PARKINSON'S DISEASE

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Abstract

Parkinson's disease is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills, speech, and other functions. Parkinson's disease affects movement (motor symptoms). Other typical symptoms include disorders of mood, behaviour, thinking, and sensation (non-motor symptoms). The symptoms of Parkinson's disease result from the greatly reduced activity of the dopaminergic neurons, which are primarily in the pars compacta region of the substantia nigra. Reviews of depression estimate its occurrence in anywhere from 20-80% of cases. PD is not considered to be a fatal disease by itself, but it progresses with time.

PREFACE

Parkinson's disease is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills, speech, and other functions.

Parkinson's disease belongs to a group of conditions called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and, in extreme cases, a loss of physical movement (akinesia). The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunction and subtle language problems. PD is both chronic and progressive.

PD is the most common cause of chronic progressive parkinsonism, a term which refers to the syndrome of tremor, rigidity, bradykinesia and postural instability. PD is also called "primary parkinsonism" or "idiopathic PD" (classically meaning having no known cause although this term is not strictly true in light of the plethora of newly discovered genetic mutations). While many forms of parkinsonism are "idiopathic", "secondary" cases may result from toxicity most notably of drugs, head trauma, or other medical disorders. The disease is named after English physician James Parkinson, who made a detailed description of the disease in his essay: "An Essay on the Shaking Palsy" (1817).[1]

SIGN AND SYMPTOM

Parkinson's disease affects movement (motor symptoms). Other typical symptoms include disorders of mood, behaviour, thinking, and sensation (non-motor symptoms). Patients' individual symptoms may be quite dissimilar and progression of the disease is also distinctly individual.

The cardinal symptoms are:

- Tremor: normally 4-6 Hz tremor, maximal when the limb is at rest, and decreased with voluntary movement. It is typically unilateral at onset. This is the most apparent and well-known symptom, though an estimated 30% of patients have little perceptible tremor; these are classified as akinetic-rigid.
- Rigidity: stiffness; increased muscle tone. In combination with a resting tremor, this produces a ratchety, "cogwheel" rigidity when the limb is passively moved.
- Bradykinesia/akinesia: respectively, slowness or absence of movement. Rapid, repetitive movements produce a

dysrhythmic and decremental loss of amplitude.
- Postural instability: failure of postural reflexes, which leads to impaired balance and falls.

Other motor symptoms include:

- Gait and posture disturbances:
  - Shuffling: gait is characterized by short steps, with feet barely leaving the ground. Small obstacles tend to cause the patient to trip.
  - Decreased arm-swing.
  - Turning "en bloc": rather than the usual twisting of the neck and trunk and pivoting on the toes, PD patients keep their neck and trunk rigid, requiring multiple small steps to accomplish a turn.
  - Stooped, forward-flexed posture. In severe forms, the head and upper shoulders may be bent at a right angle relative to the trunk (camptocormia).[3]
  - Festination: a combination of stooped posture, imbalance, and short steps. It leads to a gait that gets progressively faster and faster, often ending in a fall.
  - Gait freezing: "freezing" is a manifestation of akinesia (an inability to move). Gait freezing is characterized by an inability to move the feet which may worsen in tight, cluttered spaces or when attempting to initiate gait.
  - Dystonia (in about 20% of cases): abnormal, sustained, painful twisting muscle contractions, often affecting the foot and ankle (mainly toe flexion and foot inversion) which often interferes with gait.

Speech and swallowing disturbances.

  - Hypophonia: soft speech. Speech quality tends to be soft, hoarse, and monotonous. Some people with Parkinson's disease claim that their tongue is "heavy" or have cluttered speech.[4]
  - Monotonic speech.
  - Festinating speech: excessively rapid, soft, poorly-intelligible speech.
  - Drooling: most likely caused by a weak, infrequent swallow and stooped posture.
  - Dysphagia: impaired ability to swallow. Can lead to aspiration, pneumonia.
- Other motor symptoms:
  - Fatigue (up to 50% of cases);
  - Masked faces (a mask-like face also known as hypomimia), with infrequent blinking;[5]
  - Difficulty rolling in bed or rising from a seated position;
  - Micrographia (small, cramped handwriting);
  - Impaired fine motor dexterity and motor coordination;
  - Impaired gross motor coordination;
  - Akathisia, the inability to sit still.

Neuropsychiatric

Parkinson's Disease causes cognitive and mood disturbances, being in many cases related.Estimated prevalence rates of depression vary widely according to the population sampled and methodology used. Reviews of depression estimate its occurrence in anywhere from 20-80% of cases.[6] Estimates from community samples tend to find lower rates than from specialist centres. Most studies use self-report questionnaires such as the Beck Depression Inventory, which may overinflate scores due to physical symptoms. Studies using diagnostic interviews by trained psychiatrists also report lower rates of depression. More generally, there is an increased risk for any individual with depression to go on to develop Parkinson's disease at a later date.[7] Seventy percent of individuals with Parkinson's disease diagnosed with pre-existing depression go

on to develop anxiety. Ninety percent of Parkinson's disease patients with pre-existing anxiety subsequently develop depression; apathy or abulia.

Cognitive disturbances include:

- Slowed reaction time; both voluntary and involuntary motor responses are significantly slowed.
- Executive dysfunction, characterized by difficulties in: differential allocation of attention, impulse control, set shifting, prioritizing, evaluating the salience of ambient data, interpreting social cues, and subjective time awareness. This complex is present to some degree in most Parkinson's patients; it may progress to:
- Dementia: a later development in approximately 20-40% of all patients, typically starting with slowing of thought and progressing to difficulties with abstract thought, memory, and behavioral regulation. Hallucinations, delusions and paranoia may develop.
- Short term memory loss; procedural memory is more impaired than declarative memory. Prompting elicits improved recall.[1]
- Non-motor causes of speech/language disturbance in both expressive and receptive language: these include decreased verbal fluency and cognitive disturbance especially related to comprehension of emotional content of speech and of facial expression.[8]
- Medication effects: some of the above cognitive disturbances are improved by dopaminergic medications, while others are actually worsened.[9]

Sleep

- Excessive daytime somnolence
- Initial, intermediate, and terminal insomnia
- Disturbances in REM sleep: disturbingly vivid dreams, and rapid eye movement behavior disorder, characterized by acting out of dream content can occur years prior to diagnosis

Perception

- Impaired visual contrast sensitivity, spatial reasoning, colour discrimination, convergence insufficiency (characterized by double vision) and oculomotor control
- Dizziness and fainting; usually attributable orthostatic hypotension, a failure of the autonomic nervous system to adjust blood pressure in response to changes in body position
- Impaired proprioception (the awareness of bodily position in three-dimensional space)
- Reduction or loss of sense of smell (hyposmia or anosmia) - can occur years prior to diagnosis
- pain: neuropathic, muscle, joints, and tendons, attributable to tension, dystonia, rigidity, joint stiffness, and injuries associated with attempts at accommodation

Autonomic

- Oily skin and seborrheic dermatitis
- Urinary incontinence, typically in later disease progression
- Nocturia (getting up in the night to pass urine) — up to 60% of cases
- Constipation and gastric dysmotility that is severe enough to endanger comfort and even health
- Altered sexual function: characterized by profound impairment of sexual arousal, behavior, orgasm, and drive is found in mid and late Parkinson disease. Current data addresses male sexual function almost exclusively.
- Weight loss, which is significant over a period of ten years. [10]

PARKINSON DISEASE CAUSES

The challenge that remains is to discover how these neurons are destroyed to cause Parkinson disease.

- Many theories have been put forward, but most researchers believe that Parkinson disease is not due to a single culprit but rather a combination of both genetic susceptibility and environmental stresses causing brain cell death.

- Studies have found that living in a rural area, drinking well water, or being exposed to pesticides, herbicides, or wood pulp mills may increase your risk for developing Parkinson disease.

- It has been demonstrated that 5-10% of people with PD have a genetic tendency. A recent study identified a specific gene mutation in a group of people who were related. Although this gene mutation is not responsible for all causes of PD, this finding may give scientists the opportunity to develop an animal model to gain insight into PD.

- Currently, one of the most promising theories is the oxidation hypothesis.

    - It is thought that free radicals may play a role in the development of Parkinson disease. Free radicals are chemical compounds with a positive charge that are created when dopamine is broken down by combining it with oxygen.

    - This breakdown of dopamine by an enzyme called monoamine oxidase (MAO) leads to the formation of hydrogen peroxide.

    - A protein called glutathione normally breaks down the hydrogen peroxide quickly. If the hydrogen peroxide is not broken down correctly, it may lead to the formation of these free radicals that then can react with cell membranes to cause cell damage and something called lipid peroxidation (when the hydrogen peroxide interacts with lipids [fat soluble substances] in the cell membrane).

    - In PD, glutathione is reduced, which may mean that you have a loss of protection against the formation of these free radicals.

    - Also, iron is increased in the brain and may help form free radicals.

    - In addition, lipid peroxidation is increased in Parkinson disease.

    - The association of Parkinson disease with increased dopamine turnover, decreased mechanisms (glutathione) to protect against free radical formation, increased iron (which makes it easier to create free radicals), and increased lipid peroxidation helps support the oxidation hypothesis.

    - If this hypothesis turns out to be correct, it still does not explain why or how a loss of the protective mechanism occurs. An answer to this question may not be required. If the theory is correct, drugs may be developed to stop or delay these events.[11]

PATHOPHYSIOLOGY

- The symptoms of Parkinson's disease result from the greatly reduced activity of the dopaminergic neurons, which are primarily in the pars compacta region of the substantia nigra (literally "black substance"). These neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement, in essence an inhibition of the direct pathway and excitation of the indirect pathway.

- Black-staining granules of neuromelanin within neurons of the substantia nigra.
- The direct pathway facilitates movement and the indirect pathway inhibits movement, thus the loss of these cells leads to a hypokinetic movement disorder. The lack of dopamine results in increased inhibition of the ventral anterior nucleus of the thalamus, which sends excitatory projections to the motor cortex, thus leading to hypokinesia.
- There are four major dopamine pathways in the brain; the nigrostriatal pathway, referred to above, mediates movement and is the most conspicuously affected in early Parkinson's disease. The other pathways are the mesocortical, the mesolimbic, and the tuberoinfundibular. Disruption of dopamine along the non-striatal pathways likely explains much of the neuropsychiatric pathology associated with Parkinson's disease.
- The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells. The alpha-synuclein-ubiquitin complex cannot be directed to the proteosome. This protein accumulation forms proteinaceous cytoplasmic inclusions called Lewy bodies. The latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles — the endoplasmic reticulum (ER) and the Golgi apparatus. Certain proteins like Rab1 may reverse this defect caused by alpha-synuclein in animal models.[12]
- Excessive accumulations of iron, which are toxic to nerve cells, are also typically observed in conjunction with the protein inclusions. Iron and other transition metals such as copper bind to neuromelanin in the affected neurons of the substantia nigra. Neuromelanin may be acting as a protective agent. The most likely mechanism is generation of reactive oxygen species.[13] Iron also induces aggregation of synuclein by oxidative mechanisms. Similarly, dopamine and the byproducts of dopamine production enhance alpha-synuclein aggregation. The precise mechanism whereby such aggregates of alpha-synuclein damage the cells is not known. The aggregates may be merely a normal reaction by the cells as part of their effort to correct a different, as-yet unknown, insult. Based on this mechanistic hypothesis, a transgenic mouse model of Parkinson's has been generated by introduction of human wild-type alpha-synuclein into the mouse genome under control of the platelet-derived-growth factor-β promoter.[14]
- A recent view of Parkinson's disease implicates specialized calcium channels that allow substantia nigra neurons, but not most neurons, to repetitively fire in a "pacemaker" like pattern. The consequent flooding of calcium into these neurons may aggrevate damage to mitochondria and may cause cell death. One study has found that, in experimental animals, treatment with a calcium channel blocker isradapine had a substantial protective effect against the development of Parkinson's disease.[15]

DIAGNOSIS

- Typically, the diagnosis is based on medical history and neurological examination conducted by interviewing and observing the patient in person using the Unified Parkinson's Disease Rating Scale. A radiotracer for SPECT scanning machines called DaTSCAN and made by General Electric is specialized for diagnosing Parkinson's Disease, but it is only marketed in Europe. Due to this, the disease can be difficult to diagnose

accurately, especially in its early stages. Due to symptom overlap with other diseases, only 75% of clinical diagnoses of PD are confirmed to be idiopathic PD at autopsy.[34] Early signs and symptoms of PD may sometimes be dismissed as the effects of normal aging. The physician may need to observe the person for some time until it is apparent that the symptoms are consistently present. Usually doctors look for shuffling of feet and lack of swing in the arms. Doctors may sometimes request brain scans or laboratory tests in order to rule out other diseases. However, CT and MRI brain scans of people with PD usually appear normal.

- Clinical practice guidelines introduced in the UK in 2006 state that the diagnosis and follow-up of Parkinson's disease should be done by a specialist in the disease, usually a neurologist or geriatrician with an interest in movement disorders.[2]

TREATMENT

Primary medical complications seen in patients with Parkinson's disease (PD) include autonomic dysfunction, cardiopulmonary impairment, dysphagia, and depression.

- Autonomic dysfunction is common in patients with PD.
  - Orthostatic hypotension often becomes a concern during the later part of the disease process. Management techniques can include elevating the head of the bed, as well as having the patient arise slowly, use pressure garments, consume a high-salt diet, and use such medications as pseudoephedrine, mineralocorticoids, and midodrine.
  - Impaired intestinal motility can lead to constipation, vomiting, and impaired absorption; treatment options include the employment of frequent, smaller meals; increased fiber; bulking agents; stool softeners; and suppositories.
  - Urinary incontinence, retention, and bladder infection can occur. Treatment usually is based on the results of investigations, such as renal function studies, urinalysis, postvoid residuals, cystoscopy, and urodynamic studies.
  - Erectile dysfunction is not uncommon. Treatment options include the use of sildenafil, prostaglandin injections, pumps, and prosthetic devices.

- Cardiopulmonary impairment
  - The patient's flexed posture can lead to kyphosis, cause a reduction in pulmonary capacity, and produce a restrictive lung disease pattern.
  - Breathing exercises, postural reeducation, and trunk exercises may be helpful.
  - Institution of a general conditioning program can increase the patient's endurance.
  - If pulmonary function progressively worsens, assisted coughing techniques, incentive spirometry, and respiratory therapy intervention may be required.

- Depression
  - Depression can occur in approximately 50% of patients with PD and should not be overlooked, as its impact on disability can be significant.
  - Depression may be related to a deficit in serotonergic neurotransmission or to decreased cortical levels of norepinephrine and dopamine.
  - Serotonergic agents often are the first antidepressants of choice in PD. If this treatment regimen is ineffective, a tricyclic antidepressant with anticholinergic side effects (eg, desipramine, nortriptyline) may be recommended.

- Dysphagia
    - If swallowing difficulties do not respond to conservative interventions by the speech therapist, more aggressive treatment may be required.
    - Such aggressive management can include invasive procedures, such as nasogastric or gastrostomy feeding tube placement.
    - Discussion should be initiated early on in the disease course to ascertain the patient's wishes about a feeding tube, in case dementia develops and the patient lacks the capacity for decision making when a feeding tube becomes medically indicated.[11]

Surgical Intervention

Increased interest has been seen in the surgical management of Parkinson's disease (PD). Three main techniques currently in use are destructive therapy (lesioning), chronic deep brain stimulation, and transplantation.

- Destructive therapy
    - Lesioning options include thalamotomy and pallidotomy.
    - Ventral intermediate nucleus thalamotomy is quite effective at relieving tremor, but its effects on the other clinical manifestations of PD seem to be less significant and more variable. Thalamotomy usually is reserved for a relatively small percentage of patients with predominantly drug-resistant tremor.
    - At present, pallidotomy is the surgical procedure most commonly used for advanced PD. The surgery employs lesioning to disrupt the abnormal activity in the globus pallidus; this disinhibits the motor thalamus and cortical motor areas, thereby improving motor functioning. Candidates for pallidotomy include patients who are disabled despite optimal medical management and who have responded to L-dopa therapy in the past but have developed complications from long-term L-dopa treatment. Rigidity, tremor, and bradykinesia all seem to respond to pallidotomy.
- Deep brain stimulation
    - Chronic deep brain stimulation seems to have emerged as an alternative to lesioning in patients with PD.
    - Stimulation has the advantages of safety, reversibility, and adaptability (ie, stimulation parameters can be adjusted as the clinical features change over time).
    - Stimulation sites include the ventral lateral thalamic nuclei (performed to decrease tremor, with a good response in 80-85% of patients), the globus pallidus (for bradykinesia, gait, speech, drug-induced dyskinesias), and the subthalamic nucleus (for bradykinesia, rigidity, tremor, gait/posture). A study of 6 male patients showed improved motor rating scores and reduced timing and spatial errors following deep brain stimulation of the internal globus pallidus.
    - Earlier subthalamic nucleus stimulation (average of 7 years after diagnosis vs 14 years for control population) has been shown to improve results and patient quality of life.
    - Subthalamic nucleus stimulation does not improve long-term mortality results.
    - Bilateral subthalamic nucleus stimulation was linked in a case report with pathologic gambling.
- Transplantation
    - Although stimulation and lesioning can improve symptoms, neither corrects the underlying pathology of the disease, which is a lack of dopamine from loss of substantia nigra neurons. Transplantation therapy offers the possibility of replacing these lost neurons.
    - Clinical trials have examined the use of 3 types of transplants: autologous

adrenal medulla transplants, fetal mesencephalon grafts, and xenografts.

- Adrenal medulla transplants are not in widespread use because of the high morbidity and mortality from adrenalectomy.
- Fetal mesencephalon grafts have shown promising early results. Trials continue, but ethical concerns, insufficient tissue, and procedural difficulties make it unlikely that the procedure will become commonplace.
- The most common xenograft used is the fetal pig mesencephalon. A trial currently is underway to determine the efficacy of this procedure.

- Human embryonic stem cell therapy and gene therapy
  - Intrastriatal transplantation of human fetal mesencephalic tissue in PD patients has demonstrated clinical efficacy, but the limited availability of tissue precludes the systematic use of this procedure.
  - Embryonic stem cells can differentiate into cells from the CNS. These cells could potentially provide a relatively unlimited source of cells for transplantation if protocols were developed to generate specific populations of neural cells.
  - Ethical concerns also play a large role in this line of research.
  - Initial results from the first human clinical trial of gene therapy for PD suggest the approach might significantly reduce symptoms of the disease and provide a 25% improvement in motor control.[11]

MEDICAL INTERVENTION

Levodopa

The most widely used form of treatment is L-dopa in various forms. L-dopa is transformed into dopamine in the dopaminergic neurons by L-aromatic amino acid decarboxylase (often known by its former name dopa-decarboxylase). However, only 1-5% of L-DOPA enters the dopaminergic neurons. The remaining L-DOPA is often metabolised to dopamine elsewhere, causing a wide variety of side effects. Due to feedback inhibition, L-dopa results in a reduction in the endogenous formation of L-dopa, and so eventually becomes counterproductive.

Carbidopa and benserazide are dopa decarboxylase inhibitors. They help to prevent the metabolism of L-dopa before it reaches the dopaminergic neurons and are generally given as combination preparations of carbidopa/levodopa (co-careldopa) (e.g. Sinemet, Parcopa) and benserazide/levodopa (co-beneldopa) (e.g. Madopar). There are also controlled release versions of Sinemet and Madopar that spread out the effect of the L-dopa. Duodopa is a combination of levodopa and carbidopa, dispersed as a viscous gel. Using a patient-operated portable pump, the drug is continuously delivered via a tube directly into the upper small intestine, where it is rapidly absorbed. There is also Stalevo (Carbidopa, Levodopa and Entacapone).

Tolcapone inhibits the COMT enzyme, thereby prolonging the effects of L-dopa, and so has been used to complement L-dopa. However, due to its possible side effects such as liver failure, it's limited in its availability. A similar drug, entacapone has not been shown to cause significant alterations of liver function and maintains adequate inhibition of COMT over time.[16]

Dopamine agonists

The dopamine agonists bromocriptine, pergolide, pramipexole, ropinirole , piribedil, cabergoline, apomorphine, and lisuride are moderately effective. These have their own side effects including those listed above in addition to somnolence, hallucinations and/or insomnia. Several forms of dopamine agonism have been linked with a markedly increased risk of problem gambling. Dopamine agonists initially act by stimulating some of the

dopamine receptors. However, they cause the dopamine receptors to become progressively less sensitive, thereby eventually increasing the symptoms.

Dopamine agonists can be useful for patients experiencing on-off fluctuations and dyskinesias as a result of high doses of L-dopa. Apomorphine can be administered via subcutaneous injection using a small pump which is carried by the patient. A low dose is automatically administered throughout the day, reducing the fluctuations of motor symptoms by providing a steady dose of dopaminergic stimulation. After an initial "apomorphine challenge" in hospital to test its effectiveness and brief patient and primary caregiver (often a spouse or partner), the latter of whom takes over maintenance of the pump. The injection site must be changed daily and rotated around the body to avoid the formation of nodules. Apomorphine is also available in a more acute dose as an autoinjector pen for emergency doses such as after a fall or first thing in the morning. Nausea and vomiting are common, and may require domperidone (an antiemetic).

MAO-B inhibitors

Selegiline and rasagiline reduce the symptoms by inhibiting monoamine oxidase-B (MAO-B), which inhibits the breakdown of dopamine secreted by the dopaminergic neurons. Metabolites of selegiline include L-amphetamine and L-methamphetamine (not to be confused with the more notorious and potent dextrorotary isomers). This might result in side effects such as insomnia. Use of L-dopa in conjunction with selegiline has increased mortality rates that have not been effectively explained. Another side effect of the combination can be stomatitis. One report raised concern about increased mortality when MAO-B inhibitors were combined with L-dopa;[36] however subsequent studies have not confirmed this finding.[17] Unlike other non selective monoamine oxidase inhibitors, tyramine-containing foods do not cause a hypertensive crisis.

PROGNOSIS

PD is not considered to be a fatal disease by itself, but it progresses with time. The average life expectancy of a PD patient is generally lower than for people who do not have the disease. In the late stages of the disease, PD may cause complications such as choking, pneumonia, and falls that can lead to death.

The progression of symptoms in PD may take 20 years or more. In some people, however, the disease progresses more quickly. There is no way to predict what course the disease will take for an individual person. With appropriate treatment, most people with PD can live productive lives for many years after diagnosis.

In at least some studies, it has been observed that mortality was significantly increased, and longevity decreased among nursing home patients as compared to community dwelling patients.[18]

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