The association between systemic autoimmune disorders and epilepsy and its clinical implications

Running Title: Systemic autoimmune disorders and epilepsy

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Abstract

Systemic autoimmune disorders (SADs) happen more frequently in people with epilepsy than in the general population, suggesting shared disease mechanisms. The risk of epilepsy is elevated across the spectrum of SADs but is highest in systemic lupus erythematosus and type 1 diabetes mellitus. Vascular and metabolic factors are the most important mediators between SAD and epilepsy. Systemic immune dysfunction can also affect neuronal excitability, not only through innate immune activation and blood–brain barrier dysfunction in most epilepsies but also adaptive immunity in autoimmune encephalitis. The presence of systemic autoimmune disorders in subjects with acute seizures warrants evaluation for infectious, vascular, toxic and metabolic causes of acute symptomatic seizures, but clinical signs of autoimmune encephalitis should not be missed. Immunosuppressive medications may have antiseizure properties and trigger certain drug interactions with antiseizure treatments. A better understanding of mechanisms underlying the co–existence of epilepsy and systemic autoimmune disorders is needed to guide new antiseizure and antiepileptogenic treatments. This review aims to summarize the epidemiological evidence for systemic autoimmune disorders as comorbidities of epilepsy, explore potential immune and non-immune mechanisms, and provide practical implications on diagnostic and therapeutic approach to epilepsy in those with comorbid systemic autoimmune disorders.

Keywords: Comorbidities, acute symptomatic seizures, seizures, autoimmunity

Abbreviations: antiphospholipid antibodies (APLA), blood-brain-barrier (BBB), central nervous system (CNS), cerebrospinal fluid (CSF), damage associated molecular patterns (DAMPs), diabetic ketoacidosis (DKA), glutamic acid decarboxylase (GAD65), hippocampal sclerosis (HS), inflammatory bowel disease (IBD), leucine–rich glioma–inactivated protein 1 (LGI1), N–

methyl–D–aspartate receptor (NMDAR), posterior reversible encephalopathy syndrome (PRES), steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT), systemic autoimmune disorders (SADs), systemic lupus erythematosus (SLE), tumour necrosis factor (TNF), type 1 diabetes mellitus (T1DM), vagus nerve stimulation (VNS).

Introduction

Comorbidities impose a heavy burden on people with epilepsy and provide opportunities for improving knowledge of disease mechanisms (Keezer *et al.*, 2016b). The investigation of epilepsy comorbidities was designated an epilepsy research benchmark (NINDS, 2014). While psychiatric comorbidities have long been recognised as an important issue, systemic comorbidities have also recently become topical. Several systemic conditions, such as cardio–vascular disease, peptic ulcer, cancer, and arthritis, are more common in people with epilepsy than in the general population (Keezer *et al.*, 2016b). There is increasing evidence that systemic autoimmune disorders (SADs) are associated with chronic epilepsy and not just with acute symptomatic seizures (Amanat *et al.*, 2018).

The epidemiological association between SADs and epilepsy provides an opportunity to improve knowledge about the role of inflammation in epileptogenesis, which has gained increasing attention as a potential target for a disease–modifying therapeutic effect (Devinsky *et al.*, 2013; Vezzani *et al.*, 2019). A plausible epidemiological link recently came from a large cohort study which showed an elevated prevalence of epilepsy amongst people with SADs (OR 3.8; 95% CI 3.6–4.0) (Ong *et al.*, 2014). Other studies have replicated these findings in individual SADs, while some failed to confirm this association (Lossos *et al.*, 1995; Pengiran Tengah *et al.*, 2004; Hanly *et al.*, 2005; O'Connell *et al.*, 2008). Probing epidemiological links carries the potential to improve the understanding of common mechanisms, which could in turn instruct the development of novel treatment approaches to epilepsy.

In this narrative review, recent epidemiological evidence for the association between individual SADs and epilepsy, and its clinical correlates are discussed. We then explore the role of vascular, metabolic, and genetic mediators in the association of epilepsy with individual SADs

and outline evidence for the impact of systemic immunological dysfunction on the brain in human epilepsy and experimental models of SADs. We synthesize these findings into a diagnostic approach for people with SADs presenting with seizures, and outline treatment implications including drug–drug interactions and the impact of treatments of one comorbidity on the other.

Individual SADs and epilepsy

Multiple SADs have been associated with an increased risk of epilepsy, yet the heterogeneity of the comorbid seizure disorders suggests that each entails different potential mechanisms for seizure development. Some systemic autoimmune conditions do not have to date a clear reported association with epilepsy (e.g. scleroderma, giant cell arteritis, and vitiligo). This may stem from a heterogeneous association between epilepsy and only certain SADs, or from the lack of appropriately powered studies to evaluate the association in these conditions. We focus here on those SADs with sufficient reports to support an association but, whenever relevant, highlight conflicting data on the presence of a comorbidity link between SADs and epilepsy. With the exception of diseases affecting only adults such as rheumatoid arthritis, the review encompasses reports from adult and paediatric populations. The conceptual distinction between chronic epilepsy, an enduring predisposition to recurrent unprovoked seizures (Fisher *et al.*, 2005), and acute symptomatic seizures, a mere symptom of an underlying brain insult (Beghi *et al.*, 2010), carries practical implications for the interpretation of reports supporting an association between seizures and SADs. We highlight throughout this review whether reports support an association between an SAD and acute symptomatic seizures, epilepsy, or both. We begin with rheumatological disorders (Table 1), followed by endocrinological disorders (Table 2), then

gastrointestinal disorders (Table 3). In each section, we introduce potential mechanisms of seizures in each disease section, then explore these in further detail in the next section, on comorbidity mechanisms.

Rheumatological disorders

Systemic lupus erythematosus

About one third of people with SLE develop neuropsychiatric lupus, a broadly defined condition in which neurological and psychiatric symptoms co–occur with SLE without other clear precipitants (Lisnevskaia *et al.*, 2014). Neuropsychiatric lupus accounts for a significant portion of the association between seizures and SLE as acute symptomatic seizures occur in up to one fourth of all cases (Table 1) (Magro-Checa *et al.*, 2017). Indeed, seizures in SLE are associated with worse systemic disease severity (Andrade *et al.*, 2008) and central nervous system (CNS) involvement, such as psychiatric comorbidity (Tsai, 2014), prior stroke (Andrade *et al.*, 2008; Tsai, 2014), and antiphospholipid antibodies (APLA) (Islam *et al.*, 2018). In large cohort studies, the majority of seizures occurred in close proximity to the diagnosis of SLE, and often resolved without long–term antiseizure medication, suggesting that the diagnosis of epilepsy did not apply (Hanly *et al.*, 2012a). Subjects with acute symptomatic seizures attributed to SLE are less likely to be followed by recurrent seizures (i.e. epilepsy) than those experiencing unexplained seizures, not attributed to neuropsychiatric lupus (Hanly et al., 2012a). Conversely, mesial temporal epilepsy accounts for above one third of chronic epilepsy in the setting of SLE and may rarely precede the diagnosis of SLE (Toyota *et al.*, 2013).

The association of SLE with seizures may be accounted for by vascular mediators, but also immune mechanisms, through antineuronal antibodies and cross reactivity of systemic

autoantibodies with neural antigens. These mechanisms are discussed below, in the "Comorbidity mechanisms" section.

Rheumatoid arthritis

Two reports from administrative databases suggest an increased risk of epilepsy in people with rheumatoid arthritis (Table 1) (Ong *et al.*, 2014; Chang *et al.*, 2015). The risk appeared to be lower and only marginally increased in the report which adjusted for comorbidities (including vascular risk factors such as hypertension and diabetes), thus indicating that vascular factors are important mediators in the relationship between rheumatoid arthritis and epilepsy (Chang *et al.*, 2015).

Endocrinological disorders

Type 1 diabetes mellitus

Four large scale population–based studies using administrative databases have shown that in those with newly diagnosed T1DM, the risk of developing seizures is up to three times greater than in controls (Table 1) (Ong *et al.*, 2014; Fazeli Farsani *et al.*, 2015; Chou *et al.*, 2016; Dafoulas *et al.*, 2017). The association may be artifactual as the peak age of onset of T1DM and epilepsy coincide (DiMeglio *et al.*, 2018; Thijs *et al.*, 2019). One may also speculate that misdiagnosis of hypoglycaemic events as seizures might have confounded large–scale epidemiological data. It is, however, unlikely that selection bias or misdiagnosis fully explains the association in view of the impact of T1DM on the developing brain (Cameron *et al.*, 2019). The onset of T1DM usually precedes the onset of epilepsy (Mastrangelo *et al.*, 2019), but detailed epilepsy profiles in T1DM are still lacking. A small scale clinical cohort study suggested that T1DM is more frequent in people with refractory epilepsy and epilepsy of unknown cause (Keezer *et al.*, 2015).

Temporal trends indicate that the incidence of epilepsy in T1DM has decreased over the past decades (Sillanpaa *et al.*, 2019). The incidence decline might be explained by improved glycemic control, which would support metabolic derangements as an important driver in the association between epilepsy and T1DM. Glutamic acid decarboxylase 65 (GAD65) antibodies are another attractive shared risk factor for the development of systemic and central nervous system (CNS) disease in T1DM and are discussed in the "Immune mediators" section below.

Hashimoto's thyroiditis

People with Hashimoto's thyroiditis have a higher risk of seizures (Table 1) (Ong *et al.*, 2014), and may present with Hashimoto's encephalopathy, a rare condition associated with an increased risk for seizures and thyroiditis with elevated levels of anti–thyroid antibodies (Laurent *et al.*, 2016). The term "steroid responsive encephalopathy associated with autoimmune thyroiditis" (SREAT) has been suggested to include treatment response as an additional criterion. Acute symptomatic seizures are the most common presenting symptom and occur in 47% of all cases (Laurent *et al.*, 2016). The existing body of knowledge is limited by the lack of standardized diagnostic criteria and precedes the availability of antineuronal antibodies. Current diagnostic criteria require the absence of well characterised antineuronal antibodies in serum and cerebrospinal fluid (CSF) to make a diagnosis of Hashimoto's encephalopathy (Graus *et al.*, 2016). SREAT should, however, be suspected when people with a history of thyroiditis present with seizures and an unexplained encephalopathy. Anti–thyroid peroxidase (TPO) antibodies have been a prerequisite for SREAT (Montagna *et al.*, 2016), but these antibodies lack specificity and occur in up to 13% of the population (Frohlich and Wahl, 2017), thus restricting their clinical use in people without a history of clinical or subclinical thyroid dysfunction (Graus *et al.*, 2016). One small study reported a correlation between high anti-TPO antibodies at the

time of diagnosis and favourable outcome with immune-targeted treatment, suggesting that titres may be helpful in predicting response, although (limited) antineuronal antibody testing was only performed in some of the patients (Litmeier *et al.*, 2016).

Gastrointestinal disorders

Coeliac disease

The strongest evidence of a relationship between coeliac disease and subsequent epilepsy stemmed from a Swedish cohort study of 28,885 subjects with biopsy–verified coeliac disease, showing a 1.42 fold risk of developing epilepsy after a diagnosis of coeliac disease over a mean follow–up of ten years (Ludvigsson *et al.*, 2012b). The risk of comorbid epilepsy appeared to be higher in children (OR 16.7) compared to adults (OR 2.5) with coeliac disease (Table 1) (Ong *et al.*, 2014). Small scale clinical studies suggested that adults with temporal lobe epilepsy with hippocampal sclerosis (HS) and children with occipital epilepsy might have a higher risk of comorbid coeliac disease (Julian *et al.*, 2018). It has been suggested that comorbid coeliac disease can present without gastrointestinal symptoms in up to 40% of people with epilepsy (Julian *et al.*, 2018). This figure, however, was based on studies with positive antibodies only, without a diagnosis confirmed by duodenal biopsy, which may overestimate the diagnosis of comorbid coeliac disease and include the controversial entity of gluten sensitivity (Julian *et al.*, 2018). While one uncontrolled study reported an association between temporal lobe epilepsy and positive coeliac antibodies without confirmatory duodenal biopsy and gastrointestinal symptoms (Peltola *et al.*, 2009), another study failed to show an association with coeliac antibodies in children without gastrointestinal symptoms, when compared to a control population without epilepsy (Giordano *et al.*, 2009). The association of epilepsy with “occult coeliac disease” without confirmatory biopsy findings is therefore unclear.

Gut dysfunction is one potential mediator of seizures in the setting of coeliac disease. Another potential mechanism is the cross reactivity of systemic antibodies (e.g. transglutaminase antibodies) to neural antigens – this is discussed below, in the "Immune mediators" section.

Inflammatory bowel disease

Case–control studies using administrative databases suggested an increased risk of epilepsy in inflammatory bowel disease (IBD) (Table 1) (Virta and Kolho, 2013; Ong *et al.*, 2014). One large case series of people with IBD, however, systematically excluded acute symptomatic seizures, and failed to identify subjects with epilepsy (Lossos *et al.*, 1995). Acute symptomatic seizures due to medication side effects (e.g. calcineurin inhibitor toxicity), metabolic disturbance (e.g. hypomagnesemia) and stroke may account for a significant proportion of seizures associated with IBD. It remains thus uncertain whether IBD is actually associated with an increased risk for epilepsy.

Comorbidity mechanisms

Immune mediators

Innate immune dysfunction exists across the spectrum of human epilepsies and represents an attractive hypothetical link to explain the comorbidity of SADs and epilepsy. Brain specimens of people with focal epilepsy who underwent epilepsy surgery (Vezzani *et al.*, 2019) and of people who died after status epilepticus (Pauletti *et al.*, 2017) exhibit innate immunity activation, similar to that shown in experimental models of acquired epilepsy. Several innate immunity-associated inflammatory mediators promote seizure generation by reducing neuronal excitability threshold (Box 1, Figure 1A) (Vezzani *et al.*, 2019). Specifically, the pro–inflammatory cytokine interleukin (IL)–1β is increased in brains of people with focal cortical dysplasia type 2, temporal lobe epilepsy, and tuberous sclerosis complex (Aronica and Crino, 2014). In those with epilepsy

following traumatic brain injury, serum and CSF IL–1β levels carry a dose–dependent effect on seizure risk (Diamond *et al.*, 2014). Damage associated molecular patterns (DAMPs), involved in the initiation of the innate immunity response, have also been found to be increased in brain tissue from individuals following epilepsy surgery (Zhang *et al.*, 2018). Systemic immune activation during gestation or post–natal development also predisposes animals to develop chronically reduced seizure thresholds, through central cytokines such as IL–1β, tumour necrosis factor (TNF) and IL–6 (Pineda *et al.*, 2013). This finding in animal models has been validated by a report showing that children of mothers but not fathers, with rheumatoid arthritis have an increased risk of childhood epilepsy (Rom *et al.*, 2016). The role of innate immune dysfunction in precipitating seizures has been validated in animal models of SADs. T1DM models exhibit BBB dysfunction and increased blood cytokine levels, which may lower seizure threshold (Yorulmaz *et al.*, 2015). Altered brain excitability and reduced seizure threshold can also be evoked by induction of experimental colitis in mice, through brain inflammatory cytokine production and enhanced BBB permeability to small molecules (Nyuyki and Pittman, 2015).

In specific epilepsy syndromes, there is an additional role for adaptive immunity, as evidenced by the brain infiltration of immune cells, characteristic of encephalitis (Bauer and Bien, 2016) (Figure 2B). For example, adaptive immunity and innate immunity coexist in Rasmussen's encephalitis, in which CD3+/CD8+ T–cells and innate immunity–related inflammatory cytokines (e.g. IL–6 and IL–1β) and DAMPs (e.g. High Mobility Group Box 1 and Toll–like receptors) can be identified (Varadkar *et al.*, 2014). Classical paraneoplastic encephalitis with antibodies against intracellular proteins, such as Hu or CV2, exhibits a similar cytotoxic T-cell response (Dalmau and Graus, 2018). These antibodies are biomarkers for an adaptive immunity response, as the neuronal damage is caused by T–cell inflammation (Dalmau

and Graus, 2018). Conversely, antibodies against extracellular synaptic or membrane proteins, such as N–methyl–D–aspartate receptor (NMDAR) and leucine–rich glioma–inactivated protein 1 (LGI1), have direct functional effects (Ohkawa *et al.*, 2013; Planaguma *et al.*, 2016). Biopsies in autoimmune encephalitis usually show only mild to moderate lymphocyte infiltration or complement deposition (Bauer and Bien, 2016). In anti–LGI1 encephalitis, some T–cell activation is also observed (Bauer and Bien, 2016), as well as progressive atrophy, indicating neuronal damage by non–IgG4–mediated pathways (Arino *et al.*, 2016; Thompson *et al.*, 2018).

While antibody–mediated encephalitis manifests with acute symptomatic seizures (Bien and Holtkamp, 2017), the prevalence of antineuronal antibodies in people with chronic epilepsy is less clear, as the proportion of those with positive antibodies ranged from three to 20% (Brenner *et al.*, 2013; Borusiak *et al.*, 2016; Wright *et al.*, 2016; Dubey *et al.*, 2017; Nobrega-Jr *et al.*, 2018; de Bruijn *et al.*, 2019a). Antibody positivity also occurs in up to one third of people in status epilepticus of unknown cause (Gaspard *et al.*, 2015). The interpretation of these studies is challenging due to the variability in inclusion criteria, such as the lack of explicit exclusion of people with overt autoimmune encephalitis phenotype who may in fact have acute symptomatic seizures rather than epilepsy, and lack of rigorous antibody testing methodology (Leypoldt *et al.*, 2017). A personal history of SAD was described in about half of a small cohort with autoimmune encephalitis and seizures (Quek *et al.*, 2012). In a chronic epilepsy cohort systematically tested for antineuronal antibodies, about half of antibody positive people had a comorbid SAD, compared to about 9% of those who were antibody negative. In this cohort, of the nine antibody positive epilepsy patients who also had an SAD, eight carried GAD65 antibodies, while another had a cell surface antibody(de Bruijn *et al.*, 2019a). If a true association between epilepsy and antineuronal antibodies in the context of SADs exists, a pure

immune mechanism may not only precipitate seizures but also cause brain lesions, such as hippocampal sclerosis (Carreno et al., 2017; Finke et al., 2017; Miller et al., 2017), which may in turn be a substrate of ongoing seizures. Immune and structural causes of epilepsy may therefore coexist in subjects with antineuronal antibodies and recurrent seizures.

Nevertheless, the association between antineuronal antibodies and epilepsy in people with SADs has been examined in the setting of a number of SADs, including T1DM and SLE. The common association between T1DM, other SADs, and autoimmune encephalitis, with GAD65 antibodies (Muñoz-Lopetegi *et al.*, 2020) suggests a possible role for autoimmunity in mediating this comorbidity, but there are numerous caveats to this hypothesis. Firstly, approximately 85% of people with newly–diagnosed T1DM and about a third of those with a duration of more than five years have GAD65 antibodies, which far exceeds the prevalence of epilepsy (DiMeglio *et al.*, 2018). Secondly, only very high titre antibodies in serum are associated with neurological dysfunction, including epilepsy (Ganelin-Cohen *et al.*, 2016). As most clinical laboratories perform GAD65 antibodies for T1DM and do not necessarily test samples at a dilution suitable to accurately determine GAD65 antibody titers, particular caution needs to be taken in the interpretation of those results. Thirdly, the response to immunotherapy in people with serological GAD65 antibodies and neurological disease is variable and often poor (Malter *et al.*, 2015). Fourthly, serum–CSF pairs are critical in GAD65 encephalitis (Bien and Holtkamp, 2017). It is possible that in some cases serum antibodies enter the brain compartment by diffusion and thus cause disease, but most studies show intrathecal synthesis of the antibodies in people with CNS disease (Gresa-Arribas *et al.*, 2015). Lastly, it is still unknown how GAD65 antibodies may cause epilepsy. Some experimental models have supported a pathogenic role for GAD65 antibodies, which when directly administered lead to cerebellar neuronal loss (Mitoma

et al., 2017). Direct administration of GAD65 antibodies to hippocampal slices did not, however, lead to neurophysiological changes, thus questioning their pathophysiological relevance to GAD65–antibody associated epilepsy (Hackert *et al.*, 2016).

Antineuronal antibodies have also been assessed in the setting of SLE. One tenth of a highly selected small cohort of people with epilepsy and SLE were reported to harbour antineuronal antibodies to known antigens in serum, with a larger proportion also carrying antibodies to unknown neuropil antigens, which are of unclear clinical significance (Karaaslan *et al.*, 2017).

Cross–reactivity between neural antigens and systemic antibodies found across SADs may be another mediator of epilepsy in SADs. For example, anti–transglutaminase antibodies seen in people in coeliac disease cross–react with neural antigens in the cerebellum and brainstem and can induce cerebellar dysfunction in animal models (Boscolo *et al.*, 2010). These findings have yet to be reproduced in experimental models relevant to epilepsy. Cross–reactivity between systemic antibodies and neural antigens was also demonstrated in the setting of SLE. Anti–double stranded DNA cross–reacts with the extracellular domain of NR2 subunits of the NMDA receptor, and NR2 antibodies lead to an inflammatory cascade and apoptosis in animal models (DeGiorgio *et al.*, 2001). The association between NR2 antibodies and neuropsychiatric lupus was replicated in one (Yang *et al.*, 2017) but not in another study of people with SLE, perhaps owing to limited specificity with the use of ELISAs (Hanly *et al.*, 2012a). Lastly, systemic antibodies (e.g. antiphospholipid antibodies) may have direct effects on cytokine production and neuronal excitability (Fleetwood *et al.*, 2018).

Non-immune mediators

Vascular disease may be an epilepsy mediator in the setting of IBD, T1DM, SLE and rheumatoid arthritis and lead to focal epilepsy. For instance, vascular comorbidities increase the risk of seizures in those with rheumatoid arthritis (Chang *et al.*, 2015). Cerebrovascular disease is also more frequent in T1DM (de Ferranti *et al.*, 2014) and IBD (Kohoutova *et al.*, 2015) than in the general population, but its relationship with epilepsy has not been assessed. Cerebral thrombosis may also mediate the development of epilepsy in SLE through the effects of APLA antibodies (e.g. anticardiolipin, lupus anticoagulant, beta-2 glycoprotein) on the coagulation cascade, leading to ischemic brain insults (Fleetwood *et al.*, 2018). Vasculitis is another rare but treatable complication of SADs, such as SLE, and can lead to cerebral ischemia (Barile-Fabris *et al.*, 2014). Ischemia is known to induce epileptogenesis in animal models, and depending on the nature of the underlying cerebrovascular disease, 3 to 30% of people who suffer a stroke will go on to develop epilepsy (Pitkanen *et al.*, 2016). Whether the risk for post stroke epilepsy is increased in people with SADs is currently unknown.

Another potential mediator of epilepsy is neuronal injury caused by metabolic disturbance in the context of T1DM. Indeed, hyperglycaemia, diabetic ketoacidosis and recurrent hypoglycaemia have all been associated with brain volume loss and cognitive impairment (Cameron *et al.*, 2019). Diabetic ketoacidosis (DKA) has also been linked to a higher risk of epilepsy (Mastrangelo *et al.*, 2019) and has been associated with morphologic and functional brain changes (Cameron *et al.*, 2014). Diffusion-weighted imaging have suggested a role for abnormal cerebral perfusion in animal models of DKA (Glaser *et al.*, 2012) and hypoglycaemia (Tong *et al.*, 2019) in precipitating brain injury. Permanent injury of the CA1, subiculum and dentate gyrus of the hippocampus have been hypothesized to correlate with reduced

neurogenesis, due to progenitor cell loss in the dentate gyrus in animal models of hypoglycaemia (Suh *et al.*, 2005).

Gut dysfunction may play a role in mediating seizures through nutrient deficiency or microbiome alterations in the setting of autoimmune gastrointestinal disorders. Specific nutrient deficiencies which could lead to seizures include vitamin B6 and folate deficiency. Outside the realm of genetically determined pyridoxine-dependent seizures presenting in infancy, vitamin B6 deficiency related acute symptomatic seizures have been reported in pregnancy (Schulze-Bonhage *et al.*, 2004) and in adults with alcohol dependence, with improvement after B6 supplementation (Gerlach *et al.*, 2011). Reports of acquired folate deficiency related seizures improving with folate supplementation are still lacking. The rare radiologic syndrome of cerebral occipital calcifications and epilepsy seen among people with coeliac disease in the Mediterranean basin (Gobbi *et al.*, 1992; Julian *et al.*, 2018) closely resembles that of cerebral folate deficiency, which raises the possibility of folate malabsorption as a mediator of brain calcifications in coeliac disease (Masingue *et al.*, 2019). The role of nutrient deficiency in mediating seizures was, however, challenged by the finding that persistent villous atrophy in coeliac disease correlates with a reduced epilepsy risk, the opposite of what might be expected if nutrient deficiency was a driver in the development of epilepsy (Kurien *et al.*, 2018). Alterations in the gut microbiome are common in coeliac disease and is an unexplored avenue of research which may explain the relationship between coeliac disease and epilepsy (Lebwohl *et al.*, 2018).

Lastly, genetic factors may be a shared disease mechanism between SADs and epilepsy. A recent genome–wide linkage analysis suggested common genetic polymorphisms between SLE and epilepsy (ILAE Consortium on Complex Epilepsies, 2018). HLA haplotypes (DQ2) may also be common to both diseases, for example in the case of mesial temporal epilepsy and

coeliac disease (Lebwohl *et al.*, 2018). Shared genetic risk factors in T1DM have largely been anecdotal and restricted to families with epilepsy and neonatal diabetes mellitus carrying certain gene mutations (Poulton *et al.*, 2011; Duong *et al.*, 2012). Shared HLA profiles might also explain the association between seizures and SADs as distinct haplotypes have been reported in some syndromes causing autoimmune encephalitis and epilepsy (Kim *et al.*, 2017b; van Sonderen *et al.*, 2017; Binks *et al.*, 2018; Mueller *et al.*, 2018). So far there is no evidence, however, that the haplotypes associated with autoimmune encephalitis also increase the risk for SAD.

Relevance and implications

Diagnostic approach to seizures

Individuals with a seizure disorder and comorbid SAD should be evaluated in the usual manner, (Thijs *et al.*, 2019) with the following additional considerations tailored to specific SADs. In all cases reversible symptomatic causes such as electrolyte disturbance (e.g. IBD or SLE with renal involvement), hypoglycaemia (e.g. T1DM) or posterior reversible encephalopathy syndrome (PRES) (e.g. due to renal disease or immunosuppressive medications) should be evaluated. Encephalopathy and infectious symptoms, such as fever and meningism, should trigger rapid investigations to rule out opportunistic CNS infections. Immunosuppressed people may not exhibit a typical infectious response, such that isolated encephalopathy may be sufficient to warrant a lumbar puncture even in the absence of fever, after a space–occupying lesion has been ruled out through urgent imaging (Sonneville *et al.*, 2017). In the setting of IBD, SLE, or antiphospholipid antibody syndrome, cerebral venous and arterial thromboembolism

should be ruled out, especially in the setting of focal neurological symptoms and sudden headache.

Identification of a vascular lesion on MRI may trigger tailored investigations for modifiable vascular risk factors. For example, post–stroke epilepsy in an individual with SLE should prompt investigations for underlying antiphospholipid syndrome, including lupus anticoagulant, anticardiolipin, and beta-2 glycoprotein 1 antibodies, to initiate appropriate secondary stroke prevention (Lisnevskaia *et al.*, 2014). The diagnosis of antiphospholipid antibody syndrome rests on a combination of clinical features and supportive antibody results, reviewed elsewhere (Miyakis *et al.*, 2006). In people with T1DM and epilepsy, timely glucose measurements in association with seizure-like events are important to determine whether seizures in them are related to hypoglycaemia, as these events are clinically indistinguishable from unprovoked epileptic seizures (Frier, 2014).

In those with SAD and focal epilepsy of unknown cause, we also recommend considering an underlying autoimmune cause, although more clinical data are needed (Quek *et al.*, 2012). Features of autoimmune encephalitis include cognitive dysfunction, psychiatric symptoms and MRI features of encephalitis (Graus *et al.*, 2016). Epilepsy characteristics such as frequent seizures (Gillinder *et al.*, 2017; Vogrig *et al.*, 2019), anti–seizure medication resistance (Dubey *et al.*, 2017; Vogrig *et al.*, 2019), and autonomic (Baysal-Kirac *et al.*, 2016) or perisylvian (Gillinder *et al.*, 2017; Steriade *et al.*, 2018) semiology may also provide suspicion for an underlying autoimmune encephalitis, as in the individual described in box 2. Some features may suggest a specific cause, such as faciobrachial dystonic seizures presenting as an early sign of LGI1 encephalitis (Thompson *et al.*, 2018). When such clues are present, antibody tests should be considered. The type and the extent of the tests should depend on the clinical presentation. In

the context of chronic focal epilepsy, GAD65, LGI1, and contactin-associated protein-like 2 are the most frequently associated antibodies, whereas status epilepticus is associated with NMDA–R, GABA–B, and GABA–A (Bien and Holtkamp, 2017; Dalmau and Graus, 2018; Vogrig *et al.*, 2019). The sensitivity of serum versus CSF varies across antibodies. For example, NMDA–receptor encephalitis can be seronegative but CSF positive in 17% of cases (Titulaer *et al.*, 2013a), while serum is more sensitive than CSF in the detection of LGI1 autoantibodies (Gadoth *et al.*, 2017). If antibody tests through clinical laboratories are inconclusive, searching for uncharacterized antibodies (Graus *et al.*, 2016) through research laboratories, and use of FDG–positron emission tomography (PET) (Baumgartner *et al.*, 2013) may be worthwhile in individuals with a clinical profile highly consistent with autoimmune encephalitis.

Screening for SAD

We suggest considering screening for coeliac disease in those with gastrointestinal symptoms and focal epilepsy of unknown cause. Amongst available celiac disease antibodies, transglutaminase antibodies are most sensitive (Lebwohl *et al.*, 2018). If transglutaminase antibodies are weakly positive, follow up testing with endomysial antibodies should be performed as they carry higher specificity (Lebwohl *et al.*, 2018). People with positive antibodies should be referred onto a gastroenterologist for further diagnostic workup and management, as a coeliac disease diagnosis can be made without biopsy if strict clinical (i.e. gastrointestinal symptoms) and serological criteria (i.e. positive transglutaminase antibodies) are met (Lebwohl *et al.*, 2018). Undiagnosed coeliac disease has not been associated with increased morbidity or mortality (Lebwohl *et al.*, 2018), such that false positive antibodies leading to unnecessary biopsies in asymptomatic individuals carries little potential benefit. For those without gastrointestinal symptoms, the evidence is still too weak to support coeliac screening. We

believe that screening of people with epilepsy without gastrointestinal symptoms should be considered in those presenting with epilepsy syndromes with a strong association with coeliac disease, which are occipital calcifications (Arroyo et al., 2002; Gobbi, 2005) or childhood occipital lobe epilepsy of unknown origin (Labate et al., 2001; Dai et al., 2014).

Treatment

Considerations in managing treatment of comorbid SAD and epilepsy include: 1) interactions between immunosuppressants and anti–seizure medications, and 2) potential benefits or risks of immunosuppressants on epilepsy and of epilepsy treatment on SADs.

Drug-drug interactions

Enzyme inducing antiseizure medications (e.g. phenytoin, carbamazepine) can reduce the levels of calcineurin inhibitors (e.g. cyclosporine, tacrolimus) and have a bidirectional relationship with glucocorticoids, with mutual induction of metabolism (Asconape, 2018). Valproate may increase the levels of mycophenolate (Asconape, 2018). The high protein–binding properties of cyclosporine can also lead to displacement of other highly protein–bound medications (e.g. valproate, phenytoin), increase in free levels, and clinical toxicity. Risks of hepatotoxicity may also be compounded when multiple medications with hepatotoxic risks are administered in conjunction (e.g. valproate and cyclosporine) (Perucca and Gilliam, 2012). Lastly, while biologics (e.g. TNF blockers) have lower rates of drug–drug interactions than the above immunosuppressive medications, there have been reports of possible effects on cytochrome P450 enzyme activity (Kenny *et al.*, 2013). Judicious medication choice and monitoring blood levels can mitigate risks associated with drug–drug interactions.

Teratogenicity should always be considered in women of childbearing age requiring treatment with antiseizure and immunosuppressive medications, although large scale studies are

needed to determine the teratogenic risks of immunosuppressants and their impact on the known risks of antiseizure medications. Of note, the degree of teratogenicity varies between antiseizure medications, such that the choice of medications with lower rates of teratogenicity (e.g. levetiracetam and lamotrigine (Tomson *et al.*, 2018)) should be considered whenever possible.

Effect of immune treatment on comorbidity

Immunosuppressants may lower the risk of developing epilepsy in people with SAD. The association of hydroxychloroquine (in SLE) (Hanly *et al.*, 2012a) and non–steroidal anti–inflammatory medications (in rheumatoid arthritis) (Ong *et al.*, 2014) with lower risks of seizures may reflect confounding with low disease severity. The association of anti–TNF agents and other biologicals with a lower risk of epilepsy among some people with SAD may pose stronger evidence for an effect of immunosuppression on epilepsy (Ong *et al.*, 2014). The lower risk may reflect confounding by indication, since TNF agents are generally used in SADs associated with lower risks of epilepsy (e.g. IBD) (Ong *et al.*, 2014). The lack of detailed datasets limits the conclusions that can be drawn from this administrative database study and the ability to address potential confounders (Ong *et al.*, 2014). Specific SAD treatments may also have effects on epilepsy. For example, a gluten–free diet might lead to improvement in seizure control, as suggested by uncontrolled, unblinded studies in coeliac disease and epilepsy (Julian et al., 2018), and can lead to lowered coeliac antibodies (Lebwohl et al., 2018). A correlation between antibody levels and seizure improvement has, however, not been ascertained in those with epilepsy and coeliac disease.

Conversely, a few epilepsy treatments may hypothetically benefit people with SAD. There is some evidence to support a systemic and central anti–inflammatory effect of vagus nerve stimulation (VNS) (Meneses *et al.*, 2016; Zila *et al.*, 2017). Preliminary data suggested an

improvement in the inflammatory profile and disease severity following VNS treatment in people with rheumatoid arthritis or Crohn's disease (Bonaz *et al.*, 2017).

Immunosuppression in acute symptomatic seizures secondary to autoimmune encephalitis

While evidence is lacking on treatment of epilepsy in the setting of SAD as a whole, immunosuppressants are often effective in controlling seizures in people with seizures and antineuronal antibodies (Thompson *et al.*, 2018; de Bruijn *et al.*, 2019b; Vogrig *et al.*, 2019). Immunosuppressants are generally initiated with one of the following first–line agents: glucocorticoids, intravenous immunoglobulins and plasmapheresis (Bien and Holtkamp, 2017; Vogrig *et al.*, 2019). If a response is seen or if a relapse occurs after withdrawal of first line immunotherapy, maintenance immunosuppression with mycophenolate mofetil or azathioprine may be initiated (Bhatia and Schmitt, 2018). In cases of seizures with definite autoimmune encephalitis without response to first line immunotherapy, second line immunotherapy with rituximab or cyclophosphamide should be considered, in view of the improved outcomes noted in anti–NMDA–receptor encephalitis (Titulaer *et al.*, 2013a), and autoimmune limbic encephalitis with and without antibodies (Lee *et al.*, 2016). The immune therapies outlined above are based on observational data, to the exception of one positive randomized controlled trial demonstrating the effect of IVIg in LGI1 and CASPR2 mediated seizures (Dubey *et al.*, 2020).

A delay to initiation of immunosuppressive treatment worsens seizure and cognitive outcomes in the setting of LGI1 antibody associated faciobrachial dystonic seizures (Thompson *et al.*, 2018) and anti–NMDA receptor encephalitis (Titulaer *et al.*, 2013b; Balu *et al.*, 2019). A robust response to steroids may support the diagnosis of SREAT (Laurent *et al.*, 2016). Similarly, the use of immunosuppressive drug trials can be used to support an autoimmune cause

of seizures when suspected clinically, although objective outcome measures should be utilized to minimize bias (Toledano *et al.*, 2014). Other immunomodulatory treatments targeting innate immunity may also have a role in the treatment of certain specific epilepsies. The use of IL–1β blockade has also anecdotally been effective in individuals with febrile–infectious related epilepsy syndrome (Kenney-Jung *et al.*, 2016; Dilena *et al.*, 2019; Sa *et al.*, 2019), and in drug–refractory epilepsies associated with inflammatory conditions (DeSena *et al.*, 2018) while TNF or IL-6 blockers benefitted a subset of people with RE in an open label pilot study (Lagarde *et al.*, 2016) or people with new onset refractory status epilepticus (Jun *et al.*, 2018; Cantarín-Extremera *et al.*, 2020), respectively. Anti-inflammatory drugs targeting IL–1β, TNF or IL-6 could be investigated as agents potentially targeting immune mediators of epilepsy in people with comorbid SADs.

Toxicity of SAD and epilepsy therapies

Neurotoxic effects of immunosuppressants are rare – for example, the incidence of PRES in people post transplantation receiving calcineurin inhbitors is estimated to be 0.49% (Bartynski *et al.*, 2008; Chen *et al.*, 2016). Evaluation for PRES with neuroimaging should considered in people with SADs developing seizures in the setting of calcineurin inhibitors (Chen *et al.*, 2016). Conversely, the risk of idiosyncratic side effects from anti–seizure medications may be heightened in people with SADs. For example, the risk of aplastic anaemia with felbamate use increases with a history of SAD (Perucca and Gilliam, 2012). Among people with LGI1 antibody mediated encephalitis, the use of aromatic antiseizure medication has been associated with relatively higher effectivity, but also higher rates of cutaneous drug reactions in multi–ethnic populations (Thompson *et al.*, 2018; de Bruijn *et al.*, 2019b). Lastly, carbamazepine, phenytoin, and phenobarbital are rarely associated with the development of clinical and serological lupus,

and subsequent resolution upon discontinuation of the drug (Perucca and Gilliam, 2012; Alvarez-Lario *et al.*, 2019). Individuals with SAD may also be at higher risk of adverse bone health outcomes with enzyme–inducing antiseizure medications, due to concurrent treatment with glucocorticoids (Frenkel *et al.*, 2015). Glucocorticoids may also increase psychiatric comorbidities, which are common in people with epilepsy (Jette *et al.*, 2017).

Conclusions and future directions

Seizures and epilepsy occur more frequently in people with SAD than in the general population (Ong *et al.*, 2014). The risk of epilepsy seems elevated across the spectrum of SADs but is highest in those with systemic lupus erythematosus and type 1 diabetes mellitus (Ong *et al.*, 2014). The relationship between epilepsy and SAD is complex and probably multifactorial. The occurrence of acute symptomatic seizures complicates this association and may occur due to neurotoxic effects of immunosuppressants (Chen *et al.*, 2016), acute vascular insults associated with an SAD (Kohoutova *et al.*, 2015; Fleetwood *et al.*, 2018), or metabolic abnormalities (Frier, 2014; Mastrangelo *et al.*, 2019). Seizures may result from structural brain injury due to metabolic (ketoacidosis or recurrent hypoglycaemia in T1DM) (Mastrangelo *et al.*, 2019) or vascular mediators (e.g. stroke in IBD, SLE, T1DM, rheumatoid arthritis), or inflammatory mechanisms (de Ferranti *et al.*, 2014; Chang *et al.*, 2015; Kohoutova *et al.*, 2015; Fleetwood *et al.*, 2018; Vezzani *et al.*, 2019). Shared genetic risk factors may confound the association between SAD and epilepsy (ILAE Consortium on Complex Epilepsies, 2018) but are still largely unknown. In the absence of vascular, toxic, genetic and metabolic mediators of seizures, central effects of systemic immunological dysfunction may play a role. Neuroinflammation is a hallmark of epileptogenesis and may be triggered not only by neuronal injury but also by

systemic immune activation (box 1). There is experimental evidence of systemic immune activation precipitating neuroinflammation and seizures (Vezzani *et al.*, 2019), but there is still too little human evidence for direct immunological dysfunction resulting in seizures among people with SADs. The role of antineuronal antibodies in the mediation of epilepsy in those with SADs is understudied (Quek *et al.*, 2012). Investigation and management of vascular, metabolic, and toxic causes of seizures in people with epilepsy and SAD should however be complemented by autoimmune investigations in those with a clinical profile consistent with autoimmune encephalitis (Box 2) (Graus *et al.*, 2016). Lastly, epilepsy and SAD treatment may bring specific risks related to medication interactions and disease modification. Conversely, immunosuppressive medications can improve seizure control in the setting of autoimmune encephalitis (Bien and Holtkamp, 2017; Vogrig *et al.*, 2019) and steroid–responsive encephalopathy with associated thyroiditis (Laurent *et al.*, 2016).

Our review only focused on those SADs with sufficient reports to support an linkage between SADs and epilepsy. Future administrative database studies are needed to clarify whether the association between epilepsy and SAD is found across the full spectrum of SADs including skin autoimmune conditions and neuromuscular conditions that do not directly affect the brain. While administrative studies have been instrumental in demonstrating various associations between epilepsy and SADs, they carry the risk for artifactual comorbidity, classification errors (distinction between acute symptomatic seizures vs. chronic epilepsy) and fail to provide detailed clinical risk profiles (Keezer *et al.*, 2016a). Administrative studies should therefore be complemented by clinical cohort studies to specify which characteristics of people with SAD bring a high susceptibility to seizures and to address the epilepsy characteristics. Conversely, the role of screening for occult SAD, particularly coeliac disease in people with epilepsy, should be

clarified. Large, longitudinal cohort studies are needed to determine whether epilepsy or autoimmune disorders arise first. Clinical studies are critically needed to define risk profiles and screening strategies but also to explore the mechanisms of the association between SAD and epilepsy, by assessing immunologic mediators including cytokines and antineuronal antibodies. These studies should also pay special attention to the specific possible mediators for each SAD. Unravelling the complex association between SAD and epilepsy may have potentially important treatment implications as this could support the investigation of targeted treatments (e.g. immunosuppressants, ketogenic diet to alter the gut microbiome (Olson *et al.*, 2018)). A better understanding of the mechanisms underlying the co–existence of epilepsy and individual SADs is a critical next step to guide new antiseizure and anti–epileptogenic treatments.

Contributors

RDT and JWS conceptualised the review which was then designed by CS and RDT. CS carried out searches and drafted the section on non-immune mediators, gastrointestinal and rheumatologic disorders as well as the "Relevance and implications" section. MT drafted the "Immune mediators" section. AV drafted the “Preclinical findings linking neuroinflammation, seizures and epileptogenesis” section. JWS drafted the introduction. RDT drafted the endocrinological disorders section and the conclusion and future directions section. The table was done by CS and RDT. All authors edited and approved the manuscript.

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Competing interests

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Box 1: Preclinical findings linking neuroinflammation, seizures and epileptogenesis

Neuroinflammation can precede and follow seizures, and accompany systemic immune activation. Animal models of acquired epilepsy or some genetic forms (absence and progressive myoclonus epilepsies) and clinical evidence suggest that an inflammatory brain response precedes epilepsy onset, and persists with seizure recurrence (Vezzani *et al.*, 2019). Neuroinflammation may result from the brain's innate immune response to the insults that can cause epilepsy. Recurrent seizures and status epilepticus in animals without pre–existing brain pathology may also induce a lasting neuroinflammatory response, which, in turn, promotes further seizures (Vezzani *et al.*, 2019). Lastly, neuroinflammation may also be a secondary brain response to a primary systemic immune activation of leukocytes, typical of SADs (Vezzani *et al.*, 2019). In the setting of systemic immune activation, neuroinflammation may be initiated by several mechanisms: the release of inflammatory mediators by activated cellular components of the BBB, the infiltration of circulating cytokines or immune cells into the brain parenchyma, and the dysregulation of the hypothalamic–pituitary–adrenal axis (O'Toole *et al.*, 2014). Once initiated, the neuroinflammatory response leads to the release of an array of inflammatory mediators and may lead to brain extravasation of leukocytes. The neuroinflammatory pathways contributing to epileptogenesis involve rapid and long–term neurophysiological changes chiefly mediated by cytokines, chemokines, prostaglandins and DAMPs. The rapid effects cause post–translational changes in neurons, such as phosphorylation of ion channel subunits by activation of protein kinases (Roseti *et al.*, 2015). The long–term effects involve gene transcription and structural changes resulting in aberrant excitatory synaptogenesis (Kim *et al.*, 2017a). Lastly, BBB dysfunction is reciprocally associated with neuroinflammation (Vezzani *et al.*, 2019). BBB dysfunction facilitates the brain extravasation of serum albumin, peripheral immune cells and inflammatory molecules, promoting neuronal

network excitability and the propensity to generate seizures (Vezzani *et al.*, 2019). The neurophysiological effects of neuroinflammation in epilepsy have not been assessed in preclinical SAD models. Figure 1A summarizes the role of neuroinflammation in epileptogenesis.

Box 2: Case study: New onset focal epilepsy in a female with a systemic autoimmune disorder

A woman aged 62 presented with new onset epilepsy. She had a personal and family history of autoimmune thyroiditis and a family history of juvenile rheumatoid arthritis. She presented to a local casualty with two focal to bilateral tonic–clonic seizures. An EEG showed left frontotemporal interictal epileptiform discharges and an MRI was unremarkable. Levetiracetam was initiated. She then started to have daily events consisting of sudden anxiety, rising abdominal sensation followed by laryngeal constriction, consistent with focal aware seizures with temporo–perisylvian semiology. Escalation in levetiracetam dose did not reduce seizure frequency. She also started forgetting recent events and had to set reminders for tasks. Cognitive symptoms had been ascribed to medication side effects. Neurological examination two months after the onset of epilepsy revealed impairment of episodic memory, with an inability to recall four out of five words despite cueing. There were no psychiatric symptoms or personality changes. Given the absence of a cause on MRI, the high seizure frequency despite antiseizure medication, perisylvian semiology, associated cognitive dysfunction, and comorbid SAD, she underwent evaluation for underlying autoimmune encephalitis. Serum testing for antineuronal antibodies revealed positive LGI1 autoantibodies. Cerebrospinal fluid evaluation did not show any abnormalities in cell count, protein or oligoclonal banding, and failed to reveal LGI1 autoantibodies. An underlying malignancy such as thymoma was ruled out by computed tomography (CT) of the chest, abdomen and pelvis. A diagnosis of anti–LGI1 encephalitis was made. She underwent treatment with steroids, in the form of a pulse of intravenous methylprednisolone, followed by high dose oral corticosteroids, with resolution of seizures and improvement in cognitive status.

Box 3: Key points

1. Seizures and epilepsy occur more frequently in people with systemic autoimmune disorders (SADs) than in the general population.
2. Immune dysfunction may mediate the relationship between SADs and epilepsy. In addition, cerebrovascular disease, genetic, metabolic, and gastrointestinal mediators may play a role.
3. Careful evaluation for infectious, vascular and metabolic causes of acute symptomatic seizures should be performed when a subject with SAD presenting with new onset seizures.
4. People with SADs may have a higher risk of autoimmune encephalitis, for which a diagnostic evaluation should be undertaken in the presence of other suggestive clinical features.
5. Immunosuppressive medications can improve seizure control in the setting of autoimmune encephalitis and steroid–responsive encephalopathy with associated thyroiditis.

Figure Legends

Figure 1. Peripheral and central nervous system instigation of neuroinflammation and its role in seizures and epileptogenesis, in the context of innate immunity (A) and cellular immunity (B).

A. The neuroinflammatory response can be initiated by peripheral immune activation and central nervous system (CNS) injury. Peripheral immune dysfunction leads to activated leukocytes and an increase in cytokine production, which may cross a dysfunctional blood-brain-barrier (BBB), which may itself promote neuroinflammation. A dysfunctional hypothalamic-pituitary-adrenal (HPA) axis may also mediate a neuroinflammatory response to peripheral inflammation. Neuronal injury itself may lead to an innate immune response, mediated by pattern recognition receptors (PRRs) and damage-associated molecular patterns (DAMPs), which in turn initiates a neuroinflammatory response through activated microglia and astrocytes. Inflammatory mediators may effect increased neuronal excitability and seizures through rapid onset channelopathic effects, and long term transcriptional changes. Seizures themselves promote further neuroinflammation.
B. Specific neurologic syndromes associated with cellular immunity may also manifest with seizures, often alongside cognitive and psychiatric changes. These syndromes can be associated with antibodies target intracellular antigens (bystanders of a predominantly cytotoxic T cell driven response), or antibodies to extracellular synaptic or membrane antigens (which directly lead to a predominantly B cell driven immune disease).

Abbreviations: BBB – blood brain barrier, DAMPs – damage-associated molecular patterns, HPA – hypothalamic-pituitary-adrenal axis, PRRs – pattern recognition receptors.

Table 1. Rheumatological autoimmune disorders and epilepsy epidemiological studies

Cohort type	Study design	Sample size	Adult vs paediatric	Selection method	Diagnosis ascertainment (epilepsy)	Diagnosis ascertainment (SAD)	Control group	Prevalence, incidence, odds ratio (OR), and/or hazard ratio (HR)	Notes
Rheumatoid arthritis (RA)									
Clinical cohorts	Case series (Hanly *et al.*, 2012b)	53 cases	Adult	Clinic registry	Registry data	Diagnostic criteria	None	0%	
Administrative databases	Nested case control (Ong *et al.*, 2014), retrospective cohort (Chang *et al.*, 2015)	22,980-32,005 cases, total cohort 2,518,034	Adult and paediatric	Nationwide health insurance claims	ICD code and/or prescription of at least 1 AED	ICD code	Subjects without RA within cohort Age, sex, year of RA diagnosis matched	OR 3·5 1·14 (cases) vs 0·90 (controls) per 1,000 person years. HR 1·2	
Systemic lupus erythrematosus (SLE)									
Clinical cohorts	Case series(Herranz *et al.*, 1994; Sanna *et al.*, 2003; Appenzeller *et al.*, 2004; Hanly *et al.*, 2005; Mikdashi *et al.*, 2005; Andrade *et al.*, 2008; Gonzalez-Duarte *et al.*, 2008; Ramsey-Goldman *et al.*, 2008; Harboe *et al.*, 2009; Hanly *et al.*, 2012b; Steup-Beekman *et al.*, 2013)	53-1631 cases	Adult and paediatric	Hospital or clinic database, multicentre registry	Chart review, questionnaire or interview, registry data	ACR diagnostic criteria	None	2·3-9·5% (28% outlier (Steup-Beekman *et al.*, 2013))	Little data on single vs recurrent seizures. Majority of seizures after onset of SLE. Lower prevalence in study excluding structural or metabolic causes (Appenzeller *et al.*, 2004).
Administrative databases	Case control (Watad *et al.*, 2018), nested case-control (Ong *et al.*, 2014), and retrospective cohort (Tsai, 2014)	5,018-32,301 cases, 25,090-129,204 controls	Adult	National database Insurance claims	ICD code and/or prescription of at least 1 AED	ICD code	Age and gender matched controls People without SLE within cohort	4% (cases) vs 0·9% (controls) OR 7·4 9·1 (cases) vs 3·18 (controls) per 10,000 person years HR 2·33	Antiphospholipid syndrome: OR 9·0 (7·7-10·5)
Sjogren's syndrome									
Clinical cohorts	Case series (Harboe *et al.*, 2009; Moreira *et al.*, 2014)	72-93 cases	Adult	Hospital or clinic	Chart review	Diagnostic criteria	None	2·2-3%	Multiple subcortical lesions on MRI in both individuals who developed seizures in a cohort of 93 subjects, prior to onset of sicca (Moreira *et al.*, 2014)
Administrative databases	Nested case control (Ong *et al.*, 2014)	3614 cases, total cohort 2,518,034	Adult and paediatric	Nationwide health insurance claims	ICD code and prescription of at least 1 AED	Not stated	Individuals without Sjogren's within cohort	OR 4·5	
Behcet's disease									

Clinical cohorts	Case series (Dutra *et al.*, 2011; Kutlu *et al.*, 2015)	42-223 cases	Adult and paediatric	Clinic	Chart review	Diagnostic criteria	None	3·9-16·7%	Higher prevalence in people with neuro-Behcet's only.

Table 2. Endocrinological autoimmune disorders and epilepsy epidemiological studies

Cohort type	Study design	Sample size	Adult vs paediatric	Selection method	Diagnosis ascertainment (epilepsy)	Diagnosis ascertainment (SAD)	Control group	Prevalence, incidence, odds ratio (OR), and/or hazard ratio (HR)	Notes
Type 1 diabetes mellitus									
Clinical cohorts	Case series (Keezer *et al.*, 2015), case control,(McCorry *et al.*, 2006) and uncontrolled retrospective cohort (O'Connell *et al.*, 2008; Ramakrishnan and Appleton, 2012; Schober *et al.*, 2012)	245-45,851 cases, 150,000 controls	Adult or paediatric	Clinic, Multicentre database	Chart review Pre-defined epilepsy per ILAE criteria or treatment with 1 AED	Not stated, self-reported diagnosis of hospital records and insulin treatment	Population based prevalence	0.99 % OR 4·4 8·7-21 per 1,000 person years	Active epilepsy vs lifetime diagnosis accounting for some of the variability.
Administrative databases	Nested case-control (Ong *et al.*, 2014), retrospective cohort (Fazeli Farsani *et al.*, 2015; Chou *et al.*, 2016; Dafoulas *et al.*, 2017)	915-43,704 cases, total cohort 2,518,034	Adult and paediatric	Nationwide health insurance claims, pharmacy data, primary care clinics	ICD code and/or prescription of at least 1 - 2 or more AEDs	ICD code or insulin prescription	Subjects without T1DM within cohort Age, gender and county matched subjects	OR 5·2 30-132 (cases) vs 10·4-44 (controls) per 10,000 person years HR 2·0-3·01	Higher risk of subsequent epilepsy in individuals with hypoglycaemic episodes. Higher epilepsy incidence in study without clearly stated criteria for epilepsy diagnosis (Dafoulas *et al.*, 2017).
Hashimoto's thyroiditis									
Administrative databases	Nested case control (Ong *et al.*, 2014)	9830 cases, total cohort 2,518,034	Adult and paediatric	Nationwide health insurance claims	ICD code and prescription of at least 1 AED	ICD code (Ong *et al.*, 2014)	Subjects without Hashimoto's within cohort	OR 2·4	

Table 3. Gastrointestinal autoimmune disorders and epilepsy epidemiological studies

Cohort type	Study design	Sample size	Adult vs paediatric	Selection method	Diagnosis ascertainment (epilepsy)	Diagnosis ascertainment (SAD)	Control group	Prevalence, incidence, odds ratio (OR), and/or hazard ratio (HR)	Notes
Coeliac disease									
Clinical cohorts	Case series (Hanly *et al.*, 1982; Kieslich *et al.*, 2001; Labate *et al.*, 2001; Pengiran Tengah *et al.*, 2004; Vaknin *et al.*, 2004; Bürk *et al.*, 2009) case-control (Chapman, 1978; Cronin *et al.*, 1998; Luostarinen *et al.*, 2001; Zelnik *et al.*, 2004; Ranua *et al.*, 2005; Dalgic *et al.*, 2006; Mavroudi *et al.*, 2007; Ruggieri *et al.*, 2008; Giordano *et al.*, 2009; Peltola *et al.*, 2009; Dai *et al.*, 2014)	48-968 cases 34-584 controls	Adult, paediatric or both	Clinic, local registry, advertisement	Chart review or questionnaire	Biopsy with or without response to diet Antibodies alone	Pregnant women, historical controls age, gender and county matched controls or unmatched healthy controls	1·1-6·3% (cases) vs 0-1·4% (controls)	Outlier studies reporting highest prevalence rates may have suffered from selection bias (Chapman, 1978; Bürk *et al.*, 2009). Coeliac disease predated epilepsy in 2/3 cases (Vaknin *et al.*, 2004). Intracranial calcifications not always associated with a diagnosis of coeliac disease (Luostarinen *et al.*, 2001) but seen in ½ of cases of childhood occipital epilepsy and coeliac disease (Labate *et al.*, 2001).
Administrative databases	Nested case-control (Ong *et al.*, 2014), retrospective cohort (Ludvigsson *et al.*, 2012a)	1885-28,885 cases, vs 143,166-2,516,149 controls	Adult and paediatric	Nationwide health insurance claims and registry	ICD code with prescription of at least 1 AED	Biopsy or ICD code	People without coeliac within cohort Age, sex, year and county matched without biopsy	OR 1·18-4·5 HR 1·42	OR higher among children (OR 16·7) than non-elderly adult (OR 2·5). Study using ICD code for diagnosis of coeliac disease found higher prevalence of epilepsy than study using biopsy result.
Inflammatory bowel disease									
Clinical cohorts	Case series (Lossos *et al.*, 1995; Elsehety and Bertorini, 1997; Oliveira *et al.*, 2008; Benavente and Morís, 2011) case control (Ben-Or *et al.*, 2015)	50-648 cases vs 42 controls	Adult and/or paediatric	Hospital database	Chart review Questionnaire then interview	Pathologically confirmed	Age and gender matched subjects	0-6·1% (cases)	Case series, acute symptomatic causes excluded, did not yield any cases of epilepsy (Lossos *et al.*, 1995)
Administrative databases	Case control (Virta and Kolho, 2013) nested case control (Ong *et al.*, 2014)	596-19,464 cases, total cohort 2,518,034	Adult and paediatric	Nationwide health insurance claims or registry	ICD code and prescription of at least 1 AED	National disability records or ICD code	People without IBD within cohort	Ulcerative colitis: OR 2·5-3·82 Crohn's disease: OR 2-3·1	Prevalence of epilepsy among children markedly higher (OR 8·4 for UC, 6·2 for Crohn's disease). (Ong *et al.*, 2014)

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