



Clinical Approach to Parkinson's Disease: Features, Diagnosis, and Principles of Management

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Parkinson's disease (PD) is one of the most common neurodegenerative disorders. The condition causes a heavy burden both on those affected, as well as their families. Accurate diagnosis is critical and remains founded on clinical grounds as no specific diagnostic test is available so far. The clinical picture of PD is typical in many instances; however, features distinguishing it from other disorders should be thoroughly sought. Monogenic forms of PD also have some distinctive characteristics in many cases. This text is a roadmap to accurate diagnosis in PD, as it approaches clinical features, diagnostic methodology, and leading differential diagnoses. Therapeutic issues are also briefly discussed.

Nearly 200 years have passed since the publication of James Parkinson's succinct observations in *An Essay on the Shaking Palsy* (Parkinson 1817, reprinted in Parkinson 2002; for more details on the history of PD see the text by Goetz 2011). Remarkably, the original clinical description of the disease remains a landmark reference, especially with regard to the motor features. Parkinson's disease (PD), as Jean Martin Charcot called it a few decades later (Lees 2007; Lanska 2010), is a common and often disabling disorder seen in people from all races and geographical locations, with clinical signs emerging also in a wide age range, including the young (Marsden 1994; Tolosa et al. 2006; Lees et al. 2009).

The epidemiological figures pertaining to PD are not accurately determined, as different studies were variable in diagnostic criteria, methodology, and study population. A prevalence of ~1%–2% in the population older than 60–65 yr, or 0.3% in the general population, is now commonly accepted (de Lau and Breteler 2006; Hirtz et al. 2007; Alves et al. 2008), with prevalence rates ranging from 65.6 to 12,500 per 100,000 population (von Campenhausen et al. 2005). In 2005, more than 4 million PD patients existed in the world (Dorsey et al. 2007). Annual incidence rates range from 8.6 to 19 per 100,000 (Twelves et al. 2003; de Lau and Breteler 2006; Alves et al. 2008). PD is the second most common neurodegenerative disorder after Alzhei-

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mer's disease, with a male-to-female ratio of about 3:2 in most studies (de Lau and Breteler 2006; Alves et al. 2008). It occurs infrequently under 40 years of age, with early onset increasing the probability that genetic causes might be involved (de Lau and Breteler 2006; Schrag and Schott 2006).

The cause of PD is unknown, although complex interactions between genetic and environmental factors are probably involved. Various risk factors have been found for sporadic PD, including exposure to pesticides and other toxins, positive family history, and oophorectomy, but age remains the most important one documented so far (de Lau and Breteler 2006; Elbaz and Moisan 2008; Bronstein et al. 2009). Thus, disease prevalence is expected to increase dramatically in the next decades as the population ages, which might raise serious issues at a worldwide level with regard to social security and health care systems. This might be particularly true for developing countries such as China or India (Dorsey et al. 2007). Conversely, there have been data showing that protective factors might exist, the most robust association with smoking, but also coffee or black tea drinking, and possibly nonsteroidal anti-inflammatory drugs (Elbaz and Moisan 2008; Bronstein et al. 2009; Gao et al. 2011). In this regard, an interesting finding concerns high uric acid levels, which seem to protect from PD, and are apparently also associated with decreased rates of disease progression (Elbaz and Moisan 2008; Schlesinger and Schlesinger 2008).

CLINICAL FEATURES

Motor Symptoms

From the motor standpoint PD is characterized by a clinical syndrome universally known as *parkinsonism*, which includes four cardinal features: bradykinesia, rest tremor, rigidity, and postural and gait impairment. One should bear in mind that these are not always observed in every patient, at least in a given time frame.

1. *Bradykinesia* refers to slowness of movements with a progressive loss of amplitude or speed during attempted rapid alternating

movements of body segments (Marsden 1982; Edwards et al. 2008a; Jankovic 2008; Rodríguez-Oroz et al. 2009). It is crucial to distinguish true bradykinesia from simple slowness, which is frequently seen in patients with decreased muscle power (paresis), spasticity, or reduced motivation (e.g., depression). In fact, failing to acknowledge this is a major source of misdiagnosis. Clinically, bradykinesia can be assessed by asking the patient to perform some repetitive movements as quickly and widely as possible, namely, opening and closing the hand, tapping thumb and index fingers, or tapping the foot on the ground (see online Movies 1 and 2 at www.perspectivesinmedicine.org). The examiner must pay attention to the emergence of progressive slowness and/or loss of amplitude, which might ultimately bring the movement to full arrest (*freezing*, see online Movie 2). Bradykinesia can also be searched for globally by observing the patient's spontaneous movements while sitting, standing up from a chair, or walking (see online Movies 3 and 4 at www.perspectivesinmedicine.org). Other clinical displays of bradykinesia are *hypomimia* (decreased facial expression and eye blinking, termed "poker face" in milder stages, see online Movie 2), *hypophonia* (softer voice), *micrographia* (progressively smaller handwriting), and difficulty swallowing.

2. *Rest tremor* (sometimes also called parkinsonian tremor) is a rhythmic oscillatory involuntary movement that comes about when the affected body part is relaxed and supported by a surface, thus removing the action of gravitational forces (Deuschl et al. 1998; Bain 2007; Edwards et al. 2008b). It vanishes with active movement, and typically can reappear after a few seconds when the arms are held outstretched (*reemergent* tremor). In PD, rest tremor frequency is usually in the low to mid-range (3–6 Hz), whereas the amplitude is quite variable, from less than 1 cm to >10 cm wide (see online Movies 1, 3, 5, and 6 at www.perspectivesinmedicine.org). The most distinguishing tremor in this dis-

order is the so-called “pill-rolling” type, a visual portrayal resulting from the simultaneous rubbing movements of thumb and index fingers against each other (see online Movie 1). Other forms of tremor movements can be seen, such as finger flexion-extension or abduction-adduction. Tremor can also be present in the lower limbs, jaw (see online Movie 5), and tongue. Head tremor is not typical of PD; in fact, it should prompt careful diagnostic reconsideration. An additional form of tremor, postural (e.g., occurs immediately on stretching out the arms), faster (6–8 Hz), can be occasionally seen in PD, but this is noncontributory to the diagnosis. In clinical practice, tremor is best observed while the patient is focused on a particular mental task (e.g., countdown from 100 with eyes closed), which facilitates limb muscle relaxation.

3. *Rigidity* refers to an increased muscle tone felt during examination by passive movement of the affected segment (limbs or neck), involving both flexor and extensor muscle groups (Edwards et al. 2008a; Jankovic 2008; Rodríguez-Oroz et al. 2009). This resistance is felt throughout the full range of movement, and does not increase with higher mobilization speed, which distinguishes it from spasticity owing to upper motor neuron lesions. When resting tremor coexists the classical “cog wheel rigidity” can be felt during passive limb mobilization, especially in the wrist. Rigidity in the examined segment is very typically increased by voluntary movement of other body parts (Froment’s maneuver), and this is a useful way to detect mild rigidity in many cases.
4. *Postural and gait impairment.* Parkinsonian patients tend to adopt a stooped posture (see online Movie 7 at www.perspectivesinmedicine.org), owing to the loss of postural reflexes, a major contributor to falls (Edwards et al. 2008a; Jankovic 2008; Sethi 2008). In some cases extreme anterior truncal flexion may supervene (*camptocormia*). Parkinsonian gait is slow, occurs on a narrow base, and is characterized by short shuffling steps, which gives the observer the impression that

the patient is chasing his own center of gravity. There is decreased arm swing, turning around is slow and performed with multiple small steps (see online Movies 3 and 5), whereas freezing of gait can occur (see online Movie 8 at www.perspectivesinmedicine.org), especially in crowded or narrow places (Edwards et al. 2008a; Sethi 2008). In certain circumstances there is *festination*, in which a very fast succession of steps is seen, with the patient at times only able to stop when meeting some sort of obstacle. Walking and turning becomes more difficult or even impossible in parkinsonian patients if an additional cognitive load is imposed (e.g., dual tasking) (Sethi 2008; Spildooren et al. 2010; Plotnik et al. 2011). Clinically, one should observe posture and gait both on an open corridor and while passing through narrow doorways or spaces. The “pull test” is performed in order to assess postural stability; the examiner stands behind the supine patient who is previously warned of the “pull” applied to his/her shoulders, then allowing him/her to step back in order to regain balance—some patients will fall without any sort of postural response.

Nonmotor Symptoms and the Premotor Phase of PD

PD has been traditionally regarded as a motor disorder, perhaps because the original account of the clinical features emphasized these symptoms, while failing to recognize the important nonmotor aspects of the disease. In addition, motor symptoms often meet the eye straightaway, even for untrained observers. However, in recent years there has been an increasing interest in nonmotor symptoms of PD (Table 1), because their recognition is useful for diagnostic purposes, but also because they are a major source of deterioration in quality of life, and warrant specific management (Poewe 2008; Chaudhuri and Schapira 2009; Lim et al. 2009; Gallagher et al. 2010).

The work from Braak and coworkers showed that disease symptoms correlate with the extension of the pathology affecting the nervous sys-

Table 1. Nonmotor symptoms in Parkinson's disease

Neuropsychiatric features

Apathy
Anxiety, panic attacks
Mood disorders, especially depression
Hallucinations, illusions, delusions
Cognitive deterioration, ranging from mild impairment to dementia

Dysautonomia

Orthostatic hypotension
Constipation
Urinary dysfunction (urgency, retention)
Sexual dysfunction
Excessive sweating
Seborrhea
Sialorrhea (i.e., drooling, also attributable to decreased swallowing movements)

Sleep disorders

Insomnia
REM behavior disorder
Restless legs syndrome
Periodic limb movements in sleep
Excessive daytime sleepiness

Sensory dysfunction

Hyposmia (i.e., loss of sense of smell)
Decreased visual contrast and color discrimination
Decreased visual motion perception
Abnormal sensations, such as paresthesias (i.e., tingling)

Pain

Fatigue

Data from Silva et al. 2005; Emre et al. 2007; Poewe 2008; Castelo-Branco et al. 2009; Chaudhuri and Schapira 2009; Lim et al. 2009; and Gallagher et al. 2010.

Abbreviation: REM, rapid eye movement.

tem (Braak et al. 2003; Hawkes et al. 2010). Because of long-term pathological progression, some of these nonmotor features may be present before any of the classical motor signs are noticeable, sometimes for years or decades, which confers them potential diagnostic utility in early disease stages, such as hyposmia, rapid eye movement (REM) behavior disorder, constipation, and depression (Lim et al. 2009; Tolosa et al. 2009; Hawkes et al. 2010; Savica et al. 2010; Schapira and Tolosa 2010). Some patients will have unexplained shoulder pain or fatigue be-

fore overt motor symptoms emerge. On the other hand, features like dementia and hallucinations occur late in the course of disease, which is useful for distinguishing PD from other disorders. Mild cognitive dysfunction is apparent in many cases from early stages, but recent data has shown that frank dementia will occur in >80% of patients after 20 years of disease (Healy et al. 2008).

DIAGNOSIS OF PD AND DIFFERENTIAL DIAGNOSIS

How to Diagnose PD

The diagnosis of PD is still largely a clinical one, as there is no definitive test able to confirm the diagnosis during life, with the exception of gene testing in a reduced number of cases. PD is a disease combining clinically defined parkinsonism with specific pathological findings, namely, dopaminergic neuron loss in the region of *substantia nigra pars compacta*, as well as the presence of intraneuronal Lewy bodies (Marsden 1994; Lees et al. 2009), although there are a few notable exceptions to this with regard to the pathological diagnosis. From a practical perspective, the first step for the diagnosis of PD is careful history taking. Thorough questioning of the patient and family should be performed, trying to define which symptoms emerged and their sequence, as well as perceived anatomical involvement. Inquiry about the presence of premotor symptoms including sleep-related REM sleep behavior, loss of smell, and constipation can be helpful if present. Drug intake history, both past and present, especially concerning drugs able to cause parkinsonian symptoms, is paramount. Likewise, possible exposure to environmental toxics should also be searched for (e.g., manganese in welders). Past and present medical disorders should be systematically recorded. Family history is also an important stage, and should include neurological disorders in other family members, as well as inquiry about ethnic ancestry as monogenic forms of PD are more prevalent in some (e.g., Ashkenazi Jewish and North African Arabs who have a higher frequency of LRRK2 genetic PD).



Clinical examination follows: this should be thorough and systematic. A note should be made if there is a typical resting pill-rolling tremor and bradykinesia. If this is present in an asymmetric fashion then it is almost pathognomonic for PD. Notably, PD parkinsonism is usually different from that seen in other parkinsonian disorders, because it emerges and progresses asymmetrically (e.g., one side of the body is more affected), with gait and balance being affected later in the course of disease. Moreover, it is important to confirm that parkinsonian features are the only clinical signs—implying that pyramidal, sensory, and cerebellar deficits should be excluded, as well as dementia (early in disease course), and other movement disorders (e.g., chorea, myoclonus, tics, unexpected type of tremor), with the exception of dystonia as this can be seen in some cases, particularly the young-onset forms of PD. Eye movements in PD should be full range and display normal latency (e.g., immediate movement after command), speed, and accuracy. Some findings should raise doubts about the diagnosis of PD, and other disorders should be considered instead, whenever any of these are observed (Table 2). In some cases who have received levodopa treatment, the presence of typical limb choreiform dyskinesias is also a useful sign suggesting IPD.

In typical circumstances, a restricted number of investigations are necessary to establish the clinical diagnosis of PD. A few treatable conditions, which might cause asthenia or “slowness” (not true bradykinesia), such as anemia and hypothyroidism, should be ruled out by appropriate laboratory testing. Other specific suspicions guide further investigations. Brain structural imaging, either by computed tomography (CT) or magnetic resonance imaging (MRI) should always be performed; where available the latter is preferred, because some positive findings occasionally reveal other diagnostic entities (Massano et al. 2008; Sitburana and Ondo 2009). CT scan should be used whenever calcium deposits are being searched for (e.g., Fahr's disease). Dopamine functional imaging might be considered to confirm that degenerative parkinsonism is the cause of symptoms. Positron emission tomography (PET) with fluoro-

Table 2. “Red flags” for an incorrect diagnosis of PD

Absence of symptom asymmetry
Severe axial or lower limb involvement, especially in early stages
Frequent falls, especially in early stages
Fast disease progression (e.g., Hoehn and Yahr stage 3 in less than 3 years)
Eye movement disorders (e.g., supranuclear palsy, dysmetric or slow saccades)
Other unexpected movement disorder, such as myoclonus, tics, and chorea
Pyramidal or cerebellar dysfunction
Bulbar or pseudobulbar features
Parietal associative sensory disturbances (agraphesthesia, astereognosis)
Apraxia
Alien limb
Severe cognitive deterioration or psychosis early in disease course
Marked autonomic dysfunction in early stages
Insufficient clinical benefit gained from adequate trial of levodopa or apomorphine

The features listed here are not typical of Parkinson's disease, and should raise suspicion about alternative diagnoses. Hoehn and Yahr staging is described in Goetz et al. 2004.

dopa is one of the technologies available, but the costs and limited accessibility make it difficult to use. In this regard, dopamine transporter (DAT) imaging with single-photon emission CT (DAT-SPECT) is a very useful approach, because it is sensitive for the detection of presynaptic dopaminergic neuron degeneration in the striatum (Kägi et al. 2010a). None of these methods is able to distinguish PD from other causes of degenerative parkinsonism, but presynaptic dopamine imaging is normal in essential tremor, dystonic tremor, drug-induced, psychogenic tremor, and psychogenic parkinsonism (for more on details on functional imaging in PD please refer to the text by Niethammer et al. 2012). In appropriate circumstances, genetic testing might be considered; whenever a pathogenic mutation is found, a definitive diagnosis of PD is achieved in vivo. Another way of sanctioning the diagnosis of PD is through the observation of the clinical benefit gained from an acute challenge of oral levodopa or subcutaneous apomorphine, which should markedly



improve the clinical symptoms—otherwise, other diagnostic possibilities should be considered, although some PD patients will only respond to long-term high doses of levodopa. Dopaminergic drugs confer a sustained benefit in PD. The UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria (the Queen Square Brain Bank criteria) are routinely used to make the diagnostic process as objective and accurate as possible. Three major steps are required for the diagnosis of PD, as depicted in Table 3.

Currently, MRI is preferred over CT, and family history is not regarded as an exclusion criterion, because a number of Mendelian forms of PD have been described.

Differential Diagnosis

PD can be confused with many disorders, and diagnostic accuracy improves with increasing clinical experience. The entities most commonly confused with PD are (Edwards et al. 2008c; Jankovic 2008; Lees et al. 2009)

1. Vascular parkinsonism: In this situation parkinsonian symptoms predominate in the lower limbs, and gait tends to be quite affected, hence the designation “lower body parkinsonism”; rest tremor is uncommon. Other signs of brain vascular lesion might be present, such as spasticity, hemiparesis, and pseudobulbar palsy, whereas response to levodopa is usually scarce (Winikates and Jankovic 1999; Edwards et al. 2008c; Lees et al. 2009; Kalra et al. 2010). Structural brain imaging is especially important to rule out or support this diagnosis.
2. Drug-induced parkinsonism (DIP): Parkinsonian signs tend to present symmetrically and a coarse postural tremor is often present. Other drug-induced disorders might be present, such as orolingual dyskinesias, tardive dystonia, or akathisia, especially in those cases in which the culprit drug is an antipsychotic. For the diagnosis of DIP it is important that symptoms have emerged after the drug has been introduced (Alvarez and Evidente 2008). In true DIP symptoms improve

Table 3. The UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria

Step 1: Diagnosis of parkinsonian syndrome

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or 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

Step 2: 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^a

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 a cerebral tumor or communicating hydrocephalus on CT scan

Negative response to large doses of levodopa (if malabsorption excluded)

MPTP exposure

Step 3: Supportive positive criteria of Parkinson’s disease

Three or more required for diagnosis of definite Parkinson’s disease:

Unilateral onset

Rest tremor present

Progressive disorder

Persistent asymmetry affecting the side onset most

Excellent response (70%–100%) to L-dopa

Severe levodopa-induced chorea

Levodopa response for 5 years or more

Clinical course of 10 years or more

Hyposmia

Visual hallucinations

^aThis criterion is no longer used (Hughes et al. 1992; Litvan et al. 2003; Lees et al. 2009).

markedly or remit a few months after complete drug withdrawal, but symptoms remain at least partially in those patients with a concomitant cause for parkinsonism (e.g., PD).

3. Tremor disorders: Essential tremor (ET) is often confused with tremulous PD (Schrag et al. 2000; Jain et al. 2006), but careful observation will result in a correct diagnosis, because the characteristics of ET are quite distinct; it is a largely symmetric postural or kinetic hand tremor reaching a frequency of up to 12 Hz, infrequently observed at rest, and unaccompanied by any parkinsonian signs or abnormal posturing (Bain et al. 1994; Deuschl et al. 1998; Edwards et al. 2008b). In a large series, Bain and coworkers (1994) found that autosomal-dominant inheritance was archetypal, with the mean age at onset of tremor being 15 years old; half of the patients displayed alcohol responsiveness, and head tremor was mild when present. A few interesting and mind provocative reflections about ET have recently been published (Quinn et al. 2011). Another group of tremor patients frequently misdiagnosed as PD were more recently characterized (Schneider et al. 2007; Schwingenschuh et al. 2010)—These patients have SWEDDs (“scans without evidence of dopaminergic deficits”), hence named owing to the fact that DAT imaging is normal, thus ruling out striatal presynaptic degeneration. In these patients, tremor at rest or asymmetry are frequent, as well as head tremor, but no true akinesia is seen, although decreased arm swing may be apparent. This group shows clinical and electrophysiological characteristics resembling dystonia, which should be actively searched for clinically (Schneider et al. 2007; Schwingenschuh et al. 2010).
4. Dementia with Lewy bodies (DLB): Dementia is the fundamental feature of this disorder, whereas parkinsonism is seen either early or along the course of the disease, in striking contrast with PD. These patients, usually elderly, suffer from marked daily fluctuations in alertness and cognition, as well as very detailed and colorful visual hallucinations, involving human figures (children is a very typical motif) and animals. Other features frequently seen are REM sleep behavior disorder, extreme sensitivity to the effects of neuroleptic drugs, and dysautonomia (Geser et al. 2005; Weisman and McKeith 2007). Because of common clinical and pathological findings, a lively debate still revolves around the fact that DLB and PD could belong to the same spectrum of a common disease or, in contrast, represent truly separate disorders.
5. Multiple system atrophy: This is one of the most common causes of degenerative parkinsonism, with age at onset of symptoms usually in the late 6th or early 7th decades. Classically, patients present with a core combination of dysautonomia, cerebellar features, and parkinsonism; in most patients the latter predominates, except in Japanese populations. A jerky postural tremor is frequently seen, as well as pyramidal signs, such as generalized hyperreflexia and extensor plantar reflexes. Parkinsonism will respond to levodopa in up to roughly a third of patients, but this is usually a suboptimal and short-lived benefit (Edwards 2008c; Gilman et al. 2008; Stefanova et al. 2009). Other suggestive features of this disorder are severe dysarthria or dysphonia, orofacial dystonia, marked antecollis, and inspiratory sighing (Gilman et al. 2008; Stefanova et al. 2009). MRI may help in the diagnosis, by disclosing findings such as cerebellar and pontine atrophy, the “hot cross bun” sign, or a hypertense rim surrounding the putamen in T2-weighted sequences (Masano et al. 2008; Sitburana and Ondo 2009).
6. Progressive supranuclear palsy: The classical phenotype (Richardson syndrome, RS) will be hardly confused with PD, as patients present with a largely symmetric akinetic-rigid syndrome, with predominant axial involvement, including impairment of gait and balance, with falls occurring as early as the first year of symptoms. Tremor is infrequently seen in these patients. Other typical signs of RS are vertical gaze supranuclear palsy (only slowing of vertical saccades is apparent



in early stages), pseudobulbar symptoms, retrocollis, and continuous activity of the frontalis muscle, with eyes permanently wide open (e.g., “staring eyes”). Frontal-subcortical cognitive deficits are usually evident. Levodopa is usually of no benefit (Warren and Burn 2007; Williams and Lees 2009). However, other patients present with a parkinsonian syndrome resembling PD: symptoms are asymmetric, at times with rest tremor, with few axial involvement, delayed onset, or no eye movement disorder, and displaying levodopa responsiveness, even if partial. This syndrome has been called PSP-P (“PSP-parkinsonism”) and survival is longer than in RS (Williams et al. 2005).

7. Fragile X-tremor ataxia syndrome (FXTAS): This is a late-onset (usually >50 years of age) neurodegenerative disorder seen in patients (especially men) who carry an abnormal number of CGG repeats in the *FMR1* gene, in the premutation range (55–200 repeats). Core symptoms are cerebellar gait ataxia and postural/intention tremor, variably accompanied by parkinsonism, dysautonomia, cognitive decline of the frontal type, and peripheral neuropathy. Disease progression is usually slow. Parkinsonian symptoms resembling the classical picture of PD have been described. Women carrying the premutation tend to display mitigated symptoms, as well as premature ovarian failure and menopause. MRI may be a useful adjunct to the diagnosis, as many patients will show T2 hyperintensities in the middle cerebellar peduncles (“MCP sign”), especially affected males. Confirmation of diagnosis is achieved through molecular testing. Children in the family of those affected with FXTAS may have the classical fragile-X syndrome, owing to meiotic repeat expansion to the full mutation range (Berry-Kravis et al. 2007; Jacquemont et al. 2007).

Many other parkinsonian disorders have been described (Table 4), and some of them are at times confused with PD, although they tend to present specific clinical features, frequently with complex phenotypes.

HEREDITARY FORMS OF PARKINSON'S DISEASE AND THEIR CLINICAL FEATURES

A small but significant number of PD patients have a family history compatible with Mendelian autosomal inheritance (10%–15%), either dominant or recessive. Many of these are classified as young-onset (<40 yr) or juvenile-onset PD (<21 yr) (Schrag and Schott 2006). A number of levodopa-responsive parkinsonian syndromes have been described and linked to a specific locus or gene in the last few years, and some of them have been classified as *PARK* syndromes (Gasser 2007; Klein et al. 2009). Some of these denote true PD, whereas others represent more complex phenotypes and dissimilar diseases. Only the former group will be briefly approached here, as the clinical phenotype may be a useful pointer for the diagnosis in daily practice, guiding subsequent molecular testing. For more details on the genetics of PD please refer to Klein and Westenberger (2012).

1. Autosomal-dominant (AD) PD:
 - a. PARK1/PARK4 (gene *SNCA*, α -synuclein): Mean age at onset of symptoms is in the 30s (PARK4) or 40s (PARK1). Progression appears to be faster than in sporadic PD and dementia is a frequent finding; at times the clinical picture resembles DLB, but mean age at onset is much lower than in sporadic cases (Polymeropoulos et al. 1997; Spira et al. 2001; Zarranz et al. 2004). PARK1 and PARK4 are attributable to *SNCA* mutations and duplications/triplications, respectively.
 - b. PARK3 (gene unknown): Researchers described a group of families with parkinsonism closely resembling that of sporadic PD, including age of onset (mean 59 yr); the locus has been mapped to 2p13. Penetrance was estimated to be below 40% (Gasser et al. 1998). It has not been clearly defined whether this represents a disease susceptibility locus or a true Mendelian form of PD.
 - c. PARK5 (gene *UCHL1*, ubiquitin carboxy-terminal hydrolase 1): Only one family has been reported with PD and a mutation in *UCHL1*, providing frail evidence that this is

Table 4. Causes of parkinsonism**Heredodegenerative**

Dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, corticobasal syndrome, fragile X-tremor ataxia syndrome, neurodegeneration with brain iron accumulation (includes pantothenate kinase-associated neurodegeneration, *PLA2G6*-associated neurodegeneration or PARK 14, neuroferritinopathy, aceruloplasminemia, and *FA2H*-associated neurodegeneration), pallido-pyramidal syndromes (includes Kufor-Rakeb disease or PARK9, and neurodegeneration associated with *FBXO7* mutations or PARK 15), Perry syndrome (*DCTN1* mutations), X-linked dystonia parkinsonism (DYT3, Lubag), dopa-responsive dystonia (DYT5), rapid-onset dystonia parkinsonism (DYT12), autosomal recessive dystonia parkinsonism (DYT16), dopamine transporter deficiency syndrome (mutations in *SLC6A3*), SENDA syndrome, Huntington's disease, Huntington disease-like type 2, chorea-acanthocytosis, MacLeod syndrome, some spinocerebellar ataxias (SCA3, SCA6, SCA8, SCA13, and SCA17), dentato-rubro-pallidoluysian atrophy, hereditary spastic paraparesis types 11 (SPG11) and 15 (SPG15), frontotemporal dementia with parkinsonism (FTDP-17), prion disease (Creutzfeldt-Jakob, Gertsman-Sträussler-Scheinker), parkinsonism-dementia-ALS complex of Guam (Lytico-Bodig), Fahr's disease, intraneuronal cytoplasmic inclusion disease, and neurofilament inclusion body disease

Structural brain lesions

Cerebrovascular disease, infectious brain lesions (e.g., cryptococcosis, neurosyphilis), postencephalitic (e.g., encephalitis lethargica), postanoxic injury, posttraumatic (e.g., dementia pugilistica), toxic (e.g., MPTP, ephedrone, manganese, carbon monoxide, cyanide), metabolic disorders (Wilson, Niemann-Pick Type C, Gaucher, GM1 gangliosidosis, phenylketonuria, cerebrotendinous xanthomatosis, maple syrup urine disease, mitochondrial disorders with striatal necrosis, ceroid neuronal lipofuscinosis), secondary Fahr's syndrome, non-Wilsonian acquired hepatocerebral degeneration, hemiparkinsonism-hemiatrophy syndrome, hydrocephalus, and intracranial tumors

Drug-induced

Typical antipsychotics (e.g., haloperidol, chlorpromazine), most atypical antipsychotics (riiperidone, olanzapine), tetrabenazine, reserpine, methyl dopa, metoclopramide, flunarizine, cinnarizine, verapamil, valproic acid, lithium, and others

Psychogenic (functional)

Table compiled with data from Schrag and Schott 2006; Wijemanne and Jankovic 2007; Alvarez and Evidente 2008; Edwards et al. 2008; Farrer et al. 2009; Klein et al. 2009; Schneider et al. 2009; Krueer et al. 2010; Schneider and Bhatia 2010; Carecchio et al. 2011; Kurian et al. 2011.

Most disorders in the first group are degenerative.

Abbreviations: ALS, amyotrophic lateral sclerosis; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

a true locus for inherited PD. The clinical picture resembles that of sporadic PD, with age at onset of symptoms around 50 years of age (Leroy et al. 1998).

- d. PARK8 (gene *LRRK2*, leucine-rich repeat kinase 2 or dardarin): Probably the most common type of inherited PD. The clinical picture resembles that of late-onset sporadic PD; abduction-adduction lower limb tremor could be a useful diagnostic hint (Wszolek et al. 2004; Healy et al. 2008). Mutation frequency may be as high as 40% in North African Arabs and Ashkenazi Jewish populations; countries from

southern Europe also have high mutation frequency (Healy et al. 2008). There is considerable neuropathological heterogeneity in these patients (Wszolek et al. 2004).

2. Autosomal recessive (AR) PD:
 - a. PARK2 (gene *Parkin*): This is by far the most common disorder in the group of the AR and one of the most common forms of monogenic PD. Age at onset of symptoms ranges from childhood to mid-50s. It accounts for most PD cases under the age of 30 yr. Typical clinical features include early prominent dystonia (especially foot dystonia), exquisite response to levodopa

and anticholinergic drugs, slow disease progression, diurnal fluctuations, sleep benefit, susceptibility to levodopa-induced peak-dose dyskinesias, and wearing-off phenomenon. Hyperreflexia is a common feature. Other possible presentations include exercise-induced dystonia, focal dystonia, tremor-predominant cases, and early impairment of gait and balance (Abbas et al. 1999; Klein et al. 2000; Lücking et al. 2000; Gouider-Khouja et al. 2003; Kahn et al. 2003; Wickremaratchi et al. 2009). Nonmotor symptoms seem to be less prevalent than in sporadic PD, except anxiety (Kägi et al. 2010b). Lewy bodies were absent in most patients that came to autopsy (Farrer et al. 2001; Gouider-Khouja et al. 2003).

- b. PARK6 (gene *PINK1*, PTEN-induced putative kinase 1): It is characterized by early onset in most patients (mean age at onset in the 30s, ranging from childhood until the seventh decade of life), dystonia at onset or symptom symmetry in some cases, slow disease progression, excellent levodopa responsiveness, early peak-dose dyskinesias; hyperreflexia has been described; rare cases with very early onset display sleep benefit and diurnal fluctuations (Valente et al. 2001, 2002; Bonifati 2005; Ibáñez et al. 2006; Leutenegger et al. 2006). Psychiatric disturbances such as depression, anxiety, and psychosis are a frequent finding (Bonifati 2005; Ibáñez et al. 2006; Steinlechner et al. 2007). Lewy bodies are a recently described neuropathological finding (Samaranch et al. 2010).
- c. PARK7 (gene *DJ-1*): This seems to be a rare disorder, with a clinical phenotype similar to PARK6. Notably, some cases have been associated with blepharospasm, whereas amyotrophic lateral sclerosis and dementia have been described in one family (van Duijn et al. 2001; Abou-Sleiman et al. 2003; Dekker et al. 2003; Clark et al. 2009; Annesi et al. 2005).

Other candidate genes have been associated with parkinsonism, namely, *Nurr1* (Le et al. 2003),

synphylin-1 (Marx et al. 2003), and *POLG* (polymerase gamma) (Davidzon et al. 2006), but further confirmation in large case series is still awaited. Exciting observations have been made in the last few years in families with members suffering from Gaucher's disease (GD), an AR disorder caused by homozygous mutations in the *GBA* gene encoding the lysosomal enzyme glucocerebrosidase. Heterozygous carriers, who do not have GD, are at higher risk of developing sporadic PD or DLB (Aharon-Peretz et al. 2004; Clark et al. 2009; Sidransky et al. 2009). Thus, interest emerged in the putative role of ceramide in the pathogenesis of Lewy body disorders (Bras et al. 2008).

PD MANAGEMENT: BRIEF CONSIDERATIONS

Comprehensive review of PD therapy is beyond the scope of this text, but a few basic thoughts must be set forth. PD is best managed in a multidisciplinary setting, to obtain satisfactory results regarding the various disabling aspects of the disease. Nonmotor symptoms should be treated accordingly, although evidence to support most treatment decisions is scarce; sildenafil should be considered for erectile dysfunction and macrogol for constipation (Zesiewicz et al. 2010). Dementia symptoms are improved by cholinesterase inhibitors or memantine (Emre et al. 2010; van Laar et al. 2011). An array of drugs is used to treat motor symptoms in PD (availability varies from country to country): levodopa plus peripheral dopa decarboxylase inhibitor (carbidopa or benserazide), dopamine agonists (ergot derivatives: bromocriptine, pergolide, cabergoline, dihydroergocryptine; non-ergot derivatives: ropinirole, pramipexole, rotigotine, apomorphine), monoamine oxidase B inhibitors (selegiline, rasagiline), catechol-O-methyltransferase inhibitors (entacapone, tolcapone), anticholinergics (trihexyphenidyl, bengtropine), and amantadine. Currently, there is no consensus on the most adequate timing and drug of choice for therapy initiation in PD, but dopaminergic therapy is usually deferred until deteriorating quality of life demands treatment, owing to the future potential motor complications brought



about by these drugs, such as peak-dose dyskinesias (see online Movie 9 at www.perspectivesinmedicine.org), wearing off, and sudden off states (Edwards et al. 2008a; Lang 2009). Levodopa seems to pose higher risks in this regard as compared with dopamine agonists, although recent data brought conflicting views on this matter (Katzenschlager et al. 2008; Holloway et al. 2009). Nevertheless, levodopa is the most effective drug in the control of motor symptoms, and PD patients typically show marked and sustained benefits from it for several years (Schapira et al. 2009). Dopamine agonists may cause peripheral edema, fibrotic reactions (most ergot derivatives), excessive daytime somnolence, and impulse control disorders (Antonini et al. 2009). In advanced PD, functional neurosurgery is a valuable therapeutic option, provided that patients are carefully selected (Lang et al. 2006). Deep brain stimulation of either the subthalamic nucleus or internal globus pallidus is an effective and generally safe procedure (Deuschl et al. 2006; Follett et al. 2010; Moro et al. 2010). In advanced PD it may be more effective for the control of motor symptoms than the best medical therapy, either alone or in combination with it (Weaver et al. 2009; Williams et al. 2010).

CONCLUDING REMARKS

PD is a common and potentially disabling disorder. Suitable efforts should be performed to achieve accurate diagnosis, communicate a plausible prognosis to the patient and family, and proceed with the best therapeutic interventions. Remarkable progress has been made in the last two decades in the field of genetics, pathophysiology, and clinical imaging, but the diagnosis of PD still sits inevitably on clinical skills and exploration, which emphasizes the importance of a solid clinical knowledge about the disease.

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