24.7.2 Parkinsonism and other extrapyramidal disea

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section 24 Neurological disorders 5946 24.7.2 Parkinsonism and other extrapyramidal diseases Elisaveta Sokolov, Vinod K. Metta, and K. Ray Chaudhuri ESSENTIALS Parkinson’s disease Parkinson’s disease affects about 0.2% of the population, including 2% of those over 80 years of age. The number diagnosed is expected to double from 4.1 million people diagnosed in 2005 to 8.7 million by 2030 owing to a rise in life expectancy and better diagnosis (Tanner CM, Brandabur M, Dorsey ER. Parkinson Report, Spring 2008). The main pathological feature is degeneration of neuromelanin- containing neurons and Lewy body inclusions in the pars compacta of the substantia nigra, which leads directly and indirectly to excessive inhibition of the thalamus and consequent bradykinesia. However, seminal studies in the early 2000s by Braak et al. suggest that the con- dition starts earlier and, from a pathological point of view, stage 1 of the disease begins with Lewy body deposition at the olfactory system and the dorsal vagal nucleus in the lower medulla, with degeneration of the olfactory bulb and the anterior olfactory nucleus. Clinically, this represents olfactory dysfunction and late-onset hyposmia is recognized as one of the earliest symptoms of Parkinson’s disease, often preceding the development of the cardinal motor signs by up to 20 years. During stage 2 there is progression of neuropathology to the nuclei of the caudal brainstem (the locus coeruleus and other nu- clei), which are key areas mediating many nonmotor symptoms such as sleep homeostasis, depression,

fatigue, cognitive problems, pain, and constipation. Several of these symptoms, particularly rapid eye movement behavioural disorder are now recognized as pre-motor features of Parkinson's disease. Stage 3 is when patients are usually referred to the clinic as the substantia nigra is involved and patients start exhibiting classical motor features. Clinical features—these include motor: (1) bradykinesia; the most disabling and progressive motor symptom; (2) resting tremor (4–7 Hz); often the presenting symptom/sign, and often unilateral; (3) rigidity; cogwheel or lead pipe; (4) postural imbalance; fixed and stooped posture; (5) gait difficulty; shuffling and small steps, with or without festination; (6) other features; hypomimia ('masked' face), freezing episodes (sudden failure of movement), seborrhoea of the scalp. Nonmotor symptoms are now considered integral to Parkinson's disease and comprise of a wide range of problems. These include: (1) hyposmia, constipation, bladder disturbance; (2) sleep disorder; (3) dementia and other cognitive dysfunctions; (4) depression and anxiety; (5) chronic and regional pain; (6) fatigue; (7) sexual and auto- nomic dysfunction; (8) drug-induced problems such as impulse con- trol disorder. Investigation and treatment—there are as yet no specific tests for Parkinson's disease and diagnosis remains largely clinical. However, single photon emission computed tomography imaging with DAT scan is a valuable adjunct to clinical suspicion of the diagnosis. First-line drug treatment remains controversial and levodopa (in combination with a decarboxylase inhibitor), dopamine agonists (oral or transdermal) or monoamine oxidase-B inhibitors are all effective and treatment needs to be individualized depending on the patient's age, occupation, dominant side affected as well as expectations/life style. Additionally, local funding policies might influence treatment decisions. Many authorities believe early treatment as soon as diag- nosis is made (usually motor diagnosis as the condition may have been present for many years manifesting nonmotor symptoms) should be started, while some believe in a 'wait and watch' policy. Advanced therapeutic options consist of apomorphine injections (for rapid and reproducible 'rescue' from predictable off periods) and infusions, deep brain stimulation of the subthalamic nucleus or globus pallidus and intrajejunal levodopa infusion. Gastrointestinal problems such as delayed gastric emptying are highly prevalent in Parkinson's disease and, as such, modern therapy has also focussed on nonoral therapies such as transdermal dopamine agonists as well as the advanced therapies. Stem cell, gene therapy-based and neuro- trophic factor-related regenerative therapies remain experimental. Other parkinsonian and extrapyramidal diseases Drug-induced parkinsonism; dopamine-blocking agents (neuro- leptics) such as prochlorperazine or chlorpromazine are the most common offending agents. Vestibular sedatives (used for motion sickness) are also implicated. Progressive supranuclear palsy; typically presents with gait dis- turbance and falls (backwards predominantly). Examination reveals supranuclear gaze palsy, particularly of downgaze, with extension and rigidity of the neck, a staring look due to lid retraction, and bradykinesia/akinesia. Multiple system atrophy—comprises a variable degree of parkin- sonism with autonomic (postural hypotension), pyramidal or cere- bellar symptoms and signs. Any response to levodopa is commonly incomplete (except the parkinsonian variant) and short-lived. Clinical variants of progressive supranuclear palsy (a parkinsonian variant re- sponding to levodopa) as well as multiple system atrophy (parkin- sonian, cerebellar, and minimal change) has been described. Dementia with Lewy bodies—manifestations include fluctuations in cognition and attention, recurrent and persistent visual hallucin- ations, and parkinsonian motor signs. Corticobasal ganglionic degeneration—characterized by progres- sive gait disturbances, cortical sensory loss, and stimulus-sensitive myoclonus which results in a jerky, useless hand. Dopa-responsive dystonia—characteristically shows marked diurnal variation; may start in childhood with an odd and unusual gait; diag- nosed by finding mutation in the GTP-cyclohydrolase gene; excellent

and sustained response to low-dose levodopa. Other rare conditions mimicking parkinsonism include genetic variants of Parkinson’s disease (autosomal dominant and recessive), Wilson’s disease, neuroacanthocytosis, vascular pseudo-parkinsonism, neuronal brain iron accumulation syndromes and neuro ferritinopathy. Other movement disorders Dystonia—a syndrome of sustained muscle contractions, which may be focal, multifocal, or generalized, genetic, or idiopathic. Particular causes include (1) generalized idiopathic torsion dystonia; (2) tardive dyskinesia; induced by long-term exposure to dopamine-blocking drugs; involuntary movements usually begin with the face and mouth. See Chapter 24.7.3 for further discussion.

24.7.2 Parkinsonism and other extrapyramidal diseases 5947 Chorea and related disorders—chorea is an irregular, rapid, uncon- trolled, involuntary, excessive movement that seems to move randomly from one part of the body to another; athetosis is a slower writhing and twisting movement. Causes include Huntington’s dis- ease and Sydenham’s chorea (associated with rheumatic fever). See Chapter 24.7.3 for further discussion. Tics—these are sudden, repetitive, stereotyped, nonrhythmic, in- voluntary movement (motor tic) or sound (phonic tic); when treat- ment is required, they generally respond to drugs that decrease dopaminergic transmission. Introduction The human basal ganglia is a complex functional organiza- tion, with important interconnections with the nigrostriatal pathway, which dominates the dopaminergic innervation of the striatum (caudate nucleus and the putamen). Additionally, the globus pallidus, thalamic nuclei, the subthalamic nucleus and the pedunculopontine nucleus all play important regulatory and excitatory/inhibitory roles. Neuronal loops also interconnect the basal ganglia with the cerebellum as well as the cortex, and function is mediated by dopamine as well as a complex array of neuropeptides such as serotonin, acetylcholine, catecholamines, adenosine, and γ-aminobutyric acid. The principal clinical syndromes are Parkinson’s disease (PD); other syndromes with parkinsonian features (including drug-induced parkinsonism); progressive supranuclear palsy; multisystem atrophy; dementia with Lewy bodies; neuroacanthosis; torsion dystonia; and chorea. Apart from the use of dopaminergic agents, several drugs have beneficial effects in the management of parkinsonism and other extra- pyramidal diseases. Parkinson’s disease Parkinson’s disease was first described by the London physician James Parkinson in 1817, and later named after him by Charcot. Parkinson’s disease is one of the most important disabling illnesses of later life. It is estimated to affect 1% of those aged 70 years, but is also seen in younger people, with 10% of cases occurring before the age of 50. Epidemiology, incidence, and prevalence The exact estimation of the incidence and prevalence of PD is problematic, because there is no ‘in-life’ marker for idiopathic PD; estimates of the annual incidence of PD are in the range of 4–20 per 100 000 individuals. A widely accepted figure for the prevalence of Parkinson’s disease is approximately 200 per 100 000 population. In the United Kingdom, there are approxi- mately 120 000 to 130 000 diagnosed cases, but there may be many more who remain undiagnosed. In the United States of America, it is estimated that between 750 000 and 1.5 million people have the condition. Both the incidence and prevalence of PD increase with age, and the prevalence may be as high as 1 in 50 for patients over the age of 80 years. Men are 1.5 times more likely than women to de- velop the condition. Hospital-based studies and a limited number of epidemiological surveys in Africa have suggested that PD is less common in the black population, although this observation remains controversial. Risk factors Although PD was first described almost 200 years ago, it remains difficult to define exactly which individuals are at risk. The ageing process is related to the development of PD but is not solely re- sponsible, because some patients develop the disease early in life. Furthermore, the type of dopamine cell loss in normal ageing differs from that in PD. Certain

personality traits and envir- onmental factors may increase the risk of PD (Box 24.7.2.1). People with a family history of Parkinson's disease, particularly first-degree relatives, are also at higher risk of developing the disease. It has been postulated that people may be affected differently by a combination of genetic and environmental factors. A possible role of an environmental toxin was triggered by the fascinating observa- tion that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), accidentally consumed as an illicit drug contaminant in the United States of America in the late 1970s and early 1980s, caused an out- break of levodopa-responsive parkinsonism. This led to the de- velopment of MPTP as an experimental agent to cause selective nigrostriatal cell loss in animal models. Recently, similar observa- tions have been made in people in the welding trade, fuelling the hypothesis that manganese may be a causative factor. There have been conflicting reports about environmental agents that may pre- dispose to PD. These are listed in Box 24.7.2.1. Genetic factors The study of monogenetic forms of PD could lead to identification of new drug targets which may translate into new treatments for sporadic PD. Individuals with a positive family history have twice the risk of developing PD and the risk for siblings is increased significantly if there is an affected sibling with young-onset PD. The risk increases further to 12–24% if both a sibling and a parent are affected (see Box 24.7.2.1). α-Synuclein was the first gene to Box 24.7.2.1 Personality trends and environmental factors Personality trends • Obsessive–compulsive disorder Environmental factors (poor association) • Drinking well water • Insecticide/pesticide exposure • Manganese exposure (welding) • N-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (strong asso- ciation in producing parkinsonian syndrome)

section 24 Neurological disorders 5948 be identified in a multigeneration Italian–American family (the Contursi family) as causing an aggressive parkinsonism. Since then several genes have been identified, with Parkin and LRRK2 being the most prevalent ones (Table 24.7.2.1). LRRK2 stands for leucine-rich repeat kinase 2 and is part of the family of Roco genes; it encodes for the protein dardarin. LRRK2 has been asso- ciated with familial late-onset PD and a few cases of sporadic late-onset disease. It is possible that LRRK2 activity influences onset of symptoms and any treatment that lowers risk in LRRK2 associated monogenic PD could delay symptom onset in sporadic PD. The precise function of these genes is unknown, although α-synuclein is the core protein in Lewy bodies whereas parkin may be active through the ubiquitin pathway. Mutations can cause autosomal dominant (SNCA, LRRK2, VPS35), or autosomal recessive (Parkin, DJ1, PINK1, ATP13A2) familial PD. Additionally some of these genes can incur polymorphisms, which are subsequent risk factors for PD. Other important and relatively common risk factors for parkin- sonism include mutations in the glucocerebrosidase (GBA) gene, which encodes the lysosomal enzyme that is deficient in Gaucher's disease. There may be a gain-of-function that promotes α-synuclein aggregation. Studies have shown that patients with PD and associ- ated Lewy body disorders had an increased frequency of GBA mu- tations when compared to controls. Patients with GBA-associated parkinsonism can present with more cognitive features and an early age of onset. DNA methylation patterns vary with age, and ageing alone is a major confounding risk factor for PD. Epigenetic modification of α-synuclein, for example, hypomethylation, is evident in sporadic PD patients' blood. The analysis of α-synuclein methylation can identify nonparkinsonian patients which offers a valuable instru- ment for researchers and clinicians. Overall, late-onset PD is affiliated with autosomal dominant forms (except SNCA triplications) and early onset PD is affiliated with autosomal recessive forms and SNCA triplication. Autosomal dominant forms often present with a prominent tremor or tremor involving the legs suggesting LRRK2, and lack of tremor is associ- ated with SNCA-related disease. These clues may give the clinician an idea of which genes to start

testing first. However, routine genetic testing for PD is not available, nor is genetic counselling currently possible. Pathophysiology The main pathological feature of PD, is the degeneration of neuromelanin-containing neurons in the pars compacta of the substantia nigra, which leads to deafferentation of the striatum. Table 24.7.2.1 Genetics of parkinsonism Symbol Inheritance Product Location Gene PARK1 AD α-Synuclein 4q21.3–q23 SNCA PARK2 AR, juvenile onset Parkin 6q25.2–q27 Parkin PARK3 AD, Lewy body Unknown 2p13 SNCA PARK4 AD, Lewy body Unknown 4p15 SNCA PARK5 AD Ubiquitin C-terminal hydrolase 1 4p14 UCHL1 PARK6 AR, early onset PTEN-induced putative kinase 1 1p35–p36 PARK7 AR, early onset DJ-1 protein 1p36 PARK8 AD Leucine-rich repeat kinase 2 (LRRK2) 12p11.2–q13.1 PARK9 AR ATPase type 13A2. Kufor-Rakeb syndrome 1p36 PARK10 Unknown 1p32 PARK11 GRB 10 interacting GYF protein 2 2q37.1 PARK12 X-linked Unknown Familial PARK13 AD HtrA serine peptidase 2 2p12 PARK14 AR PLA2G6 22q13.1 PARK15 Susceptibility locus F-box protein 7 1q32 PARK16 AR Glucocerebrosidase 1q21 Heterozygous mutations appear to confer susceptibility for classic PD, while homozygous mutations cause Gaucher’s disease DCTN1 AD Dynactin 1 Perry syndrome DYT12 AD Dystonia 12 Rapid onset dystonia parkinsonism VPS35 Vacuolar sorting protein 35 p.Asp620Asn (D620N) EIF4G1 Eukaryotic translation initiation
factor 4 γ-1 Reported in monogenic and sporadic PD. Unclear as to its pathogenicity

24.7.2 Parkinsonism and other extrapyramidal diseases 5949 Normally, it has been suggested that the basal ganglia exert their motor and nonmotor effects through a complex circuitry. The two main pathways are the direct (stimulatory) and indirect (inhibi- tory) pathways, a balance in favour of the direct pathway being kept by regulatory control exerted by dopamine manufactured in the substantia nigra. In PD, dopamine cell degeneration leads to overexcitation of the direct circuit, and the resultant bradykinesia, by a complex pathway that also involves paradoxical excitation of the subthalamic nucleus and internal segment of the globus pallidus. The net result of both the direct and indirect pathways in the ab- sence of dopamine is overexcitation of the medial globus pallidus, leading to excessive inhibition of the thalamus. Thalamic input to the motor cortex is excitatory and thus thalamocortical inhibition leads to akinesia and other symptoms of PD (Fig. 24.7.2.1). Lewy bodies are intracytoplasmic eosinophilic inclusion bodies, typically found in the neurons of the substantia nigra. The patho- physiological basis of PD has recently been re-explored by Heiko Braak, who has suggested that Lewy body formation, a hallmark of dopaminergic cell degeneration in PD, actually occurs in the brainstem, in the lower medulla and the olfactory bundle (stage 1 Parkinson’s disease—Fig. 24.7.2.2a). In stage 2 more dorsal medulla and pons are involved (Fig. 24.7.2.2b) whereas it is at stage 3 that the midbrain and the substantia nigra are involved (Fig. 24.7.2.2c). According to this hypothesis, therefore, clinical Parkinson’s disease is being detected only at stage 3. In support of this observation is the fact that several nonmotor features of PD, for example, olfac- tory loss and sleep disorders such as rapid eye movement disorder (RBD), seem to occur from the brainstem and olfactory bundle in- volvement, and in fact precede the development of motor PD. A list of such nonmotor features that may actually precede the develop- ment of motor signs of PD and may in future detect people ‘at risk’ of Parkinson’s disease is listed in Box 24.7.2.2. A recent twist to the pathophysiological basis of Parkinson’s disease is the observation that positron emission tomography (PET) of the brain in Parkinson’s disease identifies neuroinflammation in the brainstem, suggesting that the pathological process in Parkinson’s disease may be initiated by an inflammatory process within the glial cells. Symptoms and signs Parkinsonism is a clinical syndrome and typically, when the condition appears to be idiopathic and in particular responds to levodopa therapy, it is referred to as Parkinson’s disease.

Often the presenting symptom is a slow resting tremor, worse at rest (4–7 Hz) and often unilateral, al- though up to 30% of cases do not have a tremor at onset of the disease. The presence of an obvious tremor often leads both patients and their carers to suspect Parkinson’s disease and self-referral. In this context, it is important to differentiate an essential tremor from a parkinsonian tremor because the former carries a more benign prognosis and is twice as common, with a prevalence of at least 400 per 100 000 (Table 24.7.2.2). Bradykinesia/akinesia is difficulty in initiating, and slowness in exe- cuting, movement. It is the most disabling and progressive motor sign of PD and is a core feature for diagnosis of PD using the United Kingdom Parkinson’s Brain Bank criteria (Box 24.7.2.3). It first affects fine move- ments such as fastening buttons and handwriting, which becomes smaller and may progressively trail off (micrographia). Associated movements suffer, and arm swing may decrease unilaterally or bilaterally. Diagnosis of parkinsonism Gait is affected in PD, with difficulty starting walking, small steps, and shuffling. ‘Festination’ occurs when the patient appears to hurry and then stops suddenly as if rooted to the ground. The face often becomes expressionless (masked face or hypomimia) with reduced blinking. Bradykinetic laryngeal movement leads to quiet, monotonous speech that is low in volume and sometimes repetitive (palilalia). Rigidity is usually detected on examination and patients tend to complain of muscular stiffness and pain. Parkinsonian rigidity, which can be activated by performing mirror movements in the opposite limb (synkinesis), presents as one of two types: 1 ‘lead-pipe’ rigidity—a constant resistance to passive movement, in the absence of tremor 2 ‘cogwheel’ rigidity—a superimposed resistance similar to a ratchet, in the presence of tremor Premotor prefrontal Suppl. motor premotor Cortex Glu DA subst P enk GABA + + + + +

- = excitatory − = inhibitory
-

++ ++ ++ −− −− −− − − − − D2 D1 Stratium STN SNr SNc Thalamus VA/VL Brainstem SC GPi Cingulate sensory motor Prefrontal insular GPe Fig. 24.7.2.1 Pathological functional anatomy of the basal ganglia in Parkinson’s disease.

section 24 Neurological disorders 5950 Clinical assessment of PD is possible using several validated PD-specific scales and questionnaires and must have regular yearly outcome measures. These include the self-rated, 30-item, nonmotor questionnaire (NMSQuest), the simple 8-item, Parkinson’s disease quality-of-life questionnaire (PDQ-8), the motor scale (Unified Box 24.7.2.2 The nonmotor symptom complex Neuropsychiatric symptoms • Depression, apathy, anxiety • Anhedonia • Attention deficit • Hallucinations, illusion, delusions • Dementia • Obsessional behaviour (usually drug-induced), repetitive behaviour • Confusion • Delirium (could be drug-induced) • Panic attacks Sleep disorders • Restless legs and periodic limb movements • REM (rapid eye movement) behaviour disorder and REM loss of atonia • Non-REM sleep-related movement disorders • Excessive daytime somnolence • Vivid dreaming • Insomnia • Sleep-disordered breathing Autonomic symptoms • Bladder disturbances: — urgency — nocturia — frequency • Sweating • Orthostatic hypotension (OH): — Falls related to OH — ‘Coat hanger’ pain • Sexual dysfunction: — Hypersexuality (likely to be drug induced) — Erectile dysfunction • Dry eyes (xerostomia) Gastrointestinal symptoms • Dribbling of saliva • Ageusia • Dysphagia/choking • Reflux, vomiting • Nausea • Constipation • Unsatisfactory voiding of bowel • Faecal incontinence Sensory symptoms • Pain • Paraesthesia • Olfactory disturbance Other symptoms • Fatigue • Diplopia • Blurred vision • Seborrhoea • Weight loss • Weight gain (possibly drug-induced) (a) (b) (c) presymptomatic phase symptomatic phase locus coeruleus dorsal IXIX nucleus locus coeruleus

locus coeruleus substantia nigra neocortex sec. + prim. neocortex association mesocortex dorsal IXIX nucleus dorsal IXIX nucleus mesocortex substantia nigra 1 2 3 4 5 6 presymptomatic phase symptomatic phase 1 2 3 4 presymptomatic phase symptomatic phase 1 2 Fig. 24.7.2.2 Proposed pathophysiological basis of Parkinson's disease. (a) Stage 1 disease—Lewy body formation in the brainstem, lower medulla, and olfactory bundle. (b) Stage 2—more dorsal medulla and pons are involved. (c) Stage 3—midbrain and substantia nigra involved (Fig. 24.7.2.2c). (Colour scale relates anatomical site(s) of involvement to disease progression.)

24.7.2 Parkinsonism and other extrapyramidal diseases 5951 Parkinson's Disease Rating Scale, UPDRS), and the nonmotor scale (NMSS) (Table 24.7.2.3). The nonmotor symptom complex A variety of nonmotor symptom complexes (NMSs) is also seen in PD from an early stage, all of which are likely to have a major ef- fect on the health-related quality of life of patients. These symptoms include depression, dementia, sleep disorders, bowel and bladder problems, fatigue, apathy, pain, and autonomic dysfunction (see Box 24.7.2.2). Confirmation of diagnosis There are no specific tests for the diagnosis of PD, which remains a clinical diagnosis (Table 24.7.2.4). DaTSCAN This is single photon emission computed tomography (SPECT) using the labelled cocaine derivative N-ω-fluoropropyl-2β- carboxymethoxy-3β-(4-iodophenyl)tropane (123I-labelled β-CIT and 123I-labelled FP-CIT (DaTSCANn, Fig. 24.7.2.3), and is re- commended in guidelines from the National Institute for Health and Clinical Excellence (NICE) and widely used to support diag- nosis and differentiate PD from essential tremor (Fig. 24.7.2.4). It labels the presynaptic dopamine transporter and this provides assessment of the presynaptic neurons, which degenerate in PD. Essential tremor is likely to show a normal DaTSCAN whereas in PD there is diminished uptake of the ligand, usually correl- ating with the clinically affected side, and DaTSCAN also appears to have a close correlation with the progression of PD. However, DaTSCAN does not differentiate between PD and other parkin- sonian syndromes. PET scan Using 18F-labelled dopa the PET scan has similar properties and better resolution but is currently available as a research tool only. More recently, transcranial ultrasonography has been used to Table 24.7.2.3 Recommended good practice guide for clinical assessment of people with Parkinson's disease A Motor assessment Hoehn and Yahr stage UPDRS (or MDS-UPDRS) B Nonmotor assessment NMS Quest (empowering patient) NMSS (measurement) PDSS HADS C Quality of life PDQ-8 PDQ-39 HADS, hospital anxiety and depression scale; NMS Quest, nonmotor symptoms questionnaire; NMSS, nonmotor symptoms scale; PDQ-8, Parkinson's disease questionnaire—8 questions (short version of PDQ-39); PDQ-39, Parkinson's disease questionnaire—39 questions; PDSS, Parkinson's disease sleep scale; UPDRS, Unified Parkinson's Disease Rating Scale. Table 24.7.2.4 Imaging modalities for pre-motor Parkinson's disease Diffusion weighted imaging of olfactory tract MIBG-SPECT Dopamine transporter SPECT Transcranial sonography 18-F Dopa PET Table 24.7.2.2 Comparison of parkinsonian tremor and essential tremor Feature Parkinsonian tremor Essential tremor Age at onset Usually >50 years

> 10 years Occurrence Incidence increases with each decade of age Incidence remains the same with each decade of age Family history Rare Common Site Usually hands, also legs and jaw; head uncommon Hands, head (a no–no or yes–yes motion), vocal Characteristics At rest; supination/pronation action reduces; mental concentration increases Postural; flexion/extension action increases; mental concentration diminishes Frequency (Hz) 4–7 8–12 Lead-pipe

> rigidity Yes No Cogwheel rigidity Yes Rare Alcohol No effect Often improves Treatment Dopaminergics β-Blockers, primidone Box 24.7.2.3 Diagnosis of parkinsonism (Parkinson's Brain Bank criteria) Essential features • Bradykinesia and two of the following: • Tremor (rest) and/or • Rigidity (cogwheel/lead pipe) • Postural imbalance, fixed, stooped posture • Gait difficulty (shuffling, short-step gait, with or without festination) Additional features • Hypomimia ('masked' face) • Freezing episodes (sudden onset failure of movement) • Seborrhoea of the scalp • Mental and cognitive disturbance

section 24 Neurological disorders 5952 reveal characteristic hyperechogenicity of the substantia nigra in patients with early PD, possibly suggestive of excessive iron de- position in the substantia nigra. However, this technique needs to be validated in large-scale studies before widespread use can be advocated. CT or MRI Scans are usually not needed for diagnosis, but a brain scan should be performed if parkinsonism is purely unilateral or otherwise atypical, or if additional signs (pyramidal) are present. Computed tomography (CT) or magnetic resonance imaging (MRI) may also be used to rule out a space-occupying lesion, vascular disease, and normal-pressure hydrocephalus. MRI brain scan is preferable to a CT brain scan. Management of Parkinson's disease When to initiate treatment is a critical question and it may indeed be best to start treatment at diagnosis (Table 24.7.2.5). The decision to treat may be dictated by the following clinical issues: • Involvement of the dominant hand relative to the nondominant hand and the effect on employment/occupation. • The particular subtype of Parkinson's disease (bradykinesia- dominant disease may require earlier treatment than tremor- dominant disease). – The individual sentiments of patients and carers (offer informed choice). – Presence of nonmotor symptoms such as pain, depression, or sleep problems. As initiating treatment, the NICE (National Institute of Health and Clinical Excellence (UK)) guidelines recommend levodopa, dopa- mine agonists, or monoamine oxidase-B inhibitors. Levodopa is a precursor to dopamine, converted to dopamine by dopa decarb- oxylation, and restores the dopamine lost due to degeneration of striatonigral cells. The addition of a peripheral decarboxylase in- hibitor that does not cross the blood–brain barrier, such as carbidopa or benserazide, inhibits dopa decarboxylase in the rest of the body (a) (b) Fig. 24.7.2.3 (a) A normal DaTSCAN showing the comma appearance. (b) DaTSCAN in Parkinson's disease showing a 'dot' appearance on one side, indicating dopaminergic loss. Postsynaptic neuron Presynaptic neuron Postsynaptic autoreceptors Presynaptic autoreceptors Synaptic cleft Glia cell Dopamine Dopamine Storage vesicle Levodopa Tyrosine MAO monoamine oxidase COMT catechol-O-methyltransferase Cell body D D D D D D D D D D Somatodentric autoreceptors Levodopa D D D D D Dopamine transporter Fig. 24.7.2.4 Dopaminergic neuronal transmission.

24.7.2 Parkinsonism and other extrapyramidal diseases 5953 and reduces side effects. The bioavailability of levodopa has been en- hanced further by the emergence of drugs such as tolcapone and entacapone that inhibit catechol-O-methyl transferase (COMT), which also breaks down dopamine. Evidence suggests that levodopa therapy should be started at the minimal effective dose (usually 50–100 mg/day), in combination with a decarboxylase inhibitor given three to four times daily. Doses at or above 600 mg/day may be associated with a dyskinesia rate as high as 17% at one year. Side effects, such as light-headedness or nausea, may be relieved by taking the medication with food or by increasing the dose of decarboxylase inhibitor or taking

domperidone, which does not cross the blood–brain barrier and hence does not cause central dopamine antagonism. Controlled- release preparations of levodopa, with addition of a COMT inhibitor (entacapone) to the traditional combination of levodopa and a de- carboxylase inhibitor (carbidopa), are now licensed for the treat- ment of later stage PD. In Parkinson's disease refractory to other forms of conventional therapies, intraduodenal/-jejunal infusion of levodopa (Duodopa) provides an alternative route of drug adminis- tration. Duodopa is effective for motor fluctuations in advanced PD and decreases dyskinesias. Dopamine agonists Dopamine agonists stimulate dopamine receptors directly and so bypass presynaptic nigrostriatal neurons which are degenerate. Five types of dopamine receptors (D1–D5) have been identified; these are divided into: D1-like and D2-like receptors. In the 1980s and 1990s ergot dopamine agonists such as bromocriptine, pergolide, and more recently cabergoline, were typically used, however now nonergot agonists are preferentially recommended due to the risk of cardiac valvular fibrosis with ergot dopamine agonists. Ropinirole and pramipexole are the main oral nonergot dopamine agonists. Rotigotine, a transdermal nonergot dopamine agonist patch, has now been released. It effectively demonstrates the concept of continuous dopaminergic stimulation and is useful when given once a day. Both ropinorole and pramipexole are available as once a day therapy which leads to improved compliance with therapy in PD (Fig. 24.7.2.4). Side effects of dopamine agonists include nausea, vomiting, postural hypo- tension, and hallucinations/psychosis in susceptible individuals or at high doses. More specifically somnolence or sudden onset of sleep has been linked to nonergot dopamine agonists, but it is clear now that somnolence can occur with progression of Parkinson's disease. Patients, therefore, need to be warned about driving when starting on these drugs. Behavioural problems demonstrating disinhibition such as compulsive gambling, hypersexuality, and a complex medley of impulsive behaviour have been linked to use of dopaminergic drugs, particularly dopamine agonists. This has been termed dopamine-dysregulation syndrome; the exact prevalence is unknown but can be up to 7% in susceptible individuals. Apomorphine injection and infusion Apomorphine is a strong nonergot dopamine agonist that is ad- ministered subcutaneously by an infusion pump in advanced Parkinson's disease when oral therapy is of no further benefit. Apomorphine can be administered as a subcutaneous injection and is usually effective within 10 minutes by-passing the stomach absorption route and is extremely effective for reversing predict- able off periods such as during early morning upon awakening. The subcutaneous infusion is delivered using a small pump and can be used from 12 to 24 hours. Subcutaneous apomorphine is particu- larly useful to control motor fluctuations and is indicated when oral or skin patch therapy is ineffective. The main side effects are skin lesions and nausea. Monoamine oxidase-B inhibitors Selegiline 10 mg once daily or 5 mg twice daily orally (or 1.25 mg once daily by buccal administration) is a selective, irreversible blocker of intra- and extraneuronal monoamine oxidase B (MAOB), and re- duces metabolism of dopamine. Rasagiline is a second-generation, irreversible, selective MAOB inhibitor that is administered orally at a dosage of 0.5–1 mg once daily. A recent study (ADAGIO) suggests a potential disease modifying effect of rasagiline. The side effects of MAOB inhibition include hallucinations, sleep disorders, agitation, postural hypotension, and withdrawal problems. Anticholinergics not recommended Anticholinergics block the action of acetylcholine against dopamine in the basal ganglia. These drugs can occasionally be used as levo- dopa adjunct therapy, helping to control rest tremor and dystonia. However, they are not routinely recommended and should be util- ized with caution in older patients with parkinsonian syndromes be- cause of the risk of precipitating a confusional state and exacerbating dementia. Other drugs The antiviral amantadine, 100–400 mg, daily has a moderate antiparkinsonian effect. It acts, partly, via increased dopamine syn- thesis and may also

be useful to manage dyskinesias. Patients who may require surgery Surgery has gained popularity in selected patients where conven- tional pharmacological therapy has failed to control symptoms. It has a morbidity rate of approximately 2% due to the risk of stroke and infection, and a mortality rate of approximately 0.5%. The oper- ation of choice is deep brain stimulation of the subthalamic nucleus, which reverses the akinesia and controls dyskinesias. Patients with severe resistant unilateral tremor may undergo single-side thalamic stimulation of the ventral intermediate nucleus. Additional surgical Table 24.7.2.5 New therapeutic options for motor complications (investigational or in clinical trial) COMT inhibition Opicapone A2A antagonists Istradefyline (approved in japan)/Vipadenant (phase 2) Glutamate antagnosits Zonisamide/Safinamide α-2 antagonists Fipamezole 5HT agonist Pimavanserine Neurotrophic factors GDNF (IP), PDGF (IV) Incretin mimetic Exenatide Synthetic amino acid precursor Droxidopa Antimuscarinic Solifenacin Adapted from Stocchi F (2014) Neurotherapeutics 11(1): 24–33.

section 24 Neurological disorders 5954 approaches, such as delivery of viral vectors to the striatum for gene therapy or neurotransplantation, are options still in research and de- velopment. Adenosine-associated virus, a nonpathogenic virus, is being used in human trials for gene delivery, including genes such as neurturin, glial-cell derived nerotrophic factor, and glutamate decarboxylase. Intrajejunal levodopa infusion It is indicated for the treatment of advanced levodopa-responsive Parkinson’s disease with severe motor fluctuations and dyskinesia. This involves giving L-dopa in a gel formulation via a jejunostomy. It has proven to be extremely effective for motor dysfunction in ad- vanced PD as well as being beneficial for some nonmotor symptoms and a subsequent health-related improvement in quality of life. Other therapies and support A multidisciplinary approach is a requirement for optimal care of the patient with Parkinson’s. Initially, the main requirement is for information and counselling. In the later stages of the disease pro- cess, coordination of the various specialists involved in care is very important for the proper management of the patient (Fig. 24.7.2.5). Other parkinsonian/extrapyramidal syndromes There are several degenerative diseases that have a more complex clinical picture than Parkinson’s disease and a poorer response to therapy. It may be impossible to distinguish idiopathic Parkinson’s disease from other parkinsonian syndromes. Drug-induced parkinsonism This is one of the most common causes of secondary parkinsonism, and is often misdiagnosed as Parkinson’s disease because clinical features may be indistinguishable. It causes rigidity, bradykinesia, tremor and gait disturbance, and may be asymmetrical. Although several medications are associated with secondary parkinsonism, dopamine-blocking agents (neuroleptics) such as prochlorperazine or chlorpromazine are the most common offending agents, and are often prescribed to older people for nonspecific complaints such as dizziness, and drug-induced parkinsonism may take up to 9 months to disappear. The incidence of drug-induced parkinsonism is es- timated to be 15–40% in patients receiving neuroleptics, and its prevalence increases with age. Vestibular sedatives are also impli- cated. Commonly used antiemetics and antidizziness pills need to be monitored. Treatment consists of withdrawal of the offending medication. If drug withdrawal is impractical, patients are dose reduced or changed to an atypical agent, such as clozapine or quetiapine. Occasionally emergence of parkinsonism may be permanent. Progressive supranuclear palsy Progressive supranuclear palsy (PSP or Steele–Richardson– Olszewski syndrome) presents with gait disturbance and falls (pre- dominantly backwards) in over 50% of cases, and is a disease of later life. The pathological hallmark is finding of tau protein-positive filamentous inclusions, known as neurofibrillary tangles, in the glia and neurons. The clinical picture consists of supranuclear gaze palsy, particularly downgaze with extension and rigidity of the neck,

a staring look due to lid retraction, and predominant truncal extensor rigidity. Varying degrees of bradykinesia, dysphagia, personality changes, and other behavioural disturbances, such as a subcortical frontal dementia, coexist. A subtype with levodopa responsiveness have been described. It has been shown that some risk variants are shared between PSP and corticobasal degeneration. In addition, it has been shown that PSP brain volume changes on vMRI capture disease progression and cognitive changes. vMRI changes may serve as a valuable biomarker or outcome to support disease modifying therapeutic efficacy in future PSP clinical trials. Multiple system atrophy Multiple system atrophy (MSA) consists of a variable combin- ation of parkinsonism with autonomic, pyramidal, or cerebellar New patient diagnosis PDNS consultation Telling the diagnosis MDT consultation Physiotherapy Occupational therapy Speech and language therapy Neuropsychology Fig. 24.7.2.5 Multidisciplinary approach.

24.7.2 Parkinsonism and other extrapyramidal diseases 5955 symptoms and signs. In the past, patients were categorized as having the striatonigral type if there were dominant parkinsonian signs, and the olivopontocerebellar type if cerebellar signs predominated. These terms are no longer in use and, currently, striatonigral- and olivopontocerebellar-type variants are called MSA-P and MSA-C, respectively. The pathological feature of MSA is α-synuclein posi- tive inclusions within neurones or glial cells. These changes result in progressive and profound neuronal loss in various parts of the brain. The parkinsonian features of MSA include progressive bradykinesia, rigidity, and postural instability, typically present bilaterally. Useful clinical clues include disproportionate anterocollis, truncal dystonia (this may resemble the so-called ‘Pisa syndrome’), characteristic sighing, and the presence of cold, blue hands. Autonomic failure, particularly postural hypotension, occurs early in MSA and is more severe than in idiopathic Parkinson’s disease. The response to levo- dopa is commonly incomplete and benefit usually declines within 1–2 years of treatment. Dementia with Lewy bodies In dementia with Lewy bodies (DLB), widespread areas of neo- cortex as well as the brainstem and diencephalic neurons have Lewy bodies. Parkinsonian DLB can be very difficult to differentiate from Parkinson’s disease, but these patients have early onset dementia (progressive cognitive decline interfering with normal social and occupational function) and may have hallucinations, delusions, and even psychosis in the absence of dopaminergic therapy, usually within two years of disease onset. Clinical criteria for diagnosis in- clude cognitive fluctuation and attention, recurrent and persistent visual hallucinations, and parkinsonian motor signs. Repeated early falls and neuroleptic sensitivity can be seen. Occasionally the pa- tients develop a supranuclear gaze palsy leading to an incorrect diag- nosis of PSP. Corticobasal ganglionic degeneration Corticobasal ganglionic degeneration, also known as cortico dentatonigral degeneration with neuronal achromasia, typically presents in the sixth or seventh decade with slowly progressive, uni- lateral development of tremor, apraxia, and rigidity in an upper limb. The condition is characterized by progressive gait disturbances, cor- tical sensory loss, and stimulus-sensitive myoclonus, which result in a jerky, useless hand. A jerky, useless lower extremity is uncommon, but may occur; it is known as the alien limb phenomenon and can occur in about 50% of patients. Gait disturbance consists of a slightly wide-based, apraxic gait rather than the typical festinating gait of Parkinson’s disease. Patients with corticobasal ganglionic degener- ation do not benefit from levodopa, and the disease course is relent- lessly progressive. Other extrapyramidal conditions that should also be considered, including the following, are fully described in Chapter 24.7.3: • Dopa-responsive dystonia • Wilson’s disease • Neuroacanthocytosis • Dystonia • Generalized idiopathic torsion dystonia • Tardive dyskinesia • Chorea and related disorders • Tics FURTHER READING Albanese A, et al. (2001). Consensus statement on the role of acute dopaminergic challenge in Parkinson’s disease. Mov Disorders, 16, 197–201. Albin RL, Frey KA

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