Original Article

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Association between type 1 diabetes mellitus and risk of epilepsy: A meta-analysis of observational studies

Dandan Yan[1], Enfa Zhao[1], Hong Zhang[2], Xiaohui Luo[1], Yajuan Du[1,*]

[1] *Department of Structural Heart Disease, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China;*
[2] *Department of Neurology, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China.*

Summary **A potential association between type 1 diabetes mellitus and subsequent epilepsy emerged in recent studies. This study aimed to evaluate the possible relationship between type 1 diabetes mellitus and epilepsy using meta-analysis. Pubmed, ISI Web of Knowledge, Embase and Cochrane Library were searched for potential studies of the association between type 1 diabetes mellitus and epilepsy from inception to February 1, 2017. Two investigators independently screened studies for inclusion and extracted related data; discrepancies were solved by consensus. Random effects model of Hazard Ratio (HR) was used to estimate the strength of association. We identified 13 papers from potentially relevant articles of which 3 cohort studies met the inclusion criteria. Random effects meta-analysis showed that type 1 diabetes mellitus was associated with an increased risk of epilepsy with HR = 3.29 (95% CI: 2.61-4.14; I^2 = 0, p = 0.689). Similar results were observed in type 1 diabetes mellitus patents younger than 18-years-old with HR = 2.96 (95% CI: 2.28-3.84; I^2 = 0, p = 0.571). Meta-analysis of 2 studies that adjusted for potential confounders yielded an increased risk of epilepsy with HR = 2.89 (95% CI: 2.26-3.70; I^2 = 0, p = 0.831). The meta-analysis indicates that type 1 diabetes mellitus is associated with a statistically significant increased risk for epilepsy compared to those without type 1 diabetes mellitus.**

Keywords: Type 1 diabetes mellitus, epilepsy, meta-analysis

1. Introduction

Type1 diabetes mellitus (T1DM) was characterized by destruction of pancreatic beta cells in the pancreatic islets and required lifelong dependence on exogenous insulin (*1*). In recent years, the incidence of T1DM has increased in children younger than 5 years and adolescents (*2*). Patients with T1DM were at an increased risk of suffering several severe health issues and mortality (*3*). Epilepsy was the most frequent serious neurological disorder. It was reported that the estimated prevalence of active epilepsy ranged from 0.2% to 4.1% (*4*). Varied causes of epilepsy were commonly reported, such as metabolic disturbances, structural, autoimmunity or genetic causes; however, the potential causes of epilepsies were still unclear (*5*). There was increased interest in a potential possible association between epilepsy and T1DM. However, the reported results were still inconsistent. Chou *et al*. found a positive association between type 1 diabetes mellitus and epilepsy with an HR of 2.84 (*6*), Dafoulas *et al*. *established* a positive association with an HR of 3.01 (*1*). Ramakrishnan *et al*. even found an almost six-fold increase in epilepsy in UK children with T1DM (*7*), whereas, some authors failed to confirm these associations (*8,9*). Thus, we conducted a meta-analysis to accurately evaluate the relationship between type 1 diabetes mellitus and risk for epilepsy.

2. Materials and Methods

2.1. *Search strategy*

We performed a systematic literature search of Pubmed, Embase, ISI Web of Knowledge and Cochrane Library from inception to February 1, 2017, for human studies of type 1 diabetes mellitus and epilepsy without a language restriction. The overall search strategy

**Address correspondence to:*
Dr. Yajuan Du, Department of Structural Heart Disease, the First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, Shaanxi 710004, China.
E-mail: xmy505@163.com

referred to medical subject heading terms and/or text words: seizures or epilepsy and type 1 diabetes mellitus or T1DM. The references list of all included studies was also manually reviewed for potential studies. Abstracts and citations were screened independently by two investigators, and all included articles had a further screen for full-text reports.

2.2. *Inclusion and exclusion criteria*

A study was included in the meta-analysis if it met the following criteria: *i*) studies for type 1 diabetes mellitus; *ii*) the study evaluated the association between type 1 diabetes mellitus and subsequent epilepsy risk; *iii*) one of the outcomes contains epilepsy; and *iv*) study must contain a reference group. Editorials, letters, systematic reviews, comments or reports lacking sufficient data were excluded. If the works were shared or duplicated in more than one study, the most recent publication was included. All identified papers were independently reviewed by two authors.

2.3. *Data extraction*

Two investigators independently extracted the following data from each study: First author, year of publication, country, study type, matching conditions, crude HR, adjusted HR, Incidence rate, follow-up period and T1DM age. Disagreements were resolved by detailed discussion, consensus and arbitration by the third author.

2.4. *Statistical analysis*

All statistical analyses were carried out with Stata version 11.0 software (StataCorp, College Station,TX). Hazard ratio (HR) with 95% confidence interval (CIs) was used to estimate the effect sizes. I^2 was used to describe the statistical heterogeneity among studies. $I^2 > 50\%$ was considered to show severe heterogeneity. A random-effect model was used if $p > 0.05$ and $I^2 < 50\%$, otherwise, a fixed-effect model was selected. We used Begg's test (rank correlation method) (*10*) to evaluate possible publication bias and a p value of < 0.1 was considered as significant statistical publication bias.

3. Results

3.1. *Characteristics of the subjects in the included studies*

Detailed studies retrieval procedures are summarized in Figure 1. A total of 487 references were preliminarily identified according to the search strategy. 284 records remained after excluding 203 duplicate articles. We screened titles and abstracts of all identified papers and 171 clearly irrelevant records were excluded. After reviewing the remaining articles in more detail, 10 of the full-text articles were excluded for 3 reviews, 3 for insufficient data, 2 without control group and 2 letters. Finally, 3 cohort studies were eventually included in the study. Characteristics of 3 eligible studies are shown in Table 1.

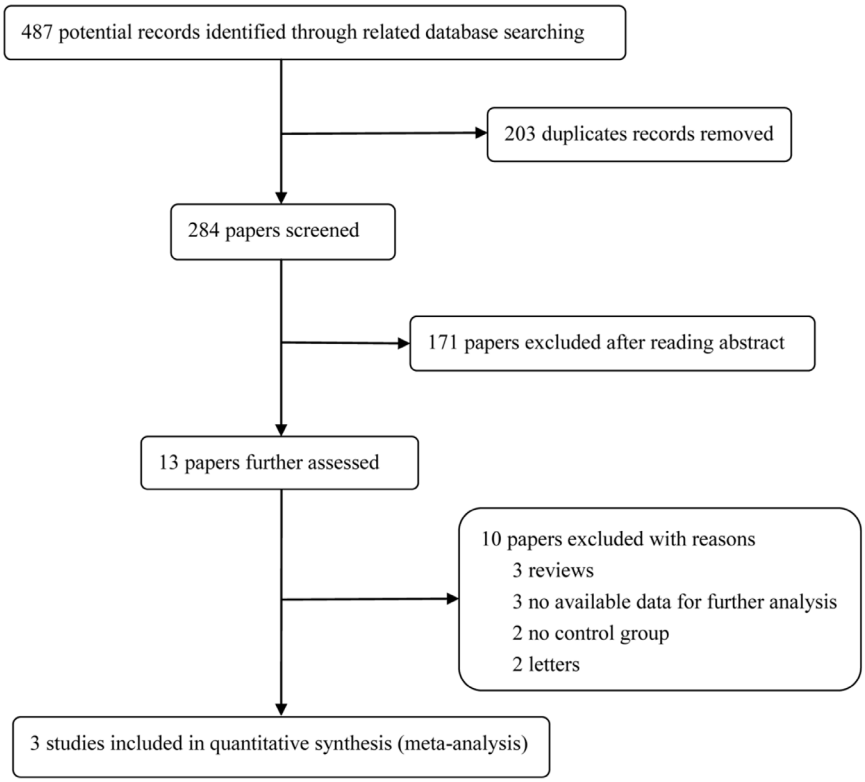

Figure 1. Flow chart of study selection process in the meta-analysis.

Table 1. Characteristics of 3 eligible studies in the meta-analysis

Author	Year	Country	Matched	Adjustment	Crude	Incidence rate (per 100,000 person-years), *n*		Follow-up	T1DM age
						Comparision cohort	T1DM cohort		
Chou C	2016	China	sex, urbanisation of residence area and index year with ten patients without type 1 diabetes	HR 2.84 [95% CI 2.11-3.83]	HR 3.26[95% CI]:(2.43, 4.37)	1.04	3.37	12 years	aged ≤ 18 years
George E	2016	UK	matched with up to four individuals without type 1 diabetes mellitus, based on age, sex and participating general practice	HR 3.01[95% CI1.93-4.68])/ HR 3.40[95% CI]: (1.97, 5.88) (≤ 18 years)	HR 3.02[95% CI]:(1.95, 4.69)/ HR 3.44[95% CI]:1.99-5.96 (≤ 18 years)	44/45 (≤ 18 years)	132/150 (≤ 18 years)	mean of 5.4 years	≤ 40 years (≤ 18 years)
McCorry D	2006	UK	age-matched patients with idiopathic generalized epilepsies (IGEs)		HR 4.4[95% CI]:(2.1-9.2)	150,000 subjects 15- to 30-year-olds	518 15- to 30-year-olds13with IGE	13 years	15-30 years

3.2. *Meta-analysis results*

As shown in Figure 2, the pooled results indicated that type 1 diabetes mellitus was associated with a statistically significant increased risk for epilepsy compared to those without type 1 diabetes mellitus. Random effects meta-analysis showed that T1DM was associated with an increased risk of epilepsy without noticeable heterogeneity with HR = 3.29 (95% CI: 2.61-4.14; $I^2 = 0$, $p = 0.689$). Similar results were observed in type 1 diabetes mellitus patients younger than 18-year-old age with HR = 2.96 (95% CI: 2.28-3.84; $I^2 = 0$, $p = 0.571$) (Figure 3). Meta-analysis of 2 studies that adjusted for potential confounders yielded an increased risk of epilepsy with HR = 2.89 (95% CI: 2.26-3.70; $I^2 = 0$, $p = 0.831$) (Figure 4).

3.3. *Publication bias*

To evaluate potential bias across studies, Begg's test with funnel plot asymmetry was used to identify small study effects of the association between T1DM and the risk of epilepsy. The funnel plot shown in Figure 5 was symmetrical, which indicated a low potential publication bias ($p = 0.526$).

4. Discussion

To our knowledge, this is the first meta-analysis that evaluated the possible effect of type 1 diabetes mellitus on subsequent epilepsy using the results of previous published studies. In this study, we found that type 1 diabetes mellitus was significantly associated with an increased risk for epilepsy compared to those without type 1 diabetes mellitus.

In recent years, there has been increasing support for the potential association between T1DM and the risk of epilepsy, although the exact mechanisms of the association remain unclear. This comorbid association was not isolated (*11*). Several hypotheses concerning the potential possible pathophysiology of the comorbidity, including genetic factors, immune abnormalities, brain lesions and metabolic abnormalities have been proposed by some researchers (*5,12*). Previously study found that glutamic acid decarboxylase antibodies (GAD-Abs) were a significant marker in TIDM patients. It was reported that GAD-Abs have been associated with T1DM and epilepsy (*13*). GAD-Abs were observed in about 60% to 70% of diabetes mellitus patients at the time of disease onset. Caietta *et al*. studied 10 T1DM children complicated with epilepsy and GAD-Abs was detected in most cases (*14*). The inactivation of gamma-amino butyric acid (GABA) receptors can also result in epilepsy (*15*). Owing to the central GABA increase in metabolism induced by hyperglycemia, GABA expression and epilepsy threshold were suppressed, thus facilitating the occurrence of seizures. Previous

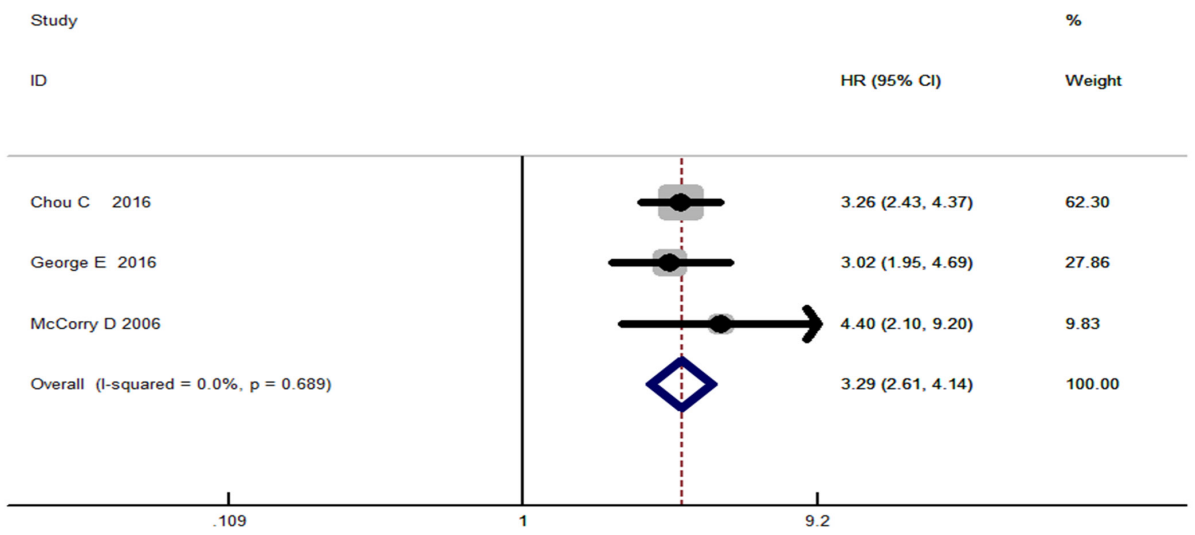

Figure 2. Pooled Hazard Ratio (HR) for the association between T1DM and epilepsy in 3 cohort studies.

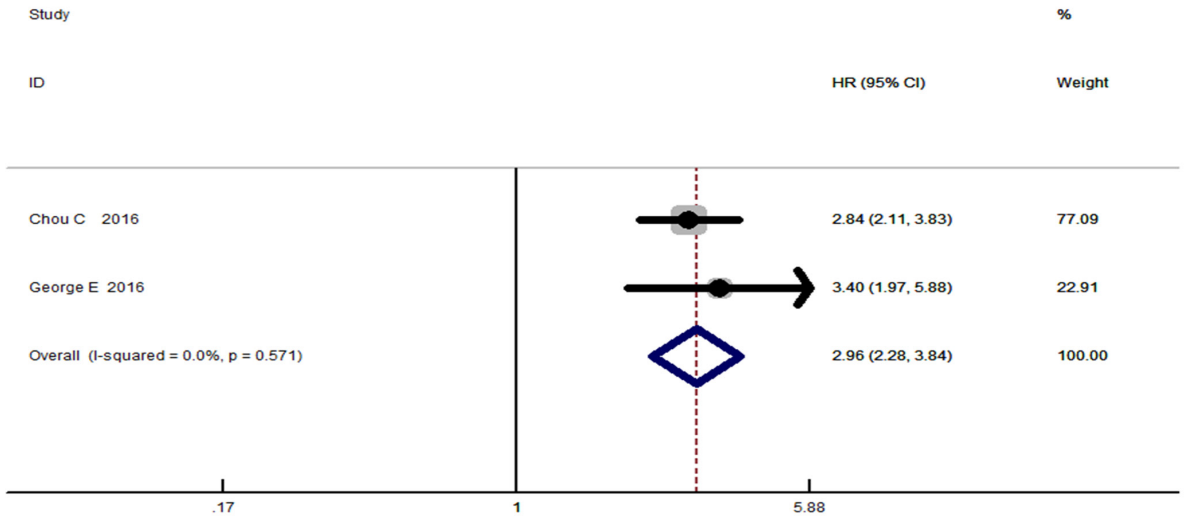

Figure 3. Pooled Hazard Ratio (HR) for the association between T1DM and epilepsy in patients younger than 18-years-old.

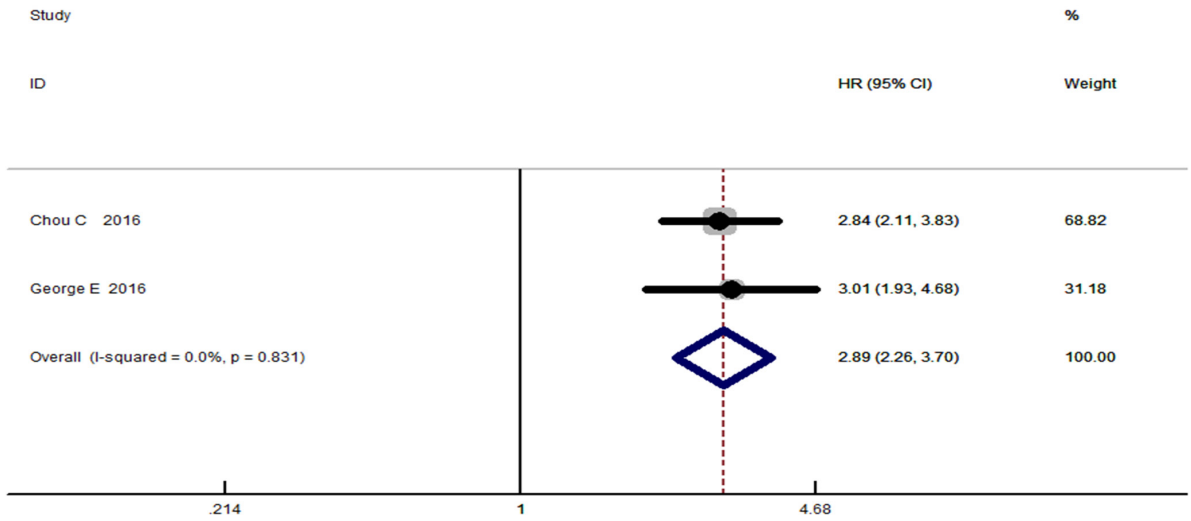

Figure 4. Pooled Hazard Ratio (HR) for the association between T1DM and epilepsy in patents adjusted for potential confounders.

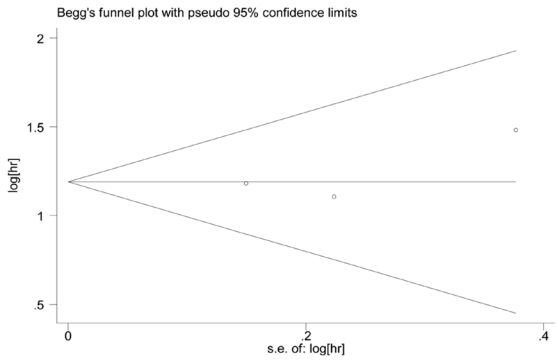

Figure 5. Funnel plot of studies evaluating the association between T1DM and epilepsy. Begg's regression asymmetry test (p = 0.526).

reports have found that approximately 15% of the diabetic patients complicated with seizures also suffered local brain damage under head computed tomography scanning. Seizures may be the result of T1DM patients' cerebrovascular complications that were commonly associated with varied types of brain damage (*6*). A possible relationship between cerebral infarction caused by diabetes mellitus and partial epilepsy has been also noted by Schomer *et al*. (*16*). Diabetes mellitus can result in pathological capillary changes, leading to neurological complications, such as epilepsy (*5*). The frequency that hypoglycemia occurred in diabetes mellitus was closely connected with the frequency of seizures (*17*). Seizures would gradually disappear when metabolic factors, such as hypoglycemia were removed. A case report found that transient hypoglycemia was caused by insulin administration and later presented with a focal seizure (*18*). The above indicated that metabolic disorders result from diabetes mellitus were closely related to epilepsy risk. Most diabetic mellitus patients complicated with seizures presented neither evident metabolic abnormalities nor serious brain damage, according to CT and MRI scanning, which indicated that there were perhaps some potential unknown pathogenesis that resulted in seizures. Previous study found that IER3IP1 mutations were the key factors, which account for the pathogenesis of early onset diabetes mellitus and infantile epilepsy. Gene mutation might act as a vital role in the pathogenesis of diabetic infantile epilepsy.

In addition, in this study, we found that T1DM patients younger than 18-years-old were also associated with an increased risk of developing epilepsy. Previous studies have demonstrated that young age, early onset and hypoglycemia can result in electroencephalographic abnormalities (*19*). The study revealed that patients who suffered electroencephalographic abnormalities were younger and had an earlier onset of diabetes (*6*). However, our meta-analysis also has limitations. However, even though we performed a systematic literature search only three studies were included. Besides, some negative studies failed to provide specific data for further analysis, which perhaps resulted in potential publication bias. Second, because of only three studies included, study quality assessment was not performed.

In conclusion, our meta-analysis indicated that patients with type 1 diabetes mellitus were associated with a higher incidence of increased risk for epilepsy compared to those without type 1 diabetes mellitus. The associations remained unchanged even when adjusted for potential confounders and in T1DM patients younger than 18-years-old. The specific mechanisms of the link between type 1 diabetes mellitus and epilepsy remained unclear. The causative factors require further investigation in future studies with a larger sample size.

References

1. Dafoulas GE, Toulis KA, McCorry D, Kumarendran B, Thomas GN, Willis BH, Gokhale K, Gkoutos G, Narendran P, Nirantharakumar K. Type 1 diabetes mellitus and risk of incident epilepsy: A population-based, open-cohort study. Diabetologia. 2017; 60:258-261.
2. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014; 383:69-82.
3. Zhao Y, Ye W, Boye KS, Holcombe JH, Swindle R. Healthcare charges and utilization associated with diabetic neuropathy: Impact of Type 1 diabetes and presence of other diabetes-related complications and comorbidities. Diabet Med. 2009; 26:61-69.
4. Ottman R, Lipton RB, Ettinger AB, Cramer JA, Reed ML, Morrison A, Wan GJ. Comorbidities of epilepsy: Results from the Epilepsy Comorbidities and Health (EPIC) survey. Epilepsia. 2011; 52:308-315.
5. Yun C, Xuefeng W. Association between seizures and diabetes mellitus: A comprehensive review of literature. Curr Diabetes Rev. 2013; 9:350-354.
6. Chou IC, Wang CH, Lin WD, Tsai FJ, Lin CC, Kao CH. Risk of epilepsy in type 1 diabetes mellitus: A population-based cohort study. Diabetologia. 2016; 59:1196-1203.
7. Ramakrishnan R, Appleton R. Study of prevalence of epilepsy in children with type 1 diabetes mellitus. Seizure. 2012; 21:292-294.
8. O'Connell MA, Harvey AS, Mackay MT, Cameron FJ. Does epilepsy occur more frequently in children with Type 1 diabetes? J Paediatr Child Health. 2008; 44:586-589.
9. Mancardi MM, Striano P, Giannattasio A, Baglietto MG, Errichiello L, Zara F, Prato G, Minuto N, Veneselli E, Lorini R, D'Annunzio G. Type 1 diabetes and epilepsy: More than a casual association? Epilepsia. 2010; 51:320-321.
10. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50:1088-1101.
11. Sander JW, Novy J, Keezer MR. The intriguing relationship between epilepsy and type 1 diabetes mellitus. Diabetologia. 2016; 59:1569-1570.
12. Keezer MR, Novy J, Sander JW. Type 1 diabetes mellitus in people with pharmacoresistant epilepsy: Prevalence and clinical characteristics. Epilepsy Res. 2015; 115:55-57.
13. Striano P, Errichiello L, Striano S. Autoantibodies to

glutamic acid decarboxylase in patients with epilepsy: What is their clinical relevance? Epilepsy Behav. 2011; 20:145.
14. Caietta E, Halbert C, Lepine A, Khammar A, Cano A, Gavaret M, Mancini J, Villeneuve N, Chabrol B, Simonin G, Reynaud R, Milh M. Association of type 1 diabetes mellitus and epilepsy in children. A cohort of 10 cases. Arch Pediatr. 2012; 19:9-16.
15. Cossette P, Liu L, Brisebois K, Dong H, Lortie A, Vanasse M, Saint-Hilaire JM, Carmant L, Verner A, Lu WY, Wang YT, Rouleau GA. Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. Nat Genet. 2002; 31:184-189.
16. Schomer DL. Focal status epilepticus and epilepsia partialis continua in adults and children. Epilepsia. 1993; 34 (Suppl 1):S29-36.
17. Lahat E, Barr J, Bistritzer T. Focal epileptic episodes associated with hypoglycemia in children with diabetes. Clin Neurol Neurosurg. 1995; 97:314-316.
18. Lapenta L, Di Bonaventura C, Fattouch J, Bonini F, Petrucci S, Gagliardi S, Casciato S, Manfredi M, Prencipe M, Giallonardo AT. Focal epileptic seizure induced by transient hypoglycaemia in insulin-treated diabetes. Epileptic Disord. 2010; 12:84-87.
19. Soltesz G, Acsadi G. Association between diabetes, severe hypoglycaemia, and electroencephalographic abnormalities. Arch Dis Child. 1989; 64:992-996.

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