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Cardiovascular autonomic impairment in GBA parkinsonian patients

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INTRODUCTION

Parkinson's disease (PD) is the second commonest neurodegenerative disorder, after Alzheimer's. (Erkkinen MG & Kim MO, n.d.). PD, described for the first time in 1817 by James Parkinson in his "An essay on shaking palsy", has been traditionally considered a movement disorder, characterized by bradykinesia, tremor, rigidity, and, in the advanced stage, postural instability. However, it is now recognized as a more complex condition that encompasses non-motor features, some of which can precede the appearance of motor symptoms by several years. (Pont-Sunyer et al., 2015). Non-motor features comprise olfactory deficits, autonomic dysfunction, pain and somatosensory disturbances, mood disorders, sleep disruptions, cognitive impairment, and dementia. Some of these symptoms, such as hyposmia, REM behaviour disorders (RBD), some neuropsychiatric alterations and dysautonomia, may be present in the premotor phase. Conversely, other non-motor symptoms emerge following diagnosis and in the later stages of the disease. (A. H. V. Schapira et al., 2017). Autonomic symptoms such as constipation or urinary urgency are frequently reported by patients at the time of diagnosis. This suggests that the recognition of dysautonomia is essential to characterize the premotor phases of the disease. Notably, it can manifest before the onset of motor symptoms, indicating that autonomic involvement may represent an early stage in the development of PD's underlying mechanisms. Existing insights into dysautonomia in PD primarily stem from research on sporadic cases of PD, with limited data available regarding dysautonomia in genetic forms of the disease.

BACKGROUND

Epidemiology

The prevalence of PD is approximately 180-200 cases per 100,000 people, with a reported occurrence in the general population of industrialized countries at 0.3%. This prevalence increases significantly in individuals over the age of 60, reaching 1%. (de Lau & Breteler, 2006). While the incidence of PD is relatively low before the age of 50, it is projected to double in the coming decades due to the aging population. Consequently, the social and economic burden of PD is poised to escalate unless disease modified therapies are discovered. (Dorsey et al., 2018). Incidence and prevalence are slightly higher in men than in women, although other studies have not found significant differences in PD occurrence between the two genders, especially in Asia (de Lau & Breteler, 2006; Pringsheim et al., 2014). Epidemiological data regarding geographic location and

ethnic groups, while possibly influenced by methodological variations, consistently indicate lower incidence rates of PD in Asian and African populations when compared to Hispanic or Caucasian populations (Van Den Eeden et al., 2003).

Neuropathology and pathophysiology

The main neuropathological findings of the disease are the degeneration of dopaminergic neurons of the substantia nigra and the presence of intracytoplasmic aggregates of alpha synuclein known as Lewy bodies (Spillantini et al., 1997). One of the most distinct anatomopathological features of PD is the loss of the neuromelanin-containing neurons in the pars compacta of the substantia nigra (SN) in the midbrain, which send dopamine-releasing terminations to the striatum. Additionally, neurodegeneration affects typically noradrenergic neurons of the locus coeruleus (Zhou et al., 2021). Indeed, clinical pathological studies reveal depigmentation of the SN and the locus coeruleus and α -synuclein abnormality is found in more than 50% of neurons in the locus coeruleus in PD (Wakabayashi et al., 2007). In the remaining neurons, eosinophilic cytoplasmic inclusions, known as Lewy bodies, can be observed. Lewy bodies are primarily composed of α -synuclein filaments and represent a major histopathological hallmark of the disease. These α -synuclein deposits and neuronal degeneration are not only limited to the monoaminergic nucleus, but they are also found in the serotonergic nucleus of Raphe, Meynert's nucleus (cholinergic), as well as olfactory system, cerebral cortex and components of the autonomic nervous system. Anatomopathological studies show a different degree of neuronal density in the substantia nigra and basal ganglia in different phases of the disease. Onset of motor symptoms is related to the reduction of dopaminergic neurons, amounting to approximately 50-60%, which is considered the threshold after which the compensation mechanisms of the early stages are no longer able to cope neuronal loss (Fearnley & Lees, 1991).

The progressive degeneration of the nigro-striatal dopaminergic pathways determines a functional impairment of the basal ganglia-thalamo-cortical circuits. These circuits originate from the projections of the primary and non-primary motor areas onto the basal ganglia, subsequently the thalamus and finally back onto the cortical areas.

In physiological conditions, the dopaminergic projections of the substantia nigra pars compacta to the striatum act on two types of dopamine receptors, D1 and D2, exerting both excitatory and inhibitory influences on the striatal output neurons. Striatum represents the origin of the two main transmission pathways of the basal ganglia circuits. The inhibitory GABAergic and excitatory glutamatergic connections, present between the different nuclei, determine a reduction in the inhibitory output of the GPi and SNr, with a consequent increase in the thalamo-cortical drive, by the

direct pathway and, on the contrary, an increase in the inhibitory output of the GPi and SN pars reticulata, with consequent reduction of the thalamo-cortical drive, by the indirect pathway. The action of the direct and indirect pathways is modulated by SNpc. Dopamine depletion, characteristic of PD, leads to a reduction in inhibition of the indirect pathway and, at the same time, a reduced activation of the direct pathway. The consequence of these alterations is an increased neuronal activity at the GPi and STN level, a reduction in the activation of the thalamus and therefore of the motor cortex (Poewe et al., 2017).

The hypothesis of alpha-synuclein propagation, as proposed by the neuropathologist Braak and colleagues, suggests a stereotypic topographic expansion of α -synuclein aggregates. Initially, during the premotor stage (stage 1 and 2), alpha-synuclein inclusions are localized in the olfactory structures, in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and in the enteric neurons. In the following years, the pathology extends to the midbrain and basal forebrain, involving the substantia nigra and leading to the emergence of motor symptoms (stage 3 and 4). As the disease progresses, Lewy bodies are also found in the cerebral cortex and the limbic system (stage 5 and 6) (Braak, Del Tredici, et al., 2003, Braak, Rüb, et al., 2003). This hypothesis is further supported by the clinical evidence that non motor features, such as gastrointestinal problems or hyposmia, are present several years before the development of dopamine -related motor symptoms in the majority of patients. (Abbott et al., 2001a; Bohnen et al., 2008)

Nevertheless, the validity of the Braak model continues to be a subject of ongoing debate in the scientific community (Brundin et al., 2016; Burke et al., 2008; Rietdijk et al., 2017). The discovery of alpha-synuclein pathology in post-mortem samples from individuals who did not exhibit clinical signs of neurodegenerative diseases (Parkkinen et al., 2005) and the identification of alternative deposition patterns in a small subset of PD patients (Zaccai et al., 2008) have given rise to questions and discussions. Moreover, when examining the neuropathology of individuals with PD who carry mutations in the gene responsible for parkin (PARK2), it is noticeable that they often exhibit significant degeneration in the nigrostriatal pathway but do not consistently show the presence of Lewy bodies (Doherty et al., 2013). These observations have also prompted inquiries into whether alpha-synuclein deposition alone is sufficient to trigger the clinical symptoms associated with the disease.

Additionally, critics argue that there is a lack of consistent progression patterns in Lewy body dementia (Kon et al., 2020), although some researchers consider it a distinct entity separate from PD (Aarsland et al., 2004). It is important to note that Braak's observations on the progression of PD did not encompass dementia with Lewy bodies (DLB).

To address this issue, some researchers have put forward an alternative model, which suggests that

Lewy pathology does not initiate in the gastrointestinal tract but instead begins within the central nervous system (CNS). For instance, it may start in regions such as the amygdala, or it might follow a distinct route, commencing with isolated olfactory entry and subsequent intracerebral propagation before spreading to other brain regions. These two contrasting views, the "body-first" and "brain-first" models, aim to provide explanations for the clinical and neuropathological variabilities observed (Adler & Beach, 2016; Borghammer et al., 2021).

To date, the molecular mechanisms that provoke neurodegeneration and α -synuclein accumulation are incompletely understood. A prevalent hypothesis is that PD may result from a complex interaction among genetics and environmental factors, which determine the impairment of several pathogenic pathways, such as protein degradation system, mitochondrial dysfunction and oxidative stress, apoptosis, and neuroinflammation (Pang et al., 2019).

Alpha synuclein aggregation

In recent years, numerous studies have demonstrated how the accumulation of α -synuclein and the altered conformation of this protein lead to the formation of toxic protofibrils that affect dopaminergic cells. The precise mechanism through which alpha-synuclein causes the degeneration of dopaminergic neurons is not yet fully understood. Lewy bodies are primarily localized at the nerve terminal, where alpha-synuclein participates in the synaptic vesicle cycle. (Burré et al., 2010) Research indicates that misfolded alpha-synuclein may disrupt synaptic transmission, intracellular trafficking, affect chaperone functions, and potentially play a role in mitochondrial dysfunction. (Bendor et al., 2013)

Pathogenic mutations in patients with hereditary forms of PD have helped shed light on the mechanisms that determine the accumulation of Lewy bodies. Some of these, such as mutations in the alpha synuclein gene (SNCA) determine an altered conformation of the protein (Siddiqui et al., 2016) while others, in genes such as PRNK or ATP13A2, compromise the molecular pathways responsible for clearing the dysfunctional proteins (Klein & Schlossmacher, 2007a). In idiopathic forms of PD, besides aging, which is regarded as a risk factor for PD (Coleman & Martin, 2022), pathways related to proteostasis and protein degradation, oxidative stress, mechanisms of neuroinflammation and alterations in the conformation of proteins, can be triggered by environmental factors that determine the typical neuropathology of the disease (Bové et al., 2005).

Prion like propagation

The Braak model initially suggested that alpha-synuclein could spread transneuronally with a caudal-

rostral propagation. Subsequently, studies by Kordower et al. and Li et al. found that embryonic mesencephalic neurons developed alpha-synuclein-positive Lewy bodies after transplantation into the brains of PD patients (Kordower et al., 2008; Li et al., 2010). Further in vivo and in vitro investigations have revealed that alpha-synuclein, whether in oligomeric or monomeric form, can be secreted into the extracellular space and then enter other neurons through various potential mechanisms such as endocytosis or intra-axonal transport. These findings have given rise to the concept that a prion-like mechanism could be responsible for the progression of synucleinopathy within the nervous system (Dunning et al., 2012; Tyson et al., 2016; Volpicelli-Daley & Brundin, 2018). However, some objections have been raised. While alpha-synuclein shares certain characteristics with prions, it is believed that these similarities may only partially contribute to the disease's progression. This view is reinforced by the observation that the speed of pathology propagation is notably slower than that seen in prion diseases, which typically have a subacute course (Bendor et al., 2013; Brundin et al., 2016).

Protein Degradation Pathways

One of the main mechanisms underlying the accumulation of misfolded alpha synuclein is primarily driven by the dysfunction of pathways involved in the repair or proteolysis of abnormal proteins (Cuervo et al., 2010). Deregulation of molecular chaperones mediated autophagies, the ubiquitin-proteasome system, and the autophagy-lysosomal pathway can determine accumulation of abnormal or toxin proteins. (Huang & Figueiredo-Pereira, 2010, Vogiatzi et al., 2008). Moreover, it has been showed that α -synuclein overexpression impairs, in turns, macroautophagy. (Winslow et al., 2010) Important insights have been gained through study on the function of some proteins involved in degradation of unfolded or misfolded proteins. Autosomal recessive mutations encoding parkin or PTEN-induced kinase 1 (PINK1) impaired the formation of a complex that activate macroautophagy degrading dysfunctional mitochondria (Deas et al., 2011; Gómez-Sánchez et al., 2016). The VPS35 gene has been identified as a causative factor of an autosomal form of late-onset familial PD (PARK17). This gene encodes for a protein primarily located on endosomes, where it forms the retromer complex by interacting with other peripheral membrane proteins. VPS35 mutations disrupt lysosomal and autophagy function, as the retromer aids the sorting of transmembrane protein cargo between the endosome and both the Golgi complex for recycling or the lysosome for degradation. (Williams et al., 2017a). Furthermore, mutations in the leucine-rich repeat kinase 2 (LRRK2), that account for the most cases of familial PD, are involved in endolysosomal pathways (MacLeod et al., 2013). Additional evidence stems from loss-of-function mutations in the lysosomal enzyme ATP13A2, which is linked to a juvenile-onset type of

Parkinsonism called Kufor-Rakeb syndrome (van Veen et al., 2020).

Mitochondrial dysfunction and oxidative stress

Mitochondrial dysfunction has been shown to play a crucial role in the pathogenesis of PD. In the 1980s, MPTP (methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a toxin found in some batches of synthetic heroin, was identified as the causative agent behind the development of a parkinsonian syndrome among drug addicts (Langston et al., 1983). This toxin leads to the deterioration of complex I, resulting in reduced ATP production and increased generation of reactive oxygen species. Oxidative stress, as one of the consequences of impaired mitochondrial function, plays a fundamental role in disrupting various metabolic pathways. This disruption leads to changes in calcium homeostasis and impairs the ubiquitin-proteasome system, which, in turn, facilitates the accumulation of alpha-synuclein. Additionally, the aggregation of alpha-synuclein further promotes mitochondrial dysfunction, setting off a cascade of events. These insights into the pivotal role of mitochondria and oxidative stress have emerged from a better understanding of the impact of specific genetic mutations associated with PD and the influence of environmental toxins on mitochondrial function (Abou-Sleiman et al., 2006; Moon & Paek, 2015).

Neuroinflammation

Chronic neuroinflammation is recognized as a pivotal feature in PD. A mounting body of evidence suggests that the overactivation of microglia results in an upsurge of pro-inflammatory factors, which in turn contributes to the deterioration of dopamine neurons in the substantia nigra pars compacta. The presence of neuroinflammation is further substantiated by changes in gut microbiota, elevated levels of pro-inflammatory cytokines in the blood and cerebrospinal fluid, and by neurohistological and neuroimaging findings in both PD patients and animal models. Additionally, epidemiological studies provide support for the idea that the use of nonsteroidal anti-inflammatory drugs can reduce the risk of developing PD. (Tansey et al., 2022; Wang et al., 2015)

Environmental risk factor

Numerous environmental factors have been investigated for their potential impact on PD. Studies have demonstrated the association between exposure to certain pesticides, such as paraquat and rotenone, as well as specific solvents and heavy metals, and an increased risk of PD. However, the precise influence of factors like dose and duration of exposure remains to be fully determined (Ascherio et al., 2006; Pezzoli & Cereda, 2013; Willis et al., 2010). Furthermore, residing in areas with elevated air pollution, particularly exposure to nitrogen dioxide, has also been linked to a

heightened risk of the disease (Cole-Hunter et al., 2023; Jo et al., 2021).

Metabolic syndrome, notably diabetes mellitus, is another well-established risk factor for both the development and progression of PD (Chohan et al., 2021; De Pablo-Fernandez et al., 2018; Nam et al., 2018). Additionally, a history of melanoma, possibly due to shared pathways involving dopamine and melanin (Liu et al., 2011; Pan et al., 2012), and traumatic brain injury are considered risk factors as well (Gardner et al., 2015).

Conversely, several protective factors have been identified that can potentially reduce the risk of PD. Adopting a healthy lifestyle, including a balanced diet (Belvisi et al., 2020; Seidl et al., 2014) and regular physical exercise (Fang et al., 2018; Hughes et al., 2019), has been associated with lower PD risk. Interestingly, substantial body of evidence suggests that individuals who consume caffeine and smokers tend to have a reduced incidence of Parkinson's, although the precise mechanisms behind these associations require further investigation (Liu et al., 2012; Noyce et al., 2012). High serum urate levels reduced the risk for PD and, in the dose-response analysis, the risk for PD was reduced by 6% (relative risk reduction) for each 1 mg/dl increment in serum urate level (Chang et al., 2022). Some authors have hypothesized a premorbid personality characterized by novelty-avoidance (Evans, 2005; Jiménez-Jiménez et al., 1992), while others suggest also the possibility of a direct neuroprotective action (Quik et al., 2012; Ren & Chen, 2020).

Considering the heightened risk of PD in patients with diabetes mellitus, several studies have indicated an inverse association between certain antidiabetic drugs and the onset of PD (Brauer et al., 2020; Paudel et al., 2020; Sportelli et al., 2020). Moreover, certain medications, including non-steroidal anti-inflammatory drugs (NSAIDs) and beta-adrenergic receptor agonists, appear to exert a neuroprotective effect (Belvisi et al., 2020).

Further epidemiological studies are necessary to fully comprehend the roles of these risk and protective factors. Indeed, this research is crucial for the development of effective preventive strategies and the advancement of our understanding of this complex condition.

Genetic of PD

While the majority of PD cases seem to be sporadic, likely resulting from a combination of genetic predisposition and environmental factors (Kalinderi et al., 2016), there is growing evidence to suggest that genetic factors contribute to the pathogenesis of PD. This genetic influence is particularly significant in cases of juvenile-onset PD, although some mutations can lead to PD even in advanced age, particularly those with autosomal dominant inheritance (Klein & Westenberger, 2012). Currently, genetic forms of PD account for approximately 5-10% of all cases (Bandres-Ciga et al., 2020). These cases can be categorized into dominant and autosomal recessive mutations, and

they exhibit variable penetrance and frequency depending on the specific ethnic group.

Autosomal dominant genes

SNCA

The SNCA gene, located on chromosome 4, encodes alpha-synuclein, and both point mutations and gene multiplications have been documented (Klein & Schlossmacher, 2007b). The discovery of this gene's association with PD in an Italian family in 1996, (Golbe et al., 1996; Polymeropoulos et al., 1996) was a pivotal moment in advancing our understanding of PD's pathogenesis.

Numerous studies have indicated that the likely pathogenic mechanism involves a gain of toxic function. Amino acid substitutions within the gene sequence lead to the production of alpha-synuclein, triggering the formation of oligomers. These oligomers tend to aggregate initially into alpha-synuclein fibrils and eventually into Lewy bodies, causing cellular toxicity, although the exact mechanisms remain to be fully elucidated. The phenotype resulting from SNCA mutations exhibits variability, not only among patients with different mutations but also within the same family (Ricciardi et al., 2016). While some forms of PD associated with SNCA mutations resemble the sporadic phenotype, especially in cases of gene duplication, more severe forms can emerge, often characterized by a rapidly progressive course and the concurrent onset of cognitive impairments and autonomic dysfunction (Petrucci et al., 2016).

LRRK2

The LRRK2 gene, located on chromosome 12, encodes a protein called leucine-rich repeat kinase-2 or dardarin. Mutations of this gene are among the most frequent, especially in Ashkenazi Jews and in North African populations. The phenotype is generally comparable to sporadic PD and presents a variable penetrance, age dependent (Brice, n.d.; Di Fonzo et al., 2005). The word “dardara” comes from the Basque language and means tremor, which is often one of the predominant motor symptoms in mutated subjects. The protein encoded by this gene has multiple functions: it is involved not only in enzymatic reactions but also in many other cellular functions such as lysosomal degradation, the constitution of the cytoskeleton, vesicle trafficking, mitochondrial dysfunction and neuroinflammation (Rideout & Stefanis, 2014).

Neuropathological studies generally show the presence of nigrostriatal degeneration (Ross et al., 2006) but cases with absence of Lewy bodies (Kalia et al., 2015) or with tau-related pathology (Henderson et al., 2019) have also been described.

VPS35

Mutations in the VPS35 (vacuolar protein sorting ortholog 35) gene, situated on chromosome 16, lead to a classic presentation of late onset PD typically. Clinically it is characterized by the development of the cardinal motor symptoms, bradykinesia, resting tremor, rigidity and postural instability (Williams et al., 2017b). The VPS35 protein plays a fundamental role as a component of the retromer complex, which is involved in the recycling of synaptic vesicles and facilitates the transport of membrane-associated proteins from endosomes to the Golgi complex (Vilariño-Güell et al., 2011; Williams et al., 2017c).

Autosomal recessive genes

PRKN

Biallelic mutations in the PRKN gene represent a major causative factor for autosomal recessive PD. The PRKN gene encodes parkin, a protein ligase responsible for ubiquitination and subsequent intracellular degradation of proteins. Recent research has revealed that parkin is also involved in mitophagy, a process aimed at removing dysfunctional mitochondria. Mutations in the parkin gene are linked to early-onset parkinsonism, typically manifesting between the second and fourth decades of life. Patients with these mutations typically exhibit a positive response to levodopa replacement therapy, and the disease progression is generally slow. Over time, motor fluctuations and dyskinesias may develop. A notable characteristic is that the clinical presentation can begin with focal dystonia, often affecting the lower limbs (Khan et al., 2003). Neuropathological studies indicate gliosis and the loss of neurons in the substantia nigra, with less significant involvement of the locus coeruleus. In many cases, there is an absence of Lewy bodies, although some exceptions have been reported (Farrer et al., 2001; Pramstaller et al., 2005; van de Warrenburg et al., 2001).

PINK1

PINK1 mutations are the second most common genetic cause of autosomal recessive familial early-onset PD, often occurring before the age of 50. As mentioned earlier, PINK1 mutations can lead to the disease by causing mitochondrial dysfunction, typically due to a loss-of-function effect (Kasten et al., 2018; Kumar et al., 2011). Patients with PINK1 mutations generally exhibit a favorable response to levodopa, but they may experience the early development of motor fluctuations and dyskinesia.

DJ-1

DJ-1 mutations, although less common than other autosomal recessive mutations, are recommended

to be screened in individuals with young-onset PD (Kasten et al., 2018).). Patients with these mutations exhibit an early onset of rigidity, dyskinesia and tremors, followed by later manifestation of psychiatric symptoms, such as psychotic disturbance, anxiety, and cognitive decline, and generally respond well to L-DOPA treatment (Repici M, Giorgini F., 2019). While the precise function of DJ-1 is not completely understood, it is primarily associated with responding to oxidative stress (Lev et al., 2006). Recent evidence also suggests that DJ-1 plays a crucial role in regulating the inflammatory and immune responses (Zhang et al., 2020).

Associated gene or risk alleles

Beyond the Mendelian genetic forms of PD, which are caused by single gene mutations, recent years have witnessed significant advancements in genetic research techniques, notably Genome-wide Association Studies (GWAS). These cutting-edge methods have unveiled a multitude of risk variants that play a pivotal role in the development and progression of the disease. Among these, one of the most noteworthy and influential factors is the presence of genetic variations within the GBA gene. This genetic discovery has shed new light on our understanding of PD pathogenesis.

GBA gene

Variants in the glucocerebrosidase gene (GBA), which encodes for the lysosomal enzyme β -glucosidase, (glucocerebrosidase or GCase, EC 3.2.1.45, MIM*606463), represent the most common genetic risk factor for PD, found in 3–20% of patients in different populations (Blauwendraat et al., 2020; Gan-Or, Amshalom, et al., 2015a; Guerreiro et al., 2018; Lesage et al., 2011). The main function of the Gcase is the degradation of glucocerebroside and glucosylsphingosine into ceramide or sphingosine and glucose (Liou et al., 2006).

Homozygous mutations in GBA gene cause Gaucher disease (GD), the most common lysosomal storage disorder, characterized by loss of function of GCase. Over 500 pathogenic GBA variants have been identified which are classified, according to the GCase activity and to the severity of GD phenotype, as complex, severe and mild. Some mutation, not previously associated to GD, are called risk variant, because they are associated with an increased risk of PD (Petrucci et al., 2020). GD can be categorized into three types based on the extent of nervous system involvement. Mild variants are associated with GD Type I, which represents the majority of GD cases. Type I is primarily a systemic disease characterized by splenic and skeletal involvement, anemia, thrombocytopenia, and respiratory problems, with no or slight neurological involvement. Severe variants of GBA mutations are linked to either Type II or Type III. Type II typically presents with an early onset and is marked by progressive central nervous system complications. In contrast,

Type III typically begins during adolescence or early adulthood and exhibits progressive central nervous system involvement (GM Pastores & Derrallynn A Hughe, n.d.; Grabowski, 2008). Interest in the GBA gene as a genetic risk factor for PD was piqued during the 1980s when clinicians observed that a cohort of patients diagnosed with type 1 Gaucher's disease (GD) exhibited the emergence of parkinsonism-related symptoms (McKeran et al., 1985), although another case was previously described (Van Bogaert L & Froehlich A., n.d.). In the following years, multiple studies confirmed these preliminary observations (Gan-Or et al., 2018; Neudorfer et al., 1996).

Among the GBA variants related to the onset of PD, the most frequent in the population were missense mutations such as N370S and L444P, classified as generally mild and severe respectively. It is interesting that the E326K variant, which in homozygosis does not determine a GD, is observed to represent an important risk factor for PD (L. Smith & Schapira, 2022).

The frequency of the mutations varies by ethnicity in PD patients and general population (Blauwendraat et al., 2020; Leija-Salazar et al., 2019), peaking at around 17% in PD patients of Ashkenazi Jewish origin (Gan-Or, Amshalom, et al., 2015b; Ruskey et al., 2019; Sidransky et al., 2009a). In an Italian cohort of PD patients, GBA variants were found in a significant percentage of patients, about 14 % (Petrucchi et al., 2020). Furthermore, GBA mutations have been associated also with increased risk of Lewy bodies dementia (Blauwendraat et al., 2020; Gan-Or, Amshalom, et al., 2015b; Lesage et al., 2011; Nalls et al., 2013).

However, it's important to note that the majority of individuals carrying GBA variants will not develop PD. This suggests the involvement of other genetic and/or environmental factors in determining the penetrance of these variants. It has been estimated that carriers have about 3- to 4-fold higher risk to develop PD. Studies exploring the penetrance of GBA variants in carriers have indicated also an age-related pattern (Anheim et al., 2012; Rana et al., 2013). Furthermore, the penetrance differs among GBA variants, with high-risk variants being associated with earlier disease onset compared to lower risk variants (Gan-Or, Amshalom, et al., 2015b).

Pathogenic mechanisms of GBA mutation

The mechanisms underlying the impact of mutations in the GBA gene on GCase function have been investigated extensively.

A widespread deficiency in GCase activity and protein levels was demonstrated in GBA-PD brains in 2012, with the most severe impairment observed in the substantia nigra (SN) and putamen (Gegg et al., 2012). These findings have been substantiated by several studies conducted on blood or cerebrospinal fluid samples, as well as induced pluripotent stem cell-derived neurons (Alcalay et al., 2015; Huh et al., 2020; Schöndorf et al., 2014).

Furthermore, some authors have indicated that the type of GBA mutations impact the enzymatic activity of β -glucocerebrosidase in PD and have established a direct correlation between the severity of GBA mutations and the decrease in β -glucocerebrosidase activity (Huh et al., 2020; Lerche et al., 2021). The presence of reduced lysosomal GCase activity in PD patients without GBA mutations suggests that the loss of GCase function contributes to the pathogenesis of PD (Alcalay et al., 2015). It is believed that the functional reduction of GCase activity is a pivotal factor leading to impaired hydrolysis of glycolipids, specifically glucosylceramide and glucosylsphingosine, resulting in their accumulation within lysosomes. This accumulation, in turn, hampers lysosomal activity and diminishes the degradation of alpha-synuclein (Blandini et al., 2019). Recent evidence also suggests an inverse relationship between reduced GCase function and the accumulation of alpha-synuclein within cells. Fernandez and colleagues hypothesized a gain-of-function mechanism for GBA mutations, showing that N370S mutation can trigger misprocessing of misfolded GCase proteins within the endoplasmic reticulum (ER), ultimately leading to an upregulation of ER stress and impairing autophagic and lysosomal functions. This dysfunction contributes to the expansion of the lysosomal compartment and to increased release of extracellular α -synuclein (Fernandes et al., 2016).

Several experiments have indeed shown that the accumulation of glucosylceramide promotes and stabilizes the formation of the insoluble form of alpha-synuclein (Blandini et al., 2019; Gündner et al., 2019; L. Smith & Schapira, 2022; Suzuki et al., 2018; Zunke et al., 2018). This sets in motion a harmful cycle that promotes the spread of the pathology (Mazzulli et al., 2011). Additionally, the accumulation of alpha-synuclein and undegraded glycolipids obstructs the trafficking of GCase to lysosomes. This further impairs lysosomal function and other protein degradation mechanisms, such as the autophagy system, leading to increased alpha-synuclein accumulation (Blandini et al., 2019). Moreover, changes in cholesterol metabolism may play a role in reducing lipid rafts, which are crucial for synaptic positioning, vesicle transport, and the maintenance of synaptic stability. Alpha-synuclein has been linked to the regulation of neuronal cholesterol levels, and cholesterol contributes to the connections between alpha-synuclein oligomers (García-Sanz et al., 2021). Another study examining interactions between alpha-synuclein and GCase revealed that alpha-synuclein oligomers lead to the fragmentation of the endoplasmic reticulum (ER) and impair the folding capacity of ER proteins, resulting in the misfolding and aggregation of immature lysosomal β -glucocerebrosidase (Stojkowska et al., 2022).

A study aimed at identifying additional genetic factors contributing to the development of PD in GBA carriers has revealed that the risk of PD in GBA carriers is influenced by specific variants in regions that are commonly associated with an increased risk of PD. Notably, these regions include

SNCA, responsible for encoding alpha-synuclein, and CTSB, responsible for encoding cathepsin B. The latter, lysosomal protease, may exert its influence through its interaction with GBA (Blauwendraat et al., 2020).

Additional mechanisms that seem to contribute to the pathogenetic process leading to PD in individuals with GBA mutations include mitochondrial dysfunction and neuroinflammation (L. Smith & Schapira, 2022). Several studies provided evidences that a reduction in GCase activity is associated with clear activation of microglia in the brain parenchyma increasing the susceptibility of the brain to neurotoxic insults (Avenali et al., 2020). Nevertheless, further studies are required to elucidate the interplay among these pathways. Some of these mechanisms serve as the focus of ongoing studies aimed at developing therapies for GBA-PD patients.

Clinical presentation of Parkinson disease

Motor symptoms

Tremor

In PD the defining tremor is known as a "rest tremor," most noticeable when the affected body part is at rest and not engaged in purposeful activities. It is often described as resembling the motion of rolling a small object between the thumb and fingers, hence the terms "pill-rolling" or "counting money". This tremor typically oscillates at a frequency between 3 to 7 times per second (Hz), with 4 to 5 Hz being the most common (Findley et al., 1981). Although patients with PD may exhibit tremors during postural changes or with specific actions, the severity usually diminishes during purposeful movement and is most pronounced at rest. In some cases, patients may experience a "re-emergent tremor," which can be distinguished from other types of action tremors by its delayed onset after assuming a specific posture (Jankovic et al., 1999).

Tremor is a prominent initial symptom in 70-80% of cases during the early stages of PD (Pagano et al., 2016), often beginning unilaterally in the distal limb and eventually spreading to the opposite side. Although initially subtle, it becomes more noticeable as the disease progresses and can affect various body parts, including the chin and tongue, typically sparing the head and voice. Stressful situations can exacerbate tremors, with latent tremors becoming apparent when patients are relaxed and distractions are minimized.

The underlying mechanisms of tremor in PD are complex and not fully understood. Evidence suggests that the basal ganglia network plays a central role in initiating tremors, while the cerebello-thalamo-cortical circuit appears to influence tremor amplitude. While dopamine depletion is critical in the onset of tremors, there is also an associated serotonin deficiency that correlates with the severity of tremors. Additionally, tremor-dominant PD patients may exhibit a relatively greater

norepinephrine activity (Abusrair et al., 2022; Hallett, 2012). Responses to dopamine replacement therapy vary, and in cases of levodopa resistance, deep brain stimulation (DBS) can be a viable therapeutic option (Groiss et al., 2009).

Bradykinesia

Bradykinesia, characterized by a general slowness of movement marked by a decrease in both the size and speed of movements, can manifest as a spectrum ranging from reduced movement amplitude (known as hypokinesia) to the most severe form, akinesia, which represents an inability to initiate movement. The complexity of these clinical and pathophysiological aspects has prompted the proposal of new terminology (Bologna et al., 2023).

In the case of the upper limbs, bradykinesia often initiates distally, impacting fine motor skills of the fingers and can also affect gait patterns. Bradykinesia is typically an early manifestation of PD, affecting approximately 80% of patients at disease onset (Pagano et al., 2016). Similar to tremor, bradykinesia in the initial stages is often asymmetric, first appearing on one side and later involving both sides, with increasing influence on proximal and axial movements.

During clinical assessments, bradykinesia can be evaluated by observing the amplitude and rhythm in the execution of tasks such as finger tapping, hand opening and closing, hand pronation-supination, and heel or toe tapping (Postuma et al., 2015). It is essential to monitor these activities for an extended period, as in mild PD, the slowing and reduced movement size may take time to become apparent. As the disease progresses, movements become less coordinated, resulting in more frequent hesitations and interruptions. Bradykinesia can also be noticed when transitioning from sitting to standing and during gait evaluations, where reduced arm swing and shorter step lengths may be observed. In the cranial region, bradykinesia is evident through decreased facial expressions (hypomimia), reduced blinking frequency, impaired saccadic movements, changes in vocal tone resulting in a more subdued and monotonous voice, and increased salivation due to decreased spontaneous swallowing. Furthermore, a notable characteristic is the diminished spontaneity in overall movements.

The pathophysiological basis of bradykinesia primarily involves a diminished output from the basal ganglia to the primary motor cortex (M1) (Berardelli et al., 2001). Further neurophysiological investigations have shown that the slowing of movement is associated with reduced excitability of M1, and the progressive reduction in movement amplitude and/or speed results in a decline in brain plasticity mechanisms (Bologna et al., 2018).

Rigidity

Rigidity is a prevalent clinical feature in PD, affecting around 75 to 90 percent of patients (Pagano

et al., 2016). Much like tremor and bradykinesia, rigidity typically originates unilaterally and is associated with the side where these symptoms first appear. During clinical examinations, an increase in muscle tone is detected when the neck and limbs are passively moved. In most cases, lead-pipe rigidity is observed, where resistance remains consistent and smooth throughout the entire range of passive movement, for the uniform involvement of the gravitational and anti-gravity muscles. However, some patients may exhibit cogwheel rigidity, which displays a ratchety pattern of resistance and relaxation when their limbs are moved passively through a full range of motion. This phenomenon is thought to result from the presence of tremor combined with heightened muscle tone. Additionally, rigidity can contribute to the development of a frozen shoulder, leading to difficulties in the proximal movements of the upper limb, often accompanied by pain. Another observable effect of rigidity is the reduced pendularity of the limbs during walking.

Postural instability

This symptom typically manifests in the later stages of the disease and is a result of impaired centrally mediated postural reflexes, leading to compromised balance and frequent falls. Given that postural instability usually doesn't appear until the advanced phases of PD, its presence in the initial stages should raise a red flag and prompt consideration of atypical parkinsonism in the diagnostic process (Postuma et al., 2015). In the more advanced stages of the disease, postural instability is a significant clinical feature. It can be evaluated by exerting a sharp backward push on the patient's shoulders to assess the normal postural response, which involves a quick recovery of balance in two steps or less. The absence of this response, where equilibrium takes two or more steps to regain or there is a total lack of response, is indicative of the postural instability associated with PD. This clinical test helps healthcare professionals gauge the severity of postural instability and assists in the disease's diagnosis and management.

Non motor symptoms

In addition to the primary motor symptoms, James Parkinson had already pointed out the simultaneous occurrence of non-motor symptoms (NMS) in his description of the disease, including issues such as sleep disturbances, urinary incontinence, pain, cognitive challenges, and neuropsychiatric problems. Nonetheless, for a significant period, their presence was largely overlooked. This oversight can be attributed to the fact that the symptoms that lead patients to seek a neurologist's care are predominantly motor in nature, which forms the cornerstone of diagnosis. Nevertheless, NMS are now recognized as an integral component within the clinical spectrum of PD. Over the past decade, numerous studies have delved into this aspect of the condition,

emphasizing that these symptoms can manifest in the early stages of the disease and throughout its entire progression.

Investigating the presence of these symptoms is fundamental, both because they impact the patient's quality of life and because, awareness of their presence, allow their management together with that of motor symptoms. However, there remains a need for substantial advancements in both characterizing these symptoms and in developing therapeutic approaches to address them. After a brief review of cognitive dysfunction, sleep disturbances, olfactory deficits, there will be a detailed presentation of the physiopathology and clinical features of dysautonomia in parkinsonian syndromes.

Cognitive dysfunction

Cognitive impairment holds a significant place within the spectrum of PD, affecting individuals from the early stages of the condition. These cognitive alterations encompass a wide array of deficits, with common manifestations spanning difficulties in executive function, attention, working memory, and visuospatial abilities (Aarsland et al., 2021). Particularly, executive dysfunction can be identified through neurocognitive testing during the initial phases of the disease, with a prevalence of approximately 24%. (Muslimovic et al., 2005) In some instances, these cognitive impairments can advance into more severe conditions, including PD dementia (PDD) (Aarsland et al., 2005). The neuropathological changes underpinning these cognitive shifts involve the accumulation of abnormal protein deposits, particularly alpha-synuclein, which tends to aggregate in regions like the parietal and temporal lobes (A. H. V. Schapira et al., 2017). In addition, tau-positive and amyloid inclusions may also be observed (Irwin et al., 2012). Furthermore, there is an increasing body of evidence suggesting that cholinergic dysfunction plays a role in the cognitive impairments associated with PD (Bohnen et al., 2003; Mattila et al., 2001). This multifaceted nature of cognitive disturbances in PD necessitates a comprehensive approach to care and management for individuals living with this condition.

Neuropsychiatric symptoms

Prospective, longitudinal studies have shown that the cumulative prevalence of most neuropsychiatric signs and symptoms in Parkinson's disease are higher than previously thought, with a cumulative frequency greater than 50% in some studies (Kim et al., 2020). These symptoms include depression, anxiety, psychosis, apathy, and impulse control disorder (Weintraub et al., 2022). Depression and anxiety are also commonly reported features of off periods, occurring as part of non-motor fluctuations, secondary to long-term levodopa

treatment, in approximately 35% of patients (van der Velden et al., 2018). These signs and symptoms are associated with excess disability, worse quality of life, a range of poorer clinical outcomes, and greater burden for caregivers. At early disease stage, signs and symptoms can occur in isolation, although they frequently co-occur (es, depression often occurs with anxiety, apathy overlaps with depression and cognitive impairment, and psychosis and depression can complicate impulse control disorders (Ou et al., 2020). In advanced disease, the aetiology of neuropsychiatric signs and symptoms is a complex interaction of biological (eg, Parkinson's disease and other neurodegenerative pathology; multiple neurotransmitter system deficits; impairments in neural circuitry subserving mental functioning; and genetics), psychological, and social factors (Hommel et al., 2020)

Olfactory disturbances

Hyposmia or anosmia rank among the earliest NMS associated with PD. Approximately 90% of individuals in the early stages of PD exhibit olfactory dysfunction, and it can manifest years before the onset of motor symptoms (Doty, 2012). Notably, this symptom is not exclusive to PD but is also observed in other neurodegenerative conditions, like Alzheimer's dementia and atypical parkinsonisms. This observation has led to the hypothesis of a shared underlying mechanism. However, in PD, olfactory dysfunction tends to manifest earlier and more severely, which can aid in the diagnostic process (Murphy, 2019; Wenning et al., 1995). Typically, the severity of this symptom is assessed through a patient's medical history or objectively by having them identify various odors, with the results compared to normative values adjusted for age and gender.

The occurrence of hyposmia preceding the emergence of motor symptoms aligns with the sequential progression model proposed by Braak. According to this hypothesis, one of the initial sites where α -syn misfolding and aggregation occur is the olfactory epithelium and the gastrointestinal system, serving as a point of origin for the disease's dissemination to other regions. Furthermore, structures that receive projections from olfactory neurons, such as the amygdala, may become involved in this process (Borghammer et al., 2021; Braak, Del Tredici, et al., 2003; Dunning et al., 2012; Hawkes et al., 2007).

However, there are alternative hypotheses aimed at elucidating the early presence of this symptom. One posits a tau-related pathology, given the discovery of neurofibrillary tangles in the structures of the anterior olfactory nucleus. Another theory suggests a dysfunction associated with deficits in certain neurotransmitters, not limited to dopamine but also encompassing norepinephrine and acetylcholine, considering the well-known early degeneration of the locus coeruleus and Meynert's nucleus, respectively. Additionally, it's proposed that the olfactory epithelium may be particularly

vulnerable to environmental factors, triggering inflammatory responses that could lead to a PD pathology (Doty, 2012).

Sleep disorders

Sleep disturbances are a common and complex issue in individuals with PD. Many Parkinson's patients experience disruptions in their sleep patterns, which can significantly impact their overall quality of life (Factor et al., 1990). These sleep disorders can take various forms, including insomnia, excessive daytime sleepiness, periodic limb movement, restless leg syndrome, and rapid eye movement sleep behaviour disorder (RBD) (Comella, 2007). RBD is a particularly notable condition where individuals physically act out their dreams during sleep, often leading to injury or distress. Numerous studies have demonstrated a higher prevalence of RBD in individuals with PD, present in up to 50% of PD patients (Comella, 2007). Furthermore, idiopathic RBD is a significant risk factor for the development of other neurodegenerative disease such as Lewy bodies (DLB) (Claassen et al., 2010). Notably, many non-motor symptoms associated with PD have been observed in individuals with RBD. For instance, hyposmia is often present in individuals with RBD (Kang et al., 2016) This association is in line with Braak's hypothesis which sees a predominance of Lewy body deposits in the initial phase of the disease in the olfactory bulbs and in the brainstem (A. H. V Schapira et al., 2017).

The causes of these sleep disturbances in Parkinson's are multifactorial, involving a combination of the underlying neurodegenerative changes in the brain, medication side effects, and the disruption of the natural sleep-wake cycle. Various neurotransmitters are involved in the development of these disorders, with dopamine, norepinephrine, and serotonin being particularly significant. The dopaminergic pathways are especially pivotal due to their extensive projections to various brain regions responsible for regulating wakefulness, including the hypothalamus and brainstem structures. Additionally, the impact of dopaminergic medications in modulating these disorders further underscores their role in managing these conditions. (A. H. V Schapira et al., 2017).

Autonomic dysfunction

Anatomy and physiology of autonomic nervous system

The main function of the vegetative nervous system is the maintenance of homeostasis, integrating and coordinating control of numerous involuntary physiological processes. Furthermore, it is characterized by ability to respond and adapt to both internal or external stimuli, triggering a series of dynamic responses.

It represents a high sophisticated system characterized by a complex interplay between peripheral visceral and somatic afferents and the central nervous system, which coordinate vegetative response by descending inputs from several areas. It comprises three distinct divisions: the sympathetic (SNS) and parasympathetic (PNS) nervous system, which have antagonist effects on the innervated organs, and enteric nervous systems.

The sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) consist of cholinergic preganglionic neurons located in the brainstem and spinal cord. These neurons, with the help of myelinated axons, form synapses with autonomic ganglia and neurons within the enteric nervous system, which, in turn, innervate target organs.

Sympathetic Nervous System

The SNS consists of preganglionic neurons located in the thoracolumbar spinal cord, in the segment from T1 to L2. The preganglionic neurons of the SNS can synapse with the postganglionic neurons which are located in proximity, or with an ascending and descending pattern articulate in synapse respectively with postganglionic neurons of the cervical (superior and middle) or stellate ganglia, or with the caudal ganglia in the lumbar area. Finally, some neurons travel into the paravertebral chain, where they release the thoracic and lumbar splanchnic nerves that reach the mesenteric, coeliac, renal, and pelvic ganglia. Some preganglionic axons end in the adrenal medulla which represents the hormonal component of the autonomic nervous system and which releases catecholamines, mainly adrenaline.

Preganglionic neurons, both sympathetic and parasympathetic, are cholinergic and synapse with nicotinic receptors. At sympathetic neuro-effector junctions, the primary neurotransmitter is noradrenaline, with the exception of the sweat glands where acetylcholine is released. For this reason, the SNS is called also the adrenergic nervous system.

In normal physiological conditions, the sympathetic nervous system innervates various target organs, regulating their functions, and plays a vital role in controlling blood pressure, heart rate, organ perfusion, thermoregulation, and the adjustment of these parameters during daily activities. In particular, at the cardiac level, the SNS increases heart rate (positive chronotropy), augments the force of ventricular contractions (positive inotropy), and accelerates conduction within the SA and AV nodes (positive dromotropy). Moreover, it's important to note that arteries and veins are solely innervated by the sympathetic nervous system. In a state of rest, the baseline vascular tone is upheld through the effects of norepinephrine, primarily acting on α_1 -adrenergic receptors, resulting in peripheral vasoconstriction, and β_2 -adrenergic receptors. In contrast, adrenaline, which is released by the adrenal gland, predominantly influences β -adrenergic receptors. Specifically, it

targets β_1 -adrenergic receptors in the heart and β_2 -adrenergic receptors primarily located in blood vessels. This leads to an increased cardiac output and promotes vasodilation, respectively.

SNS has a fundamental role in triggering autonomic responses to potentially dangerous, known as the "fight or flight" response, or emotional situations, such as fear, through the release of norepinephrine.

Parasympathetic nervous system

The parasympathetic nervous system can be divided into two main components:

Cranial component: preganglionic parasympathetic fibers originate in the nuclei of cranial nerves within the brainstem (III, VII, IX and X). The fibers directed to the ciliary ganglion run together with the 3rd cranial nerve and reach the ciliary ganglion where they control the photomotor and accommodation reflex. The other preganglionic fibers run with the VII, to reach the pterygopalatine and submandibular ganglion which innervate the nasal and lacrimal glands and the submandibular glands respectively and, via the IX cranial nerve to reach the otic ganglion, from which the post ganglion fibers depart for the innervation of the parotid.

The main output of the cranial PNS is constituted by the vagus nerve. This, through the preganglionic fibers originate in the dorsal motor nucleus and in the nucleus ambiguus, contributes to the visceral innervation of the entire digestive tract up to the descending colon, lungs, heart and other visceral organs. In particular concerning cardiac innervation, the preganglionic fibers join the cardiac plexus at the thoracic level, which is also composed of sympathetic post-ganglionic neurons originating from the stellate ganglion. The parasympathetic axons establish synapses with the neurons located within the intracardiac ganglia, near the sinoatrial (SA) and atrioventricular (AV) nodes, which subsequently give rise to the short parasympathetic postganglionic neurons responsible for innervating the myocardial muscle tissue. The release of acetylcholine onto muscarinic receptors, resulting in the activation of these nodes. This action leads to a decrease in heart rate (negative chronotropy), a reduction in the force of atrial contractions (negative inotropy), and a slowing of conduction within the SA and AV nodes (negative dromotropy).

Sacral component: preganglionic fibers originate in the sacral metameres of the medulla (S2-S4) and, via the pelvic ganglion and the mural ganglia of the distal colon and rectum, control micturition, defecation and sexual function. The effects of the parasympathetic system predominate in conditions of stability and rest: it promotes digestive functions, reduces heart rate, blood pressure and overall performs an anabolic function.

The enteric nervous system

The enteric nervous system is recognized as the third constituent of the autonomic nervous system, encompassing the Auerbach (myenteric) and Meissner (submucosal) ganglionated plexuses. It forms a network of neurons that oversee the functioning of the gastrointestinal tract through a reflex mechanism. It distinguishes itself as an autonomous entity capable of operating independently from the sympathetic and parasympathetic nervous systems, although it can be subject to their influence. Intriguingly, enteric neurons employ a broad spectrum of essential neurotransmitters, including serotonin, as integral components of their functioning.

Central circuits

The central components of the autonomic nervous system, namely the central autonomic network, encompasses various areas in the cerebral cortex, including the frontal premotor region, hippocampal cortex, insular cortex, anterior cingulate gyrus, and anteromedial prefrontal cortex. Additionally, key structures involved in autonomic regulation are the hypothalamus, amygdala, diencephalon, and specific brainstem regions such as the midbrain periaqueductal gray nuclei, parabrachial nucleus in the pons, and nucleus of the solitary tract in the medulla, as well as the reticular substance in the medulla. The hypothalamus plays a central role in integrating autonomic and endocrine functions, governing biological rhythms, thermoregulation, sexual function, and behaviour.

Crucially, the central and peripheral elements of the autonomic nervous system are interconnected. This connectivity involves sympathetic and parasympathetic ganglia, along with their associated pre-ganglionic and post-ganglionic fibers, linked through ascending and descending neural pathways.

Clinical features of dysautonomia

Urinary dysfunction

Urinary dysfunction is a common occurrence in individuals with PD, affecting up to approximately 80% of patients. The most frequently reported urinary symptoms include nocturia, followed by increased frequency and urgency (Blackett et al., 2009a; Yeo et al., 2012). Some studies suggest that the presence of urinary symptoms may serve as an indicator of more advanced disease progression (Picillo et al., 2017). The urgency of micturition, or the sudden compelling need to urinate, has been attributed to reduced inhibition within the dopamine basal ganglia-frontal circuit. This circuit typically suppresses the micturition reflex. Under normal circumstances, micturition is regulated by the sacral spinal autonomic reflex, with the sympathetic nervous system promoting urine storage and parasympathetic fibers facilitating voiding through the contraction of

the detrusor muscle. Central control of this process involves a complex cortical circuit that encompasses regions such as the hypothalamus, cerebellum, basal ganglia, frontal cortex, grey periaqueductal matter, and the pontine micturition and storage centres. The degeneration of the substantia nigra is believed to play a role in this process by reducing the D1R-mediated output from the basal ganglia to the pontine micturition center (Blackett et al., 2009b; Sakakibara et al., 2012). Moreover, research utilizing single photon emission computed tomography (SPECT), conducted by Winge et al., demonstrated a correlation between the severity of urinary dysfunction and the loss of nigrostriatal dopaminergic neurons (Winge et al., 2005).

Gastrointestinal disturbances

The gastrointestinal tract exhibits two common autonomic symptoms in PD: constipation and gastrointestinal dysmotility. Constipation is a highly prevalent symptom, affecting approximately 80-90% of patients (Poirier et al., 2016; Sauerbier & Ray Chaudhuri, 2014). Notably, constipation can appear well before the onset of motor symptoms, emerging as an early autonomic dysfunction in the disease, sometimes up to 15.3 years before motor features (Fasano et al., 2015). Interestingly, a reduced bowel motility may be associated with an increased risk of developing PD (Abbott et al., 2001b)

The precise mechanisms underlying constipation in PD remain unclear. However, the presence of Lewy bodies or Lewy neurites in the gastrointestinal tract, including the enteric nervous system (Lebouvier et al., 2008; Wakabayashi et al., 1989), and the decreasing gradient of alpha-synuclein deposits along the rostral-caudal axis (Beach et al., 2010) have established a correlation between these symptoms and pathological changes observed in the dorsal nucleus of the vagus.

Gastrointestinal dysmotility, in addition to causing various symptoms like nausea, an early feeling of fullness and malnutrition, also complicates the management of PD. This is especially true in the advanced stages, where it interferes with the proper absorption of medications, thereby complicating the clinical management of the disease (Chen et al., 2020).

Sexual dysfunction

This is a frequently overlooked issue in PD, often due to both physicians feeling uncomfortable addressing these symptoms and patients hesitating to discuss them. In both men and women, a decrease in libido is a common occurrence, with some studies indicating a prevalence of up to 80% (Santa Rosa Malcher et al., 2021). This reduction in sexual desire is primarily associated with alteration in the central dopaminergic circuits (Santa Rosa Malcher et al., 2021). Patients undergoing dopaminergic therapy, especially with dopamine agonists, may be susceptible

to experiencing a dopamine dysregulation syndrome, which can manifest as hypersexuality and compulsive sexual behaviours (Batzu et al., 2022).

Male patients often encounter issues related to erectile dysfunction and problems with ejaculation (Bronner et al., 2004), while their female counterparts may experience a lack of lubrication, vaginal tightness, difficulty achieving orgasm, and involuntary urination during sexual intercourse (Welsh et al., 1997). These autonomic dysfunctions are linked to the presence of alpha-synuclein inclusions not only in the sacral parasympathetic nucleus within the spinal cord but also in the pelvic plexus and ganglia (Batzu et al., 2022).

Thermoregulatory dysfunction

Prevalence of sweating disturbances in PD varies widely ranging from 30 to 70% (Coon & Low, 2018). It may occur at any time during the course of PD and may precede the development of the classic motor features by more than 10 years. The existence of Lewy bodies within the hypothalamus and alpha-synuclein accumulation in preganglionic neurons in the intermediolateral cell column of the spinal cord and in the sympathetic ganglia supports the presence of a central component as do reports of hyperhidrosis being triggered by subthalamic deep brain stimulation (Pfeiffer, 2020). Conversely, small fiber peripheral neuropathy, with reduced innervation of blood vessels, sweat glands, and erector pili muscles, has been reported by multiple investigators in patients with PD, although its etiology remains uncertain. Hyperhidrosis in PD often is episodic and may occur unpredictably, sometimes at night. More often, however, it is related to motor function, occurring either as an off phenomenon or during episodes of severe dyskinesia.

Hyperhidrosis may be associated with a dysautonomia dominant subtype of PD. Hypohidrosis typically is less bothersome than hyperhidrosis to affected individuals, but it leaves them at increased risk of heat intolerance (van Wamelen et al., 2019).

Cardiovascular Dysautonomia in PD

Cardiovascular dysautonomia is a common occurrence in PD. In fact, more is known about the biomarkers, underlying mechanisms, and treatment of cardiovascular dysautonomia in PD than any other form of dysautonomia in the same context. Orthostatic hypotension (OH) is a commonly observed nonmotor symptom in PD. A systematic review conducted by Velseboer estimated its prevalence to be around 30% (Velseboer et al., 2011), while Hiorth Y and other authors found varying prevalence rates, with orthostatic hypotension reported in 65.4% of cases and clinically significant OH in 29.2% (Hiorth et al., 2019). Interestingly, OH can manifest before the onset of motor symptoms in as many as 60% of patients (Goldstein, 2006). The symptoms and signs of OH

typically include dizziness or postural vertigo, a sensation of feeling faint, and occurrences of falls, sometimes with loss of consciousness, all resulting from reduced blood flow to the brain. These symptoms can significantly impact a patient's daily activities and quality of life. Furthermore, individuals with PD and OH tend to have more pronounced motor dysfunction (Chen et al., 2020). Additionally, OH has been linked to cognitive impairment (Longardner et al., 2020). Orthostatic hypotension is defined by an international consensus statement (“Consensus Statement on the Definition of Orthostatic Hypotension, Pure Autonomic Failure, and Multiple System Atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology.” 1996) as a sustained drop in systolic blood pressure (SBP) of at least 20 mm Hg and/or diastolic blood pressure (DBP) of at least 10 mm Hg within 3 minutes of active testing while standing or during a head-up tilting table test inclined at an angle of at least 60°. Besides the classic OH, which occurs within 30 seconds to 3 minutes of assuming an upright position, two other variants have been identified: initial OH (occurring within 15 seconds of standing) and delayed OH (occurring after several minutes of standing).

In cases where patients exhibit supine hypertension, with a blood pressure equal to or greater than 160 mmHg, some authors recommend defining orthostatic hypotension as a drop in systolic blood pressure of at least 30 mmHg. This adjustment takes into account the variation in blood pressure reduction based on the patient's baseline blood pressure (Fedorowski et al., 2009).

In PD, orthostatic hypotension can be linked to a reduction in total peripheral resistance and the absence of a compensatory rise in heart rate. This lack of a compensatory response leads to an insufficient adjustment to restore blood pressure to normal levels when transitioning to a standing position (Gibbons et al., 2017; Tzur et al., 2019). An important criterion to support the diagnosis of neurogenic OH is an increase in heart rate of <15 bpm suggests a diagnosis of neurogenic OH (Gibbons et al., 2017). Recently, more promising index for assessment has been introduced, which focuses on the ratio between heart rate and systolic blood pressure (SBP) changes occurring at the 3-minute mark of the tilt test ($\Delta HR/\Delta SBP$) (Norcliffe-Kaufmann et al., 2018).

The Valsalva maneuver (VM) serves as the gold standard for determining whether OH has a neurogenic basis. The absence of the anticipated increase in blood pressure during the second part of the expiratory strain (late phase II) and, notably, the absence of a blood pressure overshoot following release (phase IV) are indicative of sympathetic neurocirculatory dysfunction (Guaraldi et al., 2020). Additionally, another commonly used indicator of adrenergic baroreflex function is the blood pressure recovery time, which measures the duration in seconds for systolic blood pressure to return to baseline values from phase III (Vogel et al., 2005).

In delayed orthostatic hypotension the potential pathophysiological mechanisms can be due to an

increased pooling of blood in the lower body capacitance vessels and the gradual deterioration of compensatory mechanisms during prolonged periods of orthostatic stress. It is typically considered a milder form of classic orthostatic hypotension and may eventually progress to the classic form (Tzur et al., 2019).

The neurogenic OH of PD patients is attributed primarily to deficiency in norepinephrine that can occur in two ways. It can originate in the peripheral nervous system, resulting from cardiovascular sympathetic denervation, as seen in conditions such as pure autonomic failure, PD, and various neuropathies. Alternatively, the deficiency can stem from central mechanisms, where viscerosensory signals fail to generate sufficient sympathetic activity to effectively stimulate intact sympathetic nerve endings, a situation commonly observed in multiple system atrophy (Loavenbruck & Sandroni, 2015).

A significant milestone in our understanding of cardiac dysautonomia was achieved with the introduction of the first neuroimaging evidence demonstrating cardiac sympathetic denervation (Goldstein et al., 1997). This breakthrough marked a pivotal moment in both scientific and clinical comprehension of the disease, allowing the characterization of dysautonomic failure and the differential diagnosis between the different alpha-synucleinopathies. Goldstein et al. showed that one of the key mechanisms behind dysautonomia in PD was the loss of post-ganglionic noradrenergic nerves responsible for cardiac innervation. This cardiac sympathetic denervation occurs to varying degrees in all PD patients and appears to be unrelated to the severity of their motor symptoms. This finding has been confirmed by numerous studies using several sympathetic neuroimaging agents. Furthermore, Haensch et al. demonstrated that MIBG (meta-iodobenzylguanidine) scintigraphy proves to be a highly sensitive and valuable diagnostic tool for detecting postganglionic sympathetic cardiac nerve abnormalities. This technique is capable of identifying these alterations even before the onset of symptoms like orthostatic hypotension, and it precedes other diagnostic methods such as the analysis of reduced heart rate variability and baroreflex insufficiency (Haensch et al., 2009).

Another important aspect to explain OH in PD patients is the failure of the arterial baroreflex. The baroreceptor reflex, represents a fundamental homeostatic mechanism within the body, contributing to the maintenance of blood pressure at a nearly constant equilibrium. This intricate reflex system operates through a swift negative feedback loop. When there is an elevation in blood pressure, it triggers a reduction in heart rate. Conversely, a decrease in blood pressure diminishes baroreflex activation, leading to an elevation in heart rate, ultimately serving to reestablish blood pressure to its desired set point. Goldstein et al. using Valsalva manoeuvre, demonstrated that PD patients without orthostatic hypotension exhibit mild baroreflex failure, while those with PD and OH

experience more pronounced baroreflex impairment (Goldstein, 2014).

The exact mechanism underlying the baroreflex deficit in PD has not been completely elucidated. While deposits of alpha-synuclein have been discovered in the locus coeruleus, the primary noradrenergic nucleus, it's worth noting that this nucleus does not project onto sympathetic preganglionic neurons. Another hypothesis posits that Lewy bodies may be situated in the rostral ventrolateral medulla, which projects to preganglionic sympathetic neurons, or within the nucleus of the solitary tract, serving as the principal site where baroreceptor afferents terminate. While the dorsal motor nucleus of the vagus nerve may indeed exhibit cell loss or the presence of Lewy bodies in PD, it's noteworthy that the nucleus ambiguus, the primary source of vagal efferents responsible for reflexive bradycardia, appears to remain unaffected by the pathology associated with PD (Jain & Goldstein, 2012).

Additionally, a complicating factor arises from the use of medication. Patients may have supine hypertension that is managed with antihypertensive drugs. Furthermore, dopaminergic therapy can induce vasodilation and hypovolemia, both of which can contribute to decreased blood pressure levels.

Another characteristic of cardiovascular dysautonomia is supine hypertension. According to Fanciulli et al., the prevalence of supine hypertension in PD is 34%, and the majority of cases are of mild intensity (71%) (Fanciulli et al., 2016a). According to the American Heart Association criteria, supine hypertension (SH) was identified when systolic blood pressure (BP) reached or exceeded 140 mmHg or diastolic BP was 90 mmHg or higher at the end of any supine phase. Mild hypertension was defined as systolic BP ranging from 140 to 159 mmHg or diastolic BP between 90 and 99 mmHg, while moderate hypertension was characterized by systolic BP levels of 160 to 179 mmHg or diastolic BP between 100 and 109 mmHg. Severe hypertension was categorized as systolic BP equal to or greater than 180 mmHg or diastolic BP at or above 110 mmHg (Chobanian et al., 2003). While typically lacking noticeable symptoms, SH can serve as a potential risk factor for cardiac or renal comorbidities, cognitive dysfunction, an increased likelihood of hemorrhagic strokes (Asahina et al., 2013; Chen et al., 2020). The mechanisms responsible for supine hypertension encompass compromised baroreflex function, inapt sympathetic activity (like heightened sympathetic response when lying down), changes in endocrine systems, and medications administered to manage orthostatic hypotension (Asahina et al., 2013).

The majority of patients may exhibit a non-dipping pattern, which is defined as the absence or reduction in nocturnal blood pressure decline. The reported prevalence of this pattern is consistently around 80% in PD patients across various studies (Berganzo et al., 2013; Sommer et al., 2011). Furthermore, many PD patients also encounter post-prandial and exercise-induced hypotension,

which results from excessive or uncompensated splanchnic and muscle blood pooling. Both of these factors have the potential to worsen orthostatic hypotension (Jansen & Lipsitz, 1995; G. D. Smith & Mathias, 1995).

Dysautonomia in other synucleinopathies

The presence of autonomic dysfunction accompanies all alpha synucleinopathies which include, in addition to PD, dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and pure autonomic failure (PAF). These disorders share the commonality of alpha-synuclein deposits at the neuropathological level. However, what sets each synucleinopathy apart is the distinct pattern of inclusion distribution and the severity of associated symptoms.

Dementia with Lewy bodies

DLB is the second most common form of neurodegenerative dementia, following Alzheimer's disease (I. McKeith, 2004). It is defined by the notable occurrence of Lewy-related pathology in neurons within the neocortex, limbic system, and Peripheral Autonomic Effectors. Additionally, there is a lesser extent of neurofibrillary tangles and A β plaques (Dickson, 2002). Clinically, DLB is distinguished by cognitive impairment, along with a range of motor and non-motor symptoms, including parkinsonism, hallucinations, REM sleep behavioural disorder, olfactory dysfunction, and dysautonomia. Autonomic dysfunction is observed in approximately 60% of DLB patients and plays a role in supporting the diagnosis (I. G. McKeith et al., 2017). Although the areas affected by Lewy bodies in DLB are similar to those in PD, especially involving the dorsal motor nucleus of the vagus, peripheral sympathetic and parasympathetic fibers, and the enteric nervous system, autonomic dysfunction is typically more pronounced. This places DLB on a spectrum between PD and Multiple System Atrophy (MSA) (Thaisethawatkul et al., 2004a). Dysautonomia is present in around two-thirds of DLB patients (Mendoza-Velásquez et al., 2019) and often appears before the onset of cognitive disturbances (Fujishiro et al., 2015). Orthostatic hypotension is observed in approximately 50-70% of individuals with DLB and can manifest with severe symptoms, including syncope (Horimoto et al., 2003; Postuma et al., 2013; Thaisethawatkul et al., 2004b). Urinary incontinence is another common feature, as is constipation, found in 97% and 86% of patients in a specific cohort (Horimoto et al., 2003).

Multiple System Atrophy

The defining neuropathological feature of Multiple System Atrophy (MSA) is the presence of oligodendroglial cytoplasmic inclusions. These alpha-synuclein deposits are primarily located in

regions of the central nervous system that regulate the autonomic nervous system. Specifically, these areas encompass the ventrolateral medulla, and additionally, the hypothalamus, periaqueductal gray, medullary raphe, dorsal motor nucleus of the vagus, nucleus ambiguus, and the pontine micturition center. Moreover, within the spinal cord, they are typically observed in sacral preganglionic neurons and, notably, in the Onuf nucleus (Coon et al., 2018)

Norepinephrine plasma levels are typically within the normal range in MSA, and Cardiac 123I-MIBG-Scintigraphy usually yields negative results, indicating presynaptic autonomic dysfunction (Bhatia & Stamelou, 2017).

Dysautonomia tends to have an early onset and is quite severe in MSA (Bhatia & Stamelou, 2017). Among the dysautonomic symptoms, orthostatic hypotension (OH) and urogenital dysfunction are the most common clinical features. Delayed OH is found in approximately 50%, while urogenital dysfunction is observed in around 96% of MSA patients (Pavy-Le Traon et al., 2016; Sakakibara et al., 2000). Additionally, about one-third of patients also experience supine hypertension, which tends to be more severe in those with the cerebellar variant of MSA (Fanciulli et al., 2016b; Wenning et al., 2012). Erectile dysfunction is prevalent in nearly all men diagnosed with definite MSA and can be an initial symptom (Jecmenica-Lukic et al., 2012; Tandon & Pradhan, 2015). However, there is a significant lack of substantial data regarding genital dysfunction in women. Constipation is another autonomic feature that can be present in MSA (C.-N. Lee et al., 2013; Savica et al., 2018)

Pure Autonomic Failure

Pure Autonomic Failure (PAF) is a rare and distinct neurological disorder primarily affecting the autonomic nervous system. Unlike other synucleinopathies, PAF is characterized by the presence of Lewy body deposits, which preferentially accumulate in the sympathetic ganglia and peripheral autonomic fibers with a post-ganglionic distribution. This specific pattern results in a reduction of plasma norepinephrine levels and, when transitioning to an upright position, an absence or only a modest increase. Additionally, sympathetic noradrenergic denervation is evident through reduced cardiac uptake of 123I-MIBG (Kashihara et al., 2006).

The cardinal feature of PAF is typically neurogenic orthostatic hypotension. Moreover, PAF patients may also experience supine hypertension, bowel and bladder disturbances, thermal dysregulation, and sexual dysfunction. Notably, in a prospective cohort study, it was demonstrated that approximately one-third of patients with PAF can progress to α -synucleinopathies. The risk of conversion was significantly higher, sevenfold, in individuals who, in addition to experiencing dysautonomic symptoms, also exhibited REM sleep behavior disorder (Kaufmann et al., 2017).

Assessment of cardiovascular dysautonomia

Clinical rating scales

Numerous clinical rating scales have been developed to assess cardiovascular dysautonomic symptoms, with a particular focus on OH and its degree of severity. These scales primarily serve as screening tools for evaluating autonomic dysfunction. Nonetheless, it is worth noting that these could potentially underestimate the presence of orthostatic hypotension (OH). This underestimation might occur because of the terminology used to describe the associated symptoms, the possibility that not all relevant symptoms are fully encompassed, or even if OH exists, it may be asymptomatic (Fereshtehnejad & Lökk, 2014; Jamnadas-Khoda et al., 2009).

A task force convened by the Movement Disorders Society conducted an evaluation of clinical rating scales designed for the assessment of non-motor symptoms. They classified a scale as "Recommended" if it had been employed in clinical trials following its development by the respective group, specifically used in reports related to PD, and demonstrated through clinimetric studies to be valid, reliable, and sensitive. The "Suggested" scales were those that met some of these criteria but did not satisfy all of them (Pavy-Le Traon et al., 2011). For the evaluation of orthostatic hypotension (OH), the MDS task force recommended using the SCOPA-AUT and the Composite Autonomic Symptom scale. Additionally, they suggested considering the New scale for non-motor symptoms and the Orthostatic Rating Scale to assess OH in individuals with PD (Pavy-Le Traon et al., 2011)

Clinical laboratory tests

Active standing

The active stand test is a simple evaluation that can be conveniently conducted, either at the patient's bedside or during a clinical visit. Initially, baseline measurements of heart rate and blood pressure are taken while the patient is in a supine position. Then, these measurements are repeated once the patient has assumed the upright, orthostatic position. When transitioning to the orthostatic position, there's compression of the lower extremity veins due to the muscular pump. This leads to an increase in venous return to the heart and an elevation in cardiac output. Simultaneously, the compression of arterial vessels results in heightened resistance. These mechanisms trigger the baroreceptor response, reducing sympathetic activity and consequently peripheral resistance, leading to a rapid drop in blood pressure. This phase typically lasts for approximately 6 to 8 seconds. Subsequently, the baroreceptors adjust the parasympathetic and sympathetic responses to optimize both blood pressure and heart rate. This test's clinical utility lies in its ability to assess the potential presence of hypotension in a real-life scenario, making it a valuable tool for bedside

evaluation. However, it is generally less sensitive than the head-up tilt test (HUT).

The head-up tilt test

The head-up tilt test stimulates the autonomic nervous system (ANS) through the application of orthostatic stress. This is achieved by passively transitioning an individual from a supine position to an upright posture within a controlled laboratory environment. In the assessment of cardiovascular dysautonomia in patients with PD, it is valuable to detect irregularities in sympathetic noradrenergic innervation of the heart. This is accomplished by examining the presence of orthostatic hypotension and distinguishing between neurogenic and non-neurogenic forms. The procedure begins with recording the patient's baseline blood pressure and heart rate while they are lying in a supine position for a few minutes. After this, the patient is swiftly tilted to a head-up position of 60-80 degrees. While in this tilted position, continuous monitoring of blood pressure and heart rate is conducted to assess any changes in frequency and pressure. It is important to take note of any symptoms reported by the patient during this period.

To ensure the test's effectiveness and minimize potential confounding factors that could influence the autonomic response, it is recommended to conduct the test under specific standard conditions. Ideally, it should be performed in the early morning, as individuals, whether healthy or affected by orthostatic hypotension, tend to have reduced tolerance to the upright position during this time of day. The room temperature during the test should be kept comfortable, neither too hot nor too cold, to ensure patient comfort.

Patients should be advised to consume a moderate or light meal before the test, as it is known that meals, especially those rich in carbohydrates, can increase the risk of post-prandial hypotension. Additionally, it's crucial to evaluate the patient's medication regimen before the test to identify and suspend any drugs that could influence the autonomic response, as well as to address potential issues that may lead to a rebound effect. The list of such drugs includes beta-adrenergic receptor agonists, alpha-adrenergic receptor antagonists, clonidine, benzodiazepines, and serotonin/norepinephrine reuptake inhibitors.

During the tilt test conducted in a cardiac physiology laboratory, a neural reflex is induced by redistributing blood to the lower limbs. This redistribution results in a decrease in venous return, subsequently leading to hypotension. Under normal physiological conditions, baroreceptors detect the drop in blood pressure and trigger a reduction in parasympathetic activity and an increase in the noradrenergic response, leading to vasoconstriction and increased cardiac contractility.

However, in patients with orthostatic hypotension, these mechanisms are impaired (Sandhu).

Valsalva maneuver

The Valsalva maneuver (VM) entails a controlled exhalation against a resistance of 30-40 mm Hg over a 15-second duration, with concurrent continuous monitoring of blood pressure and heart rate. VM induces an abrupt and prolonged increase in intrathoracic pressure, which subsequently instigates alterations in both cardiac pressure and heart rate. These alterations provide us with valuable metrics for assessing the functionality of the sympathetic and parasympathetic systems. To facilitate the analysis of these changes, VM is divided into four phases:

Phase I: during this initial phase, there is a notable increase in intrathoracic and intra-abdominal pressures, resulting in the mechanical compression of the aorta. Consequently, there is a transient rise in blood pressure along with a decrease in heart rate. Phase I typically has a duration of approximately 2 to 4 seconds.

Phase II is further subdivided into two segments: early Phase II (IIe) and late Phase II (III).

Early Phase II (IIe): after Phase I, there is compression of the vena cava, resulting in a decreased venous return to the heart, thereby reducing preload and cardiac output. This decrease in blood pressure activates baroreceptors, subsequently initiating an efferent sympathetic discharge. This sets the stage for *late Phase II (III)*, during which the aortic and arterial baroreceptors stimulate the activation of sympathetic vasomotor nerves. This activation leads to an increase in total peripheral resistance and blood pressure. These fluctuations in blood pressure are accompanied by an elevation in heart rate. Initially, the rising heart rate is due to the withdrawal of cardiovagal activity, and subsequently, it's driven by increased sympathetic activation. The combination of an increasing heart rate and heightened peripheral systemic resistance prevents further decline in blood pressure. This ultimately results in a recovery of blood pressure, often surpassing the baseline level. Phase II concludes after the 15-second forceful expiration period.

Phase III: this phase is initiated when the expiratory effort ceases, causing a decrease in intrathoracic pressure owing to the sudden expansion of intrathoracic vessels. The heart rate remains elevated.

Phase IV: during this phase, the restoration of venous return brings about a continuous elevation in diastolic heart filling, thus enhancing cardiac function. Simultaneously, systemic resistance remains elevated due to the earlier sympathetic activity during the maneuver. The substantial volume of blood ejected into the constricted systemic circulation leads to a notable increase in arterial pressure, commonly referred to as the "blood pressure overshoot," surpassing the baseline level. In tandem, there is a decline in heart rate due to the stimulation of baroreceptors. Phase IV typically persists for about 10-20 seconds.

Analyzing the distinct phases can yield valuable insights into the evaluation of adrenergic and

vagal functions. In individuals with sympathetic adrenergic dysfunction, the blood pressure drop in early Phase II does not abate after 4-7 seconds, as observed in healthy subjects, but may instead decline significantly. Late Phase II is reflective of vasoconstriction, which may be attenuated in patients with sympathetic failure. However, it's worth noting that this index may also be reduced in some elderly individuals with otherwise normal health, limiting its diagnostic specificity (Low et al., 1997). In more severe cases of sympathetic dysfunction, blood pressure may plummet dramatically in early Phase II, with no subsequent recovery in late Phase II.

Another crucial marker of adrenergic dysfunction is the absence of the "overshoot" in blood pressure.

Additionally, a novel index, referred to as "blood pressure recovery time," is calculated. This index signifies the duration it takes for blood pressure to return to baseline from the conclusion of Phase III. Importantly, this index demonstrates a strong correlation with both late Phase II and Phase IV (Vogel et al., 2005).

During the Valsalva maneuver, the data related to heart rate is meticulously collected and subsequently subjected to analysis. This analysis involves the computation of a crucial metric known as the "Valsalva ratio." This ratio is derived by comparing the maximum heart rate achieved during the expiratory phase with the minimum heart rate attained during the subsequent relaxation phase, which unfolds within a 30-second timeframe. The Valsalva ratio serves as a precise and quantifiable gauge of cardiac parasympathetic function. In essence, it provides a numerical representation of how well the parasympathetic nervous system is functioning in regulating cardiac activity. A higher Valsalva ratio is indicative of superior overall parasympathetic function, signifying a more effective and balanced control over heart rate, contributing to the stability of cardiovascular dynamics. This metric plays a pivotal role in assessing autonomic nervous system health and cardiac function.

Deep breathing

Deep breathing enables the assessment of heart rate variability through controlled breathing at a rate of 6 respiratory cycles per minute. To establish a baseline heart rate, the mean heart rate is determined for one minute before commencing the test. Heart rate variability is assessed by calculating the difference between the highest heart rate observed during inspiration and the lowest heart rate observed during expiration over the course of six respiratory cycles within one minute.

Typically, there is an increase in heart rate during inspiration primarily due to the influence of baroreceptors and chemoreceptors on parasympathetic fibers. Conversely, a decrease in heart rate is observed during expiration. This phenomenon is known as sinus arrhythmia and is

intensified by a reduction in respiratory frequency. This test serves as a valuable tool for evaluating parasympathetic function.

Isometric hand-grip test

The isometric handgrip exercise involves the sustained contraction of muscles, resulting in a significant elevation in arterial blood pressure and heart rate, primarily driven by sympathetic activation. This maneuver triggers a metaboreflex, which is initiated by the activation of muscle chemoreceptors highly sensitive to the metabolic byproducts generated during muscular contraction. These chemoreceptors, in turn, stimulate both small myelinated and unmyelinated nerve fibers, ultimately culminating in an adrenergic response within the cardiovascular system. Afferent nerve fibers play a critical role in relaying this information, facilitating the initiation of sympathetic responses throughout the cardiovascular system (Fu et al., 2002)

Cold face test (CFT)

In contrast, the Cold Face Test (CFT) involves the application of a cold stimulus to the face, resulting in bradycardia, primarily brought about by cardiovagal activation, and an increase in blood pressure, predominantly driven by peripheral vasoconstriction. The initiation of this reflex can be attributed to cutaneous thermoreceptors and nociceptors, which transmit signals through unmyelinated C-fibers. This test represents an alternative method for studying the cardiovagal response, distinct from the baroreceptor's involvement (Fu et al., 2002; Heath & Downey, 1990).

Heart Rate Variability Analyses

Spectral analysis is a powerful method employed for examining the frequency components of a signal, facilitating the revelation of its underlying characteristics. It relies on the decomposition of a complex signal, which offers a method for recurring patterns to be unveiled, concealed structures to be revealed, and the existence of specific frequencies within it to be assessed. Over the last two decades, there has been a growing utilization of spectral analysis in PD research, particularly for investigating the autonomic nervous system (Heimrich et al., 2021). This analytical approach enables the assessment of potential dysfunction in both the sympathetic and parasympathetic nervous systems, even in the early stages of the disease. Furthermore, it provides insights into the interaction between these two components of the autonomic nervous system. To ensure a uniform approach, in 1996, a task force consisting of the European Society of Cardiology and the North American Society of Pacing Electrophysiology formulated guidelines aimed at standardizing methods of measurement, physiological interpretation, and clinical application (Electrophysiology, 1996). Heart rate variability (HRV) analysis is a non-invasive and readily available method for

assessing the overall activity of the autonomic nervous system. It enables the separate evaluation of both sympathetic and parasympathetic nerve functions. HRV represents changes in heart rate across a defined time frame, providing insights into how the sympathetic and parasympathetic nervous systems influence heart rate. These interactions are characterized by non-linear dynamics and involve a rather intricate and complex interplay. To conduct an accurate analysis, the heart rate at any given moment, or the intervals between successive normal QRS complexes, known as normal-to-normal (NN) intervals, are measured. It is crucial to eliminate ectopic beats or premature ventricular contractions, as they can introduce artifacts and distort the analysis. This can be accomplished manually or with the assistance of suitable algorithms (Fujiwara et al., 2021).

They are mainly distinguished in time domains and frequency domains.

The principal time domains are RMSSD, or Root Mean Square of Successive Differences and pNN50, or Percentage of Differences in Successive NN (normal-to-normal) Intervals Greater than 50 ms. Both represents a measure of short-term heart rate variability. Other index include the SDNN, SDRR, SDANN, SDNN Index, NN50, HR Max – HR Min, the HRV triangular index (HTI), and the Triangular Interpolation of the NN Interval Histogram which are more accurate in long recordings, over 24 h (Shaffer & Ginsberg, 2017). These values can be presented either in their original units or, alternatively, as the natural logarithm (Ln) of the original units. This logarithmic transformation helps achieve a distribution that aligns more closely with a normal pattern (Shaffer & Ginsberg, 2017).

- RMSSD is computed by first calculating the squared-difference between consecutive NN intervals, and their average. Then, the square root of this average is taken to derive the RMSSD value, in ms. RMSSD quantifies the fastest components of variability and has a particular sensitivity to parasympathetic (vagal) activity. An increase in parasympathetic influence leads to enhanced fast beat-to-beat heart rate variability, resulting in higher RMSSD values. Elevated RMSSD values are often associated with a well-functioning autonomic nervous system. Conversely, lower RMSSD values may suggest diminished vagal tone potentially signalling various medical conditions.
- Regarding pNN50+, this index is computed by initially measuring the differences between successive NN intervals. Differences exceeding 50 milliseconds (ms) are counted and pNN50+ is calculated as their percentage relative to the total number of NN intervals. Since pNN50+ quantifies the fast heart rate decelerations due to the vagal nervous discharge, higher values indicate a more responsive parasympathetic autonomic nervous system. pNN50+ was introduced by Ewing as a means to quantify the frequency of vagal (parasympathetic) influence on the sinus node by monitoring sudden reductions in heart

rate. It is commonly used as an index to evaluate cardiac parasympathetic activity (Ewing et al., 1984).

Frequency-domain indexes are used to assess the frequency components of HRV. It provides insights into the distribution of power across different frequency bands within the HRV signal, using mathematical algorithms, allowing for a more detailed understanding of autonomic nervous system activity. The frequency index typically involves the following components:

- **Very Low-Frequency (VLF) Power:** This represents the lowest frequency range in the HRV signal, with frequencies lower than 0.04 Hz. VLF power is associated with long-term regulatory mechanisms and is influenced by factors like circadian rhythms, physical activity, thermoregulation, and hormonal fluctuations (Shaffer & Ginsberg, 2017). There is a lack of clarity concerning the physiological mechanisms that drive activity in this frequency band. The heart's inherent nervous system seems to play a role in generating the VLF rhythm, while the SNS affects both the amplitude and rate of its fluctuations. The use of atropine eliminates this activity, indicating that it involves a parasympathetic efferent pathway (Shaffer & Ginsberg, 2017).
- **Low-Frequency (LF) Power:** LF power is defined within the frequency range from 0.04 to 0.15 Hz. It is thought to represent a blend of sympathetic and parasympathetic activity and is linked to the baroreflex, which primarily influences this frequency during periods of rest (Shaffer & Ginsberg, 2017).
- **High-Frequency (HF) Power:** HF power spans the frequency range from 0.15 to 0.4 Hz. This frequency band primarily reflects parasympathetic (vagal) activity and includes the oscillations linked to the respiratory sinus arrhythmia, the heart rate variation that occurs with each breath. HF power is a valuable marker of parasympathetic control. Indeed, heart rate increases during inhalation and decreases during exhalation. When we inhale, the cardiovascular center suppresses the vagal outflow, leading to an acceleration of heart rate. In contrast, during exhalation, it reinstates vagal outflow, causing heart rate to decrease through the release of acetylcholine (Eckberg & Eckberg, 1982). Almost complete vagal blockade effectively eliminates high-frequency oscillations and reduces the power in the low-frequency range (Shaffer et al., 2014).
- **LF/HF powers ratio** represents the sympathovagal balance as the relative dominance of low-frequency (LF) over the high-frequency (HF) components of HRV. The LF/HF ratio is often used as an index of sympathovagal balance because the LF power is influenced by the cardiac sympathetic modulations while the HF power only reflects the parasympathetic activity. A higher LF/HF ratio indicates a relative predominance of sympathetic activity or

reduced parasympathetic influence. It's essential to consider that the interpretation of the LF/HF ratio is not always straightforward, and its clinical significance can vary depending on the context and specific research questions.

GBA phenotype

Numerous investigations have sought to define the characteristics of patients carrying the GBA mutation. These studies have consistently indicated that GBA-PD is distinguished by an early onset, often with a family history of PD (Alcalay et al., 2012; Brockmann et al., 2015; Malek et al., 2018a; Sidransky et al., 2009b). In its initial stages, the phenotype may closely resemble that of individuals with sporadic PD (Maple-Grødem et al., 2021; Winder-Rhodes et al., 2013). While resting tremor is also a common symptom, most research points to a higher prevalence of a rigid, akinetic phenotype and a faster disease progression (Brockmann et al., 2011; Gan-Or et al., 2010; Goker-Alpan et al., 2008; Jesús et al., 2016; Lesage et al., 2011; Malek et al., 2018b), coupled with reduced survival rates (Cilia et al., 2016; Stoker et al., 2020a). Several authors have noted that individuals with GBA mutations frequently experience motor fluctuations and dyskinesias (Clark et al., 2007; Iwaki et al., 2019; Lesage et al., 2011).

Additionally, individuals with GBA mutations exhibit a significant prevalence of NMS (Brockmann et al., 2011; Sidransky et al., 2009b).

Notably, cognitive decline is a common feature, observed in certain cohorts even during the early stages of the disease and progressing to dementia as the disease advances (Alcalay et al., 2012; Setó-Salvia et al., 2012; Winder-Rhodes et al., 2013). A greater incidence of neuropsychiatric alterations such as anxiety, depression and hallucinations has also been reported (Brockmann et al., 2011; Cilia et al., 2016; Creese et al., 2018; Jesús et al., 2016; Neumann et al., 2009). The underlying pathological basis for these features remains unclear. Although some authors have hypothesized that they are due to widespread Lewy body disease, the results of neuropathological studies have been inconsistent (Mata et al., 2016) and further investigations are warranted. To date, some neuroimaging studies have identified reduced cortical activity in occipital and posterior parietal regions, including the precuneus (Cilia et al., 2016; Goker-Alpan et al., 2012; Oeda et al., 2015a), aligning with the reported visuospatial and non verbal memory dysfunctions described by some researchers (Alcalay et al., 2012; Mata et al., 2016; Zokaei et al., 2014).

GBA-PD patients may present olfactory dysfunction and RBD, although their prevalence does not seem to be consistently higher compare to non-carriers (Alcalay et al., 2012; Gan-Or, Mirelman, et al., 2015; Lopez et al., 2022; Malek et al., 2018a; McNeill et al., 2012). A good response to dopaminergic therapy is generally reported in various case series (Goker-Alpan et al., 2008; Rossi

etal., 2022). The data regarding the greater appearance of motor fluctuations and dyskinesias are conflicting (Cilia et al., 2016; Iwaki et al., 2019; Maple-Grødem et al., 2021). Some authors also report a greater predisposition to the development of impulsive-compulsive behavior disorders (Amami et al., 2021; Petrucci et al., 2020; Simuni et al., 2020). Considering the early onset of symptoms, the response to levodopa, and the emergence of motor fluctuations, one of the therapeutic options is represented by deep brain stimulation. While it demonstrates efficacy in addressing motor symptoms, it's worth noting that some authors have documented a higher occurrence of cognitive impairment (Lythe et al., 2017; Mangone et al., 2020; Pal et al., 2022).

A substantial body of evidence has emerged indicating that individuals carrying the GBA mutation are more prone to experiencing autonomic disorders. The majority of these findings are derived from studies employing questionnaires. In a 2011 study by Brockman et al., comparing 20 GBA mutation carriers to 20 non-carriers, an increased prevalence of orthostatic symptoms, urinary dysfunction, and gastrointestinal disturbances was noted using the Unified Multiple System Atrophy Rating Scale. An elevated incidence of dysautonomia was also observed in an Italian cohort, with dysautonomic symptoms manifesting in 53.8% of GBA-PD patients compared to 43.2% of idiopathic PD (I-PD) patients (Brockmann et al., 2011). Specifically, in a single-center study using the UPDRS Part IV scale, the presence of orthostatic hypotension was reported in 18.5% of GBA-PD patients compared to 10.6% of I-PD patients (Cilia et al., 2016). Conversely, a comprehensive multicenter study, as documented by Sidranski, did not uncover any significant disparities in orthostatic blood pressure changes between GBA carriers and non-carriers (Sidransky et al., 2009c).

There have been relatively few studies that have conducted instrumental assessments. In a prospective analysis of 33 GBA-PD patients versus 313 I-PD patients, Usnich administered an active standing test and found that GBA-PD patients exhibited a higher incidence of orthostatic hypotension (37.5% vs. 12.9%). These authors did not identify any differences in systolic and diastolic values or heart rate frequency, and no significant demographic or clinical distinctions were reported (Usnich et al., 2022).

Moreover, a separate study, which included spectral and symbolic analysis of heart rate variability, involved 15 I-PD, 15 GBA-PD, and 15 healthy controls. This study revealed a higher resting heart rate in GBA-PD patients. It also indicated a diminished heart rate increase in response to active standing, suggesting a reduced or absent vagal response to orthostatic challenges in GBA-PD patients compared to I-PD patients. Nevertheless, there were no differences in resting heart rate between GBA-PD and I-PD patients, and the LF/HF power at rest was similar in both groups, with both displaying higher resting heart rates compared to the control group. The HF/LF ratio during

active standing was not reported (Carandina et al., 2022).

In a recent single-center study, both spectral analysis and a full battery of autonomic tests were conducted on 21 GBA-PD patients compared to 24 matched controls. Devigili et al. suggested an impaired sympathovagal balance in GBA-PD, as indicated by time domain indices in spectral analysis, which were lower in the GBA-PD group. They also hypothesized a greater efferent baroreflex failure in GBA-PD, as they observed an inadequate increase in the HF/LF ratio during the head-up tilt test, though not statistically significant except for the seventh minute. However, significant differences in most sympathetic and parasympathetic indices of autonomic tests were not found. Additionally, they identified a preserved late phase IIb in the GBA-PD group, suggesting that sympathetic reflex vasoconstriction during orthostasis remains relatively intact, and the reduced increase in the HF/LF ratio during tilt may be attributed to a sympathovagal demodulation. Moreover, they discovered reduced sweat production in GBA-PD patients, indicative of sympathetic-cholinergic dysfunction (Devigili et al, 2023).

Objectives of the study

Our understanding of the molecular mechanisms underlying neurodegeneration in PD remains incomplete. While monogenic forms of PD, resulting from specific gene mutations, account for less than 10% of all PD cases, recent advances in genetic technologies like genome-wide association studies (GWAS) and next-generation sequencing (NGS) have shed light on the role of highly penetrant genetic variants in influencing the age of disease onset, clinical presentation, and disease progression.

To develop clinical practice guidelines, it is crucial to establish correlations between a patient's genetic makeup and the observable traits of PD, referred to as the phenotype. Such understanding can help clinicians select appropriate clinical and laboratory tests and tailor therapy.

Notably, individuals with GBA-PD, a specific subtype linked to mutations in the GBA gene, tend to exhibit a higher prevalence of non-motor symptoms. This raises questions about whether autonomic dysfunction, a component of these symptoms, is not only more common but also distinct in GBA-PD patients. Data from patient questionnaires on autonomic function have suggested that carriers of GBA mutations may have an increased risk of OH and other autonomic disturbances, which may manifest at an earlier stage in this genetic subgroup. Recent laboratory findings have corroborated these observations.

To delve deeper into this, we conducted a case-control study aimed at evaluating cardiovascular autonomic function in GBA-PD patients in comparison to those with I-PD. Our primary goal was to determine the prevalence and severity of cardiovascular dysautonomia in GBA-PD patients relative

to the I-PD group. Our secondary objectives included assessing postganglionic cardiac ¹²³I-MIBG binding between the two groups and exploring whether cardiovascular dysautonomia primarily affects the sympathetic, parasympathetic nervous systems. Additionally, we conducted a genotype - phenotype analysis to determine if individuals with so-called severe GBA variants are at a higher risk of experiencing cardiovascular dysautonomia.

Methods

We obtained two cohorts of patients diagnosed with clinically definite Parkinson's disease (PD) from the Humanitas genetic database. Inclusion criteria included a diagnosis of clinically definite Parkinson's disease according to the 2015 diagnostic criteria provided by the Movement Disorder Society (MDS). One group exhibited variants in the GBA gene, while the other group, referred to as idiopathic PD (I-PD), had normal genetic test results and showed no evidence of genetic variants associated with PD.

Exclusion criteria

Patients with a medical history of heart disease, hypertension, neuropathy, or any conditions that could potentially impact autonomic function, such as diabetes, hematological disorders, or malignancies, were excluded from the study. Additionally, individuals with cognitive impairment, as indicated by a Mini-Mental Status Examination score below 26, were not included in the analysis.

Clinical evaluation

All patients underwent a comprehensive neurological examination. The severity of motor symptoms was assessed using the motor portion of the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS). To evaluate autonomic dysfunction, symptoms were documented for each patient using the SCOPA-AUT questionnaire. Furthermore, the levodopa equivalent dose (LED) was calculated based on a well-established conversion algorithm.

Molecular genetic analysis

Standard genomic DNA extraction methods were employed using peripheral blood samples from the patients. Subsequently, DNA analysis was conducted using a custom gene panel called Nextera Rapid Capture Custom Enrichment. This panel encompasses 23 genes associated with PD, including ATP13A2, DNAJC13, DNAJC6, EIF4G1, FBX07, GBA, GCH1, GYGYF2, GRN, HTRA2, LRRK2, MAPT, PRKN, DJ1, PINK1, PLA2G6, SNCA, VPS35, SYNJ1, UCHL1, TMEM230, and RAB39B. The design of this gene panel was executed through the Illumina Design

Studio tool, targeting the Coding sequence (CDS) and the adjacent ± 20 base pairs of intronic regions to accommodate potential splicing mutations. The prepared libraries were then subjected to analysis using the Illumina Miseq system, ensuring an effective mean depth of 50X. The resulting reads were aligned to the human genome assembly hg19, and any identified variants were annotated using the Variant-Studio by Illumina.

In the filtering process, a focus was placed on rare variants, defined as those with a minimum allele frequency of less than 1% in databases like the 1000 Genome Project, ExAc, and Exome Sequencing Project. Additionally, variants causing potential protein function disruptions, as determined by tools such as Polyphen2, SIFT, and Mutation Taster, were considered. To further investigate the conservation of altered amino acids and nucleotides, BLAST and PhyloP tools were employed, respectively. Variants were subsequently confirmed using Sanger sequencing. Furthermore, MLPA analysis was conducted in accordance with provided instructions (SALSA MLPA P051 and P052, MRC-Holland).

Cardiovascular autonomic tests

To assess cardiovascular autonomic reflex function, the evaluations were performed in the morning under controlled conditions, including a quiet environment and stable temperature. The procedures adhered to current guidelines. Prior to testing, subjects refrained from consuming caffeine-containing beverages, cigarettes, and alcohol for at least 24 hours. Participants were assessed while taking their usual antiparkinsonian medications, with the withdrawal of drugs that could modify autonomic responses, such as alpha or beta-adrenoceptor blockers, in advance of three times the drug's half-life before the autonomic assessment.

Continuous noninvasive hemodynamic assessments were carried out using the Task Force Monitor device from CNSystems Medizintechnik GmbH, Austria. Additionally, intermittent blood pressure measurements were taken at predetermined intervals using a validated automated cuff sphygmomanometer over the brachial artery. The autonomic assessment battery included the head-up tilt test, Valsalva maneuver, and deep breathing. All participants gave their informed written consent.

Assessment of the sympathetic noradrenergic system included the measurement of heart rate and blood pressure responses during head-up tilt (HUT) and the blood pressure (BP) response to the Valsalva maneuver. Key sympathetic parameters considered in this evaluation were the presence of the overshoot and the duration of pressure recovery time (PRT). For the assessment of parasympathetic function, the Valsalva Ratio and Heart Rate during deep breathing were measured.

Sympathetic function test

- *Tilt-Hup Test*

To perform the tilt up test, the patient was positioned on a motorized reclining bed, with straps securing their hips and legs to ensure stability. The test began with the patient lying flat in a supine position for five minutes. Subsequently, at the end of the fifth minute, the bed was adjusted to an almost vertical position at an angle of 65° relative to the ground, maintaining the patient in a passive upright posture for ten minutes. Following this, the patient was returned to the supine position for another five minutes.

Orthostatic hypotension (OH) was defined as a significant drop in systolic blood pressure (SBP) of at least 20 mmHg or a reduction in diastolic blood pressure (DBP) of 10 mmHg or more after 10 minutes of passive standing, considering early (within 3 minutes) and delayed (till 10 minutes) orthostatic hypotension.

The neurogenic nature of orthostatic hypotension (NOH) was confirmed by the presence of an $\Delta\text{HR}/\text{systolic: } \Delta\text{SBP (ratio)} < 0.495$ at 3rd minute.

- *Valsalva Maneuver*

Patients were positioned in a supine posture with their head inclined at 15°. They were instructed to exhale forcibly for 15 seconds against a sealed system (with an intra-oral pressure maintained at 40 mmHg) followed by a resting phase of 20 seconds. At least three Valsalva maneuvers were performed, each separated by a 2-minute rest interval, and the best-executed maneuver was chosen for data collection. To assess cardio-adrenergic innervation, we analyzed the blood pressure response during the Valsalva maneuver. The following indexes were calculated:

- reduction of mean BP in phase II early (>20 or 40 mmHg)
- return to baseline of mean BP in phase II I
- systolic pressure recovery time (PRT) (< 4 ms, or in the range between 4-5 ms, 6-9 ms, =/>10 ms)
- detection of overshoot in the phase IV, defined as the highest systolic blood pressure value within the 20 seconds following the commencement of phase IV. An increase in SBP that was less than the baseline SBP level was considered abnormal.

Parasympathetic function test

- *Valsalva Maneuver*

To assess cardio-vagal innervation, we computed the Valsalva Ratio (VR). This ratio represents the

division of the longest RR-interval following the maneuver, typically seen during the bradycardic response in phase IV, by the shortest RR-interval, which corresponds to the highest heart rate observed during the Valsalva maneuver, usually occurring in phases II late or III.

- *Deep breathing*

To establish a baseline, the mean heart rate for one minute before the test was calculated. Patients were then instructed to inhale for 5 seconds and exhale for 5 seconds, repeating this 10-second respiratory cycle six times. The E/I difference, which is the discrepancy between the mean of the longest RR intervals during each expiration and the mean of the shortest RR intervals during each inspiration, is considered abnormal if it falls below 15 bpm. This test provides insights into autonomic function and cardiac health.

In both tests, VR values and E/I differences were compared to those of healthy individuals, categorized by age and gender, as presented by Low et al., to assess their normalcy.

Evaluation of CASS score

The Composite Autonomic Severity Score (CASS) is utilized to evaluate the severity of autonomic disturbances in patients based on the outcomes of laboratory tests assessing autonomic function, which encompass cardiovascular and sudomotor function tests (Low PA 2023).

In our study, sudomotor tests were not conducted. Consequently, we computed the cardiovascular subscore (cv-CASS), as illustrated in Table 1.

Dysautonomia was considered to occur when the cardiovascular section of Composite Autonomic Severity Score (cv-CASS) was >1 . Patients with a total score ranging from 1 to 3 were classified as having mild dysautonomia, those with scores from 4 to 5 were categorized as moderate, and individuals scoring from 6 to 7 were deemed to have severe dysautonomia.

Results	Degree of abnormality	Score	
Adrenergic score			
Normal		0	
Abnormal	Mild	1	Valsalva maneuver: early phase II drop reduction > 20 and < 40 mmHg or late phase II does not return to baseline or systolic PRT 4-5 seconds
	Moderate	2	Valsalva maneuver: early phase II drop reduction > 40 mmHg and absent phase II or absent phase IV (overshoot) or systolic PRT 6-9 seconds
	Severe	3	Tilt test: Orthostatic hypotension or Valsalva maneuver: early phase II drop reduction > 40 mmHg plus absent phase II plus absent phase IV (overshoot) or absent phases II and IV and systolic PRT = 10 seconds
		4	Tilt (OH) + Valsalva maneuver score 3
Cardiovagal score			
Normal		0	
Abnormal	Mild	1	Deep breathing or Valsalva ratio reduced but $\geq 50\%$ of minimal normal value
	Moderate	2	Deep breathing or Valsalva ratio reduced to < 50% of minimal normal value
	Severe	3	Both deep breathing and Valsalva ratio reduced to < 50 % of minimal normal value

Table 1. Calculation of adrenergic and cardiovagal score.

Spectral analysis

To evaluate the sympatho-vagal balance and vagal tone in both the supine and standing positions, spectral analysis of HRV was performed. This analysis involved electrocardiographic recordings (two-lead ECG with sampling rate =1 kHz). ECG tracings were individually examined to identify and remove motion artifacts or premature beats, resulting in a series of normal-to-normal intervals

(NNI). Time domain indices were calculated, including the RMSSD and pNN50. As for frequency domain indices, the NNI beat-to-beat series were interpolated to 5 Hz. The power spectral density (PSD) was estimated using the Welch periodogram method (this method splits the period of analysis into 90% overlapped Hann windows, each of 120 s duration, calculates the power spectrum in each window by Fast Fourier Transform, and averages the spectra over all the windows).

From the PSD, powers in the very low frequency (VLF) range (0.003 - 0.04 Hz), low frequency (LF) range (0.04 - 0.15 Hz), and high frequency (HF) range (0.15 - 0.45 Hz) were calculated. The ratio between LF/HF powers and the normalized LF powers, represented as $LF_{nu} = LF/(LF+HF)$, were computed as indices of sympathetic/vagal balance.

These analyses were conducted and compared in both the supine rest (SUP) and head-up tilt (HUT) positions.

Imaging of cardiovascular dysautonomia

The evaluation of postganglionic sympathetic nerve terminals in the heart was performed using 123I-MIBG myocardial single-photon emission CT. The radiotracer was injected intravenously, and imaging of cardiac uptake was taken 15 minutes and 4 hours after injection, using a dual-head γ -camera SPECT. The heart to mediastinum ratio of 123I-MIBG uptake was calculated according to a standard methodology (Xu, D. et al.2018).

Statistical analysis

Data were presented as either the number and percentage for categorical variables or as the mean and standard deviation for continuous variables. To assess differences between groups, the chi-square test was employed, with Fisher's correction applied if necessary for categorical data. For continuous data that approximated a Gaussian distribution, the t-student test was used. When data did not meet the assumptions of normality, the Mann-Whitney test was utilized. Linear regression analysis was employed to explore the relationship of cv-CASS scores with other variables, and results were expressed as coefficients with 95% confidence intervals. All calculations were performed using Stata 15, with a significance level set at $p < 0.05$.

Regarding spectral analysis, the sample's normality was initially assessed for each index separately in both conditions (SUP, HUT) for each group (GBA-PD and I-PD) using the Shapiro-Wilks test. Analysis of variance (ANOVA) was used to assess the significance of differences between groups (GBA vs I-PD), differences between postures (SUP vs. HUT), and the interaction between these factors, which indicates whether the difference between SUP and HUT is dependent on the group considered (GBA vs I-PD). Post-hoc tests were conducted using Fisher's LSD procedure.

In cases where normality tests failed, nonparametric tests were applied to determine the significance of differences between groups within SUP and HUT separately (Mann-Whitney U Test) and differences between postures within M and NM (Wilcoxon Test).

The spectral powers and the RMSSD index were found to have skewed distributions, as they cannot have negative values and exhibit a highly asymmetric right tail. Consequently, the Shapiro-Wilks test was conducted after logarithmic transformation on RMSSD, VLF, LF, HF, LF/HF, and LFnu to assess their normality. The entire "broadband" spectrum was compared between the GBA and I-PD groups separately in the SUP and HUT postures by calculating the Student's T variable for each spectral line.

Results

A total of 34 GBA-PD and 33 I-PD patients fulfilling inclusion criteria were recruited. Among our cohort of patients, we identified four individuals with 'Mild' GBA variants, 11 with 'Risk' variants, nine with 'Severe' variants, seven with 'Unknown' variants, and two with 'Complex' variants, based on the classification (Figure 1). Thirty-two GBA-PD patients had a monoallelic mutation, whereas 2 GBA-PD patients had biallelic mutations (Table 2).

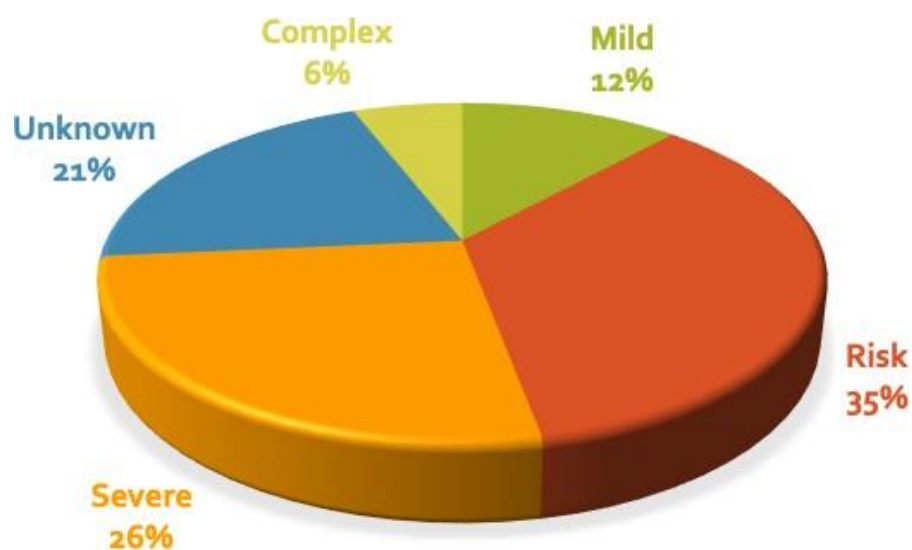


Figure 1. Classification of variants present in our cohort of GBA patients.

N° of GBA patients	GBA gene variants
7	p.Glu326Lys (c.5309G>A) (E326K)
5	p.Leu483Pro (c.1448T>C) (L444P)
3	c.1223C>T; p.Thr408Met - T369M
3	p.Asn409Ser (c.1226A>G) (N370S)
2	c.1093G>A p.Glu365Lys (Glu326Lys)
1	c.1279G>A p.Glu388Lys
1	c.1260C>C p.rp420Cys (W381C) (esone 9)
1	c.1483g>a (p.Ala495Pro)
1	c.508C>T; p.(Arg170Cys) - R131C
1	c.370A>G p.Met124Val (p.Met85Val) (esone 5)
1	c.703C>T; p.Ser235Pro (p.Ser196Pro) (esone 6)
1	c.754T>A (F213I) (esone 6)
1	c.407C>A (S97*) (esone 4)
1	c.886C>T (p.Arg296*)
1	c.715C>T (p.Gln239Ter) - Q200X
1	c.882T>G; p.His294Gln (H255Q)
1	c.762-18T>G (introne 7)
1	c.1448T>C; p.Leu483Pro (p.Leu444Pro) - c.1483G>C; p.Ala495Pro (p.Ala456Pro) - c.1497G>C; p.Val499Val (p.Val460Val)
1	c.882T>G (p.His294Gln) (esone 7) - c.1342 G>C (p.Asp448His) (esone 9)

Table 2. GBA variants in our cohort

There were no significant differences between the two groups in terms of gender, disease duration, Levodopa equivalent dose (LED), or the severity of motor symptoms. Only age at disease onset was significantly younger in the GBA-PD group compared to PD group (Table 3).

	GBA-PD (N=34)	I-PD (N=33)	p value
<i>Demographic characteristics</i>			
Male Gender	21 (61.8%)	24 (72.7%)	0.34
Age (yoa)	61.1 ±8.6	62.8 ±8.8	0.43
Age at onset (yoa)	52.8 ±12.0	58.5 ±9.3	0.016
Disease duration (years)	6.33 ±4.31	4.64 ±2.41	0.11
MDS-UPDRS Motor Score	16.7 ±7.4	15.8 ±6.6	0.63
Levodopa Equivalent Dose (mg)	569 ±464	528 ±398	0.88

Table 3: Demographic and clinical features of GBA-PD and I-PD patients. Abbreviations: MDS-UPDRS

In the Head-Up Tilt test, autonomic assessment revealed that individuals with GBA-PD had a higher resting heart rate while lying down, and this higher heart rate persisted when they transitioned to an upright position.

It is noteworthy that there were no significant differences between the two groups in terms of the occurrence of OH. Specifically, four GBA carriers experienced early OH compared to one in the I-PD group, while four GBA carriers and one I-PD patient had delayed OH.

Concerning the evaluation of sympathetic function during the Valsalva maneuver, there were no notable distinctions in the occurrence of overshoot absence or abnormal PRT between the two groups. Both groups had a similar number of patients experiencing sympathetic failure, and the extent of adrenergic dysfunction was comparable. Conversely, when examining parasympathetic indices such as the Valsalva ratio and heart rate during Deep Breathing, a trend towards greater impairment was observed in the GBA group compared to the I-PD group, although this difference did not reach statistical significance (Table 4).

<i>Autonomic assessment</i>	GBA-PD (N=34)	I-PD (N=33)	p-value
<i>Supine Rest</i>			
Heart Rate (bpm $\pm$ SD)	71.3 $\pm$ 9.9	66.7 $\pm$ 8.5	0.047
Systolic BP (mmHg, IQR)*	118.0 [8.5]	119.0 [17.5]	0.73
Diastolic BP (mmHg, IQR)*	77.5 [7]	81.0 [14]	0.17
<i>Head-up Tilting</i>			
3'-Heart Rate (bpm $\pm$ SD)	81 $\pm$ 11	73 $\pm$ 9	0.004
3'-Systolic BP (mmHg, IQR)*	117.5 [19.75]	120.0 [12.5]	0.43
3'-Diastolic BP (mmHg, IQR)*	78.5 [12]	83.5 [14]	0.07
10'-Heart Rate (bpm $\pm$ SD)	81 $\pm$ 11	74 $\pm$ 10	0.021
10'-Systolic BP (mmHg, IQR)*	114.0 [17.0]	117.0 [14.0]	0.57
10'-Diastolic BP (mmHg, IQR)*	80.0 [11.0]	84.0 [13.0]	0.09
Classic Orthostatic Hypotension (patients, %)*	4 (11.8%)	1 (3.3%)	0.36
Delayed Orthostatic Hypotension (patients, %)*	4 (12.1%)	1 (3.4%)	0.36
<i>Valsalva Maneuver</i>			
Detectable Overshoot (patients, %)	21 (61.8%)	25 (75.8%)	0.29
Pressure Recovery Time (s, $\pm$ SD)	8.0 $\pm$ 6.8	7.7 $\pm$ 7.5	0.74
Pressure Recovery Time >5s (patients, %)	17 (50.0%)	15 (45.5%)	0.71
Valsalva Ratio (ratio $\pm$ SD)	1.45 $\pm$ 0.21	1.54 $\pm$ 0.32	0.51
Abnormal Valsalva Ratio (patients, %)	13 (38.2%)	9 (27.3%)	0.34
<i>Deep Breathing</i>			
Abnormal E-I difference (patients, %)	16 (47.1%)	10 (30.3%)	0.16

Table 4. Results of laboratory autonomic assessment in the two study populations. Values are reported as mean $\pm$ standard deviation (SD), or number of individuals (%). Significant values

($p < 0.05$) are shown in bold. Abbreviations: BP = blood pressure; IQR, Interquartile range. *Brachial cuff BP measures available in 34 GBA-PD and 30 I-PD patients at 3', and in 33 GBA-PD and 29 I-PD patients at 10'.

Examination of the instrumented measurements using cv-CASS uncovered a notably abnormal parasympathetic sub-score within the GBA-PD group ($p = 0.041$). Correspondingly, the GBA-PD group had a greater number of patients displaying parasympathetic abnormalities in the cv-CASS score (23 individuals compared to 13 in the non-GBA-PD group), and this difference was statistically significant ($p = 0.020$). While the total cv-CASS score showed a somewhat higher result in the GBA-PD group, this variation did not reach statistical significance. Interestingly, the sympathetic sub-score did not exhibit discrepancies between the two groups, and the number of patients with abnormal results in tests of sympathetic function was also similar (Table 4). Furthermore, in the subjective assessment of dysautonomic symptoms using the SCOPA-AUT questionnaire, GBA-PD patients exhibited higher total scores, along with elevated scores in both the cardiovascular and extra-cardiovascular sub-categories, in comparison to the I-PD group (Table 5).

	GBA-PD (N=34)	I-PD (N=33)	p-value
SCOPA-AUT scale			
Total score ($\pm$ SD)	16.5 $\pm$ 10.1	6.8 $\pm$ 5.8	<0.001
Cardiovascular Sub-score ($\pm$ SD)	1.91 $\pm$ 1.66	0.58 $\pm$ 0.94	<0.001
cv-CASS score			
Total score ($\pm$ SD)	1.83 $\pm$ 1.40	1.39 $\pm$ 0.70	0.085
Sympathetic score ($\pm$ SD)	1.03 $\pm$ 1.03	0.90 $\pm$ 1.02	0.47
Parasympathetic score ($\pm$ SD)	0.90 $\pm$ 0.70	0.52 $\pm$ 0.71	0.041
Abnormal total score (patients, %)	28 (82.4%)	20 (60.6%)	0.06
Abnormal sympathetic score (patients, %)	22 (64.7%)	17 (51.5%)	0.27
Abnormal parasympathetic score (patients, %)	23 (67.6%)	13 (39.4%)	0.020

Table 5. Clinical autonomic scores in the two study populations. Values are reported as mean $\pm$ standard deviation, or number of individuals (%). Significant values ($p < 0.05$) are shown in bold.

Spectral Analysis

NNI

The NNI values showed that the GBA-PD group is significantly more tachycardic than the I-PD group in both SUP and HUT. (Figure 2).

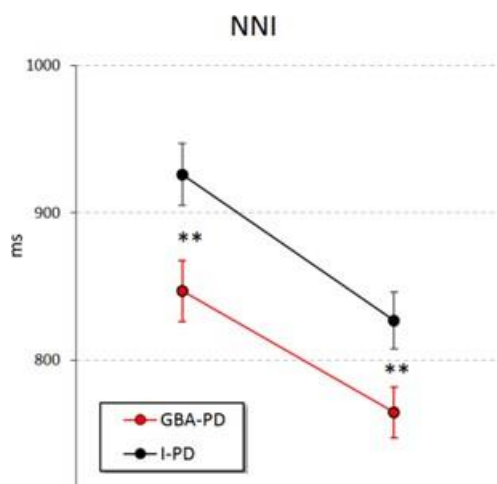


Figure 2: Cardiac interval in the GBA-PD and I-PD groups during SUP and HUT. Post-hoc analysis with Fisher LSD: ** indicate differences significant between postures with $< 1\%$. Values are reported as mean $\pm$ sem.

Time domain analysis

RMSSD

Concerning time-domain analysis, RMSSD index, after logarithmic transformation, showed a Gaussian distribution, as shown in table 6:

	GBA-PD group		I-PD group	
	SUP	HUT	SUP	HUT
RMSSD	0.67	0.094	0.34	0.92

Table 6: Significance of the normality test for RMSSD using Shapiro-Wilks test and of their interaction.

The RMSSD index decreases from SUP to HUT position in both groups. The GBA-PD group consistently demonstrates lower values in both postures. The interaction between factors shows borderline significance ($p=0.06$), and it appears that the trends for the two groups diverge from SUP to HUT, with the difference between the groups becoming more pronounced in the HUT position (Tab.7 and Fig. 3).

Factors and their interaction	Significance (p)
Case (GBA-PS vs I-PD)	0.002
Postures (SUP vs HUT)	<0.001
Case x Posture	0,06

Table 7: Significance of factors (case and postures) and their interaction. Significant values ($p<0.05$) are shown in bold.

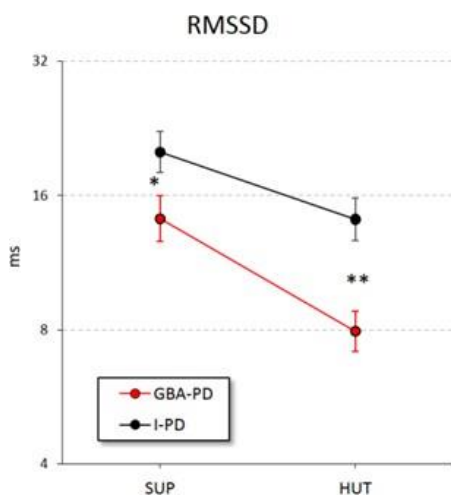


Figure 3: Root mean square of successive differences (RMSSD). Values are reported as geometric mean $\pm$ geometric sem, separately in the GBA-PD and I-PD groups in supine (SUP) and head-up tilt (HUT) postures. The * and ** indicate statistically significant differences between groups at 5% and 1% significance levels after one-way repeated measures ANOVA with Fisher LSD post-hoc comparison.

pNN50+

In the case of pNN50+, the index did not meet the criteria for normal distribution, as indicated by the p-value $< 10^{-5}$ for each condition and group. Consequently, the statistical results are presented in the form of medians [1st-3rd quartile]. The significance of the comparison between groups was calculated using the Mann-Whitney test, while the comparison between conditions was assessed using the Wilcoxon test. The difference between groups was significant in both conditions, with pNN50+ being higher in the I-PD patients' group. In both groups, the index was lower in the HUT position compared to the SUP position (Table 8).

	GBA-PD group	I-PD group	p value MW
SUP	0% [0% - 1.05%]	1.05% [0% - 3.85%]	0.027
HUT	0% [0% - 0.10%]	0.20% [0% - 0.875%]	0.016
p value Wc	0.0096	0.0078	

Table 8: Statistical analysis for pNN50+. Significant values ($p < 0.05$) are shown in bold.

Frequency-domain analysis:

After applying a logarithmic transformation, all spectral powers and the LF/HF power ratio pass the normality test. However, LFnu does not pass the test even after the log transformation, as shown in table 9.

p Shapiro Wilk	GBA-PD group		I-PD group	
	SUP	HUT	SUP	HUT
log VLF	0.35	0.72	0.72	0.08
log LF	0.75	0.30	>0.99	0.77
log HF	0.83	0.12	0.55	0.67
log LF/HF	0.43	0.93	0.39	0.57
LFnu	0.02	0.04	0.08	0.11
Log LFnu	<0.01	<0.01	<0.01	<0.01

Table 9: Significance of the Normality test for spectral indices using Shapiro-Wilk test. Significant values ($p < 0.05$) are shown in bold.

The ANOVA showed the presence of significance for the HF powers and the LF/HF ratio (Table 10). HF powers were lower in the HUT than SUP position. They were also lower in the GBA-PD group than in the I-PD group in both SUP and HUT, with a more significant difference in the HUT posture. The ratio between LF/HF powers increased from SUP to HUT in the GBA group, while it remained relatively stable in the I-PD group. This difference is significantly greater in the GBA group, but only in HUT. The trend of the spectral indices with significant "CASE" factor (HF powers and the LF/HF ratio) is shown in figure 4.

	VLF	LF	HF	LF/HF
Case (GBA-PD x I-PD)	0.13	0.12	0.001	0.010
Posture (SUP x HUT)	0.007	<0.001	<0.001	0.021
Posture×Case	0.35	0.21	0.039	0.18

Table 10: The statistical significance of the factors in the ANOVA test for spectral powers.

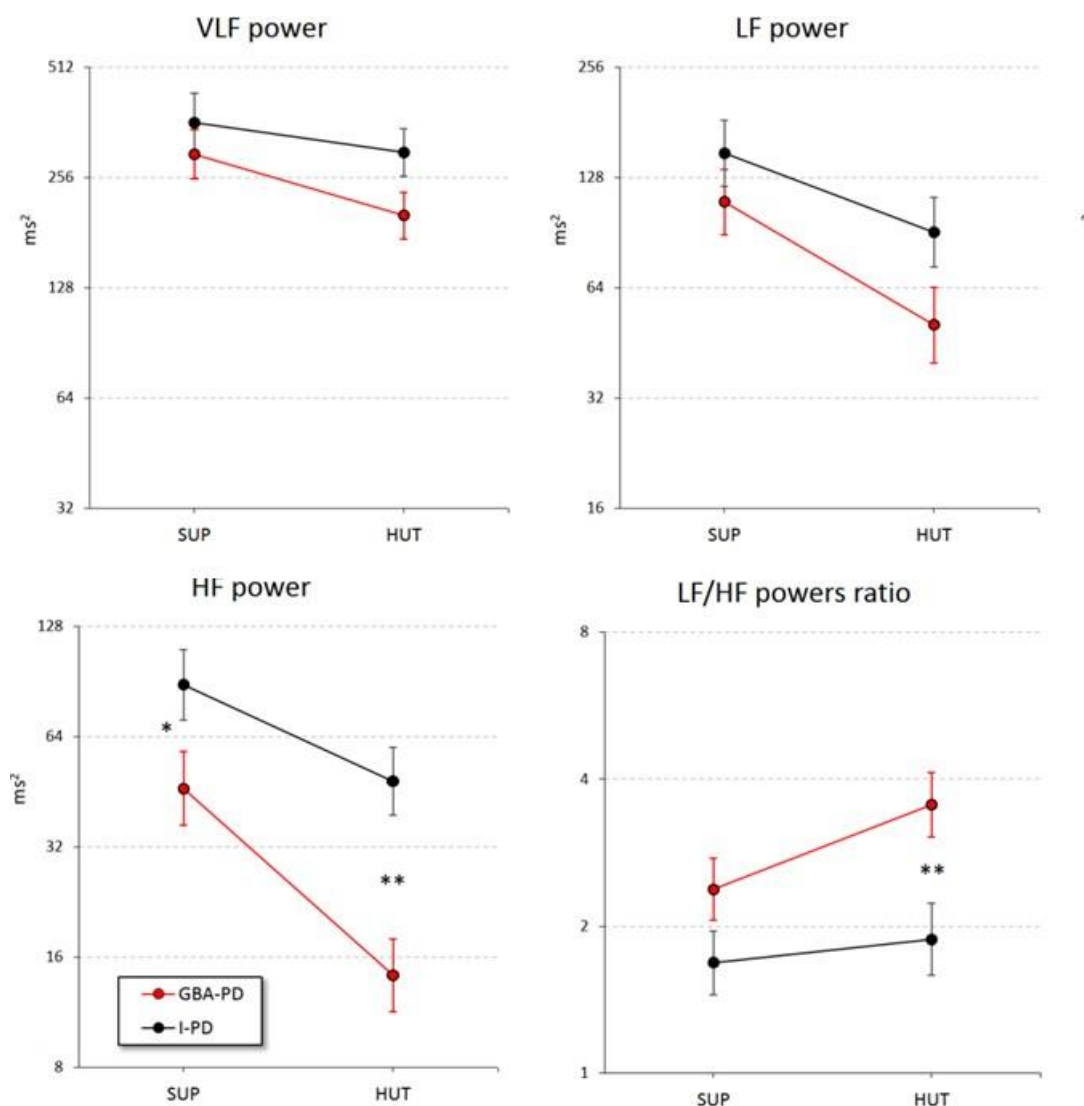


Figure 4: Upper panels, from left to right: spectral powers in the very-low frequency (VLF), low-frequency (LF). Lower panel: high-frequency (HF) bands, ratio between low and high frequency powers (LF/HF). Values are reported as geometric mean $\pm$ geometric sem, separately in the GBA-PD and I-PD groups in supine (SUP) and head-up tilt (HUT) postures. The * and ** indicate statistically significant differences between groups at 5% and 1% significance levels after one-way repeated measures ANOVA with Fisher LSD post-hoc comparison.

The LFnu statistic, was presented as a median [1st-3rd quartile]. The results were consistent with what was observed for LF/HF. In particular, this scale demonstrated a significant increase in sympatho/vagal balance from SUP to HUT, but only in the GBA group. It was greater in the GBA

group compared to the I-PD group, but this difference was significant only during the HUT condition (Table 11).

	GBA-PD group	I-PD group	p value MW
SUP	0.72 [0.61 - 0.82]	0.64 [0.51 - 0.77]	0.12
HUT	0.77 [0.65 - 0.87]	0.68 [0.52 - 0.76]	0.008
p value Wc	0.047	0.022	

Table 11: Statistical analysis for LFnu. Significant values ($p < 0.05$) are shown in bold.

^{123}I -MIBG myocardial scintigraphy was carried out on a subgroup of patients, specifically in 9 out of 34 GBA-PD and 28 out of 33 I-PD patients, being positive in 77.78% of the GBA-PD patients and 67.86% of the I-PD patients. It's worth noting that this discrepancy did not reach statistical significance ($p = 0.695$).

Finally, we performed a thorough statistical examination to identify any potential associations between classification of GBA variants of our cohort (Mild, Risk, Severe, Unknown, and Complex) and various parameters. There were no significant differences observed among the classes of GBA variants concerning the CASS total score, its subscores, or any of the individual laboratory measures we investigated.

Discussion

We present evidence of autonomic dysfunction in both the GBA-PD and I-PD groups, with a particular emphasis on parasympathetic impairment within the GBA-PD population. This evidence is supported by a range of instrumental assessments as well as the SCOPA-AUT questionnaire. These findings expand upon earlier clinical observations, which had already indicated a higher prevalence of autonomic dysfunction in GBA-PD patients (Blandini et al., 2019; Carandina et al., 2022; Cilia et al., 2016; Devigili et al., 2023; Petrucci et al., 2020; Usnich et al., 2022). Previously, studies assessing dysautonomia in GBA-PD predominantly relied on clinical scales and focused on symptoms related to orthostatic hypotension. While there may have been variations in terminology and methodology across these studies, they consistently suggested that parasympathetic dysfunction is a prominent feature in the GBA-PD group. Furthermore, several studies reported a higher incidence of orthostatic hypotension in GBA-PD patients compared to those with I-PD. However, it is important to note that data from questionnaires may not fully capture the presence of dysautonomia, as up to 50% of patients may not report symptoms (Chaudhuri et al., 2007). Moreover, there is a possibility of underestimating the

occurrence of cardiovascular dysautonomia due to the fact that approximately 75% of individuals with orthostatic hypotension may exhibit no symptoms (H. Lee et al., 2017).

Previous research also indicated evidence of sympatho-vagal imbalance in GBA-PD compared to i-PD. For instance, one study demonstrated reduced vagal tone in GBA-PD patients (Carandina et al., 2022), while another found a more impaired baroreflex function in GBA-PD (Devigili et al., 2023). These observations align with our study's consistent evidence of parasympathetic dysfunction in GBA-PD. We found that GBA-PD patients exhibited a reduced vagal tone, as evidenced by higher supine and orthostatic heart rates and lower scores in parasympathetic domains of autonomic tests.

Additionally, our analysis of HRV revealed significant reductions in HRV, indices associated with vagal modulation, in the GBA group, in both time and frequency domains. These findings support the hypothesis of impaired cardiac vagal control in GBA-PD, with more pronounced alterations during the HUT position.

The higher LF/HF ratio in the GBA group compared to I-PD during the transition from supine to HUT suggests that GBA patients may experience a distinctive response, potentially related to sympathetic dominance. Further research is needed to explore these aspects of sympathetic autonomic control and sympatho/vagal balance, especially through the analysis of blood pressure tracings.

While limited research has delved into the examination of the parasympathetic system in individuals with PD (Nakamura et al., 2007), it remains uncertain whether this impairment is interconnected with simultaneous sympathetic dysfunction (Suzuki et al., 2017). Spectral analysis studies suggest that parasympathetic dysfunction tends to escalate with advancing age (Heimrich et al., 2021b).

Our study found no significant differences between the groups in the prevalence of orthostatic hypotension (OH) diagnoses. It's noteworthy that the overall prevalence of OH in both groups was lower than previously reported (Velseboer et al., 2011). This lower prevalence may be due to the strict criteria for neurogenic OH, which required an abnormal blood pressure response to the Valsalva maneuver and blunted heart rate response to tilt. From a physiological perspective, orthostatic hypotension in PD has been attributed to postganglionic sympathetic dysfunction, particularly reduced noradrenergic response leading to impaired peripheral vasoconstriction (Goldstein & Orimo, 2009). Our findings indicate a considerable degree of peripheral origin in GBA-PD-related dysautonomia, similar to I-PD. Although sympathetic dysfunction was present, it did not reach symptomatic levels in our study. The absence of significant differences in pericardiac MIBG uptake, which was consistently reduced in both groups, further confirms the similarity in

sympathetic impairment between GBA-PD and I- PD patients. This data aligns with previous studies that did not find differences in pericardiac sympathetic innervation between the two groups (Oeda et al., 2015b).

However, the higher scores on the SCOPA-AUT questionnaire in the GBA-PD group are in line with parasympathetic dysautonomia. The prominence of parasympathetic dysfunction in GBA-PD supports the intriguing hypothesis that GBA-related parkinsonism may represent a "body-first subtype" of Parkinson's disease. According to this hypothesis, the pathology originates in the peripheral nervous system, subsequently spreading along the vagus nerve to the brainstem and, ultimately, to the striatum. This subtype is hypothesized to involve a greater accumulation of α -synuclein in the peripheral nervous system and extra-nigral regions, which may contribute to the higher prevalence of non-motor symptoms observed in GBA mutation carriers (Kim et al, 2023; Krohn et al., 2020).

The correlation between genotype and phenotype in GBA-related Parkinson's disease is a subject of conflicting evidence. Some studies have reported that individuals carrying severe mutations exhibit more pronounced autonomic dysfunction than those without GBA mutations. However, no discernible differences have been observed in autonomic dysfunction between individuals with mild GBA mutations and those with I-PD (Cilia et al., 2016). Our examination did not reveal any correlation between the severity of GBA mutations and cardiovascular autonomic dysfunction. It's important to note that this classification is based on the GD phenotype. Notably, the p.E326K mutation, even though it does not lead to GD in a homozygous form, has been associated with a mild reduced Gcase activity and is linked to a more rapid progression of cognitive dysfunction, postural instability, and gait disturbances in PD patients (Davis et al., 2016). Nonetheless, these mechanisms require further elucidation (Montfort et al., 2004; Stoker et al., 2020b).

While our study represents a significant advancement in sample size compared to previous research efforts, it is important to note that the sample size remains relatively small due to its basis on a genetic cohort. This limitation is inherent to the nature of our study population and the available data. Some other limits of our study are the absence of a healthy control group and the use of a cross-sectional analysis. To establish the early and predominant vagal dysfunction in patients with GBA variants, it is imperative to conduct longitudinal studies. In conclusion, our study provides substantial evidence of parasympathetic dysfunction in GBA-PD patients.

Conducting multicenter studies is essential to undertake prospective research with a sufficiently large and diverse sample.

References:

- Aarsland, D., Ballard, C. G., & Halliday, G. (2004). Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? *Journal of Geriatric Psychiatry and Neurology*, 17(3), 137–145. <https://doi.org/10.1177/0891988704267470>
- Aarsland, D., Batzu, L., Halliday, G. M., Geurtsen, G. J., Ballard, C., Ray Chaudhuri, K., & Weintraub, D. (2021). Parkinson disease-associated cognitive impairment. *Nature Reviews Disease Primers*, 7(1), 47. <https://doi.org/10.1038/s41572-021-00280-3>
- Aarsland, D., Zaccai, J., & Brayne, C. (2005). A systematic review of prevalence studies of dementia in Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, 20(10), 1255–1263. <https://doi.org/10.1002/mds.20527>
- Abbott, R. D., Petrovitch, H., White, L. R., Masaki, K. H., Tanner, C. M., Curb, J. D., Grandinetti, A., Blanchette, P. L., Popper, J. S., & Ross, G. W. (2001a). Frequency of bowel movements and the future risk of Parkinson's disease. *Neurology*, 57(3), 456–462. <https://doi.org/10.1212/wnl.57.3.456>
- Abbott, R. D., Petrovitch, H., White, L. R., Masaki, K. H., Tanner, C. M., Curb, J. D., Grandinetti, A., Blanchette, P. L., Popper, J. S., & Ross, G. W. (2001b). Frequency of bowel movements and the future risk of Parkinson's disease. *Neurology*, 57(3), 456–462. <https://doi.org/10.1212/wnl.57.3.456>
- Abou-Sleiman, P. M., Muqit, M. M. K., & Wood, N. W. (2006). Expanding insights of mitochondrial dysfunction in Parkinson's disease. *Nature Reviews Neuroscience*, 7(3), 207–219. <https://doi.org/10.1038/nrn1868>
- Abusrair, A. H., Elsekaily, W., & Bohlega, S. (2022). Tremor in Parkinson's Disease: From Pathophysiology to Advanced Therapies. *Tremor and Other Hyperkinetic Movements (New York, N.Y.)*, 12, 29. <https://doi.org/10.5334/tohm.712>
- Adler, C. H., & Beach, T. G. (2016). Neuropathological basis of nonmotor manifestations of Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, 31(8), 1114–1119. <https://doi.org/10.1002/mds.26605>
- Alcalay, R. N., Caccappolo, E., Mejia-Santana, H., Tang, M.-X., Rosado, L., Orbe Reilly, M., Ruiz, D., Ross, B., Verbitsky, M., Kisselev, S., Louis, E., Comella, C., Colcher, A., Jennings, D., Nance, M., Bressman, S., Scott, W. K., Tanner, C., Mickel, S., ... Marder, K. (2012). Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. *Neurology*, 78(18), 1434–1440. <https://doi.org/10.1212/WNL.0b013e318253d54b>
- Alcalay, R. N., Levy, O. A., Waters, C. C., Fahn, S., Ford, B., Kuo, S.-H., Mazzoni, P., Pauciulo, M. W., Nichols, W. C., Gan-Or, Z., Rouleau, G. A., Chung, W. K., Wolf, P., Oliva, P., Keutzer, J., Marder, K., & Zhang, X. (2015). Glucocerebrosidase activity in Parkinson's disease with and without GBA mutations. *Brain : A Journal of Neurology*, 138(Pt 9), 2648–2658. <https://doi.org/10.1093/brain/awv179>
- Amami, P., De Santis, T., Invernizzi, F., Garavaglia, B., & Albanese, A. (2021). Impulse control behavior in GBA-mutated parkinsonian patients. *Journal of the Neurological Sciences*, 421, 117291. <https://doi.org/10.1016/j.jns.2020.117291>

- Anheim, M., Elbaz, A., Lesage, S., Durr, A., Condroyer, C., Viallet, F., Pollak, P., Bonaiti, B., Bonaiti-Pellie, C., & Brice, A. (2012). Penetrance of Parkinson disease in glucocerebrosidase gene mutation carriers. *Neurology*, 78(6), 417–420. <https://doi.org/10.1212/WNL.0b013e318245f476>
- Asahina, M., Vichayanrat, E., Low, D. A., Iodice, V., & Mathias, C. J. (2013). Autonomic dysfunction in parkinsonian disorders: assessment and pathophysiology. *Journal of Neurology, Neurosurgery & Psychiatry*, 84(6), 674–680. <https://doi.org/10.1136/jnnp-2012-303135>
- Ascherio, A., Chen, H., Weisskopf, M. G., O'Reilly, E., McCullough, M. L., Calle, E. E., Schwarzschild, M. A., & Thun, M. J. (2006). Pesticide exposure and risk for Parkinson's disease. *Annals of Neurology*, 60(2), 197–203. <https://doi.org/10.1002/ana.20904>
- Avenali, M., Blandini, F., & Cerri, S. (2020). Glucocerebrosidase Defects as a Major Risk Factor for Parkinson's Disease. *Frontiers in Aging Neuroscience*, 12, 97. <https://doi.org/10.3389/fnagi.2020.00097>
- Bandres-Ciga, S., Diez-Fairen, M., Kim, J. J., & Singleton, A. B. (2020). Genetics of Parkinson's disease: An introspection of its journey towards precision medicine. *Neurobiology of Disease*, 137, 104782. <https://doi.org/10.1016/j.nbd.2020.104782>
- Batzu, L., Titova, N., Bhattacharyya, K. B., & Chaudhuri, K. R. (2022). The pathophysiology of sexual dysfunction in Parkinson's disease: An overview. *International Review of Neurobiology*, 162, 21–34. <https://doi.org/10.1016/bs.irn.2022.01.001>
- Beach, T. G., Adler, C. H., Sue, L. I., Vedders, L., Lue, L., White Iii, C. L., Akiyama, H., Caviness, J. N., Shill, H. A., Sabbagh, M. N., Walker, D. G., & Arizona Parkinson's Disease Consortium. (2010). Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. *Acta Neuropathologica*, 119(6), 689–702. <https://doi.org/10.1007/s00401-010-0664-3>
- Belvisi, D., Pellicciari, R., Fabbrini, G., Tinazzi, M., Berardelli, A., & Defazio, G. (2020). Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: What do prospective studies suggest? *Neurobiology of Disease*, 134, 104671. <https://doi.org/10.1016/j.nbd.2019.104671>
- Bendor, J. T., Logan, T. P., & Edwards, R. H. (2013). The Function of α -Synuclein. *Neuron*, 79(6), 1044–1066. <https://doi.org/10.1016/j.neuron.2013.09.004>
- Berardelli, A., Rothwell, J. C., Thompson, P. D., & Hallett, M. (2001). Pathophysiology of bradykinesia in Parkinson's disease. *Brain : A Journal of Neurology*, 124(Pt 11), 2131–2146. <https://doi.org/10.1093/brain/124.11.2131>
- Berganzo, K., Díez-Arrola, B., Tijero, B., Somme, J., Lezcano, E., Llorens, V., Ugarriza, I., Ciordia, R., Gómez-Esteban, J. C., & Zarranz, J. J. (2013). Nocturnal hypertension and dysautonomia in patients with Parkinson's disease: are they related? *Journal of Neurology*, 260(7), 1752–1756. <https://doi.org/10.1007/s00415-013-6859-5>
- Bhatia, K. P., & Stamelou, M. (2017). *Nonmotor Features in Atypical Parkinsonism* (pp. 1285–1301). <https://doi.org/10.1016/bs.irn.2017.06.001>
- Blackett, H., Walker, R., & Wood, B. (2009a). Urinary dysfunction in Parkinson's disease: a review. *Parkinsonism & Related Disorders*, 15(2), 81–87. <https://doi.org/10.1016/j.parkreldis.2007.10.016>
- Blackett, H., Walker, R., & Wood, B. (2009b). Urinary dysfunction in Parkinson's disease: a review. *Parkinsonism & Related Disorders*, 15(2), 81–87. <https://doi.org/10.1016/j.parkreldis.2007.10.016>

- Blandini, F., Cilia, R., Cerri, S., Pezzoli, G., Schapira, A. H. V, Mullin, S., & Lanciego, J. L. (2019). Glucocerebrosidase mutations and synucleinopathies: Toward a model of precision medicine. *Movement Disorders : Official Journal of the Movement Disorder Society*, 34(1), 9–21. <https://doi.org/10.1002/mds.27583>
- Blauwendraat, C., Reed, X., Krohn, L., Heilbron, K., Bandres-Ciga, S., Tan, M., Gibbs, J. R., Hernandez, D. G., Kumaran, R., Langston, R., Bonet-Ponce, L., Alcalay, R. N., Hassin-Baer, S., Greenbaum, L., Iwaki, H., Leonard, H. L., Grenn, F. P., Ruskey, J. A., Sabir, M., ... Singleton, A. B. (2020). Genetic modifiers of risk and age at onset in GBA associated Parkinson's disease and Lewy body dementia. *Brain*, 143(1), 234–248. <https://doi.org/10.1093/brain/awz350>
- Bohnen, N. I., Kaufer, D. I., Ivanco, L. S., Lopresti, B., Koeppe, R. A., Davis, J. G., Mathis, C. A., Moore, R. Y., & DeKosky, S. T. (2003). Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. *Archives of Neurology*, 60(12), 1745–1748. <https://doi.org/10.1001/archneur.60.12.1745>
- Bohnen, N. I., Studenski, S. A., Constantine, G. M., & Moore, R. Y. (2008). Diagnostic performance of clinical motor and non-motor tests of Parkinson disease: a matched case-control study. *European Journal of Neurology*, 15(7), 685–691. <https://doi.org/10.1111/j.1468-1331.2008.02148.x>
- Bologna, M., Espay, A. J., Fasano, A., Paparella, G., Hallett, M., & Berardelli, A. (2023). Redefining Bradykinesia. *Movement Disorders*, 38(4), 551–557. <https://doi.org/10.1002/mds.29362>
- Bologna, M., Guerra, A., Paparella, G., Giordo, L., Alunni Fegatelli, D., Vestri, A. R., Rothwell, J. C., & Berardelli, A. (2018). Neurophysiological correlates of bradykinesia in Parkinson's disease. *Brain*, 141(8), 2432–2444. <https://doi.org/10.1093/brain/awy155>
- Borghammer, P., Horsager, J., Andersen, K., Van Den Berge, N., Raunio, A., Murayama, S., Parkkinen, L., & Myllykangas, L. (2021). Neuropathological evidence of body-first vs. brain-first Lewy body disease. *Neurobiology of Disease*, 161, 105557. <https://doi.org/10.1016/j.nbd.2021.105557>
- Bové, J., Prou, D., Perier, C., & Przedborski, S. (2005). Toxin-induced models of Parkinson's disease. *NeuroRx : The Journal of the American Society for Experimental NeuroTherapeutics*, 2(3), 484–494. <https://doi.org/10.1602/neurorx.2.3.484>
- Braak, H., Del Tredici, K., Rüb, U., de Vos, R. A. I., Jansen Steur, E. N. H., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*, 24(2), 197–211. [https://doi.org/10.1016/s0197-4580\(02\)00065-9](https://doi.org/10.1016/s0197-4580(02)00065-9)
- Braak, H., Rüb, U., Gai, W. P., & Del Tredici, K. (2003). Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *Journal of Neural Transmission (Vienna, Austria : 1996)*, 110(5), 517–536. <https://doi.org/10.1007/s00702-002-0808-2>
- Brauer, R., Wei, L., Ma, T., Athauda, D., Girges, C., Vijiaratnam, N., Auld, G., Whittlesea, C., Wong, I., & Foltynie, T. (2020). Diabetes medications and risk of Parkinson's disease: a cohort study of patients with diabetes. *Brain*, 143(10), 3067–3076. <https://doi.org/10.1093/brain/awaa262>
- Brice, A. (n.d.). How much does dardarin contribute to Parkinson's disease? *Lancet (London, England)*, 365(9457), 363–364. [https://doi.org/10.1016/S0140-6736\(05\)17841-6](https://doi.org/10.1016/S0140-6736(05)17841-6)
- Brockmann, K., Srulijes, K., Hauser, A. K., Schulte, C., Csoti, I., Gasser, T., & Berg, D. (2011). GBA-associated PD presents with nonmotor characteristics. *Neurology*, 77(3), 276–280. <https://doi.org/10.1212/WNL.0b013e318225ab77>

- Brockmann, K., Srulijes, K., Pflederer, S., Hauser, A., Schulte, C., Maetzler, W., Gasser, T., & Berg, D. (2015). GBA -associated Parkinson's disease: Reduced survival and more rapid progression in a prospective longitudinal study. *Movement Disorders*, 30(3), 407–411. <https://doi.org/10.1002/mds.26071>
- Bronner, G., Royter, V., Korczyn, A. D., & Giladi, N. (2004). Sexual dysfunction in Parkinson's disease. *Journal of Sex & Marital Therapy*, 30(2), 95–105. <https://doi.org/10.1080/00926230490258893>
- Brundin, P., Ma, J., & Kordower, J. H. (2016). How strong is the evidence that Parkinson's disease is a prion disorder? *Current Opinion in Neurology*, 29(4), 459–466. <https://doi.org/10.1097/WCO.0000000000000349>
- Burke, R. E., Dauer, W. T., & Vonsattel, J. P. G. (2008). A critical evaluation of the Braak staging scheme for Parkinson's disease. *Annals of Neurology*, 64(5), 485–491. <https://doi.org/10.1002/ana.21541>
- Burré, J., Sharma, M., Tsetsenis, T., Buchman, V., Etherton, M. R., & Südhof, T. C. (2010). Alpha-synuclein promotes SNARE-complex assembly in vivo and in vitro. *Science (New York, N.Y.)*, 329(5999), 1663–1667. <https://doi.org/10.1126/science.1195227>
- Carandina, A., Lazzeri, G., Rodrigues, G. D., Franco, G., Monfrini, E., Arienti, F., Frattini, E., Trezzi, I., da Silva Soares, P. P., Bellocchi, C., Furlan, L., Montano, N., Di Fonzo, A., & Tobaldini, E. (2022). Dysautonomia in Parkinson's Disease: Impact of Glucocerebrosidase Gene Mutations on Cardiovascular Autonomic Control. *Frontiers in Neuroscience*, 16, 842498. <https://doi.org/10.3389/fnins.2022.842498>
- Chang, H., Wang, B., Shi, Y., & Zhu, R. (2022). Dose-response meta-analysis on urate, gout, and the risk for Parkinson's disease. *Npj Parkinson's Disease*, 8(1), 160. <https://doi.org/10.1038/s41531-022-00433-5>
- Chaudhuri, K. R., Martinez-Martin, P., Brown, R. G., Sethi, K., Stocchi, F., Odin, P., Ondo, W., Abe, K., Macphee, G., Macmahon, D., Barone, P., Rabey, M., Forbes, A., Breen, K., Tluk, S., Naidu, Y., Olanow, W., Williams, A. J., Thomas, S., ... Schapira, A. H. V. (2007). The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. *Movement Disorders : Official Journal of the Movement Disorder Society*, 22(13), 1901–1911. <https://doi.org/10.1002/mds.21596>
- Chen, Z., Li, G., & Liu, J. (2020). Autonomic dysfunction in Parkinson's disease: Implications for pathophysiology, diagnosis, and treatment. *Neurobiology of Disease*, 134, 104700. <https://doi.org/10.1016/j.nbd.2019.104700>
- Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jones, D. W., Materson, B. J., Oparil, S., Wright, J. T., & Roccella, E. J. (2003). Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*, 42(6), 1206–1252. <https://doi.org/10.1161/01.HYP.0000107251.49515.c2>
- Chohan, H., Senkevich, K., Patel, R. K., Bestwick, J. P., Jacobs, B. M., Bandres Ciga, S., Gan-Or, Z., & Noyce, A. J. (2021). Type 2 Diabetes as a Determinant of Parkinson's Disease Risk and Progression. *Movement Disorders : Official Journal of the Movement Disorder Society*, 36(6), 1420–1429. <https://doi.org/10.1002/mds.28551>
- Cilia, R., Tunesi, S., Marotta, G., Cereda, E., Siri, C., Tesi, S., Zecchinelli, A. L., Canesi, M., Mariani, C. B., Meucci, N., Sacilotto, G., Zini, M., Barichella, M., Magnani, C., Duga, S., Asselta, R., Soldà, G., Seresini, A., Seia, M., ... Goldwurm, S. (2016). Survival and dementia in GBA-associated Parkinson's disease: The mutation matters. *Annals of Neurology*, 80(5), 662–673. <https://doi.org/10.1002/ana.24777>

- Claassen, D. O., Josephs, K. A., Ahlskog, J. E., Silber, M. H., Tippmann-Peikert, M., & Boeve, B. F. (2010). REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. *Neurology*, 75(6), 494–499. <https://doi.org/10.1212/WNL.0b013e3181ec7fac>
- Clark, L. N., Ross, B. M., Wang, Y., Mejia-Santana, H., Harris, J., Louis, E. D., Cote, L. J., Andrews, H., Fahn, S., Waters, C., Ford, B., Frucht, S., Ottman, R., & Marder, K. (2007). Mutations in the glucocerebrosidase gene are associated with early-onset Parkinson disease. *Neurology*, 69(12), 1270–1277. <https://doi.org/10.1212/01.wnl.0000276989.17578.02>
- Cole-Hunter, T., Zhang, J., So, R., Samoli, E., Liu, S., Chen, J., Strak, M., Wolf, K., Weinmayr, G., Rodopolou, S., Remfry, E., de Hoogh, K., Bellander, T., Brandt, J., Concini, H., Zitt, E., Fecht, D., Forastiere, F., Gulliver, J., ... Andersen, Z. J. (2023). Long-term air pollution exposure and Parkinson's disease mortality in a large pooled European cohort: An ELAPSE study. *Environment International*, 171, 107667. <https://doi.org/10.1016/j.envint.2022.107667>
- Coleman, C., & Martin, I. (2022). Unraveling Parkinson's Disease Neurodegeneration: Does Aging Hold the Clues? *Journal of Parkinson's Disease*, 12(8), 2321–2338. <https://doi.org/10.3233/JPD-223363>
- Comella, C. L. (2007). Sleep disorders in Parkinson's disease: An overview. *Movement Disorders*, 22(S17), S367–S373. <https://doi.org/10.1002/mds.21682>
- Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. (1996). *Neurology*, 46(5), 1470. <https://doi.org/10.1212/wnl.46.5.1470>
- Coon, E. A., Cutsforth-Gregory, J. K., & Benarroch, E. E. (2018). Neuropathology of autonomic dysfunction in synucleinopathies. *Movement Disorders : Official Journal of the Movement Disorder Society*, 33(3), 349–358. <https://doi.org/10.1002/mds.27186>
- Coon, E. A., & Low, P. A. (2018). Thermoregulation in Parkinson disease. *Handbook of Clinical Neurology*, 157, 715–725. <https://doi.org/10.1016/B978-0-444-64074-1.00043-4>
- Creese, B., Bell, E., Johar, I., Francis, P., Ballard, C., & Aarsland, D. (2018). Glucocerebrosidase mutations and neuropsychiatric phenotypes in Parkinson's disease and Lewy body dementias: Review and meta-analyses. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics*, 177(2), 232–241. <https://doi.org/10.1002/ajmg.b.32549>
- Cuervo, A. M., Wong, E. S. P., & Martinez-Vicente, M. (2010). Protein degradation, aggregation, and misfolding. *Movement Disorders*, 25(S1). <https://doi.org/10.1002/mds.22718>
- Davis, M. Y., Johnson, C. O., Leverenz, J. B., Weintraub, D., Trojanowski, J. Q., Chen-Plotkin, A., Van Deerlin, V. M., Quinn, J. F., Chung, K. A., Peterson-Hiller, A. L., Rosenthal, L. S., Dawson, T. M., Albert, M. S., Goldman, J. G., Stebbins, G. T., Bernard, B., Wszolek, Z. K., Ross, O. A., Dickson, D. W., ... Zabetian, C. P. (2016). Association of GBA Mutations and the E326K Polymorphism With Motor and Cognitive Progression in Parkinson Disease. *JAMA Neurology*, 73(10), 1217–1224. <https://doi.org/10.1001/jamaneurol.2016.2245>
- de Lau, L. M. L., & Breteler, M. M. B. (2006). Epidemiology of Parkinson's disease. *The Lancet. Neurology*, 5(6), 525–535. [https://doi.org/10.1016/S1474-4422\(06\)70471-9](https://doi.org/10.1016/S1474-4422(06)70471-9)
- De Pablo-Fernandez, E., Goldacre, R., Pakpoor, J., Noyce, A. J., & Warner, T. T. (2018). Association between diabetes and subsequent Parkinson disease: A record-linkage cohort study. *Neurology*, 91(2), e139–e142. <https://doi.org/10.1212/WNL.0000000000005771>

- Deas, E., Wood, N. W., & Plun-Favreau, H. (2011). Mitophagy and Parkinson's disease: The PINK1-parkin link. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, 1813(4), 623–633. <https://doi.org/10.1016/j.bbamcr.2010.08.007>
- Devigili, G., Straccia, G., Cereda, E., Garavaglia, B., Fedeli, A., Elia, A. E., Piacentini, S. H. M. J., Prioni, S., Amami, P., Invernizzi, F., Andreasi, N. G., Romito, L. M., Eleopra, R., & Cilia, R. (2023). Unraveling Autonomic Dysfunction in <scp>GBA</scp>-Related Parkinson's Disease. *Movement Disorders Clinical Practice*. <https://doi.org/10.1002/mdc3.13892>
- Di Fonzo, A., Rohé, C. F., Ferreira, J., Chien, H. F., Vacca, L., Stocchi, F., Guedes, L., Fabrizio, E., Manfredi, M., Vanacore, N., Goldwurm, S., Breedveld, G., Sampaio, C., Meo, G., Barbosa, E., Oostra, B. A., & Bonifati, V. (2005). A frequent LRRK2 gene mutation associated with autosomal dominant Parkinson's disease. *The Lancet*, 365(9457), 412–415. [https://doi.org/10.1016/S0140-6736\(05\)17829-5](https://doi.org/10.1016/S0140-6736(05)17829-5)
- Dickson, D. W. (2002). Dementia with Lewy bodies: neuropathology. *Journal of Geriatric Psychiatry and Neurology*, 15(4), 210–216. <https://doi.org/10.1177/089198870201500406>
- Doherty, K. M., Silveira-Moriyama, L., Parkkinen, L., Healy, D. G., Farrell, M., Mencacci, N. E., Ahmed, Z., Brett, F. M., Hardy, J., Quinn, N., Counihan, T. J., Lynch, T., Fox, Z. V., Revesz, T., Lees, A. J., & Holton, J. L. (2013). Parkin Disease. *JAMA Neurology*, 70(5), 571. <https://doi.org/10.1001/jamaneurol.2013.172>
- Dorsey, E. R., Sherer, T., Okun, M. S., & Bloem, D. B. (2018). The emerging evidence of the Parkinson pandemic. In *Journal of Parkinson's Disease* (Vol. 8, Issue s1, pp. S3–S8). IOS Press. <https://doi.org/10.3233/JPD-181474>
- Doty, R. L. (2012). Olfactory dysfunction in Parkinson disease. *Nature Reviews. Neurology*, 8(6), 329–339. <https://doi.org/10.1038/nrneurol.2012.80>
- Dunning, C. J. R., Reyes, J. F., Steiner, J. A., & Brundin, P. (2012). Can Parkinson's disease pathology be propagated from one neuron to another? *Progress in Neurobiology*, 97(2), 205–219. <https://doi.org/10.1016/j.pneurobio.2011.11.003>
- Eckberg, D. L., & Eckberg, M. J. (1982). Human sinus node responses to repetitive, ramped carotid baroreceptor stimuli. *The American Journal of Physiology*, 242(4), H638–44. <https://doi.org/10.1152/ajpheart.1982.242.4.H638>
- Electrophysiology, T. F. of the E. S. of C. the N. A. (1996). Heart Rate Variability. *Circulation*, 93(5), 1043–1065. <https://doi.org/10.1161/01.CIR.93.5.1043>
- Erkkinen MG, & Kim MO. (n.d.). *Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases*.
- Evans, A. H. (2005). Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 77(3), 317–321. <https://doi.org/10.1136/jnnp.2005.065417>
- Ewing, D. J., Neilson, J. M., & Travis, P. (1984). New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. *British Heart Journal*, 52(4), 396–402. <https://doi.org/10.1136/hrt.52.4.396>
- Factor, S. A., McAlarney, T., Sanchez-Ramos, J. R., & Weiner, W. J. (1990). Sleep disorders and sleep effect in Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, 5(4), 280–285. <https://doi.org/10.1002/mds.870050404>

- Fanciulli, A., Göbel, G., Ndayisaba, J. P., Granata, R., Duerr, S., Strano, S., Colosimo, C., Poewe, W., Pontieri, F. E., & Wenning, G. K. (2016a). Supine hypertension in Parkinson's disease and multiple system atrophy. *Clinical Autonomic Research*, 26(2), 97–105. <https://doi.org/10.1007/s10286-015-0336-4>
- Fanciulli, A., Göbel, G., Ndayisaba, J. P., Granata, R., Duerr, S., Strano, S., Colosimo, C., Poewe, W., Pontieri, F. E., & Wenning, G. K. (2016b). Supine hypertension in Parkinson's disease and multiple system atrophy. *Clinical Autonomic Research : Official Journal of the Clinical Autonomic Research Society*, 26(2), 97–105. <https://doi.org/10.1007/s10286-015-0336-4>
- Fang, X., Han, D., Cheng, Q., Zhang, P., Zhao, C., Min, J., & Wang, F. (2018). Association of Levels of Physical Activity With Risk of Parkinson Disease: A Systematic Review and Meta-analysis. *JAMA Network Open*, 1(5), e182421. <https://doi.org/10.1001/jamanetworkopen.2018.2421>
- Farrer, M., Chan, P., Chen, R., Tan, L., Lincoln, S., Hernandez, D., Forno, L., Gwinn-Hardy, K., Petrucelli, L., Hussey, J., Singleton, A., Tanner, C., Hardy, J., & Langston, J. W. (2001). Lewy bodies and parkinsonism in families with parkin mutations. *Annals of Neurology*, 50(3), 293–300. <https://doi.org/10.1002/ana.1132>
- Fasano, A., Visanji, N. P., Liu, L. W. C., Lang, A. E., & Pfeiffer, R. F. (2015). Gastrointestinal dysfunction in Parkinson's disease. *The Lancet. Neurology*, 14(6), 625–639. [https://doi.org/10.1016/S1474-4422\(15\)00007-1](https://doi.org/10.1016/S1474-4422(15)00007-1)
- Fearnley, J. M., & Lees, A. J. (1991). Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain : A Journal of Neurology*, 114 (Pt 5), 2283–2301. <https://doi.org/10.1093/brain/114.5.2283>
- Fedorowski, A., Burri, P., & Melander, O. (2009). Orthostatic hypotension in genetically related hypertensive and normotensive individuals. *Journal of Hypertension*, 27(5), 976–982. <https://doi.org/10.1097/hjh.0b013e3283279860>
- Fereshtehnejad, S.-M., & Lökk, J. (2014). Orthostatic hypotension in patients with Parkinson's disease and atypical parkinsonism. *Parkinson's Disease*, 2014, 475854. <https://doi.org/10.1155/2014/475854>
- Fernandes, H. J. R., Hartfield, E. M., Christian, H. C., Emmanoulidou, E., Zheng, Y., Booth, H., Bogetofte, H., Lang, C., Ryan, B. J., Sardi, S. P., Badger, J., Vowles, J., Evetts, S., Tofaris, G. K., Vekrellis, K., Talbot, K., Hu, M. T., James, W., Cowley, S. A., & Wade-Martins, R. (2016). ER Stress and Autophagic Perturbations Lead to Elevated Extracellular α -Synuclein in GBA-N370S Parkinson's iPSC-Derived Dopamine Neurons. *Stem Cell Reports*, 6(3), 342–356. <https://doi.org/10.1016/j.stemcr.2016.01.013>
- Findley, L. J., Gresty, M. A., & Halmagyi, G. M. (1981). Tremor, the cogwheel phenomenon and clonus in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 44(6), 534–546. <https://doi.org/10.1136/jnnp.44.6.534>
- Fu, Q., Levine, B. D., Pawelczyk, J. A., Ertl, A. C., Diedrich, A., Cox, J. F., Zuckerman, J. H., Ray, C. A., Smith, M. L., Iwase, S., Saito, M., Sugiyama, Y., Mano, T., Zhang, R., Iwasaki, K., Lane, L. D., Buckey, J. C., Cooke, W. H., Robertson, R. M., ... Biaggioni, I. (2002). Cardiovascular and sympathetic neural responses to handgrip and cold pressor stimuli in humans before, during and after spaceflight. *The Journal of Physiology*, 544(2), 653–664. <https://doi.org/10.1113/jphysiol.2002.025098>
- Fujishiro, H., Nakamura, S., Sato, K., & Iseki, E. (2015). Prodromal dementia with Lewy bodies. *Geriatrics & Gerontology International*, 15(7), 817–826. <https://doi.org/10.1111/ggi.12466>
- Fujiwara, K., Miyatani, S., Goda, A., Miyajima, M., Sasano, T., & Kano, M. (2021). Autoencoder-Based Extrasystole Detection and Modification of RRI Data for Precise Heart Rate Variability Analysis. *Sensors (Basel, Switzerland)*, 21(9). <https://doi.org/10.3390/s21093235>

- Gan-Or, Z., Amshalom, I., Kilarski, L. L., Bar-Shira, A., Gana-Weisz, M., Mirelman, A., Marder, K., Bressman, S., Giladi, N., & Orr-Urtreger, A. (2015a). Differential effects of severe vs mild GBA mutations on Parkinson disease. *Neurology*, 84(9), 880–887. <https://doi.org/10.1212/WNL.0000000000001315>
- Gan-Or, Z., Amshalom, I., Kilarski, L. L., Bar-Shira, A., Gana-Weisz, M., Mirelman, A., Marder, K., Bressman, S., Giladi, N., & Orr-Urtreger, A. (2015b). Differential effects of severe vs mild GBA mutations on Parkinson disease. *Neurology*, 84(9), 880–887. <https://doi.org/10.1212/WNL.0000000000001315>
- Gan-Or, Z., Bar-Shira, A., Mirelman, A., Gurevich, T., Kedmi, M., Giladi, N., & Orr-Urtreger, A. (2010). LRRK2 and GBA mutations differentially affect the initial presentation of Parkinson disease. *Neurogenetics*, 11(1), 121–125. <https://doi.org/10.1007/s10048-009-0198-9>
- Gan-Or, Z., Liong, C., & Alcalay, R. N. (2018). GBA-Associated Parkinson's Disease and Other Synucleinopathies. *Current Neurology and Neuroscience Reports*, 18(8), 44. <https://doi.org/10.1007/s11910-018-0860-4>
- Gan-Or, Z., Mirelman, A., Postuma, R. B., Arnulf, I., Bar-Shira, A., Dauvilliers, Y., Desautels, A., Gagnon, J.-F., Leblond, C. S., Frauscher, B., Alcalay, R. N., Saunders-Pullman, R., Bressman, S. B., Marder, K., Monaca, C., Högl, B., Orr-Urtreger, A., Dion, P. A., Montplaisir, J. Y., ... Rouleau, G. A. (2015). GBA mutations are associated with Rapid Eye Movement Sleep Behavior Disorder. *Annals of Clinical and Translational Neurology*, 2(9), 941–945. <https://doi.org/10.1002/acn3.228>
- García-Sanz, P., M F G Aerts, J., & Moratalla, R. (2021). The Role of Cholesterol in α -Synuclein and Lewy Body Pathology in GBA1 Parkinson's Disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, 36(5), 1070–1085. <https://doi.org/10.1002/mds.28396>
- Gardner, R. C., Burke, J. F., Nettiksimmons, J., Goldman, S., Tanner, C. M., & Yaffe, K. (2015). Traumatic brain injury in later life increases risk for Parkinson disease. *Annals of Neurology*, 77(6), 987–995. <https://doi.org/10.1002/ana.24396>
- Gegg, M. E., Burke, D., Heales, S. J. R., Cooper, J. M., Hardy, J., Wood, N. W., & Schapira, A. H. V. (2012). Glucocerebrosidase deficiency in substantia nigra of parkinson disease brains. *Annals of Neurology*, 72(3), 455–463. <https://doi.org/10.1002/ana.23614>
- Gibbons, C. H., Schmidt, P., Biaggioni, I., Frazier-Mills, C., Freeman, R., Isaacson, S., Karabin, B., Kuritzky, L., Lew, M., Low, P., Mehdirad, A., Raj, S. R., Vernino, S., & Kaufmann, H. (2017). The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. *Journal of Neurology*, 264(8), 1567–1582. <https://doi.org/10.1007/s00415-016-8375-x>
- GM Pastores, & Derrallynn A Hughe. (n.d.). *Gaucher Disease - GeneReviews*.
- Goker-Alpan, O., Lopez, G., Vithayathil, J., Davis, J., Hallett, M., & Sidransky, E. (2008). The Spectrum of Parkinsonian Manifestations Associated With Glucocerebrosidase Mutations. *Archives of Neurology*, 65(10). <https://doi.org/10.1001/archneur.65.10.1353>
- Goker-Alpan, O., Masdeu, J. C., Kohn, P. D., Ianni, A., Lopez, G., Groden, C., Chapman, M. C., Cropp, B., Eisenberg, D. P., Maniawang, E. D., Davis, J., Wiggs, E., Sidransky, E., & Berman, K. F. (2012). The neurobiology of glucocerebrosidase-associated parkinsonism: a positron emission tomography study of dopamine synthesis and regional cerebral blood flow. *Brain*, 135(8), 2440–2448. <https://doi.org/10.1093/brain/aws174>

- Golbe, L. I., Di Iorio, G., Sanges, G., Lazzarini, A. M., La Sala, S., Bonavita, V., & Duvoisin, R. C. (1996). Clinical genetic analysis of Parkinson's disease in the Contursi kindred. *Annals of Neurology*, 40(5), 767–775. <https://doi.org/10.1002/ana.410400513>
- Goldstein, D. S. (2006). Orthostatic hypotension as an early finding in Parkinson's disease. *Clinical Autonomic Research*, 16(1), 46–54. <https://doi.org/10.1007/s10286-006-0317-8>
- Goldstein, D. S. (2014). Dysautonomia in Parkinson disease. *Comprehensive Physiology*, 4(2), 805–826. <https://doi.org/10.1002/cphy.c130026>
- Goldstein, D. S., Holmes, C., Cannon, R. O., Eisenhofer, G., & Kopin, I. J. (1997). Sympathetic cardioneuropathy in dysautonomias. *The New England Journal of Medicine*, 336(10), 696–702. <https://doi.org/10.1056/NEJM199703063361004>
- Goldstein, D. S., & Orimo, S. (2009). Cardiac sympathetic neuroimaging: summary of the First International Symposium. *Clinical Autonomic Research : Official Journal of the Clinical Autonomic Research Society*, 19(3), 137–148. <https://doi.org/10.1007/s10286-009-0002-9>
- Gómez-Sánchez, R., Yakhine-Diop, S. M. S., Bravo-San Pedro, J. M., Pizarro-Estrella, E., Rodríguez-Arribas, M., Climent, V., Martín-Cano, F. E., González-Soltero, M. E., Tandon, A., Fuentes, J. M., & González-Polo, R. A. (2016). PINK1 deficiency enhances autophagy and mitophagy induction. *Molecular & Cellular Oncology*, 3(2), e1046579. <https://doi.org/10.1080/23723556.2015.1046579>
- Grabowski, G. A. (2008). Phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet (London, England)*, 372(9645), 1263–1271. [https://doi.org/10.1016/S0140-6736\(08\)61522-6](https://doi.org/10.1016/S0140-6736(08)61522-6)
- Groiss, S. J., Wojtecki, L., Südmeyer, M., & Schnitzler, A. (2009). Deep brain stimulation in Parkinson's disease. *Therapeutic Advances in Neurological Disorders*, 2(6), 20–28. <https://doi.org/10.1177/1756285609339382>
- Guaraldi, P., Baschieri, F., Barletta, G., Cecere, A., Cortelli, P., & Calandra-Buonaura, G. (2020). Validation of the new index of baroreflex function to identify neurogenic orthostatic hypotension. *Autonomic Neuroscience*, 229, 102744. <https://doi.org/10.1016/j.autneu.2020.102744>
- Guerreiro, R., Ross, O. A., Kun-Rodrigues, C., Hernandez, D. G., Orme, T., Eicher, J. D., Shepherd, C. E., Parkkinen, L., Darwent, L., Heckman, M. G., Scholz, S. W., Troncoso, J. C., Pletnikova, O., Ansorge, O., Clarimon, J., Lleo, A., Morenas-Rodriguez, E., Clark, L., Honig, L. S., ... Bras, J. (2018). Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. *The Lancet Neurology*, 17(1), 64–74. [https://doi.org/10.1016/S1474-4422\(17\)30400-3](https://doi.org/10.1016/S1474-4422(17)30400-3)
- Gündner, A. L., Duran-Pacheco, G., Zimmermann, S., Ruf, I., Moors, T., Baumann, K., Jagasia, R., van de Berg, W. D. J., & Kremer, T. (2019). Path mediation analysis reveals GBA impacts Lewy body disease status by increasing α -synuclein levels. *Neurobiology of Disease*, 121, 205–213. <https://doi.org/10.1016/j.nbd.2018.09.015>
- Haensch, C.-A., Lerch, H., Jörg, J., & Isenmann, S. (2009). Cardiac denervation occurs independent of orthostatic hypotension and impaired heart rate variability in Parkinson's disease. *Parkinsonism & Related Disorders*, 15(2), 134–137. <https://doi.org/10.1016/j.parkreldis.2008.04.031>
- Hallett, M. (2012). Parkinson's disease tremor: pathophysiology. *Parkinsonism & Related Disorders*, 18 Suppl 1, S85–6. [https://doi.org/10.1016/S1353-8020\(11\)70027-X](https://doi.org/10.1016/S1353-8020(11)70027-X)
- Hawkes, C. H., Del Tredici, K., & Braak, H. (2007). Parkinson's disease: a dual-hit hypothesis. *Neuropathology and Applied Neurobiology*, 33(6), 599–614. <https://doi.org/10.1111/j.1365-2990.2007.00874.x>

- Heath, M. E., & Downey, J. A. (1990). The cold face test (diving reflex) in clinical autonomic assessment: methodological considerations and repeatability of responses. *Clinical Science (London, England : 1979)*, 78(2), 139–147. <https://doi.org/10.1042/cs0780139>
- Heimrich, K. G., Lehmann, T., Schlattmann, P., & Prell, T. (2021a). Heart Rate Variability Analyses in Parkinson's Disease: A Systematic Review and Meta-Analysis. *Brain Sciences*, 11(8), 959. <https://doi.org/10.3390/brainsci11080959>
- Heimrich, K. G., Lehmann, T., Schlattmann, P., & Prell, T. (2021b). Heart Rate Variability Analyses in Parkinson's Disease: A Systematic Review and Meta-Analysis. *Brain Sciences*, 11(8), 959. <https://doi.org/10.3390/brainsci11080959>
- Henderson, M. X., Sengupta, M., Trojanowski, J. Q., & Lee, V. M. Y. (2019). Alzheimer's disease tau is a prominent pathology in LRRK2 Parkinson's disease. *Acta Neuropathologica Communications*, 7(1), 183. <https://doi.org/10.1186/s40478-019-0836-x>
- Hiorth, Y. H., Pedersen, K. F., Dalen, I., Tysnes, O.-B., & Alves, G. (2019). Orthostatic hypotension in Parkinson disease. *Neurology*, 93(16), e1526–e1534. <https://doi.org/10.1212/WNL.0000000000008314>
- Hommel, A. L. A. J., Meinders, M. J., Lorenzl, S., Dodel, R., Coelho, M., Ferreira, J. J., Laurens, B., Spampinato, U., Meissner, W., Rosqvist, K., Timpka, J., Odin, P., Wittenberg, M., Bloem PhD, B. R., Koopmans, R. T., Schrag, A., & Care of Late-Stage Parkinsonism Consortium. (2020). The Prevalence and Determinants of Neuropsychiatric Symptoms in Late-Stage Parkinsonism. *Movement Disorders Clinical Practice*, 7(5), 531–542. <https://doi.org/10.1002/mdc3.12968>
- Horimoto, Y., Matsumoto, M., Akatsu, H., Ikari, H., Kojima, K., Yamamoto, T., Otsuka, Y., Ojika, K., Ueda, R., & Kosaka, K. (2003). Autonomic dysfunctions in dementia with Lewy bodies. *Journal of Neurology*, 250(5), 530–533. <https://doi.org/10.1007/s00415-003-1029-9>
- Huang, Q., & Figueiredo-Pereira, M. E. (2010). Ubiquitin/proteasome pathway impairment in neurodegeneration: therapeutic implications. *Apoptosis*, 15(11), 1292–1311. <https://doi.org/10.1007/s10495-010-0466-z>
- Hughes, K. C., Gao, X., Molsberry, S., Valeri, L., Schwarzschild, M. A., & Ascherio, A. (2019). Physical activity and prodromal features of Parkinson disease. *Neurology*, 93(23), e2157–e2169. <https://doi.org/10.1212/WNL.0000000000008567>
- Huh, Y. E., Chiang, M. S. R., Locascio, J. J., Liao, Z., Liu, G., Choudhury, K., Kuras, Y. I., Tuncali, I., Videnovic, A., Hunt, A. L., Schwarzschild, M. A., Hung, A. Y., Herrington, T. M., Hayes, M. T., Hyman, B. T., Wills, A.-M., Gomperts, S. N., Growdon, J. H., Sardi, S. P., & Scherzer, C. R. (2020). β -Glucocerebrosidase activity in GBA-linked Parkinson disease: The type of mutation matters. *Neurology*, 95(6), e685–e696. <https://doi.org/10.1212/WNL.0000000000009989>
- Irwin, D. J., White, M. T., Toledo, J. B., Xie, S. X., Robinson, J. L., Van Deerlin, V., Lee, V. M.-Y., Leverenz, J. B., Montine, T. J., Duda, J. E., Hurtig, H. I., & Trojanowski, J. Q. (2012). Neuropathologic substrates of Parkinson disease dementia. *Annals of Neurology*, 72(4), 587–598. <https://doi.org/10.1002/ana.23659>
- Iwaki, H., Blauwendraat, C., Leonard, H. L., Liu, G., Maple-Grødem, J., Corvol, J.-C., Pihlstrøm, L., van Nimwegen, M., Hutten, S. J., Nguyen, K.-D. H., Rick, J., Eberly, S., Faghri, F., Auinger, P., Scott, K. M., Wijeyekoon, R., Van Deerlin, V. M., Hernandez, D. G., Day-Williams, A. G., ... Nalls, M. A. (2019). Genetic risk of Parkinson disease and progression:: An analysis of 13 longitudinal cohorts. *Neurology Genetics*, 5(4), e348. <https://doi.org/10.1212/NXG.0000000000000348>

- Jain, S., & Goldstein, D. S. (2012). Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. *Neurobiology of Disease*, 46(3), 572–580. <https://doi.org/10.1016/j.nbd.2011.10.025>
- Jamnadas-Khoda, J., Koshy, S., Mathias, C. J., Muthane, U. B., Ragothaman, M., & Dodaballapur, S. K. (2009). Are current recommendations to diagnose orthostatic hypotension in Parkinson's disease satisfactory? *Movement Disorders : Official Journal of the Movement Disorder Society*, 24(12), 1747–1751. <https://doi.org/10.1002/mds.22537>
- Jankovic, J., Schwartz, K. S., & Ondo, W. (1999). Re-emergent tremor of Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 67(5), 646–650. <https://doi.org/10.1136/jnnp.67.5.646>
- Jansen, R. W., & Lipsitz, L. A. (1995). Postprandial hypotension: epidemiology, pathophysiology, and clinical management. *Annals of Internal Medicine*, 122(4), 286–295. <https://doi.org/10.7326/0003-4819-122-4-199502150-00009>
- Jecmenica-Lukic, M., Poewe, W., Tolosa, E., & Wenning, G. K. (2012). Premotor signs and symptoms of multiple system atrophy. *The Lancet Neurology*, 11(4), 361–368. [https://doi.org/10.1016/S1474-4422\(12\)70022-4](https://doi.org/10.1016/S1474-4422(12)70022-4)
- Jesús, S., Huertas, I., Bernal-Bernal, I., Bonilla-Toribio, M., Cáceres-Redondo, M. T., Vargas-González, L., Gómez-Llamas, M., Carrillo, F., Calderón, E., Carballo, M., Gómez-Garre, P., & Mir, P. (2016). GBA Variants Influence Motor and Non-Motor Features of Parkinson's Disease. *PLoS One*, 11(12), e0167749. <https://doi.org/10.1371/journal.pone.0167749>
- Jiméanez-Jiméanez, F. J., Mateo, D., & Giméanez-Roldan, S. (1992). Premorbid smoking, alcohol consumption, and coffee drinking habits in Parkinson's disease: A case-control study. *Movement Disorders*, 7(4), 339–344. <https://doi.org/10.1002/mds.870070407>
- Jo, S., Kim, Y.-J., Park, K. W., Hwang, Y. S., Lee, S. H., Kim, B. J., & Chung, S. J. (2021). Association of NO₂ and Other Air Pollution Exposures With the Risk of Parkinson Disease. *JAMA Neurology*, 78(7), 800. <https://doi.org/10.1001/jamaneurol.2021.1335>
- Kalia, L. V., Lang, A. E., Hazrati, L.-N., Fujioka, S., Wszolek, Z. K., Dickson, D. W., Ross, O. A., Van Deerlin, V. M., Trojanowski, J. Q., Hurtig, H. I., Alcalay, R. N., Marder, K. S., Clark, L. N., Gaig, C., Tolosa, E., Ruiz-Martínez, J., Martí-Masso, J. F., Ferrer, I., López de Munain, A., ... Marras, C. (2015). Clinical correlations with Lewy body pathology in LRRK2-related Parkinson disease. *JAMA Neurology*, 72(1), 100–105. <https://doi.org/10.1001/jamaneurol.2014.2704>
- Kalinderi, K., Bostantjopoulou, S., & Fidani, L. (2016). The genetic background of Parkinson's disease: current progress and future prospects. *Acta Neurologica Scandinavica*, 134(5), 314–326. <https://doi.org/10.1111/ane.12563>
- Kang, S. H., Lee, H. M., Seo, W.-K., Kim, J. H., & Koh, S.-B. (2016). The combined effect of REM sleep behavior disorder and hyposmia on cognition and motor phenotype in Parkinson's disease. *Journal of the Neurological Sciences*, 368, 374–378. <https://doi.org/10.1016/j.jns.2016.07.057>
- Kashihara, K., Ohno, M., Kawada, S., & Okumura, Y. (2006). Reduced cardiac uptake and enhanced washout of 123I-MIBG in pure autonomic failure occurs conjointly with Parkinson's disease and dementia with Lewy bodies. *Journal of Nuclear Medicine : Official Publication, Society of Nuclear Medicine*, 47(7), 1099–1101.
- Kasten, M., Hartmann, C., Hampf, J., Schaake, S., Westenberger, A., Vollstedt, E.-J., Balck, A., Domingo, A., Vulinovic, F., Dulovic, M., Zorn, I., Madoev, H., Zehnle, H., Lembeck, C. M., Schawe, L., Reginold, J., Huang, J., König, I. R., Bertram, L., ... Klein, C. (2018). Genotype-Phenotype Relations for the

Parkinson's Disease Genes Parkin, PINK1, DJ1: MDSGene Systematic Review. *Movement Disorders : Official Journal of the Movement Disorder Society*, 33(5), 730–741.
<https://doi.org/10.1002/mds.27352>

- Kaufmann, H., Norcliffe-Kaufmann, L., Palma, J.-A., Biaggioni, I., Low, P. A., Singer, W., Goldstein, D. S., Peltier, A. C., Shibao, C. A., Gibbons, C. H., Freeman, R., Robertson, D., & Autonomic Disorders Consortium. (2017). Natural history of pure autonomic failure: A United States prospective cohort. *Annals of Neurology*, 81(2), 287–297. <https://doi.org/10.1002/ana.24877>
- Khan, N. L., Graham, E., Critchley, P., Schrag, A. E., Wood, N. W., Lees, A. J., Bhatia, K. P., & Quinn, N. (2003). Parkin disease: a phenotypic study of a large case series. *Brain : A Journal of Neurology*, 126(Pt 6), 1279–1292. <https://doi.org/10.1093/brain/awg142>
- Kim, R., Shin, J. H., Park, S., Kim, H.-J., & Jeon, B. (2020). Longitudinal evolution of non-motor symptoms according to age at onset in early Parkinson's disease. *Journal of the Neurological Sciences*, 418, 117157. <https://doi.org/10.1016/j.jns.2020.117157>
- Klein, C., & Schlossmacher, M. G. (2007a). Parkinson disease, 10 years after its genetic revolution: Multiple clues to a complex disorder. *Neurology*, 69(22), 2093–2104.
<https://doi.org/10.1212/01.wnl.0000271880.27321.a7>
- Klein, C., & Schlossmacher, M. G. (2007b). Parkinson disease, 10 years after its genetic revolution: multiple clues to a complex disorder. *Neurology*, 69(22), 2093–2104.
<https://doi.org/10.1212/01.wnl.0000271880.27321.a7>
- Klein, C., & Westenberger, A. (2012). Genetics of Parkinson's disease. *Cold Spring Harbor Perspectives in Medicine*, 2(1), a008888. <https://doi.org/10.1101/cshperspect.a008888>
- Kim MS, Park DG, An YS, Yoon JH. Dual-phase ¹⁸F-FP-CIT positron emission tomography and cardiac ¹²³I-MIBG scintigraphy of Parkinson's disease patients with GBA mutations: evidence of the body-first type? *Eur J Neurol*. 2023 Feb;30(2):344-352. doi: 10.1111/ene.15615.
- Kon, T., Tomiyama, M., & Wakabayashi, K. (2020). Neuropathology of Lewy body disease: Clinicopathological crosstalk between typical and atypical cases. *Neuropathology : Official Journal of the Japanese Society of Neuropathology*, 40(1), 30–39. <https://doi.org/10.1111/neup.12597>
- Kordower, J. H., Chu, Y., Hauser, R. A., Freeman, T. B., & Olanow, C. W. (2008). Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nature Medicine*, 14(5), 504–506.
<https://doi.org/10.1038/nm1747>
- Krohn, L., Ruskey, J. A., Rudakou, U., Leveille, E., Asayesh, F., Hu, M. T. M., Arnulf, I., Dauvilliers, Y., Högl, B., Stefani, A., Monaca, C. C., Abril, B., Plazzi, G., Antelmi, E., Ferini-Strambi, L., Heidebreder, A., Boeve, B. F., Espay, A. J., De Cock, V. C., ... Gan-Or, Z. (2020). GBA variants in REM sleep behavior disorder. *Neurology*, 95(8), e1008–e1016. <https://doi.org/10.1212/WNL.0000000000010042>
- Kumar, K. R., Djarmati-Westenberger, A., & Grünwald, A. (2011). Genetics of Parkinson's disease. *Seminars in Neurology*, 31(5), 433–440. <https://doi.org/10.1055/s-0031-1299782>
- Langston, J. W., Ballard, P., Tetrud, J. W., & Irwin, I. (1983). Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science (New York, N.Y.)*, 219(4587), 979–980.
<https://doi.org/10.1126/science.6823561>
- Lebouvier, T., Chaumette, T., Damier, P., Coron, E., Touchefeu, Y., Vrignaud, S., Naveilhan, P., Galmiche, J.-P., Bruley des Varannes, S., Derkinderen, P., & Neunlist, M. (2008). Pathological lesions in colonic biopsies

- during Parkinson's disease. *Gut*, 57(12), 1741–1743. <https://doi.org/10.1136/gut.2008.162503>
- Lee, C.-N., Kim, M., Lee, H. M., Jang, J.-W., Lee, S.-M., Kwon, D.-Y., Park, K.-W., & Koh, S.-B. (2013). The interrelationship between non-motor symptoms in Atypical Parkinsonism. *Journal of the Neurological Sciences*, 327(1–2), 15–21. <https://doi.org/10.1016/j.jns.2013.01.034>
- Lee, H., Low, P. A., & Kim, H. A. (2017). Patients with Orthostatic Intolerance: Relationship to Autonomic Function Tests results and Reproducibility of Symptoms on Tilt. *Scientific Reports*, 7(1), 5706. <https://doi.org/10.1038/s41598-017-05668-4>
- Leija-Salazar, M., Sedlazeck, F. J., Toffoli, M., Mullin, S., Mokretar, K., Athanasopoulou, M., Donald, A., Sharma, R., Hughes, D., Schapira, A. H. V., & Proukakis, C. (2019). Evaluation of the detection of GBA missense mutations and other variants using the Oxford Nanopore MinION. *Molecular Genetics & Genomic Medicine*, 7(3), e564. <https://doi.org/10.1002/mgg3.564>
- Lerche, S., Schulte, C., Wurster, I., Machetanz, G., Roeben, B., Zimmermann, M., Deuschle, C., Hauser, A.-K., Böhringer, J., Krägeloh-Mann, I., Waniek, K., Lachmann, I., Petterson, X.-M. T., Chiang, R., Park, H., Wang, B., Liepelt-Scarfone, I., Maetzler, W., Galasko, D., ... Brockmann, K. (2021). The Mutation Matters: CSF Profiles of GCase, Sphingolipids, α -Synuclein in PDGBA. *Movement Disorders : Official Journal of the Movement Disorder Society*, 36(5), 1216–1228. <https://doi.org/10.1002/mds.28472>
- Lesage, S., Anheim, M., Condroyer, C., Pollak, P., Durif, F., Dupuits, C., Viallet, F., Lohmann, E., Corvol, J.-C., Honoré, A., Rivaud, S., Vidailhet, M., Dürr, A., Brice, A., & French Parkinson's Disease Genetics Study Group. (2011). Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease. *Human Molecular Genetics*, 20(1), 202–210. <https://doi.org/10.1093/hmg/ddq454>
- Lev, N., Roncevic, D., Ickowicz, D., Melamed, E., & Offen, D. (2006). Role of DJ-1 in Parkinson's disease. *Journal of Molecular Neuroscience : MN*, 29(3), 215–225. <https://doi.org/10.1385/jmn:29:3:215>
- Li, J.-Y., Englund, E., Widner, H., Rehncrona, S., Björklund, A., Lindvall, O., & Brundin, P. (2010). Characterization of Lewy body pathology in 12- and 16-year-old intrastriatal mesencephalic grafts surviving in a patient with Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, 25(8), 1091–1096. <https://doi.org/10.1002/mds.23012>
- Liou, B., Kazimierczuk, A., Zhang, M., Scott, C. R., Hegde, R. S., & Grabowski, G. A. (2006). Analyses of Variant Acid β -Glucosidases. *Journal of Biological Chemistry*, 281(7), 4242–4253. <https://doi.org/10.1074/jbc.M511110200>
- Liu, R., Gao, X., Lu, Y., & Chen, H. (2011). Meta-analysis of the relationship between Parkinson disease and melanoma. *Neurology*, 76(23), 2002–2009. <https://doi.org/10.1212/WNL.0b013e31821e554e>
- Liu, R., Guo, X., Park, Y., Huang, X., Sinha, R., Freedman, N. D., Hollenbeck, A. R., Blair, A., & Chen, H. (2012). Caffeine intake, smoking, and risk of Parkinson disease in men and women. *American Journal of Epidemiology*, 175(11), 1200–1207. <https://doi.org/10.1093/aje/kwr451>
- Loavenbruck, A., & Sandroni, P. (2015). Neurogenic orthostatic hypotension: roles of norepinephrine deficiency in its causes, its treatment, and future research directions. *Current Medical Research and Opinion*, 31(11), 2095–2104. <https://doi.org/10.1185/03007995.2015.1087988>
- Longardner, K., Bayram, E., & Litvan, I. (2020). Orthostatic Hypotension Is Associated With Cognitive Decline in Parkinson Disease. *Frontiers in Neurology*, 11, 897. <https://doi.org/10.3389/fneur.2020.00897>
- Lopez, G. J., Lichtenberg, J., Tayebi, N., Ryan, E., Lecker, A. L., & Sidransky, E. (2022). Longitudinal evaluation

- of olfactory function in individuals with Gaucher disease and GBA1 mutation carriers with and without Parkinson's disease. *Frontiers in Neurology*, 13. <https://doi.org/10.3389/fneur.2022.1039214>
- Low, P. A., Denq, J. C., Opfer-Gehrking, T. L., Dyck, P. J., O'Brien, P. C., & Slezak, J. M. (1997). Effect of age and gender on sudomotor and cardiovascular function and blood pressure response to tilt in normal subjects. *Muscle & Nerve*, 20(12), 1561–1568. [https://doi.org/10.1002/\(sici\)1097-4598\(199712\)20:12<1561::aid-mus11>3.0.co;2-3](https://doi.org/10.1002/(sici)1097-4598(199712)20:12<1561::aid-mus11>3.0.co;2-3)
- Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. *Mayo Clin Proc.* 1993 Aug;68(8):748-52. doi: 10.1016/s0025-6196(12)60631-4. PMID: 8392653.
- Lythe, V., Athauda, D., Foley, J., Mencacci, N. E., Jahanshahi, M., Cipolotti, L., Hyam, J., Zrinzo, L., Hariz, M., Hardy, J., Limousin, P., & Foltynie, T. (2017). GBA-Associated Parkinson's Disease: Progression in a Deep Brain Stimulation Cohort. *Journal of Parkinson's Disease*, 7(4), 635–644. <https://doi.org/10.3233/JPD-171172>
- MacLeod, D. A., Rhinn, H., Kuwahara, T., Zolin, A., Di Paolo, G., McCabe, B. D., Marder, K. S., Honig, L. S., Clark, L. N., Small, S. A., & Abeliovich, A. (2013). RAB7L1 interacts with LRRK2 to modify intraneuronal protein sorting and Parkinson's disease risk. *Neuron*, 77(3), 425–439. <https://doi.org/10.1016/j.neuron.2012.11.033>
- Malek, N., Weil, R. S., Bresner, C., Lawton, M. A., Grosset, K. A., Tan, M., Bajaj, N., Barker, R. A., Burn, D. J., Foltynie, T., Hardy, J., Wood, N. W., Ben-Shlomo, Y., Williams, N. W., Grosset, D. G., Morris, H. R., & PRoBaND clinical consortium. (2018a). Features of GBA-associated Parkinson's disease at presentation in the UK Tracking Parkinson's study. *Journal of Neurology, Neurosurgery, and Psychiatry*, 89(7), 702–709. <https://doi.org/10.1136/jnnp-2017-317348>
- Malek, N., Weil, R. S., Bresner, C., Lawton, M. A., Grosset, K. A., Tan, M., Bajaj, N., Barker, R. A., Burn, D. J., Foltynie, T., Hardy, J., Wood, N. W., Ben-Shlomo, Y., Williams, N. W., Grosset, D. G., Morris, H. R., & PRoBaND clinical consortium. (2018b). Features of GBA-associated Parkinson's disease at presentation in the UK Tracking Parkinson's study. *Journal of Neurology, Neurosurgery, and Psychiatry*, 89(7), 702–709. <https://doi.org/10.1136/jnnp-2017-317348>
- Mangone, G., Bekadar, S., Cormier-Dequaire, F., Tahiri, K., Welaratne, A., Czernecki, V., Pineau, F., Karachi, C., Castrioto, A., Durif, F., Tranchant, C., Devos, D., Thobois, S., Meissner, W. G., Navarro, M. S., Cornu, P., Lesage, S., Brice, A., Welter, M. L., ... Burbaud, P. (2020). Early cognitive decline after bilateral subthalamic deep brain stimulation in Parkinson's disease patients with GBA mutations. *Parkinsonism & Related Disorders*, 76, 56–62. <https://doi.org/10.1016/j.parkreldis.2020.04.002>
- Maple-Grødem, J., Dalen, I., Tysnes, O.-B., Macleod, A. D., Forsgren, L., Counsell, C. E., & Alves, G. (2021). Association of GBA Genotype With Motor and Functional Decline in Patients With Newly Diagnosed Parkinson Disease. *Neurology*, 96(7), e1036–e1044. <https://doi.org/10.1212/WNL.0000000000011411>
- Mata, I. F., Leverenz, J. B., Weintraub, D., Trojanowski, J. Q., Chen-Plotkin, A., Van Deerlin, V. M., Ritz, B., Rausch, R., Factor, S. A., Wood-Siverio, C., Quinn, J. F., Chung, K. A., Peterson-Hiller, A. L., Goldman, J. G., Stebbins, G. T., Bernard, B., Espay, A. J., Revilla, F. J., Devoto, J., ... Zabetian, C. P. (2016). GBA Variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, 31(1), 95–102. <https://doi.org/10.1002/mds.26359>
- Mattila, P. M., Røyttä, M., Lönnberg, P., Marjamäki, P., Helenius, H., & Rinne, J. O. (2001). Choline acetyltransferase activity and striatal dopamine receptors in Parkinson's disease in relation to cognitive impairment. *Acta Neuropathologica*, 102(2), 160–166. <https://doi.org/10.1007/s004010100372>

- Mazzulli, J. R., Xu, Y.-H., Sun, Y., Knight, A. L., McLean, P. J., Caldwell, G. A., Sidransky, E., Grabowski, G. A., & Krainc, D. (2011). Gaucher disease glucocerebrosidase and α -synuclein form a bidirectional pathogenic loop in synucleinopathies. *Cell*, 146(1), 37–52. <https://doi.org/10.1016/j.cell.2011.06.001>
- McKeith, I. (2004). Dementia with Lewy bodies. *Dialogues in Clinical Neuroscience*, 6(3), 333–341. <https://doi.org/10.31887/DCNS.2004.6.3/imckeith>
- McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J.-P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C. G., Bayston, A., Beach, T. G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., ... Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, 89(1), 88–100. <https://doi.org/10.1212/WNL.0000000000004058>
- McKerian, R. O., Bradbury, P., Taylor, D., & Stern, G. (1985). Neurological involvement in type 1 (adult) Gaucher's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 48(2), 172–175. <https://doi.org/10.1136/jnnp.48.2.172>
- McNeill, A., Duran, R., Proukakis, C., Bras, J., Hughes, D., Mehta, A., Hardy, J., Wood, N. W., & Schapira, A. H. V. (2012). Hyposmia and cognitive impairment in Gaucher disease patients and carriers. *Movement Disorders : Official Journal of the Movement Disorder Society*, 27(4), 526–532. <https://doi.org/10.1002/mds.24945>
- Mendoza-Velázquez, J. J., Flores-Vázquez, J. F., Barrón-Velázquez, E., Sosa-Ortiz, A. L., Illigens, B.-M. W., & Siepmann, T. (2019). Autonomic Dysfunction in α -Synucleinopathies. *Frontiers in Neurology*, 10, 363. <https://doi.org/10.3389/fneur.2019.00363>
- Montfort, M., Chabás, A., Vilageliu, L., & Grinberg, D. (2004). Functional analysis of 13 GBA mutant alleles identified in Gaucher disease patients: Pathogenic changes and “modifier” polymorphisms. *Human Mutation*, 23(6), 567–575. <https://doi.org/10.1002/humu.20043>
- Moon, H. E., & Paek, S. H. (2015). Mitochondrial Dysfunction in Parkinson's Disease. *Experimental Neurobiology*, 24(2), 103–116. <https://doi.org/10.5607/en.2015.24.2.103>
- Murphy, C. (2019). Olfactory and other sensory impairments in Alzheimer disease. *Nature Reviews. Neurology*, 15(1), 11–24. <https://doi.org/10.1038/s41582-018-0097-5>
- Muslimovic, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*, 65(8), 1239–1245. <https://doi.org/10.1212/01.wnl.0000180516.69442.95>
- Nakamura, T., Hirayama, M., Ito, H., Takamori, M., Hamada, K., Takeuchi, S., Watanabe, H., Koike, Y., & Sobue, G. (2007). Dobutamine stress test unmasks cardiac sympathetic denervation in Parkinson's disease. *Journal of the Neurological Sciences*, 263(1–2), 133–138. <https://doi.org/10.1016/j.jns.2007.07.005>
- Nalls, M. A., Duran, R., Lopez, G., Kurzawa-Akanbi, M., McKeith, I. G., Chinnery, P. F., Morris, C. M., Theuns, J., Crosiers, D., Cras, P., Engelborghs, S., De Deyn, P. P., Van Broeckhoven, C., Mann, D. M. A., Snowden, J., Pickering-Brown, S., Halliwell, N., Davidson, Y., Gibbons, L., ... Sidransky, E. (2013). A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. *JAMA Neurology*, 70(6), 727–735. <https://doi.org/10.1001/jamaneurol.2013.1925>
- Nam, G. E., Kim, S. M., Han, K., Kim, N. H., Chung, H. S., Kim, J. W., Han, B., Cho, S. J., Yu, J. H., Park, Y. G., & Choi, K. M. (2018). Metabolic syndrome and risk of Parkinson disease: A nationwide cohort study. *PLoS*

Medicine, 15(8), e1002640. <https://doi.org/10.1371/journal.pmed.1002640>

- Neudorfer, O., Giladi, N., Elstein, D., Abrahamov, A., Turezkite, T., Aghai, E., Reches, A., Bembi, B., & Zimran, A. (1996). Occurrence of Parkinson's syndrome in type 1 Gaucher disease. *QJM*, 89(9), 691–694. <https://doi.org/10.1093/qjmed/89.9.691>
- Neumann, J., Bras, J., Deas, E., O'Sullivan, S. S., Parkkinen, L., Lachmann, R. H., Li, A., Holton, J., Guerreiro, R., Paudel, R., Segarane, B., Singleton, A., Lees, A., Hardy, J., Houlden, H., Revesz, T., & Wood, N. W. (2009). Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. *Brain : A Journal of Neurology*, 132(Pt 7), 1783–1794. <https://doi.org/10.1093/brain/awp044>
- Norcliffe-Kaufmann, L., Kaufmann, H., Palma, J.-A., Shibao, C. A., Biaggioni, I., Peltier, A. C., Singer, W., Low, P. A., Goldstein, D. S., Gibbons, C. H., Freeman, R., Robertson, D., & Autonomic Disorders Consortium. (2018). Orthostatic heart rate changes in patients with autonomic failure caused by neurodegenerative synucleinopathies. *Annals of Neurology*, 83(3), 522–531. <https://doi.org/10.1002/ana.25170>
- Noyce, A. J., Bestwick, J. P., Silveira-Moriyama, L., Hawkes, C. H., Giovannoni, G., Lees, A. J., & Schrag, A. (2012). Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Annals of Neurology*, 72(6), 893–901. <https://doi.org/10.1002/ana.23687>
- Oeda, T., Umemura, A., Mori, Y., Tomita, S., Kohsaka, M., Park, K., Inoue, K., Fujimura, H., Hasegawa, H., Sugiyama, H., & Sawada, H. (2015a). Impact of glucocerebrosidase mutations on motor and nonmotor complications in Parkinson's disease. *Neurobiology of Aging*, 36(12), 3306–3313. <https://doi.org/10.1016/j.neurobiolaging.2015.08.027>
- Oeda, T., Umemura, A., Mori, Y., Tomita, S., Kohsaka, M., Park, K., Inoue, K., Fujimura, H., Hasegawa, H., Sugiyama, H., & Sawada, H. (2015b). Impact of glucocerebrosidase mutations on motor and nonmotor complications in Parkinson's disease. *Neurobiology of Aging*, 36(12), 3306–3313. <https://doi.org/10.1016/j.neurobiolaging.2015.08.027>
- Ou, R., Lin, J., Liu, K., Jiang, Z., Wei, Q., Hou, Y., Zhang, L., Cao, B., Zhao, B., Song, W., & Shang, H. (2020). Evolution of Apathy in Early Parkinson's Disease: A 4-Years Prospective Cohort Study. *Frontiers in Aging Neuroscience*, 12, 620762. <https://doi.org/10.3389/fnagi.2020.620762>
- Pagano, G., Ferrara, N., Brooks, D. J., & Pavese, N. (2016). Age at onset and Parkinson disease phenotype. *Neurology*, 86(15), 1400–1407. <https://doi.org/10.1212/WNL.0000000000002461>
- Pal, G., Mangone, G., Hill, E. J., Ouyang, B., Liu, Y., Lythe, V., Ehrlich, D., Saunders-Pullman, R., Shanker, V., Bressman, S., Alcalay, R. N., Garcia, P., Marder, K. S., Aasly, J., Mouradian, M. M., Link, S., Rosenbaum, M., Anderson, S., Bernard, B., ... Goetz, C. G. (2022). Parkinson Disease and Subthalamic Nucleus Deep Brain Stimulation: Cognitive Effects in GBA Mutation Carriers. *Annals of Neurology*, 91(3), 424–435. <https://doi.org/10.1002/ana.26302>
- Pan, T., Zhu, J., Hwu, W.-J., & Jankovic, J. (2012). The role of alpha-synuclein in melanin synthesis in melanoma and dopaminergic neuronal cells. *PloS One*, 7(9), e45183. <https://doi.org/10.1371/journal.pone.0045183>
- Pang, S. Y.-Y., Ho, P. W.-L., Liu, H.-F., Leung, C.-T., Li, L., Chang, E. E. S., Ramsden, D. B., & Ho, S.-L. (2019). The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease. *Translational Neurodegeneration*, 8(1), 23. <https://doi.org/10.1186/s40035-019-0165-9>
- Parkkinen, L., Kauppinen, T., Pirttilä, T., Autere, J. M., & Alafuzoff, I. (2005). Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. *Annals of Neurology*, 57(1), 82–91. <https://doi.org/10.1002/ana.20321>

- Paudel, Y. N., Angelopoulou, E., Piperi, C., Shaikh, Mohd. F., & Othman, I. (2020). Emerging neuroprotective effect of metformin in Parkinson's disease: A molecular crosstalk. *Pharmacological Research*, 152, 104593. <https://doi.org/10.1016/j.phrs.2019.104593>
- Pavy-Le Traon, A., Amarenco, G., Duerr, S., Kaufmann, H., Lahrmann, H., Shaftman, S. R., Tison, F., Wenning, G. K., Goetz, C. G., Poewe, W., Sampaio, C., Schrag, A., Stebbins, G. T., & Rascol, O. (2011). The Movement Disorders task force review of dysautonomia rating scales in Parkinson's disease with regard to symptoms of orthostatic hypotension. *Movement Disorders*, 26(11), 1985–1992. <https://doi.org/10.1002/mds.23742>
- Pavy-Le Traon, A., Piedvache, A., Perez-Lloret, S., Calandra-Buonaura, G., Cochen-De Cock, V., Colosimo, C., Cortelli, P., Debs, R., Duerr, S., Fanciulli, A., Foubert-Samier, A., Gerdelat, A., Gurevich, T., Krismer, F., Poewe, W., Tison, F., Tranchant, C., Wenning, G., Rascol, O., ... European MSA Study Group. (2016). New insights into orthostatic hypotension in multiple system atrophy: a European multicentre cohort study. *Journal of Neurology, Neurosurgery, and Psychiatry*, 87(5), 554–561. <https://doi.org/10.1136/jnnp-2014-309999>
- Petrucci, S., Ginevrino, M., Trezzi, I., Monfrini, E., Ricciardi, L., Albanese, A., Avenali, M., Barone, P., Bentivoglio, A. R., Bonifati, V., Bove, F., Bonanni, L., Brusa, L., Cereda, C., Cossu, G., Criscuolo, C., Dati, G., De Rosa, A., Eleopra, R., ... ITA-GENE-PD Study Group. (2020). GBA-Related Parkinson's Disease: Dissection of Genotype-Phenotype Correlates in a Large Italian Cohort. *Movement Disorders : Official Journal of the Movement Disorder Society*, 35(11), 2106–2111. <https://doi.org/10.1002/mds.28195>
- Petrucci, S., Ginevrino, M., & Valente, E. M. (2016). Phenotypic spectrum of alpha-synuclein mutations: New insights from patients and cellular models. *Parkinsonism & Related Disorders*, 22, S16–S20. <https://doi.org/10.1016/j.parkreldis.2015.08.015>
- Pezzoli, G., & Cereda, E. (2013). Exposure to pesticides or solvents and risk of Parkinson disease. *Neurology*, 80(22), 2035–2041. <https://doi.org/10.1212/WNL.0b013e318294b3c8>
- Pfeiffer, R. F. (2020). Autonomic Dysfunction in Parkinson's Disease. *Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics*, 17(4), 1464–1479. <https://doi.org/10.1007/s13311-020-00897-4>
- Picillo, M., Palladino, R., Barone, P., Erro, R., Colosimo, C., Marconi, R., Morgante, L., Antonini, A., & PRIAMO Study Group. (2017). The PRIAMO study: urinary dysfunction as a marker of disease progression in early Parkinson's disease. *European Journal of Neurology*, 24(6), 788–795. <https://doi.org/10.1111/ene.13290>
- Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkman, J., Schrag, A.-E., & Lang, A. E. (2017). Parkinson disease. *Nature Reviews. Disease Primers*, 3, 17013. <https://doi.org/10.1038/nrdp.2017.13>
- Poirier, A.-A., Aubé, B., Côté, M., Morin, N., Di Paolo, T., & Soulet, D. (2016). Gastrointestinal Dysfunctions in Parkinson's Disease: Symptoms and Treatments. *Parkinson's Disease*, 2016, 6762528. <https://doi.org/10.1155/2016/6762528>
- Polymeropoulos, M. H., Higgins, J. J., Golbe, L. I., Johnson, W. G., Ide, S. E., Di Iorio, G., Sanges, G., Stenroos, E. S., Pho, L. T., Schaffer, A. A., Lazzarini, A. M., Nussbaum, R. L., & Duvoisin, R. C. (1996). Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. *Science (New York, N.Y.)*, 274(5290), 1197–1199. <https://doi.org/10.1126/science.274.5290.1197>
- Pont-Sunyer, C., Hotter, A., Gaig, C., Seppi, K., Compta, Y., Katzenschlager, R., Mas, N., Hofeneder, D., Brücke, T., Bayés, A., Wenzel, K., Infante, J., Zach, H., Pirker, W., Posada, I. J., Álvarez, R., Ispierto, L., De

- Fàbregues, O., Callén, A., ... Tolosa, E. (2015). The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). *Movement Disorders : Official Journal of the Movement Disorder Society*, 30(2), 229–237. <https://doi.org/10.1002/mds.26077>
- Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, 30(12), 1591–1601. <https://doi.org/10.1002/mds.26424>
- Postuma, R. B., Gagnon, J.-F., Pelletier, A., & Montplaisir, J. (2013). Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies. *Movement Disorders : Official Journal of the Movement Disorder Society*, 28(5), 597–604. <https://doi.org/10.1002/mds.25445>
- Pramstaller, P. P., Schlossmacher, M. G., Jacques, T. S., Scaravilli, F., Eskelson, C., Pepivani, I., Hedrich, K., Adel, S., Gonzales-McNeal, M., Hilker, R., Kramer, P. L., & Klein, C. (2005). Lewy body Parkinson's disease in a large pedigree with 77 Parkin mutation carriers. *Annals of Neurology*, 58(3), 411–422. <https://doi.org/10.1002/ana.20587>
- Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. L. (2014). The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Movement Disorders : Official Journal of the Movement Disorder Society*, 29(13), 1583–1590. <https://doi.org/10.1002/mds.25945>
- Quik, M., Perez, X. A., & Bordia, T. (2012). Nicotine as a potential neuroprotective agent for Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, 27(8), 947–957. <https://doi.org/10.1002/mds.25028>
- Rana, H. Q., Balwani, M., Bier, L., & Alcalay, R. N. (2013). Age-specific Parkinson disease risk in GBA mutation carriers: information for genetic counseling. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, 15(2), 146–149. <https://doi.org/10.1038/gim.2012.107>
- Ren, X., & Chen, J.-F. (2020). Caffeine and Parkinson's Disease: Multiple Benefits and Emerging Mechanisms. *Frontiers in Neuroscience*, 14. <https://doi.org/10.3389/fnins.2020.602697>
- Repici M, Giorgini F. DJ-1 in Parkinson's Disease: Clinical Insights and Therapeutic Perspectives. *J Clin Med*. 2019 Sep 3;8(9):1377. doi: 10.3390/jcm8091377. PMID: 31484320; PMCID: PMC6780414.
- Ricciardi, L., Petrucci, S., Di Giuda, D., Serra, L., Spanò, B., Sensi, M., Ginevrino, M., Cocciolillo, F., Bozzali, M., Valente, E. M., & Fasano, A. (2016). The Contursi Family 20 Years Later: Intrafamilial Phenotypic Variability of the SNCA p.A53T Mutation. *Movement Disorders : Official Journal of the Movement Disorder Society*, 31(2), 257–258. <https://doi.org/10.1002/mds.26549>
- Rideout, H. J., & Stefanis, L. (2014). The neurobiology of LRRK2 and its role in the pathogenesis of Parkinson's disease. *Neurochemical Research*, 39(3), 576–592. <https://doi.org/10.1007/s11064-013-1073-5>
- Rietdijk, C. D., Perez-Pardo, P., Garssen, J., van Wezel, R. J. A., & Kraneveld, A. D. (2017). Exploring Braak's Hypothesis of Parkinson's Disease. *Frontiers in Neurology*, 8. <https://doi.org/10.3389/fneur.2017.00037>
- Ross, O. A., Toft, M., Whittle, A. J., Johnson, J. L., Papapetropoulos, S., Mash, D. C., Litvan, I., Gordon, M. F., Wszolek, Z. K., Farrer, M. J., & Dickson, D. W. (2006). Lrrk2 and Lewy body disease. *Annals of Neurology*, 59(2), 388–393. <https://doi.org/10.1002/ana.20731>

- Rossi, M., Castillo-Torres, S. A., & Merello, M. (2022). Early motor response to dopamine replacement therapy in Parkinson's disease patients carrying GBA variants. *Journal of the Neurological Sciences*, 440, 120354. <https://doi.org/10.1016/j.jns.2022.120354>
- Ruskey, J. A., Greenbaum, L., Roncière, L., Alam, A., Spiegelman, D., Liong, C., Levy, O. A., Waters, C., Fahn, S., Marder, K. S., Chung, W., Yahalom, G., Israeli-Korn, S., Livneh, V., Fay-Karmon, T., Alcalay, R. N., Hassin-Baer, S., & Gan-Or, Z. (2019). Increased yield of full GBA sequencing in Ashkenazi Jews with Parkinson's disease. *European Journal of Medical Genetics*, 62(1), 65–69. <https://doi.org/10.1016/j.ejmg.2018.05.005>
- Sakakibara, R., Hattori, T., Uchiyama, T., Kita, K., Asahina, M., Suzuki, A., & Yamanishi, T. (2000). Urinary dysfunction and orthostatic hypotension in multiple system atrophy: which is the more common and earlier manifestation? *Journal of Neurology, Neurosurgery, and Psychiatry*, 68(1), 65–69. <https://doi.org/10.1136/jnnp.68.1.65>
- Sakakibara, R., Tateno, F., Kishi, M., Tsuyuzaki, Y., Uchiyama, T., & Yamamoto, T. (2012). Pathophysiology of bladder dysfunction in Parkinson's disease. *Neurobiology of Disease*, 46(3), 565–571. <https://doi.org/10.1016/j.nbd.2011.10.002>
- Santa Rosa Malcher, C. M., Roberto da Silva Gonçalves Oliveira, K., Fernandes Caldato, M. C., Lopes Dos Santos Lobato, B., da Silva Pedroso, J., & de Tubino Scanavino, M. (2021). Sexual Disorders and Quality of Life in Parkinson's Disease. *Sexual Medicine*, 9(1), 100280. <https://doi.org/10.1016/j.esxm.2020.10.008>
- Sauerbier, A., & Ray Chaudhuri, K. (2014). Non-motor symptoms: the core of multi-morbid Parkinson's disease. *British Journal of Hospital Medicine (London, England : 2005)*, 75(1), 18–24. <https://doi.org/10.12968/hmed.2014.75.1.18>
- Savica, R., Boeve, B. F., & Mielke, M. M. (2018). When Do α -Synucleinopathies Start? An Epidemiological Timeline: A Review. *JAMA Neurology*, 75(4), 503–509. <https://doi.org/10.1001/jamaneurol.2017.4243>
- Schapira, A. H. V., Chaudhuri, K. R., & Jenner, P. (2017). Non-motor features of Parkinson disease. *Nature Reviews Neuroscience*, 18(7), 435–450. <https://doi.org/10.1038/nrn.2017.62>
- Schapira, A. H. V., Chaudhuri, K. R., & Jenner, P. (2017). Non-motor features of Parkinson disease. *Nature Reviews. Neuroscience*, 18(7), 435–450. <https://doi.org/10.1038/nrn.2017.62>
- Schöndorf, D. C., Aureli, M., McAllister, F. E., Hindley, C. J., Mayer, F., Schmid, B., Sardi, S. P., Valsecchi, M., Hoffmann, S., Schwarz, L. K., Hedrich, U., Berg, D., Shihabuddin, L. S., Hu, J., Pruszek, J., Gygi, S. P., Sonnino, S., Gasser, T., & Deleidi, M. (2014). iPSC-derived neurons from GBA1-associated Parkinson's disease patients show autophagic defects and impaired calcium homeostasis. *Nature Communications*, 5, 4028. <https://doi.org/10.1038/ncomms5028>
- Seidl, S. E., Santiago, J. A., Bilyk, H., & Potashkin, J. A. (2014). The emerging role of nutrition in Parkinson's disease. *Frontiers in Aging Neuroscience*, 6, 36. <https://doi.org/10.3389/fnagi.2014.00036>
- Setó-Salvia, N., Pagonabarraga, J., Houlden, H., Pascual-Sedano, B., Dols-Icardo, O., Tucci, A., Paisán-Ruiz, C., Campolongo, A., Antón-Aguirre, S., Martín, I., Muñoz, L., Bufill, E., Vilageliu, L., Grinberg, D., Cozar, M., Blesa, R., Lleó, A., Hardy, J., Kulisevsky, J., & Clarimón, J. (2012). Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. *Movement Disorders : Official Journal of the Movement Disorder Society*, 27(3), 393–399. <https://doi.org/10.1002/mds.24045>
- Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. *Frontiers in Public Health*, 5, 258. <https://doi.org/10.3389/fpubh.2017.00258>

- Shaffer, F., McCraty, R., & Zerr, C. L. (2014). A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Frontiers in Psychology*, 5, 1040. <https://doi.org/10.3389/fpsyg.2014.01040>
- Siddiqui, I. J., Pervaiz, N., & Abbasi, A. A. (2016). The Parkinson Disease gene SNCA: Evolutionary and structural insights with pathological implication. *Scientific Reports*, 6, 24475. <https://doi.org/10.1038/srep24475>
- Sidransky, E., Nalls, M. A., Aasly, J. O., Aharon-Peretz, J., Annesi, G., Barbosa, E. R., Bar-Shira, A., Berg, D., Bras, J., Brice, A., Chen, C.-M., Clark, L. N., Condroyer, C., De Marco, E. V., Dürr, A., Eblan, M. J., Fahn, S., Farrer, M. J., Fung, H.-C., ... Ziegler, S. G. (2009a). Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *The New England Journal of Medicine*, 361(17), 1651–1661. <https://doi.org/10.1056/NEJMoa0901281>
- Sidransky, E., Nalls, M. A., Aasly, J. O., Aharon-Peretz, J., Annesi, G., Barbosa, E. R., Bar-Shira, A., Berg, D., Bras, J., Brice, A., Chen, C.-M., Clark, L. N., Condroyer, C., De Marco, E. V., Dürr, A., Eblan, M. J., Fahn, S., Farrer, M. J., Fung, H.-C., ... Ziegler, S. G. (2009b). Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *The New England Journal of Medicine*, 361(17), 1651–1661. <https://doi.org/10.1056/NEJMoa0901281>
- Sidransky, E., Nalls, M. A., Aasly, J. O., Aharon-Peretz, J., Annesi, G., Barbosa, E. R., Bar-Shira, A., Berg, D., Bras, J., Brice, A., Chen, C.-M., Clark, L. N., Condroyer, C., De Marco, E. V., Dürr, A., Eblan, M. J., Fahn, S., Farrer, M. J., Fung, H.-C., ... Ziegler, S. G. (2009c). Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *The New England Journal of Medicine*, 361(17), 1651–1661. <https://doi.org/10.1056/NEJMoa0901281>
- Simuni, T., Brumm, M. C., Uribe, L., Caspell-Garcia, C., Coffey, C. S., Siderowf, A., Alcalay, R. N., Trojanowski, J. Q., Shaw, L. M., Seibyl, J., Singleton, A., Toga, A. W., Galasko, D., Foroud, T., Nudelman, K., Tosun-Turgut, D., Poston, K., Weintraub, D., Mollenhauer, B., ... Parkinson's Progression Markers Initiative Investigators. (2020). Clinical and Dopamine Transporter Imaging Characteristics of Leucine Rich Repeat Kinase 2 (LRRK2) and Glucosylceramidase Beta (GBA) Parkinson's Disease Participants in the Parkinson's Progression Markers Initiative: A Cross-Sectional Study. *Movement Disorders : Official Journal of the Movement Disorder Society*, 35(5), 833–844. <https://doi.org/10.1002/mds.27989>
- Smith, G. D., & Mathias, C. J. (1995). Postural hypotension enhanced by exercise in patients with chronic autonomic failure. *QJM : Monthly Journal of the Association of Physicians*, 88(4), 251–256.
- Smith, L., & Schapira, A. H. V. (2022). GBA Variants and Parkinson Disease: Mechanisms and Treatments. *Cells*, 11(8), 1261. <https://doi.org/10.3390/cells11081261>
- Sommer, S., Aral-Becher, B., & Jost, W. (2011). Nondipping in Parkinson's disease. *Parkinson's Disease*, 2011, 897586. <https://doi.org/10.4061/2011/897586>
- Spillantini, M. G., Schmidt, M. L., Lee, V. M., Trojanowski, J. Q., Jakes, R., & Goedert, M. (1997). Alpha-synuclein in Lewy bodies. *Nature*, 388(6645), 839–840. <https://doi.org/10.1038/42166>
- Sportelli, C., Urso, D., Jenner, P., & Chaudhuri, K. R. (2020). Metformin as a Potential Neuroprotective Agent in Prodromal Parkinson's Disease-Viewpoint. *Frontiers in Neurology*, 11, 556. <https://doi.org/10.3389/fneur.2020.00556>
- Stojkovska, I., Wani, W. Y., Zunke, F., Belur, N. R., Pavlenko, E. A., Mwenda, N., Sharma, K., Francelle, L., & Mazzulli, J. R. (2022). Rescue of α -synuclein aggregation in Parkinson's patient neurons by synergistic enhancement of ER proteostasis and protein trafficking. *Neuron*, 110(3), 436–451.e11. <https://doi.org/10.1016/j.neuron.2021.10.032>

- Stoker, T. B., Camacho, M., Winder-Rhodes, S., Liu, G., Scherzer, C. R., Foltynie, T., Evans, J., Breen, D. P., Barker, R. A., & Williams-Gray, C. H. (2020a). Impact of GBA1 variants on long-term clinical progression and mortality in incident Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 91(7), 695–702. <https://doi.org/10.1136/jnnp-2020-322857>
- Stoker, T. B., Camacho, M., Winder-Rhodes, S., Liu, G., Scherzer, C. R., Foltynie, T., Evans, J., Breen, D. P., Barker, R. A., & Williams-Gray, C. H. (2020b). Impact of GBA1 variants on long-term clinical progression and mortality in incident Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 91(7), 695–702. <https://doi.org/10.1136/jnnp-2020-322857>
- Suzuki, M., Nakamura, T., Hirayama, M., Ueda, M., Katsuno, M., & Sobue, G. (2017). Cardiac parasympathetic dysfunction in the early phase of Parkinson's disease. *Journal of Neurology*, 264(2), 333–340. <https://doi.org/10.1007/s00415-016-8348-0>
- Suzuki, M., Sango, K., Wada, K., & Nagai, Y. (2018). Pathological role of lipid interaction with α -synuclein in Parkinson's disease. *Neurochemistry International*, 119, 97–106. <https://doi.org/10.1016/j.neuint.2017.12.014>
- Tandon, R., & Pradhan, S. (2015). Autonomic predominant multiple system atrophy in the context of Parkinsonian and cerebellar variants. *Clinical Neurology and Neurosurgery*, 130, 110–113. <https://doi.org/10.1016/j.clineuro.2014.09.018>
- Tansey, M. G., Wallings, R. L., Houser, M. C., Herrick, M. K., Keating, C. E., & Joers, V. (2022). Inflammation and immune dysfunction in Parkinson disease. *Nature Reviews Immunology*, 22(11), 657–673. <https://doi.org/10.1038/s41577-022-00684-6>
- Thaisetthawatkul, P., Boeve, B. F., Benarroch, E. E., Sandroni, P., Ferman, T. J., Petersen, R., & Low, P. A. (2004a). Autonomic dysfunction in dementia with Lewy bodies. *Neurology*, 62(10), 1804–1809. <https://doi.org/10.1212/01.wnl.0000125192.69777.6d>
- Thaisetthawatkul, P., Boeve, B. F., Benarroch, E. E., Sandroni, P., Ferman, T. J., Petersen, R., & Low, P. A. (2004b). Autonomic dysfunction in dementia with Lewy bodies. *Neurology*, 62(10), 1804–1809. <https://doi.org/10.1212/01.wnl.0000125192.69777.6d>
- Tyson, T., Steiner, J. A., & Brundin, P. (2016). Sorting out release, uptake and processing of alpha-synuclein during prion-like spread of pathology. *Journal of Neurochemistry*, 139(S1), 275–289. <https://doi.org/10.1111/jnc.13449>
- Tzur, I., Izhakian, S., & Gorelik, O. (2019). Orthostatic hypotension: definition, classification and evaluation. *Blood Pressure*, 28(3), 146–156. <https://doi.org/10.1080/08037051.2019.1604067>
- Usnich, T., Hanssen, H., Lohmann, K., Lohse, C., Klein, C., Kasten, M., Brüggemann, N., & EPIPARK Study Group. (2022). Pronounced Orthostatic Hypotension in GBA-Related Parkinson's Disease. *Journal of Parkinson's Disease*, 12(5), 1539–1544. <https://doi.org/10.3233/JPD-223197>
- Van Bogaert L, & Froehlich A. (n.d.). *Un cas de maladie de Gaucher de l'adulte avec syndrome de Raynaud, pigmentation, et rigidité du type extra-pyramidal aux membres inférieurs.*
- van de Warrenburg, B. P., Lammens, M., Lücking, C. B., Denèfle, P., Wesseling, P., Booij, J., Praamstra, P., Quinn, N., Brice, A., & Horstink, M. W. (2001). Clinical and pathologic abnormalities in a family with parkinsonism and parkin gene mutations. *Neurology*, 56(4), 555–557. <https://doi.org/10.1212/wnl.56.4.555>
- Van Den Eeden, S. K., Tanner, C. M., Bernstein, A. L., Fross, R. D., Leimpeter, A., Bloch, D. A., & Nelson, L. M.

- (2003). Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *American Journal of Epidemiology*, 157(11), 1015–1022. <https://doi.org/10.1093/aje/kwg068>
- Van der Velden, R. M. J., Broen, M. P. G., Kuijf, M. L., & Leentjens, A. F. G. (2018). Frequency of mood and anxiety fluctuations in Parkinson's disease patients with motor fluctuations: A systematic review. *Movement Disorders : Official Journal of the Movement Disorder Society*, 33(10), 1521–1527. <https://doi.org/10.1002/mds.27465>
- van Veen, S., Martin, S., Van den Haute, C., Benoy, V., Lyons, J., Vanhoutte, R., Kahler, J. P., Decuypere, J.-P., Gelders, G., Lambie, E., Zielich, J., Swinnen, J. V., Annaert, W., Agostinis, P., Ghesquière, B., Verhelst, S., Baekelandt, V., Eggermont, J., & Vangheluwe, P. (2020). ATP13A2 deficiency disrupts lysosomal polyamine export. *Nature*, 578(7795), 419–424. <https://doi.org/10.1038/s41586-020-1968-7>
- van Wamelen, D. J., Leta, V., Podlowska, A. M., Wan, Y.-M., Krbot, K., Jaakkola, E., Martinez-Martin, P., Rizos, A., Parry, M., Metta, V., & Ray Chaudhuri, K. (2019). Exploring hyperhidrosis and related thermoregulatory symptoms as a possible clinical identifier for the dysautonomic subtype of Parkinson's disease. *Journal of Neurology*, 266(7), 1736–1742. <https://doi.org/10.1007/s00415-019-09325-w>
- Velseboer, D. C., de Haan, R. J., Wieling, W., Goldstein, D. S., & de Bie, R. M. A. (2011). Prevalence of orthostatic hypotension in Parkinson's disease: A systematic review and meta-analysis. *Parkinsonism & Related Disorders*, 17(10), 724–729. <https://doi.org/10.1016/j.parkreldis.2011.04.016>
- Vilariño-Güell, C., Wider, C., Ross, O. A., Dachsel, J. C., Kachergus, J. M., Lincoln, S. J., Soto-Ortolaza, A. I., Cobb, S. A., Wilhoite, G. J., Bacon, J. A., Behrouz, B., Melrose, H. L., Hentati, E., Puschmann, A., Evans, D. M., Conibear, E., Wasserman, W. W., Aasly, J. O., Burkhard, P. R., ... Farrer, M. J. (2011). VPS35 mutations in Parkinson disease. *American Journal of Human Genetics*, 89(1), 162–167. <https://doi.org/10.1016/j.ajhg.2011.06.001>
- Vogel, E. R., Sandroni, P., & Low, P. A. (2005). Blood pressure recovery from Valsalva maneuver in patients with autonomic failure. *Neurology*, 65(10), 1533–1537. <https://doi.org/10.1212/01.wnl.0000184504.13173.ef>
- Vogiatzi, T., Xilouri, M., Vekrellis, K., & Stefanis, L. (2008). Wild type alpha-synuclein is degraded by chaperone-mediated autophagy and macroautophagy in neuronal cells. *The Journal of Biological Chemistry*, 283(35), 23542–23556. <https://doi.org/10.1074/jbc.M801992200>
- Volpicelli-Daley, L., & Brundin, P. (2018). Prion-like propagation of pathology in Parkinson disease. *Handbook of Clinical Neurology*, 153, 321–335. <https://doi.org/10.1016/B978-0-444-63945-5.00017-9>
- Wakabayashi, K., Takahashi, H., Takeda, S., Ohama, E., & Ikuta, F. (1989). Lewy bodies in the enteric nervous system in Parkinson's disease. *Archives of Histology and Cytology*, 52 Suppl, 191–194. https://doi.org/10.1679/aohc.52.suppl_191
- Wakabayashi, K., Tanji, K., Mori, F., & Takahashi, H. (2007). The Lewy body in Parkinson's disease: Molecules implicated in the formation and degradation of α -synuclein aggregates. *Neuropathology*, 27(5), 494–506. <https://doi.org/10.1111/j.1440-1789.2007.00803.x>
- Wang, Q., Liu, Y., & Zhou, J. (2015). Neuroinflammation in Parkinson's disease and its potential as therapeutic target. *Translational Neurodegeneration*, 4, 19. <https://doi.org/10.1186/s40035-015-0042-0>
- Weintraub, D., Aarsland, D., Chaudhuri, K. R., Dobkin, R. D., Leentjens, A. F., Rodriguez-Violante, M., & Schrag, A. (2022). The neuropsychiatry of Parkinson's disease: advances and challenges. *The Lancet*

Neurology, 21(1), 89–102. [https://doi.org/10.1016/S1474-4422\(21\)00330-6](https://doi.org/10.1016/S1474-4422(21)00330-6)

Welsh, M., Hung, L., & Waters, C. H. (1997). Sexuality in women with Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, 12(6), 923–927. <https://doi.org/10.1002/mds.870120614>

Wenning, G. K., Granata, R., Krismer, F., Dürr, S., Seppi, K., Poewe, W., Bleasdale-Barr, K., & Mathias, C. J. (2012). Orthostatic hypotension is differentially associated with the cerebellar versus the parkinsonian variant of multiple system atrophy: a comparative study. *Cerebellum (London, England)*, 11(1), 223–226. <https://doi.org/10.1007/s12311-011-0299-5>

Wenning, G. K., Shephard, B., Hawkes, C., Petrukevitch, A., Lees, A., & Quinn, N. (1995). Olfactory function in atypical parkinsonian syndromes. *Acta Neurologica Scandinavica*, 91(4), 247–250. <https://doi.org/10.1111/j.1600-0404.1995.tb06998.x>

Williams, E. T., Chen, X., & Moore, D. J. (2017a). VPS35, the Retromer Complex and Parkinson's Disease. *Journal of Parkinson's Disease*, 7(2), 219–233. <https://doi.org/10.3233/JPD-161020>

Williams, E. T., Chen, X., & Moore, D. J. (2017b). VPS35, the Retromer Complex and Parkinson's Disease. *Journal of Parkinson's Disease*, 7(2), 219–233. <https://doi.org/10.3233/JPD-161020>

Williams, E. T., Chen, X., & Moore, D. J. (2017c). VPS35, the Retromer Complex and Parkinson's Disease. *Journal of Parkinson's Disease*, 7(2), 219–233. <https://doi.org/10.3233/JPD-161020>

Willis, A. W., Evanoff, B. A., Lian, M., Galarza, A., Wegrzyn, A., Schootman, M., & Racette, B. A. (2010). Metal emissions and urban incident Parkinson disease: a community health study of Medicare beneficiaries by using geographic information systems. *American Journal of Epidemiology*, 172(12), 1357–1363. <https://doi.org/10.1093/aje/kwq303>

Winder-Rhodes, S. E., Evans, J. R., Ban, M., Mason, S. L., Williams-Gray, C. H., Foltynie, T., Duran, R., Mencacci, N. E., Sawcer, S. J., & Barker, R. A. (2013). Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. *Brain : A Journal of Neurology*, 136(Pt 2), 392–399. <https://doi.org/10.1093/brain/aws318>

Winge, K., Friberg, L., Werdelin, L., Nielsen, K. K., & Stimpel, H. (2005). Relationship between nigrostriatal dopaminergic degeneration, urinary symptoms, and bladder control in Parkinson's disease. *European Journal of Neurology*, 12(11), 842–850. <https://doi.org/10.1111/j.1468-1331.2005.01087.x>

Winslow, A. R., Chen, C.-W., Corrochano, S., Acevedo-Arozena, A., Gordon, D. E., Peden, A. A., Lichtenberg, M., Menzies, F. M., Ravikumar, B., Imarisio, S., Brown, S., O'Kane, C. J., & Rubinsztein, D. C. (2010). α -Synuclein impairs macroautophagy: implications for Parkinson's disease. *Journal of Cell Biology*, 190(6), 1023–1037. <https://doi.org/10.1083/jcb.201003122>

Yeo, L., Singh, R., Gundeti, M., Barua, J. M., & Masood, J. (2012). Urinary tract dysfunction in Parkinson's disease: a review. *International Urology and Nephrology*, 44(2), 415–424. <https://doi.org/10.1007/s11255-011-9969-y>

Zaccai, J., Brayne, C., McKeith, I., Matthews, F., Ince, P. G., & MRC Cognitive Function, A. N. S. (2008). Patterns and stages of alpha-synucleinopathy: Relevance in a population-based cohort. *Neurology*, 70(13), 1042–1048. <https://doi.org/10.1212/01.wnl.0000306697.48738.b6>

Zhang, L., Wang, J., Wang, J., Yang, B., He, Q., & Weng, Q. (2020). Role of DJ-1 in Immune and Inflammatory Diseases. *Frontiers in Immunology*, 11, 994. <https://doi.org/10.3389/fimmu.2020.00994>

Zhou, C., Guo, T., Bai, X., Wu, J., Gao, T., Guan, X., Liu, X., Gu, L., Huang, P., Xuan, M., Gu, Q., Xu, X., Zhang, B.,

- & Zhang, M. (2021). Locus coeruleus degeneration is associated with disorganized functional topology in Parkinson's disease. *NeuroImage. Clinical*, 32, 102873. <https://doi.org/10.1016/j.nicl.2021.102873>
- Zokaei, N., McNeill, A., Proukakis, C., Beavan, M., Jarman, P., Korlipara, P., Hughes, D., Mehta, A., Hu, M. T. M., Schapira, A. H. V., & Husain, M. (2014). Visual short-term memory deficits associated with GBA mutation and Parkinson's disease. *Brain : A Journal of Neurology*, 137(Pt 8), 2303–2311. <https://doi.org/10.1093/brain/awu143>
- Zunke, F., Moise, A. C., Belur, N. R., Gelyana, E., Stojkovska, I., Dzaferbegovic, H., Toker, N. J., Jeon, S., Fredriksen, K., & Mazzulli, J. R. (2018). Reversible Conformational Conversion of α -Synuclein into Toxic Assemblies by Glucosylceramide. *Neuron*, 97(1), 92-107.e10. <https://doi.org/10.1016/j.neuron.2017.12.012>