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ESSENTIALS Neurodegenerative disorders are associated with a progressive loss of structure and function of neurones that leads to neuronal death. Their aetiology combines ageing, genetic susceptibility, and risk factors including environmental exposure, balanced against protective factors. They present with varying combinations of progressive cognitive, emotional, motor, autonomic and periph- eral symptoms, and clinical signs. Neurodegenerative conditions are all likely to have a preclinical prodromal period, followed by slow initial decline during which there is clinical presentation, followed by a further steady decline and an eventual accelerated decline. The rate of progression of these disorders varies greatly, but they are all inevitably progressive, currently have no cure, and require symptomatic treatment. This chapter focuses on the clinical presentation, diagnosis, and management of Parkinson's disease as perhaps the best example of an age-related neurodegenerative condition. It explains the par- ticular challenges of the disease in the context of ageing, the use of the multidisciplinary team, and the management of the nonmotor symptoms. Introduction Neurodegenerative disorders are associated with a progressive loss of structure and function of neurones that leads to neuronal death. They present with varying combinations of progressive cognitive, emotional, motor, autonomic, and peripheral symp- toms and clinical signs. These conditions include Alzheimer's dis- ease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and frontotemporal dementia (FTD). The aetiology of neurodegenerative disorders combines ageing, genetic susceptibility, and risk factors including environmental ex- posure, balanced against protective factors. Pathologically, neurodegenerative disorders all exhibit abnor- malities of protein handling, leading to the intracellular depos- ition of abnormal proteins in a variety of patterns associated with distinct patterns of cell loss. The deposition of proteins gives rise to pathological markers such as the Lewy body, due to α-synuclein protein (e.g. PD), or plaques and tangles due to Tau protein (e.g. AD). The conditions can be

divided according to the predominant protein deposition into α-synucleinopathies (PD, dementia with Lewy bodies, and multiple system atrophy) and tauopathies (AD, progressive supranuclear palsy, corticobasal degeneration, and frontotemporal dementia). Cell death is the culmination of a cascade of complex processes. Many of these processes parallel the changes which occur in ageing, although the detailed pattern differs. Pathologically some of these conditions are interrelated such that the presence of one increases the risk of the development of another. There is often mixed degen- erative pathology combined independently with vascular disease, which may contribute to cognitive and physical decline. This can be seen, for example, in the pathological overlap between PD and AD transitioning through PD dementia and dementia with Lewy bodies with increasing AD pathology (Fig. 6.10.1). 6.10 Neurodegenerative disorders in older people John Hindle AD DLB Vascular PD PDD Limbic and cortical Lewy bodies Fig. 6.10.1 Neuropathological overlap in neurodegenerative disease in older people. AD, Alzheimer' disease; DLB, dementia with Lewy bodies; PD, Parkinson's disease; PDD, Parkinson's disease dementia.

602 Section 6 Old age medicine Neurodegenerative conditions are all likely to have a preclinical prodromal period, followed by slow initial decline during which there is clinical presentation, followed by a further steady decline and an eventual accelerated decline (Fig. 6.10.2). The rate of pro- gression of these disorders varies greatly, but they are all inevit- ably progressive, currently have no cure, and require symptomatic treatment. This chapter focuses on the clinical presentation, diagnosis, and management of PD as perhaps the best example of an age-related neurodegenerative condition. It explains the particular challenges of PD in the context of ageing, the use of the multidisciplinary team, and the management of the nonmotor symptoms. Each section highlights where symptoms and management strategies are also applicable to other neurodegenerative disease of older people. For further discussion of neurodegenerative disorders, see chapters on movement disorders (24.7.1–4), inherited neurodegenerative disorders (24.17), higher cerebral function (24.4.1–2), and neuro- psychiatric disorders (26.5.3). Parkinson's disease and ageing Aetiology The specific aetiology of PD is not known, hence the term idio- pathic. In general, the earlier the onset of PD the more likely it is to be associated with genetic abnormalities, although an abnormality of the Leucine Rich Repeat kinase 2 (LRRK-2) gene may be associated with a few late onset cases. In future it is likely that susceptibility genes will be identified that predis- pose to late onset PD. Several environmental risk factors have been identified, including rural living, exposure to pesticides and herbicides, and well water drinking. Other factors may be protective, including use of nonsteroidal drugs, drinking coffee, and smoking. Age is still, however, the largest risk factor for the development of PD. Epidemiology Parkinson's disease is largely a disease of older age, with the mean age of onset in the early 70s, and an incidence of around 11 cases of PD and 17 cases of parkinsonism per 100 000 popula- tion per year. Age-adjusted prevalence in the United Kingdom is around 150–200 per 100 000 population (compared with c.1000 per 100 000 for AD). The pattern of increasing prevalence with age is remarkably similar across most European and Western countries. Pathogenesis Pathologically, PD is characterized by the formation of Lewy bodies and a distinct pattern of cell loss. The pathogenesis consists of a cascade of events leading to cell death. It is now recognized that the spread of pathology may occur through transmission of abnor- mally folded proteins across the synapse commencing in the brain- stem and spreading to the cortex, as described in Chapter 24.7.2. The very earliest changes occur in the vagal nucleus and in the ol- factory bulb, the latter being associated with loss of sense of smell. Brainstem pathology may produce autonomic dysfunction, and limbic involvement may produce mood changes. Extension of pathology to the cortex and hippocampus may lead to

cognitive changes and dementia. Despite the presence of significant path- ology, even in the early stages of PD, the brain adopts compensatory mechanisms that delay the clinical presentation. In older people the reduced reserve brought about through ageing and associated pathologies such as vascular disease, overwhelms these compensa- tory mechanisms leading to a relatively earlier clinical decline than would be caused by PD-specific pathology alone. Clinical features The diagnosis of PD or other neurodegenerative disorders should be confirmed by a specialist, either a neurologist or geriatrician, although it is still revised later in about 10% of cases. The clinical symptoms and signs can be divided into motor and nonmotor fea- tures, with the latter being increasingly important in older age. The characteristic motor phenotype includes bradykinesia, rigidity, tremor, and the loss of postural reflexes. Nonmotor symptoms in- clude anosmia, neuropsychiatric problems, autonomic dysfunc- tion, sleep disturbances, gastrointestinal, and bladder problems. Prodromal symptoms including depression, anxiety, anosmia, restless legs, and sleep behaviour disorder may precede the onset of the typical motor syndrome. Motor signs and symptoms The onset of motor symptoms may be subtle, and these are easily missed or mistaken for age-related changes by the patient or doctor. All of the motor symptoms are characteristically asymmetrical. Bradykinesia is a fatigable slowing of movement and alteration of its rhythm and amplitude. It may be associated with slowness of axial movements, giving difficulty turning in bed. Reduced facial movement and slowness of expression may lead to a mask-like face. Rigidity is typically irregular through passive movement and is termed cogwheel. There is also background continuous rigidity de- scribed as lead-pipe rigidity. The tremor of PD is usually a rhythmic rest tremor of around 4–7 cycles per second, but some patients may also have this tremor on sustained posture. Hand tremor often emerges when walking. The gait characteristically has a delay in ini- tiation, hesitancy and shortening of stride length, the use of extra steps to turn round, and associated loss of arms swing and stooping. The gait pattern needs to be differentiated from the hesitant gait often seen in older people who have developed a fear of falling. A very marked stoop on standing, which disappears on lying down, can sometimes develop due to a spinal dystonia known as camptocormia. This may be associated with other spinal pathology or myopathy. An early onset sideways stoop, often called the Pisa syndrome, is more characteristic of multiple system atrophy. Minimal decline-prodromal period Symptom onset Diagnosis Steady decline Accelerated decline Susceptibility Time/age Function Fig. 6.10.2 Common neurodegeneration disease model.

6.10 Neurodegenerative disorders in older people 603 Postural instability may be present, even on diagnosis, particu- larly in older people. Absence of other neurological signs supports a diagnosis of PD, but coincidental neurological signs such as brisk reflexes or extensor plantar responses are common in older people. With disease progression motor signs become bilateral, as- sociated with increased axial rigidity, postural changes, instability, and falls. Abnormal movements in the form of dyskinesia associated with medication are more prevalent in younger onset PD, and when they occur in older age they are usually less severe. The motor symptoms of PD may worsen in periods of intercurrent illness or following major procedures or anaesthesia. Other disorders of movement Cerebellar dysfunction is common in multiple system atrophy, and when present the condition is termed multiple system atrophy-C in contrast to multiple system atrophy-P which has predominant parkinsonism. Myoclonic jerks can be present as a late phenom- enon in PD and AD, but commonly develop earlier in dementia with Lewy bodies and corticobasal degeneration. Dystonia can occur related to fluctuations in drug response in PD. Unilateral dystonia is a common feature in corticobasal degeneration. Differential diagnosis Ageing Mild parkinsonian signs can occur sporadically in a few very elderly people without an established neurological disorder. They can be

distinguished by symmetrical signs, an absence of rest tremor, and a lack of response to dopaminergic therapy. They may reduce functional capacity and are associated with increased likelihood of mild cognitive impairment. These signs are likely to be multifactorial in origin, including age-associated decline in dopaminergic activity, deep white matter disease, and ‘incidental’ Lewy body pathology (not amounting to PD) that can also be present without clinical signs and symptoms. Ageing can also be associated with axial impairment of gait and postural control, sometimes called age-related gait disturbance (Table 6.10.1). Drug-induced Parkinsonism Increasing age is associated with increasing sensitivity to side effects of dopamine blocking agents, producing drug-induced parkinsonism. It is more common in women and in those with a family history of PD and affective disorders. Symptoms may come on within a few weeks of commencement of the causal agent in 50% of cases, but others may take many years to develop. Drug-induced parkinsonism has less tremor and is more likely to be symmetrical. When there is marked asymmetry it may be due to an unmasking of subclinical PD, which then progresses in the typical pattern. The commonest agents causing drug-induced parkinsonism are given in Table 6.10.2. If possible, withdrawal of the causal drug should be considered, although this must be done very slowly to avoid precipitating a tardive movement disorder (dyskinesia or dystonia). In 60% of cases improvement will occur within two months, but it may take much longer. Essential tremor Essential tremor is more common with increasing age and is associated with symmetrical postural tremor at higher fre- quency (8–12 hz) than in PD. There may be a family history and response to alcohol. Differentiation from PD can some- times be difficult because some people with PD will have a noticeable postural tremor. β-blockers are the most effective treatment for postural tremor, with improvement occurring in over 50%, although intolerance of, and contraindications to, the use of β-blockers are more common in older patients. Other agents including primidone, other anticonvulsants and benzodiazepines are more likely to cause side effects in older people. Other dementias An early presentation of dementia, prior to the onset of motor symptoms, may be due to dementia with Lewy bodies, which is now thought to be part of a spectrum that includes PD. Dementia with Lewy bodies is particularly associated with fluctuating cognition, visual hallucinations, language difficul- ties, and marked sensitivity to dopamine blocking drugs. The motor signs are similar to PD. There may be some response to L-dopa, but doses need to be kept extremely low to avoid ex- acerbation of hallucinations. Autonomic problems, particularly orthostatic hypotension, are common in dementia with Lewy bodies. Frontotemporal dementia mainly affects those under the age of 65 years and usually presents with behavioural changes and/or disturbances of language and memory. AD can have associated parkinsonism leading to diagnostic confusion. The parkinsonism may be due to the development of associated Lewy body pathology. Vascular parkinsonism Cerebrovascular disease, in particular deep white matter changes, increases with age and may be associated with parkin- sonism. This typically affects the lower body, producing pre- dominant gait symptoms and postural instability. Small steps with a rapid cadence give a characteristic ‘marche à petits pas’. Table 6.10.1 Differentiating age-related motor changes from Parkinson’s disease (PD) Parkinson’s disease Mild parkinsonian signs ‘Age-related’
gait disturbance Tremor Rest Absent in 90% Absent Rigidity Typical cogwheel or lead pipe Variable Musculoskeletal Bradykinesia Typical with fatigue Variable General slowness Gait and balance disturbance Late Early Axial impairment gait and posture Symmetry Asymmetrical Symmetrical Symmetrical Dementia risk Increased Slightly increased Age-related L-dopa response Good Poor None

 Occasionally, acute vascular lesions of the basal ganglia can give rise to asymmetrical parkinsonism. Although vascular parkinsonism is characterized by a relatively poor response to L-dopa, some patients with vascular parkinsonism, particu- larly those with lesions close to the nigrostriatal pathway, may respond to L-dopa. Multisystem degenerations Other multisystem degenerations may occur in older people. These conditions have a more rapid progression requiring com- plex multidisciplinary management and early palliative care. Progressive supranuclear palsy is associated with early falls and injury, planning difficulties, vertical gaze palsies, swallowing dif- ficulties, and poor response to L-dopa. People with progressive supranuclear palsy also show difficulty suppressing ongoing move- ment, such as continuing clapping when asked to clap three times (applause sign). Multiple system atrophy, although usually presenting at an earlier age than PD or progressive supranuclear palsy, can occur in older age and is associated particularly with autonomic dysfunc- tion, cerebellar symptoms, and a more rapid progression. Urinary symptoms are particularly common at onset. Initially, these are commonly urgency, frequency, and incontinence, but voiding problems may develop later. Corticobasal degeneration may present with marked asym- metry of motor signs including dystonia, myoclonus and limbs moving outside voluntary control (alien limb phenomenon), asso- ciated with cognitive impairment and dyspraxia. It may also pre- sent with dementia. The condition is probably underdiagnosed, with the persistent asymmetry leading to misdiagnosis as vas- cular disease or stroke. The differentiating features of the neurodegenerative conditions are given in Table 6.10.3. Investigations There is no single diagnostic test for PD since it is a clinical diagnosis. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain are not recommended routinely, but in older patients it is more common to find coincidental vascular and deep white matter changes. An isotope brain scan highlighting dopamine nerve terminals (ioflupane iodine-123 injection—DaTscan) may help differentiate degenerative parkin- sonism from essential tremor or drug-induced parkinsonism (see Chapter 24.7.2). Treatment Multidisciplinary treatment Anyone with suspected PD should be referred for specialist assess- ment, enabling access to a specialist multidisciplinary team. Early referral should be considered to a PD nurse specialist, physiother- apist, occupational therapist, speech and language therapist, and later possible referrals may include dietician, psychologist, and psychiatrist (Table 6.10.4). Drug treatment Older people tend to be more sensitive to the cognitive and psychi- atric side effects of PD drugs treatments (Table 6.10.5). The focus of drug therapy for motor dysfunction in older people with PD is L-dopa (plus dopamine decarboxylase inhibitor, e.g. carbidopa in Co-careldopa or benserazide in Co-beneldopa). There is no reason to delay initiation of L-dopa in older people. The starting dose is smaller in older than younger patients, with more gradual incre- ments and regular monitoring of response. Anticholinergic drugs should be avoided since they may cause hallucinations and cognitive decline. In older patients who de- velop wearing off from the response to L-dopa there is benefit from adjunctive therapy, such as addition of a monoamine oxidase B inhibitor (rasagiline, selegiline), catechol-O-methyltransferase inhibitor (entacapone) or small doses of a direct acting dopamine agonist (ropinirole, rotigotine, pramipexole). Patients may still benefit from the use of more complex ther- apies such as subcutaneous apomorphine or intrajejunal L-dopa. Patients over the age of 70 years are much less likely to be suitable for brain stimulation. Other degenerative Parkinsonisms do not respond well to drug treatment. Management of falls Falls are common in PD, particularly with increasing stage of the disease and ageing, and may occur in 50% over a three-month period. They may occur even in moderate disease, affect quality of life and increase fracture risk (Table 6.10.6). Falls occur very early in the course of progressive supranuclear palsy.

Table 6.10.2 Agents causing drug-induced parkinsonism Drugs commonly causing parkinsonism

Drug less commonly causing parkinsonism Drug rarely causing parkinsonism Drug type/ usage Examples Drug type/ usage Examples Drug type/ usage Examples Typical Neuroleptics Chlorpromazine Trifluoperazine Flupentixol Haloperidol Pimozide Sulpiride Atypical Neuroleptics Aripiprazole Amisulpiride Olanzapine Risperidone Atypical neuroleptics Clozapine Quetiapine Antiemetic Metoclopramide Anticonvulsants Sodium valproate Antidepressants Paroxetine Vestibular sedative Prochloperazine Antiarrhythmic Amiodarone Dopamine depleters Tetrabenazine Travel sickness Cinnarazine Anticonvulsants Lamotrigine

6.10 Neurodegenerative disorders in older people 605 Table 6.10.3 Features of neurodegenerative conditions Synucleinopathies Tauopathies Other PD DLB MSA AD PSP CBD FTD ET Common age of onset 60–70

> 65 50–60 65 70 variable 45–65 All ages Pathological marker Lewy bodies Lewy bodies Glial cytoplasmic inclusion bodies, gliosis Plaques and tangles Tangles Tangles Pick bodies Variable Clinical motor Extrapyramidal Asymmetrical parkinsonism, tremor common Symmetrical parkinsonism Symmetrical parkinsonism in MSA-P Late onset parkinsonism Symmetrical parkinsonism in PSP-P Marked asymmetrical parkinsonism Late: overlap with PSP or CBD None Gait Slow, short stride, reduced arm swing, narrow base, stoop, falls late Slow, short stride, reduced arm swing Slow, short stride, reduced arm swing, narrow base, marked stoop, ataxia, syncope causing falls Normal Upright posture, wide base, motor recklessness, early falls Marked asymmetrical reduced arm swing and dystonia Late changes Normal Other movements Occasional myoclonic jerks, dystonia Myoclonic jerks common Cerebellar dysfunction Myoclonic jerks late onset Applause sign Alien limb, myoclonic jerks, dystonia Late abnormal movements None Gaze palsy None None Horizontal > vertical None Vertical > horizontal Horizontal = vertical None or overlap with PSP None Clinical neuropsychiatric Cognition Dementia late Dementia at presentation Dementia rare Dementia at presentation Planning problems early Variable: dyspraxia, language problems Dementia at presentation, language problems Normal Behaviour Hallucinations later Hallucinations early. Challenging behaviour Normal Hallucinations late Challenging behaviour Reckless behaviour in some Variable Early behavioural and personality changes Normal Other problematic nonmotor features Wide variety Autonomic Autonomic predominate Variable Apathy, swallow problems Variable Aphasia, None Treatment Drugs L-dopa good response Some response to L-dopa but doses kept low Poor response to L-dopa Poor response to L-dopa Poor response to L-dopa Poor response to L-dopa Poor response to L-dopa β-block MDT priorities Motor function then all nonmotor symptoms Mental health Autonomic impairment Mental health Falls, swallow problems Mental health, motor symptoms Mental health Tremor Prognosis: survival Normal to slight reduction Reduced 10 yr Reduced 6 yr 6 yr 8 yr Normal AD, Alzheimer’s disease; CBD, corticobasal degeneration; ET, essential tremor; FTD, frontotemporal dementia; DLB, Lewy body dementia; MDT, multidisciplinary team; MSA, multiple system atrophy; PD, Parkinson’s disease; PSP, progressive

> supranuclear palsy.

606 Section 6 Old age medicine It is important to monitor risk of falls in older people with PD (Table 6.10.7). Those at risk should be screened for fracture risk using a standard fracture risk calculator (e.g. Q-Fracture) and treated accordingly. Interventions also include ensuring good motor control and avoidance of ‘off’ periods, a reduction in dys- kinesia, and avoiding postural hypotension. The standard strength and balance exercise approaches to prevention may be insufficient, and there is some evidence for the use of specialized physiotherapy utilizing cueing strategies, cognitive strategies, environmental changes, and assistive devices. A full multidisciplinary assessment is vital in the management of falls in PD and is particularly im- portant in progressive supranuclear palsy. Nonmotor signs and symptoms The number and severity of nonmotor symptoms increases both with age and disease progression. Nonmotor symptoms, particu- larly mental health symptoms, significantly impact quality of life and need special consideration in older people. Many of the nonmotor symptoms arise secondary to autonomic dysfunction, including constipation, urinary symptoms, orthostatic hypoten- sion and sweating (Table 6.10.7).
Table 6.10.4 The multidisciplinary team (MDT) referral and roles Team member Referral Some of the key roles of team members General practitioner Initiates referral Early recognition, referral, continuity of care, prescribing and medicines management, managing comorbidity, link with primary healthcare team Specialist doctor (geriatrician or neurologist) At diagnosis Diagnosis, drug treatment, symptom management, coordination of MDT, education and information, research Specialist nurse At diagnosis Assessment of needs, communication, symptom management, medicines management, support and counselling, education, integration of the service, managing case load, independent prescribing Physiotherapist At diagnosis and active review Monitor and identification of rehabilitation priorities, exercise programme, restoration and compensation of function Occupational therapist Early referral after diagnosis Patient and carer centred assessment, development of goals, address physical and psychosocial problems, enhance participation in everyday activities and self-care Speech and language therapist Early referral after diagnosis Improvement of vocal loudness and pitch range, optimize intelligibility, effective communication, assistive technologies, assess and manage swallowing Dietician Nutrition and weight loss Nutritional screening, advice on weight, review fluid and fibre intake, avoidance of constipation, dietary advice, altered texture of food, food supplements Psychologist Cognition, management of neuropsychiatric symptoms Assessment of cognition, mood and neuropsychiatric symptoms, diagnosis of cognitive impairment, cognitive therapies for cognitive impairment and mood Social worker When care needs increase Nonmedical care needs, advice about services and eligibility, coordination of service providers, advice about care provision Pharmacist Prescription of drug treatments Advice about medications and potential interactions or contraindications, dispense medications, medication reviews, independent prescribing Voluntary body support group Throughout the disease Information and support for patients, carers, and liaison with MDT
Table 6.10.5 Drug treatment: do’s and don’ts for motor symptoms in the older patient Do Do not • Start with L-dopa: low dose, slow titration • Prescribe anticholinergics • Consider increased dose and frequency of L-dopa for motor fluctuations • Suddenly stop treatments • Consider adjunctive drugs; COMT, MAOB, or cautious use of dopamine agonist, for motor fluctuations • Consider apomorphine or intrajejunal L-dopa for advanced treatment • Consider the use of acetylcholinesterase inhibitors for dementia • Ensure patients admitted to hospital get medications

on time COMT, catechol-O-methyltransferase inhibitors; MAOB, Monoamine oxidase B inhibitors. Table 6.10.6 Falls in PD and other neurodegenerative conditions Factors contributing to increasing falls risk in patients with PD Clinical predictors of falls Nonspecific PD-specific • Increasing age • Increasing motor severity • Presence of a previous fall in the last year • Cognitive impairment • Axial rigidity • Evidence of freezing of gait in the last month • Polypharmacy • Freezing of gait • Reduced self-selected gait (less than 1.0 m/second) • Sarcopenia • Motor
fluctuations • Slow timed up and go test
(e.g. taking longer than
12 seconds) • Joint disease • Postural changes • Cardiac • Side effects of PD medications • Visual impairment
and hearing
loss • Autonomic impairment • Co-morbidities • Cognitive
changes

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glycopyrrolate Topical antiperspirant often not effective Suitable clothing and environment Depression Can be early or before PD symptoms and throughout disease SSRI antidepressants. Avoid tricyclic antidepressants Exercise, peer support, group therapy, cognitive therapy Anxiety Can be early or before PD symptoms and throughout disease SSRI antidepressants (those licensed for anxiety) Exercise, peer support, group therapy, cognitive therapy, relaxation Psychosis Illusions and visual experiences common in first 5 years—full psychosis later Reduction in PD drugs Atypical antipsychotics Acetylcholinesterase inhibitor Counselling patients and carer Dementia Mild cognitive impairment common early in older people Dementia later Acetylcholinesterase inhibitor Memantine Multidisciplinary support, liaison with psychiatry a Notes—see Table 6.10.8. MSA, multiple system atrophy; PD, Parkinson's disease; SALT, speech and language therapist; SSRI, selective serotonin reuptake inhibitor. Table 6.10.8 Constipation in PD and related conditions Causes Mechanisms • Changes in the neural plexus of the colon • Colonic dysmotility • Autonomic changes • Anorectal dysfunction • Reduced mobility • A combination of the two • Reduced fluid intake • Poor diet

608 Section 6 Old age medicine neurodegenerative conditions because of the risk of aspiration. The speech therapist will teach compensatory strategies to patients to reduce dribbling and to aid swallowing. In cases with problematic dribbling the use of Botulinum toxin A or B to the parotid and saliva glands can be considered. Anticholinergics are limited by side effects and increased confusion in older people with PD, hence use of sublingual atropine or topical hyoscine should be avoided. There is limited evidence for oral glycopyrrolate (which does not cross the blood brain barrier) and some interest in ipratropium bromide, and the unlicensed use of glycopyrrolate 1–2 mg twice to three times per day can be considered under specialist supervision. L-dopa possibly improves the volitional phase of swallowing. In acutely ill cases short-term enteric feeding might be required. For longer term management, there needs to be consideration and discussion about the potential benefits and burdens of enteral feeding in those with severe swallowing difficulties in late stage disease. Delayed gastric emptying may be helped by advice about meal size and content, and the use of liquid L-dopa. There is no specific management available for the delay in small-bowel transit time. Colonic dysmotility may be helped by increasing fibre and fluid intake and use of osmotic laxatives (macrogol). It is important to ensure regular rather than intermittent use of laxatives to avoid constipation with overflow diarrhoea, although laxatives may ex- acerbate anorectal dysfunction, which may be helped by improve- ment in dopaminergic therapy. It is also important to assess nutritional state and consider re- ferral to a dietician. Appetite may be reduced and food enjoyment changed due to loss of smell. Altering the overall volume and con- sistency of food is likely to reduce food adequacy unless specific adjustments and/or supplements are provided. Urogenital symptoms Sexual dysfunction is common in PD, which is associated with loss of libido and erectile dysfunction. The cause of sexual dysfunction is due to combination of autonomic impairment, mood changes, psychosocial changes, comorbidity, and (in men) age-related tes- tosterone deficiency. Urinary symptoms are common with increasing age but are more prevalent in PD, where they affect up to half of all patients. Symptoms of bladder overactivity include frequency and urgency of micturition. A weak detrusor combined with sphincter dysfunc- tion causes hesitancy and a weak stream of urine. Dysfunction of the sphincter and pelvic floor muscles exacerbate all symptoms. In older men, symptoms commonly overlap with prostatism. Urinary symptoms early in the course of parkinsonism raises the suspicion of the diagnosis of multiple system atrophy, particularly if there is post-voidal residual volume greater than 100 ml. The nature of and cause of sexual dysfunction in older people should be explored through a

specialist clinic. The role of androgen or oestrogen replacement in older people is unclear. For erectile dysfunction, the use of phosphodiesterase inhibitors such as sildenafil can be considered, although they may cause hypotension. In cases of detrusor overactivity, urgency, and frequency, anti- cholinergic drugs that are less likely to cross the blood brain barrier should be considered, such as tolterodine, trospium, or solifenacin. Drugs such as oxybutynin are more likely to cross the blood brain barrier and should be avoided in older people due to their tendency to cause confusion. For patients who have not responded to, or are not suitable for, anticholinergics, the β-3 agonist mirabegron or bladder wall botulinum toxin may also be considered. The results of prostatic surgery and effects on continence in older men with PD are unpredictable. Intermittent self-catheterization may be needed in multiple system atrophy. Cardiovascular symptoms Cardiovascular autonomic dysfunction is common as PD advances, is present early in multiple system atrophy, and is very common in dementia with Lewy bodies. Symptoms include dizziness and light-headedness, falls, loss of confidence when walking, fatigue, and feeling muddled or confused. Patients may also experience pain over the shoulders and into the neck (coat hanger pain), and even angina like pain. Postprandial dizziness is also common. It is important to monitor blood pressure regularly because orthostatic (postural) hypotension may occur in half PD patients. It should be checked after lying for up to 10 minutes (or sitting if this is not feasible), and then on standing at one and again at three minutes. A drop in systolic blood pressure of greater than 20 mm Hg or to below 100 mm Hg, or a drop of 10 mm diastolic, is considered ab- normal. Orthostatic hypotension may be associated with cognitive impairment and dementia. Patients with PD and particularly de- mentia with Lewy bodies may develop neurovascular instability, with associated fluctuations in blood pressure and carotid sinus sensitivity, leading to syncope. The simplest assessment for cardiovascular autonomic dys- function is 24-hour blood pressure monitoring, which will show a reversal of the normal diurnal variation in blood pressure with daytime hypotension interspersed with periods of marked hyper- tension when recumbent or at night. The investigation and man- agement of syncope is considered in more detail in Chapters 6.8 and 16.2.2. Tilt table testing may be undertaken with or without glyceryl trinitrate (GTN) provocation, but detailed tests of auto- nomic function are not normally undertaken in daily practice. Practical management of symptoms includes nonpharmaco- logical interventions as the first line. While drugs may increase standing systolic blood pressure, they may also increase postural blood pressure drop and exacerbate recumbent and nocturnal hypertension. There is little evidence that treatments affect symp- toms, functional ability, or quality of life. The most commonly used drug is fludrocortisone, whose most likely side effect is oedema. The sympathomimetic vasoconstrictor midodrine may be used under specialist supervision with the last dose given in late after- noon to avoid exacerbating night-time hypertension. Other drugs such as pyridostigmine, droxydopa, or desmopressin are restricted to clinical trials. Sleep disorders Sleep disorders may precede the motor symptoms of PD, ultimately affecting over 50% of patients, and they are also common in de- mentia with Lewy bodies and multiple system atrophy. Daytime sleepiness is common in PD, may be more common with increasing age, and is increased by the use of dopaminergic drugs, particularly direct acting agonists. These symptoms are important since they may affect safety, particularly with driving. The use of modafinil may be considered if other causes of sleepiness have been excluded. Rapid eye movement sleep behaviour disorder may also precede

 PD, dementia with Lewy bodies, and multiple system atrophy. In this condition the normal atonia seen in rapid eye movement sleep is lost,

allowing the person to move and shout in sleep, which can be problematic during aggressive dreams. It is important to distin- guish this from night-time hallucinations. Good daytime control of symptoms and control of motor symp- toms in the evening and overnight will enhance sleep quality. The use of long acting L-dopa last thing at night may help night- time symptoms. Continued use of night-time sedation should be avoided due to possible increased risk of falls. Direct acting dopa- mine agonists may be associated particularly with daytime sleepi- ness and should be reduced carefully where this occurs, especially when causing sudden onset of sleepiness. The effects on driving should be reviewed. Rapid eye movement sleep behaviour disorder may benefit from the use of 0.5–1 mg of clonazepam at night. Thermo-regulation Peripheral autonomic dysfunction linked with hypothalamic dopa- mine deficiency is associated with abnormalities of temperature control. This presents with bouts of sweating in over 60% people with PD and may be associated with motor fluctuation. Patients may be noted to have fluctuation in temperature when monitored in hospital. The sweating affects the whole body and is therefore not amenable to local control with antiperspirants. Good control of motor function is the mainstay of treatment. Unlicensed specialist use of the oral glycopyrrolate may be considered. Respiratory problems The ultimate cause of death in many people with PD is broncho- pneumonia and it is suspected that respiratory dysfunction in Parkinson’s may predispose to this condition, along with an in- creased risk of aspiration due to swallowing difficulties. There may be a combined obstructive and restrictive pattern, which often goes unrecognized. Stridor may be a feature of multiple system atrophy. It is important to ensure good motor control, promote physical activity, facilitate good sitting posture, recognize the risk of aspir- ation, ensure care during anaesthesia, and consider pulmonary rehabilitation. Pain Pain is a common symptom and is often unrecognized. It may be due to abnormal central pain mechanisms, neuropathy, dystonia, dyskinesia, and musculoskeletal problems. Shoulder pain can be a presenting feature of PD. Good control of motor function and attention to posture and musculoskeletal symptoms is important. The usual pain pathway should be followed, and patients may need the support of specialist pain services. Neuropsychiatric problems In many ways the maintenance of mental health in PD and other neurodegenerative conditions may be more important than the physical state, since neuropsychiatric problems adversely affect quality of life. Depression and dementia are associated with in- creased mortality. The risk of developing dementia in PD is considerably higher than that of age-matched controls, affecting over 80% of patients in the long term. Dementia is associated with spread of pathology into cortical areas, often associated with an increasing burden of AD and vascular pathology associated with a significant cholin- ergic deficiency. Subtle cognitive impairment may be detected early on in the disease, particularly in older patients. Cognitive impair- ment in PD particularly affects planning or executive function, visuospatial function and attention, rather than memory functions (nonamnestic dementia), whereas in AD the dementia affects pref- erentially memory (amnestic dementia). Dementia and (particu- larly) dyspraxia can be early features of corticobasal degeneration. Dopaminergic medication may help improve cognition in early disease but later may have an adverse effect. Management of de- mentia in PD is similar to the principles involved in the management of other forms of dementia, supported by a specialist multidiscip- linary team with mental health expertise. Acetylcholinesterase in- hibitors such as rivastigmine should be considered under specialist guidance, following pulse and electrocardiogram screening to avoid cardiovascular complications. Memantine may be considered for those intolerant of acetylcholinesterase inhibitors. Although there is great interest in the possible use of nonpharmacological interventions, evidence is currently lacking. Psychosis Hallucinations occur in up to 50% of people with PD and are very common in dementia with Lewy bodies. Drug treatment

adds to the effects of visual disturbances, changes in sleep, cognitive impair- ment and effects of light and shadows to precipitate hallucinations (Fig. 6.10.3). Hallucinations may be visual, usually of animals or people, but occasionally may also be auditory. They may be associ- ated with the secondary development of delusions. People with PD are also prone to delirium, particularly during acute illness, with hallucinations as part of this. An explanation of the nature of the experiences to the patient and carer can often alleviate concerns about hallucinations. Consider gradual reduction of dopaminergic drugs under the supervision of a specialist, particularly focusing on drugs most likely to precipi- tate hallucinations such as anticholinergic drugs or direct acting dopamine agonists (Fig. 6.10.4). It is, however, important to avoid sudden reduction of dopaminergic treatment as this may be asso- ciated with development of hyperpyrexia. Achieving a balance be- tween the benefits of motor control with the risk of hallucinations Brain neurochemical abnormalities Visual dysfunction Environment PD medications Cortical pathology PD psychosis Brainstem/ sleep dysfuntion Fig. 6.10.3 Aetiology of psychosis in Parkinson’s disease (PD).

 will be impacted by individual patient tolerance of symptoms. In the presence of cognitive impairment acetylcholinesterase inhibi- tors may reduce hallucinations. Occasionally low-dose atypical neuroleptics may need to be considered, such as short-term use of quetiapine or specialist use of clozapine. Mood Depression and anxiety are common in PD and other neuro degenerative conditions and may affect 50% of patients. Anxiety may be associated with motor fluctuation. Depression is often under-recognized, particularly in older patients. Dopaminergic therapy should be optimized to reduce motor fluctuations. Nonpharmacological interventions including anx- iety management and cognitive approaches should be considered. Selective serotonin reuptake inhibitors antidepressants may be considered in appropriate cases, but tricyclic antidepressants are usually avoided. There is a potential interaction between se- lective serotonin reuptake inhibitors and tricyclic antidepressants with monoamine oxidase B (MAOB) inhibitors, which can cause hyperpyrexia. Prognosis All neurodegenerative conditions are progressive: no treatment available can modify disease progression, but treatment can sig- nificantly improve quality of life. Progression is usually slow, al- though multiple system atrophy, progressive supranuclear palsy, and (occasionally) dementia with Lewy bodies can progress more rapidly. The final stages of PD, AD, and dementia with Lewy bodies are remarkably similar, with a combination of dementia, psychosis, immobility due to parkinsonism and a requirement for compre- hensive personal and nursing care. Palliative care As neurodegenerative conditions advance it is important to rec- ognize the palliative needs of patients and the support required for carers. Advanced care planning decisions related to complex interventions such as enteric feeding or life-support may need to be considered, and this needs to be done earlier in the more ac- celerated course of progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration. With the development of increasingly severe motor disability, nonmotor problems such as dysphagia, and dementia, the focus of treatment should be on sup- portive care with the minimization of aggressive treatments and interventions. Management should be focused on comfort and quality of life. Many people in the advanced stages of disease may require nursing at home or in a nursing home. Although clinic attendance becomes impossible, ongoing involvement of clinical staff with relevant expertise remains necessary. Close liaison with specialist palliative care services should be considered. Areas of future research In future there will be a greater concentration on research into the relationship between ageing and neurodegeneration and the pre- clinical prodromal periods of all these conditions, since it is hoped that early preventative intervention will reduce progression. There will be an increased understanding of the contribution

of risk fac- tors and susceptibility genes to the aetiology of neurodegenerative conditions in older people, perhaps allowing preventative strat- egies for those at risk of the conditions. It is clear that these con- ditions are extremely complex and the prospect of a single cure for each is unrealistic, but it is more likely that a better understanding of the conditions will lead to a variety of individualized preventa- tive and treatment strategies. FURTHER READING Aarsland D, et al. (2007). The effect of age of onset of PD on risk of dementia. J Neurol, 254, 38–45. Berg D, et al. (2014). Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. Mov Disord, 29, 454–62. Burn DJ (2010). The treatment of cognitive impairment associated with Parkinson's disease. Brain Pathol, 20, 672–8. Campbell N, et al. (2009). The cognitive impact of anticholinergics: a clinical review. Clin Interv Aging, 4, 225–33. Chaudhuri KR, Healy D, Schapira AHV (2006). The non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol, 5, 235–45. Emre M, et al. (2004). Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med, 351, 2509–18. Halliday G, et al. (2008). The progression of pathology in longitudin- ally followed patients with Parkinson's disease. Acta Neuropathol, 115, 409–15. Hawkes CH (2008). Parkinson's disease and aging: same or different process? Mov Disord, 23, 47–53. Hindle JV (2010). Ageing, neurodegeneration and Parkinson's dis- ease. Age Ageing, 39, 156–61. Jenner P, et al. (2013). Parkinson's disease—the debate on the clin- ical phenomenology, aetiology, pathology and pathogenesis. J Parkinsons Dis, 3, 1–11. Kalra S, Grosset DG, Benamer HT (2010). Differentiating vascular parkinsonism from idiopathic Parkinson's disease: a systematic review. Mov Disord, 25, 149–56. Mattson MP, Magnus T (2006). Ageing and neuronal vulnerability. Nat Rev Neurosci, 7, 278–94. McKeith IG, et al. (2005). Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology, 65, 1863–72. Anticholinergics Tricyclics Amantidine Dopamine agonists Apomorphine Other antidepressants COMT MAOB L-dopa Fig. 6.10.4 Stepwise drug adjustment and withdrawal in psychosis in PD.

 Mosimann UP, et al. (2006). Characteristics of visual hallucinations in Parkinson disease dementia and dementia with lewy bodies. Am J Geriatr Psychiatry, 14, 153–60. Muzerengi S, Clarke CE (2015). Initial drug treatment in Parkinson's disease. BMJ, 351, h4669. National Institute for Health and Clinical Excellence (NICE) (2017). Parkinson's disease in adults. [NG71]. https://www.nice.org.uk/ guidance/ng71 Petrou M, et al. (2015). Amyloid deposition in Parkinson's disease and cognitive impairment: a systematic review. Mov Disord, 30, 928–35. Playfer J, Hindle J (eds). Parkinson's disease in the older patient, 2nd edition. Radcliffe, Oxford. Scottish Intercollegiate Guideline Network (2010). Diagnosis and pharmacological management of Parkinson's disease. Guideline No. 113. Shin HW, Chung SJ (2012). Drug-induced parkinsonism. J Clin Neurol (Seoul, Korea), 8, 15–21. Srivanitchapoom P, et al. (2014). Drooling in Parkinson's disease:
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