Seizures and type 1 diabetes mellitus: current state of knowledge

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Abstract
In this review, we will try to analyze the possible coexistence between epilepsy or seizures and type 1 diabetes mellitus (T1DM), in order to establish if there is more than a casual association, and to investigate possible mechanisms underlying this link. Anti-glutamic acid decarboxylase antibodies (GAD-Abs) have been associated with T1DM and a great number of neurological diseases such as epilepsy. Epilepsy can be a feature of a large variety of autoimmune or inflammatory disorders. GAD-Abs can have a role at the basis of the possible link between epilepsy and T1DM, although their real pathogenetic mechanism in neurological diseases is still unknown. Metabolic conditions such as hypoglycemia and hyperglycemia, common problems in diabetic patients, may be also implicated, even if their underlying mechanism is minimally understood.

Background
Type 1 diabetes mellitus (T1DM) is characterized by a chronic, progressive, and immune-mediated destruction of the insulin-producing beta-cells (β-cells) in the pancreatic islets of Langerhans. It may occur in association with other autoimmune diseases involving other endocrine tissues, such as thyroid and adrenal glands, or non-endocrine tissue, such as gastric and intestine mucosa (1).

Seizures or epilepsy are observed in many autoimmune or inflammatory disorders, and are linked to the primary disease or secondary to the proinflammatory processes. There could be specific pathogenic antibodies that react with neuronal antigens, causing the central nervous system (CNS) disorder in a subpopulation of patients. Their coexistence may indicate a genetic predisposition common to the two disorders or a simple coincidence (2).

Metabolic abnormalities of diabetes mellitus such as hyperglycemia and hypoglycemia could have a damaging effect on the CNS (3), which may cause seizure; indeed, in endocrine disorders, seizures could be the result of neuroinflammation, autoimmunity, or of metabolic disturbances (2).

Epilepsy is one of the most frequent neurological disorders; the estimated prevalence for active epilepsy ranges from 0.2 to 4.1% (4). Different causes of epilepsy are commonly being identified, such as structural, metabolic, or genetic causes; however, the majority of epilepsies have unknown etiology (5). Over the last few years, there has been increasing support for the hypothesis that some forms of epilepsy with unknown etiology may have an autoimmune component. Recently, autoantibodies have been found in many CNS disorders often characterized by recurrent seizures (6).

There is increased interest in a possible link between epilepsy and diabetes mellitus. The two conditions have been observed in individuals more frequently than might be expected by chance (7).

This review discusses current understanding of the possible coexistence between seizures or epilepsy and diabetes mellitus in relation to autoimmunity, electroencephalogram (EEG) abnormalities, and glycemic variations, in order to establish if there is more than a casual association, and to investigate possible mechanisms underlying this link.

Epidemiology
Few epidemiological analyses were performed studying the association between T1DM and epilepsy. There is great interest in the study of McCorry et al. (7), who compared the population prevalence of T1DM in 150,000 subjects 15- to 30-year-olds with a cohort of 518 age-matched patients with idiopathic generalized epilepsies (IGEs), founding a greatly significant surplus of T1DM in the IGE cohort, with an odds ratio of 4.4.

Successively, O’Connell et al. did not confirm these results, observing that type of epilepsy and prevalence...
in children and adolescents with T1DM are similar to those in the general pediatric population. The prevalence of active epilepsy in the pediatric diabetic population (1384 active patients, aged 0–19 years) of the Diabetes Clinic at the Royal Children’s Hospital, Melbourne, Australia was therefore 8.7/1000 or 0.9% (epilepsy in 15 patients) (8).

Mancardi et al. (9) reviewed 249 T1DM patients (145 male; mean age 16.3 ± 0.2 years, mean age at disease onset 7.7 ± 6.9 years) attending the Diabetes Clinic, where a collaborative network provides epidemiologic data by an active surveillance model. Six of 249 T1DM patients showed epilepsy. The high proportion of IGE observed (four of 249, 1.6%) supports the data of McCorry et al. In all patients but one, the epilepsy onset was preceded by T1DM with a mean of 2.8 years. This may reflect different age of onset of the two conditions or alternatively, it could support an autoimmune mechanism starting with T1DM and, then, affecting the CNS (7, 10). On the other hand, it is possible that recurrent episodes of hypoglycemia can result in seizures. In agreement with this hypothesis, Eeg–Olofsson previously demonstrated that in 11% of children with T1DM an increased prevalence of paroxysmal epileptiform activity compared with 2.7% of normal controls, noting that marked generalized paroxysmal slow-wave abnormalities were confined to children with recurrent hypoglycemic seizures history (7, 11, 12).

Epileptic seizures in diabetic patients are mostly reported as focal seizures (13, 14, 15, 16, 17, 18, 19) with or without secondary generalization; epilepsy partialis continua (EPC) (20, 21, 22, 23, 24, 25, 26, 27, 28), occipital seizures (29, 30, 31, 32, 33), and reflex seizures (34, 35, 36) have also been described. However, some cases of generalized epilepsy (childhood absence epilepsy, juvenile absence epilepsy, tonic-clonic seizures on wakening, and juvenile myoclonic epilepsy) associated with T1DM have also been reported (7, 9, 37, 38). From the published cases, it seems that focal seizures are frequently reported as the result of metabolic disturbances, while generalized seizures are mostly linked to autoimmune diseases.

The link between focal seizures and hyperglycemia was first reported in 1965 (14). The phenomenon may not be rare; in a review of 158 cases of non-ketotic hyperglycemia (NKH) 19% had focal motor seizures (15). The focal character of the seizures described during hyperglycemia has been reported consistently over the years (13, 14, 16, 17, 18, 19). In 1997 Whiting et al. reported the development of intractable focal seizures in three teenagers with previously well-controlled epilepsy. T1DM was diagnosed; glucose levels were high in all patients, with mild ketosis and acidosis only in one patient, and there was prompt cessation of seizures after institution of insulin. The authors concluded that hyperglycemia should be considered in children with epilepsy who develop intractable seizures (19).

EPC is an uncommon, localization-related seizure, characterized by simple focal motor seizures with repetitive clonic jerks, detected in many cortical lesions and metabolic disorders as diabetes mellitus (20). EPC was also observed in the pediatric age group, as a rare manifestation of T1DM (26). Olson et al. (28) described a 6-year-old boy who developed EPC 6 months after diagnosis of T1DM. Lately, Baglietto et al. (27) observed a 3-year-old boy who presented EPC 5 months after T1DM onset, resulting in drug-resistant epilepsy with continuous spike-waves during slow sleep and severe behavioral impairment.

Schober et al., in a very recent study, have estimated the prevalence of epilepsy and possible risk factors in children and adolescents with diabetes mellitus, searching for the concomitant diagnosis of epilepsy or epileptic convulsions and for antiepileptic medication; they have conducted an observational cohort study based on the Diabetes Patienten Verlaufsdokumentation database including data from 45 851 patients (52% male) with T1DM, aged 13.9 ± 4.3 years (duration of diabetes mellitus 5.4 ± 4.2 years). Seven hundred and five patients with epilepsy were identified, giving a prevalence of 15.5 of 1000, of which 375 patients treated with antiepileptic therapy and 330 not treated ones. The authors concluded that there is an increased prevalence of epileptic seizures in children and adolescents with diabetes mellitus (39).

The great number of case reports described by international literature increases the enthusiasm for McCorry et al.’s results, supporting the hypothesis that, behind the coexistence of epilepsy and diabetes in the same patient, there is more than a casual association.

Focal neurological deficits associated with hypoglycemia have been frequently observed in diabetic adults, while in children this association was little described. One report presented a series of 19 episodes in seven children with diabetes (40) and another study reported focal motor seizures, followed by ipsilateral hemiparesis associated with hypoglycemia (41).

**Autoimmunity as the possible link between epilepsy and T1DM**

Epileptologists are becoming increasingly interested in autoimmune processes and in the search for pathogenic antibodies (42). In particular, anti-glutamic acid decarboxylase antibodies (GAD-Ab) have been associated with T1DM and a large variety of neurological conditions, including epilepsy (43, 44). GAD-Ab have been detected in 80% of patients with new diagnosis of T1DM, in about 80% of patients with the stiff-man syndrome (SPS) and in some patients with cerebellar ataxia, late-onset autoimmune diabetes mellitus and polyendocrine autoimmunity, palatal myoclonus and epilepsy, and drug-refractory temporal lobe epilepsy (TLE) (44).
GAD catalyzes the conversion of glutamic acid, the main excitatory amino acid in the brain, to the main inhibitory amino acid gamma-aminobutyric acid (GABA) (2, 45). GABA-secreting neurons and pancreatic beta cells (which may also secrete GABA as a paracrine signal molecule) mostly express GAD (37). Neuronal discharges and seizures may be the result of an imbalance between excitation and inhibition caused by inhibition of GAD activity by autoantibodies (45, 46, 47).

The full spectrum of neurological syndromes associated with GAD-Ab is not well established. To clarify these issues, Saiz et al. reviewed the clinical and immunological features of patients in whom high GAD-Ab levels were detected in a reference center for T1DM. High levels of GAD-Ab were found in 61 patients; 36% had SPS, 28% cerebellar ataxia, 18% other neurological disorders, and 18% isolated T1DM. Epilepsy was observed in four (7%) patients. In one of them, GAD-Ab were measured after the recent onset of an isolated downbeat nystagmus, while in the other three patients, GAD-Ab were detected many years after the onset of the epilepsy, at the time of diagnosis of late-onset T1DM (44). The frequency of high GAD-Ab levels in epileptic patients ranges from 0 to 4% (37, 44, 48, 49, 50).

Peltola et al. investigated the prevalence of GAD-Ab in patients with therapy-resistant localization-related epilepsy (n = 51) and generalized epilepsy (n = 49). GAD-Ab were found in eight patients with localization-related epilepsy; high levels of GAD-Ab were observed in two patients, while the remaining six had significantly lower titers, which is a feature of T1DM. The authors concluded that GAD autoimmunity may be associated with refractory localization-related epilepsy (37), although it is important to remember that the majority of epidemiological data suggests that high GAD-Ab levels were found in diabetic patients with IGE. Moreover, there are few studies that detected GAD-Ab in cerebrospinal fluid (CSF). The presence of serum GAD-Ab is not a precise marker of intrathecal production of antibodies in these patients; to analyze this aspect, the evaluation of CSF antibodies is more sensitive. The lack of strict correlation between serum GAD-Ab levels and intrathecal synthesis must be taken into consideration when these immunological data are evaluated.

Several studies confirmed elevated GAD-Ab in patients with refractory focal seizures (27, 28, 51).

In contrast, Kwan et al., measuring serum GAD-Ab in 105 patients with idiopathic or symptomatic epilepsy, did not find any difference in the absolute titer of GAD-Ab between patients with controlled and uncontrolled epilepsy. On the other hand, four uncontrolled epileptic female patients had levels over three times higher than the highest found in the seizure-free group, three of whom were also positive for pancreatic islet cell antibodies (48).

McKnight et al. (49) studied sera obtained from 139 patients and found increased GAD-Ab in five patients (3.6%); all of them had drug-resistant epilepsy, onset in childhood or early teens (<15 years), duration of disease for 3 years or greater, and focal abnormalities on EEG. Very high GAD-Ab levels were found in three patients (2%) and one of these had hypothyroidism and T1DM.

In another study, GAD-Ab were measured in a series of consecutive unselected epileptic patients observed over a 2-year period: 233 patients (121 women, age range: 6–78) were recruited. GAD-Ab were detected in six (2.58%) patients; two had IGE associated with T1DM, and the other four patients suffered from cryptogenic temporal epilepsy and no history or signs of T1DM. The authors confirm that GAD autoimmunity may be associated with some forms of epilepsy, with preferential identification in patients with cryptogenic temporal epilepsy (52).

Liimatainen et al. analyzed GAD-Ab in sera of 253 epileptic patients and 200 control subjects, detecting GAD-Ab in 15 patients (5.9%) and in three control subjects (1.5%) (P = 0.026). Seven patients (2.8%) showed high GAD-Ab titers, six of whom had TLE; low titers were found in all three GAD-Ab-positive control subjects. Intrathecal synthesis of GAD-Ab was observed in two of the five patients with high GAD-Ab titers and available CSF samples; one patient had CSF oligoclonal bands. The prevalence of increased GAD-Ab levels seems to be higher in patients with TLE. The autoimmune origin of the epilepsy is suggested by the immunologic profile of these patients: a positive intrathecal synthesis of GAD-Ab may be an immune response marker (53).

Striano et al. (38) confirmed previous reports, finding the absence of GAD-Ab in isolated IGE and retrospectively identifying two patients with T1DM among their IGE population aged 15 years or older (n = 199) with high levels of GAD-Ab.

In another study, investigators selected serum from a GAD-Ab-positive epileptic patient, a GAD-positive diabetic case, two epileptic GAD-Ab-negative patients, and a normal control and registered post-synaptic inhibitory potentials on hippocampal neurons in culture, before and after the application of diluted sera in a patch-clamp study. The frequency of post-synaptic inhibitory potentials significantly increased after application of GAD-positive epileptic serum, while no effect was observed using negative controls’ sera: this suggests interference with GABA function and with neuronal inhibition, supporting a pathogenetic role of GAD-Ab in the development of epilepsy (47).

There are few evidences on the pathogenetic role of GAD-Ab in neurological diseases. The most important concern is that during GABA exocytosis GAD is never exposed to the outer side of the cell membrane, because it is located in pancreatic beta cells and in neuron cytoplasm. Consequently, it is improbable that GAD-Ab have access from serum and CSF to their target molecule in intact cells, in contrast with the hypothesis...
of in vivo inhibition of GABA synthesis caused by GAD-Ab. On the other hand, antibodies may penetrate cells as often happens with neurons (54). Two mechanisms have been previously suggested for the antibodies-induced suppression of GABA release: reduction of GABA synthesis in the nerve terminal or interference with exocytosis of GABA. Some investigators also assume that GAD-Ab directed to the catalytic site of the molecule may not need to access GAD to display a function because the antibodies could mimic the structure of GABA and cross-react with GABA binding sites accessible on the neuronal surface (54).

Other investigators have demonstrated that circulating antibodies can reach intracellular antigens in two possible ways through the IgG internalization by neurons (55) and through the HSP 70 protein binding, recognized by the immune system making a complex linked to the synaptic vesicle membrane (56). GAD-Ab pathogenicity inside the CNS can be supported by the GAD-Ab intrathecal synthesis, but actually only a few studies have systematically measured the GAD-Ab titer in the CSF of GAD-Ab-positive epileptic patients (37, 46, 52, 53). Intrathecal synthesis of GAD-Ab was calculated in paired serum/CSF samples. Values higher than the IgG index were considered indicators for positive GAD-Ab-specific intrathecal synthesis (44). GAD-Ab may be the biological basis of the association between epilepsy and T1DM (38, 57, 58).

Important antigenic differences between the epitopes recognized by GAD-Ab of diabetic patients and of neurological ones are described by Kim et al. (59), explaining the results' heterogeneity among studies using different GAD-Ab. Low GAD-Ab titers were observed in T1DM patients, while in patients with neurological disorders (cerebellar degeneration or SPS) they may be 25- to 500-fold higher (57, 60).

As epilepsy often afflicts SPS patients (61), GAD-Ab could have a similar pathogenic role to that suggested for SPS. Magnetic resonance spectroscopy (MRS) studies in SPS patients (62) demonstrated a significant GABA level decrease in the motor cortex, suggesting that the imbalance of inhibitory and excitatory neurotransmitters equilibrium (with consequent excitatory neurotransmitters predominance) could be secondary to GAD-Ab presence (46). These findings could extend an evidence of the relationship between GAD autoimmunity and seizures, but the implications of this study must be considered with caution because, although interesting, these are the results of only one study.

To test whether the antibodies were associated with changes in cortical GABA levels, Stagg et al. used MRS in four patients with epilepsy and high serum GAD-Ab levels and 10 healthy controls. Patients had significantly lower GABA concentrations within the cortex compared with the control group. The hypothesis that GAD-Ab are markers of a specific disease process with a role for immune-mediated GABergic dysfunction is supported by the demonstration of an association between high serum GAD-Ab and low cortical GABA levels in patients with epilepsy (45).

Recently, a patient with sudden onset of refractory status epilepticus, in the presence of strong intrathecal GAD-Ab synthesis, was successfully treated with cyclophosphamide (63).

A T-cell-mediated mechanism may be implicated in GAD-Ab-associated neurological disorders, as suggested by the detection of GAD-65 epitopes by peripheral blood T-cells of patients affected by SPS, considering that T1DM with GAD-Ab positivity is a T-cell-mediated disease (54).

A very recent study observed that the deletion of the genes for IA-2 and IA-2β, present in the brain neuroendocrine cells, affected the content and secretion of neurotransmitters and hormones as insulin, FSH, and LH, resulting in a secretion impairment that caused behavioral and learning disturbances, seizures, and reduced life span (64).

Although the real pathogenetic mechanism of GAD-Ab in neurological diseases is still unknown, this extensive analysis of the literature suggests the important role of autoimmunity as the basis of the possible link between epilepsy and T1DM, summarized in the Fig. 1.

Seizures and glycemic variations

Glucose plays a critical role in brain functions because it represents the main source of metabolic energy generation (65). Focal motor epileptic episodes may be associated with hypoglycemia and NKH; however, these do not occur with ketotic hyperglycemia, probably because of the anticonvulsant action of ketosis (41). Most published reports on diabetic hyperglycemia are concerned with non-ketotic hyperosmolar diabetic coma accompanied by severe hyperglycemia, hyperosmolality, and dehydration, with minimal or no ketoacidosis (21, 66), a severe condition which represents one extreme of a biochemical continuum. In practice, actually, diabetics show a spectrum of hyperglycemia and they are often detected before the development of severe hyperosmolality (18). Although occipital focal seizures have also been described (29, 31), the clinical features of focal seizures in NKH are usually those of frontal lobe epilepsy (21). The explanation of this condition by hyperglycemia alone is unsatisfactory, because seizures are rare in diabetic ketoacidosis. It was hypothesized that hyperglycemia leads to a decrease in epileptic seizure threshold by increasing metabolism of GABA and accordingly decreasing the level of GABA, so resulting in a reduction in the seizure threshold (17, 18). Another hypothesis involves decrease of seizure threshold due to metabolic disturbance. Hyperosmolality and dehydration associated with hyperglycemia can be considered to be triggers for EPC or other focal seizures, and may lead
to neurological deficit in some patients (23); in fact, some experimental studies adduced to show that hypertonic solutions will activate existing seizures foci, in particular a potential mechanism is the hyperosmolar irritation of neurons rendered ischemic by an enhanced tendency to vascular disease and by an acute reduction in cerebral blood flow secondary to hyperglycemia and dehydration (41, 67). Focal seizures can be symptomatic of structural lesions within the brain; for this reason other authors (18) suggested that a previously existing cortical lesion of ischemic nature might lead to these seizures after acquiring an epileptogenic characteristic under altered metabolic conditions. Some studies (30, 68) also described several transient changes in magnetic resonance imaging following seizures. These brain parenchymal changes are typically hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. Nevertheless, some patients without evidence of brain damage have been reported (18, 21, 23). In sum, during hyperglycemia, a focal reduction in blood flow may occur with consequent focal seizures; however, there is no constant relationship between blood glucose levels and the frequency or severity of neurological symptoms (41).

Focal epilepsy may be the first symptom of diabetes in some patients and various studies (17, 18) reported cases in which focal seizures can occur in the acute setting of hyperglycemia and can lead to the discovery of diabetes mellitus. While acute hyperglycemia seems to be implicated in the development of frontal lobe epilepsy as EPC (21), prolonged uncontrolled hyperglycemia may be the key to the development of occipital seizures (29), but further studies are needed to clarify how prolonged hyperglycemia contributes to seizures.

As regards ketoacidosis, it has been suggested that ketosis and acidosis have an anticonvulsant effect and therefore a ketogenic diet is thought to be beneficial for epileptic children, although the exact mechanism for
this is still not clearly understood. It has been hypothesized that in this case, intracellular acidosis elevates GABA level by increasing activity of GAD, which leads to a corresponding elevation of seizure threshold (17, 21). According to these hypotheses, the presence of seizures in patients with ketoacidosis may indicate the existence of cerebral lesions (69).

However, a very recent study conducted on T1DM children and adolescents without any underlying neurological disease found an association between epilepsy and diabetic ketoacidosis, observing almost double the risk for diabetic ketoacidosis in patients with epilepsy compared with T1DM alone ones (39).

Hypoglycemia is a common problem in diabetic patients treated with insulin and can induce various neurological disturbances, such as confusion, motor restlessness, hypotonia, and epileptic seizures, which represent a relatively common acute symptom (41, 70).

The association between hypoglycemia and epilepsy or seizures has not yet been fully understood. A significantly low glucose level can alter cortical excitability so determining a disproportion between excitation and inhibition. Indeed, several experimental studies have shown that the loss of high-energy substrates leads to the release of excitatory amino acids that result in hyperexcitability and consequent excitotoxicity (71). These effects may be more pronounced in some brain regions than in others, the temporal lobe and hippocampus appearing to be particularly susceptible (72).

EEG abnormalities and glycemic control

Patients with T1DM can show EEG abnormalities (74, 75, 76, 77). There are conflicting opinions regarding the role of diabetic ketoacidosis (DKA) in the development of seizures; however, the first report of EEG changes in children with DKA or ketosis dates back to 1981 (78). Several studies reported the association between severe hypoglycemia (SH) and EEG abnormalities in diabetic children and adolescents (3, 74, 76, 79, 80). Haumont et al. described one of the first reports of a significant positive correlation between EEG abnormalities and degree of diabetic control, but no definite increase was noted in relation to the duration of diabetes (79, 80). In 1983, 270 juvenile children from the Montreal Children’s Hospital Diabetic Clinic were reviewed. Numbers of epileptiform EEG abnormalities were significantly increased in the initial EEG of diabetic patients who later had a hypoglycemic convulsion (81).

In the same year, Halonen et al. (82) recorded 498 EEGs from 195 diabetic children; the children were divided into stable and labile groups according to diabetes control. The labile children had significantly more abnormal EEGs than the stable children. In 1989, Soltesz & Acsadi (3) described the EEG abnormalities in 70 diabetic children and 70 normal controls. Twenty-six percent had abnormal electroencephalograms, while these abnormalities were found in only 7% of the 70 healthy children; moreover, about 80% of the children with previous SH presented abnormal EEG, compared with only 30% in the non-hypoglycemic group. In another study (75), quantitative EEGs of 44 insulin-dependent diabetic patients were compared with normal controls, and a correlation between high values of HbA1c and decreased relative power of the alpha
Epilepsy can be a feature of diabetic patients. The available evidence suggests that specific pathogenic antibodies can react with neuronal antigens in a subpopulation of diabetic patients. GAD-Ab can be at the basis of the possible link between epilepsy and T1DM, although there are questions regarding the relative role of these antibodies. In fact, the pathogenicity of these antibodies needs to be clarified to determine if they are causative or simply a marker of underlying inflammatory processes. Efforts should be applied to identifying new antibodies which could help to better understand the link between epilepsy and T1DM. Further studies are needed to look for GAD-Ab and other autoantibodies in additional cohorts and to define any clinical phenotype that might be associated with these autoantibodies. Moreover, it is likely that both metabolic extremes, SH and severe hyperglycemia, may contribute to the development of epilepsy in patients with T1DM.

Diabetic patients need a multidisciplinary approach that involves pediatric endocrinologists and neurologists in order to optimize therapeutic management and follow-up.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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### References


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