International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

A REVIEW ON PARKINSON'S DIAGNOSIS AND IT'S NEW APPROACHES

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ABSTRACT

Parkinsons disease is a neurodegenerative disorder which is difficult to diagnose. There are no confirmatory laboratory tests or imaging techniques available for its diagnosis. An experienced or specialized neurologist diagnoses the disease by considering the patient's clinical presentations which include 4 cardinal signs (resting tremors,Bradykinesia, Rigidity of limbs, Postural instability). Presence of any two or more than two of the above signs makes the physician to suspect that patient might be having PD. Other than 4 cardinal signs a PD patient may also present with different signs and symptoms which may be either motor or non-motor. New approaches are being made to diagnose PD through laboratory findings like α- synuclein levels in plasma and CSF and epigenetic biomarkers.

KEY WORDS: Parkinson's disease, 4 cardinal signs, PD, α- synuclein, epigenetic biomarkers.

INTRODUCTION

PD is a progressive neurodegenerative disorder which mainly effects the dopamine generating cells of substantia nigra which is present in the mid brain.

Dopamine, a neurotransmitter mainly controls the reward motivation behavior, motor activities. It also shows effect on different systems like gastrointestinal tract(reduces GI motility), renal system(regulates sodium excretion) and also dilates blood vessels, inhibits insulin secretion in pancreas.

The diagnosis of PD is mainly done or made on the basis of clinical presentation of the patient.

For this it requires a specialized neurologist. In few cases, even the experienced neurologist may also face difficulties in diagnosing the PD patients or differentiating it from other neurodegenerative disorders.

The clinical presentation of PD is based on cardinal signs which include resting tremors, bradykinesia, rigidity of limbs, postural instability. The physician makes provisional diagnosis, if the patient shows any of the 2 or more than two of the above cardinal signs.

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The physician also considers secondary motor symptoms which include freezing, micrographia, hypomimia. Few patients may also show kyphotic posture, bradyphrenia, dystonia, akathesia, sexual dysfunction, drooling, dysarthria.

The non-motor symptoms in PD patients include loss of sense of smell, REM behavior disorder, orthostatic hypotension, vision and dental problems. Sometimes dementia and confusion.(1,2)

The neurologist also considers the medical history of the patient, past and current medication history to check whether those medications can cause symptoms similar to PD.

The physician also asks the patient to perform tasks to apprise the alacrity of the arms and legs, stride, muscle tone and balance of the patient.

Certain imaging techniques are also recommended for further elucidation of disease. Eg: PET scan, SPECT scan[1].

DISCUSSION

It is always difficult to diagnose a neurodegenerative disorder. Parkinson's disease diagnosis is primarily based on its symptoms. The symptoms are always examined thoroughly by a neurologist and for further conformation other imaging techniques like PET and SPECT scans are considered[1,4].

The symptoms of PD which form basis for diagnosis are discussed below.

There are four cardinal signs that are based on which the PD diagnosis is made. They are-
1. Resting tremor
2. Bradykinesia
3. Rigidity
4. Postural instability

Resting Tremor

Parkinsonian tremor is primarily a rest tremor with a frequency in 3-7 Hz range, it is episodic in time, can be modulated by motor or cognitive activity.

The occurrence of parkinsonian tremor is naturally related to dopaminergic degeneration, the network, the cellular and synaptic mechanisms of parkinsonian tremor are not clear[5].

Bradykinesia

It is the slowness of performed movement which is often used synonymously with other two terms; Akinesia and Hypokinesia.

Akinesia - It is the poverty of spontaneous movement (Eg: in facial expression) or associated movement (Eg: arm swing during walking).

Hypokinesia – It is the slow movement as well as smaller movements than desired, as in the micrographia of patient handwriting[6].

Rigidity

It is an increased resistance while stretching the muscle passively and is commonly associated with bradykinesia. It is present in about 90-99% of PD patients.

Muscular rigidity can be unilateral or bilateral[7,8].

Postural Instability

Postural stability is one of the axial symptom of PD and is due to the loss of postural reflexes.

Postural instability is impairment in balance which is not frequentin early stages of PD, but becomes the most common distressing factor in later stages[7].

● These are the four cardinal signs on which the diagnosis of PD relies on and aid the physician in making a provisional diagnosis.

In few cases, the physician may also consider secondary motor symptoms and other non-motor symptoms.

The secondary symptoms include freezing, micrographia, hypomimia, kyphotic posture, dystonia etc.

Non-motor symptoms include sexual dysfunction, drooling etc.

SECONDARY MOTOR SYMPTOMS
Freezing:
It is seen in patients with mild stage to advanced PD.

It is involuntary inability to move which is seen temporarily.

All the PD patients mayn't experience this symptom but those who do have a greater risk of falling.

It usually lasts only a few seconds. Freezing episodes are seen at any time but more often seen when the patient initiates or starts to move[9].

Micrographia
It is an acquired disorder where there is abnormally small, cramped handwriting or the progression to continually smaller handwriting[10].

Hypomimia
It is also said to be mask-like expression.

It includes reduced facial movements, slowed blinking, slowed eye movements and reduced facial expression.

These symptoms are seen because PD effects the muscles that control facial movement[12].

Kyphotic Posture/Stooped Posture/ Posture Changes In PD
i. Bent posture – In this, the tendency to flex/bend to oneside or to flex /bend forward is seen.

This may be due to many factors including rigidity of muscles, brain changes that control posture or dystonia.

ii. Change in awareness of posture – In this, the patient feel like his/her posture is straight but it is not.

The standing straight may seen like an over correction and may sometimes make the patient feel like he/she is falling backwards.

iii. Camptocormia – It is severe but an uncommon problem.

It is severe bending of thoracolumbar spine (middle of back) or lowerback.

This is seen during standing and walking which improves while lying flat[13].

Dystonia
It is characterized by painful, prolonged muscle contractions that cause involuntary repetitive twisting and sustained muscle contractions which likely results of dysfunction of the basal ganglia although the ultimate cause is unknown.

It is a prominent symptom in patients who have mutation in Parkin gene[14].

Bradyphrenia
It is a mental slowness characterized by slowness of thought, impaired tension and motivation, inflexibility and lack of spontaneity.

11-51 % of PD patients exhibit mental slowness.

Akathesia
It is an intolerable feeling of inner restlessness that objectify the patient to move.

For example, the patient may repeatedly rise and sit from the chair or paces in place.

In this condition, the patient remaining immobile is impossible.

The patient feels like asperity (rage), feeling like he must fight against the world[15].

Dysarthria
It is a speech impedement that prevents a person from speaking clearly because the muscles that control their mouth are not functioning properly.

These muscles could be in the tongue, lips or even the diaphragm.

Hypokinetic dysarthria – It is usually due to PD which results from lesions on the substantia nigra.[1]

NON-MOTOR SYMPTOMS
Sexual Dysfunction
It is a common non-motor symptom seen in people with PD.

In men, common sexual problems are erectile dysfunction, decreased libido (sexual drive),

premature or delayed ejection and inability to orgasm.

Women may experience decreased libido, lack of sexual arousal, inability to orgasm and decreased lubrication and/or pain with intercourse[16].

Drooling

It is excessive pooling and spill over of saliva out of the oral cavity.

It is a non-motor symptom that produces various physical and social consequences for the patients as well as their caregivers.

It is due to the abnormality of salivary production or insufficient salivary clearance.[17].

Diagnosis of PD

As discussed earlier there are no objective tests for parkinson's diagnosis. So, the neurologist always considers the past medical history of the patient and performs a comprehensive neurological examination to check for the presence of two or more cardinal signs.

● The physician also observes the response of the patient to parkinson's medications.

● The food and drug administration (FDA) in the year 2011 approved a specific technique called DaTscan that captures detailed images of dopamine system in the brain.

● PET scan also helps in the diagnosis of parkinson's[18].

PET scan and SPECT (DAT) scan

These scans would not add any new information and therefore likely to be unnecessary. They are recommended to conform whether it is essential tremor or parkinson's.

These are performed only by experienced neurologists who have executed a large volume of parkinson's disease scans.

The procedure of this scans is as follows-

● The person first receives a radiopharmaceutical agent/imaging agent generally an injection of Ioflupane I_{123} (Phenyltropine).

● The compound is then examined by a special detector called a Gamma camera.

● This helps in measuring the dopamine transporter (DaT) and it helps in the differentiation of essential tremor and parkinson's disease or another parkinsonism.

● PET scans and DaT/SPECT scans examine the "function" of brain rather than its anatomy.

● This is important because unlike in strokes and tumors, the brain anatomy of PD patient is largely normal.

● The PET and DaT scans will determine the changes in brain chemistry, such as decrease in dopamine, which identify PD and other kinds of parkinsonism.

● PET scans typically focus on glucose metabolism and DaT/SPECT scans focus on the activity of dopamine transporter.

● The new DaT scans use a substance that "tags" a part of neuron in the brain where dopamine attaches to it, showing the density of healthy dopamine neurons.

● Thus, the more of the picture that "lights-up", the more surviving of brain cells.

● If the parts of the brain where dopamine cells remain dark in colour, it is diagnosed as early brain degeneration. This could either mean PD or parkinsonism.

● There is a common pattern seen in people with parkinson's with the cell loss starting on just one side, towards the back of basal ganglia and deep down[19].

NEW APPROACHES IN PD DIAGNOSIS:

In PD, α-synuclein a 140 aminoacid protein levels are abundantly increased. So, levels of α-synuclein in CSF can be used as biomarker for PD diagnosis. Researches are being made to ameliorate α-synuclein as a biomarker [20].

PD diagnosis is almost based only on its hallmark motor symptoms. It is found that by the time a PD patient shows these symptoms almost 70% of neuronal death is already seen. This biomarkers

help in early diagnosis of PD before excessive neuronal death has occurred [21].

α-synuclein is also present in other body fluids like blood. Researches have been conducted to measure plasma α-synuclein level which is served as surrogate biomarker for PD diagnosis.

The levels of α-synuclein in CSF and plasma are measured by ELISA and new technique called immune-magnetic reduction (IMR), an ultra-sensitive Immunoassay has been developed by researchers to detect α-synuclein[22].

➢ Newer studies propose that epigenetic marks may be a new source of biomarkers for PD.

Epigenetics refer to heritable and acquired alterations in gene activity and expression without changes in DNA sequence.

Proposed epigenetic biomarkers are -
 1. DNA methylation at select loci
 2. SNPs with allele – specific methylation
 3. Epigenetic clock
 4. Epigenetic predictors of endopheno types
 5. mt DNA methylation.[23]

Figure 1: Example of micrographia in a patient with IPD. As the sentence, "Today is a sunny day in California" is repeatedly handwritten, progressive diminution of letter size occurs (micrographia). The height of each lined row is approximately 5/16 inches (8 mm). (Courtesy of Jack J. Chen, PharmD, and David M. Swope, MD).(11)
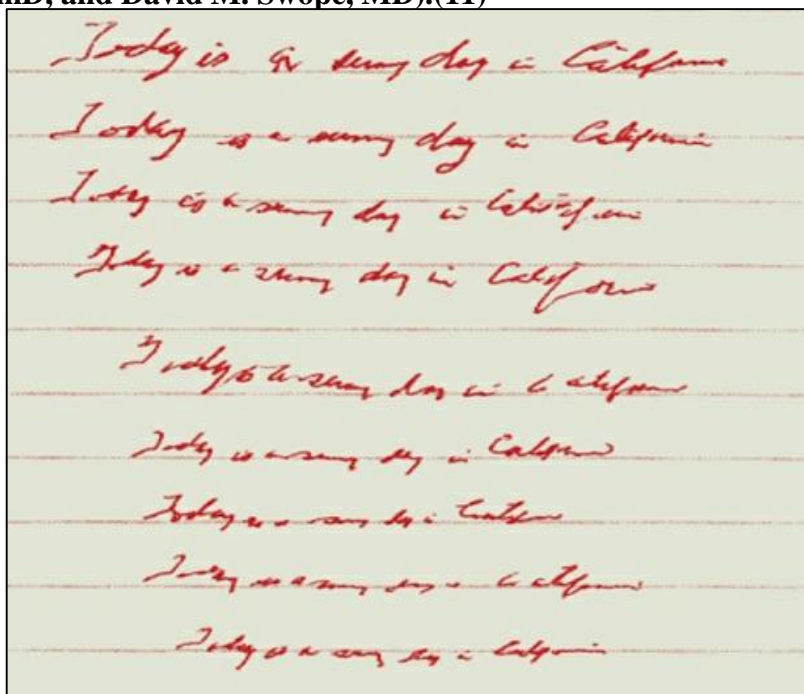
CONCLUSION

Diagnosis of PD often becomes difficult even for a specialized neurologist. The four cardinal signs of PD (Tremors, Rigidity, Bradykinesia, Postural instability) are considered while diagnosing the patient. PET scans and SPECT scans are done to differentiate essential tremor from parkinsonian tremor, which gives a confirmation about the disease.

New approaches are being made like α-synuclein levels in CSF and plasma and epigenetic biomarkers for the diagnosis of PD.

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