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ORIGINAL PAPERS

Further Studies on the Neurological Component of Irritable Bowel Syndrome.

I. The Connections Between Parkinson's Disease Pathology and Irritable Bowel Syndrome Manifestations

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Abstract

Although a complex neurodegenerative condition, Parkinson's disease etiology and pathogenic mechanisms remain incompletely understood. Irritable bowel syndrome is one of the most common gastrointestinal functional disorder with the gastrointestinal symptoms being one of the most common non-motor features of Parkinson's disease. In this way, although the prevalence of Irritable bowel syndrome in Parkinson's disease patients has not been entirely evaluated, recent reports revealed that Irritable bowel syndrome could be associated with an increased risk of developing PD. Thus, in the present mini-review we focused our atention on the possbile connections that could exist between these two patologies.

Key words*:* Parkinson's disease, Irritable bowel syndrome, neurological.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease [1]. As a general rule, the onset of the disease is between 40 and 70 years, with a peak in the 6th decade [2], with a prevalence of about 1% at the age of 65 and 3.5% at the age of 85 [3]. An Asian study conducted in 2001, indicated the probability of increasing the prevalence and incidence of this disease by up to 30% by 2013, which is quite alarming if we consider that this can affect both society and the economy regarding the costs involved [4].

The clinical features of the disease include a significant movement disorder such of bradykinesia, resting tremor, rigidity and, in a more advanced stage of the disease, postural instability [5]. Although the cause of PD is still not known,

several genetic risk factors have been identified, as well as a number of genes which cause some rare forms of PD [6]. Aside the motor features of the disorder, non-motor symptoms of Parkinson's disease draw attention, especially gastrointestinal symptoms such as constipation, with a prevalence of 46.7-52.5 %, and abdominal pain in about 28% of the cases. [7].

Irritable bowel syndrome (IBS) is a chronic functional dysfunction, with a variable pattern of symptoms, characterized by abdominal pain or discomfort, with the occurrence of intestinal transit changes. Symptoms include bloating, constipation, diarrhea, a sensation of incomplete defecation or the presence of mucus in the stool [8]. This condition in one of the main causes of presentation to the clinician, giving the fact that it has a high prevalence in western European countries (e.g. between 10 – 25% of the population) [9].

Although the real pathophysiology of IBS is not fully understood, studies incriminated the involvement of bidirectional dysregulation of brain–gut axis [10]. Moreover, psychosocial, environmental, or/and genetic factors can easily influence the brain, facilitating the neurotransmitters release, in order to alter the gastro-intestinal tract motility [11].

Giving the fact that brain–gut axis is potentially involved in both PD and IBS, we aim to reveal the existing relationship between these two conditions. The perspectives of a link between them, can generate the focus on these two conditions simultaneously in clinical practice.

General aspects regarding Parkinson's disease

Regarding the etiopathogenesis, primary Parkinson's disease is the consequence of a diffuse neuronal degenerative process of the central nervous system, in which the first lesions appear in the lower brainstem [12]. As they progress, at one point, they cause degeneration to the dopaminergic cells of the mesencephalic black substance (pars compacta), large enough to disorganize the control system of motor activity in the basal ganglia. In this process, both the direct and, especially, the indirect pathway from the co-stripe-pallial cortical circuits are affected, with the involvement (disinhibition) of the subthalamic Luys nucleus [13].

Clinical diagnosis of PD is based on the presence of bradykinesia defined as a slow movement speed. Because the clinical differentiation of bradykinesia from hypokinesis is sometimes difficult to achieve, as they are characteristics of the motor act that are largely intertwined, in clinical practice only the term bradykinesia is used, in a broader sense. Also, the presence of resting tremor or rigidity are investigated in order to establish a diagnostic [5].

The cellular degenerative phenomena that lead to these functional changes is caused by structural alterations of some cellular proteins, in some cases by a demonstrated genetic defect [14], sometimes by a possible toxic factor that leads

to a series of molecular pathogenic links [14] (incompletely identified so far, but in which oxidative stress plays an important role), in cell death through apoptosis.

Studies regarding neurodegeneration of the gut-brain axis revealed the existence of Lewy bodies and alpha-synuclein in neurons and neuritis in patients with Parkinson's disease, although, unfortunately, pathopshysiology of non-motor symptoms are not entirely recognized in clinical practice [15].

A study conducted in 2003 proposed that pathological process in the brain begins in the brainstem dorsal motor nucleus of the vagal nerve, and not in the substantia nigra of the midbrain. And from this, arised the question whether PD could begin outside the central nervous system, especially from the enteric nervous system [16]. Starting from this premise, the study which included examination of brain and stomach tissues from 150 autopsy cases, revealed that the brains of 120 cases (80%) showed no alpha-synuclein pathology. The remaining 30 cases (20%) demonstrated PD-associated alpha-synuclein at varying stages of disease progression. In this way, they concluded that the stomach is not the first region within the enteric nervous system (ENS) to become involved in PD. On the other hand, the size of the stomach makes it difficult to be truly certain that a negative finding can indicate the absence of any alpha-synuclein[16]. In this regard, the attention focused on whether the peripheral sympathetic or parasympathetic nervous system becomes involved prior to the central nervous system.

Irritable bowel syndrome, microbiome and Parkinson's disease

As stated by Drossman in the overview of the Rome IV criteria, which is the standard method for assessing functional gastrointestinal disorders such as irritable bowel syndrome, 'It is a group of disorders classified by gastrointestinal symptoms related to any combination of the following: motility disturbance visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing'[17]. An elevated risk of PD has been linked to diagnosis of IBS [18]. Although, a detailed assessment of IBS symptoms in PD patients vs. control subjects has not been published previously, it was hypothesized that a subgroup of PD patients with constipation might suffer from a wider spectrum of bowel symptoms, equivalent to an IBS-like phenotype. Moreover, it was speculated that the presence of other non-motor symptoms and even the alterations of gut microbiome, could be associated with the presence of IBS-like symptoms in PD patients [18].

Also, findings suggested that IBS-like symptoms could be a manifestation of a more generalized dysautonomic phenotype of PD [19]. It was previously indicated the link between IBS pathogenesis and symptoms and the alterations of the microbiome or the dysregulation of the gut-brain axis [20]. Regarding gut microbiome, several studies have reported an increased abundance of *Firmicutes* to the detriment of B*acteroidetes* and *Bifidobacteria* in IBS patients [21].

However, the results for the abundance of *Prevotella* have not been consistent [21], [22]. On the other hand, *Prevotella* emerged as a key species related to PD, and also to PD-associated IBS-like symptoms [23].

In any case, it must be taken into account the fact that PD patients suffer from multiple comorbidities that can alter the microbiome and [24], comparing previous results contrasting IBS patients and healthy controls can be challenging.

Linked to IBS, changes in the microbiome might lead to inflammation and increased permeability of the gut mucosa [25], [26]. Also, gut mucosal changes occurred in PD and it has been speculated by Braak and his team that this could initiate αsynuclein associated neurodegeneration in the enteric nervous system, and then the spreading to the central nervous system [27], [28]. Giving the fact that IBS has been proposed as a risk factor for PD [18], gut microbiome in the premotor stage of the disease should be further studied in order to establish a valid biomarker or even a therapeutic target.

Vagotomy and Parkinson's disease

One major route of disease progression in PD is suggested to be represented by the vagus nerve. This route has an active retrograde transport of α synuclein from the enteric nervous system, ascending the vagus nerve and then reaching the dorsal motor nucleus of the vagus in the lower brainstem [29]. This hypothesis is sustained by subdiaphragmatic truncal vagotomy, which seems to be associated with a decreased risk for subsequent PD [30]. Moreover, axonal-predominant α-synuclein pathology has been found not only in the glossopharyngeal-vagus and spinal nerve roots, but in cervical and pharyngeal sections of the vagus nerve in PD patients too [31], [32].

Regarding the mentioned truncal vagotomy, a study conducted in Denmark brought to the forefront the idea that this procedure has a protective effect over PD progression as compared to super-selective vagotomy which has a minor effect. This assumption suggests that the vagal nerve may be critically involved in the pathogenesis of PD[30]

Also, a recent study demonstrated the existing bilateral atrophy of the vagus nerve but not of the spinal accessory or the phrenic nerves in PD patients as compared to age-matched controls, using High-Resolution Ultrasonography. Moreover, findings suggested that viscero-afferent and viscero-efferent vagal fibers are predominantly affected in PD [33].

Conclusions

Although a complex neurodegenerative condition, PD's etiology and pathogenic mechanisms remain incompletely understood. IBS is one of the most common gastrointestinal disorder. Gastrointestinal symptoms are one of the most common non-motor features of Parkinson's disease. Although the prevalence of

IBS in PD patients has not been entirely evaluated, recent reports revealed that IBS may be associated with an increased risk of developing PD. Moreover, research pointed out the hypothesis according to which vagotomy procedure has a protective effect over PD progression as compared to super-selective vagotomy which has a minor effect and that the vagal nerve may be critically involved in the pathogenesis of PD.

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References

[1] L. V Kalia and A. E. Lang, "Parkinson's disease.," *Lancet (London, England)*, vol. 386, no. 9996, pp. 896–912, Aug. 2015.

[2] C. M. Tanner and S. M. Goldman, "Epidemiology of Parkinson's disease.," *Neurol. Clin.*, vol. 14, no. 2, pp. 317–335, May 1996.

[3] R. L. Nussbaum and C. E. Ellis, "Alzheimer's disease and Parkinson's disease.," *N. Engl. J. Med.*, vol. 348, no. 14, pp. 1356–1364, Apr. 2003.

[4] R. C. Chen *et al.*, "Prevalence, incidence, and mortality of PD: a door-to-door survey in Ilan county, Taiwan.," *Neurology*, vol. 57, no. 9, pp. 1679–1686, Nov. 2001.

[5] C. H. Williams-Gray and P. F. Worth, "Parkinson's disease," *Medicine (Baltimore).*, vol. 44, no. 9, pp. 542–546, Sep. 2016.

[6] D. G. Healy *et al.*, "Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study.," *Lancet. Neurol.*, vol. 7, no. 7, pp. 583–590, Jul. 2008.

[7] T. Kozlovski *et al.*, "Hierarchical Data-Driven Analysis of Clinical Symptoms Among Patients With Parkinson's DiseaseData_Sheet_1.docx," *Front. Neurol.*, vol. 10, May 2019.

[8] G. Goldsmith and J. S. Levin, "Effect of sleep quality on symptoms of irritable bowel syndrome.," *Dig. Dis. Sci.*, vol. 38, no. 10, pp. 1809–1814, Oct. 1993.

[9] A. V Golubeva *et al.*, "Prenatal stress-induced alterations in major physiological systems correlate with gut microbiota composition in

adulthood," *Psychoneuroendocrinology*, vol. 60, pp. 58–74, 2015.

[10] T. Mach, "The brain-gut axis in irritable bowel syndrome - Clinical aspects," *Med. Sci. Monit.*, vol. 10, pp. RA125-31, Jul. 2004.

[11] P. Katiraei and G. Bultron, "Need for a comprehensive medical approach to the neuro-immuno-gastroenterology of irritable bowel syndrome," *World J. Gastroenterol.*, vol. 17, no. 23, pp. 2791–2800, Jun. 2011.

[12] D. W. Dickson, "Parkinson's disease and parkinsonism: neuropathology.," *Cold Spring Harb. Perspect. Med.*, vol. 2, no. 8, Aug. 2012.

[13] R. Katzenschlager, J. Head, A. Schrag, Y. Ben-Shlomo, A. Evans, and A. J. Lees, "Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD.," *Neurology*, vol. 71, no. 7, pp. 474–480, Aug. 2008.

[14] H. Deng, P. Wang, and J. Jankovic, "The genetics of Parkinson disease.," *Ageing Res. Rev.*, vol. 42, pp. 72–85, Mar. 2018.

[15] I. Ferrer, I. Lopez-Gonzalez, M. Carmona, E. Dalfo, A. Pujol, and A. Martinez, "Neurochemistry and the non-motor aspects of PD.," *Neurobiol. Dis.*, vol. 46, no. 3, pp. 508–526, Jun. 2012.

[16] H. Braak, K. Del Tredici, U. Rub, R. A. I. de Vos, E. N. H. Jansen Steur, and E. Braak, "Staging of brain pathology related to sporadic Parkinson's disease.," *Neurobiol. Aging*, vol. 24, no. 2, pp. 197–211, 2003.

[17] D. A. Drossman, "Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV.," *Gastroenterology*, Feb. 2016.

[18] S.-W. Lai, K.-F. Liao, C.-L. Lin, and F.-C. Sung, "Irritable bowel syndrome correlates with increased risk of Parkinson's disease in Taiwan.," *Eur. J. Epidemiol.*, vol. 29, no. 1, pp. 57–62, Jan. 2014.

[19] A. Sauerbier, P. Jenner, A. Todorova, and K. R. Chaudhuri, "Non motor subtypes and Parkinson's disease," *Parkinsonism Relat. Disord.*, vol. 22, pp. S41–S46, 2016.

[20] K. N. Lee and O. Y. Lee, "Intestinal microbiota in pathophysiology and management of irritable bowel syndrome.," *World J. Gastroenterol.*, vol. 20, no. 27, pp. 8886–8897, Jul. 2014.

[21] G. Major and R. Spiller, "Irritable bowel syndrome, inflammatory bowel disease and the microbiome," *Curr. Opin. Endocrinol. Diabetes. Obes.*, vol. 21, no. 1, pp. 15–21, Feb. 2014.

[22] V. Shankar *et al.*, "The networks of human gut microbe–metabolite associations are different between health and irritable bowel syndrome," *ISME J.*, vol. 9, no. 8, pp. 1899–1903, 2015.

[23] T. H. Mertsalmi *et al.*, "More than constipation - bowel symptoms in Parkinson's disease and their connection to gut microbiota.," *Eur. J. Neurol.*, vol. 24, no. 11, pp. 1375–1383, Nov. 2017.

[24] F. Scheperjans *et al.*, "Gut microbiota are related to Parkinson's disease and clinical phenotype," *Mov. Disord.*, vol. 30, no. 3, pp. 350–358, Mar. 2015.

[25] H. Tornblom, G. Lindberg, B. Nyberg, and B. Veress, "Full-thickness of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome," *Gastroenterology*, vol. 123, pp. 1972–1979, Jan. 2003.

[26] E. Quigley, "Gut Permeability in Irritable Bowel Syndrome: More Leaks Add to Slightly Inflamed Bowel Syndrome Conspiracy Theory," *Gastroenterology*, vol. 137, no. 2, pp. 728–730, Aug. 2009.

[27] N. P. Visanji, P. L. Brooks, L.-N. Hazrati, and A. E. Lang, "The prion hypothesis in Parkinson's disease: Braak to the future," *Acta Neuropathol. Commun.*, vol. 1, p. 2, May 2013.

[28] C. B. Forsyth *et al.*, "Increased intestinal permeability correlates with sigmoid mucosa alpha-synuclein staining and endotoxin exposure markers in early Parkinson's disease.," *PLoS One*, vol. 6, no. 12, p. e28032, 2011.

[29] K. Del Tredici and H. Braak, "Review: Sporadic Parkinson's disease: development and distribution of alpha-synuclein pathology.," *Neuropathol. Appl. Neurobiol.*, vol. 42, no. 1, pp. 33–50, Feb. 2016.

[30] E. Svensson *et al.*, "Vagotomy and subsequent risk of Parkinson's disease.," *Ann. Neurol.*, vol. 78, no. 4, pp. 522–529, Oct. 2015.

[31] L. Mu *et al.*, "Alpha-synuclein pathology and axonal degeneration of the peripheral motor nerves innervating pharyngeal muscles in Parkinson disease.," *J. Neuropathol. Exp. Neurol.*, vol. 72, no. 2, pp. 119–129, Feb. 2013.

[32] K. Nakamura *et al.*, "alpha-Synuclein pathology in the cranial and spinal nerves in Lewy body disease.," *Neuropathology*, vol. 36, no. 3, pp. 262–269, Jun. 2016.

[33] U. Walter, P. Tsiberidou, M. Kersten, A. Storch, and M. Löhle, "Atrophy of the Vagus Nerve in Parkinson's Disease Revealed by High-Resolution Ultrasonography," *Front. Neurol.*, vol. 9, p. 805, Sep. 2018.