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ORIGINAL ARTICLE

Diabetes mellitus: a risk factor for seizures in the elderly—a population-based study

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Abstract
Aims To evaluate the association between diabetes mellitus (DM) and risk of seizures in a well-defined elderly population.
Methods The administrative databases of the Lombardy region (a 10 million population area in Northern Italy) were used to identify persons aged 65 years or older with DM (defined by prescription of antidiabetic drugs and/or through ICD-9 CM code and/or exemption code for diabetes) during the year 2002. Seizure-free DM subjects were followed until 2012 in search of individuals with incident seizures (identified through ICD-9 CM codes for epilepsy/seizures or ATC codes for antiepileptic drugs associated with the prescription of an electroencephalogram). To adjust for confounding, comorbidities having epileptogenic potential were also identified through the ICD-9 CM codes.
Results The population at risk included 1,494,071 persons. Of these, 136,941 seizure-free patients had DM. At the end of follow-up, the cumulative time-dependent incidence of seizures was 3.0% in DM patients and 1.9% in No-diabetic individuals (hazard ratio, HR 1.47; 95% confidence interval, 1.41–1.53, adjusted for age classes, sex, comorbidities and number of hospital admission). The HR was unchanged in patients with no history of stroke. The cumulative incidence of seizures after DM increased with the number of hospital admissions.
Conclusions DM is an independent risk factor for seizures in elderly individuals. In diabetic patients, the risk of seizures increases with the number of comorbidities, supporting the role of vascular disease as a cause of seizures.

Keywords Diabetes mellitus · Epilepsy · Seizures · Elderly

Introduction

Diabetes mellitus (DM) is a chronic clinical condition followed by complications in various organs, including neurological disorders. Epilepsy is a common disease of the brain having structural, metabolic or genetic origin. Theoretically, an association between DM and epilepsy cannot be excluded and has, in fact, been postulated on the basis of several case reports and small series [1]. However, these studies have been carried out mostly in children and adolescents with type 1 DM with inconsistent results. Some cohort studies have in fact shown an association between type 1 DM and the risk of seizures [2–4], whereas other studies did not support this association [5].

The association between DM and epilepsy has been also investigated in some studies in adult populations. In a

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clinic-based study carried out in the UK in patients aged 15 through 30 years, an association was found between type 1 DM and idiopathic generalized epilepsy [2]. A case–control study conducted using the population-based Stockholm Incidence Registry of Epilepsy (SIRE) reported a population attributable risk percent (PAR%) of 1.9% for DM diagnosis [6]. A study investigating the association between diabetes and severity of epileptic seizures in adults found that patients with HbA1c $> 9\%$ (poor glycemic control) had a significantly higher risk of seizure recurrence (44.8% vs 8.3%) in comparison with those with HbA1c $\leq 9\%$ [7].

DH is one of the most common serious metabolic disorders and may represent a precipitating factor as well as a major complication of associated comorbidities, especially in the elderly with DM. To the best of our knowledge, there are no studies investigating the association between DM and seizures in the elderly, a fraction of the population in which both diseases are most prevalent [8, 9]. The aim of our study was to evaluate the association between DM and the risk of developing seizures in a large elderly population resident of Lombardy, the most heavily populated Italian region in Northern Italy, comprising urban, industrial and rural areas.

Methods

Data source

Health care in Italy is publicly funded for all residents, irrespective of social class or employment, and everyone is assigned a personal identification number kept in the National Civil Registration System. Citizens are cared for by general practitioners (GPs) and community and hospital specialists as part of the National Health System (NHS). Medical acts are recorded in linkable Lombardy health administrative databases which include a population registry with the demographic data of all residents and detailed information on diagnostic tests, drug prescriptions and hospital admissions. Data were available from 2000 to 2012 for a total of about 2 million inhabitants. The pharmacy prescription database contains the medication name and anatomic therapeutic chemical (ATC) classification code, quantity and date of dispensation. The hospital discharge database contains information on date of hospital admission, date of discharge or death, in-hospital procedures and discharge diagnosis. Laboratory tests and specialist medical examinations done on an outpatient basis are also recorded.

In Italy, all persons with DM are entitled to antihyperglycemic drugs, visits and ad hoc devices free of charge from the NHS, provided that they have a certified diagnosis from a physician working in a public health institution. This certification is recorded in a database called the disease-specific exemption registry.

For each patient, we linked the information from all databases, using a single identification code. To protect privacy, in accordance with Italian laws for the treatment of confidential data, each identification code was automatically converted to an anonymous code. Reversal of this process was prevented by deletion of the conversion table.

In Italy, approval from an ethics committee was not required to analyze encrypted administrative data and no informed consent is required according to the national law.

Study population

The population was divided in two groups, DM and No-DM, according to their status on January 1, 2002. All people 65 years or older were included in this analysis in 2002 and followed up until 2012.

Subjects with DM were identified whether they met at least one of the following criteria in 2002:

- a prescription of an oral antihyperglycemic drug (OAD) or insulin according to the ATC code A10*
- a diagnostic code of the International Classification of Disease, Ninth Revision DM (ICD-9-CM code 250.xx) in one hospital admission;
- DM diagnosis certification in the exemption registry (ER 013.250).

We could not distinguish between type 1 and type 2 DM since this information was not included in our database. Subjects without DM were individuals 65 years or older residents in Lombardy region who did not meet these criteria in the year of entering the cohort and during follow-up.

All subjects receiving a diagnosis of seizures or epilepsy in the two years (2000–2001) before entering the cohort were removed from the study (see paragraph below for the procedure to define the presence of seizures or epilepsy).

Outcomes

Subjects were defined as having incident seizures: (a) if they had a hospital admission with a diagnosis of seizure or epilepsy (as primary and secondary position of the hospital discharge record) or (b) if they underwent an EEG examination and received a prescription of antiepileptic drugs (6 months before or after the EEG examination) (see Appendix—Supplementary Information). A combination of EEG and antiepileptic drugs was found by us to be the most valid tracer of patients with seizures not incurring in hospital admissions, with a sensitivity of 85.9% and a specificity of 99.8% [10].

The follow-up to identify the incidence of seizures started on January 1, 2002, and ended when the subjects experienced seizures or were censored. Reasons to be censored and relative data were emigration (date of emigration), admission to the nursing home (01/01/year), development of DM (01/01/year) or death (date of death). Subjects admitted to the nursing homes were censured because we did not have access to their drug prescription data.

Comorbidities

The following comorbidities were traced through their respective ICD-9 codes during hospital admissions in the two years before entering study (2000–2001): chronic heart disease, myocardial infarction, heart failure, atrial fibrillation, cerebrovascular disease, stroke, kidney disease, hypoglycemia, brain tumor, inflammatory disease of the central nervous system (CNS), traumatic brain injury (TBI) and mental disorder.

The following comorbidities having etiologic significance for seizures or epilepsy in the elderly were considered as covariates: cerebrovascular disease, inflammatory CNS disease, mental disorder, brain tumor and TBI. Age, sex and number of hospital admissions in the years 2000 and 2001 were also considered as covariates. All ICD-9 diagnostic codes are listed in Appendix (see Supplementary material).

Statistical analysis

Age was divided in six classes (<70, 70–74, 75–79, 80–84, 85–89, ≥90 years), taking the youngest as the reference group. The number of hospital admissions in the years 2000 and 2001 (a proxy for the hospital admissions in the following years) was divided into four groups (0, 1–2, 3–4, ≥5) taking the class without hospitalizations as the reference category. Males were the reference category for sex. "Comorbidities were dichotomized. Reference category was absence of disease".

Baseline characteristics of DM and No-DM subjects were compared by the Chi-square test for categorical variables and the Student's *t* test for age.

Cumulative incidence of seizures in patients with and without DM was plotted using Kaplan–Meier estimates. The significance of differences between the Kaplan–Meier curves was assessed with the log-rank test. Hazard ratios (HRs), with 95% confidence intervals (CIs), for seizures in DM patients compared to No-DM subjects were analyzed using univariable and a multivariable Cox proportional hazards regression models adjusted for sex, age classes, cerebrovascular disease, inflammatory diseases of the central nervous system, mental disorders, brain tumor, TBI and number of hospital admissions, so as to avoid overestimation of the incidence of seizures in DM patients compared to No-DM due to more frequent hospitalizations. To control the presence of stroke, a major cause of seizures in the elderly population, a similar model was fitted in a subgroup of patients not diagnosed with stroke during the entire period. In a further analysis, patients were classified according to the presence and the number of cardio-cerebrovascular comorbidities (coronary heart disease, atrial fibrillation, heart failure and cerebrovascular disease) in the years 2000 and 2001 into five groups (No-DM subjects and no comorbidities, No-DM subjects with comorbidities, DM subjects with no comorbidities, DM subjects with one comorbidity and DM with two or more comorbidities). The first group was taken as the reference group.

A two-sided value of $p \leq 0.05$ was considered significant. Analyses were done with Stata 13.0 (Stata Corp LP, College Station, TX, USA), JMP Pro 12.0 (SAS Institute Inc., Cary, NC, USA) and SAS software, version 9.4 (SAS Institute).

Results

The study population included 1,494,071 persons aged 65 years or older in 2002 (Figure S1). Of these, the 62,504 (4.2%) individuals who received a diagnosis of seizures or epilepsy in the previous two years were excluded.

A total of 136,941 subjects (9.56%) fulfilled our diagnostic criteria of DM. From 2002 to 2012, a total of 18,981(1.3%) subjects had a diagnosis of seizure (or epilepsy), 2493 (1.8%) within DM subjects and 16,488 (1.3%) within No-DM subjects.

The general characteristics of the sample are illustrated in Table 1. Compared to the rest of the study population, patients with DM were slightly older and had a higher proportion of men and a predominant number of all comorbidities, including TBI, brain tumor and mental disorder, with the only exception of inflammatory disease of the CNS. The number of hospital admissions was also higher among DM subjects (45.3%) compared to No-DM individuals (31.6%).

At the end of follow-up (mean follow-up period, 7.66 years, total person-years, 10,741,070), the cumulative time-dependent incidence of seizures was 3.0% (95% CI 2.92–3.17) in DM subjects and 1.9% (95% CI 1.85–1.91) in No-DM individuals (Fig. 1). In DM subjects, the incidence of seizures was 0.4% (95% CI 0.41–0.48) at 2 years and 1.2% (95% CI 1.12–1.25) at 5 years. The corresponding values for No-DM subjects were 0.3% (95% CI 0.28–0.30) and 0.8% (95% CI 0.75–0.79) at 2 and 5 years, respectively. The overall period unadjusted risk of seizures among DM subjects was 1.60 (95% CI 1.54–1.67). The risk

Table 1 Baseline characteristics and comorbidities of subjects with or without diabetes

Variable	Overall population (no. = 1,431,567)	Subjects with diabetes (no. = 136,941)	Subjects without diabetes (no. = 1,294,626)	*P* value
Age, year (±SD)	75.92 (±6.94)	76.06 (±6.59)	75.90 (±6.98)	<0.001
Male sex, No. (%)	557,017 (39.0)	60,980 (44.5)	49,6037 (38.3)	<0.001
Age classes (years), No. (%)				
<70	286,386 (20.0)	24,162 (17.6)	262,224 (20.2)	<0.001
70–74	423,353 (29.6)	40,111 (29.3)	383,242 (29.6)	
75–79	331,817 (23.2)	34,588 (25.3)	297,229 (23.0)	
80–84	201,586 (14.1)	21,276 (15.5)	180,310 (14.0)	
85–89	114,578 (8.0)	11,165 (8.1)	103,413 (8.0)	
≥90	73,847 (5.2)	5639 (4.1)	68,208 (5.3)	
Comorbidity[a], No. (%)				
Coronary heart disease	68,864 (4.81)	13,454 (9.82)	55,410 (4.28)	<0.001
Myocardial infarction	10,755 (0.75)	2290 (1.67)	8465 (0.65)	<0.001
Heart failure	27,473 (1.92)	6089 (4.45)	21,384 (1.65)	<0.001
Atrial fibrillation	40,352 (2.82)	5860 (4.28)	34,492 (2.66)	<0.001
Cerebrovascular disease	51,813 (3.62)	9156 (6.69)	42,657 (3.29)	<0.001
Stroke	14,335 (1.00)	2667 (1.95)	11,688 (0.90)	<0.001
Kidney disease	19,342 (1.35)	5503 (4.02)	13,839 (1.07)	<0.001
Hypoglycemia	518 (0.04)	388 (0.28)	130 (0.01)	<0.001
Inflammatory diseases of the central nervous system	178 (0.01)	22 (0.02)	156 (0.01)	0.205
Mental disorder	11,024 (0.77)	1472 (1.07)	9552 (0.74)	<0.001
Brain tumors	794 (0.06)	133 (0.10)	661 (0.05)	<0.001
Traumatic head injury	3941 (0.28)	480 (0.35)	3461 (0.27)	<0.001
Number of hospital admission[a], No. (%)				
0	960,595 (67.10)	74,954 (54.7)	88,5641 (68.4)	<0.001
1–2	372,301 (26.01)	44,923 (32.8)	327,378 (25.3)	
3–4	72,380 (5.06)	11,763 (8.6)	60,617 (4.7)	
>4	26,291 (1.84)	5301 (3.9)	20,990 (1.6)	

Baseline characteristics of DM and No-DM subjects were compared using the Chi-square test for categorical variables and the Student's *t*-test for age

DM diabetes mellitus

[a] Comorbidity and hospital admission were collected in the two years (2000–2001) before entering the cohort study

remained higher in DM subjects (1.47, 95% CI 1.41–1.53) after adjusting for all considered variables and was also predominant in men, in patients with comorbidities, and increased exponentially with the number of hospital admissions (Table 2). Considering the diagnosis of seizures as hospital admission or as EEG examination and antiepileptic drug separately, the HR remained similar: 1.46 (95% CI 1.38–1.54) and 1.34 (95% CI 1.26–1.42), respectively.

The HR observed in the subgroup of patients without stroke during the entire period was 1.45 (95% CI 1.38–1.53). The cumulative incidence of seizures in DM and No-DM subjects by comorbidity status is reported in Fig. 2. The incidence in No-DM individuals and no cardio-cerebrovascular comorbidities was 1.8%. The incidence increased to 2.8% in DM subjects without comorbidities, to 3.2% in No-DM subjects with at least one comorbidity, to 4.1% DM subjects with one comorbidity and to 4.9% in DM subjects with 2 or more comorbidities. A similar trend was also observed when adjusting for sex and age (Fig. 2).

Discussion

Our study shows that DM is an independent risk factor for seizures in elderly patients. The cumulative incidence of seizures was 3.0% in DM subjects as compared to 1.9% in No-DM individuals. The disease carried a 1.47-fold increased risk of seizures after adjusting for age, sex and

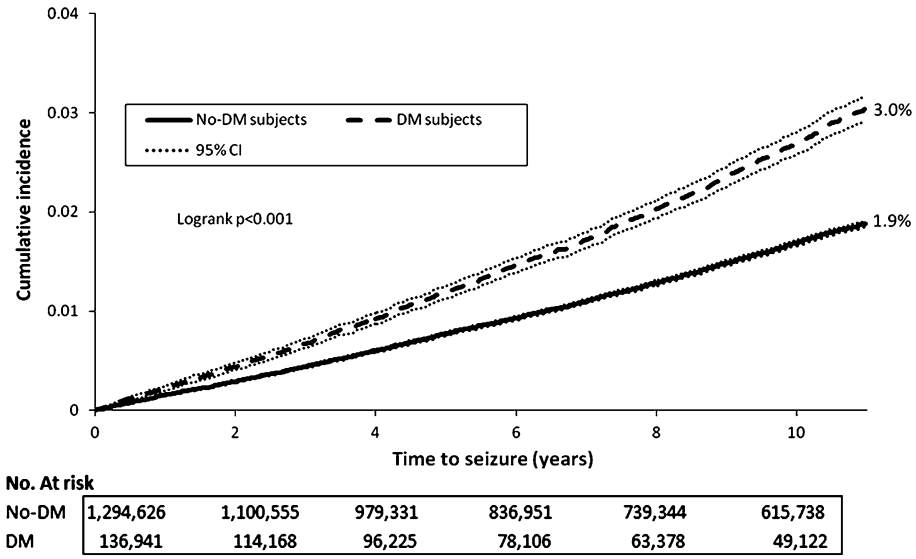

Fig. 1 Cumulative incidence curves for seizures in subjects with or without diabetes. *DM* diabetes mellitus

Table 2 Unadjusted and adjusted hazard ratio of incidence of seizures according to the presence of diabetes

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
DM	1.60 (1.54–1.67)	1.47 (1.41–1.53)
Sex	1.18 (1.15–1.21)	1.16 (1.12–1.19)
Age classes (years),		
70–74	1.20 (1.15–1.25)	1.18 (1.14–1.23)
75–79	1.37 (1.31–1.43)	1.32 (1.27–1.38)
80–84	1.44 (1.37–1.52)	1.38 (1.31–1.45)
85–89	1.55 (1.45–1.66)	1.48 (1.38–1.58)
≥90	1.26 (1.14–1.40)	1.24 (1.12–1.38)
Comorbidities		
Cerebrovascular disease	3.25 (3.08–3.44)	2.28 (2.14–2.42)
Inflammatory CNS disease	3.84 (1.83–8.05)	2.21 (1.05–4.64)
Mental disorder	4.19 (3.68–4.77)	2.30 (2.02–2.63)
Brain tumor	5.77 (4.31–7.74)	3.37 (2.51–4.52)
Traumatic brain injury	2.20 (1.79–2.72)	1.41 (1.15–1.77)
Number of hospital admissions		
1–2	1.44 (1.39–1.48)	1.24 (1.20–1.28)
3–4	1.91 (1.80–2.02)	1.46 (1.37–1.55)
>4	2.39 (2.17–2.63)	1.70 (1.54–1.87)

Reference was male for sex, <70 years for age classes and zero for number of hospital admission

DM diabetes mellitus, *CNS* central nervous system

[a] HR: Hazard ratio; IC: 95% confidence interval; Cox regression model was adjusted for sex, age classes, comorbidities and number of hospital admissions

Comorbidities and number of hospital admissions were collected in the two years (2000–2001) before entering the cohort

major comorbidities. DM HR was lower than HR for brain tumors, inflammatory CNS disorders, cerebrovascular disease and mental disorders.

Although data investigating the association between diabetes and seizures in the elderly are scarce, our findings are in keeping with other reports. In the Stockholm study [6], patients with unprovoked seizures had a 1.9 higher risk of having been hospitalized with DM. The fourfold risk of seizures (higher than ours) shown in another study in adults [2] could be explained by the different population at risk (individuals aged 15–30 years with or without idiopathic generalized epilepsy).

In the UK, 20 of 2016 patients with pharmacoresistant epilepsy admitted to a tertiary medical center had type 1

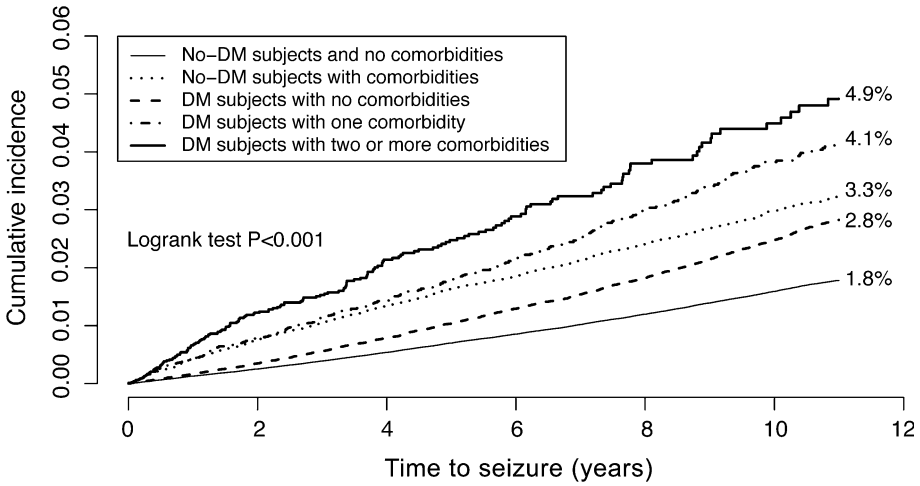

Fig. 2 Cumulative incidence of seizures and adjusted hazard ratio in DM and No-DM subjects by comorbidity status. *DM* diabetes mellitus

DM (point prevalence of 9.9 per 1000 population) [11]. This finding represents a more than twofold increase relative to published prevalence estimates of type 1 DM in the general population.

There are several possible explanations for the association between seizures and DM. The disease shares several pathogenic mechanisms with other putative causes of seizures in the elderly. These include, among others, microvascular brain injuries, immune abnormalities and metabolic factors [1]. The importance of maintaining a good glycemic control over time to decrease the incidence of micro- and macrovascular complication in subjects with diabetes has been demonstrated [12–14]. The hyperglycemic state causes cell damage by promoting advanced glycation end products, activating protein kinase C, and through polyol pathway activation, which might play an important role in the development of diabetes atherosclerosis [15]. Atherosclerosis in elderly patients with diabetes can be caused by chronic hyperglycemia, dyslipidemia, hypertension and hyperinsulinemia. Increased levels of molecular mediators, such as circulating vascular cell adhesion molecule-1, plasminogen activator inhibitor-1, tissue factor and increased platelet activation, are also implicated in the development of atherosclerosis and all contribute to vascular dysfunction with ischemia/hypoxia [15].

In our study, we observed an increased risk of developing seizures in patients with cardio-cerebrovascular comorbidities (coronary heart disease, atrial fibrillation, heart failure and cerebrovascular disease). The presence of two or more comorbidities, in patient with DM, conferred a higher risk. The increasingly higher seizure risk in patients with 1, 2 or more comorbidities is in keeping with others [16] and supports the role of vascular disease as a major cause of epilepsy in the elderly [17].

Autoimmune diseases also carry an increased risk of seizures. The role of immunity and inflammatory processes in epilepsy is increasingly recognized [18]. Glutamic acid decarboxylase (GAD) antibodies are important markers in type 1 DM [19]. Although autoimmunity is a well-known pathogenic component of type 1 DM, the pathogenesis of type 2 DM also encompasses autoimmune aspects based on the presence of circulating autoantibodies against β cells, self-reactive T cells and also on the glucose lowering efficacy of some immunomodulatory therapies [20].

Along with hyperglycemia, also hypoglycemia is a common occurrence in elderly patients with diabetes. These metabolic derangements alter the balance between excitation and inhibition of neural networks [21–23]. Diabetic ketoacidosis has been also associated with an increased risk of seizures in children and adolescents with type 1 DM (3). Metabolic factors, such as hyperglycemia and hypoglycemia, may have a damaging effect on the CNS, leading to EEG abnormalities and epileptic seizures [22, 24].

The major strength of the study is the use of administrative data from a large unselected cohort, which allow an unbiased assessment of the epidemiology of diseases, since in Italy everyone is assisted by the NHS, with a high level of completeness regarding drug prescriptions, diagnosis and follow-up. Administrative data are increasingly used in public health research because they are readily available, collected over time in a standardized way and inexpensive. The study, however, has some limitations. First of all, the diagnoses of DM and seizures could not be verified in our cases. This leaves room to a certain degree of over- and under-ascertainment. Although the diagnosis of seizures and epilepsy in Italy is generally confirmed by a neurologist and the diagnosis of DM must be confirmed by a specialist before being entitled for exemption, we cannot exclude

undiagnosed cases. Second, DM, seizure and epilepsy types could not be identified in the administrative records. Thus, we cannot confirm whether the purported association between DM and seizures in the elderly involves all patients or is limited to specific subcategories of the two diseases. Third, given the available data, we cannot exclude that some patients experiencing acute symptomatic seizures (caused by hyper- or hypoglycemia) could be erroneously given the diagnosis of epilepsy. However, patients' characteristics are not available (such as glycemic control, lifestyle habits, CV risk factors) that could influence the rate of hospital admissions for seizures or epilepsy.

Fourth, the administrative records do not include patients hosted in nursing homes. However, with the inclusion of these patients the association between DM and seizures might have been even stronger. Last, although we did our best to adjust for relevant comorbidities, the possibility cannot be excluded that the association between DM and seizures is due to other factors (e.g., dementia and microvascular diseases such as retinopathy or peripheral neuropathy, difficult to identify from administrative records).

In conclusion, our findings provide fairly robust evidence that DM is an independent predictor of seizures in the elderly. Poor glycemic control adds to vascular disease and is thus an additional risk factor for seizures and epilepsy in this fragile population. An adequate control of metabolic parameters is even more needed not only to decrease the vascular complications of DM but also to prevent this serious complication.

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Authors' contribution Guarantor's name: All authors take responsibility for the contents of the article. BE, BM, RMC and TM took part in study concept and design, and interpretation of data. FI, BA and ML performed acquisition of data. VT and TM carried out analysis of data. BE, BM and RMC drafted the manuscript. All authors participated in critical revision of the manuscript for important intellectual content.

Compliance with ethical standards

Conflict of interest Ettore Beghi received personal fees from Viropharma to participate in an Advisory Board, research grants from UCB-Pharma, EISAI, Shire, the Italian Drug Agency (AIFA), the Italian Ministry of Health, the American ALS Association and the Borgonovo Foundation. The other authors have nothing to declare.

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Human and animal rights In Italy, approval from an ethics committee is not required to analyze encrypted administrative data according to the National law.

Informed consent In Italy, informed consent is not required to analyze encrypted administrative data according to the National law.

References

1. Yun C, Xuefeng W (2013) Association between seizures and diabetes mellitus: a comprehensive review of literature. Curr Diabetes Rev 9:350–354
2. McCorry D, Nicolson A, Smith D et al (2006) An association between type 1 diabetes and idiopathic generalized epilepsy. Ann Neurol 59:204–206
3. Schober E, Otto KP, Dost A et al (2012) Association of epilepsy and type 1 diabetes mellitus in children and adolescents: is there an increased risk for diabetic ketoacidosis? J Pediatr 160:662–666
4. Chou IC, Wang CH, Lin WD et al (2016) Risk of epilepsy in type 1 diabetes mellitus: a population-based cohort study. Diabetologia 59:1196–1203
5. O'Connell MA, Harvey AS, Mackay MT et al (2008) Does epilepsy occur more frequently in children with type 1 diabetes? J Paediatr Child Health 44:586–589
6. Adelöw C, Andersson T, Ahlbom A et al (2011) Prior hospitalization for stroke, diabetes, myocardial infarction, and subsequent risk of unprovoked seizures. Epilepsia 52:301–307
7. Huang CW, Tsai JJ, Ou HY et al (2008) Diabetic hyperglycemia is associated with the severity of epileptic seizures in adults. Epilepsy Res 79:71–77
8. Forsgren L, Beghi E, Oun A et al (2005) The epidemiology of epilepsy in Europe—a systematic review. Eur J Neurol 12:245–253
9. Monesi L, Baviera M, Marzona I et al (2012) Prevalence, incidence and mortality of diagnosed diabetes: evidence from an Italian population-based study. Diabet Med 29:385–392
10. Franchi C, Giussani G, Messina P et al (2013) Validation of health care administrative data for the diagnosis of epilepsy. J Epidemiol Community Health 67:1019–1024
11. Keezer MR, Novy J, Sander JW (2015) Type 1 diabetes mellitus in people with pharmacoresistant epilepsy: prevalence and clinical characteristics. Epilepsy Res 115:55–57
12. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 353:2643–2653
13. Holman RR, Paul SK, Bethel MA (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 359:1577–1589
14. Gaede P, Lund-Andersen H, Parving HH et al (2008) Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 358:580–591
15. Umemura T, Kawamura T, Hotta N (2017) Pathogenesis and neuroimaging of cerebral large and small vessel disease in type 2 diabetes: a possible link between cerebral and retinal microvascular abnormalities. J Diabetes Investig 8(2):134–148
16. Pugh MJ, Knoefel JE, Mortensen EM et al (2009) New-onset epilepsy risk factors in older veterans. J Am Geriatr Soc 57:237–242
17. Li X, Breteler MM, de Bruyne MC et al (1997) Vascular determinants of epilepsy: the Rotterdam Study. Epilepsia 38:1216–1220
18. Nabbout R (2012) Autoimmune and inflammatory epilepsies. Epilepsia 53(Suppl 4):58–62
19. Pociot F, Lernmark Å (2016) Genetic risk factors for type 1 diabetes. Lancet 387:2331–2339

20. Itariu BK, Stulnig TM (2014) Autoimmune aspects of type 2 diabetes mellitus—a mini-review. Gerontology 60:189–196
21. Maheandiran M, Mylvaganam S, Wu C et al (2013) Severe hypoglycemia in a juvenile diabetic rat model: presence and severity of seizures are associated with mortality. PLoS One 8:e83168. doi:10.1371/journal.pone.0083168
22. Schwechter EM, Velísková J, Velísek L (2003) Correlation between extracellular glucose and seizure susceptibility in adult rats. Ann Neurol 53:91–101
23. Kirchner A, Velísková J, Velísek L (2006) Differential effects of low glucose concentrations on seizures and epileptiform activity in vivo and *in vitro*. Eur J Neurosci 23:1512–1522
24. Soltész G, Acsádi G (1989) Association between diabetes, severe hypoglycaemia, and electroencephalographic abnormalities. Arch Dis Child 64:992–996