

Gut-Microbiota Link in Parkinson's Disease: Current Perspectives

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Abstract: Parkinson's disease (PD) is a metacentric neurodegenerative disorder results with accumulation and aggregation of alpha-synuclein (α -Syn) (or alpha-synucleinopathy) in the substantia nigra in the central nervous system (CNS). Contributory factors include pesticide exposure, head injury and agriculture background. PD has been considered to be a non-genetic disorder, however around 15% individuals with PD have first-degree relative who has the disease. Mutations in genes including SNCA, LRRK2 and glucocerebrosidase (GBA) found to be risk factor for sporadic PD. Brain cells could be lost due to an abnormal accumulation of the protein alpha-synuclein. This insoluble protein accumulates inside neurons forming inclusions called Lewy bodies. Other cell death mechanisms include proteasomal and lysosomal system dysfunction, but the mechanisms are not fully understood. Brain-gut axis (GBA) refers to central nervous system (CNS) control of the enteric nervous system (ENS) through vagus nerve intervention. PD is characterized by alpha-synucleinopathy affecting all levels of the brain-gut axis. Both clinical and neuropathological evidences indicate the neurodegenerative changes in PD are accompanied by gastrointestinal symptoms that may precede or follow the central nervous system impairment. Frequent symptoms in PD include tremor, rigidity, slowness of movement and difficulty with walking. Treatment with L-DOPA (levodopa), with dopamine agonist, medications become less effective and produce complications. Research studies recommend new therapeutic approach in PD based on modification of the gut microbiota with probiotics, prebiotics, or even fecal microbiota transplantation.

Keywords: Parkinson's disease, Brain-gut axis, Enteric nervous system, Gut-microbiota.

I. Introduction

Parkinson's disease (PD) is a long term degenerative disorder of the central nervous system [1]. The main motor symptoms are collectively called "parkinsonism" or a "parkinsonian syndrome" [2]. In 2013, PD was present in 5.3 million people and resulted in about 103,000 deaths globally [3]. PD typically occurs in people over the age of 60, of which about one per cent are affected [1]. Males are more affected than females [4]. When it is seen in people before the age of 40 or 50, it is called young onset [5]. PD is a multicentric neurodegenerative disorder characterized by the accumulation and aggregation of alpha-synuclein (α -syn) in the substantia nigra in the central nervous system (CNS) and in other neural structures [6]. It has become evident that different levels of the brain-gut axis (BGA) including the autonomic nervous system (ANS) and enteric nervous system (ENS) may be affected in PD [7]. Recently it has been also recognized that BGA interaction may be essentially influenced by the gut microbiota [8]. The dysregulation of the brain-gut-microbiota axis in PD result in GI dysregulation, which is present in over 80% of PD subjects [9]. This regulation of GI may also significantly contribute to the pathogenesis of PD itself, supporting the hypothesis that pathological process is spread from the gut to the brain [7]. The symptoms generally come on slowly over time. Early in the disease, the most common obvious are shaking, rigidity, slowness of the movement, and difficulty with walking [1]. There is no cure for Parkinson's disease [1]. Treatment with anti-Parkinson medication L-DOPA (levodopa), with dopamine agonists being used once levodopa becomes less effective. Medications become less effective and produce complications marked by involuntary writhing movements [2]. The paper reviews the role of brain-gut axis and current concepts in management of Parkinson's disease.

II. Epidemiology

Parkinson's disease is the most common neurodegenerative disorder after Alzheimer's disease and affects approximately seven million people globally and one million people in the United States [10]. The proportion in population at a given time is about 0.3% in the industrialized countries. PD is more common in the

elderly and rates rises from 1% over 60 years of age to 4% of the population over 80[11].The mean age of onset is around 60 years, although 5-10% of cases, classified as young onset PD, begins between the ages 20 and 50[12].PD may be less prevalent in those African and Asian ancestry, although this finding is disputed[11].Some studies have proposed that it is more common in men than women, but others failed to detect and differences between the two sexes[11].The number of new cases per of PD is between 8 and 18 per 100,000 person-years[11].

Many risk factors and protective factors have been proposed in relation to theories concerning possible mechanisms of the disease; however, none have been conclusively related to PD by empirical evidence. When epidemiological studies have been carried out in order to test the relationship between given factor and PD, they have often been flawed and their results have in some cases been contradictory[11].The most frequently replicated relationships are an increased risk of PD in those exposed to pesticides, and a reduced risk in smokers[11].

III. History and Historical Cases

Several early sources, including an Egyptian papyrus, an Ayurveda medical treatise, the Bible, and Galen's writings, describe symptoms resembling those of PD[13].After Galen there are no references unambiguously related to PD until 17th century[13].In the 17th and 18th centuries, several authors wrote about elements of the disease, including Sylvius, Gaibius, Hunter and Chomel[14].In 1817 an English doctor, James Parkinson, published his essay reporting six cases of paralysis agitans[15].An *Essay on the Shaking Palsy* described the characteristics resting tremor, abnormal posture and gait, paralysis and diminished muscle strength, and the way the disease progresses over time[16].Early neurologist who made further additions to the knowledge of the disease include Trousseau, Gowers, Kinnier Wilson and Erb, and most notably Jean-Martin Charcot, whose studies between 1868-1881 were landmark in the understanding of the disease[15], including renaming of the disease in honor of James Parkinson[15].

In 1912 Frederic Lewy described microscopic particles in affected brains, later named "Lewy bodies"[15].In 1991 Konstantin Tretiakoff reported that substantia nigra was the main cerebral structure affected, but his findings was not widely accepted until it was confirmed by further studies published by Rolf Hassler in 1938[15].In 1997, alpha-synuclein was found to be the main component of Lewy bodies by Spillantini, et al[17].Levodopa was first synthesized in 1911 by Casimir Funk. It entered the clinical practice in 1967 and brought about a revolution in the management of PD [18].By the late 1980s deep brain stimulation introduced by Alim Louis Benabid and colleagues at Grenoble, France, emerged as a possible treatment[19].

Historical Cases

Actor Michael J Fox had PD and has greatly increased the public awareness of the disease[20].He has written autobiographies in which his fight against the disease plays a role[21].The Michael J Fox Foundation aims to develop a cure for Parkinson's disease[21].Fox received an honorary doctorate in medicine from Karolinska Institute for his contributions to research in PD[22].Professional cyclist and Olympic medalist Davis Phinney, who was diagnosed with young onset PD at age 40, started the Davis Phinney Foundation in 2004 to support PD, focusing on quality of life for people with the disease[23].Legendary boxer Muhammad Ali showed signs of PD when he was 38, but was not diagnosed until he was 42, and he was called the "World's most famous Parkinson's patient"[24].Whether he had PD or a parkinsonism related to boxing is unresolved[25].

IV. Contributory Factors

The cause of PD is generally unknown, but believed to involve both genetic and environmental factors. Those with family members affected are more likely to get the disease themselves [4].

External factors: External or environmental factors have been associated with an increased risk of PD, including pesticide exposure, head injuries, and living in the country or farming[26].Rural environments and drinking of well water may be risks, as they are indirect measures of exposure to pesticides[11].Implicated agents include insecticides, primarily chlorpyrifos and organochlorines[27], and pesticides, such as rotenone, paraquat, and herbicides, such as Agent Orange and ziram[11].Exposure to heavy metals has been proposed to be a risk factor, through possible accumulation in the substantia nigra, but studies on the issue have been inconclusive [11].

Genetic factors: PD traditionally has been considered a non-genetic disorder, however, around 15% of individuals with PD have a first-degree relative who has the disease [12].At least 5% of people are now known to have forms of the disease that occur because of a mutation of one of several genes[28].

Mutations in specific genes have been conclusively shown to cause PD. These genes code for alpha-synuclein (SNCA), parkin (PRKN), leucine-rich repeat kinase (LRRK2 or dardarin), PTEN-induced putative kinase 1 (PINK), DJ-1 and ATP13A2[29,28].In most cases, people with these mutations will develop PD. With exception of LRRK2, however, they account for only a small minority of cases of PD[29].The most extensively

studied PD-related genes are SNCA and LRRK2. Mutations in genes including SNCA, LRRK2 and glucocerebrosidase (GBA) have found to be risk factor for sporadic PD. Mutations in GBA are known to cause Gaucher's disease [28]. Genome-wide association studies, which search for mutated alleles with low penetration in sporadic cases, have now yielded many positive results [30].

The role of the SNCA gene is important in PD, because the alpha-synuclein protein is the main component of Lewy bodies [28]. Missense mutations of the gene (in which a single nucleotide is changed), and duplications and triplications of the locus containing it have been found in different groups with familial PD [28]. Missense mutations are rare [29]. On the other hand, multiplications of the SNCA locus accounts for around 2% of the familial cases [28]. Multiplication has been found in asymptomatic carriers, which indicate the penetrance is incomplete or age-dependent [28].

LRRK2 gene (PARK8) encodes a protein called dardarin. The name dardarin was taken from a Basque word for tremor, because this gene was first identified in families from England and the north of Spain [29]. Mutations in LRRK2 are most common known cause of familial and sporadic PD, accounting for approximately 5% of individuals with family history of the disease and 3% of sporadic cases [29, 28 rpt]. There are many mutations described in LRRK2, however unequivocal proof of causation only exists for a few [28]. Several Parkinson-related genes are involved in the function of lysosomes, or organelles that digest cellular waste products. It has been suggested that some forms of Parkinson may be caused by lysosome dysfunction that reduce the ability of cells to break down alpha-synuclein [3].

V. Pathophysiology

The primary symptoms of Parkinson's disease result from greatly reduced activity of dopamine-secreting cells caused by cell death in the compacta region of the substantia nigra [32]. There are five major pathways in the brain connecting other brain areas with basal ganglia. These are known as the motor, oculomotor, associative, limbic and orbitofrontal circuits, with names indicating the main projection area each circuit [32]. All of them are affected in PD, and their disruption explains many of the symptoms of the disease, since these circuits are involved in a wide variety of functions, including movement, attention and learning [32]. Scientifically, the motor circuit has been examined most extensively [32]. Drugs that are used to treat PD, conversely, may produce excessive dopamine activity, allowing motor systems to be activated at inappropriate times and thereby producing dyskinesias [32].

Degeneration and brain cell death

There is speculation of several mechanisms by which the brain cells could be lost [33]. One mechanism consists of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells. This insoluble protein accumulates inside neurons forming inclusions called Lewy bodies [29, 17]. According to Braak staging, a classification of the disease based on pathological findings, Lewy bodies first appear in the olfactory bulb, medulla oblongata and pontine tegmentum, with individuals at this stage being asymptomatic. As the disease progresses, Lewy bodies later develop in the substantia nigra, areas of the midbrain and basal forebrain, and in a last step the neocortex [29, 17]. These brain sites are the main places of neuronal degeneration in PD, however, Lewy bodies may not cause cell death and may be protective [33, 17]. People with dementia, a generalized presence of Lewy bodies is common in cortical areas. Neurofibrillary tangles and senile plaques, characteristic of Alzheimer disease, are not common unless the person is demented [34]. Other cell-death mechanisms include proteasomal and lysosomal system dysfunction and reduced mitochondrial activity [33]. Iron accumulation in the substantia nigra is typically observed in conjunction with protein inclusions. It may be related to oxidative stress, protein aggregation and neuronal death, but the mechanisms are not fully understood [35].

VI. Gut-microbiota link in PD

Brain-gut axis (BGA) refers to central nervous system (CNS) control of the enteric nervous system (ENS) through vagus nerve innervation [36]. The gastrointestinal tract is unique among mammalian organ systems in that it possesses its own nervous system. The ENS controls GI motility, blood flow and water and electrolyte transport. Many enteroenteric reflexes bypass CNS control [37]. PD is characterized by alpha-synucleinopathy affecting all levels of the brain-gut axis. Both clinical and neuropathological evidences indicate that neurodegenerative changes in PD are accompanied by gastrointestinal symptoms that may precede or follow the central nervous system impairment [38].

Bidirectional communication between CNS and GI tract—the brain gut axis—occurs both in health and disease. The neural network for the control of GI functions involves the intrinsic and extrinsic nervous systems and forms a hierarchic four level integrative organization [39]: The first level is the ENS represented by neurons of the myenteric (Auerbach's) and submucosal (Meissner's) plexi and enteric glial cells (EGCs) [40]. The second level is the prevertebral ganglia modulating many peripheral visceral reflexes [41].

The third level is ANS (autonomic nervous system) within the spinal cord [origin of the sympathetic (T5-L2) and sacral (S2-S4) parasympathetic nervous systems] and the brain-stem with the nucleus tractus solitarius (NTS) and dorsal motor nucleus of the vagus nerve (DMVN), which receives and gives origins to the afferent and efferent fibers of the vagus nerve (VN), respectively. The DMVN influence is most prominent in the upper GI tract, where cholinergic myenteric neurons mediate vagal excitatory effect, and VIP/NO neurons mediate inhibitory reflexes [42].

The fourth level includes higher brain centers. Information from the cortical and subcortical centers, including the basal ganglia, funnels down to specific brainstem from where many GI functions are controlled. Disturbances at every level of that neural control may affect modulation of the GI functions including mechanisms at the local enteric reflexes, and extrinsic neural control [43].

Under physiological conditions α -syn is abundantly expressed in the CNS and involved in the regulation of neurotransmission. Insoluble fibrils of phosphorylated α -syn have been implicated in several neurodegenerative disorders, such as PD and Alzheimer [17]. Accumulated evidence shows that α -syn plays a crucial role in neuroinflammation by triggering and/or potentiating astrological and microglial activation [44]. Recent studies have also shown that dysfunction of EGCs at the ENS level occurs in PD [45]. EGCs, which represent in the digestive tract counterpart for brain astrocytes may be critically involved in gut inflammation and modulation of intestinal epithelial barrier integrity [46]. Devos et al found that expression of pro-inflammatory cytokines and glial markers are increased in colonic biopsies from PD patients and that they are correlated with disease duration [46].

Both clinical and neurological evidences indicate that neurodegenerative changes are accompanied by GI symptoms may precede or follow the CNS impairment [47]. Based on these observations a mechanistic hypothesis presenting gut as the gateway in neurodegenerative diseases has been proposed [48]. Accordingly the ENS seems to play a critical role in the pathophysiology of PD representing a route of entry of entry for a putative environmental factor to initiate the pathological process. Furthermore, regarding the parallel manifestations of neuropathologies in ENS and CNS, the ENS may provide a more accessible target for studies of neural function, histopathology, and biochemistry in PD [47]. Thus, the ENS can be considered not only as "the second brain", but also a window towards "the first brain" [49].

Among many causes of parkinsonism, including multiple system atrophy, progressive supranuclear palsy or corticobasal degeneration, GI symptoms have been best characterized in the classical PD [9]. In the study of Edwards et al. [50] evaluating the frequency of various GI symptoms in 98 patients with PD abnormal salivation, dysphagia, nausea, constipation and defecatory dysfunction were present in 70%, 52%, 29% and 66% of the subjects respectively. Among the studied parameters, only PD activity and duration correlated with GI dysfunction. No correlation was found between GI symptoms and patient's age, gender, anti-parkinsonism treatment, level of activity or dietary fiber intake [50].

Changes in the gut microbiota composition may cause alterations in the gut barrier function and intestinal permeability, affecting not only GI epithelial cells and immune system, but also the ENS including both neurons and glial cells [51]. The bidirectional brain-gut-microbiota axis interactions modulates pro- and anti-inflammatory responses [52]. It has been suggested that gut microbiota changes associated with intestinal inflammation may contribute to initiation of α -syn misfolding [46]. There is growing number of evidence confirming that the gut microbiota alterations precede or occur during course of PD [53]. However, the casual relationship between the microbiota changes and the pathogenesis of PD remains unclear [38]. Gastrointestinal dysfunction in PD includes:

(a). Hypersalivation typical in PD results not from salivary hypersecretion (in fact saliva production is even diminished), but from decreased swallowing frequency. Swallowing dysfunction may be symptomatic in up to 50% of PD patients [54].

(b). Impaired gastric emptying is an important manifestation of PD and is characterized by symptoms such as postprandial bloating or abdominal discomfort, early satiety and nausea [55].

(c). Uncomfortable sensation of abdominal bloating experienced by some individuals with PD especially as an "off" phenomena, could be the consequence of small bowel dysmotility shown by manometry [56].

(d). Constipation the most prominent GI dysfunction of PD seems to be an early manifestation of the disease process itself [9].

(e). Defecatory dysfunction characterized by excessive straining and incomplete evacuation are another common distressing problems in PD [57].

The study by Scheperjans and colleagues showed a reduced abundance of the *Prevotellaceae* bacteria family in PD patients compared with healthy controls and greater abundance of Enterobacteriaceae among those patients with the postural instability and gait difficulty phenotype compared to those with tremor-dominant PD [58]. *Prevotellaceae* bacteria are commensals are involved in musin synthesis in the gut mucosal layer and production of neuroactive short-chain fatty acids (SCFA) through fiber fermentation [59].

The potential role of *Helicobacter pylori*(HP) in PD both with regard to the pathogenesis of PD itself and the development of motor system fluctuation, remains controversial[60].Moreover, there is an increased mortality from PD amongst livestock farmers, which has been associated with *Helicobacter suis* being the most common zoonotic *Helicobacter* in man[61].An association between *Mycobacterium avium* ss.Paratuberculosis(MAP) and several inflammatory diseases including Crohn's disease has been suggested. Genetic studies concerning the polymorphism of CARD15 gene revealed a link between PD and Crohn's disease [62].

Recent studies reported a great inter-individual variation among elderly regarding the gut microbiota composition, and a significant relationship between microbiota, diet and institution or community living. Fiber-rich diet enhances the growth of colonic bacteria that produce SCFA, which have systemic anti-inflammatory effect[63,64].Therefore intervention studies with probiotics and prebiotics offer promising way to bring benefits in elderly's health[38].*Agata Mulak and associates concluded that a better understanding of the brain gut-microbiota axis interactions should bring a new insight in the pathophysiology of PD, permit an earlier diagnosis with a focus on peripheral biomarkers within ENS as well as lead to novel therapeutic options in PD. Further studies on a new therapeutic approach in PD based on the modification of the gut microbiota with probiotics, prebiotics, or even fecal microbiota transplantation are awaited [38].*

VII. Clinical manifestations and Diagnosis

Parkinson's disease affects movement, producing motor symptoms[65].Non-motor symptoms, which include autonomic dysfunction, neuropsychiatric problems (mood, cognition, behavior or thought alterations),and sensory and sleep difficulties, are also common. Some of these non-motor symptoms are often present at time of diagnosis and can precede motor symptoms [65].Four motor symptoms are considered cardinal in PD:(a) Tremor (b) Rigidity (c)Slowness of movement and (d) Postural instability[65].

Diagnosis:The most widely known criteria come from UK Parkinson's Disease Society Brain Bank and the U.S.National Institute of Neurological Disorders and Stroke[65].The PD Brain Bank Society criteria require slowness of movement(bradykinesia) plus either rigidity. resting tremor or postural instability[65].Computed tomography (CT) and conventional magnetic resonance imaging(MRI) brain scans of people with PD usually appear normal[66].These techniques are nevertheless useful to rule out other diseases that can be secondary causes of parkinsonism, such as basal ganglia tumor, vascular pathology and hydrocephalus[66].

VIII. Management, Prognosis and Prevention

There is no cure for Parkinson's disease, but medications,surgery, and multidisciplinary management can provide relief from the symptoms. The main families of drugs useful for treating motor symptoms are levodopa(usually combined with a dopadecarboxylase inhibitors or COMT inhibitor that does not cross the blood-brain barrier),dopamine agonists and MAO-B(monoamine oxidase B) inhibitors[67].Levodopa preparations lead in the long term to the development of motor complications characterized by involuntary movements called dyskinesias and fluctuations in the response to medications[67].

Levodopa and protein use the same transportation system in the intestine and the blood-brain barrier, thereby competing for access [68].When they are taken together, this results in a reduced effectiveness of the drug[68].Therefore, when levodopa is introduced, excessive protein consumption is discouraged and well balanced Mediterranean diet is recommended. In advanced stages, additional intake of low-protein products such as bread or pasta is recommended for similar reason [68].Palliative care should involve earlier, rather than later in the disease course[69].Palliative care specialists can help with physical symptoms, emotional factors such as loss of function and jobs, depression, fear, and existential concerns[69].

Prognosis:PD invariably progresses with time. A severity rating method known as the Unified Parkinson's disease rating scale (UPDRS)[70].Medications has improved the prognosis of motor symptoms, while at the same time it is a new source of disability, because of the undesired effects of levodopa after years of use[70].Finally, after ten years most people, with the disease have autonomic disturbances, sleep problems, mood alterations, and cognitive decline[70].

Prevention:Exercise in the middle age reduces the risk of Parkinson's disease later in life[71].Caffeine also appears protective with greater decrease in risk occurring with larger intake of caffeinated beverages such as coffee[72].Although tobacco smoke causes adverse health effects, decreases life expectancy and quality of life, it may reduce the risk of PD a third when compared to nonsmokers[11t].The basis of this effect is not known, but possibilities include as effect of nicotine as a dopamine stimulant [11].Antioxidants, such as vitamins C and D, have been proposed to protect against the disease, but results of studies have been contradictory and no positive effect has been proven[11].Also there have been preliminary indications of possible protective role of estrogens and anti-inflammatory drugs[11].

IX. Economic impact

The costs of PD to society are high, but precise calculations are difficult due to methodological issues in research differences between countries [73]. The economic cost in UK is estimated to be between 449 million and 3.3 billion pounds. In the United States the economic burden of PD is at least 14.4 billion [74], while the cost per patient per year in U.S. is probably around \$10,000 and the total around 23 billion [74]. In Australia the financial cost of PD in 2014 was almost A\$1.1 billion, the amount has doubled since 2005 (A\$527.8 million) [75]. While in Germany PD is a costly disease not only to the individual and society in general but it affects the national budget [76]. The largest share of direct cost comes from inpatient care and nursing homes, while the share coming from medication is substantially lower [74]. The indirect costs are high, due to reduced productivity and burden on caregivers [74]. In addition to economic costs, PD reduces quality of life of those with the disease and their caregivers [74].

X. Conclusion

Parkinson's disease a neurodegenerative disorder. There is a need for better understanding of the brain gut-microbiota axis interactions should bring a new insight in the pathophysiology of PD, with an earlier diagnosis with a focus on peripheral biomarkers within ENS as well as lead to novel therapeutic options in PD. Further research on a new therapeutic approach in PD based on the modification of the gut microbiota with probiotics, prebiotics, or even fecal microbiota transplantation are awaited.

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