Intriguing Association of Parkinson's Disease and Epileptic Seizures

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We read with interest the article by Gruntz et al.[1] These authors suggest that incident Parkinson's disease (PD) is associated with an increased risk of incident epileptic seizures. This observation is a very important contribution, which will be useful in future studies, and we want to acknowledge these authors for their efforts. However, some issues raise concerns and merit a more detailed examination.

First, Gruntz et al's case selection is based on a large data set from a primary care setting. The same group, using the same data set in previous articles, specified that only a small percentage (1%) of all cases were referred to a neurologist to confirm the diagnosis,[2] and that seizure diagnosis is not formally validated in the data set.[3] Other disorders with prominent signs and symptoms of transient loss of consciousness (TLOC), such as syncope, may be confused with seizures. The reliability of the diagnosis of the first TLOC is therefore surprisingly low,[4] and this may particularly be the case in a primary care setting, such as the one used for this study.

Second, for case selection, one of the engaged criteria was usage of antiepileptic drugs (AEDs) in combination with diagnostic codes indicating a suspected epileptic seizure as a surrogate for the diagnosis of epileptic seizure. However, AEDs can be indicated for many conditions other than epilepsy, which may lead to misclassification.

In a sensitivity analysis, these authors applied a definition of incident epilepsy that they used in another study with the same data set.[5] However, that study[5] used criteria of AED prescriptions in conjunction with diagnostic codes for epilepsy and not with codes for suspected epileptic seizures.

Finally, this study utilized a conditional logistic regression analyses to explore the "real association" between PD and the risk of epileptic seizures. Nevertheless, these authors essentially presented only the results of a univariate logistic regression. A univariate analysis should be only the first step in any model building process. Despite the fact that this study matched controls for many variables, there can still be effect modifiers, and a multivariate analysis could examine potential statistical interactions between each of the selected variables.

Overall, the association of PD and epileptic seizures is intriguing, and we strongly support further investigation in this area. However, considerable caution is necessary in making causal inferences from case-control studies.

Potential Conflicts of Interest

Nothing to report.

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References

1. Gruntz K, Bloechliger M, Becker C, et al. Parkinson disease and the risk of epileptic seizures. Ann Neurol 2018;83:363–374.
2. Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR. Seizures in patients with Alzheimer's disease or vascular dementia: a population-based nested case-control analysis. Epilepsia 2013;54:700–707.
3. Bloechliger M, Ceschi A, Rüegg S, et al. Lifestyle factors, psychiatric and neurologic comorbidities, and drug use associated with incident seizures among adult patients with depression: a population-based nested case-control study. Eur J Epidemiol 2016;31:1113–1122.
4. Hoefnagels WAJ, Padberg GW, Overweg J, Roos RAC. Syncope or seizure? A matter of opinion. Clin Neurol Neurosurg 1992;94: 153–156.
5. Hesdorffer DC, Ishihara L, Webb DJ, et al. Occurrence and recurrence of attempted suicide among people with epilepsy. JAMA Psychiatry 2016;73:80–86.

DOI: 10.1002/ana.25257

Reply to "Intriguing Association of Parkinson Disease and Epileptic Seizures"

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We thank Dr Lukić et al for their comments on our study on Parkinson disease (PD) and incident epileptic seizures.

The authors correctly point out that epileptic seizures are not formally validated in the Clinical Practice Research Datalink (CPRD) and that other medical conditions could occasionally be misdiagnosed as epileptic seizures. We dealt with the uncertainty of seizure diagnoses in the CPRD in several ways.

First, diagnoses in the CPRD are generally of high validity, and specialist and hospital care are routinely reported to the general practitioners (GPs). Thus, at least some of the diagnoses were initially made in specialist care and then referred to the GP, despite another study by our group, which reported that only a small percentage of patients in the CPRD had a record of a referral to a neurologist after the GP record of epileptic seizures.[1]

Second, the most likely sources of potential misclassification of epileptic seizures in our study population are discussed in the article, none of which would explain the observed association between PD and epileptic seizures. Random misclassification leads to bias to the null and would not explain the elevated risks reported in our study.

Third, we conducted a sensitivity analysis in which we applied more rigorous criteria, namely those mentioned in the

study by Hesdorffer et al.[2] As this sensitivity analysis yielded results closely similar to the main analysis, we are confident that our results are robust.

We agree that univariate regression models would not yield a valid association between PD and epileptic seizures. We thus adjusted for confounding factors using multivariate conditional regression in the nested case–control analysis, and we stratified by important potential confounders or effect modifiers, both valid methods to deal with confounding and effect modification in epidemiologic studies. Both adjusted and stratified analyses were provided in the paper.

Lastly, it is true that epidemiologic studies cannot prove causality, regardless of the study design, because of the nature of real life medical practice where exposures are not randomly allocated as in randomized controlled trials. Patient characteristics, comorbidities, and concomitant medications may bias the association between the study exposure and outcome. It is the case, however, that epidemiologic research is sometimes the only option to study associations between exposures and outcomes when the exposure cannot be randomly allocated. Observational research has contributed substantially and repeatedly to a better understanding of disease risk factors and unintended drug effects.

Potential Conflicts of Interest

Nothing to report.

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References

1. Imfeld P, Bodmer M, Schuerch M, et al. Seizures in patients with Alzheimer's disease or vascular dementia: a population-based nested case-control analysis. Epilepsia 2013;54:700–707.
2. Hesdorffer DC, Ishihara L, Webb DJ, et al. Occurrence and recurrence of attempted suicide among people with epilepsy. JAMA Psychiatry 2016;73:80–86.

DOI: 10.1002/ana.25252