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Hepatitis B and C virus infection as a risk factor for Parkinson's disease in Israel-A nationwide cohort study

Lilach Goldstein[a,b], Haya Fogel-Grinvald[c], Israel Steiner[a,b,*]

[a] Department of Neurology, Rabin Medical Center, Beilinson Campus, Petach Tikva, Israel
[b] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[c] School of occupational Therapy, The Hebrew University of Jerusalem, Jerusalem, Israel

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ABSTRACT

Objective: To study the association between hepatitis C and B viruses and Parkinson's disease (PD) in Israel.
Methods: A retrospective cohort study was performed by analyzing the computerized database of Clalit Healthcare Service in Israel. Cohorts of people with hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection and nonalcoholic steatohepatitis (NASH) were constructed and compared to a reference cohort for prevalence of PD.
Results: The prevalence of PD in Israel was found to be 0.5% in the general population. The M-H (Mantel-Haenszel) odds ratio (OR) of PD for HBV-positive patients was 1.08 (95% CI: 1.00–1.16). The M-H OR of PD for HCV-positive patients was 1.18 (95% CI: 1.04–1.35). The M-H OR of PD for patients infected with both hepatitis C and B was 1.13 (95% CI: 0.87–1.47). The M-H OR of PD for patients diagnosed with nonalcoholic steatohepatitis (NASH) was 1.13 (95% CI: 1.08–1.19).
Conclusions: We report evidence supporting a minor increased risk for PD in patients with HCV. Co infection of HCV and HBV was not associated with an increased risk for PD. The increased risk for PD in the group of patients with NASH, raises the possibility that liver disease per se is a risk factor for PD rather than viral infection. In addition, it cannot be ruled out that the association is, at least in part, the result of the occurrence of cirrhosis induced parkinsonism that was misclassified as PD.

1. Introduction

Parkinson's disease (PD) is the second-most prevalent neurodegenerative disorder, with reported prevalence in industrialized countries of 0.3% in the general population, 1.0% in people older than 60 years, and 3.0% in those aged 80 years and above [1]. A recent study that sought to estimate the prevalence of PD in North America found an overall prevalence among those aged ≥45 years was of 572 per 100,000 [2]. The neuropathological hallmarks of the disease are neuronal loss in the substantia nigra pars compacta, which causes striatal dopamine deficiency, and the presence of intracellular inclusions containing aggregates of α-synuclein, the Lewy bodies. The etiopathogenesis of the disease is complex and still elusive [1,3].

Hepatitis C virus (HCV) is a positive stranded RNA virus that belongs to the flaviviridae family, which includes other neurotropic viruses such as Japanese encephalitis, yellow fever, dengue and tick-borne encephalitis viruses [4]. The prevalence of chronic HCV infection ranges between 0.3 and 4% for most parts of the world. HCV infection is associated with cognitive dysfunction, fatigue and depression, which do not correlate with the severity of liver disease and cannot be accounted for by hepatic encephalopathy or drug abuse [5]. Negative-strand HCV RNA, which is a viral replicative intermediary, was detected in autopsied brain tissue of HCV-infected patients raising the possibility of direct association between central nervous system HCV infection and brain dysfunction [6]. Brain microvascular endothelial and brain endothelial cells were found to express all the recognized HCV entry receptors [7]. Evidence of HCV-induced neuronal toxicity was documented in rats [4]. Monoaminergic neurotransmission has been shown to be altered in HCV-infected patients with chronic fatigue and cognitive impairment [8].

The aggregation of aberrantly polymerized, misfolded proteins in the brain is a hallmark of several neurodegenerative disorders, including PD. One of the intriguing theories for the pathogenesis of PD is propagation of synuclein protein per continuum in a manner suggestive of an infectious process through the triggering of misfolding in normally folded proteins [9]. This mechanism, found to have similarities

* Corresponding author at: Department of Neurology, Rabin Medical Center, Beilinson Campus, 49100 Petach Tikva, Israel.
E-mail address: israels@ekmd.huji.ac.il (I. Steiner).

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with prion diseases, raises the possibility that infectious agent might have a role in the ethiopathogenesis of PD. It is possible that viral hepatitis itself is the causative infection, or it is a marker for other pathogen as a cause for PD. Nevertheless, there is no evidence for transmission of neurodegenerative disorders through blood transfusion [10]. Those observations raised the possibility of a potential ethiopathogenetic link between HCV infection and PD.

Human hepatitis B virus (HBV) is a member of the Hepadnaviridae family. The infectious virion contains a partially double stranded, relaxed circular DNA (rcDNA) genome. The worldwide estimated prevalence of chronic HBV infection in 2016 was 3·5% [11]. The pathophysiology of HBV-associated extrahepatic manifestations usually involves indirect consequences of immune-mediated mechanisms triggered by the virus replication. Strong evidence of brain HBV replication is missing and direct invasion of HBV into the nervous system symptoms has been rarely reported [12].

Two epidemiologic studies from Taiwan have found an association between HCV infection and increased risk of PD. [4,13] A community-based cohort concluded that HCV seropositive patients exhibited a significantly increased risk of developing PD with adjusted odds ratio (OR) = 1.39 (95% CI, 1.07–1.80) [4]. In a larger Taiwan nationwide cohort study utilizing the National Health Insurance Research Database, an adjusted hazard ratio of PD following HCV infection of 1.29 (95% CI 1.06–1.56) was observed [13]. The most significant association between HCV and PD was noted in male patients younger than 65 years, and in those that exhibited a combination of co morbidities. Neither of the studies found evidence of an association between HBV infection and PD following adjustment for potential confounding factors [4,13]. The associations between viral hepatitis viruses and PD, was evaluated also by analyzing linked English National Hospital Episode Statistics and mortality data in a retrospective cohort study. It came up with an association between HCV infection and PD. Relative risk (RR) of PD following HCV infection was 1.51 (95% CI 1.18–1.9). The standardized RR of PD following HBV infection in the English study was 1.76 (95% CI 1.28–2.37) [14]. This finding is in contrast to the Taiwan studies with the finding of no association of PD with hepatitis B [4,13]. There were no significant elevations of PD rates in patients with other forms of chronic liver disease such as autoimmune hepatitis, chronic active hepatitis, or HIV cohorts [14]. A meta-analysis found that the risk of Parkinson's disease was significantly higher among patients with HCV infection compared with those without HCV infection with the pooled OR of 1.35 (95% CI: 1.19–1.52) [15].

Based on the previously reported, the aim of the current study was to re-evaluate and verify the association between PD and HCV and/or HBV infection on a larger sample size by conducting a community-based epidemiologic study in Israel.

As a comparison group we used a cohort of patients diagnosed with Non- alcoholic steatohepatitis (NASH), in order to asses if an increased risk for PD is specific for viral hepatitis infection rather than a result of hepatic disease from different etiology.

NASH is a non-infectious liver disease, occurring in patient without history of excessive alcohol consumption. It is characterized by hepatic fat deposition with inflammation, accumulating fibrosis and ultimately, liver cirrhosis [16].

2. Materials and methods

Data source was the computerized database of Clalit Healthcare Service, the largest healthcare provider in Israel. Clalit Healthcare Service covers 4.5 million individuals, consisting of 55% of the Israeli population. Clalit Healthcare Service insurance program has no exclusion criteria for enrollment and providers are accessible throughout the country. Disease identification was based on the Clalit Healthcare Service coding system and/or by recorded positive serologic tests for HCV or HBV. The identities of the insurant in the Clalit Healthcare Service were recoded before their release to researchers.

Standard protocol approvals, registrations, and patient consents. This study was approved by the institutional review board of Rabin Medical Center and the review board of Clalit Healthcare Service. The review board waived the consent requirement.

Patients: Patients were divided into different cohorts according to their hepatitis status: HCV seropositive group, HBV seropositive group, HCV and HBV co-infection group and NASH group. Patients without the above diagnoses were included in the reference group. In each cohort, patients were stratified according to whether or not they were diagnosed with PD.

Statistical analysis: The prevalence of PD was determined in each of the hepatitis cohorts and the control cohort. OR were calculated using the Mantel-Haenszel test. Analyses of PD rates were further stratified, according to gender and age in a 20-year age groups (< 20, 20–39, 40–59, 60–79, > 80 years). All statistical analyses were performed using the WinPepi Statistical Software version 11.65 for Windows.

Data availability statement: The data used and analyzed during the current study is available on request.

3. Results

A total of 4,514,807 individuals were in the sample where 21,010 (0.5%) had PD. The prevalence was 2.4% in people older than 60 years, and 5.8% in those aged 80 years and above (Table 1).

There were 71,188, 24,394, 5258 and 151,433 individuals in the HBV-infected, HCV-infected, both hepatitis C and B infected and NASH, cohorts, respectively. The prevalence was 1.6%, 0.5%, 1.2% and 3.4% for hepatitis B, hepatitis C, both hepatitis C and B and NASH respectively (Table 2). The prevalence of PD among patients with different type of hepatitis is summarized in Table 1.

The M-H (Mantel-Haenszel) OR of PD for hepatitis B positive patients was 1.08 (95% CI: 1.00–1.16). The M-H OR of PD for hepatitis C positive patients was 1.18 (95% CI: 1.04–1.35). The M-H OR of PD for patients infected with both hepatitis C and B was 1.13 (95% CI: 0.87–1.47). The M-H OR of PD for patients diagnosed with NASH was 1.13 (95% CI: 1.08–1.19) (Table 3).

Significant association between HCV, HBV, NASH and PD was observed in males and females patients aged 40–59. Female patients between 60 and 79 years old diagnosed with HCV or NASH had significant increased prevalence of PD. Co infection with HCV and HBV was correlated with PD only in the subgroup of 20–39 years old males. Patients with NASH between the ages 20–39 years of both genders also had increased prevalence of PD.

4. Discussion

The prevalence of PD in the Israeli general population has not been reported before. Our study enabled to provide this information since Clalit Healthcare Service ensures 4.5 million individuals in the country.

Table 1
Prevalence of PD in the whole Clalit Healthcare Service cohort and by type of hepatitis, stratified by age and gender.

Age	Gender	% with PD				
		HCV	HBV	HCV & HBV	NASH	Total all patients
0–19	Male	0.0%	0.0%	0.0%	0.0%	0.0%
	Female	0.0%	0.0%	0.0%	0.0%	0.0%
20–39	Male	0.0%	0.0%	0.2%	0.1%	0.0%
	Female	0.0%	0.0%	0.0%	0.1%	0.0%
40–59	Male	0.3%	0.2%	0.3%	0.2%	0.1%
	Female	0.3%	0.2%	0.3%	0.3%	0.1%
60–79	Male	1.5%	1.8%	1.6%	1.8%	1.7%
	Female	1.7%	1.4%	1.8%	1.4%	1.2%
80 +	Male	7.5%	6.4%	5.2%	7.0%	6.7%
	Female	5.4%	5.1%	5.4%	5.7%	5.2%

Table 2
Prevalence of HCV, HBV, HCV&HBV and NASH in the Clalit Healthcare Service cohort by age and gender.

Age	Gender	HCV	HBV	HCV & HBV	NASH
0–19	Male	0.0%	0.1%	0.0%	0.1%
	Female	0.0%	0.0%	0.0%	0.1%
20–39	Male	0.4%	1.0%	0.1%	2.0%
	Female	0.4%	1.1%	0.0%	1.1%
40–59	Male	1.5%	3.4%	0.4%	6.7%
	Female	0.9%	2.8%	0.2%	5.3%
60–79	Male	1.1%	4.4%	0.3%	9.1%
	Female	0.9%	3.5%	0.2%	11.1%
80 +	Male	0.8%	3.5%	0.2%	6.5%
	Female	0.9%	2.5%	0.2%	7.7%

Table 3
Odds ratio (OR) and 95% confidence intervals (CIs) for PD in people with hepatitis compared with the reference cohort.

Hepatitis	OR (95% CI)	*P* Value
HCV	1.18 (1.04–1.35)	$p = .011$
HBV	1.08 (1.00–1.16)	$p = .037$
HCV & HBV	1.13 (0.87–1.46)	$p = .395$
NASH	1.13 (1.08–1.19)	$p < .001$

This cohort spans about 55% of the Israeli population. Patients covered by this medical insurance are distributed between all ethnic and age groups and are representative of the general population of Israel. The size of study cohort is the main advantage of this approach as it enables to deliver more precise estimates than can be produced by studies that contact people directly [2]. Our findings suggest a prevalence of 0.5% of PD patients in the general population, 2.4% in people older than 60 years, and 5.8% in those aged 80 years and above (Table 1). These rates are higher than those reported in the past in other countries: 0.3%, 1.0% and 3.0% in the general population, people older than 60 years, and in those aged 80 years and above, respectively [1]. This larger reported prevalence of PD might be a result of the increase in life expectancy in Israel as PD prevalence is increasing with aging of the population all over the world [2]. In addition, genetic forms of PD with mutation in the LRRK2 gene or in the glucocerebrosidase (GBA) gene, are much more common in patients of Ashkenazi Jewish ancestry with sporadic and familial PD than in the non-Jewish population [16]. Askenazi Jewish population is much more prevalent in Israel than in other countries. Another possibility is that the diagnosis of PD is based on clinical features and not on specific marker(s) of any sort. This may lead to discrepancies between stringency of diagnosis of PD in different nations.

The prevalence of HCV-seropositive patients in our cohort is 0.5% (Table 2). This rate is in the range reported before, 0.3 to 4% for most parts of the world [5] and therefore strengthen the validity of our findings of a minor increased risk for PD in patients with HCV. The OR calculated for PD in HCV-positive patients in our cohort is 1.18 (95% CI: 1.04–1.35). While this is in line with the recently reported association between HCV and PD in Taiwan and England [4,13,14] the OR in our study is lower than reported in these studies but is within the reported 95% CI.

We found only marginal increased in the prevalence of PD in HBV positive patient with OR 1.08 CI [1.00–1.16]. Indeed, previously reported results were inconsistent [4,13,14].

The OR of PD for patients infected with both hepatitis C and B was not statistically significant elevated: 1.13 (95% CI: 0.87–1.47). Thus, the co infection with HBV and HCV was not found to have synergistic effect on the risk for PD. The finding may be attributed to the possibility that HBV and HCV have a similar mechanism of increasing the risk of PD. This may consist of shared genetic or environmental susceptibility, sequelae of hepatitis and hepatic injury, or a consequence of treatment. If this is not the case, the lack of an accumulative effect may suggest that the effect is limited and eventually reaches a plateau.

We examined the effect of NASH on the development of PD (Table 3). After stratification for gender and age, the effect was significant for males 20–59 and females 20–79 years old (Table 1). The increased risk for PD in this group of patients raises the possibility that liver disease per se is a risk factor for PD.

The use of routinely collected data from medical records or health system claims has well recognized limitations. Mainly the lack of clinical data to confirm code based diagnosis. HBV and HCV tests were not performed in all subjects insured by the Clalit Healthcare Service which could cause a bias. Our data was corrected for age and gender but we were unable to control for lifestyle factors such as smoking or alcohol and other potential confounders.

Last, extrapyramidal syndrome associated with liver cirrhosis is well known [17–20]. Our data was not adjusted for prevalent of cirrhosis because clinical information was unavailable. Hence, it cannot be ruled out that the association between hepatitis viruses and PD is, at least in part, the result of the occurrence of cirrhosis induced parkinsonism that was misclassified in Clalit Healthcare records as PD.

Disclosure

The authors report no disclosures relevant to the manuscript.

Appendix A

Name	Location	Role	Contribiution
Lilach Goldstein	Rabin Medical Center, Petach Tikva, Israel	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Haya Fogel-Grinvald	The Hebrew University, Jerusalem	Author	Preformed all statistical analyses
Israel Steiner	Rabin Medical Center, Petach Tikva, Israel	Author	Interpreted the data; revised the manuscript for intellectual content

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