelitis	19%–67%?
Behçet's Disease	2.2–5% (Middle Eastern and Asian); 27% (UK)	Generalized tonic–clonic (most common); complex partial; simple partial including <i>epilepsia partialis continua</i>	Paranchymatous lesions (meningoencephalitis and brainstem lesions); vascular (thrombosis of large veins and less often arteries, dural venous sinus thrombosis); intracranial hypertension	10% (within 10 years of the onset); 23% (in UK)
Hashimoto's Encephalopathy	66%	Generalized tonic–clonic; complex partial; simple partial including <i>epilepsia partialis continua</i> ; absence status; myoclonic	Encephalopathy; delirium; depression; psychosis; stroke like; dementia; ataxia; chorea; myoclonus; tremor	100%



gluten protein in wheat and other grains (e.g., rye and barley) (36). The disorder has a large genetic component, as most patients have the HLA-DQ2 allele. The inflammatory response injures the villi and can lead to malabsorption and gastrointestinal symptoms. The diagnosis is often made serologically with IgA or IgG anti-gliadin antibodies or autoantibodies such as IgA anti-transglutaminase or anti-endomysial antibodies. In patients with IgA deficiency, IgG anti-endomysial antibodies are often positive. A small intestinal biopsy is the gold standard for diagnosis. The only treatment is a gluten-free diet. Celiac disease can cause neurological disorders in ~10% of cases (37), including ataxia, neuropathy (often carpal tunnel syndrome), vestibular dysfunction, seizures, migraine, and dementia. In cases with biopsy-proven celiac disease, neurological symptoms such as cerebellar ataxia are well documented (38). Compared to controls, children with celiac disease have only a slightly increased frequency of neurological symptoms (e.g., headache, mental retardation, neuropathy, and bipolar disorder), but ataxia is very rare (39). Vitamin E deficiency with improvement in neurological symptoms occurs in a minority of patients (40). Antigliadin antibodies cross react with synapsin (1), providing a potential explanation for neurological symptoms (41). The prevalence of epilepsy in CD ranges from 1% (42) to 5% (43). Seizures are often generalized tonic-clonic, but partial and occasionally absence seizures are also reported (42, 44). A recent epidemiologic study of nearly 29,000 subjects with CD and 143,000 controls found that CD increased by risk of epilepsy by 1.4-fold (47). The etiology of seizures in CD is not entirely known, but gluten neurotoxicity (48), or pyridoxine or folate deficiency (45) are suspected. In isolated patients with celiac disease and epilepsy refractory to AEDs, seizure control has been obtained with a gluten-free diet (48). In one study of 75 children with biopsy-proven celiac disease, 20% showed bilateral T2 white matter lesions, identified on MRI (49). There was no correlation between MRI findings and seizures (6/75; febrile 3, single TCS – 2; absence – 1) (49).

In rare and geographically limited regions (i.e., mainly Italy, Spain, Argentina), celiac disease is associated with occipital calcifications and epilepsy (50). Less than 200 cases of this disorder have been reported; occipital seizures are most common. In many cases, seizures are easily controlled; in others, the epilepsy is drug-resistant, and patients may progress to develop epileptic encephalopathy (50). The effectiveness of a gluten-free diet appears to decline with increasing duration of epilepsy and age. A gluten-free diet can halt the growth of the calcifications. CSF anti-gliadin antibodies may be present; most patients have the typical HLA phenotype. Celiac disease induced folic acid deficiency or environmental factors may interact with genetic susceptibility to cause calcifications (50).

Crohn's Disease

Crohn's disease is a T-cell mediated autoimmune disorder characterized by a chronic granulomatous inflammation of the intestines, although it can affect any portion of the gastrointestinal tract. Neurological and neuropsychiatric manifestations occur in 33% to 67% of Crohn's patients (51, 52). Among Crohn's disease patients, central demyelination occurs in 9% to 10% (53), epilepsy occurs in 3.5% to 5.9%, and stroke occurs in 4.7% to 7.1% but is usually unrelated to seizures (53, 54). Inflamma-

tory, hypercoagulable, and genetic factors were suggested as potential mechanisms for seizures (55). In one epilepsy clinic, 4 out of 150 patients had Crohn's disease (55). One-fifth of epilepsy patients had seizures during a flare of inflammatory bowel disease. One-third of patients had one seizure for which they did not receive AEDs but had a recurrent seizure during an exacerbation. Seizures are usually tonic-clonic but complex partial seizures also occur. MRI studies are usually normal.

Behçet's Disease

Behçet's disease is an autoimmune disorder that usually causes ulcers in mucous membranes (mouth, genitals) and inflammatory eye disease (uveitis, iritis, retinal vasculitis). Symptoms often relapse and remit. The skin, intestines, lungs, musculoskeletal system, and brain can be affected. The disease is most common in the Middle East and Central Asia (the "Silk Road" disease) and is linked to HLA-B51. The main pathological finding in most organs is vasculitis. Neurologic involvement occurs in ~10% of cases, often 1 to 10 years after initial presentation (mean 3–6 years), and affects males ~2.8 times as frequently as females (56–60). Neurologic involvement may coincide with onset of other features but rarely precede them (60). Neurologic involvement is most common between ages 20 to 40 years and usually affects the brain, either parenchymal or nonparenchymal (60). Parenchymal involvement is mainly an immune-mediated meningoencephalitis with brainstem lesions. Nonparenchymal involvement is vascular, with thrombosis of large veins and less often arteries (60) but can also involve the basal ganglia, thalamus, cortex and white matter, spinal cord, or cranial nerves; second, as a consequence of thrombosis within the dural venous sinuses. Half of neuro-Behçet patients have parenchymal lesions, and a third have intracranial hypertension (61).

Seizures and epilepsy occur in 2.2% to 5% of Middle Eastern and Asian cases (62–64), paralleling the low frequency of cortical involvement seen on MRI65 and neuropathology (66). Notably, among patients in the UK who were not ethnically from high-risk regions, neurologic involvement was more common (23%), and seizures were the more common feature of neuro-Behçet's (27%) (67). Similarly, in a Brazilian cohort of 178 Behçet's patients, 40 (22.5%) had neurological involvement, and epilepsy occurred in 7 (17%) of these patients, but only 4% of the overall sample (68). Tonic-clonic seizures predominate, but partial seizures, including *epilepsia partialis continua*, can occur (64, 69, 70). Cortical vein thrombosis is rarely complicated by seizures, possibly because hemorrhage is not typical (60). A recent report suggests that early aggressive treatment with corticosteroids and cytotoxic drugs may substantially improve the outcome of neuro-Behçet's disease (71).

Hashimoto's Encephalopathy

Hashimoto's encephalopathy (HE) is a rare, often underdiagnosed, life-threatening condition characterized by relapsing and remitting encephalopathy, associated with antithyroid antibodies, particularly antithyroid peroxidase. HE is also referred to as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT). Brain and colleagues described the first case of HE in 1966 (72). The prevalence is estimated to be 2.1 out of 100,000 (73). HE affects both



children and adults; the mean age at onset is 44 years (74, 75). The clinical presentations are very heterogeneous and range from acute onset of impairment of consciousness, delirium, seizures, and stroke-like episodes to a more insidious presentation of chronic cognitive decline, dementia and other psychiatric disorders such as agitation, depression, and psychosis (74). Involuntary movements (choreoathetosis, myoclonus, and tremors) and ataxia can occur. Most patients are clinically euthyroid. More recently, new autoantibodies directed against the NH₂-terminal of alpha-enolase (NAE) were discovered in 44% of HE patients (76). The most common presentation of patients with alpha-enolase (NAE) was acute encephalopathy (76).

Seizures affect 66% of HE patients (74, 75, 77). Seizures are either generalized tonic-clonic or complex partial, but simple partial, absence, and myoclonic seizures also occur. Convulsive and non-convulsive status epilepticus (SE) occur rarely in HE patients (78). We found only 7 HE patients with SE: 4 with convulsive SE, 2 with complex partial SE, and 1 each with absence SE and *epilepsia partialis continua*. Recurrent complex partial SE in a young woman with HE two weeks after missing scheduled intravenous immunoglobulin infusion, was also reported (79).

EEG abnormalities are present in 98% of HE patients (74). While EEG abnormalities may be non-specific (74, 80) (focal or diffuse slowing, FIRDA, triphasic waves, and epileptiform discharges), their severity often parallels the severity of encephalopathy. These EEG changes are often reversible with immunotherapy. CSF is reported to be abnormal in 80% cases (81), often with elevated protein (74, 81) and occasional oligoclonal bands and lymphocytic pleocytosis (81). Brain MRI is often normal but may show focal or diffuse atrophy, subcortical white matter changes (74), or edema (79).

The pathophysiology of HE and HE-associated seizures remains uncertain. A direct role of antithyroid antibodies has not been clearly established. These antibodies are often viewed as a biomarker of underlying autoimmunity rather than being pathogenic, despite the detection of these antibodies in the CSF (82). Other postulated mechanisms include circulating immune complexes (82) or neuronal autoantibodies, such as anti-glutamic acid decarboxylase antibodies and autoantibodies targeting a 36kD antigen derived from the cerebral cortex (83). Autoimmune vasculitis was also proposed as a possible etiology of HE, based on the presence of alpha-enolase antibodies that occur with other vasculitic syndromes such as Kawasaki disease (84, 85), the SPECT findings of cerebral hypoperfusion (74) in HE cases, and the limited neuropathological reports for HE (85).

Glucocorticosteroids are the mainstay treatment for HE, and the response is frequently prompt. The dose and duration of steroid treatment are titrated to the clinical response and the risk of relapse rather than to the antithyroid antibodies titers. For steroid-resistant or dependent cases, intravenous immunoglobulins, immunosuppressant drugs, or plasma exchange might be effective. During the relapsing phase of HE, the role of antiepileptic medications alone in controlling seizures is often limited, unless inflammation is controlled. Antithyroid antibodies should be obtained in patients with subacute encephalopathy and unexplained seizures or atypical neuropsychiatric manifestation.

Conclusions

Seizures often complicate systemic autoimmune disorders through a variety of mechanisms. These include primary immunological effects on brain tissue (e.g., antineuronal antibodies, immune complexes, cytokines), effects of vascular disease (e.g., prothrombotic state, anticardiolipin antibody, emboli, vasculitis), metabolic disorders, infection, and complications of therapy. Understanding the pathophysiology of epileptogenesis in these patients may help provide therapeutic targets for specific patients and more broadly, for epilepsy patients without systemic autoimmune disorders. Further, the expanding group of autoimmune encephalitides (e.g., auto-antibodies to the NMDA, GABA-B and AMPA receptors and to LGI1, CASPR2 and Contactin-2, components of the voltage-gated potassium channel complex) may be relevant to some of the epilepsies complicating systemic autoimmune disorders. Supporting this notion, animal models using anti-NMDA receptor antibodies can induce neuropsychiatric changes that mimic cognitive and behavioral disorders in SLE.⁸⁶

References

1. Postal M, Costallat LTL, Appenzeller S. Neuropsychiatric manifestations in systemic lupus erythematosus: Epidemiology, pathophysiology and management. *CNS Drugs* 2011;25:721–736.
2. Appenzeller S, Cendes F, Costallat LT. Epileptic seizures in systemic lupus erythematosus. *Neurology* 2004;63:1808–1812.
3. Andrade RM, Alarcón GS, González LA, Fernández M, Apte M, Vilá LM, McGwin G Jr, Reveille JD; LUMINA Study Group. Seizures in patients with systemic lupus erythematosus: Data from LUMINA, a multiethnic cohort (LUMINA LIV). *Ann Rheum Dis* 2008;67:829–834.
4. Ward MM, Pyun E, Studenski S. Causes of death in systemic lupus erythematosus. Long-term followup of an inception cohort. *Arthritis Rheum* 1995;38:1492–1499.
5. West SG. Neuropsychiatric lupus. *Rheum Dis Clin North Am* 1994;20:129–158.
6. González-Duarte A, Cantú-Brito CG, Ruano-Calderón L, García-Ramos G. Clinical description of seizures in patients with systemic lupus erythematosus. *Eur Neurol* 2008;59:320–323.
7. Mikdashi J, Krumholz A, Handwerker B. Factors at diagnosis predict subsequent occurrence of seizures in systemic lupus erythematosus. *Neurology* 2005;64:2102–2107.
8. Zhang YX, Liu JR, Ding MP, Huang J, Zhang M, Jansen O, Deuschl G, Eschenfelder CC. Reversible posterior encephalopathy syndrome in systemic lupus erythematosus and lupus nephritis. *Intern Med* 2008;47:867–875.
9. Sanna G, Bertolaccini ML, Cuadrado MJ, Laing H, Khamashta MA, Mathieu A, Hughes GR. Neuropsychiatric manifestations in systemic lupus erythematosus: Prevalence and association with antiphospholipid antibodies. *J Rheumatol* 2003;30:985–992.
10. Cimaz R, Meroni PL, Shoenfeld Y. Epilepsy as part of systemic lupus erythematosus and systemic antiphospholipid syndrome (Hughes syndrome). *Lupus* 2006;15:191–197.
11. Ranua J, Luoma K, Peltola J, Haapala AM, Raitanen J, Auvinen A, Isojärvi J. Anticardiolipin and antinuclear antibodies in epilepsy—A population-based cross-sectional study. *Epilepsy Res* 2004;58:13–18.
12. Liimatainen S, Peltola M, Fallah M, Kharazmi E, Haapala AM, Peltola J. The high prevalence of antiphospholipid antibodies in refractory focal epilepsy is related to recurrent seizures. *Eur J Neurol* 2009;16:134–141.



13. Bluestein HG, Williams GW, Steinberg AD. Cerebrospinal fluid antibodies to neuronal cells: Association with neuropsychiatric manifestations of systemic lupus erythematosus. *Am J Med* 1981;70:240–246.
14. Arinuma Y, Yanagida T, Hirohata S. Association of cerebrospinal fluid anti-NR2 glutamate receptor antibodies with diffuse neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum* 2008;58:1130–1135.
15. Kozora E, West SG, Maier SF, Filley CM, Arciniegas DB, Brown M, Miller D, Grimm A, Zhang L. Antibodies against N-methyl-D-aspartate receptors in patients with systemic lupus erythematosus without major neuropsychiatric syndromes. *J Neurol Sci* 2010;295:87–91.
16. Yoshio T, Hirata D, Onda K, Nara H, Minota S. Antiribosomal P protein antibodies in cerebrospinal fluid are associated with neuropsychiatric systemic lupus erythematosus. *J Rheumatol* 2005;32:34–39.
17. Malik S, Bruner GR, Williams-Weese C, Feo L, Scofield RH, Reichlin M, Harley JB, Sawalha AH. Presence of anti-La autoantibody is associated with a lower risk of nephritis and seizures in lupus patients. *Lupus* 2007;16:863–866.
18. Bautista JF, Kelly JA, Harley JB, Gray-McGuire C. Addressing genetic heterogeneity in complex disease: Finding seizure genes in systemic lupus erythematosus. *Epilepsia* 2008;49:527–530.
19. Yu HH, Lee JH, Wang LC, Yang YH, Chiang BL. Neuropsychiatric manifestations in pediatric systemic lupus erythematosus: A 20-year study. *Lupus* 2006;15:651–657.
20. Steinlin MI, Blaser SI, Gilday DL, Eddy AA, Logan WJ, Laxer RM, Silverman ED. Neurologic manifestations of pediatric systemic lupus erythematosus. *Pediatr Neurol* 1995;13:191–197.
21. Devinsky O, Petito CK, Alonso DR. Clinical and neuropathological findings in systemic lupus erythematosus: The role of vasculitis, heart emboli, and thrombotic thrombocytopenic purpura. *Ann Neurol* 1988;23:380–384.
22. Harboe E, Tjensvoll AB, Maroni S, Gøransson LG, Greve OJ, Beyer MK, Herigstad A, Kvaløy JT, Omdal R. Neuropsychiatric syndromes in patients with systemic lupus erythematosus and primary Sjögren syndrome: A comparative population-based study. *Ann Rheum Dis* 2009;68:1541–1546.
23. Delalande S, de Seze J, Fauchais AL, Hachulla E, Stojkovic T, Ferribri D, Dubucquoi S, Pruvot JP, Vermersch P, Hatron PY. Neurologic manifestations in primary Sjögren syndrome: A study of 82 patients. *Medicine* 2004;83:280–291.
24. Nishino H, Rubino FA, DeRemee RA, Swanson JW, Parisi JE. Neurological involvement in Wegener's granulomatosis: An analysis of 324 consecutive patients at the Mayo Clinic. *Ann Neurol* 1993;33:4–9.
25. Moore BM, Rothman SM, Clark HB, Vehe RK, Laguna TA. Epilepsy: An anticipatory presentation of pediatric Wegener's granulomatosis. *Pediatr Neurol* 2010;43:49–52.
26. Ricker W, Clark M. Sarcoidosis: A clinical pathological review of 300 cases. *Am J Clin Pathol* 1949;19:725–749.
27. Delaney P. Neurologic manifestations in sarcoidosis: A review of the literature, with a report of 23 cases. *Ann Intern Med* 1977;87:336–345.
28. Stern BJ, Krumholz A, Johns C, Scott P, Nissim J. Sarcoidosis and its neurological manifestations. *Arch Neurol* 1985;42:909–917.
29. Mirfakhraee M, Crofford MJ, Guinto FC Jr, Nauta HJ, Weedn VW. Virchow-Robin space: A path of spread in neurosarcoidosis. *Radiology* 1986;158:715–720.
30. Shah R, Roberson GH, Curé JK. Correlation of MR imaging findings and clinical manifestations in neurosarcoidosis. *Am J Neuroradiol* 2009;30:953–961.
31. Nowak DA, Widenka DC. Neurosarcoidosis: A review of its intracranial manifestation. *J Neurol* 2001;248:363–372.
32. Joseph FG, Scolding NJ. Neurosarcoidosis: A study of 30 new cases. *J Neurol Neurosurg Psychiatry* 2009;80:297–330.
33. Baumann RJ, Robertson WC Jr. Neurosarcoid presents differently in children than in adults. *Pediatrics* 2003;112:e480–486.
34. Terushkin V, Stern BJ, Judson MA, Hagiwara M, Pramanik B, Sanchez M, Prystowsky S. Neurosarcoidosis: Presentations and management. *Neurologist* 2010;16:2–15.
35. Malmgren K, Lycke J, Engman E, Hedström A, Jönsson L, Rydenhag B, Nordborg C. Successful epilepsy surgery in a patient with neurosarcoidosis. *Epilepsia* 2010;51:1101–1103.
36. McGowan KE, Castiglione DA, Butzner JD. The changing face of childhood celiac disease in North America: Impact of serological testing. *Pediatrics* 2009;124:1572–1578.
37. Cooke WT, Smith WT. Neurological disorders associated with adult coeliac disease. *Brain* 1966;89:683–722.
38. Bürk K, Farecki ML, Lamprecht G, Roth G, Decker P, Weller M, Ramnensee HG, Oertel W. Neurological symptoms in patients with biopsy proven celiac disease. *Mov Disord* 2009;24:2358–2362.
39. Ruggieri M, Incorpora G, Polizzi A, Parano E, Spina M, Pavone P. Low prevalence of neurologic and psychiatric manifestations in children with gluten sensitivity. *J Pediatr* 2008;152:244–249.
40. Freeman HJ. Neurological disorders in adult celiac disease. *Can J Gastroenterol* 2008;22:909–911.
41. Alaadini A, Okamoto H, Briani C, Wollenberg K, Shill HA, Bushara KO, Sander HW, Green PH, Hallett M, Latov N. Immune cross-reactivity in celiac disease: Anti-gliadin antibodies bind to neuronal synapsin I. *J Immunol* 2007;178:6590–6595.
42. Pengiran Tengah DS, Holmes GK, Wills AJ. The prevalence of epilepsy in patients with celiac disease. *Epilepsia* 2004;45:1291–1293.
43. Chapman RW, Laidlow JM, Colin-Jones D, Eade OE, Smith CL. Increased prevalence of epilepsy in coeliac disease. *Br Med J* 1978;2:250–251.
44. Fois A, Vascotto M, Di Bartolo RM, Di Marco V. Celiac disease and epilepsy in pediatric patients. *Childs Nerv Syst* 1994;10:450–454.
45. Ludvigsson JF, Zingone F, Tomson T, Ekbohm A, Ciacci C. Increased risk of epilepsy in biopsy-verified celiac disease: A population-based cohort study. *Neurology* 2012;78:1401–1407.
46. Hadjivassiliou M, Grünewald RA, Davies-Jones GA. Gluten sensitivity as a neurological illness. *J Neurol Neurosurg Psychiatry* 2002;72:560–563.
47. Lea ME, Harbord M, Sage MR. Bilateral occipital calcification associated with celiac disease, folate deficiency, and epilepsy. *Am J Neuroradiol* 1995;16:1498–1500.
48. Canales P, Mery VP, Larrondo FJ, Bravo FL, Godoy J. Epilepsy and celiac disease: Favorable outcome with a gluten-free diet in a patient refractory to antiepileptic drugs. *Neurologist* 2006;12:318–321.
49. Kieslich M, Errázuriz G, Posselt HG, Moeller-Hartmann W, Zanella F, Boehles H. Brain white-matter lesions in celiac disease: A prospective study of 75 diet-treated patients. *Pediatrics* 2001;108:E21.
50. Gobbi G. Coeliac disease, epilepsy, and cerebral calcifications. *Brain Dev* 2005;27:189–200.
51. Lossos A, River Y, Eliakim A, Steiner I. Neurologic aspects of inflammatory bowel disease. *Neurology* 1995;45:416–421.
52. Gondim FA, Brannagan TH, Sander HW, Chin RL, Latov N. Peripheral neuropathy in patients with inflammatory bowel disease. *Brain* 2005;128:867–879.
53. Benavente L, Moris G. Neurologic disorders associated with inflammatory bowel disease. *Eur J Neurol* 2011;18:138–143.
54. Elsehety A, Bertorini TE. Neurologic and neuropsychiatric complications of Crohn's disease. *South Med J* 1997;90:606–610.



55. Hussain MS, Ahmed SN. Epilepsy and Crohn's disease. *Pak J Neurol Sci* 2006;1:132–135.
56. Akman-Demir G, Serdaroglu P, Tasci B; The Neuro-Behçet Study Group. Clinical patterns of neurological involvement in Behçet's disease: Evaluation of 200 patients. *Brain* 1999;122:2171–2182.
57. Kidd D, Steuer A, Denman AM, Rudge P. Neurological complications in Behçet's syndrome. *Brain* 1999;122:2183–2194.
58. Serdaroglu P. Behçet's disease and the nervous system. *J Neurol* 1998;245:197–205.
59. Farah S, Al-Shubaili A, Montaser A. Behçet's syndrome: A report of 41 patients with emphasis on neurological manifestations. *J Neurol Neurosurg Psychiatry* 1998;64:382–384.
60. Al-Araji A, Kidd DP. Neuro-Behçet's disease: Epidemiology, clinical characteristics, and management. *Lancet Neurol* 2009;8:192–204.
61. Al-Araji A, Sharquie K, Al-Rawi Z. Prevalence and patterns of neurological involvement in Behçet's disease: A prospective study from Iraq. *J Neurol Neurosurg Psychiatry* 2003;74:608–613.
62. Al-Fahad SA, Al-Araji AH. Neuro-Behçet's disease in Iraq: A study of 40 patients. *J Neurol Sci* 1999;170:105–111.
63. Siva A, Kantarci OH, Saip S, Altintas A, Hamuryudan V, Islak C, Koçer N, Yazici H. Behçet's disease: Diagnostic and prognostic aspects of neurological involvement. *J Neurol* 2001;248:95–103.
64. Aykutlu E, Baykan B, Serdaroglu P, Gökyigit A, Akman-Demir G. Epileptic seizures in Behçet disease. *Epilepsia* 2002;43:832–835.
65. Akman-Demir G, Bahar S, Coban O, Tasci B, Serdaroglu P. Cranial MRI in Behçet's disease: 134 examinations of 98 patients. *Neuroradiology* 2003;45:851–859.
66. Totsuka S, Hattori T, Yazaki M, Nagao K, Mizushima S. Clinicopathologic studies on neuro-Behçet's disease. *Folia Psychiatr Neurol Jpn* 1985;39:155–166.
67. Joseph FG, Scolding NJ. Neuro-Behçet's disease in Caucasians: A study of 22 patients. *Eur J Neurol* 2007;14:174–180.
68. Dutra LA, Braga-Neto P, Pedroso JL, Guedes Bde V, de Souza LT, Gonçalves CR, de Souza AW, Gabbai AA, Barsottini OG. Epilepsy and Behçet's disease: Cortical and hippocampal involvement in Brazilian patients. *J Neurol Sci* 2011;309:1–4.
69. Aktekin B, Doğan EA, Oğuz Y, Karaali K. Epilepsia partialis continua in a patient with Behçet's disease. *Clin Neurol Neurosurg* 2006;108:392–395.
70. Mead S, Kidd D, Good C, Plant G. Behçet's syndrome may present with partial seizures. *J Neurol Neurosurg Psychiatry* 2000;68:392–393.
71. Shahien R, Bowirrat A. Neuro-Behçet's disease: A report of sixteen patients. *Neuropsychiatr Dis Treat* 2010;6:219–225.
72. Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. *Lancet* 1966;2:512–514.
73. Ferracci F, Bertiato G, Moretto G. Hashimoto's encephalopathy: Epidemiologic data and pathogenetic considerations. *J Neurol Sci* 2004;217:165–168.
74. Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy: Syndrome or myth? *Arch Neurol* 2003;60:164–171.
75. Vasconcellos E, Piña-Garza JE, Fakhoury T, Fenichel GM. Pediatric manifestations of Hashimoto's encephalopathy. *Pediatr Neurol* 1999;20:394–398.
76. Matsunaga A, Yoneda M. Anti-NAE autoantibodies and clinical spectrum in Hashimoto's encephalopathy. *Rinsho Byori* 2009;57:271–278.
77. Arain A, Abou-Khalil B, Moses H. Hashimoto's encephalopathy: Documentation of mesial temporal seizure origin by ictal EEG. *Seizure* 2001;10:438–441.
78. Tsai MH, Lee LH, Chen SD, Lu CH, Chen MT, Chuang YC. Complex partial status epilepticus as a manifestation of Hashimoto's encephalopathy. *Seizure* 2007;16:713–716.
79. Mayer T, Devinsky O. Seizures, cognitive abnormalities, and abnormal magnetic resonance imaging findings in a 19-year-old woman. *Rev Neurol Dis* 2006;3:190,195–197.
80. Henchey R, Cibula J, Helveston W, Malone J, Gilmore RL. Electroencephalographic findings in Hashimoto's encephalopathy. *Neurology* 1995;45:977–981.
81. Kothbauer-Margreiter I, Sturzenegger M, Komor J, Baumgartner R, Hess CW. Encephalopathy associated with Hashimoto thyroiditis: Diagnosis and treatment. *J Neurol* 1996;243:585–593.
82. Ferracci F, Moretto G, Candeago RM, Cimini N, Conte F, Gentile M, Papa N, Carnevale A. Antithyroid antibodies in the CSF: Their role in the pathogenesis of Hashimoto's encephalopathy. *Neurology* 2003;60:712–714.
83. Oide T, Tokuda T, Yazaki M, Watarai M, Mitsuhashi S, Kaneko K, Hashimoto T, Ohara S, Ikeda S. Anti-neuronal autoantibody in Hashimoto's encephalopathy: Neuropathological, immunohistochemical, and biochemical analysis of two patients. *J Neurol Sci* 2004;217:7–12.
84. Chun, JK, Lee TJ, Choi, KM, Lee KH, Kim DS. Elevated anti-alpha-enolase antibody levels in Kawasaki disease. *Scand J Rheumatol* 2008;37:48–52.
85. Schiess N, Pardo CA. Hashimoto's encephalopathy. *Ann NY Acad Sci* 2008;1142:254–265.



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