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M. paratuberculosis and Parkinson's disease – Is this a trigger

Coad Thomas Dow *

McPherson Eye Research Institute, University of Wisconsin-Madison, 9431 WIMR, 1111 Highland Avenue, Madison, WI 53705, United States
Chippewa Valley Eye Clinic, 2715 Damon Street, Eau Claire, WI 54701, United States

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ABSTRACT

Genetic linkage studies and genome wide analysis have provided insights into complex medical diseases. *Mycobacterium avium* ss. *paratuberculosis* (MAP) causes Johne's disease, an important enteric inflammatory disease mostly studied in ruminant animals. MAP is also the putative cause of Crohn's disease. Moreover, MAP has been linked to other inflammatory diseases: sarcoidosis, Blau syndrome, autoimmune diabetes, autoimmune thyroiditis and multiple sclerosis. Genetic studies reveal an association between Parkinson's disease (PD), leprosy and Crohn's disease and since discovered, these findings have been considered "surprising". Autophagy and ubiquitin–proteosome systems are cellular systems that both fight intracellular pathogens (xenophagy) and maintain cellular protein quality control. PD is a common neurodegenerative disease that manifests clinically as a profound movement disorder. The recognized genetic defects of PD create disruption of cellular homeostasis that result in protein folding abnormalities of PD called Lewy bodies. Those same genetic defects are associated with susceptibility to intracellular pathogens, including mycobacteria. It is now understood that PD Lewy body pathology starts in the enteric nervous system and "spreads" to the brain in a retrograde fashion via the vagus nerve. This is the same process by which prions affect the brain. Lewy body pathology of the enteric nervous system predates the Lewy body pathology of the central nervous system (CNS) by years or even decades. This article proposes that genetic defects associated with PD also result in a permissive environment for MAP infection – ineffective xenophagy. It postulates that beginning as an enteric infection, MAP – via the vagus nerve – initiates a pathologic process that results in a targeted neuroinvasion of the CNS. The article proposes that MAP infection and resultant PD pathology are due, in the genetically at-risk and age dependant, to the consumptive exhaustion of the protein quality control systems.

Introduction

Genome wide analysis and genetic linkage studies have suggested an association between *Mycobacterium avium* ss. *paratuberculosis* (MAP) and several inflammatory diseases. Polymorphisms of the CARD15 and SLC11a1 genes have been central to these investigations [1]; genes that harbor defects imparting susceptibility to both mycobacterial infection and inflammatory diseases have provided a "genetic trail" that has linked MAP to Crohn's disease [2–4] sarcoidosis [5], Blau syndrome [6], autoimmune diabetes [7–9], autoimmune thyroiditis [10–12] and multiple sclerosis [13,14]. Interestingly, a parallel trail is emerging that provides a link between MAP and Parkinson's disease (PD). Polymorphisms of the LRRK2 and PARK genes are associated with PD and polymorphisms of the same genes are associated with susceptibility to mycobacterial infection: PD genes are "surprisingly" involved with leprosy (M. leprae) and Crohn's disease (putatively, MAP) [15–19].

M. avium ss. paratuberculosis (MAP)

M. avium ss. *paratuberculosis* (MAP) is the cause of an enteric inflammatory disease mostly studied in ruminant animals, Johne's disease. MAP is the putative cause of the very similar human enteric inflammatory disease, Crohn's disease [2–4]. MAP is present in pasteurized milk [20,21], infant formula made from pasteurized milk [22]. A recent study reported testing infant formula for MAP in 65 samples from 18 countries: greater than 40% tested positive for viable MAP [23]. MAP is found in surface water [24,25], soil [26], cow manure "lagoons" that can leach into surface water, cow manure in both solid and liquid forms that is applied as fertilizer [25,26], and municipal tap water [27,28], all providing routes of transmission to humans.

* Address: Chippewa Valley Eye Clinic, 2715 Damon Street, Eau Claire, WI 54701, United States. Tel.: +1 715 834 8471; fax: +1 715 834 0373.
E-mail address: ctdow@me.com

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Parkinson's disease

Parkinson's disease (PD) is a common, progressive degenerative disease of the nervous system that manifests clinically as motor symptoms: slowness of movement, tremor, rigidity and difficulties with balance and walking. These symptoms occur after the pathology already has reached an advanced stage [29–31]. A prerequisite for the postmortem diagnosis of both the pre-symptomatic and symptomatic phases of the pathological process underlying PD is evidence of specific inclusion bodies called Lewy bodies [32–35]. In PD, only a few specific types of nerve cells are prone to develop the lesions. The major component of Lewy bodies is an aggregated form of the normally pre-synaptic protein – synuclein [36]. Lewy bodies target the dopamine producing cells of the brain particularly the substantia nigra [37].

Anatomic staging of PD progression suggests that an unidentified neurotropic pathogen in the intestinal lumen triggers abnormal synuclein aggregation that, in turn, initiates a "prion-like" process in the enteric nervous system (ENS) eventually achieving access to the central nervous system (CNS) via the vagus nerve (cranial nerve X) [36–41]. This protein aggregation, manifest as Lewy bodies, targets and destroys dopamine producing cells resulting in both the classic motor and non-motor symptoms of PD [41,42]; with the non-motor symptoms predating the motor symptoms by years, or even decades [43].

While retrograde Lewy body progression entering the brain at the dorsal motor nucleus of the vagus is considered the main route of neuroinvasion, an alternative route is ante-grade progression via the olfactory nerve (cranial nerve I). Loss of the sense of smell is so early and common in PD that it has been postulated that PD is primarily an olfactory disorder [44]. While the pathology burden of the colon corresponds to PD severity, olfactory dysfunction is unrelated [45]. This additional/alternative route of neuroinvasion via the olfactory nerve does not eliminate MAP from consideration as the environmental triggering agent; MAP is competent as a bioaerosol [24,46–48].

Infectious and toxic triggers of Parkinson's disease

There are known infectious and toxic triggers of "parkinsonism," which is acute motor symptoms evocative of PD. The most commonly studied toxic trigger of PD is MPTP, an identified contaminant of IV drug abusers that resulted in acute parkinsonism. The discovery of MPTP resulted in the creation of an MPTP animal model that has greatly increased the knowledge of PD [49]. Of infectious triggers, *Nocardia asteroides* is the most studied. As a member of Actinobacteria this bacterium is phylogenetically related to MAP. The finding of immunosuppressed patients with *Nocardia* neuroinfection presenting with acute symptoms of PD and demonstrating *Nocardia* in the substantia nigra has prompted exhaustive study of this bacterium and PD and also resulted in a useful animal model [50].

With *Nocardia* animal models, the infection, given parenterally, attacks the substantia nigra. A movement disorder ensues that responds to dopamine [51]. The Nocardia bacterium can exist there in a cell wall deficient (spheroplast) form [52]. Spheroplasts have been found in the substantia nigra of PD patients – however, these spheroplasts have been shown to not be *Nocardia* [53]. MAP is well known to form spheroplasts [54].

Iron and Parkinson's disease

PD patients have excessive iron deposition in the substantia nigra [55]. While it is unknown if iron is a cause or an effect of PD, evidence suggesting a causative role of PD is drawn from rare genetic disorders that interfere with normal iron pathways. Elevated iron in aceruloplasminemia, Neurodegeneration with Brain Iron Accumulation (NBIA1) and neuroferritinopathy all can result in a Parkinson presentation [56]. Several sources for this iron deposition have been postulated [57]. Iron accumulation and concentration are essential to pathogenic mycobacteria. MAP is very well known for its unique iron requirements for in vitro growth [58], and its specific functions aimed at acquiring iron [59]. This article suggests that the concentration of iron in the substantia nigra of PD patients is due to the presence of MAP in its spheroplast form.

Discussion

The gut is the natural point of entry for MAP. This article suggests that MAP, in some form perhaps as a sheroplast, matriculates to the brain via the vagus nerve and triggers the pathologic protein aggregation of Lewy bodies. There is an animal model of neuroinvation via a cranial nerve: neuro-infection by Neisseria has been demonstrated via cranial nerve I (Olfactory) [60]. If MAP is found to be a trigger for PD it may be that the gut is just the more susceptible site of initial infection and MAP's extension to the brain is a later event possibly breaching the blood brain barrier. Alternatively, it may be that the presence of MAP in the gut precipitates a domino effect of protein aggregation and that the observed spheroplasts in the brain are unrelated or inconsequential to the etiopathology.

A rational and straightforward first step in researching MAP and PD would be to subject gut biopsy tissues testing positive for Lewy bodies [61,62] to PCR in attempt to detect MAP.

How can genes associated with neurodegeneration play a role in the host defense against bacterial infections? In addition to autophagy, the PD genes parkin and LRRK2 also promote xenophagy, an autophagic pathway involved in the removal of intracellular pathogens [17,63]. Indicting MAP in a causative role in PD would shed light on a couple of additional "surprising" findings: the anti-mycobacterial rifampicin has a protective function in PD [64]. Mycobacterial heat shock protein 65 and 70 (HSP65, HSP70) have been found in the cerebral spinal fluid of PD patients [65], and BCG vaccination partially preserves substantia nigra integrity in an animal model of PD [66].

This article proposes these same genetic polymorphisms associated with PD allow persistent infection of MAP and that MAP is the "unidentified enteric pathogen" that triggers synuclein aggregation. The cell wall deficient forms that are found in the substantia nigra of PD patients – found to not be *Nocardia* – may be MAP. It is postulated that the iron concentration in PD substantia nigra is due to sequestered iron in MAP spheroplasts. Moreover, it is postulated that the loss of function leading to protein aggregation (Lewy bodies) is due to iron toxicity and/or to "consumptive exhaustion" of the processes that both maintain cellular protein homeostasis and effect removal of intracellular pathogens.

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Conflict of interest statement

The author has no conflict of interest.

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