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A glossary of terms

Jolyon Meara

As our knowledge of Parkinson's disease and parkinsonism increases considerable confusion can arise in relation to the terms used to describe these conditions. To maintain consistency in the text the following definitions will be used.

Parkinsonism

A clinical syndrome of akinesia accompanied by rigidity and often tremor. Akinesia includes difficulty with voluntary motor actions, difficulty performing sequential or concurrent motor actions, slowness of voluntary movement, and abnormal fatigability of repetitive motor actions. Rigidity, or 'stiffness', can be defined as the resistance encountered by an examiner when passively stretching relaxed muscles around a joint. Rigidity in parkinsonism can often be detected in the axial skeleton and upper limbs by the examiner performing passive flexion/extension movements of the neck and wrist joint. Tremor is often present at rest when the muscles are fully relaxed and is usually first noted in the upper limb involving the hand and fingers. Leg and jaw tremor may less commonly occur. Parkinson's disease is the most common cause of parkinsonism and arises sporadically and is of unknown cause. Known causes of parkinsonism include drugs, cerebrovascular disease, other sporadic and inherited neurodegenerative disease, infections, head trauma, hydrocephalus, and metabolic diseases, amongst others.

Parkinson's disease (PD)

Levodopa-responsive parkinsonism resulting in a characteristic clinical picture and natural history. When present, a typical 'pill rolling' tremor involving the thumb and index finger is almost pathognomic for PD or drug-induced parkinsonism. The primary neuropathological findings consist of degeneration of cells in the substantia nigra pars compacta resulting in striatal dopamine deficiency and the presence in surviving cells of inclusions called Lewy bodies. Other discrete areas of the brain also demonstrate cell loss and Lewy bodies.

Late stage PD

Late stage PD is associated with significant functional disability and the onset of increasing dependency. The clinical picture in late stage disease is dominated by features that do not respond to dopaminergic drugs, such as poor mobility, falls, confusion, drowsiness, dementia, sialorrhoea, dysarthria, impaired communication, dysphagia, and weight loss.

Late onset PD

Late onset PD can be arbitrarily defined as PD presenting for the first time in subjects who are aged 70 years or older. Even after adjusting for age, late onset PD appears to progress faster and to be associated with the earlier development of cognitive impairment and possibly depression. In late onset disease gait and balance problems appear early in the course of the illness. The pattern of disease at presentation in elderly subjects may reflect the more widespread loss of nigral cells due to aging in addition to the more circumscribed loss due to PD.

Drug-induced parkinsonism (DIP)

Parkinsonism resulting from exposure to antidopaminergic drugs, usually due to blocking of dopamine receptors. The clinical picture can be indistinguishable from PD. Neuroleptic drugs are by far the most common cause of DIP.

Vascular parkinsonism

Parkinsonism resulting from vascular disease of the brain. The clinical picture is dominated by gait disturbance, truncal ataxia with relative sparing of the upper limb and the absence of tremor. There may be associated evidence of upper motor neurone involvement (pseudobulbar palsy, pyramidal deficits) and a history of stroke events. A history of hypertension is often present and brain imaging may demonstrate extensive deep white matter ischaemic changes. Akinesia of the upper limb is absent in most cases. However, basal ganglia infarcts may rarely give rise to a clinical picture indistinguishable from PD.

Parkinsonism in multisystem neurodegenerative disease

Parkinsonism can arise from sporadic disease such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, Alzheimer's disease and dementia with Lewy bodies. Inherited degenerative diseases such as Huntington's

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disease can cause parkinsonism and familial parkinsonism, although very rare, is now well described. Progressive supranuclear palsy and multiple system atrophy may be mistaken for PD early in the natural history of the disease as both these conditions may initially respond to levodopa treatment.

Dementia with Lewy bodies (DLB)

A progressive fluctuant dementia associated with variable degrees of parkinsonism, visual hallucinations, falls, transient loss of consciousness and neuroleptic sensitivity. Cortical Lewy bodies are prominent at postmortem, particularly in the limbic areas of the mesial temporal lobe. Subcortical changes identical to those found in PD may also be present.

Gait apraxia

Gait apraxia results from a failure of integration of cerebral activity involving high-level sensorimotor systems. The difficulty in walking cannot be explained by motor or sensory abnormalities that can be detected by bedside neurological examination. The term 'high level gait disorder' is often preferred. Lesions of the premotor area, the supplementary motor area, the basal ganglia and their connections appear to be related to the development of gait apraxia.

Essential tremor (ET)

The most common movement disorder in elderly people. A bilateral, persistent postural tremor involving the hands and forearms of longstanding duration is required for a definite diagnosis of ET. A kinetic tremor on movement may also be present. A family history of tremor is elicited, as is a short term improvement of tremor after alcohol. The head, voice and legs may also be involved with decreasing frequency. In elderly subjects ET is commonly misdiagnosed as PD.

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Diagnosis of parkinsonism in the elderly

Robert L Rodnitzky

The diagnosis of parkinsonism depends on recognizing its component clinical features. Parkinsonism includes Parkinson's disease (PD) and all the varied conditions with clinical features resembling those of PD. To identify patients with parkinsonism correctly it is important to be able to recognize the cardinal clinical features of PD, namely akinesia, lead-pipe rigidity, rest tremor, and postural instability. The next critically important step is to determine whether they suggest PD or one of the other non-PD causes of parkinsonism (see Table 2.1). This latter distinction will enable effective treatment strategies to be devised and a meaningful discussion of prognosis and genetic implications to be undertaken. The entire process of identifying parkinsonism and assigning a specific clinical diagnosis is particularly challenging in the elderly because many of the motor changes associated with normal ageing resemble parkinsonism. Additionally, several medical conditions that are common in this age group can result in parkinsonism that may incorrectly be considered evidence of PD.

The clinical signs of PD

Of the cardinal motor signs of PD, akinesia is perhaps the most disabling. Slowness, difficulty in initiation, and a reduction in the amount or amplitude of voluntary movement (Rodnitzky and Uc 1997) characterize akinesia (see Table 2.2). A great variety of clinically recognizable signs result from akinesia. A lack of facial expression attended by reduced blink rate is one of the most apparent manifestations of akinesia. Additional findings are diminished arm swing on one or both sides of the body, difficulty arising from a chair, a slow, short stepped gait, en bloc turning, and soft, poorly articulated speech (hypophonia). The clinical signs of akinesia are so striking that their presence alone has been considered by some to be sufficient to establish a diagnosis of PD (Quinn 1995). The more usual view is that additional motor findings are necessary to establish a diagnosis of PD. Rigidity is another common finding in patients with PD (see Table 2.3). Rigidity is felt by an examiner as an increased resistance to passive movement of joints in the fully relaxed limb.

5 **Diagnosis****Table 2.1** Stages in the diagnosis of parkinsonism**Stage 1**

- Is there clinical evidence of parkinsonism?
- Akinesia must be present for this diagnosis.

Stage 2

- What type of parkinsonism is present?

Table 2.2 Clinical features of PD**Akinesia**

- Reduction in spontaneous voluntary motor activity, slow movements, difficulty with sequential and concurrent motor acts, abnormal early fatigability and reduction in amplitude of movements

Table 2.3 Clinical features of PD**Lead-pipe rigidity**

- Abnormal resistance which remains constant throughout the range of movement and is felt when passively stretching muscles around a joint in a relaxed subject

Cog-wheel rigidity

- A ratchet type of fluctuating resistance felt at the wrist in synchrony with tremor bursts

Resistance is unchanged throughout the range of movement of the joint and can be distinguished from spasticity, in which resistance is greatest at the onset of passive movement and then suddenly gives way (clasp knife phenomenon). Often, a ratchet like quality (cog-wheeling) is present as the joint is moved especially when tremor is present. Subtle rigidity can be enhanced by utilizing reinforcement techniques such as instructing the patient to execute repetitive forceful movements in the contralateral limb. True rigidity must be distinguished from gegenhalten in which patients with diffuse encephalopathy or frontal lobe dysfunction exert a force opposite in direction to the examiner's attempted passive movement.

Rest tremor is one of the most easily recognizable signs of PD (see Table 2.4). It usually appears at a frequency of 3–6 Hz when the limb is fully supported and motionless. It also appears in the hands when the arms are suspended at the sides during walking. Typically, the tremor is reduced or totally disappears during action. In PD, tremor is often unilateral at the onset of the illness and remains asymmetrical even though ultimately spreading to the contralateral limbs. The presence or absence of rest tremor is a major consideration when attempting to determine

Table 2.4 Clinical features of PD**Rest tremor**

- Classically a 4–5 Hz oscillation involving the distal portion of the upper limb of ‘pill rolling’ type. Atypical rest tremor can occur and rest tremor is often accompanied by postural and kinetic tremors. The head and trunk are usually spared

whether a patient has PD or another form of parkinsonism. Rest tremor is present in the great majority of patients with PD, but in only a smaller percentage of those with other forms of parkinsonism. The distribution of tremor is also important in helping to establish a diagnosis of PD. The tremor of PD commonly begins in the hands and is slightly less common in the lower extremities and mandible. It almost never affects the head or the muscles of articulation. When present, a ‘pill rolling’ tremor at rest involving the thumb and index finger very strongly suggests a diagnosis of PD or drug-induced parkinsonism. Postural instability has a great number of potential causes other than PD, particularly in the elderly. Patients manifesting this dysfunction are at increased risk of falling since they are unable to generate normal reflex movement to counter even the slightest perturbation to their posture. The clinician can safely demonstrate an absence of postural reflexes by standing behind the patient and applying a brisk backward directed push on the sternum.

Episodes of freezing, also referred to as ‘motor blocks’, most commonly involve gait. The patient’s feet appear ‘glued’ to the floor when attempting to initiate gait, during turns, or when approaching a real or imagined obstacle such as a narrow passageway or an entrance to a room. Whether this phenomenon represents a severe form of akinesia or is physiologically separate is not known. It is common in late stage PD, but in some other forms of parkinsonism it can be an early, or even a presenting clinical sign (Giladi et al. 1991). Several guidelines have been suggested for utilizing clinical signs to establish a diagnosis of clinically probable PD. Definite diagnosis strictly requires postmortem confirmation of PD. Most guidelines require a certain number of the cardinal motor signs of parkinsonism to be present to make a diagnosis of PD in life. For example, the UK Parkinson’s Disease Society Brain Bank criteria (Hughes et al. 1992a) requires the presence of akinesia plus *one* other clinical sign from among rigidity, rest tremor, and postural instability. Koller (1995), on the other hand, suggested that any two of three motor findings from among rigidity, akinesia, and tremor is sufficient to establish a clinical diagnosis of PD. While these criteria increase diagnostic accuracy, they are far from infallible. Several studies have suggested a high level of diagnostic inaccuracy compared to postmortem findings, even when the clinical diagnosis of PD is made by experienced neurologists (Rajput et al. 1991a, Hughes et al. 1992a, de Rijk et al. 1997).

Rajput et al. (1991a) found that only 76% of patients with a final clinical diagnosis of PD during life had evidence of the disease when examined at autopsy. Hughes et al. (1992a) examined 100 brains of patients with a final clinical diagnosis of PD and could confirm such a diagnosis in only 76% of cases. The diagnosis in the remainder included conditions such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and Alzheimer's disease (AD). The clinicians in this study had utilized clinical criteria of their choice in arriving at a diagnosis of PD. When systematized diagnostic clinical criteria were retrospectively applied to cases in this study diagnostic accuracy improved to 82%. In clinical practice diagnostic accuracy is likely to be much lower than these figures suggest since these studies only looked at final diagnosis. However, all patients in these studies died at least 10 years ago and in the interim diagnostic awareness may have improved as is suggested by the most recent clinicopathological series (Ansorge et al. 1997). When applying additional computer generated criteria with a high predictive value for diagnostic accuracy (asymmetrical onset, no atypical features and no other possible etiology), the diagnostic accuracy was further increased to 93%, but 32% of pathologically confirmed cases were rejected on this basis. A further study compared eight different sets of diagnostic criteria that might be applied to prevalence studies of PD and found some sets too inclusive and others too restrictive (de Rijk et al. 1997). These authors concluded that the most reasonable inclusion criteria for PD was two of the three cardinal features (tremor, akinesia and rigidity) in the absence of other apparent causes of parkinsonism. It is clear from these studies that PD can be distinguished from other forms of parkinsonism on clinical grounds alone with high, but not total, accuracy. Using the most stringent diagnostic criteria reduces misdiagnosis, but at the expense of misclassifying a significant number of true cases of PD.

Controversy still exists over the condition of 'tremor dominant' PD. In this situation tremor is an isolated finding and this can easily lead to misdiagnosis with the most common cause of isolated tremor, essential tremor. Rest tremor, accompanying the more usual postural and kinetic tremor, can be a late manifestation of essential tremor in elderly subjects (Rajput et al. 1993). Tremor dominant cases of presumed PD could usefully be assessed with an apomorphine challenge test to help distinguish PD from other causes of isolated tremor.

Atypical features suggesting diagnoses other than PD

Despite the caveat that diagnostic criteria can be made so specific as to reduce their clinical utility, the usefulness of incorporating a careful search for atypical features as an exclusionary criterion for PD deserves special mention. Atypical features not only alert the clinician to the possibility that the diagnosis may not be PD, but in a

positive sense may suggest another form of parkinsonism and lead the clinician to the correct diagnosis. In this regard it is important to understand which facets of the natural history or clinical examination are to be considered highly atypical for PD as well as which of them singly or in combination strongly suggest another clinical diagnosis within the spectrum of parkinsonism.

There is a reasonably well defined body of clinical signs and symptoms that are distinctly unusual in PD. When one or more of these signs appear in the akinetic-rigid or tremulous patient, they should prompt the clinician to question the diagnosis of PD. The following discussion describes the most important of these atypical signs and indicates which alternative diagnoses each one suggests. Several of these atypical features are much more likely to occur in elderly subjects, making their identification and proper interpretation even more important in this age group.

Early dementia

Dementia is common in PD, having been found in as many as 65% of patients by the age of 85 years (Mayeux et al. 1990). However, the dementia of PD seldom appears at the onset of the illness. Early dementia in the akinetic-rigid patient should prompt consideration of a variety of other syndromes with parkinsonian features, including dementia with Lewy bodies (DLB), PSP, corticobasal ganglionic degeneration (CBGD), normal pressure hydrocephalus, Creutzfeldt-Jacob disease, or AD. The confusion with AD arises from the fact that parkinsonism can appear in some patients with AD (Hughes et al. 1992a, Hulette et al. 1995). These signs are usually thought to occur late in the illness and are most likely to be seen in the elderly patient with severe cognitive impairment (Lopez et al. 1997). However, in the study of Hughes et al. (1992a) AD was a common cause of diagnostic error in PD and it appears from this study that AD, particularly when AD pathology involves the corpus striatum, can present with parkinsonism sufficient to lead to diagnostic confusion with PD. The development of mild parkinsonian features one or more years after the onset of otherwise clinically typical AD, especially in an elderly patient, should be considered to be a case of AD with parkinsonism, rather than PD with dementia. In the elderly patient, the possibility of the concurrent appearance of both PD and AD should also be given consideration, taking into account the high prevalence of both of these conditions in this age group. In this circumstance, the presence of a rest tremor or a significant improvement in parkinsonism after treatment with levodopa lends some support to a diagnosis of PD, rather than parkinsonism due to AD alone.

Certain clinical characteristics of the dementia may also be atypical for PD. Marked fluctuations in cognitive impairment consisting of periods of confusion alternating with lucidity, for example, should suggest DLB (Byrne et al. 1989, Mega

et al. 1996). The differentiating characteristics of the dementia associated with AD and those found in PD have been well studied. The dementia of AD is more likely to be associated with abnormalities of memory and language and the presence of anosognosia while that of PD is more commonly characterized by impairment of visuospatial and executive functions (Mohr et al. 1990, Starkstein et al. 1996, Mahieux et al. 1998).

Early hallucinations have implications similar to those of early dementia. Hallucinations occurring in PD typically appear late in the course of the illness and are almost always associated with the chronic use of antiparkinsonian drugs. Hallucinations occurring prior to the initiation of such drugs or with the first administration of these agents strongly suggests another diagnosis, particularly DLB. This phenomenon points out the importance of accurately distinguishing between PD and DLB. Compared to PD, DLB patients are much more likely to suffer behavioural side effects from dopaminergic or anticholinergic agents.

Early falls and postural instability

Falling in PD is typically the result of impaired postural reflexes, postural hypotension or severe large amplitude dyskinesias. Severe freezing with inability to check forward propulsion of the upper trunk is another possible cause. These causes of falling typically appear in late stage PD and seem to occur earlier with late onset PD. However, a variety of other conditions with parkinsonian features may present with early falling.

The condition among those most likely to present with falling is PSP (Jankovic et al. 1990). In these patients, the gait abnormality is quite different from that seen in PD. In PSP patients there is akinesia associated with axial rigidity and nuchal dystonia, often in extension, vertical supranuclear gaze palsy and impaired postural reflexes. This combination results in frequent and early falling. The early appearance of gait freezing in PSP, which sometimes antedates the other motor signs of this condition, is also a major contributing factor to the occurrence of early falling. Postural instability is much more common early in the course of MSA than in PD. These patients may have marked akinesia with a loss of postural reflexes, sometimes associated with truncal dystonia. Wenning et al. (1997) in a review of 203 pathologically proven cases of MSA found that 38% had presented with ataxia. The term 'lower body parkinsonism' has been used to describe a severe isolated gait disorder associated with diffuse cerebral vascular disease (Fitzgerald and Jankovic 1989). This form of vascular parkinsonism is characterized by isolated involvement of the lower extremities and severe freezing of gait, often leading to falls. Normal pressure hydrocephalus can present with an early and predominant gait disorder associated with frequent falls. In this condition the gait is characterized by inability to lift the feet from the floor, short shuffling steps, imbalance while walking,

difficulty turning, and gait ignition failure (Marsden and Thompson 1997, Graff-Radford and Godersky 1997, and see Chapter 6).

Severe autonomic dysfunction

Severe autonomic dysfunction early in the course of the illness is not typical of PD. Late in the course of PD patients may develop mild to moderate symptoms of autonomic insufficiency such as constipation, urinary incontinence, orthostatic hypotension, impotence, or impaired lacrimation (Goetz et al. 1986, Beattie et al. 1993). Anticholinergic drugs used to treat PD may contribute to the appearance of constipation or bladder dysfunction, while dopaminergic agents can cause or exacerbate hypotension and, to a lesser extent, constipation. The possibility of MSA should be considered in patients with evidence of early autonomic dysfunction in the absence of other diseases and drug treatments known to effect the autonomic system (Magalhaes 1995). In MSA autonomic dysfunction can predate signs of parkinsonism by several years. In one study of MSA autonomic signs antedated motor symptoms by one to two years in a quarter of cases (Wenning et al. 1994). Two techniques, electromyography of the urethral sphincter (Pramstellar et al. 1995) and formal urodynamic studies (Bonnett et al. 1997) are available to objectively distinguish the autonomic dysfunction of MSA from that of PD. The urethral sphincter is invariably denervated in MSA patients with incontinence, but not in PD patients with similar symptoms. In PD, urodynamic studies reveal an urgency to void without chronic retention, associated with detrusor hyperreflexia and normal urethral sphincter function. In MSA there is often chronic urinary retention, a hypoactive detrusor muscle and lower urethral pressures.

Poor or transient benefit from drug treatment

Dopaminergic drugs, especially levodopa, usually improve the signs of PD. The vast majority of PD patients benefit from levodopa therapy. In one series of pathologically proven cases of PD, 94% had responded to levodopa during life (Rajput et al. 1990). The response rate to levodopa in other causes of parkinsonism is much lower. As many as 65% of MSA patients have been reported to respond, at least initially, to levodopa (Hughes et al. 1992b), although in most studies the response is closer to one third (Rajput et al. 1990). Even among those with an initial response, fewer than 5% may continue to benefit in the advanced stages of the illness (Wenning et al. 1997). In PSP, a levodopa response rate of 38% has been reported (Nieforth and Golbe 1993). Patients with multisystem degenerative disease who are initially responsive to levodopa commonly experience a rapid disappearance of benefit within one to two years. In CBDG early benefit from dopaminergic agents is much less common than that seen in PSP or MSA. In other causes of parkinsonism such as vascular parkinsonism and normal pressure hydrocephalus, lack of