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PARKINSON'S DISEASE

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Abstract: Parkinson's disease (PD) is a neurodegenerative illness and has a common onset between the ages of 55 and 65 years. There is progressive development of both motor and non-motor symptoms, greatly affecting one's overall quality of life. While there is no cure, various treatments have been developed to help manage the symptoms of PD. Management of PD is a growing field and targets new treatment methods, as well as improvements to old ones. Pharmacological, surgical, and treatments have allowed physicians to treat not only the main motor symptoms of PD but also target patient-specific problems as they arise.

Keywords: Levodopa, dopamine agonists, apomorphine, substantia nigra, basal ganglia, lewy bodies.

INTRODUCTION:

Parkinson's disease (PD), or paralysis agitans, is a common neurodegenerative condition, which typically develops between the ages of 55 and 65 years. This disease was first named and described by James Parkinson in 1817. The progression of this disease is gradual and prolonged. It has a plausible familial incidence, although the estimates of these occurrences are low and usually sporadic.[1]
This disease is organized into two classifications: genetic and sporadic. Genetic PD follows Mendelian inheritance. Sporadic PD, which accounts for about 90% of all Parkinson's cases, is a more complex category in which the pathogenic mechanisms that underlie it are not yet fully understood. [2]

General risk factor:

Research studies have linked theories regarding the outbreak of PD to both environmental and genetic circumstances. These theories propose associations between PD and chemical reactions, neurotoxins, and genetic susceptibility or predisposition. [3]
Environmental determinants positively associated with PD include factors such as injuries to the head, rural living, pesticides, anxiety and/or depression, and intake of dairy products; whereas physical inactivity, smoking, consumption of coffee and/or alcohol, and serum uric acid concentration are reported as having an inverse relationship to PD. Though it is undisputed that familial factors play a role in this disease, the extent of heritability is heavily debated. As of yet, 41 different genetic loci have been linked to PD pathogenesis through the completion of 6 large meta-analysis studies.[4]

General symptoms:

A precedent for the clinical diagnosis of PD, according to the Movement Disorder Society, is centralized on a motor syndrome, Parkinsonism, and is based on three overriding motor symptoms (MS): bradykinesia, rigidity, and resting tremor. The onset of motor manifestations usually begins unilaterally with asymmetrical effects enduring on the side of commencement. [5]
Symptoms include resting tremors, bradykinesia, gait, speech difficulties, hypophonia, muscle dystrophy, postural deformities, and instability. Pain, stiffness or numbness in limbs, bradykinesia, tremors, a decline in facial expressions, and hypophonia are motor symptoms seen in the early stages of this disease's onset. [6]
Late-stage motor features may include motor fluctuations, dyskinesia, gait freezing, and falling. Initial diagnosis may be made based on the evaluation of clinical features of patient history and examination. Positive or negative responses to dopamine agents may also be used in the diagnosis of PD over time. [7]

Pathology of idiopathic Parkinson's disease:

The dominant pathology of idiopathic Parkinson's disease (PD) is primarily a loss of dopamine-producing cells in the substantia nigra in the midbrain, followed by degeneration of the nigrostriatal pathway, depriving basal ganglia of dopamine required to facilitate all motor activities. [8]
The current theory explaining PD pathology was put forward by Braak et al., suggests that pathology starts in the gut, then utilizing the vagus nerve, it ascends to the olfactory bulb and vagal motor nucleus at the caudal medulla oblongata, progressing up the brainstem and diencephalon to the cortex. It is estimated that more than 50% of the nigrostriatal dopamine-producing neurons have degenerated before the first motor symptom appears.[9]

Diagnosis of PD:

PD diagnosis relies on the UK Parkinson's Disease Society Brain Bank criteria. To diagnose Parkinson's disease, the patient must satisfy the diagnostic criteria for Parkinsonism first. Parkinsonism is diagnosed when bradykinesia is present, plus any of the other core features, muscular rigidity, resting tremor, or postural instability. Then, the patient must fulfil other supportive criteria listed in Table 1. [10]

Table 1: UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.

Step : Diagnosis of Parkinsonian syndrome :
* Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed
and amplitude of repetitive actions)
* And at least one of the following:
Muscular rigidity
4-6 Hz rest tremor
Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive
dysfunction.
Step2 : Exclusion criteria for Parkinson's disease
* History of repeated strokes with stepwise progression of parkinsonian features
* History of repeated head injury
* History of definite encephalitis
* Oculogyric crises
* Neuroleptic treatment at onset of symptoms
* More than one affected relative
* Sustained remission
* Strictly unilateral features after 3 years
* Supranuclear gaze palsy
* Cerebellar signs
* Early severe autonomic involvement
* Early severe dementia with disturbances of memory, language, and praxis
* Babinski sign
* Presence of cerebraltumor or communicating hydrocephalus on CT scan
* Negative response to large doses of levodopa (if malabsorption excluded)
* MPTP exposure
Step3: Supportive prospective positive criteria for Parkinson'sdisease
(Three or more required for diagnosis of definite Parkinson'sdisease)
* Unilateralonset
* Resttremorpresent
* Progressive disorder
* Persistent asymmetryaffectingside of onset.
* Excellent response (70-100%) to levodopa
* Severelevodopa-inducedchorea
* Levodoparesponse for 5 years or more
* Clinical course of 10 years or mor

CLINICAL PRESENTATION

The clinical presentation of PD represents a nexus of four major components: motor symptoms, cognitive changes, behavioural /neuropsychiatry changes, and symptoms related to autonomic nervous system failures. Individual variation affects the area(s) that become(s) more prominent. Each aspect will be discussed. The cardinal motor features of PD are tremor, bradykinesia, rigidity and postural instability. The latter symptom develops more with disease progression over time. A mnemonic is sometimes used to encapsulate the major motor symptoms: T-R-A-P. It stands for Tremors(resting), Rigidity (possibly cogwheel jerking), Akinesia(or Bradykinesia), and Posture (stooped shuffling gait). [11]

Pathological and neuroimaging studies suggest that motor signs of PD only develop when 50-70% of substantia nigra neurons have degenerated. LBD,PSP, CBD, and MSA are clinical syndromes that have differing clinical presentations from classic PD.

The "pill rolling" rest tremor of idiopathic PD is most noticeable when the body part is not engaged in purposeful movement. Usually unilateral initially, PD often progresses to bilateral rest tremor overtime. Rest tremor is the presenting symptom in over 70 percent of PD patients. Bradykinesia or slowness of movement is often described as tiredness or weakness by patients. It is manifested in lessened finger manual dexterity shuffling steps or difficulty getting out of a chair (2). Difficulty with opening packages or containers is commonly reported.Rigidity is seen in almost all PD patients. It can beginuni laterally but moves to the other side. When joint range of motion is examined, the PD patient often demonstrates a"cogwheel" rigidity that is similar to the ratchet pattern of agear.

Later in the disease course, patients with PD willlikely display postural instability with an increased risk offalling. Falling early in the course of PD suggests another disorder such as PSP. Another manifestation may be"festination" where patients take much quicker and shorter steps, assuming a running gait. Notably, postural instability responds least well to dopamine treatments.[12]

Motor symptoms:
PD is associated with resting tremor (initially unilateral), bradykinesia (slow movements), rigidity,shuffling gait, and postural instability. The onset is insidious where individuals may attribute the symptoms to aging processes. PD symptoms are progressive but rates of motor progression are highly variable. Also, sub types of PD occur wherein tremor, rigidity, or postural instability dominate .
In addition to the "classic" motor symptoms previously described, other motor manifestations are observed. These include masked facial expression(hypomimia), decreased eye blink rate, blurred vision ,impaired upward gaze, dystonia, stooped posture, difficulty turning in bed, kyphosis, scolosis, shuffling gait, "freezing"(inability to move) and speech impairment, such ashypophonia (increasingly soft voice), or palilalia (repetition of word or phrase). [13]

Non-motor symptoms:
Non-motor symptoms of PD include cognitive changes, behavioral/neuropsychiatric changes autonomic nervous system failure, sensory and sleep disturbances (See Table 1). Non-motor symptoms can represent some of the greatest challenges to quality of life and appropriate management in PD since they usually do not respond to dopamine therapy as well as motor symptoms. Notably, a number of non-motor features can precede the motor symptoms of PD by years, even decades. However, it is known that almost 90% of PD patients experience non-motor symptoms during the course of the disease. [14]

Drug therapy of PD motor symptoms:
For an early to moderate stage of PD, available symptomatic therapies include anticholinergics, amantadine, MAO-B inhibitors (selegiline and rasagiline), dopamine agonists and levodopa. The main decision point is when to start a dopaminergic drug, and whether that agent is a dopamine agonist or levodopa. Levodopa introduction in 1967 has revolutionized PD therapeutics and has changed the landscape of PD treatment(18, 19). Delaying levodopa, when patients need it, to avoid loss of effect, has no clinical evidence to support it. All patients lose effect with time, and they will require increasingly larger doses to obtain a satisfactory motor response. When compared to dopamine agonists, levodopa is more effective, and is less associated with impulse control disorders (ICDs) than dopamine agonists. ICDs include compulsive shopping, gambling, hyper sexuality, punding ,dopamine dysregulation syndrome and compulsive eating.[15]
In its 2002 guidelines on initiating treatment in PD, which was reviewed in 2006, the American Academy of Neurology suggested there was not enough evidence to use dopamine agonists first. It concluded it is reasonable to initiate treatment with levodopa, dopamine agonist or an MAO-B inhibitor. When Parkinson's disease advances, side effects of dopaminergic therapy start accumulating. The commonest of these side effects is a loss of efficacy before the next dose is scheduled (wearing off), levodopa-induced dyskinesia,and ICDs.
Long-term use of levodopa leads to motor fluctuations and dyskinesia. Development of dyskinesia is related to levodopa dose and duration. The higher the levodopa dose and the longer the duration it is used, the more likelihood dyskinesias develop. Reasons for levodopa-induced dyskinesia include short half-life of levodopa, the need to dose it frequently, coupled with degeneration of the nigrostriatal neurons that store and slowly release dopamine.Delayed gastric emptying is thought to play a major role in dose failure, as well as decrease the efficacy of oral therapy. [16]

Drug therapy of PD Non-motor symptoms:

Non-motor symptoms(NMS), including constipation, rapid eye movement (REM) sleep behavior disorder (RBD),anosmia, anxiety, and depression can predate the motor symptoms with a decade or two. They were largely over shadowed by motor features, especially in early clinical trials, which were mostly geared towards motor features control. Over the last twenty years or so, NMS have been recognized as a major source of concern to patients, and grading scales have been developed and incorporated into clinical trials.
Hallucinations are common in later stages of PD. They start with friendly non-threatening imagery, then they become frightening. Treatment is not needed if hallucinations are non-threatening. When caregivers or patients indicate a need for treatment, eliminating culprit drugs with less motoric benefit and more hallucinating potential is the first step. [17]
Clozapine has the most clinical evidence in treating PD associated psychosis. It is plagued by the need to monitor patients for neutropenia frequently. Quetiapine has no evidence supporting its use. Nonetheless, anecdotal reports and single patients' experiences show it works. It has no serious side effects, and it needs no monitoring,apart from corrected QT interval (QTc). Pimavanserin, a select serotonin 5-HT2A inverse agonist, could become the first-line therapy, especially after the promising results it showed in Cummings et al., study. Typical antipsychotics should be avoided, as they worsen PD symptoms. [18]
Constipation can predate PD diagnosis with a decade or two(45). Gastric emptying is slowed by over 40%(27), with delayed absorption. Subsequently, oral medications become less effective. Constipation, untreated, can lead to bowel obstruction and death in PD patients. [19]

Device-assisted therapy:
Continuous levodopa delivery has emerged as a practical means to treat motor fluctuations and oral levodopa-induced dyskinesias. Levodopa intestinal gel infusion (LIGI), is an infusion of levodopa gel via an external pump ,through a percutaneous gastro jejunal tube. Apomorphine, a rapid onset D1/D2 dopamine, agonist is used to treat freezing by subcutaneous injection. It is infused continuously via a subcutaneous route through a small pump held externally by the patient. It is effective for smoothing out motor fluctuations as well as a host of non-motor symptoms. [20]
Deep brain stimulation (DBS) is a two-step neurosurgical procedure. First, an electrode is placed deep in a selected target in the brain, followed by implanting a neurostimulator in the pectoral region and connecting it to the electrode. LIGI, apomorphine pump and DBS are used for patients with motor fluctuations and other advanced complications of oral therapy, and are better left to specialists in tertiary care centers with enough volume and expertise . The selection of the appropriate patients and modality need careful consideration. These modalities are invasive and expensive. [21]

Treatment Approaches:

Though the exact cause of Parkinson's disease has not been identified, treatment discoveries have been progressive. There is no known cure for the disease, so treatments seek to manage symptoms rather than prevent or slow the progression of the disease. Treatments can vary from drugs, surgeries, therapy, oral combination of different treatments [Table 1]. They must also be adjusted throughout the course of the disease, as some common treatments, such as L-DOPA lose effectiveness over time. Treatment of PD using available drugs has positive symptomatic effects; however, there are no disease-modifying or neuroprotective therapies available to slow the progression of the disease .Therefore, treatment begins at the discretion of the patient and the physician when symptoms begin to impair function or provide social embarrassment. No one drug is more beneficial than the other for initial treatment, but instead the disease itself must be looked at in terms of severity and time of on set.PD is a disease that affects multiple neural pathways in the brain. While L-DOPA may treat motor problems caused by low dopamine levels, it will not treat motor problems caused by low acetylcholine levels in other pathways. Additionally, each sub type responds differently to drugs. It is up to the discretion of the doctor to choose a plan that works for an individual patient based on responsiveness and symptom. [22]

DRUG TREATMENTS:

Dopaminergic medications

Dopaminergic medications are the typical treatment method for motor symptoms in PD, and L-DOPA ,the most potent anti-parkinsonian drug currently available, remains the "gold standard" for PD therapy .Because the lack of dopamine available for communication in the nigrostratial pathway is at the root of many PD symptoms, specifically movement-based ones, dopaminergic medications are used to help increase or mimic dopamine levels. Dopamine does not easily pass through the blood brain barrier, but its precursor, L-DOPA . It is metabolized in the small intestine and is converted to dopamine by aromatic-L-amino-acid decarboxylase (AADC) and catechol-O-methyltransferase (COMT), which can then be stored in the nigrostratial terminals. In contrast, dopamine agonists act directly on post synaptic receptors, mitigating the need for dopamine production[23].

Responsiveness to L-DOPA occurs in 80% of patients with idiopathic PD, reducing bradykinesia and rigidity. However, it is ineffective or unsatisfactory at treating several prominent PD symptoms: posture and gait problems, speech problems, freezing, autonomic dysfunction, cognitive disorders, affective disorders ,and sleep problems.

As previously mentioned about early-onset PD, there are concerns about L-DOPA-related dyskinesia. While dyskinesia is correlated with L-DOPA usage, the disease itself (PD) and a pulsatile drug delivery are both required for dyskinesia to develop. L-DOPA does not usually induce dyskinesia in Parkinsonism with post- synaptic involvement, and intestinal gel delivery has shown to reduce pre-existing dyskinesia. Therefore ,it may be more appropriate to view dyskinesia as a result of the method of administering levodopa rather than an intrinsic effect of CL-DOPA itself. [24]

Monoamine oxidase inhibitors, Catechol O-methyltransferase inhibitors, and N-methyl D-aspartate receptor antagonists

Monoamine oxidase inhibitors (MAOIs), like rasagiline or selegiline, and COMT inhibitors, like entacapone, work to inhibit the breakdown of dopamine and L-DOPA to prolong their effects. MAOI s reduce the amount of dopamine broken down in the synapse. COMT inhibitors prevent COMT from prematurely converting L-DOPA into dopamine. It reduces peripheral loss of L-DOPA before it can reach the brain. Patients with mild symptoms may be treated with MAOIs first, due to their milder side effects ,less frequent doses and to delay the treatment of dopaminergic drugs.

Anticholinergics for early on

The first pharmacological agents used in PD therapy were anticholinergic drugs. They reduce the activity of acetylcholine by acting as antagonists at choline receptors, hoping to restore the balance between dopamine and acetylcholine levels that was disturbed by PD. These drugs have largely been replaced by L-DOPA and other centrally acting dopaminergic agonists, but they still remain available for use in the treatment of PD. Benztropine, biperiden, diphenhydramine, ethopropazine, orphenadrine, procyclidine, and trihexyphenidyl are included in this therapeutic class of drugs, though there is little pharmacokinetic information available on them because of their low plasma drug concentrations. [25]

Neurotrophic factors

Nerve cells require neurotrophic factors (NTFs), which are small natural proteins, for their development and continued survival. In addition, NTFs help maintain the morphological and functional phenotype of nerve cells. Neuronal networks require the release of NTFs at the target structures. NTFs are taken up by the nerve terminals and moved retrogradely to the soma of the projecting neurons for their formation and preservation. This is described by the "neurotrophic hypothesis". Neuronal survival and phenotype specification is stimulated by the induction of a gene upon the arrival of NTFs at the nucleus. There have been several proteins that have been classified as NTFs based on the effects they have on neuronal survival ,differentiation, maturation of electrophysical properties, and plasticity. The functional roles of NTFs provide promising possible benefits in the treatment of neurodegenerative diseases, including PD. Glial cell line-derived neurotrophic factor (GDNF) is one of the more closely related NTFs associated with PD as a result of the potent trophic action it has on cultured dopaminergic neurons. Production of GDNF is done by striatal neurons and is required for the sustenance of adult nigrostriatal dopaminergic neurons and other central and peripheral nuclei affected in PD. Exogenous administration of GDNF has also shown neurotoxic damage preventative abilities of dopaminergic neurons in the midbrain, and noradrenergic neurons in the locus coeruleus. Evidence of GDNF and its effect on the latter neurons implies that the stimulation of endogenous GDNF generation and/or administration of exogenous GDNF could serve as competent therapeutic strategies for PD. [26]

Nanomedicine

Nanomedicine and the manipulation of compounds on the nanometric scale is being investigated for the improvement of drug delivery systems, specifically to improve drug bioavailability, half-life, or achieve more sustained levels of circulation. The most widely used approach is to increase the ability of drugs to be transported across the blood brain barrier. This is particularly important with L-DOPA and dopamine agonists because the process with which they are mediated through the blood brain barrier can also occur in peripheral tissues. [27]

SURGICAL TREATMENTS

There are three major surgical treatments for PD: ablative surgery, deep brain stimulation (DBS), and grafting faetal mesencephalic cells into the striatum.

Ablative surgery

Ablative surgery is the oldest of the three major surgical treatments and holds the greatest risks.

Pallidotomy, thalamotomy, and sub thalamotomy are available surgeries. Because of the loss of dopaminergic innervation ,internal globus pallidus and substantia nigra reticulata have hyperactivity leading to excessive inhibitory output. The inhibitory output interferes with the movement-related centre in the thalamus and generates hypokinetic PD symptoms. Ablative surgery tries to alleviate these symptoms by creating alesion within the internal globus pallidus, thalamus, or subthalamic nucleus to stop the overactive pathway

either near the start, as in pallidotomies, or further down the line in thalamotomies [Figure 1]. In one study, stereotactic posteroventral pallidotomies were performed on 38 patients, giving complete or almost complete relief of rigidity and hypokinesia in 92% of patients. As well, 32 patients had suffered tremors before the surgery, and 81% of them had complete or almost complete relief of tremor, post-surgery. Gait and speech volume also saw improvement. However, seven patients (roughly 18%) had complications, with six patients presenting with permanent partial homonymous hemianopsia; one of those patients also had

transient dysphagia and facial weakness. The other patient developed transitory hemiparesis 1 week after the surgery. Thalamotomy is an option for patients that have long-standing tremor as the main clinical manifestation, and it cannot be controlled by drugs. Thalamotomy is less common than pallidotomy, with less than 5% of patients having the thalamus as the preferable target for thalamotomy or DBS. Ablative surgeries have lost prevalence because of concerns over high incidence of side-effects with bilateral ablative procedures. At experienced centre, unilateral pallidotomy is equally safe as unilateral DBS, though bilateral DBS is likely safer than bilateral pallidotomy. Therefore, while DBS may be more common now, pallidotomy and other ablative surgeries are still viable options when DBS is not available nor feasible. [28]

Deep brain stimulation

Deep brain stimulation (DBS) developed Deep brain stimulation (DBS) developed as an alternative to risky bilateral ablative surgeries. It is applied in the internal globus pallidus, subthalamic nucleus, and thalamus. It is similar to ablative surgeries in terms of the pathway and symptoms that DBS is trying to mitigate. Conventional DBS is open-loop, with the implants delivering electrical impulses continuously and without feedback. [29]

Surgical therapies with transplantation and gene therapy

Cell transplantation is regarded as a potential future PD treatment. There have been trials using autologous and non-autologous cells. Human embryonic stem cells and induced pluripotent stem cells are few of the cells that have been included in these transplantation studies. One of the concerns with cell transplantation using stem cells is the ethical bounds that must be considered .Since the first clinical trial in 1987 involving the transplantation of dopaminergic- neuron-rich human featal mesencephalic tissue into PD patients' striatum, more research has aimed to explore whether the grafted dopaminergic neurons will live and form connections in the brain, if the patient's brain can harmonize and make use of the grafted neurons, and if the grafts can generate significant clinical improvement. [30]

CONCLUSION:

L-DOPA remains the most accepted form of treatment for PD, as it is used as a dopamine replacement for this neurodegenerative disease. While other dopamine agonists are successful at controlling symptoms of PD early on in the onset of the disease, L-DOPA is the most effective pharmaceutical at helping to improve QoL, especially once symptoms become more unmanageable with other anti-parkinsonian medications. There is no known cure for PD, but alternative drug, surgical and behavioral therapies exist for the treatment of PD, and new therapies are being developed to help mitigate the side effects and symptoms of this progressive disease. Physical, occupational, and speech therapies provide non-drug alternatives that can be used in adjunct with medications, or separately for those who prefer more natural approaches. They can help treat individual symptoms as they arise. There is still a need to further explore other treatments, and more studies can delve into the under-researched therapies for PD, but the future of PD treatment is promising for patient-specific care that is more effective and with minimal side effects.

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