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Review Article

The Essentials in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder that affects millions of patients worldwide. In the last years, important advances have been made in reference to the etiology, pathogenesis, epidemiology, neuroimaging and treatment strategies. PD is now recognized as a heterogeneous condition, characterized by motor and non-motor symptoms. According to the temporal profile, three stages can be considered: 1-preclinical, 2-prodromal and 3-clinical. The clinical phase can be subdivided into early and late, from the appearance of motor and neuropsychiatric complications. Despite its progressive nature, it is one of the few neurodegenerative diseases whose symptoms reverse after chronic administration of dopaminergic therapy. Initially considered a movement disorder, PD is a multisystem disease. At present there is no definitive cure for PD, so we must wait for new advances in the field of scientific knowledge.

Keywords: *Parkinson; Diagnosis; Treatment*

Introduction

PD, with a chronic and progressive course, is in frequency the second neurodegenerative disease, only surpassed by Alzheimer's disease (AD). It is characterized by severe motor and non motor disorders. The clinical picture includes cardinal signs of bradykinesia, tremor, rigidity, postural disorders and minor signs like depression, freezing of gait, sialorrhea, decreased blinking, hypophonia, bradylalia, festinating gait, reduced arm swing while walking, triple flexed posture, decreased facial expression and micrographia [1].

History

Four thousand years before Christ, in an ancient medical system of India called Ayurveda, PD was referred to as Kampavata (kampa: means tremor and vata: refers to movement). James Parkinson (Figure 1), an English physician, described in 1817 in his monograph named "An Essay on the Shaking Palsy" (Figure 2), the clinical features of the disease. He mentioned a triad of cardinal motor signs

(tremor, rigidity and postural disorders), minor motor signs (gait disturbance) and non motor signs (sleep disorders and constipation). He also described the progressive nature of PD and the degree of disability that the disease entails [2]. Five decades later, Jean Martin Charcot (Figure 3), a French physician, added bradykinesia to the constellation of cardinal signs and named the condition as "Parkinson's Disease" [3]. In France, while Brissaud was studying the neuropathological findings in a tuberculosis patient who develops hemiparkinsonism and dies, found a tuberculous granuloma in the contralateral substantia nigra (SN). This finding laid the pathological foundations of PD. Later, Tretiakoff carried out some neuropathological studies on patients with PD and described a depigmentation and a depopulation of neurons in the SN. These findings confirmed the existence of the intracytoplasmic inclusion bodies discovered by Lewy. In 1957, Carlsson developed a model of akinetic-rigid parkinsonism after the administration of reserpine to experimental animals. He observed that the clinical picture went into remission after the administration of L-Dopa (the precursor to dopamine) paving the way for its use as a treatment for Parkinson's disease [4].

Figure 1: *James Parkinson.*

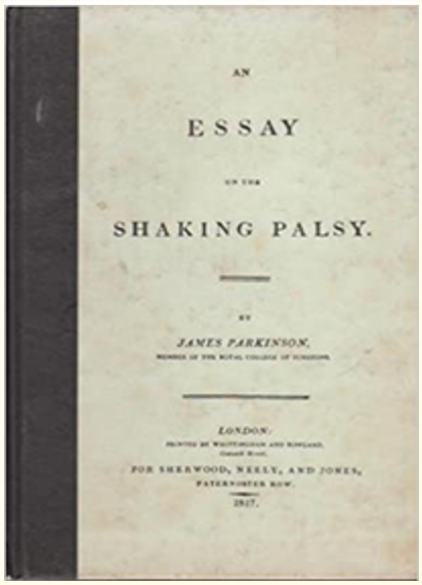


Figure 2: *An Essay of the Shaking palsy.*

Figure 3: *Jean Martin Charcot.*

In 1961, Birkmayer and Hornykiewicz demonstrated a lack of dopamine (DA) in the striatum of patients with PD, so they suggested the potential benefit of an intravenous dopaminergic replacement therapy. In 1967, Cotzias., *et al*. prescribed oral doses of DL-dihydroxyphenylalanine (DOPA) to patients with PD, achieving encouraging results [5]. L-dopa combined with an inhibitor of peripheral aromatic amino acid decarboxylase becomes the mainstay of medical therapy, in force today. In the late 20th and early 21st century, important advances in the pathophysiology of PD took place, as well as in the development of various treatment options. Neurosurgical treatments were developed to control symptoms refractory to pharmacological treatment, which include lesion surgeries and later deep brain stimulation (DBS). The 21st century has witnessed rapid progress in the field of neurogenetics and its role in the etiology of PD. Currently, the outcome of neurorestorative and neuroprotective therapies is being studied, as well as immunotherapy [6].

Epidemiology

PD affects millions of patients in the world, which could double by the year 2030 [7]. This disease affects 1% of people over the age of 60. The lifetime risk of suffering from PD is 2% in men and 1.3% in women older than 40 years. The incidence of Parkinson's disease is low in populations younger than 50 years, increasing thereafter with age [8]. Men are more susceptible to PD than women [9].

Clinical picture

PD is characterized by tremor, rigidity, bradykinesia, and postural disturbances [10]. Resting tremor is the main reason for consultation. It is of the distal and asymmetrical type, and involves one limb more intensely than the other, and may compromise all four limbs. It is regular and has low frequency (4 to 6 cycles per second). It adopts the clinical form "pill-rolling tremor", "adduction-abduction movement" of the fingers in the axis of the middle finger, a "prono-supination movement" of the hands or the combination between them. Being a resting tremor, it can be seen when the patient is sitting, relaxed, with their hands resting on both thighs or while walking. Furthermore, tremor can appear after a few seconds as a postural tremor when extending both upper limbs (re-emergent tremor) [11]. Rigidity implies the active resistance offered by the different body segments against a passive stretch and this can be observed in the large joints (wrists, elbows, shoulders, hips, knees or ankles) when making flexion-extension, adduction-abduction or rotation movements (Figure 4). The examiner can objectify a resistance as small jumps, called "cogwheel rigidity" [12].

Figure 4: *Examination of wrist rigidity.*

Bradykinesia is characterized by a pronounced slowness in the initiation and/or continuation of voluntary movements, which can lead to true akinesia (absence of movement). It is verified by examining the speed that the patient performs digital pincer movements between the thumb and index finger (Figure 5), pronosupination of both hands, flexion-extension of the fingers and the index-nose maneuver. Bradykinesia results from the association of hypokinesia (decreased range of motion) and bradykinesia itself (slowing down in the execution of voluntary movement).

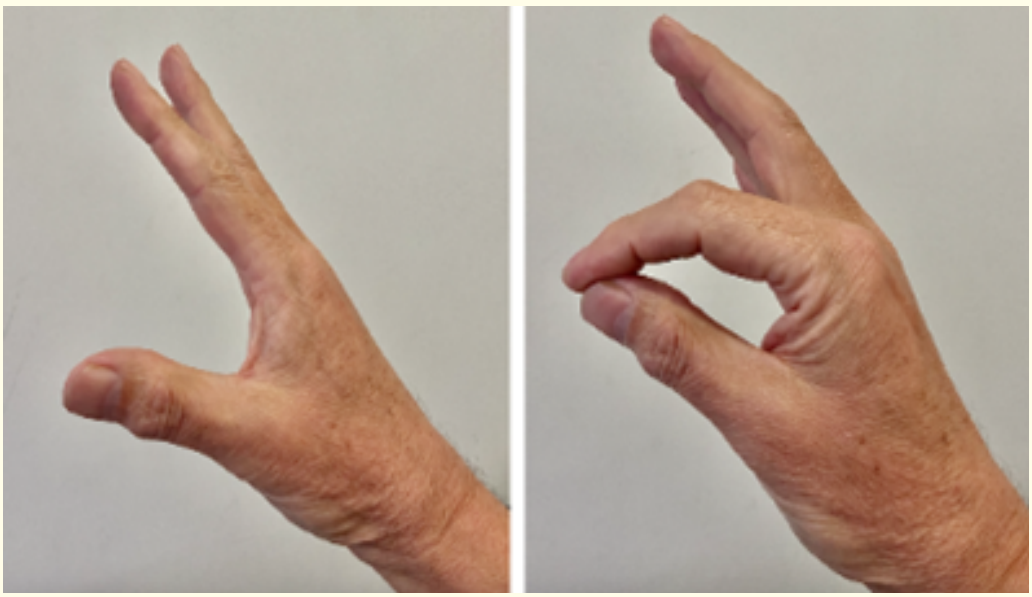


Figure 5: *Thumb-index finger tapping test.*

In the lower limbs, slowness can be observed when standing up or walking. If the patient is asked to strike the heels on the floor or to tap it with the toe of the foot (tapping) while seated, the movement becomes slow or even blocked. Bradykinesia and rigidity reduce facial expression to hypomimia, which, associated with intense seborrheic secretion, makes the patient's face as expressionless as a mask (poker face). Arm swing is lost when walking, usually asymmetrically, and predominantly in the side of the body most affected by the disease. The postural disorder appears a few years later. It is due to the marked flexor hypertonia of the trunk and extremities that the typical triple flexion posture is produced (inclination of the trunk forward, associated with flexion of the elbows and knees), added to the extension of the neck. Finally, the postural disorder compromises the gait that becomes unstable. Postural disorders can be objectified through the "pull test", which consists of pushing the standing patient forward from the shoulders, thus falling in a block towards the examiner. It is a symptom usually resistant to L-dopa and one of the main causes of falls. Postural disorders contribute to fractures, loss of independence and the consequent institutionalization of the patient with PD. The asymmetry of PD is maintained throughout the course of the disease. Consequently, the most affected body segment indicates where the PD began and will be the seat of the various motor complications (fluctuations and/or dyskinesias) due to chronic L-dopa therapy [13].

Non-motor symptoms

Most patients experience non-motor symptoms during PD. The impact of non-motor symptoms on the patient's quality of life is greater than motor symptoms, due to their lack of recognition and poor response to treatment [14]. Neuropsychiatric symptoms include anxiety, depression, impulse control disorders (ICD), hallucinations, delusions, mood disorders and apathy. Cognitive symptoms include executive dysfunction, memory disorders, and cognitive decline that may progress to dementia. Dysautonomia includes orthostatic hypotension, constipation, urinary incontinence, sexual dysfunction, altered cardiac reflexes, and profuse sweating. Sleep disorders are observed, namely insomnia, daytime sleepiness, restless legs syndrome, periodic movements of the extremities during sleep and rapid eye movement (REM) sleep behavior disorder. Sensory abnormalities include acroparesthesia and numbness in the extremities, pain, fatigue, and anosmia. Non-motor state fluctuations can be observed [15]. During "off" states, patients may experience worsening mood, anxiety, dysautonomia, including sweating, and body temperature irregularities. Non-motor states include paranoia, mania, agitation, delusions, and impulsivity [16].

Premotor symptoms

Premotor symptoms precede the motor symptoms of PD and include depression, constipation, anosmia, and REM sleep behavior disorder [17].

Etiopathogenesis PD is characterized by 1- degeneration and depopulation of dopaminergic neurons in the pars compacta of the Substantia Nigra (SN) and 2- presence of Lewy bodies in the brainstem. Motor symptoms become evident when 60% to 80% of these neurons degenerate. Depigmentation of the SN is observed (Figure 6). The SN projects its axons to the striatum (caudate nucleus and putamen), interacting over the direct and indirect pathways of basal ganglia circuits.

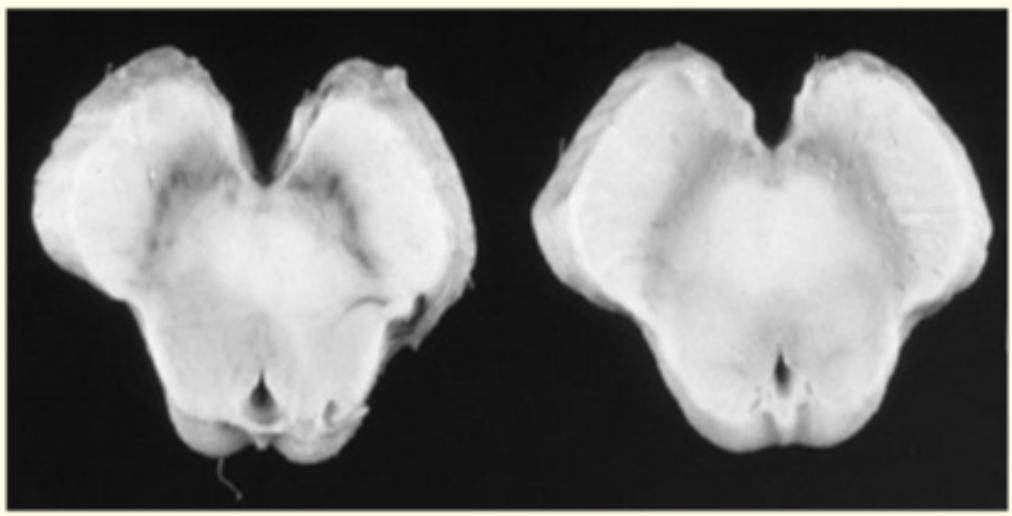


Figure 6: *Macroscopic section of the cerebral peduncles: normal pigmentation of the SN in a healthy person (left) and depigmentation of the SN in a PD patient (right).*

Consequently, the inhibitory effects of the indirect pathway and the excitatory effects of the direct pathway are reduced, leading to the clinical manifestations of PD, although other neurotransmitters (noradrenaline, serotonin, substance P and/or acetylcholine) would be involved. Lewy bodies are intracytoplasmic inclusion bodies, eosinophilic in sections stained with hematoxylin-eosin, and located in dopaminergic neurons of the SN as well as other nuclei (dorsalis vagus, locus coeruleus, and/or Meynert). These aggregations are caused by the intracellular accumulation of an abnormal misfolded protein called alpha-synuclein (Figure 7). Other synucleins have recently been described: beta-synuclein and non-alpha/non-beta-synuclein [18].

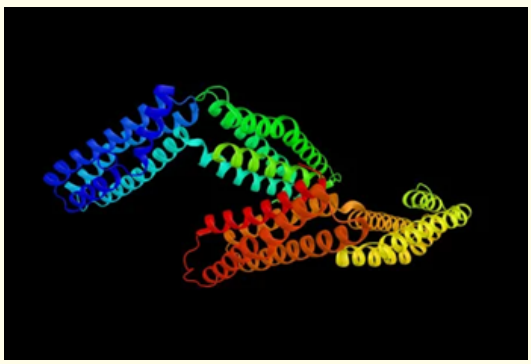


Figure 7: *Three-dimensional structure model of alpha synuclein (ASN).*

PD is part of the group of so-called alpha synucleinopathies. With the progression of the disease, Lewy bodies extend throughout the central nervous system (CNS) and involve the structures of the olfactory pathway, to the dorsal nucleus of the vagus nerve (autonomic manifestations), then extend along the brainstem affecting SN, locus coeruleus and finally limbic cortex and neocortex (Figure 8 and 9). PD is a heterogeneous disorder with various clinical forms of presentation, age of onset, types of motor and non-motor symptoms, and different rates of progression [19-20].

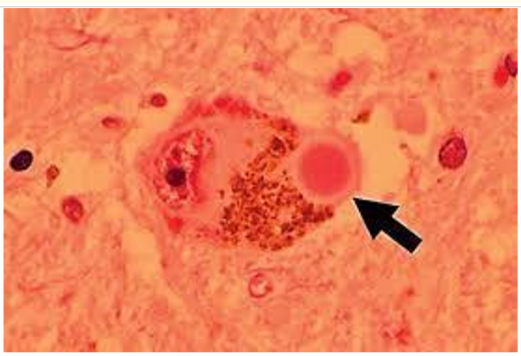


Figure 8: *Lewy bodies (LB).*

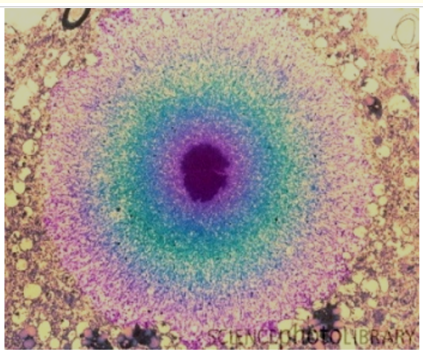


Figure 9: *LB by electron microscopy.*

Genetics and PD

Many factors are involved in the degeneration of dopaminergic neurons that occurs in PD. Between 5% and 10% of PD cases have a genetic etiology. Monogenic forms of PD include the PARK-SNCA, PARK-LRRK2, and PARK-VPS35 genes, among others. Another genetic risk factor for PD and for the Ashkenazi Jewish population in particular, is the gene for glucocerebrosidase, or GBA1, responsible for Gaucher disease [21]. GBA1 induces the biosynthesis of the glucocerebrosidase protein, involved in lysosomal activity. A genetic defect in GBA1 causes a reduction in glucocerebrosidase activity and consequently an increase in glucosylceramide. This condition leads to the accumulation of α-synuclein, increasing the possibility of developing PD. Future genetic sequencing studies will provide information on the role of genetics in the genesis of PD [22].

Environment and PD

In the late 1980s in the United States, the toxic effect of MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine), a synthetic derivative of heroin, on addicted patients was described. This substance produces selective damage to dopaminergic neurons in the SN, laying the foundations for parkinsonism due to an environmental neurotoxic effect. Some of the environmental factors and toxic exposures that may be associated with PD include pesticides (rotenone and paraquat); heavy metals (manganese, lead and copper); well water; head trauma; other substances, including polychlorinated biphenyls, trichlorethylene, perchlorethylene, carbon tetrachloride, and rural life. Exposure to carbon monoxide, organic solvents and cyanide, have been implicated as environmental risk factors. Smoking and caffeine intake reduce the risk of developing PD [23].

Diagnosis The diagnosis of PD is clinical. The correct diagnosis of PD can be difficult due to the various clinical forms of the disease [24]. PD begins gradually and it is difficult for the patient to define it. When the first motor symptoms appear, it is estimated that PD has a decade of evolution, usually preceded by non-motor symptoms. The finding of resting tremor, rigidity, and/or asymmetric bradykinesia with a favorable response to dopaminergic therapy, suggest the diagnosis. Clinical features that cast doubt on the diagnosis of PD include: severe autonomic disturbances, early-stage hallucinations, cognitive impairment preceding motor symptoms, postural disturbances, and freezing of gait within the first 3 years of diagnosis [25]. Diagnostic criteria are based on the "United Kingdom Parkinson's disease Society Brain Bank Clinical Criteria", which sets out diagnostic criteria for parkinsonian syndromes, exclusion criteria and supporting criteria, for the diagnosis of PD (Table 1) [26].

Temporal profile of PD

PD is characterized by having an invariably progressive course. Three stages are recognized in early PD: 1-preclinical phase: neurodegeneration begins but patients lack clinical symptoms; 2-prodromal phase: symptoms are present but insufficient to make a diagnosis of PD; and 3- clinical phase: clinical symptoms become evident and recognizable [27]. The first stage of PD (approx. the first five years) is described as a true "honeymoon", where the patient responds effectively to dopaminergic therapy. Later, between 5 and 10 years after diagnosis, motor complications appear. After a decade, severe postural disorders with frequent falls ensue. Over time, motor complications due to chronic L-dopa therapy (fluctuations and dyskinesias), speech and swallowing disorders, frostbite, and unsteadiness worsen. Patients with juvenile-onset PD develop early motor complications induced by L-dopa. Patients with late-onset PD often develop cognitive and autonomic disorders [28].

Complementary studies in PD

Ultrasound: Bilateral mesencephalic ultrasound, recorded through the temporal bone squama, using a 2.5 Hz cardiology transducer, makes it possible to study the echogenicity of SN, which is hyperechoic in PD and hypoechoic in atypical parkinsonism (Figure 10).

Step 1. Diagnosis of parkinsonian syndrome
Bradykinesia (slowness in the initiation of voluntary movements with progressive reduction in speed and amplitude of repetitive actions) At least one of the following: - Muscular stiffness - Resting tremor of 4 - 6 Hz - Postural instability not caused by visual, vestibular, cerebellar, or proprioceptive impairment
Step 2. Exclusion criteria
History of repeated strokes or gradual progression of parkinsonian signs Repeated history of head trauma History of encephalitis Oculogyric seizures Neuroleptic treatment at the onset of symptoms More than one affected relative Sustained remission Unilateral symptoms after three years of evolution Supranuclear gaze palsy Cerebellar signs Autonomic manifestations in early phase Early dementia with amnesia, aphasia and apraxia Babinski's sign Presence of brain tumor or communicating hydrocephalus on CT Lack of response to adequate doses of levodopa (if malabsorption is excluded) Exposure to MPTP
Step 3. Criteria that support the diagnosis of PD*
Unilateral start Resting tremor Progressive course Persistent asymmetry that more compromises the side where it started Excellent response (70-100%) to levodopa Levodopa-induced severe chorea Response to levodopa for more than five years Clinical course of 10 years or more
*Three or more are required for a definitive diagnosis of PD.

Table 1: *United Kingdom parkinson's disease society brain bank clinical criteria.*

Computed tomography (CT) and magnetic resonance imaging (MRI): High-fidelity CT and MRI studies of the brain do not reveal structural alterations, except for MRI in certain atypical parkinsonisms: 1-cruciform hyperintensity in the pons, the "hot-cross bun" sign in multiple system atrophy (MSA), 2-"hummingbird" sign in progressive supranuclear palsy (PSP) or 3-an asymmetric fronto-parietal cortical retraction in corticobasal degeneration (CBD) (Figure 11) [29].

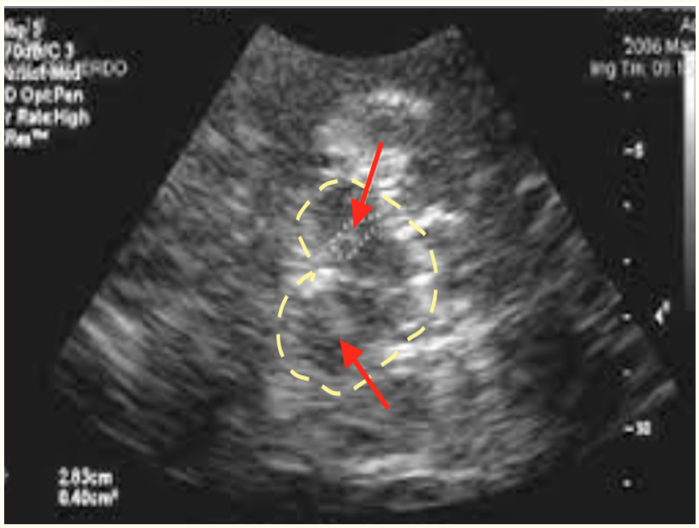


Figure 10: *Mesencephalic ultrasonography. The cerebral peduncles and echogenic features of the SN are shown (red arrows).*

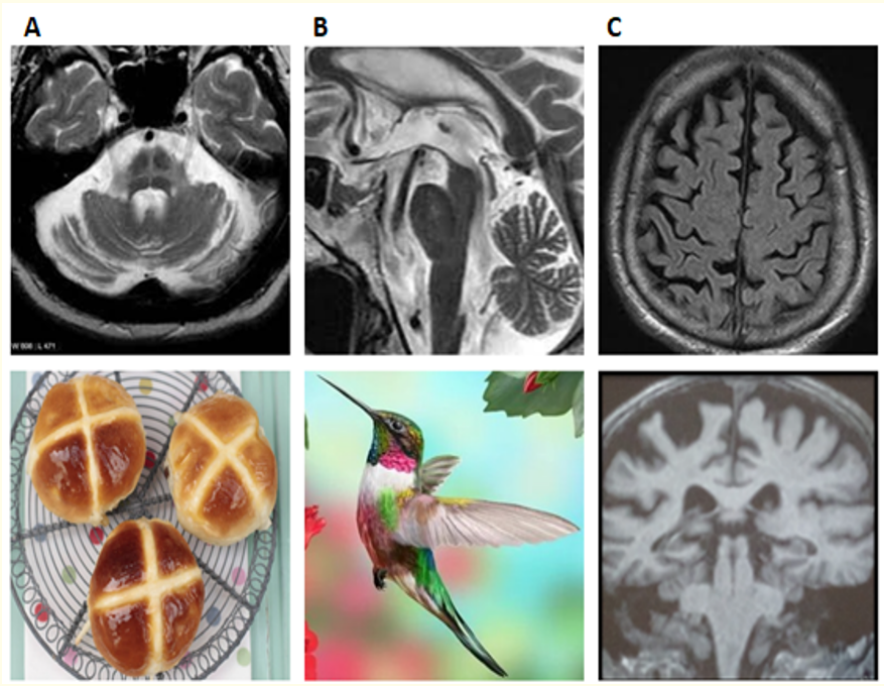


Figure 11: *Atypical parkinsonisms: MSA (A), PSP (B) and CBD (C).*

Single-photon emission computed tomography (SPECT): Single-photon emission computed tomography (SPECT) of the dopamine transporter with contrast injection may be helpful in the diagnosis of PD and is considered an adjunct at diagnosis [30]. Dopamine transporter SPECT does not confirm the diagnosis of PD nor does it allow the differential diagnosis to be established with other parkinsonisms including atypical parkinsonisms. This procedure has high sensitivity (87% to 98%) and specificity (80% to 100%) in differentiating PD from benign essential tremor (BET). Dopamine transporter SPECT orients to achieve a diagnosis on patients with a tremor of unknown origin (PD or TEB) (Figure 12) [31,32].

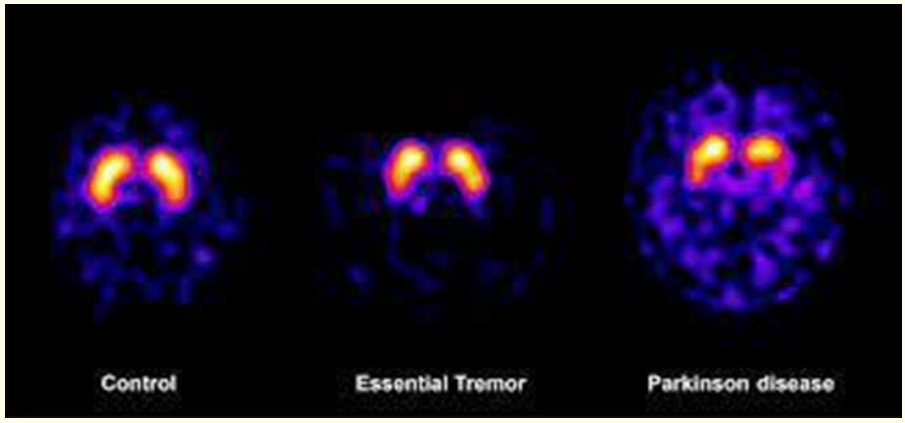


Figure 12: *Molecular imaging of the dopamine transporter (DAT).*

DAT SPECT with 123I-FP-CIT shows the normal availability of striatal DAT in patients with essential tremor, while asymmetric loss of DAT is observed in a patient with PD [33].

Positron emission tomography (PET): Positron emission tomography with injection of a radiotracer (fluorodopa) is an excellent mark of the severity of PD (Figure 13).

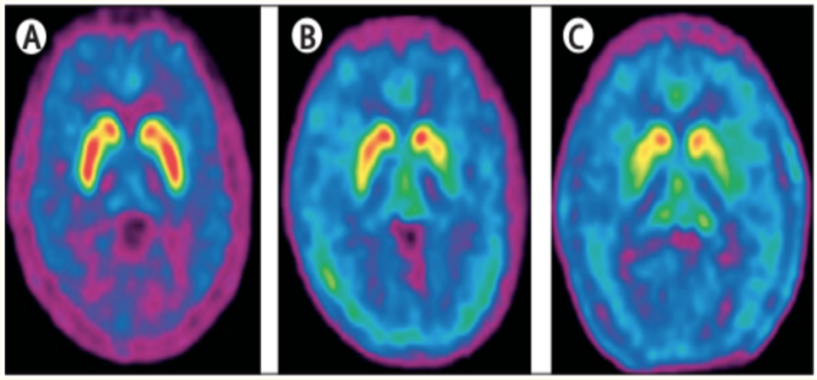


Figure 13: *PET with 18F-fluorodopa of a healthy individual (A), and of a patient with PD at the time of diagnosis (B) and after 12 years of evolution (C) [34].*

Differential diagnosis

The diagnosis of PD is not easy. A margin of error of 25% is registered, even in specialized centers.

Differential diagnoses should include TEB, atypical parkinsonisms, tremor, secondary parkinsonisms, or other movement disorders (Table 2). Atypical parkinsonisms constitute the most difficult differential diagnosis in clinical practice, for which the following clinical findings must be considered: 1- early onset speech disorders, 2- instability, 3- absence of tremor (acineto-rigid forms), 4- symmetry of symptoms (except DCB) and 5- a failure to respond to L-dopa. Atypical parkinsonisms include progressive supranuclear palsy (PSP), corticobasal degeneration (CDB), Lewy body disease (LBD), and multiple system atrophy (MSA) of the cerebellar, parkinsonian, or autonomic types. Atypical parkinsonisms present characteristic symptoms such as dysautonomia (MSA), vertical axis conjugate gaze palsy (Parinaud's sign) (PSP), and marked apraxia/dystonia or myoclonus of one limb correlated with contralateral parietal cortical retraction (CBD) [35].

Idiopathic Parkinson's disease
Genetic
Sporadic
Lewy body dementia
Atypical parkinsonisms
Multiple system atrophies (MSA)
Cerebellar type (MSA-c)
Parkinsonian type (MSA-p)
Autonomic type (MSA-a)
Progressive Supranuclear Palsy (PSP)
Corticobasal degeneration (CBD)
Fronto-temporal dementia (FTD)
Secondary Parkinsonisms
Drug induced
Tumor
Infectious
Vascular
Adult normal pressure hydrocephalus (Hakim Adams)
Trauma
Hepatocellular failure
Toxins
Other neurodegenerative diseases
Wilson's disease
Huntington's disease
Niemann and Pick disease type C
Dystonia-ataxia-parkinsonism (DYT12)
Neurodegeneration with brain iron accumulation
SCA 3 (Machado Joseph ataxia)
Fragility of the X chromosome
Parkinsonism/ataxia/tremor
Prion disease (JC)
Parkinsonism associated with dementia of the Alzheimer type (DTA)

Table 2: *Differential diagnosis of parkinsonisms.*

PD assessment scales

Clinical rating scales are useful for monitoring the progression of PD. They are used in clinical trials. The Unified Parkinson's Disease Rating Scale (UPDRS) [36], developed by the Parkinson Disease and Movement Disorder Society (MDS) and recently revised (MDS-UPDRS) [37], is a validated scale and widely used. It is subdivided into four parts: 1- cognition and mood, 2- activities of daily living, 3- motor examination, and 4- motor complications. The Unified Dyskinesia Rating Scale (UDysRS) allows the evaluation of motor complications (dyskinesia) that occur with the progression of PD [38]. The Hoehn and Yahr scale describes five stages of PD, namely I: unilateral symptoms, II: bilateral symptoms, III: axial symptoms (postural instability), IV: worsening of symptoms with inability to live independently, and V: assistance in a wheelchair or in bed [39]. Other clinical rating scales are: the Schwab and England Scale of Activities of Daily Living [40], the PD Questionnaire (PDQ-39 and PDQ-8) [41] and the Non-Motor Disease Symptoms Questionnaire of Parkinson (PD NMS) [42]. Patients can be encouraged to write how they feel in a personal diary and provide extremely important information about the daily profile of motor complications (fluctuations and/or dyskinesias) associated with taking the medication.

Pharmacological treatment of PD

L-dopa, a precursor to dopamine, has been shown to be effective in reversing the symptoms of PD. Other drugs have been used, such as dopamine agonists, which act on pre and postsynaptic dopamine receptors in the region of the basal ganglia and the cerebral cortex, and MAO-B and COMT inhibitors to prevent dopamine catabolism. In special situations, amantadine and/or anticholinergic drugs may be prescribed. These drugs increase central dopaminergic transmission and act on different dopamine pathways. Non-motor manifestations do not respond effectively or only partially to currently available dopaminergic drugs. The clinical manifestations of PD vary from patient to patient, progress over time, and consequently the various treatment strategies must be dynamically adapted to each clinical situation [43].

L-dopa

DA does not cross the blood-brain barrier (BBB), therefore L-dopa, its precursor, introduced in clinical practice since 1969, is used as a pharmacological strategy for PD. Clinical trials carried out over the next decade confirmed its clinical value, revolutionizing the treatment of PD. L-dopa is administered in combination with an aromatic amino acid decarboxylase inhibitor (carbidopa and/or benserazide) to prevent its peripheral metabolism to DA and the appearance of adverse effects (nausea/vomiting) due to activation of dopamine receptors (DR) in the area postrema of the medulla oblongata, not protected by the BBB. Currently, there are various formulations of L-dopa available: 1-standard oral formulation associated with carbidopa/benserazide, 2-formulation soluble in a fast-absorbing acidic medium, 3-extended-release formulation, 4-associated with an inhibitor of the catechol-O-methyltransferase (COMT) enzyme, which prolongs its effect, 5-gel formulation suitable for enteral administration and 6-inhalation formulation. L-dopa is the most effective symptomatic treatment currently available for PD. No medical or surgical treatment exceeds the benefits achieved with this drug; that allows the remission of the characteristic motor symptoms of PD, reduces disability, prolongs independence, improves activities of daily living, and increases life expectancy. The lack of response to a clinical trial with L-dopa casts doubt on the diagnosis of PD. There are limitations in chronic therapy with L-dopa. Acute adverse effects (nausea, vomiting, and orthostatic hypotension) may be observed and can be avoided by titrating L-dopa progressively. If it persists, domperidone, a peripheral DR blocking agent, can be administered. The progressive nature of PD leads to the appearance of motor and non-motor symptoms such as falls, freezing, autonomic dysfunction, sleep disturbances, and cognitive decline. These clinical manifestations do not respond adequately to L-dopa and constitute a source of disability and institutionalization of patients in advanced stages. Early in drug therapy with L-dopa, the benefits are long-lasting and three daily doses can be administered, despite having a relatively short half-life (60 - 90 minutes). This is due to the buffering capacity of the patient in his remaining presynaptic dopaminergic terminals. In chronic form, the duration of benefit after a single dose progressively shortens and approaches the half-life of

the drug. This loss of efficacy is known as "end-of-dose deterioration" or "wearing off". In severe cases, patients may experience a delayed onset (delayed "on") or no response to a given dose (no "on"). After the first few years of chronic L-dopa therapy, motor complications ensue, consisting of fluctuations in motor response ("on" episodes when the drug is working and "off" episodes when parkinsonian symptoms return) and involuntary movements known as dyskinesias (Table 3).

1-"On": Expected response after taking the dose of L-dopa with improvement of symptoms.
2-Start of dose: Expected response after 30-40 minutes of taking the dose of L-dopa.
3-Peak dose: Time of maximum response to the dose of L-dopa.
4-End of dose: Moment in which the effect of L-dopa decays.
5-"Off": The patient experiences parkinsonian symptoms, with no response to L-dopa.
6-Magnitude of the motor response: Difference of the motor state between the "off" and "on" periods

Table 3: *Definition of the "on" and "off" periods in response to L-dopa.*

Dyskinesias occur at the time of maximum plasma L-dopa concentration and maximum clinical benefit (peak dose dyskinesia). These usually present in the form of chorea, dystonia, myoclonus, tics and/or stereotypes. When these are mild, they are generally well tolerated by the patient, but in severe cases they can be truly disabling, limiting the daily dose of L-dopa with the consequent difficulty in controlling the clinical manifestations of PD. In advanced stages, patients alternate "on'' periods with disabling dyskinesias and "off" periods in which they suffer from severe parkinsonism and painful dystonic postures. Patients may experience "biphasic dyskinesias", which are seen at the onset and decline of the response curve to L-dopa. These dyskinesias typically consist of transient, stereotyped, and rhythmic movements that predominantly affect the lower extremities associated with parkinsonian manifestations in other regions of the body (trunk and upper limbs). The etiology of the motor complications induced by L-dopa is unknown. Phenomena related to the pharmacokinetics and pharmacodynamics of L-dopa would be involved, being observed more frequently in young individuals, with severe PD and in those patients who have received sustained high doses of L-dopa. The classical model of basal ganglia pathophysiology has been useful in understanding the origin of motor features in PD, but it does not unequivocally justify the origin of motor complications. As dopaminergic neurons degenerate, striatal concentration of dopamine depends on peripheral L-dopa availability, which varies with exogenous oral administration. Intermittent doses of L-dopa result in fluctuating plasma levels due to the variability in the transit of the drug from the stomach to the duodenum where it is absorbed and the short half-life of the drug, which ranges from 60 to 90 minutes. This variability results in variable exposure of DR to fluctuating and not stable high or low concentrations of DA. A new formulation of extended-release L-dopa-carbidopa (IPX066) was designed for easy administration, rapid absorption, and a longer duration of clinical benefit [44]. IPX066 has been clinically shown to improve dyskinesia-free time and reduce "off" time in advanced PD [45]. An inhaled powder formulation of L-dopa has recently been approved by the US Food and Drug Administration (FDA) for the intermittent treatment of inactive episodes in PD patients under a chronic L-dopa treatment regimen. The "continuous dopaminergic stimulation" model lays the foundations for a treatment strategy that could prevent the development of motor complications. A gel formulation of L-dopa-carbidopa has been designed that can be administered intestinally by continuous infusion using a percutaneous endoscopic gastrostomy-jejunal extension tube (J-PEG) [46]. Clinical trials have shown that L-dopa/carbidopa intestinal gel reduces fluctuations in plasma L-dopa and increases dyskinesia-free "on" time compared to standard oral L-dopa formulations. L-dopa-carbidopa intestinal gel may be recommended for patients with PD who experience motor complications refractory to oral formulations and for patients with advanced PD who are not amenable to surgical treatment [47]. Cases of sensory polyneuropathy and even severe Guillain Barré type have been reported in patients who have received L-dopa intestinal gel [6,48]. In the course of chronic treatment with L-dopa, patients may develop behavioral disorders, namely: 1-dopaminergic dysregulation syndrome, in which patients take frequent and unnecessary doses of L-dopa in an addictive way, 2-pounding, observe stereotyped and purposeless behaviors such as mindless assembling, collecting, and sorting objects, similar to that seen in chronic amphetamine addicts, 3-Impulse Control Disorders (ICD) such as hypersexuality, compulsive shopping or gambling [49].

Fluctuations

The fluctuations are due to a decrease in motor response. These can be subdivided into predictable, which correlate with taking the L-dopa dose, and non-predictable when they do not correlate with taking the dose. Also, these can be motor or non-motor. A motor fluctuation is defined as a change in the patient's motor status that goes from a phase of good mobility ("on" period), to a phase of motor deficit or immobility ("off" period). Different clinical forms of motor fluctuations have been described, ranging from simple and predictable (the "off" period appears when the next dose of L-dopa is due) to complex and unpredictable (when there is no chronological relationship between taking the dose of L-dopa and the onset of the "off" period). The risk of appearance of these complications is 10% per year of treatment with L-dopa and they affect the patient's quality of life. The pattern of motor fluctuations changes over the course of PD, due to changes in pharmacokinetics (initially taking large and spaced doses of L-dopa and then small and frequent doses) and pharmacodynamics (loss of buffering capacity at presynaptic dopaminergic terminals) (Table 4) [50,51].

1-Lack of response: little or no response to L-dopa even when it is administered in high doses.
2-Suboptimal clinical response: less than expected clinical response after administration of the dose of L-dopa.
3-Delayed dose response: patients begin to experience a delayed onset of dose response to L-dopa.
4-Deterioration at the end of the dose (wearing off): the response to L-dopa decreases earlier than expected (it does not reach the next dose). This initially predictable deterioration then adopts a less predictable pattern, being able to advance or delay the dose of L-dopa.
5-No"on": An unpredictable failure in the dose response is displayed.
6-"On-off" phenomenon: Unpredictable changes in the motor response not related to taking the medication are observed. These changes occur suddenly, just as a light switch is turned on or off.
7-Freezing phenomenon: A transient suppression in the expected motor response in the "on" or "off" phase.

Table 4: *Fluctuations. Clinical considerations.*

Dyskinesias

L-dopa induced dyskinesias (DIL) are involuntary movements such as chorea, dystonias, ballismus, myoclonus, tics or stereotypes, that appear in any period of the dose-response curve to L-dopa. These can manifest: 1- at the beginning of the dose, 2- at the peak of the dose, 3-during the benefit, 4- at the end of dose, 5- at the beginning and at the end of the dose (biphasic) (See figure 14) [52]. The most frequent dyskinesias in clinical practice should be considered (Table 5).

Peak dose dyskinesias
Biphasic dyskinesia (beginning and end of dose)
Dystonia in the "off" period or due to end-of-dose deterioration

Table 5: *Dyskinesias due to chronic therapy with L-dopa.*

Peak dose dyskinesias: These manifest themselves in coincidence with the maximum therapeutic effect obtained after taking a dose of L-dopa and correlate with the maximum plasma level which corresponds to the greatest benefit in motor status. These compromise the orolingual region and the body area most compromised by PD. When these are severe they can cause disability, but not when they are mild.

Biphasic dyskinesias: They manifest at the beginning and at the end of the effect of a dose of L-dopa. They affect lower limbs as repetitive and stereotyped movements of flexion-extension, adduction-abduction of ankles, knees or hips. They can affect the trunk as severe dystonia in extension. During dyskinesias, motor status is deficient. The patient lives with dyskinesias and in an "off" motor status (rigidity/bradykinesia). They are associated with autonomic changes such as profuse sweating.

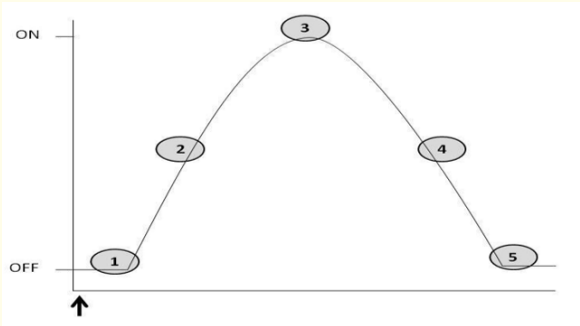


Figure 14: *Response curve to L-dopa, at the start of oral treatment.*

Dystonias "off": These are observed in line with decreased plasmatic levels of L-dopa and appear as a painful dystonia (dystonia of the hallux in extension or flexion, accompanied by a fanning of the rest of the toes). These appear in the morning, before taking the first dose of L-dopa. It is a frequent manifestation in parkinsonisms due to mutations in the parkin protein gene or in juvenile-onset PD, which can recur throughout the day [53].

Temporal profile of motor complications

Motor complications usually adopt a certain temporal profile throughout the course of PD. At first, morning akinesia on awakening is usually observed. Then, "off" periods appear at the end of each intake, called end-of-dose deterioration (wearing off). Before the appearance of peak dose dyskinesias (generally of a choreic type), the frequency of taking L-dopa should be increased and the dose amount decreased. This gives rise to the development of complex fluctuations accompanied by dyskinesias of various kinds. Biphasic dyskinesias and "on" phase dystonia may appear. Subsequently, in the "off" phase foot dystonias are observed in the early morning, with worsening of motor status at the end of the day. The occurrence of various types of dyskinesias and fluctuations determines a temporal profile, characteristic of each patient with PD throughout the day and variable throughout the disease. There is a correlation between the magnitude and duration of treatment with L-dopa and the development of motor complications. The main goal in the treatment of motor complications is to decrease the duration of the "off" periods and increase the "on" periods throughout the day [54,55].

Dopamine agonists

Dopamine agonists (DA) interact directly on the DR. The first DAs were developed from ergotamine (ergot derived DA) such as pergolide, bromocriptine, and cabergoline. Ergotamine side effects (ergotism) including valvular and subvalvular sclerosis of the aortic and/or mitral valves have been reported. A second generation of non-ergot DA like pramipexole, ropinirole, and rotigotine, were introduced in an attempt to reduce the side effects seen with ergot derived DA. DA have lower clinical efficacy compared to L-dopa. These were introduced as an adjunct to L-dopa in an attempt to improve motor function and reduce "off" time in patients with motor fluctuations. DA are drugs less likely to induce motor complications, due to their long half-life. Consequently, they were prescribed as initial therapy, although due to their low efficacy even at high doses, supplemental L-dopa is required in patients with severe PD. Ropinirole and pramipexole are marketed in immediate release and/or extended release oral formulations, in the latter case being able to be administered as a single daily dose. Rotigotine is administered as a transdermal patch in variable doses (2 mg, 4 mg, 6 mg or 8 mg), once a day, and more than one patch can be applied, increasing the dose/day, in exceptional cases reaching 16 or 24 mg/day. Patients must be informed how to apply the patch to prevent its detachment (Figure 15).

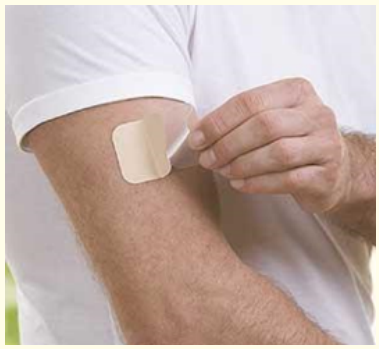


Figure 15: *Transdermal patch of rotigotine.*

Apomorphine is a non ergot DA with efficacy comparable to L-dopa. It is administered parenterally (subcutaneously), and has a very short half-life and duration of therapeutic action (45 min). It is prescribed as a rescue agent or in the treatment of severe "off" episodes, refractory to L-dopa. Apomorphine can be administered as a continuous subcutaneous infusion (apomorphine pump), demonstrating a clear reduction in "off" time in patients with severe PD. A variety of adverse effects associated with the prescription of DA in the acute and chronic phase have been described. Acute side effects due to dopaminergic action include nausea, vomiting and orthostatic hypotension, which can be avoided by slowly and progressively titrating the medication. Side effects after chronic administration of DA include visual hallucinations, cognitive impairment, sleep attacks (while driving), unilateral or bilateral lower limb edema, and impulse control disorders (ICD). ICD include pathological gambling, hypersexuality, and compulsive shopping. The adverse effects observed chronically are related to extended-release DA formulations and can be avoided or minimized by switching to lower-dose immediate-release DA formulations. The decrease in the dose of DA should be done gradually. Lower limb edema is reabsorbed after several weeks of suspending the DA and during the reabsorption, the patients alter the rhythm of diuresis (nocturia). Apomorphine injections and rotigotine patch administration can be complicated by the development of skin lesions (erythema) at the application sites [56].

Monoamine oxidase-B inhibitors

The Monoamine oxidase-B inhibitors (MAO-B I), prevent the degradation of L-dopa in the brain and limit its reuptake. Selegiline and rasagiline are relatively selective inhibitors of the MAO-B enzyme. Selegiline is a selective and irreversible MAO-B I used as an adjunctive medication to L-dopa. Rasagiline, a second-generation MAO-B I, lacks the amphetamine metabolites of selegiline and can be used as monotherapy and/or adjunctive therapy. Safinamide is another potent and reversible MAO-B I that has recently been approved as a treatment for PD patients who develop motor fluctuations. MAO B I, can be prescribed as monotherapy in early PD and reduce "off" time when used as an adjunct to L-dopa in patients with motor fluctuations [50]. They are well-tolerated and safe drugs. They can exacerbate dyskinesias in patients taking L-dopa, which subsides after lowering the L-dopa dose. Inhibition of the MAO-A isoform prevents tyramine metabolism in the intestine, leading to a hypertensive reaction, known as the "cheese effect" precipitated by foods high in tyramine such as some cheeses, red meats, and red wine. The doses of selegiline and rasagiline prescribed in clinical practice do not functionally inhibit MAO-A and consequently the "cheese effect" is unusual. In depressive PD patients treated with MAO-B I and selective serotonin reuptake inhibitor (SSRI) antidepressant drugs, there is a potential risk of developing serotonin syndrome which is uncommon in clinical practice. MAO-B I have aroused interest due to their potential disease-modifying effect (neuroprotective effect). MPTP (synthetic heroin derivative) toxicity can be prevented experimentally by co-administration of an MAO-B I that blocks its conversion to the toxic pyridinium ion MPP+, and can potentially block the oxidative metabolism of dopamine and prevent oxidative stress. The DATATOP study has shown that

selegiline significantly delays the onset of disability while delaying the introduction of L-dopa into the treatment regimen. It is unknown whether it is due to the neuroprotective effect that slows the progression of the disease or to the symptomatic effect that masks the ongoing neurodegeneration [57]. The ADAGIO study has recently shown that early-phase treatment of PD with rasagiline 1 mg/day, provides benefits that could not be achieved when treatment with the same drug is started in advanced phase, consistent with a disease-modifying effect, however the long-term significance of these findings is uncertain [58]

Catechol O methyltransferase inhibitor drugs

Catechol O methyltransferase inhibitor (COMT-I) reduces the degradation of L-dopa to 3-O-methyldopa and improves the availability of L-dopa at the central level. Administration of L-dopa associated with COMT-I, reduces "off" time and prolongs "on" time in patients with motor fluctuations while improving motor status scores [59]. Two COMT-I drugs have been tested: tolcapone and entacapone. A combination tablet of L-dopa, carbidopa, and entacapone, in variable doses, is currently available. The side effects of COMT-I are mainly dopaminergic (nausea, vomiting, exacerbation of dyskinesias) although they can be controlled by reducing the dose of L-dopa by 20 - 30%. Adverse effects such as severe and persistent diarrhea have been described with tolcapone and to a lesser extent with entacapone, in which case the medication should be withdrawn. Cases of acute fulminant toxic hepatitis with severe hepatocellular failure have been reported after tolcapone administration, requiring periodic monitoring of liver function [60]. This problem has not been reported with entacapone. COMT-I produces changes in urine color (orange), due to the accumulation of a metabolite, but it lacks clinical significance. It has been proposed to initiate drug treatment with L-dopa associated with a COMT-I in the context of a more continuous administration of L-dopa at frequent intervals and reduce the risk of motor complications, although this postulation has not been confirmed in clinical trials (SPRIDE-PD). Currently, the main value of COMT-I centers on patients who experience motor fluctuations of the end-of-dose impairment type, difficult to manage pharmacologically [61].

Amantadine

In the 1960s, amantadine was introduced into clinical practice as an antiviral agent. It has an antiparkinsonian effect, linked to its antagonistic properties on the N-methyl-d-aspartate (NMDA) receptor. It is prescribed in patients with early-stage PD where it reverses mild symptoms or in those with advanced-stage PD as an antidyskinetic agent. In fact, it is the only oral agent that has been shown in controlled studies to be effective in reducing dyskinesias without worsening the motor condition, although the benefits may be relatively transient. It can induce cognitive impairment similar to anticholinergic drugs. Other adverse effects include livedo reticularis, edema in the ankle region, and weight gain. Amantadine should be tapered gradually because patients may experience withdrawal symptoms. A new extended-release formulation of amantadine, ADS-5102, has been developed and can be prescribed for the management of L-dopa-induced dyskinesias [62].

Anticholinergics

Trihexyphenidyl and biperiden are centrally acting anticholinergic drugs, historically prescribed in the treatment of PD. Since the development of new dopaminergic agents, their use has been reduced in practice to particular situations. Its main clinical effect is the reduction of tremor, which adds to the benefit obtained with agents such as L-dopa, MAOI B and DA, and are specially useful in those patients with predominantly tremorous clinical forms. Its use is limited in elderly patients, due to the appearance of central or peripheral adverse effects such as urinary dysfunction, glaucoma, cognitive impairment, visual hallucinations, etc.

New drugs

The pending issue regarding the pharmacological treatment of PD includes the development of new drugs that can potentially 1-improve the antiparkinsonian effects, 2-reduce the "off" time and 3-treat or prevent dyskinesias. These include: 1- nicotinic agonists, 2-5-H1A agonists, 3- adenosine A2A antagonists and 4- glutamate antagonists.

Neuroprotection

PD is a neurodegenerative disorder that leads to a severe degree of disability. A neuroprotective therapy involves slowing or stopping the progression of the disease. No drug has reliably demonstrated such an effect. Clinical trials with certain drugs (selegiline and rasagiline), have provided positive results consistent with a theoretical PD-modifying effect. However, it is not possible to determine whether the positive results were due to neuroprotection that slows disease progression or symptomatic effects that mask PD progression [63].

Treatment strategies for PD in the early phase

The treatment of PD consists of a dopamine replacement strategy (dopaminergic therapy). There is no benefit in delaying treatment in a patient with symptomatic PD, so it should be prescribed after diagnosis. The pharmacological treatment scheme must consider the degree of motor and non-motor compromise considering to: 1-age of the patient, 2-associated comorbidities, 3-family and work status and 4-quality of life. Patients can consult due to presenting any of the cardinal signs, being unaware of their disease or seeking a second opinion on the diagnosis or prescribed treatment. When communicating the diagnosis, the presence of a family member is convenient, in order to alleviate the emotional impact. On the other hand, it is advisable to promote the confidence of the recently diagnosed patient towards the health team so that they can evacuate any possible doubts or fears that may arise after their diagnosis. Initially and during the first years of treatment, L-dopa is a reliable, safe and effective drug in remitting the symptoms of PD. In this first stage of the disease, the development of motor complications is infrequent. The initial and subsequent dose of L-dopa associated with a peripheral decarboxylase inhibitor is usually low (100 to 300 mg L-dopa/d). During outpatient follow-up, this dose may be increased according to the clinical response. In patients under 65 years of age, MAO-B I or/and DA may be tested as a monodrug therapy, together (MAO B I + DA) or associated with standard formulations of L-dopa (MAO-B I+ DA + L-dopa), in accordance with the severity of the clinical picture (L-dopa saving strategies). High doses of DA can be limited in those patients with PD who develop adverse effects. In patients older than 65 years, who show excessive daytime sleepiness, cognitive impairment or other comorbidities, it will be appropriate to start treatment with standard formulations of L-dopa. DA, MAO-B I, and anticholinergics are more likely to cause cognitive/behavioral disturbances in elderly patients than L-dopa. Physiotherapy rehabilitation and physical exercise (strength training exercises, yoga, dance, and music therapy) should be encouraged. Neurocognitive rehabilitation should be considered in those patients with cognitive complaints [64,65].

Treatment strategies for advanced-stage PD

In advanced-stage PD, the storage capacity (buffer) and release of endogenous dopamine is reduced. This situation leads to a reduction in the benefit time of each dose of L-dopa. The space between each dose, initially every 6 hours, is gradually reduced until reaching a half-life that ranges from 60 to 90 minutes. Patients experience a decrease in the effectiveness of the medication and symptoms return before the next dose, known as "end-of-dose deterioration". Subsequently, motor fluctuations and L-dopa induced (LID) appear. In the chronic course, complex and unpredictable dyskinesias occur for much of the day. Pulsatile stimulation of DR plays an important role in the genesis of motor fluctuations [66]. In the advanced phase, autonomic dysfunction and consequent slow gastric emptying ensue, further contributing to uneven drug absorption. Non-motor fluctuations involve the neuropsychiatric spectrum with symptoms such as depression, fatigue, and anxiety. The objective of the treatment of PD in advanced phase is to optimize the "on" time, reduce the "off" time and attenuate the motor complications induced by L-dopa. The "off" time can be improved by shortening the intervals between doses of L-dopa. Another strategy involves the use of prolonged release L-dopa formulations, adding an I-COMT, a MAO-B I, or adding an immediate or extended release DA, which allows for a more stable response. The pharmacological approach to motor complications must be done jointly with the patient and the family or caregivers in order to adapt the best treatment strategy. The redistribution of medication doses and the change from immediate release formulations to extended release formulations significantly improve these motor complications. Amantadine reverses dyskinesias induced by L-dopa. A sustained-release formulation is now available, which reduces LID and downtime.

In those patients with advanced PD who receive suboptimal treatment despite trying various pharmacological strategies, other treatment alternatives can be considered: 1- new oral formulations, 2- intestinal gel of L-dopa-carbidopa, 3- continuous infusion of subcutaneous apomorphine or 4- deep brain stimulation surgery. MRI-guided ultrasound lesion treatment opens up a new spectrum of therapeutic possibilities [67].

Treatment of non-motor symptoms

The non-motor symptoms (NMS) of PD are usually observed 1- in the premotor phase (hyposmia, constipation, depression, REM sleep disorders), 2- at the onset of motor symptoms and 3- during the course or in the late phase of the disease (psychosis, hallucinations, dementia). NMS may have a slowly progressive or fluctuating course throughout the day, known as non-motor wearing-off. The treatment of mental manifestations such as hallucinations and delusions, implies the management of precipitating factors (infection, dehydration, alterations of the internal environment), withdrawal of medication that may aggravate the clinical picture or administration of atypical antipsychotic drugs to control the symptoms (clozapine, quetiapine, olanzapine). Pimavanserin, a new antipsychotic drug with a different pharmacological profile, has recently been introduced, which is effective in controlling hallucinations refractory to atypical antipsychotics. The adverse effects of these drugs should be monitored in the medium or long term. Some patients develop Impulse Control Disorders (ICD). Other patients develop a dopaminergic dysregulation syndrome, characterized by the compulsive use of medication, associated with aggressiveness, restlessness, or self-injurious behaviors, which subsides when the medication is gradually reduced. Depression improves after administration of tricyclic antidepressants or selective serotonin reuptake inhibitors. Cognitive impairment can progress to dementia and can be partially reversed with a choline acetyltransferase inhibitor such as donepezil or rivastigmine, in variable doses for each case [68].

Continuous dopaminergic stimulation strategies

L-dopa/carbidopa intestinal gel

Nyholm., *et al.* (2005) administered a gel formulation of L-dopa through a catheter in the abdominal wall [69]. That gel formulation, initially approved in Europe, was approved in 2015 by the FDA in the USA. It constitutes a treatment option in patients with advanced PD with refractory symptoms that compromise their quality of life. The intrajejunal infusion of the gel is very useful in the treatment of motor fluctuations [70,71]. The gel is administered while awake, using a portable pump, through an indwelling tube that passes through the abdominal wall, stomach, and small intestine, a technique known as percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). Continuous infusion achieves stable plasma levels of L-dopa, thus reducing motor complications. Inclusion criteria include: 1- cardinal symptoms of PD must respond to high-dose oral formulations of L-dopa, 2- have at least 25% symptom-free time in the awake state, 3- have tried various treatment options including standard formulations of L-dopa, MAO-B I, COMT I and DA in immediate and extended release formulations, without enough benefit. Exclusion criteria include: 1-failure to respond to oral formulations of L-dopa; 2-suffering from psychosis or severe dementia. Before starting treatment, the patient is evaluated by a multidisciplinary team that determines the suitability of the procedure. A demonstration of the PEG-J, infusion pump, and medication cassette should be provided to the patient and family members, explaining the risks, benefits and limitations of such therapy, and cross-referenced with the patient's expectations. Before the start of therapy, the patient must undergo the insertion of a naso-jejunal tube for a few days to see the degree of response to the gel. If it is favorable, the patient should be referred to a gastroenterologist to evaluate the possibility of performing the PEG-J. L-dopa gel is administered continuously during the awake state. The pump is turned on in the morning and turned off at night. The L-dopa gel infusion system consists of four parts: 1- outer PEG tube, 2- inner J-tube, which is placed inside the PEG tube through the stomach into the jejune, 3- CADD pump, which delivers the gel continuously, 4- cassette, consisting of a container holding the L-dopa gel, connected to the pump, in a 4 to 1 ratio (2,000 mg of L-dopa/ 500 mg of carbidopa) (Figure 16).

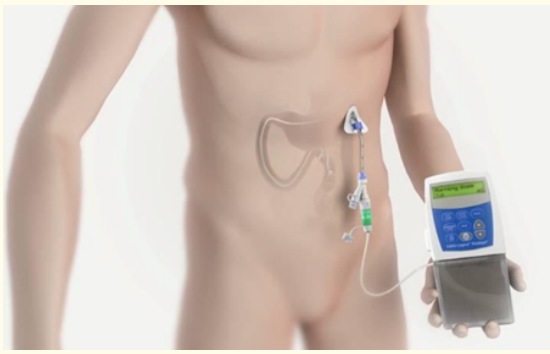


Figure 16: *Device for intrajejunal infusion of L-dopa gel.*

The cassette should be stored in the refrigerator and changed once a day. The implantation of the device consists of two stages namely: 1-A combination of two tubes (PEG-J) is inserted into your stomach through the abdominal wall to the small intestine, 2-After two to three weeks after PEG-J insertion, therapy with L-dopa gel is started. The CADD pump with the medication cassette is connected to the PEG tube, being observed by the neurologist who will adjust the medication dose. Dosing regimens are programmed into the pump individually. Complications may be seen at the percutaneous implant site. Side effects such as ileus, colon perforation, pneumoperitoneum, perforating ulcer or gastrointestinal bleeding have been described. A clinical trial compared the effect of the gel to an equivalent oral formulation of L-dopa and it was effective in reducing the "off" time and extending the "on" time, without generating problematic dyskinesias [72]. Intrajejunal infusion is a therapeutic option in patients with motor complications refractory to conventional drug treatment [73]. In a clinical trial developed in Italy, patients treated with intrajejunal infusion of L-dopa were evaluated, observing a clear improvement in motor symptoms and a significant reduction in dyskinesias [74].

Continuous subcutaneous apomorphine infusion (CSAI)

Apomorphine, the oldest and most potent DA drug, activates striatal DR, D1 and D2 [75]. It is soluble in water and can be administered parenterally. It is rapidly absorbed after subcutaneous injection and has a short half-life, achieving a rapid clinical response within 10 minutes of administration. It has been prescribed as an analgesic, in insomnia, chronic alcoholism and/or psychosis. It is used as a rescue drug to overcome the "off" states. It is administered subcutaneously or sublingually. It induces vomiting and prior to its administration, a drug with an antiemetic effect (domperidone) should be prescribed, 10 mg in 3 doses /day, for 3 days. In the US, the FDA approved subcutaneous injection of apomorphine to overcome "off" episodes. In Europe it is used by continuous subcutaneous infusion, to provide a stable response in those patients who fluctuate between "dyskinetic" and "off" states (Figure 17) [76]. Apomorphine has an antiparkinsonian effect similar to L-dopa. An improvement in the "off" time and a reduction in the appearance of dyskinesias were reported [77]. The introduction of DA, MAO-B I and COMT I, allowed the development of L-dopa saving strategies, delaying the appearance of motor complications. CSAI as monotherapy is only effective in high doses (100 mg/d), not without side effects in the behavioral sphere. The addition of an oral formulation of L-dopa changes stable drug levels to a pulsatile way, with recurrence of dyskinesias. The effect of CSAI was compared to deep brain stimulation surgery in a clinical trial. Each cohort of patients had a similar magnitude of "off" time and dyskinesias at baseline.

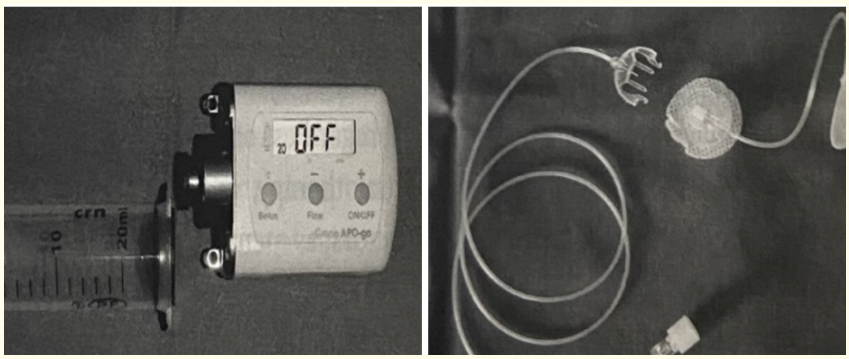


Figure 17: *Continuous subcutaneous apomorphine infusion pump (CSAI).*

After twelve months, clinical and neuropsychological evaluation demonstrated a 50% reduction in "off" time/day and a 30% reduction in L-dopa dose/day, with no change in the incidence of dyskinesias. The neuropsychiatric evaluation did not show behavioral changes or cognitive functions [78]. In the two-year follow-up of CSAI, a drop in motor response was observed, as well as the appearance of ICD and behavioral changes: gambling, internet addiction, hypersexuality, suspending treatment. When CSAI is indicated, oral DAg must be interrupted. The infusion begins by administering 1 mg/hour, maintaining the dose/day of L-dopa. Then the dose of apomorphine is increased, while the dose of L-dopa is reduced until it is withdrawn. Adverse effects for CSAI were reported: 1-subcutaneous nodules, 2-sedation and drowsiness, 3-nausea and vomiting, 4-orthostatic hypotension [36]. The inclusion criteria are: 1-patients who respond to L-dopa and with motor complications refractory to the various treatment options. The exclusion criteria are: 1-cognitive impairment, 2-neuropsychiatric disorders, 3-old age, 4-severe complications, 5-psychiatric complications induced by dopaminergic drugs. It is important that patients with PD who choose CSAI have a supportive family group that cares for them primarily at the beginning of treatment [79].

High intensity focused ultrasound (HIFU)

HIFU constitutes a new form of non-invasive ablative surgery of basal ganglia. It consists of releasing acoustic energy (ultrasound) in the tissues, which generates focused lesions by concentrating ultrasound beams on the chosen target. The HIFU equipment is mounted on a high field resonator (3 Tesla). Before the procedure, the patient is evaluated by CT and MRI to rule out structural brain lesions and visualize the target where the ultrasound will be directed in real time. Ultrasound is applied guided by MR imaging (Figure 18), which allows treatment monitoring, including temperature control. During the procedure, the patient remains awake and is constantly examined by the neurologist who is verifying clinical improvement in situ. A stereotactic frame is used, which allows the correct localization of the objective within the cranial cavity. The patient is located in the resonator (Figure 19) and his head is covered with a cooling water membrane, avoiding damage from high temperatures. Ultrasound beams are applied increasing the temperature until reaching 50ºC and in case of a favorable response, the temperature is increased up to 60ºC. It constitutes a non-invasive and precision procedure for the treatment of patients with ET and its use has currently been extended to patients with PD. However, further clinical trials must be awaited [80].

Surgical treatment

Surgical treatment of PD should be considered in those patients in whom the different pharmacological options prescribed do not achieve adequate control of the symptoms or when refractory motor or non-motor complications occur.

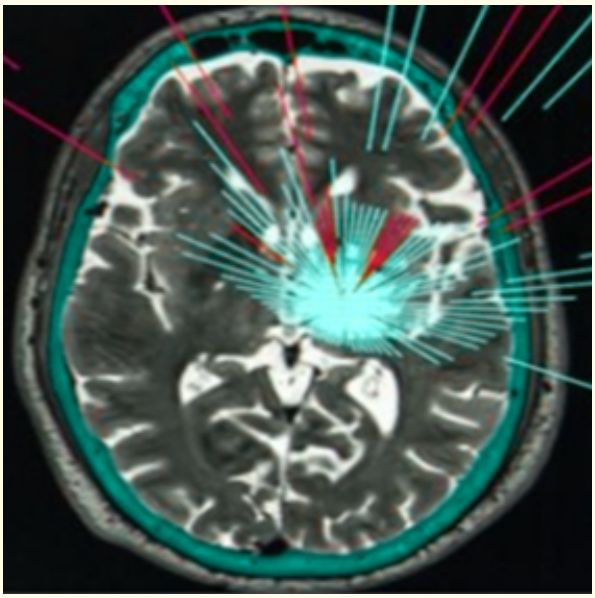


Figure 18: *Ultrasound beams are displayed.*

Figure 19: *Positioning the patient on the MRI.*

Lesion surgeries

Lesion surgery is another surgical treatment option but it is not currently used (VIM nucleus thalamotomy), subthalamotomy or pallidotomy (unilateral). Ablative procedures are associated with irreversible adverse effects such as damage to the internal capsule or the visual pathway after pallidotomies or dysphagia, dysarthria, and cognitive failures resulting from bilateral lesions. Surgery lesions preclude future deep brain stimulation (DBS) treatments that require indemnity of basal nuclei structures.

Deep brain stimulation

DBS consists of modulating brain circuits through electrical stimulation (electrical field), from an implanted current source [81]. It was developed in 1987 (Alim Benabid, Grenoble), by stimulating the thalamus and observing the remission of a tremor in the contralateral hemibody [82]. Since then to date, more than 150,000 patients in the world have undergone DBS surgery. The current development of DBS is due to a better understanding of the pathophysiology of the basal ganglia involved in movement control: STN (subthalamic nucleus), GPi (globus pallidus internus), VIM (ventral intermediate thalamus) and PPN (pontine nuclei). DBS has shown marked improvement in tremor, dyskinesias, and motor fluctuations. It constitutes a programmable and reversible procedure. The correct selection of the patient

and the implantation of the electrode in the optimal target are keys to surgical success. Most DBS procedures are performed within 10 years of PD diagnosis, but the EARLY STIM trial (Controlled Trial of Deep Brain Stimulation in Patients with Early Parkinson's Disease) suggests that PD may be indicated in the early phase of the disease when the severity of the condition so indicates [81]. The exclusion criteria for DBS include: 1- presence of atypical parkinsonism, 2- neuropsychiatric manifestations refractory to medical treatment, 3- PD in an advanced phase with severe cognitive impairment, 4- comorbidities that may compromise the intra and postoperative period, 5- advanced age. The choice of a particular target must be individualized and for this, the following elements must be considered: 1- the predominant symptoms in each patient such as tremor, rigidity, bradykinesia and/or postural disorders, 2- the clinical characteristics of the motor complications observed as fluctuations (end-of-dose deterioration, morning akinesia or off-period dyskinesia) or dyskinesias (peak dose type and/or biphasic dyskinesias), 3- the cognitive status of the patient with PD, 4- associated neuropsychiatric disorders, 5- absence of structural lesions in neuroimaging studies, 6- absence of associated comorbidities that could make surgery difficult, 7- need to reduce the daily requirements of dopaminergic medication (STN), 8- possibility of controlling excessive dyskinesias or dystonias (GPi) or severe postural and gait disorders (NPP) [83]. Surgical planning for DBS requires preoperative multiplanar T1, T2, and Flair images of brain MRI with IV gadolinium. The target is identified through the patient's specific anatomy (direct targeting) with or without reference to the stereotactic coordinates established for each target (indirect targeting) and the electrode trajectory is planned to avoid vascular structures.

Advances in neurosurgical techniques through the development of a stereotactic framework (Figure 20A) and the best quality in the acquisition of Computed Tomography (CT) and Magnetic Resonance (MR) images of the brain (Figure 20B), have made it possible to reduce the margin of error of these procedures [84].

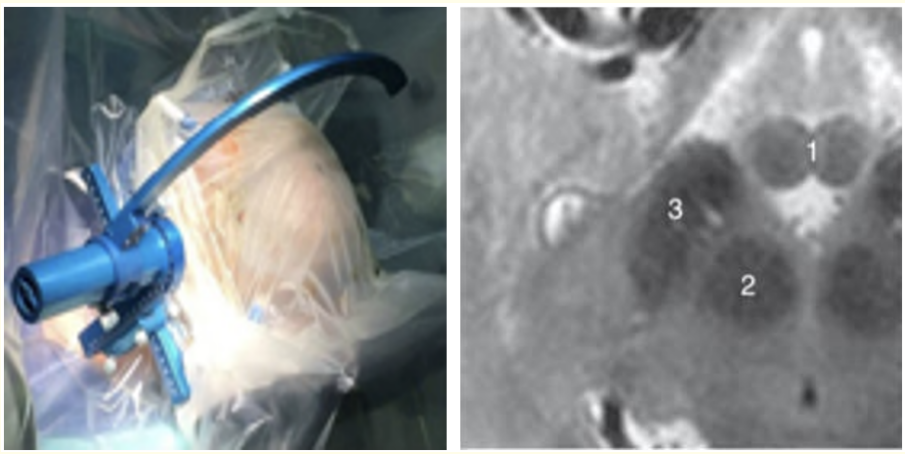


Figure 20A: *Stereotactic frame.* ***Figure 20B:*** *MRI 1. Mammillary tubercles, 2. N.R., 3. STN.*

DBS consists of the introduction of unilateral or bilateral electrodes (Figure 21A and 21B) in various targets according to the symptoms that predominate in each patient. During the surgical procedure, an intraoperative micro-recording (MER) is performed (Figure 22A and 22B) that allows the exact location of the electrode to be established.

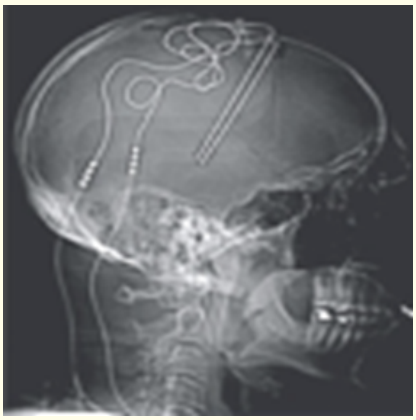


Figure 21A: *Implanted device.*

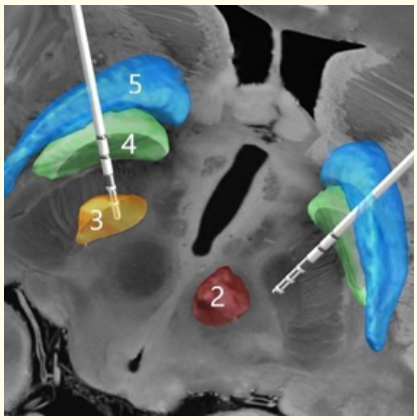
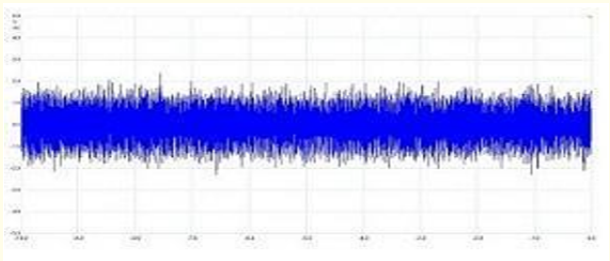
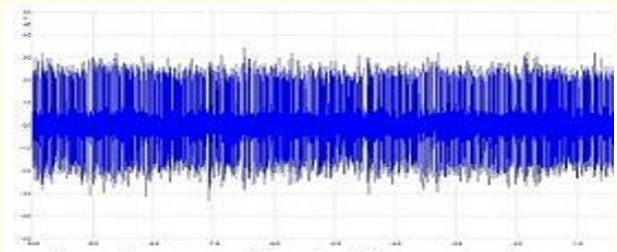


Figure 21B: *Implanted electrodes (STN).*



A. Micro electrode recording (MER) STN



B. Micro electrode recording (MER) GPi

Figure 22A and 22B: *Intra-operative micro-registration images. DBS Surgery.*

During the surgical procedure, once the MER is finished, intra-operative stimulation is performed. This makes it possible to identify the best contact that remits the symptoms. The DBS electrodes are implanted in the optimal target chosen. That electrode generates a micro lesion, and it is connected by a wire to an implanted impulse generator (IPG) under the skin near the clavicle. Two to three weeks after surgery, when the effect of the micro lesion and the perilesional edema subside, the implanted IPG is turned on and programmed. It is

programmed with stimulation parameters designed to deliver current to the appropriate areas, making symptoms disappear. The parameters of frequency, voltage and pulse width are configured in each electrode, choosing the stimulation point that improves the patient's symptoms. The pharmacological treatment should be adapted, taking into account that the DBS of the subthalamic nucleus saves L-dopa while the DBS of the Gpi remits dyskinesias. DBS does not cause damage to the brain parenchyma (the electrodes have a diameter of less than 1 mm) and therefore brain stimulation procedures can be carried out in both cerebral hemispheres in order to obtain the maximum benefit in the contralateral hemi-body and the least effects adverse. DBS achieves effective control of the motor symptoms of the disease as well as the motor complications derived from chronic L-dopa therapy. The DBS allows, through a different programming in each electrode, to compensate the usual asymmetry of PD and to unify the symptoms in both sides of the body. Pharmacological treatment is not excluded and consequently the symptoms of PD require the summative effect of both treatment strategies (medical and surgical) for their control [85]. The DBS depends on the accumulated energy in the battery, so it must be replaced periodically. Batteries with a life of more than a decade have been developed, and there are even rechargeable batteries similar to cell phones that need to be recharged weekly. DBS is considered a treatment strategy that should be added to pharmacological and rehabilitation treatment. To date, however, there are non-motor symptoms that are refractory to all types of treatment. Patients undergoing DBS may present medical complications: 1- myocardial infarction, 2- pneumonia, 3- deep vein thrombosis, 4- pulmonary thromboembolism. Surgical complications may present: 1- cerebral hematoma, 2- cerebrovascular accident, 3- seizures, 4- infections, and 5- hardware dysfunction, all reported in a small percentage of patients. Side effects include paresthesias, dysarthria, ataxia, and mood dysregulation, generally reversible by changing pacing parameters [86,87].

Ambulatory control

For years, the neurologist must monitor the patient on an outpatient basis, establishing a close doctor-patient relationship. Motor and non-motor symptoms should be recognized, including unsteadiness and falls, swallowing disorders, constipation, and mood disorders such as depression. The progressive nature of PD implies periodic adjustments of the medication. An exhaustive questioning and physical examination will make it possible to adjust the doses of dopaminergic and/or symptomatic medication. The patient can keep a journal to write the time of taking each dose and the pattern of response, thus being able to establish the necessary time corrections to adjust the medication. The pharmacokinetics and pharmacodynamics of the prescribed drugs should be considered: 1- how long does it take for the dose of medication to take effect, 2- how long does the effect of each dose last, 3- note the appearance of dyskinesias after taking a dose of L-dopa, 4- if the dyskinesia appear at the beginning, during or at the end of the dose interval, 5- if the effect of a dose decays before taking the next dose of medication, 6- how much time elapses between the loss of the effect of a dose and the favorable response of the next dose, 7- if patient experience dystonia or pain in the hallux early in the morning, 8- how much time elapses between taking the 1st dose of medication and the disappearance of the painful morning dystonia, 9- dystonia occurs at other times of the day, 10- if patient notice a drop in response to medication during the day, 11- if these periods are observed close to meals. Based on the information received, the changes in the dosage are established, which allows increasing the ''on'' periods and reducing the ''off'' ones. Various switching strategies should be considered: 1- if a predictable decrease in effect occurs, the medication dose may need to be increased or dosed more frequently, or another formulation of L-dopa may be used, 2- if dystonia occurs early in the morning, patients may benefit from an extended-release formulation of L-dopa at bedtime, 3- if patients report lack of medication efficacy after a protein-rich meal, they are advised to take smaller doses of protein throughout the day, 4- severe dyskinesias, which compromise quality of life, can be mitigated with an NMDA antagonist, by redistribution of the dose of L-dopa, or through surgery of deep brain stimulation (Gpi bilateral) [39]. Rehabilitation has a determining role in the chronic management of patients with PD. It is carried out by a multidisciplinary team that includes speech therapy, psychotherapy, psychiatry, occupational therapy, kinesiology, neurocognitive therapy, nutritional counseling and active participation in self-help groups [88].

Immunity and PD

The role of immunity in PD is evaluated establishing a new treatment strategy called immunotherapy. Since the common end event in PD patients results from the abnormal accumulation and dissemination of alpha-synuclein (ASN) in dopaminergic neurons at different levels of the CNS, neuronal clearance of ASN is of particular importance (anti-ASN immunotherapy). This type of therapy involves immunization (active or passive), being the active one that induces the patient to generate antibodies against a certain antigen or passive by administering to the patient antibodies directed against known antigens. As an example of this, administering a monoclonal antibody against ASN (passive) or administering a vaccine made from peptides that mimic the molecular structure of ASN and consequently the patient generates its antibodies (active). To date, clinical trials with active or passive immunotherapy in PD have not yielded conclusive results [89].

Emerging therapies

PD results from an interaction between genome and environmental factors. Approximately 10% of PD cases are linked to known genetic abnormalities. An early phase treatment strategy could slow down or prevent the neurodegenerative process. The GBA gene encodes a glucocerebrosidase (GCase) enzyme, responsible for lipid metabolism in the lysosomes. Between 5 to 15% of the patients with PD have mutations in the GBA gene. These mutations cause a decrease in GCase activity, affecting the metabolism of alpha-synuclein and consequently its intracellular accumulation. The GCase protein is used in various investigations as a target to prevent neurodegeneration. Two promising therapies consist of 1- enzyme replacement (ERT) and 2- substrate reduction (SRT). ERT is based on the administration of an active recombinant GCase protein that increases the levels of the enzyme, preventing the accumulation of alpha synuclein. SRT reduces the intracellular accumulation of GCase substrates. These molecules do not cross the blood-brain barrier (BBB). Techniques are tested to incorporate peptides that allow them to do so and, in this way, reach the neuronal environment. A gene therapy approach is being explored that allows intracerebral active recombinant GCase protein to be delivered by a viral vector [90,91]. The LRRK2 gene codes for the Dardarin protein, which, through its kinase activity, controls several important cellular pathways for immune functions such as the secretion of inflammatory mediators and chemotaxis-mediated migration. The LRRK2 gene, a positive modulator of neuroinflammation forms the pathophysiological substrate for the development of PD. Immunotherapy models in which an LRRK2 inhibitor is administered to decrease the neuronal pro-inflammatory state are being explored [92] (Figure 23).

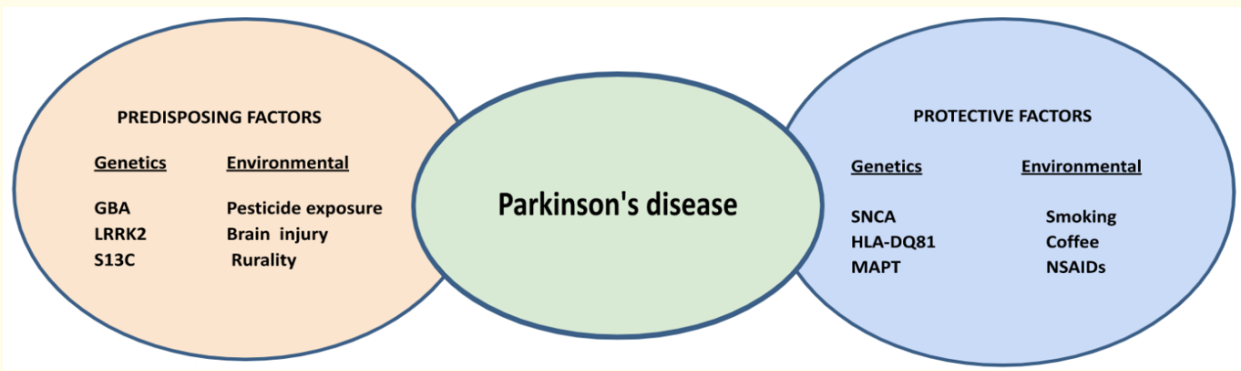


Figure 23: *Exposure to certain environmental factors would modify the risk of developing PD. Certain genes would be involved in the development of PD (GBA and LRRK2) [93].*

Conclusion

PD is a heterogeneous and progressive neurodegenerative disease. It affects millions of people in the world and its prevalence increases with age. The diagnosis is clinical and there is no biological marker or complementary study that allows arriving at a certain diagnosis. Genetic causes involve 10% of cases, while the genetic and environmental component responsible for the rest is unknown. Cardinal and minor symptoms, motor and non-motor, should be recognized. PD is divided into preclinical, prodromal, and clinical phases. Various neuroimaging studies: PET/SPECT with radioactive markers for DA and mesencephalic ultrasonography, make it possible to differentiate PD from other neurological conditions. New drugs and new formulations of dopaminergic drugs have been developed in an attempt to alleviate motor and non-motor symptoms. Patients respond effectively to L-dopa which continues to be the drug of choice. Within the differential diagnoses, atypical parkinsonisms (PSP, MSA and/or DCB) and their characteristic lack of response to L-dopa should be recognized. Clinical rating scales are useful for monitoring response to treatment and assessing the progression of PD. The chronic and progressive nature of PD implies an exhaustive clinical follow-up that allows adapting the different treatment strategies. The definitive cure for PD is currently unknown, so treatment continues to be symptomatic. The treatment is based on optimizing the "on" time and reducing the "off" time. The development of effective biomarkers will allow, in the future, knowledge of PD from its preclinical phase. Neuroprotective and neuronal restoration therapies should be investigated. The role of immunity within the new treatment options is studied. When pharmacological strategies exhaust their spectrum of action and refractory motor and non-motor complications occur, new therapies with intrajejunal L-dopa gel or subcutaneous apomorphine by continuous infusion pump can be used. Surgical treatment (lesion or DBS) should be considered in those patients with PD whose symptoms are refractory to the various medical treatment strategies. HIFU is a new non-invasive lesion treatment option currently under study.

Dedication

To our beloved families, for their love and constant support.

Comment

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