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Point of view

A punch in the gut – Intestinal inflammation links environmental factors to neurodegeneration in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is an etiologically heterogeneous disorder. Experimental, clinical and epidemiological data suggest that intestinal inflammation contributes to the pathogenesis of PD. This article reviews recent literature on gut microbiota and intestinal inflammation in PD. We propose that intestinal inflammation links environmental factors (e.g. an altered gut microbiota composition) to neurodegeneration in (genetically susceptible) PD patients. In addition, there is an epidemiological and genetic overlap between PD and inflammatory bowel disease. This overlap provides an opportunity to develop new treatment strategies for at least a subgroup of PD patients.

1. Introduction

Parkinson's disease (PD) comprises heterogeneous etiologies and is not a single entity [esupp ref 1]. A monogenic inheritance pattern accounts for a small minority of PD cases, while the majority of PD cases cannot be attributed to mutations or variants of a single gene. Several susceptibility genes for PD have been identified and an interaction of biological susceptibility and environmental factors is regarded as relevant for the development of non-monogenic forms PD. In this context, the gut is of particular interest: nutrients, microbiota and the (genetically defined) individual's immune system interact on the huge surface of the gastrointestinal tract; they can alter the intestinal permeability and modulate the activity of the enteric nervous system (ENS). The ENS, in turn, modulates the local immune response, secretion of peptides, the gut's motility and exerts remote effects via the gut-brain axis.

More than 200 years ago, James Parkinson described gastrointestinal symptoms as non-motor features of the disease in his *Essay on the Shaking Palsy*. Many years later, the discovery of an involvement of the ENS in PD [1] provided the potential pathoanatomical correlate for gastrointestinal symptoms in PD. Based on the observation that gastrointestinal symptoms, e.g. constipation, frequently precede the diagnosis of PD and based on his cross-sectional anatomical studies, Heiko Braak and his colleagues proposed as part of their dual-hit hypothesis of PD [2] that a yet unknown factor might cause aggregation of alpha-synuclein in the ENS which then spreads in a prion-like way to the brain using the vagal nerve as anatomical route. Experimental data and two large register studies on vagotomy and the subsequent risk for PD [3,4] seemed to endorse this hypothesis of an ascending neurodegenerative process. However, the conclusions drawn from these post-vagotomy studies are highly debated: Firstly, the reduced risk for PD was only observed in a subgroup, i.e. in subjects with a long post-vagotomy follow-up and a truncal (not a selective or superselective) vagotomy. Secondly, the effect was at the borderline of statistical significance. Thirdly, an independent group re-analyzed the data of one of the studies with a different methodological approach and could not reproduce the initially reported statistical significance [esupp ref 2]. In addition, experimental data indicate that there is also the possibility of a descending route of alpha-synuclein transmission via the vagal nerve [esupp ref 3]. Hence, the suggested caudo-rostral (ascending) propagation of alpha-synuclein from the ENS to the central nervous system is not an exclusive explanation. The question concerning a possible route of transmission and the origin has not been settled yet and has been recently reviewed by Lionnet and colleagues [esupp ref 4]. While the exact temporo-spatial pattern remains to be clarified, it is widely accepted that the gut is involved in the pathogenesis of PD.

2. Chronic intestinal inflammation might trigger aggregation of alpha-synuclein in the ENS

One of PD's histopathological hallmarks are Lewy bodies that

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consist in part of aggregated alpha-synuclein. Alpha-synuclein is a protein which is mainly expressed in neuronal cells and which is involved in vesicular transport [esupp ref 5]. Its physiological function has still not been completely revealed, but recent data suggest that alpha-synuclein might also be important for the innate immune response in the gut [5]: on the one hand, intestinal infections with *Helicobacter pylori* or norovirus increased alpha synuclein expression in the ENS. On the other hand, alpha-synuclein seems to have chemoattractant effects that enhance the local immune response. Hence, under certain conditions alpha-synuclein might be part of a self-sustaining inflammatory process in the gut. A potential role for alpha-synuclein in connecting environmental factors to the nervous system has been recently described in a paper which identified a possible key role for enteroendocrine cells in this circuit: Chandra et al. showed that several subtypes of enteroendocrine cells (which are epithelial cells and therefore encounter numerous contacts with the intraluminal content of the gut, including toxins, microbial metabolites and other environmental influences) express alpha-synuclein and are able to transmit it to connected enteric nerves [esupp ref 6]. Based on these data it seems reasonable to hypothesize that chronic or repeated intestinal infections (that might increase the expression of alpha-synuclein) favor a process that leads to pathological aggregation of alpha-synuclein in the ENS. Indeed, the increased expression of alpha-synuclein (induced by inflammatory conditions, etc. see above) might then ignite the process described by Braak and colleagues in their dual-hit hypothesis [2]. However, as discussed above, the temporo-spatial pattern of the pathogenetic process underlying PD has not yet been settled.

3. Human in vivo data support the hypothesis of intestinal inflammation in PD

Intestinal inflammation has been long time discussed as a contributing factor in the pathogenesis of PD (reviewed by Dobbs and colleagues [6]). Indeed, there is increasing evidence (including human in vivo data) that supports the hypothesis of intestinal inflammation in PD:

Colonic biopsies obtained from PD patients show an increased expression of pro-inflammatory cytokines (compared to controls) [7]. Recently, increased concentrations of inflammatory markers have also been shown in fecal samples of early PD [8] arguing that inflammation is an early (and not a secondary) phenomenon in the pathogenesis of PD. The finding of increased markers indicating inflammation is in accordance with a pro-inflammatory mucosa-associated microbiome in PD [9]. Yet, it remains to be shown that pro-inflammatory, mucosa-associated microbiota are the cause for the observed inflammation and not an epiphenomenon.

Fecal calprotectin, a sensitive and robust marker for gastrointestinal inflammation, is also increased in PD patients (compared to age-matched controls) [10,11]. Calprotectin even reflects subclinical inflammatory activity: e.g. patients with ulcerative colitis who are in clinical and endoscopic remission but with a histologically proven active inflammation have elevated fecal calprotectin concentrations [esupp ref 7]. Hence, intestinal inflammation can occur even in the absence of clinically overt signs and symptoms.

4. Altered gut microbiota composition – cause or effect?

A recent finding is the altered composition of gut microbiota in PD patients compared to age-matched controls. Despite differences in patients' characteristics (disease duration, geographic background, diet, medication, etc.) and differences in methodology across studies, there are some striking common findings: e.g. an increase in the abundance of Akkermansia [9,12–16] and Lactobacillus [14,15,17–19] and a decreased abundance of Prevotella [12,15–17,19] and Faecalibacterium [14,16,19]. The common finding of a reduced abundance of Prevotella (and Faecalibacterium) is of special interest as these bacteria are capable of producing short chain fatty acids (SCFA). SCFA have been shown to enhance gastrointestinal motility and can exert anti-inflammatory effects (reviewed by Agata Mulak [20]). Hence, the decreased abundance of SCFA-producing bacteria and decreased fecal concentrations of SCFA in PD [16] indicate reduced anti-inflammatory effects and might therefore be clinically and pathologically relevant.

Sampson and colleagues elaborately investigated the role of gut microbiota and SCFA in a mouse model of PD [21]: Using alpha-synuclein overexpressing mice, Sampson and colleagues showed in a number of different experiments that microbiota are required for the PD-typical phenotype and alpha-synuclein aggregation in this model [21]. In addition, the investigators described a central role for SCFA in this process [21]. Even though these animal data cannot be directly translated into the human situation, it is remarkable that colonization of mice with microbiota from PD patients led to a more severe phenotype compared to microbiota transplants from healthy controls [21].

Notably, one study reported a similar shift in gut microbiota (as in established PD) already in a prodromal stage of PD, i.e. in REM sleep behavior disorder [13]. This study suggests that the shift in gut microbiota is not a secondary event (e.g. induced by the dopaminergic therapy). Yet, the exact mechanisms that lead to the altered gut microbiota composition in early (pre-motor) PD and the subsequent events as well as their role in the pathogenesis of PD are still to be revealed. On the one hand, an altered gut microbiota composition might favor chronic intestinal inflammation; on the other hand, an enhanced local immune response or a genetically dysregulated gut immune system might predispose subjects to alterations in the composition of gut microbiota.

Thus, the causality between the composition of gut microbiota and intestinal inflammation could be either way.

5. Epidemiological overlap between PD and IBD

Besides the finding of increased fecal markers indicating intestinal inflammation in PD [10,11], there are additional overlaps between the neurodegenerative disorder PD and inflammatory bowel disease (IBD): Genome-wide association studies revealed an overlap between gene loci relevant for autoimmune diseases as well as PD raising the assumption of a common genetic background [esupp ref 8]. A finding of recent interest is hereby the epidemiological association between PD and Crohn's disease (CD): an epidemiologic study from Taiwan reported a significant association between CD and the risk to develop PD [22], this finding was reproduced by a US American study [23] that analyzed databases that contained more than 170 million persons and found an increased incidence of PD among patients with IBD (including CD). Yet, not all studies reported an increased co-incidence of PD and IBD [24,25]. One explanation for these divergent observations might be the anti-inflammatory therapy (in IBD) as a confounding factor: interfering with the local inflammatory process in the gut (as therapy for IBD) ameliorates intestinal inflammation and consecutively might reduce the risk for subsequent PD. Indeed, the recent study by Peter and colleagues nicely showed that an immunomodulatory treatment with TNF-alpha blockers substantially reduces the risk for PD among patients with IBD [23].

6. A common genetic background in PD and IBD (NOD2, LRRK2)

Regarding a) the epidemiological link between PD and inflammatory bowel disease (IBD) and b) the hypothesis of intestinal inflammation in PD, one protein of interest is nucleotide-binding oligomerization domain-containing protein 2 (NOD2). NOD2 is a pattern recognition receptor and ignites an inflammatory and antibacterial response upon binding to muramyl-dipeptide (MDP, a compound of bacterial cell walls). NOD2 was the first genetic risk locus for CD to be identified [esupp ref 9, 10]. Genetic variants of NOD2 are associated with an altered composition of gut microbiota and an inflammatory

microenvironment.

Data on NOD2 variants in PD are controversial [26–28], but existing evidence suggests a potential role for some variants (R702W, G908R, 3020insC [27] and P268S [28]) in a subgroup of PD patients. Interestingly, the NOD2 variant identified in Chinese PD patients (P268S) [28] is also reported to be associated with CD in the Chinese population [29]. This finding endorses the hypothesis of intestinal inflammation as a contributing factor in the etiopathogenesis of PD and a common pathway in PD and IBD.

The second gene of interest is leucine-rich repeat kinase 2 (LRRK2): On the one hand, LRRK2 variants are a well-known genetic risk factor for familial and sporadic PD; on the other hand, LRRK2 variants have also been described in other diseases, including inflammatory bowel disease like CD (reviewed by Ref. [30]).

Dysregulated signaling pathways of the gut immune system (e.g. those caused by NOD2 variants) could explain the susceptibility to intestinal inflammation and alterations in gut microbiota composition in PD. Intensified research on this topic is a crucial next step towards a better understanding of the cause-effect context and the identification of mere epiphenomena:

Are some PD patients predisposed genetically to a specific pattern of gut microbiota and consecutive intestinal inflammation?

Is the altered gut microbiota composition an independent event but ignites an enhanced inflammatory response in PD?

How do intrinsic (genetic) factors and extrinsic factors (gut microbiota composition) interact in the development of PD?

7. Challenges and opportunities

Most studies that investigated gastrointestinal inflammation in PD were cross-sectional. Hence, despite accumulating evidence for intestinal inflammation in PD, the cause-effect context and the temporal pattern of intestinal inflammation (early hit, intermittent or continuous) has not yet been resolved. As discussed previously, available evidence argues that intestinal inflammation might be an early feature.

In distinction to other neurodegenerative disorders, PD provides the opportunity of a well characterized prodromal phase (pre-motor PD). Even subjects at risk for PD (without presumed early nigral degeneration) can be identified (e.g. by transcranial sonography or by polysomnography in the case of REM sleep behavior disorder). Hence, PD could be a model disease in longitudinal studies investigating the link between intestinal inflammation and early stages of neurodegeneration.

A prospective long-term follow-up of those IBD patients who are at high risk for neurodegeneration (e.g. determined by SN sonography, early-premotor features, other risk factors for PD) seems to be another promising approach. Such a study would be able to clarify (in a prospective way) whether or not the anti-inflammatory therapeutic regime (for IBD) modifies the risk for PD.

Conflicts of interest

The authors declare that there is no conflict of interest regarding this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.09.032.

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