TITLE

The riveting relationship between epilepsy and type 1 diabetes

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LETTER TO THE EDITOR (max 1000 words)

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 (DM1).[1] They were compared to a matched control group in the same administrative database, allowing the investigators to estimate that people with DM1 were on average 2.8 times more likely to develop epilepsy than those without DM1.

The study has numerous strengths, including its foundation in a large, population-based sample effectively including all Taiwan residents as well as sound statistical methods. The study was not free of challenges. The diagnostic algorithms for DM1 and epilepsy are not validated. This is often unavoidable in such large-scale studies. The investigators correctly considered hypoglycaemia as a potential confounder. They did not, however, consider hyperglycaemia. This was possibly because it less often requires medical attention and therefore, translates into a recorded diagnosis. 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 percent less likely to have epilepsy than those less than 6 years. Fifty-nine people were reported to have "developed" epilepsy over the course of the study, but 30% (18 of 59) had a prior epilepsy history, 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 DM1 and epilepsy. Prior studies have produced conflicting results in part due to inconsistent attempts to distinguish between DM1 and type 2 diabetes.[2] Only two previous studies specifically defined which individuals were with DM1. Both showed that the prevalence

of DM1 was roughly two-fold 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 DM1 and epilepsy: metabolic abnormalities, cerebrovascular disease, genetic factors, and autoimmune-related. 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 sufficient severity could produce a permanent cortical lesion which could then go on to become epileptogenic, but we would consider this to be a rare occurrence. If resultant cerebrovascular disease were the reason for the majority of new onset epilepsy, it would be reasonable to expect that 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: 30% in the present study, 20% in a similar series.[2] Such findings are, at least to some measure, 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 potential future research. Another highly relevant potential factor, as mentioned, is a shared auto-immune aetiology, in particular anti-glutamic acid decarboxylase (GAD) antibodies. Anti-GAD antibodies are found in 80% of people with DM1 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. There are 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 GABA receptors.[8]

We congratulate Chou et al for their impressive study. We 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.

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