

Seizures as a Clinical Manifestation in Somatic Autoimmune Disorders

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Abstract

The risk of epileptic seizures seems increased in several systemic autoimmune disorders including systemic lupus erythematosus, type 1 diabetes mellitus, myasthenia gravis, celiac disease, rheumatoid arthritis, Hashimoto's encephalopathy, psoriasis, multiple sclerosis, neuromyelitis optica, and bullous pemphigoid. Immune dysfunction may be partly responsible for this association. Elevated levels of pro-inflammatory cytokines, autoantibodies seen in these autoimmune disorders and antibodies against neuronal antigens may contribute to the etiopathogenesis of seizures and epilepsy associated to immune conditions. Other unknown factors, the effect of different co-morbid conditions of epilepsy as well as shared risk factors such as common etiological factors, environmental triggers, or a common genetic predisposition may also explain the association. We review different autoimmune disorders which may present with co-morbid seizures and discuss possible underlying mechanisms of this co-occurrence focusing on a potential role of immune system dysfunction.

Keywords: comorbidity, epilepsy, cytokines, lupus erythematosus, type 1 diabetes mellitus

1. Introduction

Epilepsy is a common neurological condition with marked psychiatric and systemic comorbidity. Recent evidence suggests that systemic auto-immune disorders are often co-morbid with epilepsy (1). A meta-analysis reported an almost 3-fold increased risk of epilepsy [odds ratio (OR): 2.66, 95% confidence interval (CI): 1.88-3.76] in people with such disorders (2). Acute symptomatic as well as unprovoked seizures have been reported in people with autoimmune disorders. Most seizures reported are either convulsions or focal in nature (3-7).

The underlying mechanisms for a possible association between autoimmune disorders and seizures are still unclear. All conceivable reasons for this association should be considered including causal mechanisms or common risk factors such as shared etiologies, environmental triggers or genetic predisposition which leads to either conditions. Coincidental events cannot be ruled out as people with epilepsy and co-morbid disease are more likely to be referred thus resulting in selection bias. This may affect hospital based cohort studies but the link has also been seen in the general population (8). Artefactual associations are therefore unlikely to explain the full picture.

1.1. Immune system dysfunction as a causality mechanism in epilepsy

Cytokines are a group of small proteins with a major role in cell signaling in the immune system including the central nervous system (CNS) where they can have inflammatory or anti-inflammatory effects. Interferon (IFN) α , β and γ , tumor necrosis factor (TNF) α , and high mobility group box (HMGB)1 are examples of cytokines with pro-inflammatory effects, while fibroblast growth factor (FGF), interleukin (IL)1ra and IL10 are anti-inflammatory. Pro-inflammatory cytokines may modulate neuronal activity by inducing the release of neuroactive molecules such as nitric oxide and prostaglandins, neurotransmitters and neurotrophins or by activating their receptors (9). An immunohistochemical study of resected brain tissues in people with temporal lobe epilepsy showed increased levels of IL1 β compared to control samples (10). It has also been showed that people with various epileptic syndromes including temporal lobe

epilepsy, focal cortical dysplasia, tuberous sclerosis, west syndrome and febrile seizures have higher levels of pro-inflammatory cytokines compared to controls (11, 12).

Effectiveness of anti-inflammatory agents in the treatment of certain pediatric syndromes (infantile spasms and electrical status epilepticus in sleep) also provides circumstantial evidence for a role of inflammation in epileptogenesis (13,14). This may parallel the clinical observation that stress may act as a trigger for seizures (15). Higher cortisol levels seem to relate closely to the incidence of epileptiform discharges in those reporting stress-sensitive seizures (16) and to impact negatively on functional connectivity (17).

Another putative causative mechanism potentially explaining the association relates to the role of antibodies causing encephalitis. Autoimmune epilepsy (AE) refers to an encephalitis caused by autoantibodies to CNS proteins with seizures as one of the core symptoms (18). Neuronal antigens can be intracellular or extracellular (19). Antibodies to intracellular proteins may be generated by an immune response to tumor antigens including CNS proteins. This onconeural association is weaker for antibodies with extracellular targets, although it may vary per antibody type. Antibodies to extracellular neuronal (or glial) surface antigens such as the N-methyl-D-aspartate (NMDAR), and other glutamate receptors, leucine-rich glutamate inactivated 1 (LGI1), contactin-associated protein like 2 (CASPR2), α -methyl-4-isoxazolepropionic acid (AMPA), dipeptidyl-peptidase-like protein 6 (DPPX), and gamma-amino butyric acid (GABA) receptors, are thought to be directly pathogenic in AE. People with these antibodies often improve with immunotherapy (20-22). This contrasts with the variable response to immunotherapy in those with AE and intracellular glutamic acid decarboxylase (GAD) antibodies (23). Some features in different types of AE may facilitate their diagnosis, including faciobrachial dystonic seizures in anti-LGI1 encephalitis, extreme delta brushes in anti-NMDAR encephalitis and multifocal MRI abnormalities in anti-GABA_AR encephalitis (18, 21,24).

In summary, two possible ties between immune dysfunction and epilepsy need consideration: (1) proinflammatory cytokines that may lower seizure threshold and trigger seizures when several factors coincide, (2) antibodies causing encephalitis.

1.2. *Other mechanisms*

The likelihood of seizures due to other common etiological factors also needs consideration. Examples include cardiovascular diseases in people with systemic lupus erythematosus (SLE) and cortical thinning in individuals with multiple sclerosis (MS). The co-occurrence of shared risk factors is also a possibility. Mutations in some genes seem associated with the occurrence of epilepsy and type 1 diabetes mellitus (T1DM) or SLE (25,26). It is also possible that environmental factors or treatment effects may play a role. For example, tobacco smoking increases the risk of various autoimmune disorders and is also more common in epilepsy (27,28). The high prevalence of seizures in people with MS using baclofen is an example of an resultant mechanism (29).

We review different autoimmune disorders which may present with co-morbid seizures and discuss possible underlying mechanisms for this co-occurrence focusing on the potential role of immune system dysfunction.

2. Method

A full search of PUBMED and GOOGLE SCHOLAR up to May 2018 identified any report in which the prevalence of seizures in autoimmune disorders and the possible mechanisms for this co-occurrence was examined. The search and revision was independently conducted by two authors (MA and MS). Only articles in English were reviewed. Search items included “seizure”, “epilep*”, “autoimmune disorders”, “systemic lupus erythematosus”, “type 1 diabetes mellitus”, “myasthenia gravis”, “celiac disease”, “rheumatoid arthritis”, “hashimoto’s encephalopathy”, “psoriasis”, “multiple sclerosis”, “neuromyelitis optica”, and “bullous pemphigoid”. After identification of each relevant

article, the reference list was reviewed for further references. Gray literature was not searched.

3. Systemic lupus erythematosus (SLE)

SLE is a multisystem autoimmune disease affecting mainly connective tissues. CNS or peripheral nervous system involvement is referred to as neuro-psychiatric systemic lupus erythematosus (NPSLE). A meta-analysis suggested that headache (28%); followed by mood disorders (20%), cognitive dysfunction (20%), and seizures (10%) were the commonest neuro-psychiatric symptoms in SLE (30).

Various reports indicated a high prevalence of seizures among people with SLE (prevalence:1.6%-16%) (3,8,31-36); and from studies including controls they seem higher than in the general population (8,33-36). A recent cross sectional study with over 5,000 people with SLE and over 25,000 controls found epilepsy 4.7 times more likely in the SLE cohort (95% CI: 3.9-5.8%) (35). One retrospective cohort study also reported that SLE was associated with 5.6-fold increased risk of epilepsy (36).

Younger age, history of stroke, African descent, history of psychosis, history of malar rash, proteinuria, neuropathy and low levels of complement 3 (C3) seem associated with increased seizure risk (33,35,37-39). Seizures are more likely to happen in the year after the diagnosis of SLE (3,37) and are not explained by infection or antiphospholipid syndrome (3). The presence of a seizure disorder affects the long term prognosis and increases the risk of premature death (40).

Acute seizures may result from associated conditions such as hypertension and posterior reversible encephalopathy (41) or from a direct CNS effect of SLE. People with SLE seem more susceptible to ischemic stroke than controls (risk ratio (RR): 2.1) (42). Vasculopathy ("lupus cerebritis") triggering cortical and subcortical ischemic injury (43) or emboli from comorbid conditions in SLE including valvular heart disease (44), coagulopathy (45) or microembolic signals (46,47), may explain the increased risk for ischemic injury. In a survey on 17 adults with SLE and epilepsy post-stroke epilepsy

appeared to be the most common cause (n=8) followed by mesial temporal sclerosis (n=7) (48).

3.1. Autoantibodies in SLE

A number of autoantibodies have been identified in SLE and some have been suggested as specific marker of NPSLE (49). A recent meta-analysis identified the highest risk factor for anti-neuronal antibodies including anti-NMDA NR2A (OR: 9.5) (50). Risk for NPSLE was even higher if these antibodies were found in the CSF (OR: 37) (50). Other autoantibodies with increased prevalence in NPSLE compared to SLE include antiphospholipid antibodies (APL) (OR: 2.1), lupus anticoagulants (OR: 1.9) and anti-cardiolipin antibodies (OR: 1.6). Smaller sized cohort studies addressed the association between antibodies and seizure disorders in SLE and suggested that anticardiolipin (aCL), APL and anti Sm antibody may increase seizure risk (38,39,51), conversely the presence of anti La antibodies might lower it (52). Large scale studies are warranted to confirm this and to clarify the exact pathomechanism. For example, APL may play a role in the occlusive vasculopathy in NPSLE but might also exert direct modulatory effects on the brain.

4. Type 1 diabetes mellitus (T1DM)

T1DM is an autoimmune condition characterized by pancreatic beta cells impairment. Two large cohorts of people with newly diagnosed T1DM suggest that the risk of developing epilepsy is up to three times greater than in controls (53-55). One population study specifically addressed the association between T1DM and genetic generalised epilepsy (GGE) and reported a fourfold increased risk for young adults with GGE (56). T1DM appears to be particularly increased in those with an intellectual disability (54) and those with epilepsy of unknown cause (7,57). In one cohort, almost all (96%) had focal epilepsy and in most (80%) T1DM preceded seizure onset (7). Hypoglycemia induced seizures appear to be rare and do not seem to explain the whole picture (58).

Once acute symptomatic seizures due to metabolic disturbances (see box) and structural brain lesions are ruled out, neuronal antibodies could be considered in view of the high prevalence of anti-GAD- antibodies in people with T1DM. Anti-GAD-antibodies have been associated with various clinical presentations including stiff person syndrome, autoimmune encephalitis, cerebellar ataxia and temporal lobe epilepsy. The role of GAD in the T1DM and epilepsy association is not fully understood as it is yet unknown how GAD antibodies may cause brain dysfunction. The major site of GAD expression is the CNS. GAD is an intracellular enzyme. GAD-antibodies cannot access the target molecule from CSF or serum (59). It has been postulated, however, that prevention of GABA synthesis in the nerve terminal, reduction of GABA exocytosis and binding to GABA receptors are possible mechanisms by which anti-GAD-antibodies could increase seizure susceptibility (60). GAD antibodies are also very common in T1DM and not all subjects with GAD antibodies are at risk of developing epilepsy. GAD antibodies are found in approximately 85% of people with newly-diagnosed T1DM and in about a third in those with a duration of more than 5 years (61). These figure exceeds the prevalence rates of epilepsy in T1DM. Antibody levels are likely critical as only high GAD levels have been associated with epilepsy (62,63). Case-series in T1DM also reported an association between the GAD epitope pattern and the occurrence of epilepsy (62,63). One recent case-control study indicated that T1DM was more likely in people with epilepsy who were anti-GAD positive compared to those who were negative (64).

5. Myasthenia gravis (MG)

MG is characterized by muscle weakness caused by antibodies directed against proteins of the neuromuscular junction. The association between MG and seizure occurrence is still controversial. One cohort study reported that about 3% of people with MG had epilepsy (65). One population-based study has shown that the risk of epilepsy in MG was 4.9-fold greater than expected (8). MG is associated with high levels of cytokines (66) which could explain the possible association but hypoxia due to respiratory failure causing CNS dysfunction or lesions may also play a role.

6. Celiac disease (CD)

CD is an immune-mediated disease affecting the intestinal villi. CD has a strong genetic component, as most subjects with CD carry the HLA-DQ2 allele (67). Neurological symptoms have been reported in about 10% of people with CD (68). Most hospital based (69-71) as well as population-based studies (8,72,73) indicated that CD is associated with an increased risk for epilepsy with ORs ranging from 1.4 to 4.5. The increased risk for epilepsy was not confirmed in one hospital based study (74).

Neurotoxicity caused by gluten and deficiency of neuroprotective factors such as folate and vitamin B12 are two possible etiologies for seizure occurrence. The co-occurrence of celiac disease (C), epilepsy (E) and calcifications (C) notably of the occipital lobe is a rare condition also known as CEC syndrome (75). Most cases reported are in children in the Mediterranean region with occipital lobe epilepsy (76,77). Little is known yet about the epilepsy characteristics of those presenting with CD and epilepsy without calcifications. Several surveys suggest that the yield of screening for subclinical CD is highest in those with occipital lobe epilepsy (76-78). One study showed that anti-gliadin antibodies can cross-react with an important cytosolic neuronal phosphoprotein, synapsin, which is associated with epilepsy (79). One recent population-based study identified that more severe villous atrophy in CD was associated with a reduced future risk of developing epilepsy (80). Further studies are needed to elucidate the mechanism as to why atrophy protects against epilepsy.

7. Rheumatoid arthritis (RA)

RA is the most common form of autoimmune arthritis manifesting as a chronic inflammatory disease with involvement of joints and synovial membrane. Two population-based studies reported an increased risk of epilepsy in people with RA compared with controls (8,81). The link between RA and epilepsy may be explained by vasculitis (82), CNS infections (83) and the use of methotrexate (84) and sulphasalazine (85). Increased cytokine levels may provide an alternative explanation. A recent population-based study reported a higher risk of early or late childhood epilepsy through

maternal exposure to RA but not paternal exposure (86). The increased risk of epilepsy in children of mothers with clinical RA was higher than in those with maternal preclinical RA (90% vs. 30%). These findings may relate to fetal transmission of cytokines from mother to child but has not been formally assessed.

8. Hashimoto's encephalopathy (HE)

HE is a rare autoimmune encephalitis associated with thyroiditis and somehow controversial. It is characterized by acute-subacute onset of neuropsychiatric manifestations with elevated levels of anti-thyroid antibodies (ATA) including anti-TPO, anti-TG and, sometimes, anti-TSH (87).

Seizures are the most frequent presentation occurring in up to two-third of individuals (88). It has been postulated that ATA may affect the CNS by binding to astrocytes which have also been identified in people with epilepsy without HE. Conversely, some evidence cast doubt on the role of ATA causing HE. For example, reports suggesting that ATA is commonly seen also in people free of neuropsychiatric symptoms (89,90). ATA is not associated with HE severity and it is possible that it may be an autoimmune epiphenomenon without considerable CNS effect (91). Vasculitis or a direct toxic effects of thyrotropin releasing hormone (TRH) may also provide alternative explanations (92). Overall, the exact pathogenesis of HE is unclear but its good response to steroids might support a role of the immune system.

9. Psoriasis

Psoriasis is an immune-mediated disease characterized by scaly skin patches. The association between psoriasis and epilepsy was first suggested by the increased use of anti-seizure medications among people with psoriasis (93). One a recent population-based study reported that the odds of epilepsy is 1.9 fold higher among people with psoriasis compared to controls (8). Epilepsy characteristics have not yet been ascertained. Cytokines play a critical role in the development of psoriasis but evidence is lacking whether these changes predispose to epilepsy (94).

10. Multiple sclerosis (MS)

MS involves chronic and immune-mediated myelin destruction with axonal degeneration and astrogliosis (95). The occurrence of seizures in people with MS has been reported since the earliest definition of MS (96). Up to 2% of all cases develop epilepsy within 10 years after diagnosis of MS (97). An association between MS and epilepsy seems plausible as evidence is accumulating that MS affects the grey matter even in the earliest phase of the disease (98,99). Evidence also suggests enhanced expression of various cytokines in MS lesions which might precipitate seizures (59). Approximately 2-3% of people with MS have epilepsy (100). Higher prevalences (up to 7%) have been reported in those using intrathecal baclofen (29). Studies suggested an increased risk of epilepsy in younger individuals and those with higher disease activity (101-103). People with active epilepsy and relapsing remitting MS (RRMS) are more likely to have secondary progressive MS compared to those with RRMS without epilepsy (102). The occurrence of epilepsy in MS seems to be associated with cortical thinning particularly of the temporal lobe, insular cortex and the cingulate gyrus (104).

10.1. Neuromyelitis optica (NMO)

NMO is an autoimmune CNS disorder sharing many clinical features with MS. Anti-aquaporin 4 (anti-AQP4) antibody seems to be associated with this condition. A small scaled study indicated that epilepsy may be more common in NMO than in MS (105). The presence of epilepsy was associated with poorer prognosis in both groups. As in MS, brain lesions and possibly increased cytokine levels could explain the increased risk for epilepsy. Animal studies indicated that AQP-4 dysfunction decreases seizure threshold (106). Other anti-neuronal autoantibodies might also contribute as indicated by a report of an individual with NMO with status epilepticus and anti-NMDA receptor antibodies (107).

11. Bullous pemphigoid (BP)

BP is an immune-mediated blistering skin disease probably caused by autoantibodies against hemidesmosomal proteins BP antigen 1 (BPAG1) (target: BP230) and BPAG2 (target: BP180 or type XVII collagen). Different neurological disorders, including dementia, stroke, Parkinson's disease and MS (108,109) have been reported as co-morbidities of BP. A higher prevalence of epilepsy was also reported in some studies (108-114).

BPAG1 has isoforms in skin and the CNS. Immunological cross-reaction of these isoforms is strongly suggested as the etiology of this co-occurrence. Pro-inflammatory cytokine levels seem to be increased in BP (115). These findings not only provide more evidence confirming the role of immune system in seizure presentation but also can suggest an immune basis of other neurologic disorders such as dementia.

12. Future Directions

Co-morbidities in epilepsy continue to be under-recognized and are often under-managed (1). Systemic screening for autoimmune disorders and autoantibodies may be beneficial particularly if not other clear cause or risk factor for epilepsy are present. Studies on autoimmune disorders and their association with a high prevalence of seizures may increase our understanding of epileptogenesis. Particularly longitudinal studies are needed to understand whether the seizure or the autoimmune disorder arose first. Cytokines and different autoantibodies may affect the brain and trigger seizures but still little is known about the precise inflammatory cascades and how these pathways can be modulated and in whom. AEDs have failed in the treatment of significant numbers of people with epilepsy. Trying to understand why epilepsy is a co-morbid condition in autoimmune disorders may also help finding new treatments for epilepsy. Future studies are needed to identify subgroups that may benefit from immunotherapy or anti-inflammatory drugs.

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15. Conflict of Interest

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Box: Possible etiologies of seizure occurrence in T1DM

<i>Etiologies</i>	<i>Explanation</i>
Metabolic disturbance	Hypo-calcemia, hypo-magnesemia and hypo- or hyper-glycemia (provoked seizures)
Brain lesions	Due to cerebrovascular disease or metabolic abnormalities.
Genetic factors	Mutations in KCNJ11, POLG1 or MELAS genes are associated with both T1DM and epilepsy
Autoimmunity	Role of GAD antibody

GAD: glutamic acid decarboxylase