THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

MEDICINE
Case report

THERE IS A POSSIBLE RELATION BETWEEN EPILEPSY AND DIABETES? THREE CASE REPORT AND GENERAL REMARKS

Rucsandra DĂNCIULESCU MIULESCU[1,2], Anna Maria TINU[2], Denisa MARGINĂ[1], Daniela GRĂDINARU[1], Anca UNGURIANU[1] and Loreta GUJA[1]

[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest
[2] "N.C. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases Bucharest
Corresponding author: Ruscsandra Dănciulescu Miulescu, 5-7 Ion Movila Street, Bucharest, District 2, Postal Code 11420, Tel: 0040748134500, Fax: 004021/2105575; rucsandra_m@yahoo.com

Accepted

Diabetes mellitus and epilepsy represent diseases with a great medical and social impact. The possible coexistence between the two conditions has been evaluated in numerous studies due to hinger prevalence of type 1 diabetes mellitus (T1DM) in patients with epilepsy and the increased prevalence of epilepsy in patients with T1DM. The relationship between epilepsy and diabetes remain undetermined. The hypotheses developed on the relationship between the two diseases involved: autoimmune and inflammatory condition, metabolic factors. We present 3 patients with diabetes and epilepsy. Of the three cases presented, epilepsy precedes diabetes in two cases. The first case presents the association between Graves' disease, epilepsy, T1DM. In the second case epilepsy is associated with type 2 diabetes (T2DM) and excess alcohol consumption and the third case associated epilepsy, T2DM and uncontrolled hypertension. Association between epilepsy, and diabetes mellitus is a challenge for the physician. Diabetic patients need a multidisciplinary consult that evaluate the patient from the metabolic and neurological point of view.

Keywords: diabetes, epilepsy, Graves' disease, alcoholism, uncontrolled hypertension.

INTRODUCTION

T1DM and epilepsy represent diseases with a great medical and social impact. According to World Health Organization epilepsy is characterized by "*recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized), and are sometimes accompanied by loss of consciousness and control of bowel or bladder function*"[1]. The possible coexistence between the two conditions has been evaluated in numerous studies due to higheer prevalence of T1DM in patients with epilepsy and the increased prevalence of epilepsy in patients with T1DM. Evaluation of the prevalence of epilepsy in 285 T1DM children (129 females and 156 males) aged less than 16 years highlights that the prevalence of epilepsy is six times greater than the prevalence of epilepsy in the general population of children in United Kingdom[2]. Mc Corry D and collaborators have investigated the prevalence of T1DM in 518 patients diagnosed with idiopathic epilepsy. The age of study participants was between 15 to 30 year and results suggest that the prevalence of T1DM is increased (four–times) in young adults with idiopathic epilepsy compared with controls[3]. Chou IC *et al.* have investigated the association between T1DM and epilepsy in 2568 Taiwan patients with T1DM. The study revealed that in diabetic patients the prevalence of epilepsy is 2.84 times greater than in the control group[4]. In a study published in 2017 in Diabetologia by Dafoulas GE *et al*, study which they included 24.610 subjects, 4.922 patients with T1DM and 19.688 controls, highlights that patients with T1DM are at three-times greater risk of developing epilepsy compared to the control group[5].

A recent study published in 2018 in Diabetes Research and Clinical Practice in which were included 751.792 patients with T2DM and 824.253 matched controls supported that T2DM may increase risk of epilepsy independent of severe hypoglycaemia[6].

CASE 1

A 34-year old woman was hospitalized at the National Institute of Diabetes, Nutrition and Metabolic Diseases "N.C. Paulescu", Bucharest for

increased blood glucose, general health alteration (epigastralgia, inappetence) in the last 2 days. At the admission the patient was characterized by blood glucose: 216 mg/dl, diabetic ketoacidosis (pH: 7.19, the partial pressure of carbon dioxide-pCO2: 15.8 mmHg, partial pressure of oxygen-pO_2: 166.5 mmHg, serum bicarbonate concentration: 5.9 mmol/l, base excess: 20, anion gap: 28.4 mmol/l), glycated hemoglobin (HbA1c): 10%. Specific treatment (endovenous infusions, repeated fast insulin) was instituted, which led to lowering of blood glucose levels and correction of diabetic ketoacidosis. In order to establish the clinical form of diabetes, determinations of pancreatic C-peptide-0.49 ng/ml (reference values: 0.8–3.1 ng/dl) and immunological markers (autoantibodies to glutamate acid decarboxylase-GAD-2000 IE/ml, reference values-<10 IE/ ml) were performed and the values confirmed the diagnosed T1DM. The patient had a history of heredocolateral diabetes and was diagnosed with Graves' disese from 15 age and left front focal epilepsy at 17 age. Epilepsy treatment was initiated with Carbamazepinum and Sodium valproate and subsequently it was associated Retigabine. The patient presented a frequency of crises of 1–2 to 3 day reason for a vagal pacemaker was implanted in 2014. At the moment of investigations the patient follows treatments with Levetiracetam 1000 mg/day, Carbamazepinum 1200 mg/day and presented a frequency of crises of 1–2/ month. Thyrotoxicosis treatment was performed with antithyroid drugs (Thiamazole). To mention that the patient presents frequent relapses at when discontinuing or reducing dose of antithyroid drugs and refused radical treatment of thyrotoxicosis. The evaluation of thyroid function revealed a suppressed value of thyroid stimulating hormone (TSH)-0.005 μIU/ml for which the antithyroid drugs dose was increased from 20 mg/day to 30 mg/day (Thiamazole) with progressive dose reduction depending on the values of TSH and free thyroxine (fT_4).

CASE 2

A 37-year old man diagnosed with T2DM from 2007 was hospitalized at the National Institute of Diabetes, Nutrition and Metabolic Diseases "N.C. Paulescu", Bucharest for clinical and metabolic evaluation. At the onset of diabetes the patient presented values of blood glucose levels: 294 mg/dl. HbA1c: 11.9%, total cholesterol: 294 mg/dl, fasting serum triglyceride 142 mg/dl, aspartate aminotransferase (AST): 83 U/l and alanine aminotransferase (ALT): 150 U/l. The patient was advised on lifestyle optimization (including reducing alcohol consumption) and oral antidiabetic therapy was initiated (Glimepirid 4 mg/day and Metformin 1500 mg/day) with a favorable initial evolution of glycemic values. Subsequently the patient presented frequently experienced of important hypoglycaemia (glucose level<54 mg/dl) for which the sulphonylurea treatment was discontinued. The patient and the family did not report severe cognitive impairment requiring assistance for recovery during the hypoglyceamia. From 2012 the patient follows hypoglycemic treatment only with Metformin. From 2008, the patient experiences generalized epileptic seizures. Treatment with Sodium valproate was initiated; treatment was followed inconsistently and for a period of time interrupted for which reason the patient presented frequent generalized epileptic seizures. From 2016 the patient follows treatments with Carbamazepine 600 mg/day. Patient had a family history of diabetes but not of epilepsy and has the right ocular prothesis.

CASE 3

A 62-year old woman diagnosed with epilepsy from 1997, hypertension from 2006 and T2DM from 2007 has been recently evaluated clinically and biologically. At the time of diagnosis of T2DM, the patience presented values of blood glucose levels: 171 mg/dl and HbA1c: 8.4%, reason for initiation of therapy with Metformin in association with lifestyle optimization. Epilepsy treatment included Carbamazepine 900 mg/day. The patient underwent hypoglycemic treatment with Metformin until 2011 when a moderately elevated blood glucose was associated with a secretagogue. Currently the patient is being treated with Gliclazide 120 mg/day and Saxagliptin+ Metformin 10/1000 mg/day. Hypotensor treatment included Indapamide 1.5 mg/day, Nebivolol 10 mg/day and Enalapril 20 mg/day. The patient presented high tensional oscillations and require multiple hospitalization in cardiology and neurology services.

GENERAL REMARKS

The relationship between epilepsy and diabetes remain undetermined. The hypotheses developed on the relationship between the two diseases involved: autoimmune and inflammatory condition as well as metabolic factors[5, 7, 8, 9, 10].

High titers of antibodies to GAD are associated with epilepsy involving the γ- gamma-aminobutyric acid (GABA)ergic ways. GABA is the major inhibitory neurotransmitter in the cerebral cortex. In GABA synthesis is involved GAD which catalyzes the decarboxylation of glutamic acid. High titers of antibodies to GAD impaired synthesis of GABA[7].

Genesis of epilepsy can be associated with inflammatory processes[10,11]. Inflammatory mediators may originate in the central nervous system or be acquired from systemic circulation. In a review published in 2018 in Journal of Neuroinflammation, the authors suggest the following mechanism of involvement in the etiopathogenesis of epilepsy: "*Peripheral and central inflammation allow the breakdown of the blood-brain barrier due the upregulation of inflammatory mediators. Blood-brain barrier breakdown permits leukocyte infiltration which generates neuronal hyper-excitability and further upregulates inflammatory mediators. Unregulated peripheral and central inflammation and breakdown of the blood-brain barrier lead to morphological synaptic changes within the hippocampus and ultimately, the development of epilepsy*"[2]. The association between diabetes and inflammation is established and inflammation has an important role in the development and progression of the disease[13, 14, 15, 16].

Metabolic factors such hyperglycemia or hypoglycemia may be involved in the etiopathogenesis of epilepsy. Studies on the implication of hyperglycemia in the genesis of epilepsy report that glucose inhibit GABA release thus facilitating the occurrence of seizures[17, 18]. Epileptic syndrome has been reported as manifestation of hyperosmolar non-ketotic hyperglycaemia[19,20,21] but not in ketoacidosis that increases content of brain GABA[20]. Case studies or animal models have revealed that the hypoglycemia was associated with the frequency of seizures[22,23]. Some mechanisms have been proposed through that hypoglycaemia can induce seizures:

1. Glucose modulate the release of GABA in the hypothalamus via the adenosine triphosphate (ATP) sensitive potassium channel (K_{ATP} channel). Animal models have shown that inhibition of GABA release may mediate the hyperexcitability associated with hypoglycemia[24, 25].
2. The sodium/potassium ATPases (Na^+/K^+-ATPases) is an enzyme that regulating the ionic balances across the plasma membrane. The enzyme play a role in neuronal excitability and its reduction may be associated with hyperexcitability in the central nervous system and seizure. Previous studies highlights that hypoglycemia decrease activity of Na+/K(+)-ATPase that enhanced the uptake of which initiates glutamate neurotoxicity[26, 27, 28].

In contrast other studies have suggested that association between hypoglycemia and epileptic seizures are rare. Halawa I and collaborators reported in a retrospective cross-sectional study in which they were included 388 individuals with glucose levels of ≤63 mg/dl that epileptic seizures are rare (3 patients). Generalized tonic–clonic seizure was seen in 1 patients at glucose levels <36 mg/dl and focal seizure were present in 2 patients wen glucose levels is below 36 mg/dl, respectively 59 mg/dl[29]. In a study published in 2014 in Journal of the Neurological Sciences in which they were included 229 patients with T1DM Falip M *et al.* conclude that hypoglycemic seizures are rare and diabetic patients suffering of hypoglycemic seizures not develop epilepsy[30].

DISCUSSIONS

Of the three cases presented epilepsy precedes diabetes in two cases.

The first patient associates epilepsy with polyglandular autoimmune syndrome type III. This syndrome includes association between T1DM and autoimmune thyroid disease[31]. GAD can be present in Graves' patients without diabetes and the predictive value of GAD for the development of T1DM remains to be elucidated. Taniyama M and collaborators investigated the appearance of T1DM in patients with Graves' disease. In the study were included 158 patients with Graves' disease of which 10 patients (6.3%) with high titers of GAD. During the 8-year followup period, T1DM developed in 2 patients with long duration of Graves' disease and uncontrollable by antithyroid drug[32]. Kusaka I *et al.* investigated characteristics of 61 patients with both diseases according to the absence (47 patients) or presence (14 patients) of GAD. In the GAD positive patients, the onset of T1DM is abrupt. In the GAD-negative patients, gradual onset of diabetes and attenuated manifestations of Graves' disease were common. In this study, Graves' disease preceded diabetes in 8 patients[33]. One study performed by Hallengren B and collaborators that followed the frequency of GAD antibodies in patients with hyperthyroidism reveals that GAD were detected at the diagnostic

of Graves' disease in patients without diabetes. The frequencies of GAD in patients with Graves' disease was significantly increased compared to patients with toxic nodular goitre/solitary toxic adenoma in the hyperthyroid state (28 *vs.* 3%)[34].

In the case of the second patient, the diagnosis of epilepsy was established 1 year after the diagnosis of diabetes. The patient presented frequently episodes of important hypoglycaemia (glucose level<54 mg/dl) secondary to hypoglycaemic therapy and excessive alcohol consumption. In 2017 the American Diabetes Association defined hypoglycemia as: level 1: glucose level<70 mg/dl, level 2: important hypoglycemia, glucose level of<54 mg/dl, level 3: severe hypoglycemia denotes severe cognitive impairment requiring external assistance for recovery[35]. Seizures were related to hypoglycemia and alcoholism. A retrospective cross-sectional study performed at Uppsala University Hospital evaluated the occurrence of seizures related to hypoglycemia. 388 patients with hypoglycemia but without a prior diagnosis of epilepsy were included. The authors concluded that epileptic seizures are rare (3 patients-2 patients complex partial seizure and 1 patient generalized tonic–clonic seizures). Co-morbidity such as alcoholism, nephropathy, cannabis addiction, advanced prostate cancer were present in patients with seizures[36]. In a prospective study performed at the Harlem Hospital Emergency Room were included 125 patients with symptomatic hypoglycemia. 9 patients presented seizures and of these 3 had known epilepsy; in other cases seizures were related to alcoholism[37]. Acute alcohol intake has in humans and animal models a biphasic effect on the central nervous system. In the first phase the alcohol generates an effect anticonvulsant. Subsequent when blood alcohol levels decline, neuronal excitability is increased which can cause the occurrence of seizures in patients with epilepsy[38, 39]. Note that the patient presents impaired adherence to antiepileptic treatment and to reducing alcohol consumption.

The third patient presents the association between epilepsy, T2DM and uncontrolled hypertension. Case studies and animal models revealed that severe hypertension increased the risk of seizure[40, 41]. A case-control study performed at Harlem Hospital Center, between 1981 and 1984 in which they were included 227 patients for a first seizure has highlighted that history of hypertension can represent risk factor for onset of seizures[42]. A cohort study published in 2013 by Chung TT and collaborators found that, patients with hypertensive encephalopathy are at an increased risk of subsequent epilepsy[43].

CONCLUSION

Prospective studies with an increased number of patients, developed over a long period of time are necessary to establish the relationship between GAD, epilepsy, diabetes and Graves' disease.

Association between epilepsy, and diabetes mellitus is a challenge for the physician. Diabetic patients need a multidisciplinary consult that evaluate the patient from the metabolic and neurological point of view.

REFERENCES

1. World Health Organization, Epilepsy, www.who.int, 2018.
2. Ramakrishnan R, Appleton R. Study of prevalence of epilepsy in children with type 1 diabetes mellitus. *Seizure,* 21(4): 292-294, 2012.
3. Mc Corry D, Nicolson A, Smith D *et al*. An association between type 1 diabetes and idiopathic generalised epilepsy. *Annals of Neurology*, 59: 204-206, 2006.
4. Chou IC, Wang CH, Lin WD *et al*. Risk of epilepsy in type 1 diabetes mellitus: A population-based cohort study. *Diabetologia*, 59:1196–1203 2016.
5. Dafoulas GE, Toulis KA, Mc Corry D *et al*. Type 1 diabetes mellitus and risk of incident epilepsy: a population-based, open-cohort study. *Diabetologia*, 60(2): 258-261, 2017.
6. Lu CL, Chang YH, Sun Y, Li CY. A population-based study of epilepsy incidence in association with type 2 diabetes and severe hypoglycaemia. *Diabetes Res Clin Pract*, 140: 97-106, 2018.
7. Verrotti A, Scaparrotta A, Olivieri C, Chiarelli F, Seizures and type 1 diabetes mellitus: current state of knowledge. *Eur J Endocrinol*, 167(6):749-758, 2012.
8. MA O'Connell, AS Harvey, MT Mackay, FJ Cameron. Does epilepsy occur more frequently in children with type 1 diabetes. *J Paediatr Child Health*, 44: 586-589, 2008.
9. Mancardi MM, Striano P, Giannattasio A *et al.* Type 1 diabetes and epilepsy: More than a casual association? *Epilepsia*, 51:320–321, 2010.
10. Alyu F, Dikmen M. Inflammatory aspects of epileptogenesis: contribution of molecular inflammatory mechanisms. *Acta Neuropsychiatrica*, 29(01):1–16, 2016.
11. Choi J, Koh S. Role of brain inflammation in epileptogenesis. *Yonsei Med J,* 49(1):1, 2008.
12. Rana A, Musto AE. The role of inflammation in the development of epilepsy. *J Neuroinflammation*, 15: 144, 2018.
13. Donath MY, Dalmas É, Sauter NS, Böni-Schnetzler M. Inflammation in obesity and diabetes: islet dysfunction and therapeutic opportunity. *Cell Metab*, 17: 860–872, 2013.
14. Ehses JA, Perren A, Eppler E *et al*. Increased number of islet-associated macrophages in type 2 diabetes. *Diabetes*, 56: 2356–2370, 2007.

15. Böni-Schnetzler M, Boller S, Debray S *et al*. Free fatty acids induce a proinflammatory response in islets via the abundantly expressed interleukin-1 receptor I. *Endocrinology*, 150: 5218–5229, 2009.
16. Richardson SJ, Willcox A, Bone AJ *et al.* Islet-associated macrophages in type 2 diabetes. *Diabetologia*, 52:1686–1688, 2009.
17. Smismans A, Schuit F, Pipeleers D. Nutrient regulation of gamma-aminobutyric acid release from islet beta cells. *Diabetologia*, 40(12):1411-1415, 1997.
18. Wang C , Kerckhofs K, Van de Casteele M *et al*. Glucose inhibits GABA release by pancreatic beta-cells through an increase in GABA shunt activity. *Am J Physiol Endocrinol Metab*, 290(3): E494-499, 2006.
19. Wang X. Nonketotic hyperglycemia-related epileptic seizures. *Chinese Neurosurgical Journal*, 3:16, 2017.
20. Wang X, Yu H, Cai Z *et al*. Nonketotic hyperglycemia-related epileptic seizures. *Epilepsy Behav Case Rep*. 1:77–78, 2013.
21. Maccario M, Messis CP, Vastola EF. Focal seizures as a manifestation of hyperglycemia without ketoacidosis. A report of seven cases with review of thw literature. *Neurology*. 15:195–206, 1965.
22. Lapenta L, Di Bonaventura C, Fattouch J *et al*. Focal epileptic seizure induced by transient hypoglycaemia in insulin-treated diabetes. *Epileptic Disord*, 12:84-87, 2010.
23. Chan O, Lawson M, Zhu W *et al*. ATP-sensitive K(+) channels regulate the release of GABA in the ventromedial hypothalamus during hypoglycemia. *Diabetes,* 56(4):1120-1126, 2007.
24. During MJ, Leone P, Davis KE *et al*. Glucose modulates rat substantia nigra GABA release in vivo via ATP-sensitive potassium channels. *J Clin Invest*, 95(5):2403-2408, 1995.
25. Sherin A, Peeyush KT, Naijil G *et al*. Hypoglycemia induced behavioural deficit and decreased GABA receptor, CREB expression in the cerebellum of streptozoticin induced diabetic rats. *Brain Res Bull*, 83(6):360-366 2010.
26. Lores Amaiz GR, Ordieres MGL. Brain Na^+, K^+-ATPase Activity In Aging and Disease. *Int J Biomed Sci*, 10(2): 85–102. 2014.
27. Less GJ. Inhibition of sodium-potassium-ATPase: a potentially ubiquitous mechanism contributing to central nervous system neuropathology. *Brain Res Rev*, 16(3):283-300, 1991.
28. Lau A, Tymianski M. Glutamate receptors, neurotoxicity and neurodegeneration. *Pflugers Arch*, 460(2):525-42, 2010.
29. Halawa I, Zelano J, Kumlien E. Hypoglycemia and risk of seizures: A retrospective cross-sectional study. *Seizure*, 25: 147–149, 2015.
30. Falip M, Miro J, Carreno M *et al*. Hypoglycemic seizures and epilepsy in type I diabetes mellitus. *J Neurol Sci*, 346(1-2):307-309, 2014.
31. Neufeld M, Maclaren N, Blizzard R. Autoimmune polyglandular syndromes. *Pediatr Ann*, 9:154–162 1980.
32. Taniyama M, Kasuga A, Nagayama C, Ito K. Occurrence of Type 1 Diabetes in Graves' Disease Patients Who Are Positive for Antiglutamic Acid Decarboxylase Antibodies: An 8-Year Followup Study. *J of Thyroid Res*, 306487, 2011.
33. Kusaka I, Nagasaka S, Fujibayashi K *et al*. Immunologically-related or incidental coexistence of diabetes mellitus and Graves' disease; discrimination by anti-GAD antibody measurement. *Endocr J*, 46(6):747-754, 1999.
34. Hallengren B, Falorni A, Landin-Olsson M *et al*. Islet cell and glutamic acid decarboxylase antibodies in hyperthyroid patients: at diagnosis and following treatment. *J Intern Med*; 239(1):63-68, 1996.
35. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the Europian Association for the Study of Diabetes, *Diabetes Care*, 40(1):155-157, 2017.
36. Halawa I, Zelano J, Kumlien E. Hypoglycemia and risk of seizures: A retrospective cross-sectional study. *Seizure*, 25:147-149, 2015.
37. Malouf R, Brust JC. Hypoglycemia: causes, neurological manifestations, and outcome. *Ann Neurol*, 17(5):421-430, 1985.
38. Ticku MK. The effects of acute and chronic ethanol administration and its withdrawal on gamma-aminobutyric acid receptor binding in rat brain. *Br J Pharmacol*, 70:403–410, 1980.
39. Hamerle M, Ghaeni L, Kowski A *et al*. Alcohol Use and Alcohol-Related Seizures in Patients With Epilepsy. *Front Neurol*, published online doi: 10.3389/fneur.2018.00401.
40. Hesdorffer DC, Hauser WA, Annegers JF, Rocca WA. Severe, uncontrolled hypertension and adult-onset seizures: a case-control study in Rochester, Minnesota. *Epilepsia*, 37(8):736-741, 1996.
41. Russo E, Leo A, Scicchitano F *et al*. Cerebral small vessel disease predisposes to temporal lobe epilepsy in spontaneously hypertensive rats. *Brain Res Bull*, 130:245-250, 2017.
42. Ng SKC, Hauser WA, Brust JCM, Susser M. Hypertension and the risk of new onset unprovoked seizures. *Neurology*, 43: 425–428, 1993.
43. Chung TT, Lin CY, Huang WY *et al*. Risks of subsequent epilepsy among patients with hypertensive encephalopathy: a nationwide population-based study. *Epilepsy Behav*, 29(2):374-37, 2013.