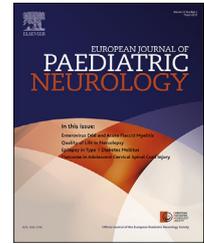




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## Review article

# Epilepsy in children with type 1 diabetes mellitus: Pathophysiological basis and clinical hallmarks



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## ABSTRACT

We provide an overview on the current knowledge about the association between epilepsy and type 1 diabetes mellitus (T1DM). People with T1DM have a 2–6-fold higher risk of epilepsy than the general population. The onset of T1DM anticipates the onset of epilepsy by a mean period between 1,5 and 2,8 years. These two disorders share four potential distinct pathogenic factors: a) genetic predisposition; b) factors involved in autoimmune responses (i.e. anti-glutamic acid decarboxylase antibodies-GADAbs); c) effects of hypo/hyperglycaemia; d) cerebrovascular damages resulting in ischaemic processes.

Seizures semiology prominently includes focal (up to patterns of epilepsy partialis continua) or secondarily generalized seizures but also reflex seizures and various forms of generalized seizures. EEG abnormalities are more common in people with an inappropriate metabolic control with a prominent involvement of fronto-temporal regions.

Epilepsy management does not differ between patients with and without diabetes and insulin, nutritional recommendations and physical activity may also produce significant benefits on seizures control. Possible therapeutic alternatives in selected cases include immunosuppressive drugs (in patients with GADAbs) and ketogenic diet.

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## Contents

1. Background .....	241
2. Epidemiological data .....	241
3. Pathophysiological mechanisms .....	241
3.1. Genetic predisposition .....	241
3.2. Factors involved in autoimmune responses .....	241
3.3. Effects of hypo/hyperglycaemia .....	244

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3.4. Cerebrovascular damages .....	245
4. Clinical aspects .....	245
5. Concluding remarks .....	246
Conflict of interest .....	246
Acknowledgements .....	246
Supplementary data .....	246
References .....	246

## 1. Background

The occurrence of epilepsy in people with childhood onset type 1 diabetes mellitus (T1DM) has been the focus for several recent studies assessing risk factors, underlying pathogenic mechanisms and clinical features of this peculiar comorbidity.<sup>1–3</sup> Various of these aspects remain controversial and epidemiological data on the strength of the association between epilepsy and T1DM are conflicting.<sup>3</sup>

Our aim is to provide an updated overview about aspects of relevant links between these two significant chronic disorders.

## 2. Epidemiological data

Epidemiological data on the association between T1DM and epilepsy is derived from four observational cohort studies, four retrospective studies based on chart reviews and one meta-analysis (Table 1).<sup>3–11</sup> These studies were focused on the risk of epilepsy in cohorts of patient with diabetes in seven cases and on the risk of T1DM in people with epilepsy in two cases (Table 1).<sup>3–11</sup> The cohort in four studies were exclusively pediatric.<sup>4,6,9,10</sup>

Several methodological issues limit the interpretation of the findings. In some cases it was not possible to differentiate epileptic seizures (which must be unprovoked according to ILAE definition) from seizures secondary to metabolic dysfunctions such as hypoglycaemia.<sup>4,10</sup> In other cases clinical details or metabolic studies of all participant were not fully available.<sup>6,9</sup>

Notwithstanding these limitations, a higher risk for epilepsy (ranging between two and six times) than in the general population has been observed in people with T1DM (Table 1).<sup>4–9</sup> This higher risk was also assessed in patients younger than 18 years even if two groups of researchers failed to confirm this result.<sup>3,5,6,9–11</sup> The prevalence of epilepsy in T1DM ranged between 8,7 and 21 per 1000 while the prevalence of T1DM increased between two and four times in patients with idiopathic generalized epilepsy if compared with the general population (Table 1).<sup>4–11</sup> The incidence of epilepsy was also higher in patients with T1DM than in controls in two different cohorts (in the United Kingdom and in Taiwan) (Table 1).<sup>5,6</sup>

On average, the onset of T1DM precedes the onset of epilepsy by 1.5–2.8 years.<sup>7,8,11</sup> Among people with T1DM specific risk factors for epilepsy occurrence and electroencephalographic abnormalities were younger age and earlier age at the onset of diabetes.<sup>6</sup> The risk for ketoacidosis was doubled in

people with T1DM with an associated epilepsy independently of the antiepileptic drugs used for treatment.<sup>9</sup> The same patients experienced less frequent serious hypoglycemic events.<sup>9</sup> No differences were found in terms of metabolic control, schedules and doses of insulin treatment, and quote of beta cell-specific autoantibodies between patients with comorbid T1DM and epilepsy and people with only T1DM.<sup>9</sup>

## 3. Pathophysiological mechanisms

Four possible pathogenic mechanisms have been suggested for the a) genetic predisposition; b) factors involved in auto-immune responses; c) effects of hypo/hyperglycaemia; d) cerebrovascular damages resulting in ischaemic processes.<sup>6,12</sup>

### 3.1. Genetic predisposition

No convincing evidences supporting the pathogenic role of various candidate genes were obtained.

Promising research fields involved genes encoding for enzymes of glucose metabolism and proteins of major histocompatibility complex (MHC). Some genes (GCK, INS, KCNJ11 and ABCC8) have been associated with neonatal onset forms of diabetes mellitus (Permanent Neonatal Diabetes Mellitus-PNDM; MIM 606176) presenting with epilepsy and often evolving into type 2 diabetes mellitus (T2DM).<sup>13</sup> About MHC proteins the only allele that was significantly associated with temporal lobe epilepsy (HLA-DRB1\*13:02) was not defined as a specific risk factor for diabetes.<sup>14</sup>

### 3.2. Factors involved in autoimmune responses

Anti-glutamic acid decarboxylase antibodies (GAD-Abs) represent the most remarkable link between epilepsy and T1DM.<sup>1</sup> Glutamic decarboxylase GAD catalyzes the conversion of glutamic acid to gamma-aminobutyric acid (GABA) in the brain and it is a crucial enzyme in GABA-mediated neuronal networks. GAD-Abs were detected in almost 80% of people with newly diagnosed T1DM and in about 4–7% of people with comorbid epilepsy and T1DM (the association with epilepsy and other neurological disorders was stronger in patients with T1DM with titers of GAD-Abs over 2000 UI).<sup>15</sup>

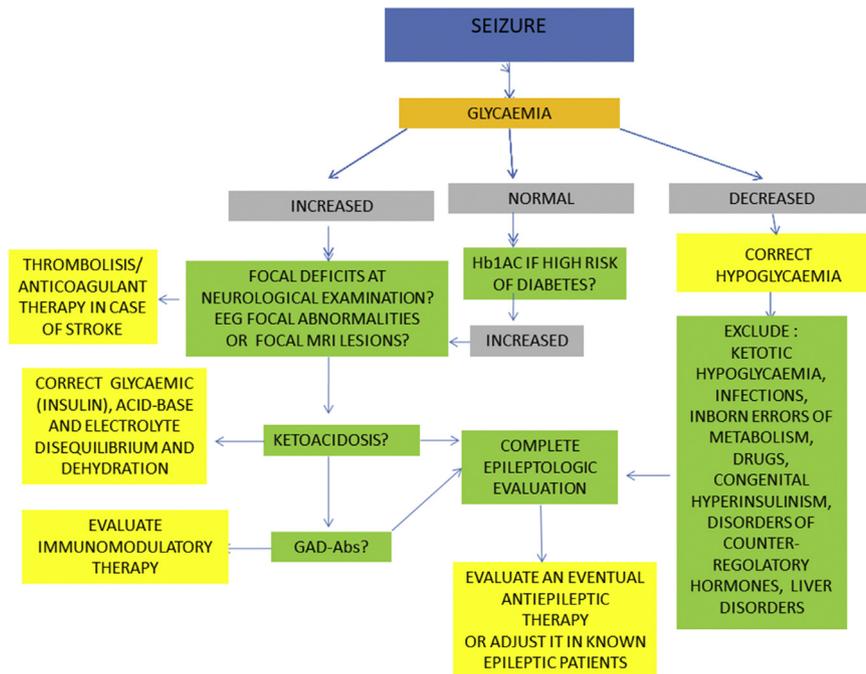
The epileptogenic mechanisms potentially triggered by GAD-Abs are still unclear but an immune-mediated impairment of GABA synthesis and release is probably involved.<sup>1,2</sup> The proposed mechanisms included: a) neutralizing action on the catalytic site of GAD after IgG GAD-Abs internalization

**Table 1 – Epidemiologic studies on the association epilepsy-T1DM in the literature.**

Author/year of publication	Type of study	Nation	Number and diseases of the patients	Age range of patients	Prevalence of epilepsy in patients with T1DM	Incidence of epilepsy in patients with T1DM	Hazard ratio	Odds ratio	Conclusions	Limits of the study
Mc Corry et al., 2006	Observational cohort study	United Kingdom	150.000 patients from the general population and 518 patients with idiopathic generalized epilepsy	15–30 years	NA (465 of 150.000 in the general population; 7 of 518 patients with idiopathic generalized epilepsy)	NA	NA	4.4 (95% CI: 2.1–9.2)	Significant excess of T1DM among patients with idiopathic generalized epilepsy if compared with the general population	Possible bias selection (patients with idiopathic generalized epilepsy were selected in a specialistic center)
O'Connel et al., 2008	Chart review	Australia	1384 patients with T1DM	0–19 years	8.7 of 1000	NA	NA	NA	Prevalence of epilepsy in patients with T1DM was similar to the ones in the general population	Retrospective design of the study Possible underestimation of the prevalence of epilepsy in patients with recurring hypoglycaemia
Mancardi et al., 2010	Chart review	Italy	249 patients with T1DM	16.3 ± 7.02 years	16 of 1000	NA	NA	NA	Prevalence of epilepsy in patients with T1DM was similar to the ones in the general population	Retrospective design of the study. Small number of patients. No control group
Ramakrishnan and Appleton, 2012	Chart review	United Kingdom	285 children with T1DM	≤16 years	21 of 1000	NA	NA	NA	Prevalence of epilepsy in patients with T1DM was six times greater than in the general population	Retrospective design of the study. Possible underestimation of the prevalence of epilepsy in patients with recurring hypoglycaemia
Shober et al., 2012	Observational cohort study	Germany and Austria	45,851 patients with T1DM	13.9 ± 4.3 years	15.5 of 1000	NA	NA	NA	Prevalence of epilepsy was higher among patients with T1DM than in the general population. The risk for diabetic ketoacidosis was double in patients with epilepsy compared with patients with T1DM alone.	No data on seizure history and semiology, blood glucose and gas analysis, EEG and MRI.

Keezer et al. 2015	Chart review	United Kingdom	2016 patients with epilepsy (20 patients with T1DM)	27–52 years	NA (prevalence of 9.9 cases of T1DM per 1000)	NA	NA	NA	NA	The prevalence of T1DM in patients with epilepsy was more than double if compared with non epileptic subjects. Patients with T1DM had a risk for developing epilepsy that was 2,84 higher than controls	Retrospective design of the study Possible bias selection (patients with epilepsy referring to a specialistic center) Retrospective design of the study Data extracted from a program that was built for administrative (not scientific) purposes No detailed data on possible known (lifestyle habits, BMI, physical activity, socioeconomic status and family history) and unknown confounders about patients clinical features
Chou et al., 2016	Population-based open-cohort study	Taiwan	2568 patients with T1DM and 25,680 comparison patients	10.4 ± 4.4	NA	33.7 per 10.000/year (10,4 per 10.000/year in controls)	2.84 [95% CI 2.11, 3.83]	NA	NA	Patients with T1DM had a risk for developing epilepsy that was 2,84 higher than controls	Retrospective design of the study Data extracted from a program that was built for administrative (not scientific) purposes No detailed data on possible known (lifestyle habits, BMI, physical activity, socioeconomic status and family history) and unknown confounders about patients clinical features
Dafoulas et al., 2017	Population-based open-cohort study	United Kingdom	4922 with T1DM (2893 younger than 18 years old) and 19,688 controls	17,9 ± 10,7 years	NA	132 per 100.000/year (44 per 100.000/year in controls)	3,01 (95% CI)	NA	NA	Patients with T1DM were three-times greater risk of developing epilepsy if compared with healthy controls. Similar risk was observed for patients younger than 18 years old	Retrospective design of the study
Dandan et al., 2017	Meta-analysis of 3 studies (Mc Corry et al., 2006; Chou et al., 2016; Dafoulas et al., 2017)	China	See above the data of the 3 selected studies	See above the data of the 3 selected studies	See above the data of the 3 selected studies	See above the data of the 3 selected studies	3.29 (95% CI: 2.61–4.14; $I^2 = 0$ , $p = 0.689$ ) in the whole sample; 2.96 (95% CI: 2.28–3.84; $I^2 = 0$ , $p = 0.571$ ) in patients younger than 18 years old	See above the data of the 3 selected studies	NA	Patients with T1DM were about three-times greater risk of developing epilepsy if compared with healthy controls. Similar risk was observed for patients younger than 18 years old	Small number of adequate studies Small selected sample

NA: not available; T1DM: Type 1 Diabetes Mellitus; CI: confidence interval.



**Fig. 1 – Suggested clinical approach to manage seizures in patients with a possible T1DM at the onset.**

by neurons; b) activation of cellulose-mediated response against synaptic vesicles of gabaergic neurons after the formation of membrane complex including GAD-Abs and the protein HSP 70; c) molecular mimicry of GABA function through a direct interaction between GAD-Abs and GABA receptors.<sup>2</sup>

Increased levels of GAD-Abs were recently observed in a small cohort of 25 patients with T1DM and epilepsy compared with 36 patients affected only by T1DM with a clear prominence in patients in whom the onset of epilepsy occurred before diabetes.<sup>16</sup> Epitope binding features for GAD-Abs overlapping with the ones of stiff person's syndrome were observed in a single 5 year's old child with T1DM, epilepsy and behavioral disturbances.<sup>17</sup> These data suggest that the routine determination of GAD-Abs and the related epitope analysis could be a useful tool to identify patients with T1DM with higher risk of developing epilepsy or other neurological disorders.<sup>17</sup>

The pathogenic role of GAD-Abs in these patients has the following therapeutic implications: a) 33–50% of the sporadic treated patients with endovenous immunoglobulins experienced a clinical improvement.<sup>12,17</sup> b) antiepileptic drugs that inhibits GABA catabolism such as vigabatrin were ineffective on seizures in sporadic reports (because GAD-Abs suppress GABAergic neurotransmission also through an interference with GABA exocytosis).<sup>18</sup>

### 3.3. Effects of hypo/hyperglycaemia

Hyperglycaemia represent a relevant risk factor for focal seizures in patients with T1DM due to an increased predisposition to cerebro-vascular dysfunctions and a secondary decrease of cerebral blood flow enhanced by neuronal hyperosmolarity and dehydration.<sup>1,2</sup> Some cerebral structures (such as frontal or occipital cortex, amygdale and hippocampus) have a lower seizure threshold as a response to glucose variations with a subsequent prominence of seizures involving the related areas

in T1DM patients.<sup>1</sup> Patients with T1DM seems more susceptible to these mechanisms especially in case of pre-existent structural lesions which could alter regional neuronal activity.<sup>1,2</sup>

The increased risk for ketoacidosis in patients with T1DM associated with epilepsy has not been properly explained to date.<sup>9</sup> These data conflict with the anticonvulsant action that have been attributed to ketosis other than diabetes-related (also including the ones obtained with a codified antiepileptic treatment such as ketogenic diet).<sup>1</sup> Suggested pathogenic mechanisms included use of carbonic anhydrase inhibitors in the antiepileptic treatment or dysfunctions of mitochondrial respiratory chain enzymes.<sup>9</sup>

Hypoglycaemia represents an acute and chronic seizure-inducing stimulus in patients with T1DM receiving insulin treatment.<sup>19</sup> Chou et al. observed an increased risk of epilepsy in T1DM patients with recurrent episodes of hypoglycaemia compared with T1DM patients without hypoglycaemia (HR 16.5 [95% CI 5.19, 52.3] versus HR 2.67 [95% CI 1.97, 3.62] in the comparison with non diabetic patients).<sup>6</sup>

In case of hypoglycaemia acute seizures induction is secondary to functional and structural injuries causing an increased cortical excitability and resulting from the lack of glucose as a source of energy for brain metabolism.<sup>19</sup> In this context some pre-clinical studies demonstrated a possible glutamate-related excitotoxicity facilitated by the reduced glucose availability.<sup>1,2</sup> These alteration could also persist after the restoration of normal glucose levels with subsequent development of EEG abnormalities or unprovoked seizures.<sup>19</sup> Patients with diabetes with recurrent hypoglycaemia may activate mechanisms of chronic adaptation based on the utilization of alternative sources of energy, such as lactate, which could support the increased neuronal metabolic requirements during seizures.<sup>19</sup> The increased production, transport and consumption of lactate and these processes could result in an increased predisposition to epilepsy.<sup>19</sup>

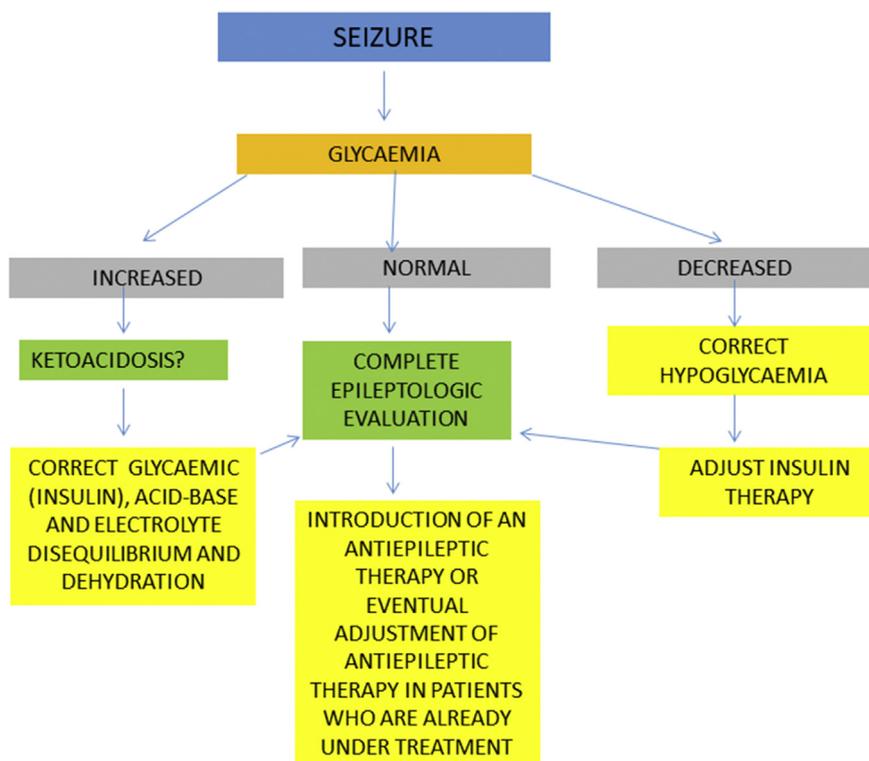


Fig. 2 – Suggested clinical approach to manage seizures in patients with a known T1DM.

### 3.4. Cerebrovascular damages

Hyperglycaemia induce different structural and functional damages in blood vessels which may could result in ischaemic events and in possible subsequent seizures secondary to impaired metabolism of endothelial nitric oxide, dysfunctions in coagulation and fibrinolytic networks, malfunctioning of recanalization or increased reperfusion injuries.<sup>20</sup> The real relevance of these mechanisms in the pathogenesis of epilepsy in patients with T1DM is controversial as atherothrombotic complications following vascular lesions are more common in people with T2DM in whom a smaller predisposition to epilepsy (35% versus 85% of patients with both the diseases) was estimated.<sup>7,20</sup>

## 4. Clinical aspects

Seizures semiology in patients with T1DM has been mainly described in sporadic case reports or case series while reliable epidemiological data from large samples lack. A total of 66 patients with focal (especially the ones originating in fronto-temporal and occipital regions) or secondarily generalized seizures were reported.<sup>2</sup> Other less common seizure patterns included *epilepsia partialis continua* (29 patients), reflex seizures (3 patients) and generalized seizures (9 patients).<sup>2</sup> Metabolic deregulations were more frequently highlighted in reported cases with focal seizures while autoimmune mechanisms were prominently involved in patients in which generalized seizures were reported.<sup>1</sup>

EEG abnormalities have been detected in different samples of patients with T1DM even if no relationships were reported

between these abnormalities and duration of diabetes.<sup>1</sup> A higher risk for their occurrence was demonstrated in patients with and an unsatisfactory metabolic control (especially in patients with recurrent events of hypoglycaemia, elevated plasma values of HbA1c or ketoacidosis).<sup>1</sup> Focal epileptiform abnormalities were located in fronto-temporal regions in most of patients with T1DM.<sup>1</sup> In an old study involving 44 patients with T1DM (compared with healthy controls) a decreased relative power of the alpha band was detected at quantitative EEG in patients with high levels of HbA1c and in patients with previous episodes of diabetic ketoacidosis (in which an increase of delta/theta band was assessed).<sup>21</sup> In a more recent study of patients with T1DM receiving insulin a decreased power of alpha, beta and gamma frequencies was reported prominently in the temporal regions at standard EEG while an increased power of theta and delta frequencies and a reduction of alpha peaks were more commonly detected in frontal regions.<sup>22</sup> A reduced alpha activity and an increased fronto-central theta activity were observed at the onset of T1DM in patients with prior episodes of severe hypoglycaemia and the same abnormalities were not confirmed in the same patients after 16 years of follow-up.<sup>23</sup> Others have shown a decreased EEG coherence following episodes of hypoglycaemia in adult T1DM series with relevant consequences on cognitive functions.<sup>24–26</sup>

Therapeutic management of epilepsy in patients with T1DM does not differ from patients without a diagnosis of T1DM and principles of therapy of diabetes (insulin, nutritional recommendations and physical activity) produce significant benefits also on seizures through an optimal metabolic control.<sup>2</sup>

Sporadic case reports suggested the usefulness of immunomodulatory therapies (corticosteroids, immunoglobulins or

immunosuppressive agents) in patients with diabetes and GAD Abs-related status epilepticus.<sup>27,28</sup>

Ketogenic diet resulted in a satisfying seizure control without increasing the risk of hypoglycaemia or complicated ketoacidosis in a few published patients with diabetes.<sup>29–31</sup> Reported patients included: a 3 year's old male with myoclonic-astatic epilepsy, a 4 year's old male with pyruvate dehydrogenase deficiency who developed T1DM after the beginning of the diet, a 2 year's old female with a previous bilateral watershed infarcts, a 3,5 year's old female with a neuronal migration disorder and a focal epilepsy.<sup>29–31</sup> All the authors suggested a strict monitoring of insulin treatment and glucose levels because of the difficulties in the distinction between starvation-induced ketosis and the ones arising from insulin deficiency.<sup>29–31</sup>

The algorithms in Figs. 1 and 2 summarize the possible clinical scenario to manage patients with the association between epilepsy and T1DM.

## 5. Concluding remarks

Epilepsy and T1DM can be considered both as casual comorbidities and disorders with common pathogenic basis (especially for subgroups of epilepsy with known autoimmune knowledges). The co-existence of two chronic disorders implies the need of a multidisciplinary approach based on a collaboration between general pediatricians, neuro-pediatricians and endocrinologists and highlights the importance of special therapeutic education programs for patients.

Available epidemiological data have recently clarified some of the most common risk factors for this association even if further studies are required to enlarge the perspective on genetic modulators and molecular mechanisms that link metabolic changes of T1DM with epileptogenesis. A better comprehension of these aspects could allow an improvement of knowledges about pathogenesis and clinical management.

## Conflict of interest

None of the authors have any conflict of interest to declare.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejpn.2018.12.006>.

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