Most physicians carry the idea that Parkinson’s disease is a disorder that is diagnosed easily at a glance and from a distance. This might be true in majority of cases but not all. There are many disorders which are “look alikes” of Parkinson’s disease and they may present immense problems in the diagnosis. James Parkinson in his historically famous book “An Essay on the Shaking Palsy” in 1817, described only six patients, of which he actually examined only three; the other three patients were in his own words, “casually met on the street” or “only seen at a distance”. But what we know about Parkinson’s disease now is a little bit different from the notion we carry. At least 10% of the patients what we call Parkinson’s disease are not Parkinson’s disease; they are something else. And this “something else” is usually a “parkinsonian plus” syndrome. This means that one out of 10 patients that we see has a disease which is different from the diagnosis we have made.

Several autopsy based studies that have looked at the final diagnosis and in these studies the characteristic histopathological finding was the basis of ultimate diagnosis of idiopathic Parkinson’s disease. The first one of these was Raiput’s study in Canada where he found that if one compared the initial diagnosis with the final diagnosis, it was wrong in 35% i.e. more than one third of cases.7 The second study was from the London Brain Bank, where the diagnosis was wrong in nearly a quarter of cases (24%).8 In a further follow up study by the London Brain Bank, on patients, all of whom were examined by “movement disorder specialists” during life, the diagnosis was wrong at autopsy 10% of the time.8 Even in the DATATOP study in North America, which included 800 patients of Parkinson’s disease all of whom were enrolled after evaluation by trained Parkinson’s disease specialists and which was designed to evaluate the efficacy of selegilines the diagnosis was found to be wrong in 8.1% cases in those who later came to autopsy. Here the diagnosis during life was based on clinical findings but there were certain clinical specifications laid before the patients were enrolled for the study. And this is the figure from those that were enrolled for the initial study and who subsequently died and were subjected to autopsy; so they are not yet final.7 Very few of these patients have died and have come to autopsy.

Regardless of the advances in anatomical and, functional neuroimaging and other techniques the diagnosis of Parkinson’s disease currently remains clinical. There are no laboratory tests to help us. There are also no universally accepted clinical criteria that are considered to be valid for diagnosis during life, which leaves only autopsy as the gold standard for the final diagnosis.6 The distinction between Parkinson’s disease and parkinsonian syndromes which are close “look alike of Parkinson’s disease can be challenging at first presentation. However speed of progression of the disease and certain subtle clinical features which have been called “red flags” by Nial Quinn and which cast doubt on the clinical diagnosis of Parkinson’s disease make things clear. This text will describe some of these “red flags”. We now know that there are a lot of different disorders, that can look like idiopathic Parkinson’s disease, but there are some including the “parkinsonism plus syndromes” of which the three most important are progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal ganglionic degeneration (CBGD). Corticobasal ganglionic degeneration is now called corticobasal degeneration (CBD) to simplify the long tortuous name. But the list of parkinsonian syndromes also includes several other conditions including Lewy body dementia, frontotemporal dementia, Alzheimer’s disease with Parkinsonism like features, drug induced parkinsonism, post encephalitic Parkinsonism, and Creutzfeldt Jakob disease. One can also see parkinsonism either at presentation or as a part of the disease later in the course of several of the spinocerebellar ataxias, prominent among which are SCA2, SCA3 and SCA12. SCA12 is particularly interesting, because it is a disease, which is typically found in a specific endogamous ethnic population in India and is more of a tremor dominant disease than ataxia dominant. Parkinsonian syndrome can also occur in chronic vascular disease of the brain, calcification of basal ganglia, juvenile Huntington’s disease, Wilson’s disease dopamine responsive dystonia as a sequelae of head injury and rarely also as a part of an intracranial tumour. There are many rare examples of parkinsonian syndromes occurring as a part of other conditions, but these are too rare.

Regardless of the criteria for the clinical diagnosis of Parkinson’s disease, there is now a growing awareness about “what is not Parkinson’s disease”.7 The three striking features that correlate most reliably during life with idiopathic Parkinson’s disease confirmed at autopsy include, (a) classic resting tremor, (b) unilateral asymmetrical onset and (c) a good sustained response to levodopa. When one sees three features, one can be highly confident, although not quite, of the diagnosis of Parkinson’s disease. In the absence of these, at least, the first two, it could still be Parkinson’s disease in a few cases because we know now...
**Table 1: List of “red flags” casting doubt on the diagnosis of Parkinson's disease.**

- Limited response to levodopa.
- Early onset falls/postural instability.
- Early onset dementia.
- Early onset hallucinations and delusions.
- Lower half parkinsonism.
- Early and prominent dysphagia and dysarthria.
- Early and prominent dysautonomia.
- Presence of cerebellar signs, lower motor neuron signs, pyramidal signs, parietal lobe signs, or aphasia.
- Presence of dystonia or myoclonus, particularly.
  - Retrocollis or anterocollis.
  - Eyelid opening apraxia and blepharospasm.
- Vertical ophthalmoparesis, including downward gaze weakness.
- Rapid progression (wheel chair sign).
- Bilaterally symmetrical onset.
- Absence of tremor.
- Presence of pseudobulbar palsy (pathological laughter or crying).
- Presence of cold dusky hands.
- Presence of palilalia/echolalia.
- Presence of perseveration/“applause sign”.
- Presence of stridor.

that a patient does not always have to have tremor or unilateral onset of the disease for the diagnosis of Parkinson's disease.

The most common diseases that look like Parkinson's disease are however the “parkinsonism plus” syndromes which as said earlier, include the two relatively common conditions, progressive supranuclear palsy and multiple system atrophy, but also a rare disorder called corticobasal degeneration. There are a number of specific criteria to diagnose each of these syndromes, but the most important approach is to look for the subtle features which have been called “red flags” or warning signals by Quinn, that tell the physician that it is more likely to be a parkinsonian syndrome rather than idiopathic Parkinson's disease. Quinn not only described many of them, but also popularized and formalized them.

There are obviously a lot of some similarities and overlaps between Parkinsonism plus syndromes and idiopathic Parkinson’s disease, particularly features like akinesia and postural instability, but there are many “red flag” features which point towards a diagnosis of parkinsonism plus syndrome, and some of them are listed in Table 1.

It must be emphasized that some of these red flags are very subtle or soft signs which are outside the nigrostriatal pathway symptomatology. But they are the real key feature, that can be used by clinicians to make the distinction between parkinsonism plus syndrome and Parkinson’s disease. It must also be realized that none of these red flags considered alone can rule out Parkinson’s disease or diagnose progressive supranuclear palsy or multiple system atrophy or corticobasal degeneration because the clinical relationship between Parkinson's disease and parkinsonism plus syndrome is indistinct, but if one takes into account the entire natural history of these patients, the preponderance of evidence favouring one over the other allows to make a fairly accurate diagnosis even during life. One must however agree, that currently the only gold standard we have for the final diagnosis of these disorder is autopsy. This means that regardless of how sure one is about the diagnosis of Parkinson's disease during life, one needs to reconsider the possibility of an alternative diagnosis at each visit and look specifically for the “red flags”. This also means that the physicians must not only concentrate on how the patients are doing on the medication they have been advised, but they must also ask at each visit the question “Does this patient still look like regular Parkinson's disease or not”. And the reason for this advice is that on first presentation a patient of progressive supranuclear palsy for example, may look like Parkinson's disease and it is only with time that a clearer picture emerges, that tells him whether he is dealing with a case of Parkinson’s disease or a parkinsonism plus syndrome. It is not uncommon to see that diagnosis of a parkinsonism plus syndrome becomes clear only in the course of follow up. It is also not uncommon to find a patient with parkinsonism who does not quite look like Parkinson's disease, but also does not have characteristic features of Parkinsonism plus syndrome either and he may turn out to be something else. Until definitive signs of one disease or the other, appear one must be content to use the term “parkinsonism not yet clearly known” and avoid giving it a specific name. Here one would have to depend entirely on the red flag features during the follow up that might give him the diagnosis, because no laboratory tests or imaging techniques are available for a definitive diagnosis of Parkinson’s disease.

As regards these red flags, one has to seek them either in the history or on examination.

**WHAT ARE THESE RED FLAGS?**

**a. Limited response to levodopa**

One of the first red flags is the “degree of response to levodopa”. Here the key features to look for are the degree and quality of response to levodopa although it is only of limited value and not quite absolute. It is commonly seen that patients with a parkinsonism plus syndrome do not respond to levodopa as strikingly as those with true Parkinson’s disease. They often show some improvement but the effect is not quite as dramatic. And often times these patients of parkinsonism plus syndrome who initially respond to levodopa to some extent, the effect often wanes off within a few months or years. The other point is that most patients with idiopathic Parkinson's disease will begin to show improvement with relatively low doses of levodopa, such as only 300 mg per day or even less; however a patient should not be declared a non-responder or a low responder until one has tried a dose of 1000 mg of levodopa per day and found that the symptoms did not improve as expected. In parkinsonism plus syndrome, the chances of a dramatic response also with doses as high as 1000 mg per day are rare. Another important point related with the good response to levodopa therapy is the development of motor fluctuations in patients with idiopathic Parkinson's disease who have been on it. Majority of patients with idiopathic Parkinson's disease eventually develop treatment related minor or major motor fluctuations, suggesting that the diagnosis is correct. On the other hand, appearance of motor fluctuation such as “on and off” phenomenon following levodopa therapy
are quite uncommon in progressive supranuclear palsy, although some patients with multiple system atrophy may develop dopa-related dyskinesia and dystonia, particularly in the face and neck region. So if there are prominent motor fluctuations, they suggest that one is dealing with a case of true Parkinson’s disease. Also in a case of idiopathic Parkinson’s disease where levodopa is very effective, as the effect of a particular dose wanes the patient knows that it is time for the next dose, which is an unlikely feature in a patient with a parkinsonism plus syndrome.

b. Appearance of early falls and postural instability
The next red flag is the history of early falls and postural instability. These are again not absolute evidence but depending upon when they appear in the course of the illness, they become important. Many patients with idiopathic Parkinson’s disease present with postural instability and falls, but they are often a late occurring feature in them. They rarely appear in the early stages of the illness. New patients with parkinsonism, who present to the physician with a history of falls in the first visit or in first few visits probably do not have idiopathic Parkinson’s disease. This is an important red flag that suggests parkinsonism plus syndrome, most likely progressive supranuclear palsy. Here it is not the presence of postural instability and falling, but the timing of its appearance in the course of the illness that is important.

c. Early appearance of dementia
This is the next important red flag. Like postural instability and falls, dementia is a common problem even in idiopathic Parkinson’s disease, but here it is a late coming complication.10 The only exception is a late onset idiopathic Parkinson’s disease, where patients present with symptoms after the age of 70, which may then complicated with features of dementia pretty early in the course of the illness.11 So the patient who has evidence of dementia early in the course of his parkinsonian disorder or where dementia occurs even before the appearance of parkinsonian syndrome, probably does not have idiopathic Parkinson’s disease. Such patients probably have something else and the list of “something else” includes many diseases, such as, Lewy body dementia, frontotemporal dementia, Alzheimer’s disease, vascular dementia, normal pressure hydrocephalus.12 Presence of prominent signs of cortical dysfunction such as aphasia, agnosia or apraxia with dementia also cast strong doubts on the diagnosis of idiopathic Parkinson’s disease.

d. Early appearance of hallucinations and delusions
Hallucinations and delusions are late appearing features in Parkinson’s disease. They are common however in advanced stages of the idiopathic disease both in untreated cases as well as those receiving levodopa but like dementia, when they are present early in the course of the illness or at the beginning, they become important red flags to steer the physician away from the diagnosis of idiopathic Parkinson’s disease.13

e. Lower body parkinsonism
When signs of parkinsonism involve exclusively or at least disproportionately, both lower limbs, it is called “lower body parkinsonism” and this is considered another important red flag. Lower half parkinsonism is typically seen in people past the age of 70 which is an age considered unusual for idiopathic Parkinson’s disease to start because most idiopathic PD patients begin to develop symptoms around 60 years of age. Here the gait is slow and shuffling, but unlike idiopathic Parkinson’s disease its base is often wide rather than narrow and the “arm swing” is not lost as it is in true Parkinson’s disease. Most of these patients often show “freezing”, early falls and “impaired postural righting reflexes”. Their upper limbs, facial appearance and speech are however quite normal. This syndrome is seen in many conditions including normal pressure hydrocephalus, vascular parkinsonism or as a primary gait disorder in the elderly where there is a gait “ignition” or “starter failure”14,15

f. Early onset dysphagia or dysarthria
Dysphagia and dysarthria can occur in patients with idiopathic Parkinson’s disease, but they are usually late features of the disease or at least they appear in the middle course of the illness. There mere presence is not enough to suggest that they are red flag signals, however when they occur early and are a prominent feature of the disease, they represent a red flag and suggest a diagnosis other than true Parkinson’s disease such as progressive supranuclear palsy or multiple system atrophy. Other than its timing and severity, the dysphagia in progressive supranuclear palsy is not very much different from what is seen in advanced Parkinson’s disease. Likewise dysarthria when present, looks very similar in true Parkinson’s disease and in parkinsonian plus syndromes except that it is again a late feature in Parkinson’s disease and usually appears early in parkinsonism plus syndromes. Some patients of progressive supranuclear palsy may have a spastic quality in their dysarthria which has been called “growling dysarthria”16 Also some patients of multiple system atrophy may show a “scanning” dysarthria, because of the prominent cerebellar dysfunction.

g. Presence of early and prominent dysautonomia
Presence of dysautonomia is often required as an essential feature for the diagnosis of multiple system atrophy, but dysautonomia can be a sign of idiopathic Parkinson’s disease as well. So it is not necessarily, presence of dysautonomia, but its timing and severity that are important. Dysautonomia appears much earlier and much more severely in multiple system atrophy than it does in idiopathic Parkinson’s disease. So dysautonomia appearing early in the course of a parkinsonian syndrome acts as a red flag that alerts the physician that it might be multiple system atrophy and not Parkinson’s disease.17

Another important point to take notice regarding dysautonomia is that the patients may not volunteer any information about their dysautonomic symptoms unless asked. It is therefore the duty of the physician to look carefully
for this red flag and interrogate patients about symptoms that suggest dysautonomia, such as erectile dysfunction in males. Similarly another important feature of dysautonomia is postural hypotension which may not always present with classic symptoms like “frank syncpe” or “near syncope” Here one has to look for minor features of orthostatic hypotension such as constipation light headedness or dizziness on change of posture. They can also have post-prandial drowsiness, visual blurring, problems in concentration. Some time these patients, complain of occipital or posterior cervical pain which is attributed to hypoperfusion of neck muscle and has been called the “coat hanger’s sign”. There it is important to check blood pressure in supine and in standing position to confirm, if there is orthostatic hypotension and if it is severe or if it appears early, it is a red flag.

h. Presence of cold dusky hands

Patients with multiple system atrophy may show cold, dusky violaceous hands and feet with slow refilling after blanching. This is a feature that has been reported by may investigators and if present, is considered a red flag. It is attributed to autonomic dysregulation of blood vessels supplying the distal parts of the extremities and is supposed to be a characteristic feature of multiple system atrophy.

i. Presence of non nigrostriatal features such as cerebellar sign lower motor neuron sign, pyramidal, parietal lobe signs and aphasia

The next important red flags are signs that suggest dysfunction outside the nigrostriatal pathway and compared to red flag sign described thus far, which have been by and large soft signs, these ones are considered “hard” signs. They suggest the involvement of cerebellar system, pyramidal tract, lower motor neuron, parietal cortex or the language function and these are generally considered fairly important. They reveal involvement of systems other than nigrostriatal pathway and their presence casts strong doubts on the diagnosis of Parkinson’s disease. One does not expect pyramidal signs such as extensor plantar response or excessively brisk deep tendon reflexes or cerebellar signs or lower motor neuron signs or parietal lobe signs or apraxia or aphasia to be present as a part of idiopathic Parkinson’s disease. If they are present, they represent important red flags that point against the diagnosis of idiopathic Parkinson’s disease. Patients with progressive supranuclear palsy have degeneration of systems other than nigrostriatal pathway. They show features suggestive of pyramidal, cerebellar, lower motor neuron, frontal and parietal lobe dysfunction. However, in this regard it is important to rule out existence of a dual pathology such as Parkinson’s disease associated with neuropathy, stroke, cervical spondylotic myelopathy or some such disorder.

An important feature is the presence of signs suggesting frontal lobe dysfunction and this is particularly noticeable in progressive supranuclear palsy. Subtle frontal lobe features include perseveration, concrete abstraction, decreased verbal fluency, executive dysfunction. There is a special type of perseveration which has been called “applause sign” which is a characteristic feature of progressive supranuclear palsy. These patients when asked to clap three times in a row exceed this number and clap for more than 3 times. Palilalia or echolalia and apathy, reduced word fluency and changes in personality are frontal lobe signs that are relatively specific for progressive supranuclear palsy. Of these, apathy is quite common in idiopathic Parkinson’s disease as well as in progressive supranuclear palsy and multiple system atrophy. Palilalia is generally not a sign of Parkinson’s disease but is often seen in progressive supranuclear palsy. Its presence is another red flag to suggest that the physician needs to think of a disease other than true Parkinson’s disease.

Parietal lobe signs such as apraxia, cortical sensory loss, “alien limb” sign, “lavitation” point towards corticobasal ganglionic degeneration. “Alien limb” sign refers to a limb with a “foreign quality” which behaves a little independently. “Lavitation” is a phenomenon where the arm floats horizontally without the patient realizing it.

j. Presence of retrocollis, anterocollis, myoclonus, blepharospasm, and eyelid opening apraxia.

There are some other movement disorders that can be seen occasionally in Parkinson’s disease, and their presence usually casts doubt on the diagnosis of idiopathic Parkinson’s disease. Dystonia and myoclonus can occasionally be a part of Parkinson’s disease particularly in the treatment phase, but their prominent presence, should lead one to question the diagnosis of idiopathic Parkinson’s disease. Prominent retrocollis suggests progressive supranuclear palsy and anterocollis suggest multiple system atrophy. One may also see blepharospasm sometime as a part of idiopathic Parkinson’s disease, but it usually occurs as a complication of levodopa treatment. However, if it is present early and prominently, it is another red flag that is more frequently seen in progressive supranuclear palsy. “Eye lid opening apraxia” which refers to “hesitancy to open the closed eyes” is another important red flag that points against the diagnosis of Parkinson’s disease. It is more frequently seen in either progressive supranuclear palsy or multiple system atrophy. The same is true of myoclonus. Sometime occasional myoclonic jerks are seen in corticobasal degeneration. It is called jerky dystonia and when present, it is typical of corticobasal degeneration and not Parkinson’s disease.

k. Presence of vertical ophthalmoparesis.

The next red flag is in the oculomotor system. There are variety of minor oculomotor signs mainly in saccadic and pursuit movements, which one can see in parkinsonian syndromes, but none of them are necessarily pathological and they do not always point to a specific diagnosis because some of them may also be seen Parkinson’s disease or as a part of normal aging. Patients with Parkinson’s disease may show hypometric saccades which simply means that the saccades do not always extend as much as they do in normal people. The saccadic velocity in this condition is however normal and there is no slowing. Saccadic intrusions which are also popularly known as “square wave jerks” and mild limitation of upward gaze, have been noted in Parkinson’s disease. These are common features of many forms of parkinsonian syndromes. However, there are some signs which are quite distinctive of certain specific parkinsonian
syndrome particularly progressive supranuclear palsy and if present they point to a direction away from the diagnosis of idiopathic Parkinson’s disease.26 Of all the parkinsonian plus syndromes, it is the progressive supranuclear palsy which has the most distinctive oculomotor abnormalities and the type of ophthalmoparesis that really distinguishes progressive supranuclear palsy from Parkinson’s disease is the impairment of downward gaze. For the clinical diagnosis of progressive supranuclear palsy downward gaze weakness is an essential requirement. If it is not present, at it is sometimes in the initial stages of the disorder, the patient under consideration is not immediately labeled as progressive supranuclear palsy. Whereas weakness of upward gaze is a nonspecific sign, the downward gaze weakness is a very specific sign favouring the diagnosis of progressive supranuclear palsy. But before downward gaze impairment becomes clinically noticeable, slowing of vertical saccades appear, which is a clinical clue that suggests that the downward gaze palsy may be in offing. This is best tested by asking the patient to shift their gaze quickly between two targets, one set located vertically and the other horizontally and comparing the speed of vertical and horizontal ocular movement and also by observing the fast phase of optokinetic nystagmus which is attenuated in progressive supranuclear palsy. It must however be remembered that the eye signs of progressive supranuclear palsy may sometime lag behind other features of the disease and very rarely may not appear at all and that makes the clinical diagnosis of progressive supranuclear palsy very problematic. Other ocular signs such as slowing of saccadic movements, overshoot ocular dysmetria and nystagmus are not normally features of a parkinsonian syndrome; they are all cerebellar signs.

1. Rapid progression of the disease (“wheel chair” sign of Quinn).
   One of the important red flags is the rapid downward progression in patients with parkinsonian plus syndrome. Many of these patients take to the wheel chair pretty early in the course of the illness and this is the reason why Quinn refers it as “wheel chair sign”, emphasizing that patients with parkinsonism plus syndrome become wheel chair bound much earlier in the course of the illness than those with, idiopathic Parkinson’s disease. Some patients of parkinsonism plus syndrome may however have a more protracted course, but most die between five and ten years of the onset. On the other hand, while most patients of Parkinson’s disease will have a slow progression, particularly when they are on levodopa therapy, those that have onset after 70 may progress a little more rapidly and come to a wheelchair stage within a few years of the onset.

m. Symmetrical onset and absence of resting tremor.
   As mentioned earlier, the most reliable sign of Parkinson’s disease are classic resting tremor, asymmetric onset (hemiparkinsonism) and a remarkably beneficial sustained response to levodopa. Only sometime Parkinson’s disease patients have a symmetrical presentation and in only about 20 to 25% they do not have a prominent tremor. This means that while absence of tremor and a symmetrical onset are certainly not by themselves against the diagnosis of Parkinson’s disease, they may lead one to reconsider the diagnosis more carefully. Also resting tremor and asymmetry have rarely been described in parkinsonian plus syndromes. The most asymmetric of the parkinsonian plus diseases is corticobasal degeneration. Multiple system atrophy and progressive supranuclear palsy rarely start unilaterally.

n. Pseudobulbar palsy (pathological laughter or crying).
   Another feature that the physicians some time notice in parkinsonian patients is emotional incontinence which means “unprovoked pathological laughter or crying” and if they are prominently present and appear early in the course of the illness they act like another red flag, which makes one think of a disease other than idiopathic Parkinson’s disease.

o. Stridor
   The is another red flag which is helpful in distinguishing idiopathic Parkinson’s disease from multiple system atrophy, of which, it is a common accompaniment. It is not only an important sign that differentiates one disease from the other, but is also important from therapeutic and prognostic points of view, because unrecognized, it may lead to dangerous airway obstruction. It is prognostically important as well, because it carries a bad prognosis when present.27 It is a sign suggesting laryngeal paralysis and dystonia.28

WHAT ARE THE CONCLUSIONS?
- The diagnosis of Parkinson’s disease is often (at least 10% of the time) incorrect and requires continuous careful monitoring.
- The most common mimickers of Parkinson’s disease are Parkinsonism plus syndromes.
- Parkinson’s disease and parkinsonism plus syndromes are very heterogeneous in their clinical features.
- Amongst the parkinsonism plus syndromes, progressive supranuclear palsy and multiple system atrophy are most common.
- Some patients with parkinsonism, who do not fit into the picture of either Parkinson’s disease or parkinsonism plus syndrome initially need not be given a specific label until the diagnosis becomes clear.
- The physician needs to know the red flags and look for their presence or absence during each visit. He must pay special attention to ocular movements, orthostatic hypotension, apraxia and dusky hands.
- There are no laboratory tests or imaging techniques to make a correct diagnosis of Parkinson disease.
- Autopsy is the gold standard not only for the final diagnosis but also for keeping us humble.
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