Contents

1 Introduction

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Neurological and neurodegenerative diseases have significant effects on functionality, independency, and overall quality of life of a patient. As the degenerative progression manifests throughout the course of these diseases, patients develop more severe symptoms, and as a consequence, many aspects of the patients' health are compromised. Unfortunately, in spite of the advance of contemporary medical technology, these diseases are, still, incurable, and none of the treatments available can slow down the degenerative process.[1]

Researchers have been focusing on achieving a deeper understanding of the mechanisms and processes of these neurological diseases and on advancing imaging techniques such as MRI. Despite ongoing research, the causes of most of these conditions are not completely known, and their pathophysiology remains poorly understood.

Parkinson disease, for example, is a chronic neuropathological disorder involving progressive degeneration of dopaminergic and non-dopaminergic neurons present in the substantia nigra.[2] This neuronal degenerative activity causes a loss of voluntary motor control, and patients develop characteristic motor symptoms.[2,3]

Multiple sclerosis (MS) is another example of a chronic autoimmune disease that affects the central nervous system (CNS), and it is characterized by the inflammation, demyelination, and scarring (sclerosis: Greek for scarring) of nerve tissues.[4,5,6] It is the most common cause of neurological disability in young adults[7] with an overall increasing prevalence worldwide regardless of age.[8]

Amyotrophic lateral sclerosis (ALS), the most common fatal neurodegenerative disease, is another example of a progressive disorder in this series.[9] ALS is a non-cell-autonomous disease that targets the motor neurons and the surrounding glia.[10]

Alzheimer disease (AD) is known as the common cause of dementia, with its insidious onset causing the progressive impairment of memory and other cognitive functions. Alzheimer's diagnosis relies primarily on the mental decline, with no motor, sensory, or coordination problems evident in the early stages. AD is a progressive, degenerative brain disease, and it affects up to 70% of people that suffer from dementia, with an estimated 115.4 million people predicted as sufferers by the year 2050.[11] Its incidence and prevalence is linked to the increase in age.[12]

This book then reviews "Stroke," which, despite being a preventable and treatable disease, has become a global epidemic of the 21st century. In 2010, an estimated 16.9 million stroke incidents occurred, of which 5.9 million lives were lost; this makes stroke the second leading cause of death after ischemic heart disease.[13] Caused by an inadequate blood supply to the brain, cerebrovascular accident or stroke can potentially lead to functional impairments, severe brain damage, and, consequently, death.[14] Common long-term effects include contralateral limb paralysis, memory loss, and cognitive impairment.[14]

Epilepsy is one of the most prevalent neurological disorders presenting with recurrent episodes of seizures, affecting an estimated 50 million individuals worldwide. They are regarded as a collection of conditions with different pathophysiologies, multiple manifestations, and diverse aetiologies.[15] It is caused by the abnormal electrical activity of the brain, specifically, uncontrolled discharges from groups of neurons—hyperexcitability of the neurons of the cerebral hemispheres.[16] Epilepsy is a disorder that can present at all ages, affecting both males and females, with males at a slightly higher risk.[16] Due to lack of consciousness following an epileptic attack, patients may seriously injure themselves, potentially leading to death. Epileptic patients may also suffer from stigma, and as a result educational and vocational impairments, which heavily affect their quality of life.[16] Therefore, in addition to an appropriate management and medication approach, a holistic

approach must be adopted—one that addresses social, educational, and psychological issues that the patient may face.

Later in this book, we also look into "Myasthenia gravis" (MG) as an autoimmune disorder of the neuromuscular junction, which is hallmarked by fatigability and weakness of all striated muscles. A health care provider is likely to encounter more than one patient with this disease throughout their career, as approximately 1 in 10,000 people carry the condition.[17] The manifestation of MG influences practitioners' approach toward treatment of patients requiring special management considerations in order to ensure safe and optimal treatment. MG is an autoimmune neuromuscular disorder marked by fluctuating degrees of weakness of the voluntary (skeletal) muscles of the body, with deterioration during periods of action and improvement following periods of rest.[18]

In the final chapter, we describe and discuss a commonly occurring medical and dental condition, "Facial Palsy." The facial nerve (cranial nerve VII) is composed of two roots, a motor and sensory root.[19] The large motor root carries the motor fibers to the muscles of facial expression and mastication. The sensory root carries general sensory fibers to parts of the external ear and the special sensation of taste. Facial paralysis varies depending on the level of facial nerve lesion. This phenomenon can be reversed spontaneously or via clinical or surgical treatment. About 20% of patients develop some form of sequelae, with unilateral and bilateral complete paralysis of facial muscle movements being the most severe outcome.[20] The global annual incidence of facial paralysis is approximately 70 cases per 100,000. Management for facial paralysis can vary broadly. This is due to the complex etiological nature of the condition. The most common cause for facial paralysis, Bell palsy, is an idiopathic disease that can only be diagnosed by exclusion, and the treatment plans depend on cause and severity of injury.[21]

Overall, there are currently no curative treatments available; however, several therapeutic drugs are being tested in clinical trials. Current treatment options for these neurological and neurodegenerative diseases, such as disease-modifying drugs or symptomatic therapies, help to manage symptoms and slow the progression of some of the diseases or relieve specific symptoms.

Therefore, multidisciplinary clinical coordination is essential for optimizing health care delivery, increasing survival rate, and enhancing the quality of life of these patients. Modifications to dental treatment are required to ensure the comfort and protection of patients. Home care oral hygiene and regular dentist visits, for example, should occur more frequently due to a higher risk of developing oral diseases.

From a large list of neurological diseases, in this book we aim to describe and discuss Parkinson disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), cerebrovascular accident (CVA) or stroke, epilepsy (and other seizure disorders), myasthenia gravis (MG), and facial paralysis, which are more commonly seen. We hope that this book offers medical and dental practitioners the required general understanding of the background and description of these neurological diseases, their epidemiology, pathogenesis and etiology, and their potential genetic components. Later, we also describe how the identification, medical history, physical examination, and laboratory testing of these diseases can help in the process of their medical management and treatment approaches. Then we focus on special management of the patients in a dental care setting, prior to and during dental treatment, while considering oral medicine aspects of those conditions. Coordination between physicians, dentists, and other health care providers is suggested and described in the final part of each chapter.

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2 Parkinson Disease

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Abstract
Parkinson disease is a chronic neuropathological disorder involving progressive degeneration of dopaminergic and non-dopaminergic neurons in the substantia nigra. It is a prevalent neurological condition affecting 2 to 3% of the population aged 65 years and older. Loss of voluntary motor control, bradykinesia, resting tremor, muscular rigidity, and postural instability are a few symptoms that are particularly experienced by the patients. These motor symptoms are collectively termed "parkinsonism" and are used as cardinal signs for diagnosis by clinicians. Due to the physical limitations in these patients and the systemic manifestations of the disease, health practitioners can play a critical role in assisting them with the maintenance of their oral health and overall well-being. Implementation of an appropriate communicating medium for coordination between dentists and physicians can help in the delivery of an optimal treatment that they provide.

Keywords: Parkinson disease, PD, epidemiology, pathogenesis, oral manifestations, medical management, treatment

2.1 Background of Parkinson Disease

Parkinson disease (PD) is a prevalent neurological condition that affects 2 to 3% of the population aged 65 years and older.[1] Patients with PD are particularly prone to oral diseases due to the physical limitations imposed on them, as well as the systemic manifestations of the disease that interfere with normal salivary functions.[2,3] Dentists, therefore, play a critical role in assisting these patients with maintenance of their oral health and overall well-being. As the population ages, dentists will inevitably encounter more patients with PD, and in order to provide proper dental care and suitable preventative measures, it is of extreme importance that dentists have a thorough understanding of the epidemiology, pathogenesis, oral manifestations, medical management, and treatment of PD.[4]

2.2 Description of Parkinson Disease

Parkinson disease is a chronic neuropathological disorder involving progressive degeneration of dopaminergic and non-dopaminergic neurons present in the substantia nigra.[5] This neuronal degenerative activity causes a loss of voluntary motor control, and patients develop characteristic motor symptoms—bradykinesia, resting tremor, muscular rigidity, and postural instability—which were first described as "shaking palsy" in 1817 by James Parkinson, after whom the disease is named.[5,6] These motor symptoms are collectively termed "parkinsonism" nowadays and are used as cardinal signs for diagnosis by clinicians.[7]

Although commonly classified as a motor disorder, the manifestation of Parkinson disease is, in fact, multisystemic and a range of nonmotor symptoms are also presented by patients. These include cognitive impairment, insomnia, dementia, psychiatric disturbances, and autonomic failures.[8,9] These multisystemic manifestations drastically diminish the patient's quality of life as they induce many detrimental secondary complications, including gastrointestinal, cardiovascular, urinary, and thermoregulatory dysfunctions that arise from dysautonomia.[10,11,12] Various psychiatric disorders that manifest due to the lack of the neurotransmitter, dopamine, are prevalent nonmotor symptoms experienced by many parkinsonian patients, and they encompass depression, psychosis, and loss of impulse control.[13,14,15] The association of these psychiatric conditions with poorer outcomes of the disease has also been found.[13]

As the degenerative progression manifests throughout the course of the disease, patients develop more severe symptoms, and as a consequence, many aspects of the patients' health are compromised. Unfortunately, in spite of the advance of contemporary medical technology, Parkinson disease is, still, an incurable condition, and none of the treatments available can slow down the degenerative process.[7]

2.3 Epidemiology of Parkinson Disease

Parkinson disease affects approximately 0.1 to 0.3% of the world's population.[16,17] One percent of the population older than 60 years are diagnosed with PD.[17,18] Results from epidemiological studies estimate the mean age among PD patients to be 70.6 years,[18] and PD is rarely present in individuals below the age of 50.[8,16,18] Where onset does occur before 50, the disease is classified as early onset Parkinson disease. This is rare, and it occurs in approximately 4% of cases.[16]

The prevalence of Parkinson disease is rising exponentially with age across the globe.[17] By virtue of the growing aging population that benefit from improved quality of life and medical advances, it is expected that the number of PD cases will continue to increase. The life expectancy of the population has increased with the advances in medical facilities, and therefore, it is expected that the number of PD cases will continue to increase. About 10 to 50 per 100,000 people in a given population are being newly diagnosed with Parkinson disease each year, and it is predicted that numbers will double by 2030.[16] Given that this disease occurs primarily in the older population, it is more common in developed countries as a result of longer average life expectancy.[8]

Age by no means is the only contributing factor to this disease. A key role of epidemiology is to translate data and statistics into the knowledge of common risk factors, progression, and prognosis in populations. Epidemiological studies have identified genetic, environmental, and lifestyle factors as likely causes of PD progression,[8] while little to no significant relationship has been established with gender. Research shows approximately 10 to 15% of patients have a family history of PD,[19] caused by monogenic mutations inherited through autosomal dominant and recessive patterns.[20] The remaining majority of those clinically diagnosed are sporadic cases, likely due to a combination of environmental and genetic factors, with no family history.[7]

Gender roles do not substantially affect the susceptibility of acquiring PD. Some studies report higher prevalence in men than women with a ratio of 1.5:1,[21,22] while other studies lack to show significant differences.[17] Parkinson disease affects all races and nationalities indiscriminately. Studies have yet to find a direct link between nationalities and prevalence of Parkinson disease. For example, Africa had reported a lower prevalence of PD cases than America yet African American and Caucasians in the United States are equally likely to develop this disease.[16,23,24] While not as significant in its contribution to the disease, the prevalence of PD varies between cultures and ethnic groups. In particular, certain genetic mutations are more prevalent in certain ethnic groups. It is thought this may be due to varying environmental factors, and distribution of susceptible genes within the gene pool of the population.[17] It appears that behavioral, genetic, and environmental factors play a larger role in the development of disease rather than gender and race.

The deleterious effect of PD in which clinical symptoms worsen with age was clearly seen when a follow-up of PD patients in a study showed a mean survival rate of 12.6 years after onset.[16] Due to the latent nature of Parkinson disease at onset, accurate diagnosis can pose a challenge. Variations and discrepancies of data collected in epidemiological studies can be ascribed to the difficulty in detection and diagnosis of PD, different methods of data collection, and necessary meticulous follow-up processes with patients and families.[25] Nevertheless, studies on the prevalence, progress, and patterns of PD in population groups lead to better knowledge of this disease in hopes to find a cure in the future.

2.4 Etiology and Pathogenesis of Parkinson Disease

2.4.1 Etiology of Parkinson Disease

Although the etiology of Parkinson disease (PD) is unknown, it is believed to be multifactorial and is likely to involve a complex interaction of environmental and genetic factors (▶ Fig. 2.1).

Traditionally, environmental factors, especially exposure to pesticides and herbicides, have demonstrated a strong association with the onset of PD, due to its dopaminergic neuron toxicity.[26] Rural residency, farming, and consumption of well water appears to increase the risk of PD and may provide further evidence in support of herbicides or pesticide as critical etiological factors.[26]

Several other environmental factors may also be considered as risk contributors of PD. Specifically, a history of head injury has been observed with PD in later life. Non-smokers and non-caffeinated beverage drinkers are believed at higher risk. Further, low blood uric acid levels tend to be associated with increased risk of PD. The mechanisms by which these contribute to PD remain unknown.[27]

Recent research has been focused on the genetic factors involved. Around 15% of individuals with PD have a first-degree relative

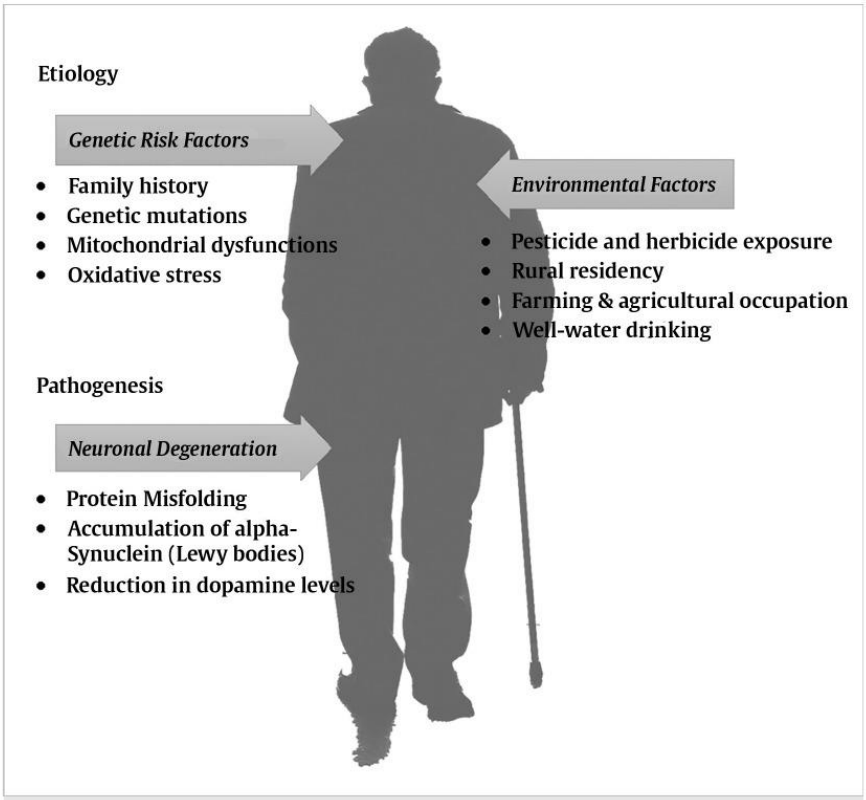

Fig. 2.1 Etiology and pathogenesis of Parkinson disease.

also suffering from the same condition.[27] Several studies of familial PD show inheritance patterns of both autosomal dominant and recessive.[26,27] Several twin studies suggest an increased concordance rate of early onset PD in monozygotic twins.[26,27,28]

Genetic mutations implicated in the development of PD are often involved in protein handling, oxidative stress, and mitochondrial function, including *LRRK2, SNCA, PINK1, PARK7, GBA, DJ1, PARK2*.[29] Again, one or several mutations in these genes alone does not determine the onset. A combination of these genetic mutations with environmental factors could affect age of onset, severity, and progression in a way that has yet to be defined.

2.4.2 Pathogenesis of Parkinson Disease

The typical characteristics of PD are neuronal cell death in the basal ganglia and formation of Lewy bodies in the damaged cells. Lewy bodies are insoluble protein inclusions that are formed through the abnormal accumulation of α-synuclein bound to ubiquitin.[26] The *SNCA* gene mentioned earlier as a genetic etiological factor encodes α-synuclein, and therefore mutation of this gene increases the risk of PD. Lewy bodies start accumulating in the substantia nigra, which is in the region of the midbrain, then spread to the basal forebrain and finally occupy the neocortex, signifying the main sites of neuron degeneration in PD.[26] The loss of neurons also causes a great reduction in dopamine levels in the regions mentioned above. The brain uses dopamine as neurotransmitters, and reduction poses inhibition of the dopamine pathway, affecting reward-motivated behaviors and motor control.[26,30]

Mitochondrial dysfunction and oxidative stress are closely interlinked in the pathogenesis of PD. Their importance has been reinforced by identification of gene mutations that induce dopaminergic cell death in some familial and sporadic PD cases.[27] Mitochondrial dysfunction involves deficiencies of respiratory chain proteins, most commonly respiratory chain protein complex I. This dysfunction can result from etiological genetic factors that encode mitochondrial proteins, for example, *PINK1*, *DJ1*, and *parkin*.[26] *PINK1* encodes PTEN-induced putative kinase I that protects neuronal cells from stress-related mitochondrial dysfunction.[26] It induces autophagy of depolarized mitochondria through the binding of parkin protein.[26] As a result of this, mutations in this gene contribute to autosomal recessive PD. Patients with *PINK1* mutation show nigrostriatal neuron cell loss and Lewy body formation. Environmental agents can also influence its function. The relationship between mitochondrial dysfunction and oxidative stress can be seen as reciprocal. Dopaminergic neurons are especially sensitive to calcium ion imbalance. Accumulation of intracellular calcium through voltage-dependent channels would result in an increase of mitochondrial free radicals and contribute to neuron death.[27,29]

Another common abnormality of PD can be manifested as proteasome inhibition. Alteration in the expression of subunits and regulatory cap induces a different organization of proteasomes, thus reducing proteasomal enzyme activity, and eventually, loss of nigral dopaminergic neurons. This degradation is achieved by a cascade of ATP-dependent peptidases.[30] Proteasome degradation has shown a strong association with mitochondrial dysfunction and oxidative stress. Free radicals impair mitochondrial respiratory chain function and increase substrate load on proteasomes.[29] Abnormal proteins then accumulate in the cytosol due to proteasome degradation. This poses potential acceleration in neuron cell dysfunction and death.

2.5 Genetic Component of Parkinson Disease

Parkinson disease is a multifactorial neurodegenerative disorder. It can be either familial or sporadic.[7] In the majority of cases, Parkinson disease occurs due to sporadic causes resulting from the interplay of both genetic mutations and environmental exposures.[7] While the

nature of the genetic involvement in PD requires further research, it is well recognized as having considerable involvement in the onset, progression, and clinical symptoms of the disease.[1,31] Whether familial or sporadic, the same pattern of dopaminergic neuron degeneration in the substantia nigra occurs.[31]

Currently, 26 genetic variations and gene loci have been identified as contributing to the risk of Parkinson disease.[32] Of these, there are six known monogenic forms of PD, accounting for 3 to 5% of sporadic and 30% of familial cases.[1,20] Inheritance follows both autosomal-dominant and autosomal-recessive patterns. The scope of research into these monogenic mutations and their relationship to Parkinson disease is outlined below.

2.5.1 Autosomal-Dominant Mutations

There are currently three genes associated with autosomal-dominant monogenic forms of Parkinson disease: SNCA, LRRK2, and VPS35.[32]

The first gene linked to PD was that of SNCA: a 140-amino acid protein encoding for α-synuclein. As mentioned above, mutations in this gene include point, duplications, and triplications, and follow an autosomal-dominant pattern of inheritance. Mutated SNCA produces a form of α-synuclein that is misfolded, insoluble, and contributes to PD pathogenesis by aggregating in the cell bodies and processes of neurons as inclusions, forming a substantial component of Lewy bodies and neurites, respectively.[7] On its own, α-synuclein does not produce such effects but is toxic in these excess aggregations.[7,33]

A hallmark characteristic in the progression of Parkinson disease is an accumulation of aggregated α-synuclein and the resulting Lewy body pathology. This follows specific patterns as the disease progresses.[34] The SNCA mutation itself causes an early onset, rapidly progressing form of Parkinson disease, which has been associated with both familial and sporadic cases.[1]

The most common genetic mutation in Parkinson disease occurs in leucine-rich repeat kinase 2 (LRRK2), which accounts for 1% of sporadic and 4% of familial occurrences.[7] This mutation results in a form of the disease with the mid-late onset and slow progression.[7] The LRRK2 protein is involved in "neurite outgrowth, synaptic morphogenesis, membrane trafficking, autophagy and protein synthesis."[7] Eight mutations of LRRK2 have been linked to PD, with the Gly2019Ser substitution being the most common.[7] LRRK2-induced Parkinson disease is highly prevalent in North African Arab and Ashkenazi Jew ethnic groups, accounting for 30% of familial, 13% of sporadic and 37% of familial, and 41% of sporadic cases, respectively.[7]

The final monogenic form of PD inherited through autosomal-dominant patterns is VPS35 (vacuolar protein sorting 35 retromolar complex). This protein is responsible for transporting proteins between endosomes and the Golgi apparatus.[32] It causes late-onset PD.

2.5.2 Autosomal-Recessive Mutations

Recessively inherited Parkinson disease has been linked to monogenic mutations in Parkin, PINK1, and DJ-1. It can be the result of homozygous or compound heterozygous mutations.[32] These genes are all associated with mitochondrial health and quality control, which provides further support for mitochondrial dysfunction as a cause of the disease.[20,35] Recessively inherited Parkinson disease is always associated with early onset.

Parkin, encoding for E3 ubiquitin ligase, was the second gene linked to PD, and the first to be associated with recessive inheritance.[20] It is the most common genetic cause of recessively inherited PD.[20] In early onset patients, it accounts for 50% of familial and 15% of sporadic cases.[7,36] The resulting clinical phenotype is associated with early onset and slow progression.

PINK1 encodes for phosphatase and tensin homolog-induced putative kinase 1. This mutation accounts for 1 to 8% of sporadic PD cases. It is involved in mitochondrial calcium homeostasis and results in Parkinson

disease with early onset and slow progression.[20,35]

DJ-1 (Parkinson disease protein 7) accounts for 1 to 2% of early onset cases. The protein produced is involved in protecting against oxidative stress.[20,35]

Genetic involvement in Parkinson disease is well founded and known to have a substantial role in the development of the disease. Further research into the nature of the genetic involvement of Parkinson disease will provide greater insight into the characteristics, pathogenesis, and progression of individual cases, improve patient prognosis, and assist in the development of more targeted treatment options.

2.6 Diagnostic Evaluation of Parkinson Disease

2.6.1 Clinical Features of Parkinson Disease

Parkinson disease is characterized by a wide range of motor and nonmotor symptoms that affect and impair function to variable degrees —depending on the onset and severity of disease, which advances with time (▶ Fig. 2.2).

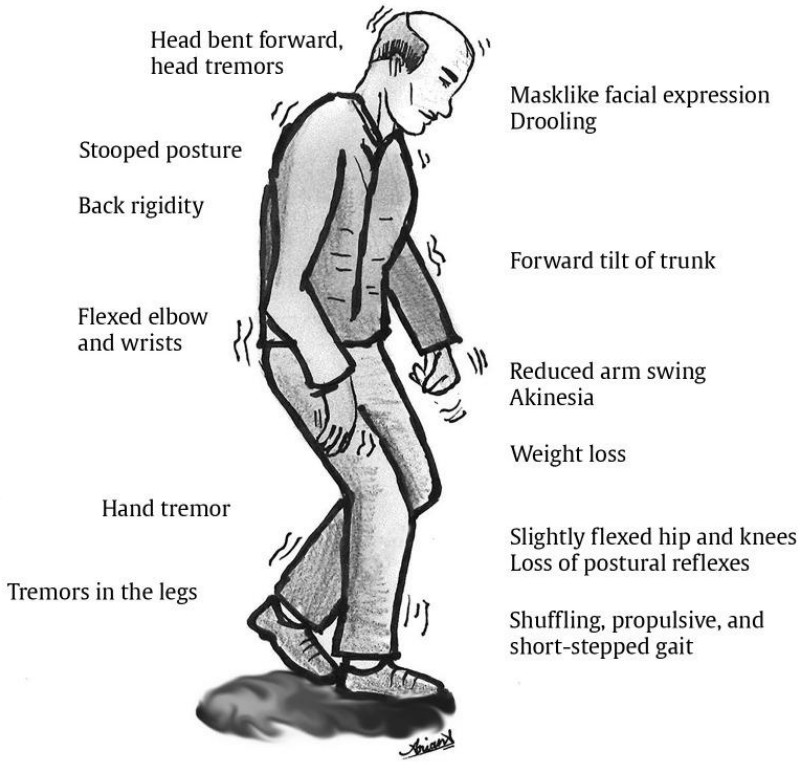

Fig. 2.2 Parkinson disease presentation.