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Review

Infection and Risk of Parkinson's Disease

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Abstract. Parkinson's disease (PD) is thought to be caused by a combination of genetic and environmental factors. Bacterial or viral infection has been proposed as a potential risk factor, and there is supporting although not entirely consistent epidemiologic and basic science evidence to support its role. Encephalitis caused by influenza has included parkinsonian features. Epidemiological evidence is most compelling for an association between PD and hepatitis C virus. Infection with *Helicobacter pylori* may be associated not only with PD risk but also response to levodopa. Rapidly evolving knowledge regarding the role of the microbiome also suggests a role of resident bacteria in PD risk. Biological plausibility for the role for infectious agents is supported by the known neurotropic effects of specific viruses, particular vulnerability of the substantia nigra and even the promotion of aggregation of alpha-synuclein. A common feature of implicated viruses appears to be production of high levels of cytokines and chemokines that can cross the blood-brain barrier leading to microglial activation and inflammation and ultimately neuronal cell death. Based on multiple avenues of evidence it appears likely that specific bacterial and particularly viral infections may increase vulnerability to PD. The implications of this for PD prevention requires attention and may be most relevant once preventive treatments for at-risk populations are developed.

Keywords: Parkinson's disease, infection, viruses, bacteria, etiology

ETIOLOGY OF PARKINSON'S DISEASE: CURRENT CONCEPTS

Numerous genetic and environmental factors have been associated with Parkinson's disease (PD), which is thought to be caused by a complex interplay of multiple factors unique to an individual. In the past decade, the number of known genetic risk factors has greatly increased with 90 risk alleles now identified [1]. However, these known loci account for only approximately 20% of PD risk [1], leaving a substantial proportion of PD unexplained on the bases of currently known genetic associations. There is an urgent need to identify the missing etiologic fraction, to develop preventive and therapeutic strategies.

There is consistent or mostly consistent evidence for several environmental associations with risk of PD (e.g., inverse associations with cigarette smoking, caffeine intake, physical activity, plasma urate and positive associations with pesticide exposure) [2] and a large number of associations with less consistent

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evidence spanning multiple categories, including dietary factors, chemical exposures, physical and emotional trauma [3]. One of the more controversial categories of risk factors is infection, bacterial or viral.

INFECTION AND PD: AN EPIDEMIOLOGIC PERSPECTIVE

The possibility of an infectious trigger or contributor to PD has gained support from several different avenues. Early observations of clusters of individuals affected by parkinsonism following infectious outbreaks provide an example of presumed viral infections followed by and thus assumed to be leading to chronic neurological disease causing parkinsonism. On example of this, recognizing that the disease is pathologically distinct from PD, is encephalitis lethargica and subsequent post-encephalitic parkinsonism that has been associated with the influenza pandemic of 1918 [4]. In addition there have been other case reports of postencephalitic parkinsonism following non-influenza infections, although these have been rare [5, 6]. More recently, the role for infection gained plausibility through the Braak hypothesis of pathological spread starting in the olfactory bulb and peripheral nerves of the gastrointestinal tract [7]. Both of these locations could be portals of entry for an environmental trigger whether toxic or infectious. Constipation and olfactory impairment are two of the most common and earliest features of the prodromal phase of PD, further supporting the importance of the olfactory pathway and gastrointestinal tract in its pathogenesis [8]. Pathologically, inflammation appears to be an early feature [9] which may be consistent with a role for an infectious agent. However, there are alternative explanations for inflammation as a component of PD pathology, and whether or not this is a cause or a consequence of the neurodegenerative process is debated.

Additional evidence for a role of an infectious trigger or risk factor for PD is found in studies showing a relationship between specific occupational exposures and PD. In some studies, occupations where there is higher interpersonal exposures (e.g., teaching, clergy) show an increased risk of developing PD [10]. There is also a significant body of literature on specific infections and subsequent risk of PD, which will be discussed later in this paper. However, there are significant challenges interpreting epidemiological evidence for etiology in PD. The very long prodromal period, spanning decades, makes measurement of initiating factors difficult due to inadequate availability of records or poor recall. In addition, there is undoubtedly a complex interplay of genetic and environmental factors influenced by the neurodegenerative process during the prodromal period that make interpretation difficult. These general challenges are amplified by the complexity of considering the timing and relative impact of multiple short infectious exposures over a lifetime, the widely varying types of infectious agents, variable severity of infections and the inevitable presence of unrecognized infections. For example, a recent epidemiological study tested the "multiple microbe" hypothesis and reported that PD risk was increased compared to healthy controls in individuals who were seropositive for five or six of the pathogens studied (CMV, EBV, HSV-1, *B. burgdorferi, C. pneumoniae*, and *H. pylori*) but not less [11].

The role of infections in PD may extend beyond being a triggering event. PD is ultimately a disease of aging and the aging nervous system is vulnerable to the direct and indirect effects of infections which can influence the manifestations of PD. Age-related increases in oxidative stress and impaired energy production can render neurons vulnerable to the toxicity of infectious agents [12]. It is well-described that the symptoms of PD and other neurodegenerative diseases worsen in the context of infection and indeed any metabolic stress [13]. As often observed in clinical practice this worsening can last months and may never return to baseline.

Viral infections and PD risk

The notion of a viral etiology to PD has been mooted for many years. One early example, and poignant today in light of the recent SARS-CoV-2 pandemic, was the emergence of a parkinsonian disorder, *encephalitis lethargica* [14], that has been linked (although not definitively causally linked) to the 1918 influenza pandemic. Viruses, particularly those that are neurotropic, are plausible causal agents of PD but have been relatively understudied compared to genetic risk factors and other environmental risk factors for PD. In this section we will consider the viruses that have been linked to PD in observational studies and evaluate the strength of evidence to support a causal link.

The most common virus associated with parkinsonism is influenza. Each strain of the influenza virus, varies in its ability to directly infect the CNS. Those

that can directly infect cells in the nervous system are considered neurotropic whereas those than cannot are thought to be non-neurotropic. Most of the influenza viruses that have circulated among humans are non-neurotropic; including the 1918 H1N1 virus (Spanish flu) [15], the 1957-1958 H2N2 (Asian flu) [16], the 1968 H3N2 (Hong Kong flu) [17] and the 2009 H1N1 (Mexican or Swine flu) [18]. Despite the lack of direct infection of the CNS, each of these pandemic outbreaks has been associated with encephalitis with parkinsonian features. The common feature of each of these influenzas was their ability to induce a significant systemic infection characterized by production of significantly high levels of cytokines and chemokines [4]. The sheer volume of this cytokine/chemokine production overwhelms the body's ability to regulate them leading to the induction of what is known as a "cytokine storm" [19]. A body of literature has demonstrated that these peripheral cytokines can pass through the blood brain barrier and communicate with the brain. In fact, inflammatory cytokines, such as TGFalpha, IFNg, and IL6, which are upregulated by influenza infection can induce activation of microglia setting off an inflammatory cascade in the brain that can lead to neuronal dysfunction and even cell death [20].

One hypothesis that has been proffered based on these findings is that the viral-based inflammation primes the CNS; thus making it more susceptible for a later insult that otherwise would have been innocuous [21]. This is often the explanation used to link the 1918 Spanish flu to development of the post-encephalitic parkinsonism [14]. In addition to signs of parkinsonism, Von Economo's encephalopathy (or encephalitis lethargica) also included other neurological symptoms such as hypersomnolence and cranial neuropathies [22]. The appearance of this influenza-associated syndrome seems to be fairly specific to the 1918 H1N1 strain of influenza, based on the lack of a significant association between influenza infection and PD in a meta-analysis combining data from 4 small, case control studies (combined OR 1.95, 95%CI 0.77–4.94 for the risk of PD following influenza infection) [23]. This suggests that not all viruses have the same potential for CNS damage and for those non-neurotropic viruses it will be critical to understand the profile of inflammatory response induced by each individual virus. This is of particular concern due to the recent outbreak of COVID-19, whose causative agent is the SARS-CoV2 coronavirus. Preliminary studies are equivocal as to the neurotropic potential of this virus. However, what is clear is that it induces a significant "cytokine storm," with the potential to induce an inflammatory reaction in the brain [24] and sensitize it to later insult; including in regions known to be affected in PD.

Hepatitis B and C viruses have also been investigated for their associations with PD in recent epidemiological studies. Understanding such associations are important given the prevalence of these infections. Hepatitis C virus (HCV) is an RNA virus of the Flavivirus family and is estimated to infect 143 million people worldwide. It primarily involves the liver with chronic infection resulting in cirrhosis and hepatocellular carcinoma [25]. Extrahepatic manifestations include a myriad of inflammatory and immune-mediated disorders [26–28].

An observational study from Taiwan, in a community setting, showed that prior diagnosis of HCV was associated with an increased risk of subsequent PD (adjusted odds ratio (OR) 1.39, 95%CI 1.07–1.80), but no similar association was observed with HBV [28]. A larger, prospective study followed in ∼0.25 million people from the Taiwan national health insurance research database which appeared to confirm these observations. It showed that prior diagnosis with HCV was associated with an increased risk of PD (adjusted hazard HR 1.29, 95%CI 1.06–1.56). Again, prior hepatitis B (HBV) infection was not associated with a similar increased risk [29]. Despite the consistency of these results, one limitation is that they had overlapping study periods, may have included some of the same participants, and that the clinical definition of PD was based only on diagnostic codes without any clinical confirmation. In a separate UK-based study, Pakpoor and colleagues used the Hospital Episode Statistics (HES) database to further assess this association. They reported associations for both HCV (RR 1.51 (95%CI, 1.18–1.9)) and HBV (RR 1.76 (95%CI 1.28–2.37) using standardised rate ratios [30], but there was no clear association with other causes of hepatitis. A systematic review and meta-analysis calculated a combined OR of 1.35 (95%CI 1.18–1.93) for HCV infection [31], and a later meta-analysis which included a further two studies gave an OR of 1.19 (95%CI 1.01–1.41) [23]. Finally, the most recent observational study (from Israel) further explored the relationship, reported an OR of 1.18 (95%CI 1.04–1.35) for HCV and OR 1.08 (95%CI 1.00–1.16) for HBV [32]. Thus, the currently available epidemiologic evidence would suggest a positive, although small, association between HCV and future development of PD. Direct evidence in support of an association between hepatitis and PD

arises from studies showing that HCV is neurotropic; and once in the brain, the predominant cell type harboring HCV infection is macrophages/microglia [27]. Additionally, *in vitro* studies examining the effects of HCV infection in cultured rat brain have shown that this agent can induce loss of dopaminergic neurons [26, 28].

If there is a causal relationship between HCV and PD, it would be expected that successful treatment of HCV infection may mitigate the risk. Two recent studies, again using the Taiwanese national health insurance database, explored the role of interferon therapy for chronic HCV infection to see whether this was associated with a lower risk of PD [33, 34]. Given the probability of considerable overlap in these studies due to near-identical study periods and potentially the same patients being included, the results were perhaps unsurprisingly similar. In the first study, the investigators selected ∼0.25 million patients with recorded HCV infection and divided them into those that were treated with interferon (plus ribavirin) and those that were not treated. In the treated group, the risk of PD was lower than the untreated group (adjusted HR 0.75, 95%CI 0.59–0.96 after 5 years of follow-up), suggesting that the increased risk associated with HCV infection may be mitigated by antiviral treatment. In the second study, HCV infection was again associated with parkinsonism; treatment with antivirals was associated with a 38% reduced risk (adjusted HR 0.62; 95%CI 0.50–0.77) [34]. The authors proposed that antiviral treatment reduces neuroinflammation, thereby reducing risk.

The human immunodeficiency virus (HIV) is acquired in similar ways to HCV and infections with the two frequently co-occur. HIV infection affects ∼37 million people worldwide and is associated with a wide spectrum of neurological disorders, either from immunodeficiency leading to opportunistic infections, malignancy, or inflammatory conditions, or direct neurological consequences of HIV, including HIV-associated neurocognitive disorders (HAND). Despite the prevalence of both HIV and PD, there are limited examples of high-quality observational studies exploring a link between them. This is despite parkinsonism (and other movement disorders) being well recognised in patients with chronic HIV infection and HAND [35, 36]. Manifestation of parkinsonism alongside cognitive impairment can be seen in the context of HIV encephalopathy or HIV-associated dementia, but there are reports of HIV patients with isolated parkinsonism and up to 5–10% of HIV patients may have PD-like motor deficits [37, 38]. Some of the early cases/series suggested that parkinsonism could be unmasked in HIV patients treated with antipsychotics or even with highly active antiretroviral therapy (HAART) [36, 37]. However, in general the prevalence of HAND has decreased in the HAART era [39]. A recent large-scale, observational study suggested relative protection against incident PD in HIV patients treated with antiretroviral drugs compared to those who were not (HR for neurocognitive impairment 0.41, 0.37–0.45) [40]. In the aforementioned study by Pakpoor and colleagues [30] using UK HES data, HIV was not associated with incident PD (RR 0.98; 95%CI 0.50–1.70). An uncontrolled, small, retrospective review of healthcare records of HIV patients in Brazil suggested that incident PD was no more frequent than in the general population [41]. HIV did not appear in a recent systematic review and meta-analysis of infections and risk of PD [23], and we are not aware of any other case-control or cohort studies evaluating the link. Thus, the evidence to date is mixed and further research is needed to understand the relationship.

Beyond the associations already described, there exist other examples of parkinsonism manifesting during acute viral infections including Coxsakie virus infection (a picornavirus), and more classically in patients suffering with Flaviviruses such as Japanese encephalitis, St Louis encephalitis, Western Equine Encephalitic virus (WEEV) and West Nile virus [22]. For these later examples, the predilection for basal ganglia involvement is evident, but parkinsonism often manifests alongside a wider spectrum of neurological signs and symptoms, rather than in isolation and it is unclear how the parkinsonism described in these reports may relate to PD with Lewy pathology.

One of the biggest impediments to drawing conclusions about the link between viral infections and PD is a severe lack of high-quality epidemiological studies. Most data come from small case-control studies, with the biases inherent in design and in likelihood of being published. High quality cohort studies are lacking and there are difficulties around exposure ascertainment, latency, duration, as well as confounding factors such as vaccination, treatment, and co-infection for several of the chronic viral infections.

Bacterial infections and PD risk

The ample spectrum of bacteria that may acutely or permanently infect the tissues of humans has been associated with the development and, to a

lesser extent, with the progression of PD. Bacterial production of pro-inflammatory and neurotoxic factors might play a major role in the development and/or in the cascade of neurotoxic events leading to degeneration. One key player in such events is the bacterial endotoxin lipopolysaccharide (LPS). LPS stimulates production of several inflammatory factors that may contribute to neurodegeneration. Tumor necrosis factor-α (TNF-α) is released from microglia; nitric oxide (NO) is released by microglia and astrocytes in and there is hyperproduction of prostagladins. All of these phenomena may lead to neurodegeneration and gliosis [42]. Given that LPS is the endotoxin of Gram-negative bacteria, theoretically, every Gram-negative infection can induce a cascade that could trigger PD; however, the evidence on bacteria is limited to a number of specific organisms.

Borrelia Budgdoferi is a Gram-negative spirochete that is the only known cause of Lyme disease in North America. *Borrelia Budgdoferi* infection can affect the central nervous system and, when active, can cause a syndrome that may resemble PD [43]. Indeed, there is some initial evidence that Lyme disease can affect dopaminergic activity, especially the dopaminergic component of the frontal reward mechanism [44]. Anecdotally, it has been reported that B. burgdorferi infection can damage of the substantia nigra [45]. However, epidemiological evidence is not supportive of a link between Lyme disease and PD; when geographic locations of Lyme disease and death due to PD were compared, no correlation was found. Given the focal distribution of Lyme disease in the United States (Midwest, Northeast and mid-Atlantic) an increase of PD was expected in those regions if there was a positive correlation, but no association was suggested [46]. In addition, a study using the Danish National registry from 1986-2016 identifying 2,607 cases of Lyme neuroborreliosis did not find a significantly increased long term risk of PD and other neurodegenerative diseases [47].

Helicobacter pylori is a Gram-negative bacterium that infects a large number of the world's population causing mostly gastrointestinal symptoms. The association with PD has been heavily explored [48]. Increased gastric and duodenal ulcers in patients with PD have been described as early as the 1960s [49]. Before the advent of antibiotic treatment of *H. pylori* infection the classical treatment of *H. pylori* was vagotomy that interestingly has been associated with a reduction of the risk of PD [50]. A large meta-analysis reported a 1.5-2-fold increased risk of developing PD after *H. pylori* infection; [51] and large case-control studies reported 2-3 times increase of PD in patients with *H. pylori* [52]. Therefore, the association between PD and *H. pylori* is confirmed although a causal relationship has not been proven. Being a gastrointestinal pathogen, a causal role is biologically plausible through a gastrointestinal "portal of entry" according to the "dual hit hypothesis" [7]. On the other hand, eradicating *H. pylori* does not seem to alter the risk of PD. [52] In addition, *H. pylori* has a critical role in the absorption of L-Dopa and therefore, in symptomatic treatments. Eradication of the infection can be important to improve the response to L-Dopa [53] and, conversely, a reduction of the response to L-Dopa requires consideration of *H. pylori* presence [54].

The potential association between PD and bacterial infection is not restricted to Gram negative organisms. *Nocardia asteroides*, a weak Gram-positive bacterium, has been reported to potentially induce PD-like pathology in mice [55]. Another study reported the possible induction of apoptosis in the substantia nigra [56] suggesting a vulnerability of dopaminergic neurons to the effects of Nocardia infection. On the other hand, a case-control study on serum of patients with PD did not report a significant association between *Nocardia asteroides* and PD [57].

It is important to consider the possible role of multiple pathogens together; in fact, when multiple bacteria are colonizing and/or are acting synergistically there could be an increased, and cumulative risk of diseases, as demonstrated in stroke [58] and Alzheimer's disease [59]. One study explored the role of the infectious burden in PD, exploring the presence of antibodies against cytomegalovirus, Epstein Barr virus, herpes simplex virus type-1, *Borrelia burgdorferi*, *Chlamydophila pneumoniae*, and *Helicobacter pylori* in serum of patients with PD and controls [11]. The study observed that the combination of the previous bacteria and viruses was associated with PD compared to controls; however, a causative role was not clarified and further studies are needed.

Notably, there is minimal evidence for associations between more severe infection such as sepsis and the future risk of PD. A recently published case-control study reported that there was no association between severe infections that required hospitalization and sepsis and the risk of PD later in life [60]. However, it is not yet clear whether an infectious condition proximate to the onset of PD or before the onset of PD can trigger or lower the threshold for the upcoming neurodegenerative process.

Understanding the gut microbiome and its role in PD in particular is an area of active study. The interest in the role of gut bacteria has been greatly promoted by pathological evidence for the involvement of the gut early in PD. Indeed, an increasing body of evidence suggests that PD may start in the gut or, at least that the gut may constitute a portal of entry into the nervous system that subsequently spreads to the brain [7]. In fact, the gastrointestinal tract may have a role in the development of synucleinopathies mediated by the bacterial activity of the gut microbiome. Endotoxins (LPS) produced by some gut bacteria (e.g., *E. coli*) have been reported to have a role in aggregating synuclein and generate toxic synuclein products that can participate in the cascade of events of PD [61–63]. The gastrointestinal tract contains about 1,000 different bacterial species, and a number of studies have shown differences in the gut microbiome between individuals with and without PD [64]. Potential mechanisms are beginning to be elucidated; an early study in mice overexpressing synuclein highlighted that microbiota extracted from PD patients caused motor symptoms and a neuro-inflammatory cascade [65]. Although the studies performed in humans have provided controversial results [66], there is increasing evidence that microbiota in patients with PD may have a significant role in the development of the disease. A recent study reported that there was a dysbiotic alteration of the microbiotic bacteria in PD in the families of *Bifidobacteriaceae*, *Christensenellaceae*, *Lachnospiraceae*, *Lactobacillaceae*, *Pasteurellaceae* and *Verrucomicrobiaceae* [67]. The study provides a possible mechanism for an indirect effect of changes in microbiota, given that this modification would cause an increase of accumulation of pesticides and other xenobiotics that are not metabolized by the modified PD microbiome; therefore, the accumulation of such molecules may lead to an increase of the risk of PD. Further studies understanding the relationship of the gut microbiome with PD are needed because the microbiome represents a potentially modifiable risk factor not only for incident disease but also disease progression.

Importantly, several studies have reported a possible reduction of risk of PD in patients with appendicectomy [68–70]. In addition, regulating and maintaining the gut flora seems to be mediated by the vermiform appendix, that is no longer considered a vestigial remnant [60]. It is indeed possible to speculate that the appendix can be not only a reservoir of synuclein but also that the lack of regulation of the appendix-mediated gut flora could be another component to increase the risk of PD.

Overall, despite the mounting evidence for a bacteria role in the development of PD (especially *H. pylori* and the gut microbiome) more studies are needed to understand their causative role and potential treatment opportunities.

MOLECULAR MECHANISMS AND BASIC SCIENCE EVIDENCE FOR THE ROLE OF INFECTION IN PD

Much of the evidence associating PD with infections, whether viral or bacterial, is based on observational studies demonstrating increased risk to develop the disease, rather than direct evidence of infection as a singular cause. In fact, due to the complexity and multifactorial etiology of PD, identifying a single point of initiation in human PD (even in cases of known genetic mutations) is often impossible. For this reason, and the impossibility of interventional studies in humans involving infectious agents, the use of preclinical animal models of PD may provide the clearest evidence for or against a role of infectious agents in the etiology of PD.

As discussed earlier in this review, a number of viral agents have been linked to PD, including influenza, Coxsackie, Japanese encephalitis B, WE EV, Herpesviruses, HCV, and HIV [22, 71]. Preclinical work examining effects of these viruses have shown significant support for their role in the etiology of PD, although in many cases, it is not known if the effects of these viral infections are direct or indirect. When viruses invade the nervous system, they are said to be neurotropic. What is interesting about these neurotropic viruses is that rather than cause a generalized infection, they often target specific regions of the nervous system. Due to this specificity, specific syndromes can often be ascribed to specific viral infections. In the case of PD, WEEV and certain strains of neurotropic influenza (e.g., H5N1) have been shown to directly infect regions affected in PD including the enteric nervous system as well as CNS regions including the substantia nigra and the olfactory bulb [72–74]. In addition to direct infection of neurons, these viruses are also gliotropic, leading to an induction of both astrogliosis and microgliosis [72, 74, 75]. What makes both influenza viruses and WEEV particularly interesting is they also induce a number of changes in the brain that are prominent in PD including induction of

an increase in expression of phosphorylated alpha-synuclein, down-regulation of dopamine production and dopaminergic neuron death in the substantia nigra pars compacta [72–74]. The induction of these specific parkinsonian pathologies appears to be specific to the viral infection. For example, using Lund human mesencephalic dopaminergic cells, H1N1 infection was found to lead to a build-up of alpha-synuclein secondary to blockade of autophagosome function and impaired cellular proteostasis [76]. What was even more interesting is that this process did not affect other proteins (tau, TDP-43) known to aggregate in neurodegenerative disease showing that each virus has the potential to produce specific proteinopathies, as well as acting as a general inflammagen.

As described above, many non-neurotropic infections (both viral and bacterial) induce a significant inflammatory response throughout the body, often referred to as the innate response. During this innate response, circulating immune cells secrete a number of different proteins including interferons, interleukins, chemokines, colony stimulating factors and TNFs [77]. What is important to recognize is that within these classes of inflammatory molecules, some are considered to be pro-inflammatory and some are anti-inflammatory. It is the balance of each, as well as the way they interact with their cognate soluble receptors that determines the ultimate outcomes of the process [78]. If the pro- inflammatory response overwhelms the anti-inflammatory response one can set off a cascade that has been commonly called a "cytokine storm" [19]. The result of this overwhelming inflammatory response is often cellular toxicity. In addition to inducing this toxicity in the periphery, many of the circulating cytokines, although large in size, appear to be able to cross the blood-brain barrier using one of several mechanisms. These mechanisms include 1) a saturable transport system [79], 2) entering through regions of decreased blood-brain barrier called circumventricular organs, and 3) increasing capillary permeability [80–82]. The latter opens up the tight junctions of the blood-brain barrier, and allowing these large proteins to bypass the protections traditionally offered by this barrier.

Once in the brain, these cytokines/chemokines/Interferons/TNFs can bind to microglial cells, which induces their "activation" [83]. In addition to this indirect effect of circulating cytokines, a number of studies have provided support for PD neurodegeneration that occurs as a direct invasion of circulating lymphocytes (including T- and B-cells) that subsequently interact with the innate inflammatory cells of the brain. A number of observational studies have found increased numbers of circulating lymphocytes and monocytes in the brains of PD patients [84, 85]. Additionally, preclinical studies have directly demonstrated the critical nature of circulating immune cells in PD pathogenesis. Early studies showed that dopaminergic toxins, such as 6-OHDA or MPTP, induced T-cell infiltration into the brain; and the importance of these cells in the induction of pathology was demonstrated by the lack of pathology in Rag-1-KO mice [84, 86, 87]. Another study examined athymic mice that were deficient in mature T-cells and were injected with AAV-alpha-synuclein. These animals showed less behavioral and anatomical pathologies compared to T-cell competent mice [88]. In aggregate, these results demonstrated that mature T-cells were necessary to induce both behavioral as well as the anatomic pathologies.

Mechanistically, what might be the link between the cells of the peripheral immune system and the innate immune system in the brain? One critical component functions through recognition of MHCII; a key antigen presenting protein [89]. MHCII is critical for the presentation of antigen to both T-cells (both inside and outside the brain) as well as microglial cells situated in the CNS [90, 91]. In regard to microglia, it is interesting to note that the SNpc contains the highest microglia:neuron ratio in the brain [92]; perhaps leading to its particular sensitivity to inflammation [93].

Antigen presentation has been shown to elicit secretion of cytokines and chemokines, both in peripheral immune cells as well as in microglia [90]. What is important in PD pathogenesis is that once chronically elevated, these proteins can both initiate and maintain glial activation [94–96]. Once microglia and astrocytes are actively expressing their inflammatory programs they themselves secrete similar cytokines and chemokines as are produced by the peripheral immune system. Again, like in the periphery, when the proinflammatory proteins are in greater quantity than anti-inflammatory cytokines the environmental milieu of neurons becomes toxic [97]. Additionally, microglia [98, 99] as well as astrocytes [100] when activated also express MHC antigens and become phagocytic.

The susceptibility of the basal ganglia to such reactions may relate to the density of microglia and astrocytes relative to neurons, which is highest in the substantia nigra of all other brain regions [92, 93, 101]. This is of particular concern as the mechanism of microglial activation can cause a feed-forward

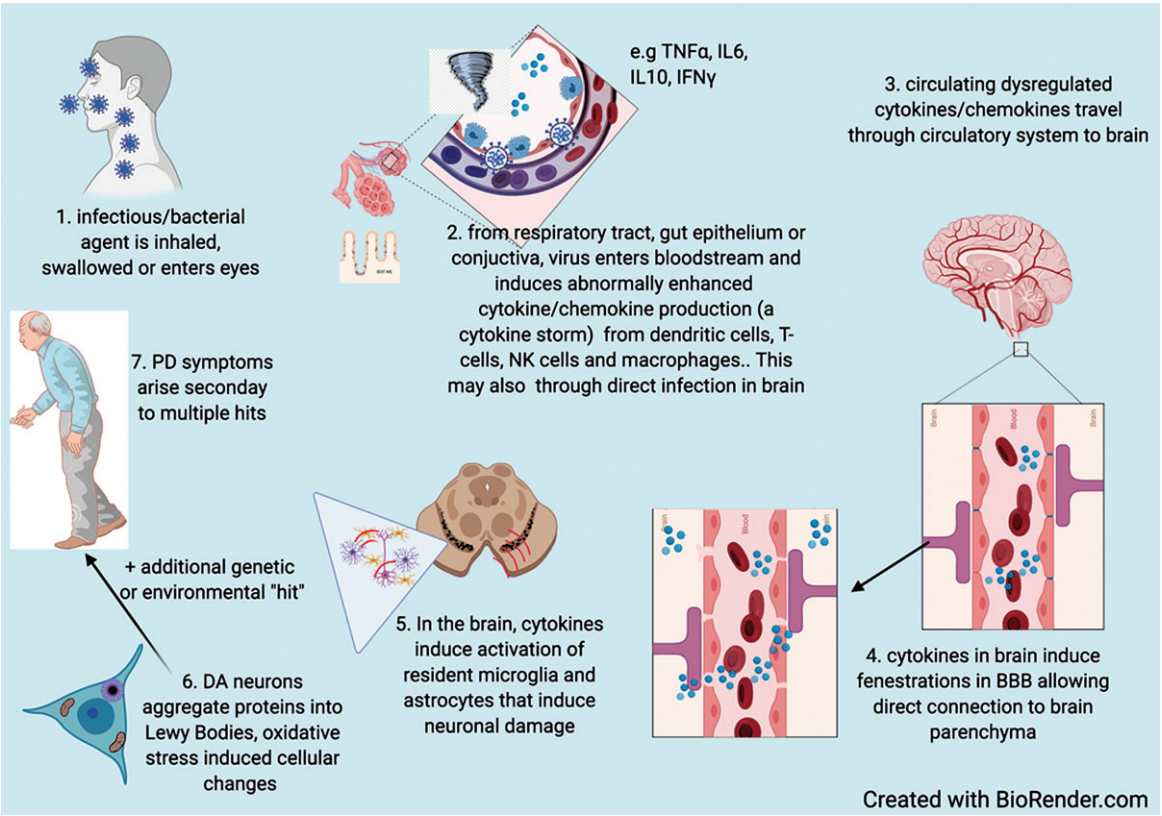

Fig. 1. Based on available evidence, hypothesized process by which infectious agents increase susceptibility to PD.

loop of clustering of microglia around dopaminergic neurons and a subsequent increase in activation [102]. Additionally, the overproduction of alpha-synuclein induced by viral infection can, in and of itself, induce activation of microglia [72]. which then sets up a feed forward cascade that perpetuates the effects of the infection. Related to alpha-synuclein, the finding of virally-increased levels of misfolded alpha-synuclein, to the detriment of native synuclein expression, may also provide a mechanism for the sensitivity of the dopaminergic neurons. Beatman et al. [103] showed that cells expressing native alpha-synuclein were resistant to West Nile Virus or Venezuelan equine encephalitis viral infection, but when this protein was removed by gene deletion the brain was much more susceptible to infection. Another study correlated expression of alpha-synuclein to viral infection and found that patients who had undergone intestinal allografts and subsequently were infected with norovirus exhibited significantly higher expression of misfolded alpha-synuclein [104] in the gut; which has been implicated as a starting site for PD pathogenesis [105, 106] Based on these finding, one could imagine a general mechanism by which the viral-induced (or PD) increased load of misfolded oligomeric alpha-synuclein could skew the overall protein pool of native synuclein downward. The lowered levels of native synuclein would make these neurons more prone to oxidative stress and subsequent death.

These observations provide plausible mechanisms to explain infection as either a susceptibility or causative factor for PD. The hypothesized process by which infectious agents increase susceptibility to PD is summarized in Fig. 1.

CONCLUSIONS

Infections are a plausible risk factor for parkinsonism and PD from both epidemiologic and basic science evidence. The magnitude of the risk is unknown for most agents but from the available epidemiologic studies appears to be overall small, with a less than doubling of risk observed in most studies. In addition, the latency from infection to PD appears to be highly variable and often long. From these data it is difficult to justify recommendations for specific

monitoring for PD in individuals with previous or ongoing infection.

On the other hand, the pathophysiological insights provided by infection and its apparent relationship to dopaminergic neuron loss and thus PD susceptibility provide important leads for treatment strategies that could be effective in the prodromal period. As suggested by epidemiologic evidence related to hepatitis C, treatment does appear to mitigate the risk. Furthermore, the mechanisms discussed above by which infection may contribute to PD are not unique to infection but share features with other environmental insults such as chemical exposures or head trauma, as each appear to induce pathology by a mechanism that has neuroinflammation as a key part of the process [42, 107–110]. Heretofore, treatments have not been routinely applied to exposed individuals with a view to managing risk of future neurodegenerative disease, but this could be a useful and feasible strategy if used in a targeted way.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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