

Viral hepatitis and Parkinson disease

A national record-linkage study

Julia Pakpoor, BA, BM
BCh*
Alastair Noyce, MRCP,
PhD*
Raph Goldacre, MSc
Marianna Selkikhova,
MRCP, PhD
Stephen Mullin, BSc,
MRCP
Anette Schrag, FRCP,
PhD
Andrew Lees, FRCP, MD
Michael Goldacre, FFPH,
FRCP

Correspondence to
Dr. Goldacre:
michael.goldacre@dph.ox.ac.uk

ABSTRACT

Objective: To study associations between viral hepatitis and Parkinson disease (PD).

Methods: A retrospective cohort study was done by analyzing linked English National Hospital Episode Statistics and mortality data (1999–2011). Cohorts of individuals with hepatitis B, hepatitis C, autoimmune hepatitis, chronic active hepatitis, and HIV were constructed, and compared to a reference cohort for subsequent rates of PD.

Results: The standardized rate ratio (RR) of PD following hepatitis B was 1.76 (95% confidence interval [CI] 1.28–2.37) ($p < 0.001$), based on 44 observed compared with 25 expected cases. The RR of PD following hepatitis C was 1.51 (95% CI, 1.18–1.9) ($p < 0.001$), based on 48.5 expected and 73 observed cases. There was no significant association between autoimmune hepatitis, chronic active hepatitis or HIV, and subsequent PD. When including only those episodes of care for PD that occurred first at least 1 year following each exposure condition, the RR for hepatitis B and hepatitis C were 1.82 (1.29–2.5) and 1.43 (1.09–1.84), respectively.

Conclusions: We report strong evidence in favor of an elevation of rates of subsequent PD in patients with hepatitis B and hepatitis C. These findings may be explained by factors peculiar to viral hepatitis, but whether it reflects consequences of infection, shared disease mechanisms, or the result of antiviral treatment remains to be elucidated. Further work is needed to confirm this association and to investigate pathophysiologic pathways, potentially advancing etiologic understanding of PD more broadly. **Neurology® 2017;88:1630–1633**

GLOSSARY

CI = confidence interval; **HCV** = hepatitis C virus; **HES** = English National Hospital Episode Statistics; **ICD-10** = *International Classification of Diseases-10*; **PD** = Parkinson disease; **RR** = rate ratio.

Parkinson disease (PD) is a common neurodegenerative disease characterized by motor and non-motor symptoms, with loss of dopaminergic neurons in the substantia nigra pars compacta and presence of Lewy body pathology.¹ The etiopathogenesis of the disease is complex, and multiple risk factors have been identified including advancing age, male sex, environmental toxins, and head trauma.¹ Two epidemiologic studies based in Taiwan have recently added to an existing body of case reports reporting an association between hepatitis C and risk of PD.^{2,3} In one of these, a nationwide cohort study utilizing the Taiwan National Health Insurance Research Database, an adjusted hazard ratio of PD following hepatitis C of 1.29 (95% confidence interval [CI] 1.06–1.56) was observed.² Neither study found evidence of a relationship between hepatitis B virus and PD following adjustment for potential confounding factors. We used a linked dataset of English national hospital records to study associations between viral hepatitis and PD, and we speculate whether any such relationship may be a reflection of viral hepatitis specifically, hepatitis more generally, or the use of antiviral therapy.

METHODS Population and data. English National Hospital Episode Statistics (HES) were analyzed in conjunction with mortality data to conduct a retrospective cohort study across 1999–2011. Utilizing HES records encompassing all episodes of day-case or inpatient care in all National Health Service hospitals in England, we built cohorts of individuals with hepatitis B, hepatitis C,

*These authors contributed equally to this work.

From the Unit of Health-Care Epidemiology (J.P., R.G., M.G.), Nuffield Department of Population Health, University of Oxford; and UCL Institute of Neurology (A.N., M.S., S.M., A.S., A.L.), Queen Square, London, UK.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

autoimmune hepatitis, chronic active hepatitis, and HIV by identifying the first episode of day-case or inpatient admission in which each of these conditions was coded (whether as the principal cause for the admission, or in any diagnostic position) (ICD-10 codes used in construction of exposure cohorts are found in the table footnotes). Individuals admitted for a variety of relatively minor medical and surgical conditions (table footnotes) were extracted to build a reference cohort. Individuals with a preexisting or co-occurring admission for PD at the time of first exposure condition were excluded.

Statistical methods. Date of entry into each of the cohorts was taken as the date of first recorded episode of day-case or inpatient care for the exposure or reference conditions. Date of first recorded episode for PD, death, or the reach of end of data collection constituted the date of cohort exit (whichever was earliest). Analyses of PD rates were stratified, and standardized, in 5-year age groups, by sex, calendar year of first recorded admission (for exposure and reference conditions), residential area, and quintile of socioeconomic status (as estimated by the standard English measure of Index of Deprivation score). Indirect standardization was applied, in which the standard population comprised the combined exposure and reference cohort. Stratum-specific rates in the standard population were applied to the number of person-days in each corresponding stratum of each exposure cohort and then, separately, to those in the corresponding stratum in the reference cohort, to calculate the expected number of cases of PD in each stratum in each cohort. In each cohort, the observed and expected numbers in each stratum were summed to provide the total for the cohort. Where O and E represent the observed and expected numbers of PD in both the exposure and reference cohorts, the formula $(O^{HEP}/E^{HEP})/(O^{REF}/E^{REF})$ provides the rate ratios (RRs). The methodology used in the calculation of CIs for RRs and calculation of χ^2 statistics in assessment of significance, and more detailed methods of analytical technique, has been described elsewhere.⁴

Standard protocol approvals, registrations, and patient consents. The build and use of the datasets for multipurpose research received ethical approval from the Central and South Bristol Research Ethics Committee (04/Q2006/176).

RESULTS There were 21,633, 48,428, 6,225, 4,234, and 19,870 individuals in the hepatitis B, hepatitis C, autoimmune hepatitis, chronic active hepatitis, and HIV cohorts, respectively. A total of 6,132,124 individuals were in the reference cohort. The standardized RR of PD following hepatitis B was 1.76 (95% CI 1.28–2.37). The RR of PD following hepatitis C was 1.51 (95% CI 1.18–1.9) (table). There were no significant elevations of PD rates in the autoimmune hepatitis, chronic active hepatitis, or HIV cohorts. In aiming to reduce the possibility of surveillance bias and of reverse causality, we subsequently included only those episodes of care for PD that occurred first at least 1 year following each exposure condition, and found a consistently elevated PD risk following hepatitis B and hepatitis C (table).

DISCUSSION We report evidence supporting a significantly increased risk of PD in patients with hepatitis B or C. Significant associations between autoimmune hepatitis, chronic hepatitis, or HIV and PD were not observed. These findings may be explained by a specific aspect of viral hepatitis (rather than a general hepatic inflammatory process or general use of antivirals) but whether this reflects shared disease mechanisms, shared genetic or environmental

Table Rate ratios (RRs) and 95% confidence intervals (CIs) for Parkinson disease (PD) in people with hepatitis or HIV compared with the reference cohort

Exposure	Overall outcome	Observed	Expected	RR (95% CI)	p Value
Hepatitis B	PD	44	25.0	1.76 (1.28–2.37)	<0.001
Hepatitis C	PD	73	48.5	1.51 (1.18–1.90)	<0.001
Autoimmune hepatitis	PD	16	10.1	1.59 (0.91–2.58)	0.087
Chronic active hepatitis	PD	18	15.7	1.15 (0.68–1.81)	0.652
HIV	PD	16	13.7	1.16 (0.67–1.89)	0.635
	Outcome at least 1 year after first exposure admission				
Exposure	Overall outcome	Observed	Expected	RR (95% CI)	p Value
Hepatitis B	PD	38	20.9	1.82 (1.29–2.50)	<0.001
Hepatitis C	PD	59	41.3	1.43 (1.09–1.84)	0.008
Autoimmune hepatitis	PD	13	7.4	1.76 (0.94–3.00)	0.061
Chronic active hepatitis	PD	13	13.7	0.95 (0.51–1.63)	0.961
HIV	PD	12	12.3	0.98 (0.50–1.70)	0.954

Exposure cohorts ICD-10 codes used were hepatitis B B16.0–B16.9, B18.0–B18.1; hepatitis C B17.1, B18.2; autoimmune hepatitis K75.4; chronic active hepatitis K73.2; HIV B20–B24; PD G20. Conditions used in the reference cohort were as follows: cataract, otitis externa/media, varicose veins, hemorrhoids, deflected nasal septum, nasal polyp, inguinal hernia, ingrowing toenail and other diseases of nail, sebaceous cyst, internal derangement of knee, bunion, appendectomy, hip replacement, knee replacement, gallbladder disease.

susceptibility, sequelae of viral hepatitis per se, or a consequence of treatment remains to be determined. These findings are in line with the recently reported association between hepatitis C and PD in Taiwan, but contrast with the finding of no association with hepatitis B.^{2,3} Explaining a relationship between viral hepatitis and PD is largely speculative. Neurotropic features of hepatitis C have been described previously and include the potential for cognitive impairment, independent of hepatic encephalopathy.⁵ Further, all essential hepatitis C virus (HCV) receptors have been shown to be expressed on the brain microvascular endothelium, which constitutes the primary component of the blood–brain barrier, thus suggesting one mechanism by which the virus may affect the CNS.⁶ This notion has been supported by the detection of HCV RNA sequence in a small study of postmortem brain tissue from infected patients.⁷ A study in rats, with and without hepatitis C, found evidence of neuronal toxicity (60% dopaminergic neuron death) induced by the virus in a midbrain neuron–glia co-culture system.³ Intriguingly, parkinsonism during combination treatment with pegylated interferon- α and ribavirin, commonly used in chronic HCV, has been described. There was no improvement following termination of HCV treatment, but clinical benefit was observed with use of levodopa, and symptom relapse upon tapering.⁸ In considering interferon as a potential contributory factor, in the Taiwanese community-based study (2000–2004) most hepatitis C–infected patients would not have been exposed to interferons (only reimbursed in Taiwan for HCV from 2004), making interferon unlikely to have an important role, at least in their data.³ We note that the rate of autoimmune hepatitis and PD was close to reaching statistical significance in this study, and thus influence of a common factor between autoimmune and viral hepatitis is possible. Parkinsonism in the context of liver cirrhosis is recognized and thought to be independent from hepatic encephalopathy–associated cognitive impairment. At least in some cases, this may be secondary to manganese deposition. We did not adjust our analyses for prevalent cases of cirrhosis because clinical data on the presence of cirrhosis was not available to us. We consider it likely that there may be many patients with hepatitis and secondary cirrhosis who never have their cirrhosis coded as a separate diagnosis in hospital, and the use of a day-case or inpatient hospital record with an ICD-10 code for cirrhosis is hence considered an unreliable tool in considering the potential presence of cirrhosis-related parkinsonism.

Limitations include that we were unable to control for lifestyle factors such as smoking or alcohol. However, notably, smokers have higher rates of viral

hepatitis but lower rates of PD (and thus would potentially mask any positive association between viral hepatitis and PD), and the association between alcohol and PD is unclear but suggests no relationship or a reduced rate of PD with high alcohol consumption.^{9,10} The use of routinely collected hospital data also means that detailed clinical data, such as that needed to confirm a PD diagnosis beyond it having been clinically coded, were not available to us. Therefore we are not able to rule out that our findings could be explained by an increased association with cirrhosis-related parkinsonism, and not PD. However, given the rare occurrence of cirrhosis-related parkinsonism, we find this unlikely. This is also not a follow-up study from the point of first diagnosis: entry into the exposure and reference cohorts is based upon the first recorded episode of hospital care for the respective conditions. We assume that the majority of patients with PD will have been coded in hospital at least once. The numbers of PD cases were often small, even when drawing upon a population of 50 million; and this study should be considered as best that could be done using a very large national hospital dataset of the HES type. As it is a hospital-based study, it is not possible to exclude the potential presence of selection bias compared to a community-based study, and it is possible that patients included in this study may represent those at the more severe end of disease spectrum. We have aimed to mitigate this as best as possible through the inclusion of a reference cohort that is also hospital-based.

We report evidence in favor of elevated rates of subsequent PD in patients with hepatitis B and hepatitis C. Acknowledging constraints of routinely collected data, we suggest that this may reflect factors associated specifically with viral hepatitis or its treatment. We encourage further work confirming this association or contributing insight into potential pathophysiologic pathways, which may be important in understanding the development of PD more broadly.

AUTHOR CONTRIBUTIONS

A.N. proposed the study. J.P. wrote the first draft of the manuscript. All authors edited the manuscript for important intellectual content. J.P., R.G., and M.J.G. designed the analysis, which was conducted by R.G. All authors contributed to the interpretation of the data. M.J.G. is the guarantor of the study.

ACKNOWLEDGMENT

The Health and Social Care Information Centre provided data on HES, and the Office for National Statistics provided data on death registrations. The Oxford record-linkage group undertook linkage of the records in constructing a time-sequenced record of successive care episode (or death, if applicable) for each person.

STUDY FUNDING

The building of the linked datasets, and the development of the analytical software used to study disease associations, was funded by the English National Institute for Health Research. This study had no specific funding. The funder had no role in study design, data collection, data analysis,

data interpretation, writing of the report, or the decision to submit for publication. The views expressed in the article do not necessarily reflect those of the funding body.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received June 29, 2016. Accepted in final form January 25, 2017.

REFERENCES

1. Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet* 2009;373:2055–2066.
2. Tsai HH, Liou HH, Muo CH, Lee CZ, Yen RF, Kao CH. Hepatitis C virus infection as a risk factor for Parkinson disease: a nationwide cohort study. *Neurology* 2016;86:840–846.
3. Wu WY, Kang KH, Chen SL, et al. Hepatitis C virus infection: a risk factor for Parkinson's disease. *J Viral Hepat* 2015;22:784–791.
4. Gold J, Goldacre R, Maruszak H, et al. HIV and lower risk of multiple sclerosis: beginning to unravel a mystery using a record-linked database study. *J Neurol Neurosurg Psychiatry* 2014;86:9–12.
5. McAndrews MP, Farcnik K, Carlen P, et al. Prevalence and significance of neurocognitive dysfunction in hepatitis C in the absence of correlated risk factors. *Hepatology* 2005;41:801–808.
6. Fletcher NF, Wilson GK, Murray J, et al. Hepatitis C virus infects the endothelial cells of the blood-brain barrier. *Gastroenterology* 2012;142:634–643.e6.
7. Radkowski M, Wilkinson J, Nowicki M, et al. Search for hepatitis C virus negative-strand RNA sequences and analysis of viral sequences in the central nervous system: evidence of replication. *J Virol* 2002;76:600–608.
8. Bersano A, Aghemo A, Rumi MG, Ballabio E, Candelise L, Colombo M. Recovery after L-DOPA treatment in peginterferon and ribavirin induced parkinsonism. *Eur J Intern Med* 2008;19:370–371.
9. Hernán MA, Takkouche B, Caamaño-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol* 2002;52:276–284.
10. Bettioli SS, Rose TC, Hughes CJ, Smith LA. Alcohol consumption and Parkinson's disease risk: a review of recent findings. *J Parkinsons Dis* 2015;5:425–442.

We're Looking for the Next Generation of Leaders— Apply for Emerging Leaders Program!

Are you looking to take your career to the next level? We're looking for *you!* Applications are now open for a prestigious and interactive six-month program designed to identify, engage, and mentor AAN members who are less than 10 years out of residency or training. Learn more and apply by the July 1 deadline at AAN.com/view/ELP.

BrainPAC

BrainPAC is the American Academy of Neurology's (AAN) federal political action committee.

- Since its inception, more than 3,600 AAN members have contributed \$2,000,000 to BrainPAC.
- BrainPAC contributed more than \$600,000 to individuals who ran for election in 2016, including several first-time candidates.
- During the 2016 congressional election, 92% of candidates supported by BrainPAC won election to the US Congress.

BrainPAC supports both Democrats and Republicans who support issues important to the practice of neurology and the care of patients with neurologic conditions. US AAN members are invited to learn more at BrainPAC.org.

Neurology[®]

Viral hepatitis and Parkinson disease: A national record-linkage study
Julia Pakpoor, Alastair Noyce, Raph Goldacre, et al.
Neurology 2017;88;1630-1633 Published Online before print March 29, 2017
DOI 10.1212/WNL.0000000000003848

This information is current as of March 29, 2017

Updated Information & Services	including high resolution figures, can be found at: http://www.neurology.org/content/88/17/1630.full.html
References	This article cites 10 articles, 2 of which you can access for free at: http://www.neurology.org/content/88/17/1630.full.html##ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://www.neurology.org/content/88/17/1630.full.html##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Infections http://www.neurology.org/cgi/collection/all_infections Cohort studies http://www.neurology.org/cgi/collection/cohort_studies Parkinson's disease/Parkinsonism http://www.neurology.org/cgi/collection/parkinsons_disease_parkinsonism Risk factors in epidemiology http://www.neurology.org/cgi/collection/risk_factors_in_epidemiology Viral infections http://www.neurology.org/cgi/collection/viral_infections
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://www.neurology.org/misc/addir.xhtml#reprintsus

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2017 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

