

# Viral hepatitis and the risk of Parkinson disease

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Parkinson disease (PD) is a chronic progressive neurodegenerative disorder with a relatively high incidence.<sup>1</sup> PD seems to result from a complicated interplay of genetic and environmental factors affecting numerous fundamental cellular processes.<sup>2</sup> However, the ultimate cause of loss of dopaminergic neurons in the substantia nigra pars compacta remains to be determined.<sup>2</sup> An outright definitive cure for the disease remains elusive, leaving both patients and their caregivers with the challenge of living with a chronic medical condition that affects their health-related quality of life.<sup>2</sup> It is therefore imperative to focus research efforts on the search for the etiology of this condition.

An increasing body of evidence suggests that neuroinflammatory processes, including activated microglia, may play an important role in the development and aggravation of PD.<sup>3</sup> Understanding the mechanisms behind the inflammatory process associated with PD could be important in primary prevention and in developing effective therapies. In this sense, some evidence suggests a possible deleterious effect of neuroinflammatory processes induced by infections in experimental models of neurodegenerative disease.<sup>4</sup>

The possible role of infections has been previously considered as an etiologic factor of PD.<sup>5</sup> Among infectious agents, hepatitis C virus (HCV) is one of the most strongly associated with PD,<sup>6,7</sup> though specific mechanisms have not been elucidated to explain this association. Links between PD and hepatitis C have been analyzed recently in 2 Taiwanese epidemiologic studies.<sup>6,7</sup> Using data from a community-based integrated screening program in Keelung, the northernmost area in Taiwan, based on a total of 62,276 persons, Wu et al.<sup>6</sup> found that the association between hepatitis C and PD was significant (adjusted odds ratio 1.39; 95% confidence interval [CI] 1.07–1.80), but not different between hepatitis B and PD. Similarly, using a nationwide population-based cohort study, based on data obtained from a dataset of the Taiwan National Health Insurance Research Database for the period 2000–2010, Tsai et al.<sup>7</sup> found an increase of risk of developing PD associated

with hepatitis C (adjusted hazard ratio 1.29, 95% CI 1.06–1.56). As in the previous study,<sup>6</sup> there was no evidence of a relationship between hepatitis B virus and PD after adjustment for potential confounding factors.

In this issue of *Neurology*®, Pakpoor et al.<sup>8</sup> studied associations between viral hepatitis and PD. For that purpose, English National Hospital Episode Statistics were analyzed in conjunction with mortality data to conduct a retrospective cohort study across 1999–2011. The results of this study are of special interest. Pakpoor et al.<sup>8</sup> found strong evidence in favor of a positive association between hepatitis C and subsequent PD (standardized rate ratio 1.51, 95% CI 1.18–1.9), but they also found it for hepatitis B (standardized rate ratio 1.76, 95% CI 1.28–2.37), although not for autoimmune hepatitis, chronic hepatitis, or HIV.

The study had several strengths, including the large sample size and a well-thought-out approach to the statistical analyses. The study was not without limitations. As noted by the authors, they could not control for lifestyle factors such as smoking or alcohol. Second, records linkage system (that is, medical records of patients evaluated at a clinic or hospital) may underestimate the numbers of patients with PD because this type of approach tends to exclude patients who do not seek medical advice.<sup>1</sup> Even if the patient seeks medical advice, the disorder may be ascribed incorrectly to other medical conditions, particularly in the elderly.<sup>1</sup> The only way to overcome this problem is to use population-based studies where any suspected patients with parkinsonism have a detailed clinical examination.<sup>1</sup> Notwithstanding, the authors were aware of the limitations and, to their credit, provided a thoughtful discussion of these issues, indicating why they thought these issues were of less concern in this study.

Leaving aside issues of strengths and limitations, the study adds evidence in favor of elevated rates of subsequent PD in patients with hepatitis B and hepatitis C. The question is why this association occurs. There is some evidence that HCV may replicate in

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the CNS, probably in cells of the macrophage/monocyte lineage.<sup>9</sup> In addition, both HCV and PD share the overexpression of inflammatory biomarkers.<sup>3,10</sup> The evidence presented here by Pakpoor et al.<sup>8</sup> justifies running deep sequencing studies in autopsy brain tissue samples from patients with PD or in their CSF to detect links with infectious agents, especially HCV. However, for the link with hepatitis virus to be conclusive, either direct-acting antiviral therapies for chronic HCV should improve PD symptoms or further well-designed epidemiologic studies should show a strong association with specific hepatitis virus.

A better understanding of the pathologic bases of PD will lead to advances in the development of more effective treatments. The research by Pakpoor et al.<sup>8</sup> should stimulate more research on how infections, especially virus, may affect the biological processes that lead to PD.

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### DISCLOSURE

The author reports no disclosures relevant to the manuscript. Go to [Neurology.org](http://Neurology.org) for full disclosures.

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