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

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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.
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) [44]. While the pathology burden of the colon corresponds to PD severity, olfactory dysfunction is unrelated to MAP. The finding of immunosuppressed patients with MAP is of specific inclusion bodies called Lewy bodies [32–35]. Lewy bodies target the dopamine producing cells of the brain particularly the substantia nigra [37].

The gut is the natural point of entry for MAP. 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 "consumptive exhaustion" of the processes that both maintain cellular protein homeostasis and effect removal of intracellular pathogens.

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References


