Diabetologia (2016) 59:1569–1570
DOI 10.1007/s00125-016-3982-8

LETTER

The intriguing relationship between epilepsy and type 1 diabetes mellitus

Josemir W. Sander[1,2,3] · **Jan Novy**[4] · **Mark R. Keezer**[1,2,3,5]

Received: 9 April 2016 / Accepted: 13 April 2016 / Published online: 18 May 2016

To the Editor: We read with great interest the article by Chou et al reporting a longitudinal cohort study of more than 2500 people with type 1 diabetes mellitus [1]. They were compared with a matched control group in the same administrative database, allowing the investigators to estimate that people with type 1 diabetes were on average 2.8 times more likely to develop epilepsy than those without type 1 diabetes.

The study has numerous strengths, including its foundation in a large, population-based sample effectively including all Taiwanese residents, as well as sound statistical methods. The study was not free of challenges. The diagnostic algorithms for type 1 diabetes and epilepsy have not been validated; this is often difficult to avoid in such large-scale studies. The investigators correctly considered hypoglycaemia as a potential confounder but did not, however, consider hyperglycaemia. This was possibly because it less often requires medical attention translating into a recorded diagnosis. In addition, the potential effect of age on epilepsy incidence was not controlled for. Those in the control group were on average 0.7 years older, which was statistically significant. This age difference is relatively small, but the data also suggested that the association between age and epilepsy is strong; those aged at least 6 years were 40% less likely to have epilepsy than those under 6 years. Fifty-nine people were reported to have 'developed' epilepsy over the course of the study, but 27% (16 of 59) had a prior history of epilepsy, which would generally make these prevalent rather than incident cases.

The findings of Chou et al are an important advance in our understanding of the relationship between type 1 diabetes and epilepsy. Previous studies have produced conflicting results in part due to inconsistent attempts to distinguish between type 1 and type 2 diabetes [2]. Only two previous studies specifically defined which individuals had type 1 diabetes, and both these showed that the prevalence of type 1 diabetes was roughly twofold greater (point-prevalence between 10 and 13 per 1000 individuals) in people with epilepsy than what is expected in the general population [2, 3]. This comorbid association is not isolated. Several studies have shown similar relationships between epilepsy and a number of conditions, including concordant ones such as migraine and dementia, as well as discordant conditions such as asthma and peptic ulcers [4]. Five mechanisms of association of the comorbidities of epilepsy are described: chance and artefactual comorbidities, causative mechanisms, resultant mechanisms, shared risk factors and bidirectional effects [4].

Chou et al present four hypotheses to explain the particular relationship between type 1 diabetes and epilepsy: metabolic abnormalities, cerebrovascular disease, genetic factors and autoimmune-related factors. We believe that some of these have more merit than others.

Seizures directly provoked by metabolic abnormalities, for example hyper- and hypoglycaemia as suggested by the authors, are inconsistent with the diagnosis of epilepsy, which is defined as the predisposition towards recurrent unprovoked seizures [5]. It is possible that a metabolic abnormality of

✉ Mark R. Keezer
mark.keezer.chum@ssss.gouv.qc.ca

1 UCL Institute of Neurology, NIHR University College London Hospitals Biomedical Research Centre, London, UK

2 Epilepsy Society, Chalfont St Peter, UK

3 Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, the Netherlands

4 Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

5 Centre Hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame, 3ième pavillon Deschamps, porte H-3110, 1560 rue Sherbrooke est, Montréal, Québec H2L 4M1, Canada

sufficient severity could produce a permanent cortical lesion which would then go on to become epileptogenic, but we consider this to be a rare occurrence. If resultant cerebrovascular disease were the reason for the majority of cases of new onset epilepsy, it would be reasonable to expect the relationship between type 2 diabetes and epilepsy to be strong (due to the comorbid effect of age), but in fact the opposite appears to be true [2]. As Chou et al also show, a large proportion of epilepsy diagnoses precede diabetes onset: 27% in the present study, 20% in a similar series [2]. Such findings are, at least to some degree, inconsistent with a vascular hypothesis.

Variable temporal sequence, where either condition may precede the other, is more suggestive of either a bidirectional relationship (each condition is apt to cause the other) or of a shared risk factor. Shared genetic factors predisposing to both epilepsy and diabetes are fascinating areas of future research. Another highly relevant potential factor, as mentioned, is a shared autoimmune aetiology, in particular autoantibodies to GAD. GAD antibodies are found in 80% of people with type 1 diabetes as well as 6% of people with epilepsy [2]. One study showed that higher anti-GAD titres are associated with more severe epilepsy [6]. There are potential therapeutic implications of this, with reports of successful treatment of anti-GAD-associated epilepsy with immunosuppressive therapy [7] while others have argued that these individuals may particularly benefit from anti-epilepsy drugs that act on γ-aminobutyric acid (GABA) receptors [8].

We congratulate Chou et al for their impressive study and look forward to future work on this important topic, with the expectation that the impact on our understanding of both diseases, and more importantly on patient care, will be great.

Acknowledgements JWS and MK are based at the University College London Hospitals NHS Foundation Trust/UCL Comprehensive Biomedical Research Centre, which received a proportion of funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

Funding The authors received no specific grant in relation to this letter from any funding agency in the public, commercial or not-for-profit sectors.

Duality of interest JWS has received research funding from Eisai, GSK and UCB, personal fees from Eisai, UCB Lundbeck and Teva, outside the submitted work. He receives research support from the Marvin Weil Epilepsy Research Fund. His current position is endowed by the Epilepsy Society, and he is a member of the editorial board of The Lancet Neurology. JN reports grants and personal fees from UCB and Pfizer. MRK reports grants and personal fees from UCB and SAGE therapeutics, outside the submitted work. He is a member of the editorial board of Epilepsia.

Contribution statement We attest that all three authors made substantial contributions to the conception, drafting, and revision of the manuscript. All three authors approved the final version to be published.

References

1. Chou IC, Wang CH, Lin WD, Tsai FJ, Lin CC, Kao CH (2016) Risk of epilepsy in type 1 diabetes mellitus: a population-based cohort study. Diabetologia doi:10.1007/s00125-016-3929-0
2. 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
3. McCorry D, Nicolson A, Smith D, Marson A, Feltbower RG, Chadwick DW (2006) An association between type 1 diabetes and idiopathic generalized epilepsy. Ann Neurol 59:204–206
4. Keezer MR, Sisodiya SM, Sander JW (2016) Comorbidities of epilepsy: current concepts and future perspectives. Lancet Neurol 15:106–115
5. Fisher RS, Acevedo C, Arzimanoglou A et al (2014) ILAE official report: a practical clinical definition of epilepsy. Epilepsia 55:475–482
6. Kwan P, Sills GJ, Kelly K, Butler E, Brodie MJ (2000) Glutamic acid decarboxylase autoantibodies in controlled and uncontrolled epilepsy: a pilot study. Epilepsy Res 42:191–195
7. Vincent A, Bien CG, Irani SR, Waters P (2011) Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol 10:759–772
8. Nemni R, Braghi S, Natali-Sora MG et al (1994) Autoantibodies to glutamic acid decarboxylase in palatal myoclonus and epilepsy. Ann Neurol 36:665–667