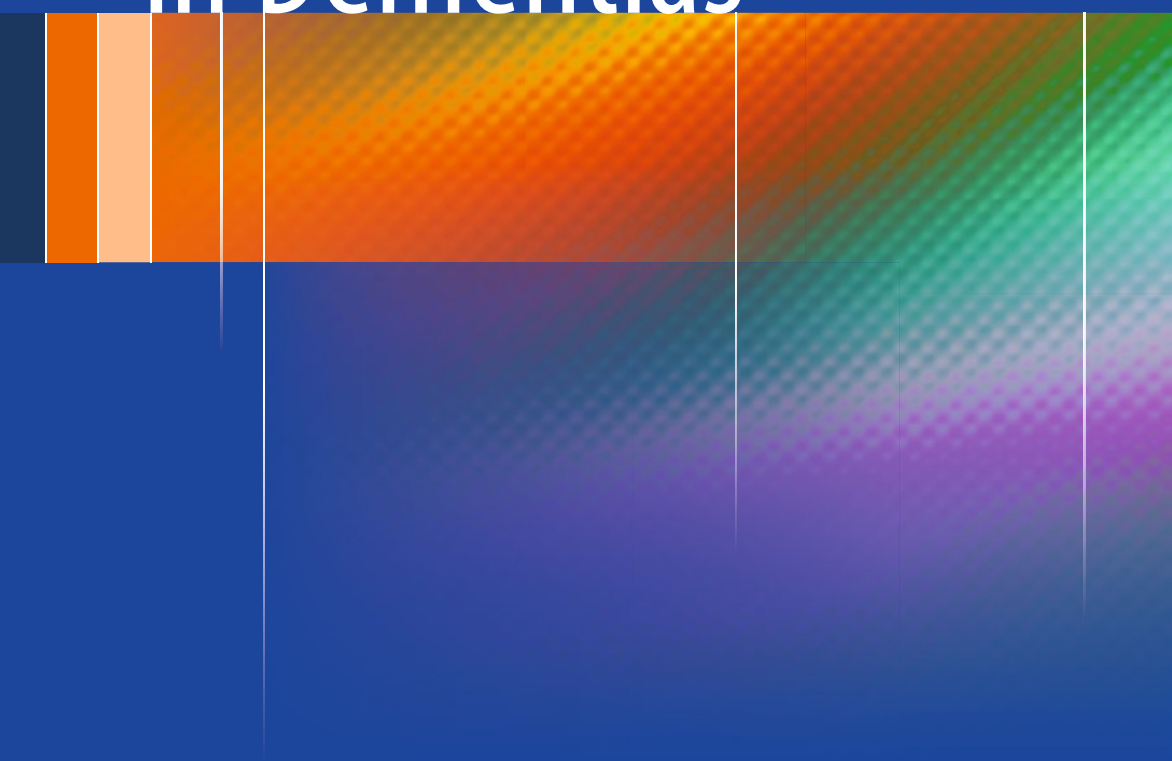
Marcelo Merello
Sergio E. Starkstein *Editors*

Movement Disorders in Dementias



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Marcelo Merello • Sergio E. Starkstein
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To our fathers, Jorge and Leonardo, and to our 20 years of uninterrupted friendship.

MM and SS

Foreword

Neurologists today need to deal in their daily practice with cognitive impairment in patients with movement disorders, particularly but not limited to those with Parkinson's disease. This book offers a somewhat opposite view, which is the occurrence of movement disorders in patients in whom dementia is the primary clinical manifestation. Movement disorders, as currently understood, comprise a large variety of conditions, not all of which are related to basal ganglia dysfunction. However, the contribution of the ascending dopaminergic projection to cognitive processing is well known, and, indeed, the now old-fashioned concept of "subcortical" dementia originated from observations in patients with progressive supranuclear palsy. On the other hand, it is now recognized that cognitive impairment very often evolves in parallel with altered gait and equilibrium and that the pathology of many neurodegenerative diseases is sufficiently widespread to impinge upon several circuits and brain regions, thus producing multiple clinical combinations. No doubt, dementia and movement disorders are a current hot topic.

Drs. Merello and Starkstein, therefore, deserve the most sincere and warm congratulation for this initiative and the outcome. This book provides a comprehensive account of a variety of different movement disorders in the setting of the major diseases and processes associated with cognitive impairment. The list of authors is impressive, as experts in the field have written each chapter. Nowadays, the world of publishing is moving quickly toward electronic editions only in what seems an inevitable trend. However, Merello and Starkstein's *Movement Disorders in Dementias* is exactly the book one wants to have on the desk to read leisurely and consult very often when thinking about specific patients with cognitive and motor impairments. I am looking forward to the smell of a new, just-printed, highly intellectual work!

Pamplona, Spain — Jose A. Obeso, MD, PhD

Preface

Since the end of the twentieth century, the cognitive and psychiatric comorbidities of movement disorders have received increasing attention. On the other hand, the study of movement disorders in dementia has been relatively neglected. To our knowledge, there are no specific books devoted to clarify the variety, mechanism, and treatment of motor problems in dementia.

It was 14 years ago that we decided to write a book on the non-motor problems of Parkinson's disease (PD). By then, research and clinical evidence were rapidly accumulating regarding the high frequency of specific cognitive deficits, affective disorders, and anxiety in PD. Apathy was also emerging as a prominent comorbid condition of PD, and the mechanism and treatment of psychotic symptoms were an area of intense investigation. We now present a book that inverts that focus, that is, it examines the motor problems in dementias due to different mechanisms.

An increasing number of studies have demonstrated a high frequency of parkinsonism and other movement disorders such as myoclonus, paratonia, and dyskinesia in Alzheimer's disease (AD). In addition, the introduction of medication to treat the cognitive impairment as well as novel antipsychotic drugs contributed to the variety and severity of movement disorders in AD. The association between dementia and movement disorders is also evident in the high proportion of patients with frontotemporal dementia and comorbid parkinsonism and the association between cognitive deficits and a variety of movement disorders such as the "alien hand syndrome" and "psychomotor" symptoms such as apraxia in corticobasal syndrome.

Cognitive dysfunction and parkinsonism are closely related, and regardless of which of them is the primary problem, the other is invariably present. For many years, dementias and parkinsonism have been separately addressed, through different specialties, by different researchers, and in different books and journals. However, emerging concepts on topics such as neurodegeneration with synucleinopathies, tauopathies, and amyloid deposit mechanisms have generated a trend to lump these disorders together.

In his masterpiece *The History of Mental Symptoms*, German Berrios asks what he considers the crucial question in the history of PD: why did it take so long for cognitive and psychiatric symptoms to be considered part and parcel of PD? The

answer to this question is that patients did not live long enough to show the non-motor comorbidities or that, following James Parkinson's description, neurologists refused to accept their presence. Perhaps a similar process occurs in dementia, with most of the focus being given to the cognitive aspects of this disorder, while the motor aspects are not so well attended. It is interesting that in his seminal paper "On the relationship between senile cerebral atrophy and aphasia," Arnold Pick already described motor problems in patients with dementia. The patient Augustus H had brisk knee reflexes and a fast clonus, a 52-year-old man developed progressive weakness of the right extremities and speech disturbance, and the third patient complained of pain in the right leg "gradually losing the use of it."

This book will mainly focus on extrapyramidal signs and symptoms in the most common or novel types of dementia and will address the issue of the artificial boundary between dementia and parkinsonism, the two most common degenerative disorders.

Recognized specialists in the field of movement disorders provided chapters on topics generally restricted to dementia experts. The first chapters address important general aspects on the relationship between motor disorders and dementia, such as the association between medications and motor problems, and motor disorders common to many types of dementia, such as gait disorders, falls, and motor manifestations of psychiatric complications of dementia. The following chapters provide an in-depth analysis on the relationship between motor and cognitive symptoms, addressing their common pathogenesis and specific treatments.

The book was timely written in 1 year, which warrants up-to-date information and views. We hope we have covered the topic widely enough, so that the book will appeal to a wide readership, including general practitioners, gerontologists, and neurologists. We expect this book to become the main reference in the field for years to come.

Buenos Aires, Argentina — Marcelo Merello, MD, PhD
Fremantle, WA, Australia — Sergio E. Starkstein, MD, PhD

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Chapter 1
Neurodegenerative Disorders: Dementia and Parkinsonism, Lumping Together or Splitting Apart?

Marcelo Merello and Malco Rossi

Abstract Neurodegenerative diseases encompass several entities characterized by variable clinical features. Clinical presentation, anatomical regions affected, neuropathology, or molecular aspects of this group of diseases overlap frequently, rendering the "perfect" classification an almost impossible mission in many cases despite presence of the hallmark molecular findings. In this chapter, we will review the different classifications of neurodegenerative disorders as well as the artificial boundaries between movement disorders and dementias.

Keywords Dementia • Parkinsonism • Amyloidopathies • Tauopathies • Synucleinopathies • FUSpathies • Filament inclusion disorders

Introduction

Neurodegenerative diseases are characterized by death and progressive loss of neurons in distinct areas of the central nervous system. Classification is based on clinical presentation, anatomical regions affected, inclusion bearing cell type, and conformational protein altered. Clinical features resulting from these mechanisms reflect which anatomical regions or functional systems are affected by neuronal damage and include cognitive decline, dementia, alteration in high-order brain functions, movement disorders, or, in the majority of cases, a combination of all of these.

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Traditionally, neurodegenerative diseases are categorized according to the specific clinical features observed and/or distinctive underlying neuropathology (Graeber et al. 1997; Duckett and Stern 1999). However, heterogeneity between them is common, and several authors have therefore questioned the validity of this classification (Armstrong 2008; Armstrong et al. 2005; Feany and Dickson 1996; Förstl 1999; Hainfellner et al. 1998). Although attempts to overcome these drawbacks have been made by putting together guidelines after agreements among leading experts on which represent the most useful clinical and pathological features for diagnosis (Litvan et al. 1996; Tierney et al. 1988), they are still not enough. The discovery of aggregates of insoluble and/or misfolded proteins has led to further molecular classifications, establishing a "hallmark molecular finding." However, even this degree of characterization has been unable to rule out overlap or coexistence of clinical and/or neuropathological features of more than one disorder in the same individual (Armstrong et al. 2005).

The Risk of Classification

In 1942, the great Argentine writer Jorge Luis Borges wrote an essay entitled "*El idioma analítico de John Wilkins*" (The Analytical Language of John Wilkins) in which he laid out the challenges of human attempts to classify the world (Borges 2001). To illustrate his argument, Borges reproduced a classification of animals purportedly found in "a certain Chinese encyclopedia entitled "Celestial [Emporium]" of Benevolent Knowledge." Borges observed that "it is clear that there is no classification of the Universe not being arbitrary and full of conjectures." It may appear odd that Borges should see conjectures in classifications, which are by definition rather explicit. This is because he considered that a full understanding of things to be classified and of their mutual relationships is necessary for the classification to make sense (Borges 2001).

Over 100 neurodegenerative disorders affect humans, among which many overlap either clinically or pathologically, rendering their practical classification most challenging. The issue is further complicated by the fact that different combinations of lesions can give rise to different clinical conditions (Luheshi and Dobson 2009; Burn and Jaros 2001). Furthermore, the same neurodegenerative processes, especially at the beginning, can affect different areas of the brain, thus varying significantly at different stages of the neurodegenerative process.

Classic categorization of neurodegenerative disorders is based on predominant lesion topography. Thus, they may be grouped, for instance, as cortical, of the basal ganglia, cerebellum, or as motoneuron disorders. Or diseases may be classified based on main clinical features into dementias, movement disorders, motoneuron disease, or ataxias. However, topographical classification of the disorders does not coincide with expected clinical manifestations. So neurodegeneration predominantly affecting the cerebral cortex may induce dementia or other non-dementing conditions, whereas diseases that predominantly involve the basal ganglia in

addition to movement disorders also produce dementia in most cases. To make things ever more confusing, accompanying signs arising from autonomic dysfunction, pyramidalism, and ocular movements are also often present.

Over the past three decades, significant advances in histological techniques such as immunohistochemistry and the incorporation of gene array, PCR, Western blot, and laser-guided micro dissection have supplemented classical histological approaches. These new techniques have improved both sensitivity and specificity of neuropathological diagnostic criteria and significantly influenced the classification. Based on the use of these novel technologies, new perspectives pushed the classification to be structured on molecular characteristics and to no longer depend on neuropathological hallmarks or clinical signs and symptoms. However, using this more modern approach, neuropathological entities that used to belong to very distinct clinical or neuropathological categories were lumped together because of a common molecular defect.

For example, disorders characterized by dementia, chorea, ataxia, or myopathy such as HD, spinal cerebellar atrophy, and myotonic dystrophy now fall into the category of the trinucleotide repeat diseases (Cummings and Zoghbi 2000); Creutzfeldt–Jakob disease and fatal familial insomnia fall into the category of the prion diseases (Prusiner 1998); PD, diffuse Lewy body dementia, and multiple system atrophy fall into the category of the synucleinopathies (Galvin et al. 2001), whereas diverse disorders such as corticobasal degeneration, progressive supranuclear palsy, frontotemporal dementia, motoneuron, and Pick disease fall into the category of the tauopathies (Goedert 2001).

Models of Neurodegenerative Diseases

The complexity linked to classifying the majority of patients seen in clinical practice testifies the extent to which the boundaries between different disorders may in reality be less distinct than previously believed and have inspired some researchers to suggest that neurodegenerative diseases characterized by abnormal protein deposits should be viewed as existing along a continuum of symptoms and pathologies, rather than as discrete entities. For instance, Armstrong et al, in an elegant review (Armstrong 2012), have postulated that different models of neurodegenerative disorders could be argued. They hypothesize that although distinct diseases may exist (“discrete” model), they may also exhibit overlapping features (“overlap” model), and the most challenging concept they put forward is that distinct diseases do not really exist, but form part of a “continuum” in which there is constant variation in clinical/pathological features from one case to another (“continuum” model). This last one would infer that many different pathways may exist through which different individuals ultimately present the same process, abnormal protein deposition. It is worth noting that the “hallmark molecular findings” themselves are not necessarily the cause of the underlying disease and clinical symptoms. Instead they may be a response to the disease processes, although at some stage the “hallmark

molecular finding" may actually begin to contribute to disease progression. A more detailed look at the pathology associated with diseases present along this spectrum reveals not only abnormal protein deposits but also widespread evidence of an underlying chronic inflammatory reaction, characterized by activated microglia and upregulation of various inflammatory markers.

Clinical Classification

Neurodegenerative diseases are usually classified depending upon the predominating clinical syndrome. Therefore, they are usually divided into those in which the main symptom is mental decline, the dementias, those where the main effect causes movement disorders like parkinsonism, or the ataxias or motoneuron diseases. When the affected anatomical region is the element taken into consideration, then they are classified according to topography as cortical, of the basal ganglia, cerebellar, and motoneuron disorders. However, while AD is by far the most frequently cited cause of dementia affecting cerebral cortex anatomy (Ott et al. 1995), it can be also observed as a prominent feature of many other diseases affecting the caudate, the putamen, the substantia nigra, the red nucleus, certain thalamic and brainstem nuclei, the cerebellum, or even the motoneurons. As is the case of Huntington's chorea, a widely known basal disorder in which dementia is a very, if not the most, common feature (Paulsen 2011), the high prevalence of dementia in Parkinson's disease (Dubois et al. 2007), ataxic patients (Braga-Neto et al. 2012; Valis et al. 2011), or even in patients with amyotrophic lateral sclerosis (Goldstein and Abrahams 2013) is no less frequent.

The opposite situation occurs in dementias with clear cortical involvement such as presenilin mutation in AD (Niwa et al. 2013), FTD (Espay and Litvan 2011), PPA (Kremen et al. 2011), Creutzfeldt–Jakob disease (Maltête et al. 2006), or even argyrophilic grain disease (Uchikado et al. 2004) in which parkinsonism is a prominent feature. Some diseases of the cerebellum can readily be grouped into pure ataxias; mixed forms where lesions affect several cerebellar and brain structures or even the spinal cord, as is the case in Friedreich ataxia; or lower and upper motor neurons, substantia nigra, and peripheral nerve in Machado–Joseph disease (Koeppen and Mazurkiewicz 2013; Rüb et al. 2008).

Movement disorders are neurologic syndromes in which there is either an excess of movement or a paucity of voluntary and automatic movements unrelated to weakness or spasticity (Fahn et al. 2011). Excessive movements or hyperkinesias, dyskinesias, and abnormal involuntary movements are terms used interchangeably. Paucity of movement is characterized by decreased amplitude of movement also referred to as hypokinesia. Slow movement or bradykinesia is a term used interchangeably with loss of movement or akinesia. The long list of causes of parkinsonian syndromes including Parkinson's disease and Parkinson´s plus are the most common and representative cause of paucity of movement, while Huntington's chorea and dystonia are the most emblematic hyperkinetic disorder syndromes (Fahn et al. 2011) (Table 1.1).

Table 1.1 Classification of movement disorders

Hypokinesias: Akinesia/bradykinesia (parkinsonism), freezing phenomenon, gait apraxia, hesitant gaits blocking (holding) tics, hypothyroid slowness, cataplexy and drop attacks, rigidity catatonia, psychomotor depression, and obsessional slowness stiff muscles
Hyperkinesias: Dyskinesias, moving toes and fingers, akathitic movements, myoclonus ataxia/asynergia/dysmetria, myokymia and synkinesis, athetosis
Myorhythmia, ballism, paroxysmal dyskinesias, chorea, periodic movements in sleep, dystonia, REM sleep behavior disorder, hemifacial spasm, restless legs
Hyperekplexia, stereotypy, hypnogenic dyskinesias, tics, jumping disorders
Tremor

Fahn et al. (2011)

Table 1.2 Classification of parkinsonian disorders

Primary (idiopathic Parkinson's disease)
Secondary (infectious, toxins, drugs, tumor, trauma, vascular, metabolic)
Parkinson´s plus syndromes (MSA, PSP, corticobasal degeneration, parkinsonism dementia complex of Guam)
Parkinsonisms of dementias (DLBD, AD, FTDP-17, CJD)
Heredodegenerative disorders (Wilson, NBIA, Huntington's, and spinocerebellar-nigral degenerations SCA 1-2-17, neuroacanthocytosis, DRPLA, neuronal inclusion body disease Niemann–Pick type C, Gaucher, PLA2G6-associated disorders)
Benign parkinsonism (Dopa-responsive dystonia, SWEDD)

Parkinson´s plus disorders is a term proposed by Stanley Fahn and refers to disorders with features of parkinsonism in addition to other neurologic feature, such as ophthalmoplegia, ataxia, dysautonomia, amyotrophy, cortical signs, cerebellar signs, or dementia. This group presents multiple system atrophies (parkinsonian, cerebellar, and mixed forms), including corticobasal degeneration, PSP, parkinsonism, and motor neuron disease. Combination of parkinsonism with dementia such as in Guamanian complex, Creutzfeldt–Jakob, Alzheimer's, and Pick, as well as various hereditary diseases in which parkinsonism and dementia can be present together, such as Wilson, NBIA, Huntington's, and spinocerebellar-nigral degenerations, are also included in the classification. Other non-degenerative disorders such as normal pressure hydrocephalus also correspond to this category. Parkinsonism occurring in dopa-responsive dystonia, also known as benign parkinsonism, which can have its onset in adults but is also seen in children, completes the group (Table 1.2).

Dementia is a clinical syndrome characterized by acquired loss of cognitive and emotional abilities, severe enough to interfere with daily functioning and quality of life. Several dementia classifications have been attempted from the clinical point of view (Table 1.3). Neuropsychological profiles of dementia reflect the impact of disease on distinctive neuroanatomic networks associated with complex cognitive domains. For example, prominent amnesia is associated with medial temporal dysfunction, whereas aphasia is a consequence of left perisylvian dysfunction. The relationship between clinical symptoms and underlying neuropathology, however, is less straightforward, as indicated by the multiple neuropathological diagnoses associated with the various clinical dementia syndromes (Mesulam 2000). It has been

Table 1.3 Classification of dementia

Dementia of Alzheimer's type (DAT)
Dementia of frontal lobe type and Pick disorders
Behavioral variant of FTD
Primary progressive aphasia
Semantic dementia
Nonfluent variant of PPA
Logopenic variant of PPA
Dementia with parkinsonism
DLBD
LB variant of AD
Progranulin mutation AD
PD-D
Dementias due to prions
Atypical dementia syndrome: CBD, progressive subcortical gliosis, PSP, Huntington's disease, cerebellar degeneration (OPCA, SCA), ALS
Non-degenerative Dementias
Vascular
Nonvascular

long said from both the clinical (Pillon et al. 1993) and etiological perspectives (Darvesh and Freedman 1996) that dementia can be split into cortical and subcortical types. The typical clinical findings of cortical dementing processes include prominent memory lost, dyscalculia, dysphasias, dyspraxias, and agnosias. The differentiating features of subcortical dementia were said to be a profound slowing of cognition, milder memory disturbances, frontal executive dysfunction, and changes in personality and affect in the absence of aphasias, apraxias, and agnosias (Cummings 1986). While this has been initially generally accepted, other authors have highlighted the difficulties with the distinction, arguing that the neuropsychological profiles of cortical and subcortical cases are not sufficiently dissimilar (Brown and Marsden 1988). Furthermore, cortical symptomatology can often occur in the so-called subcortical disease and vice versa (Hughes et al. 1993). Perhaps constant redefinition and reclassification of the frontotemporal syndromes represent the best example of overlap and lack of boundaries between cortical and subcortical motor and cognitive disorders. The psychiatric manifestations of subcortical disease come primarily in the form of personality changes and affective disorders. Apathy and irritability are particularly common (Aarsland and Karlsen 1999), and depression is said to be significantly more common in subcortical disorders such as Parkinson's disease than in Alzheimer's (Aarsland and Karlsen 1999). While amnestic symptoms of dementia have the highest likelihood of being associated with dementia of AD type (DAT) pathology, early aphasia, progressive visuospatial deficits, and changes in personality are usually seen in primary progressive aphasias, semantic dementia, or behavioral forms of frontotemporal dementia, which can also be associated with AD neuropathology (Figs. 1.1 and 1.2). As dementia progresses from early to late stages, symptom domain boundaries become blurred, and distinctive profiles disappear, with dementia becoming a single terminal clinical entity.

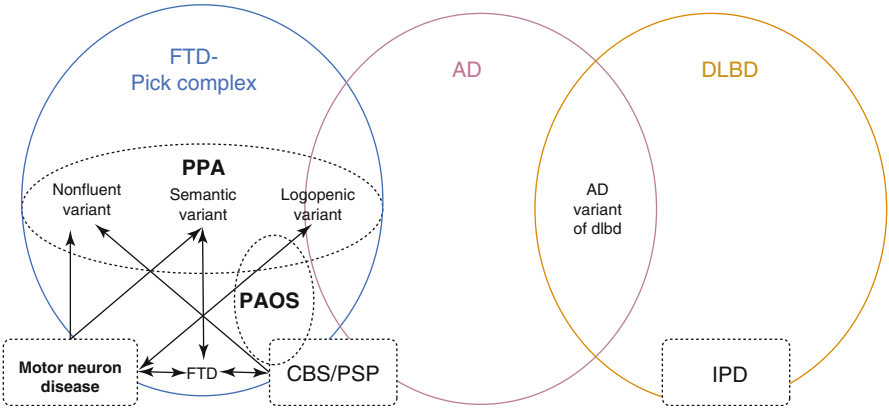

Fig. 1.1 Clinical and molecular relationship within the main types of dementia (*circles*) and between them and the major movement disorders syndromes (*squares*). *FTP* frontotemporal dementia, *AD* Alzheimer's disease, *DLBD* dementia with Lewy bodies disease, *PPA* primary progessive aphasia, *PAOS* progressive apraxia of speech, *CBS* vorticobasal syndrome, *PSP* progressive supranuclear palsy, *IPD* idiopathic Parkinson's disease

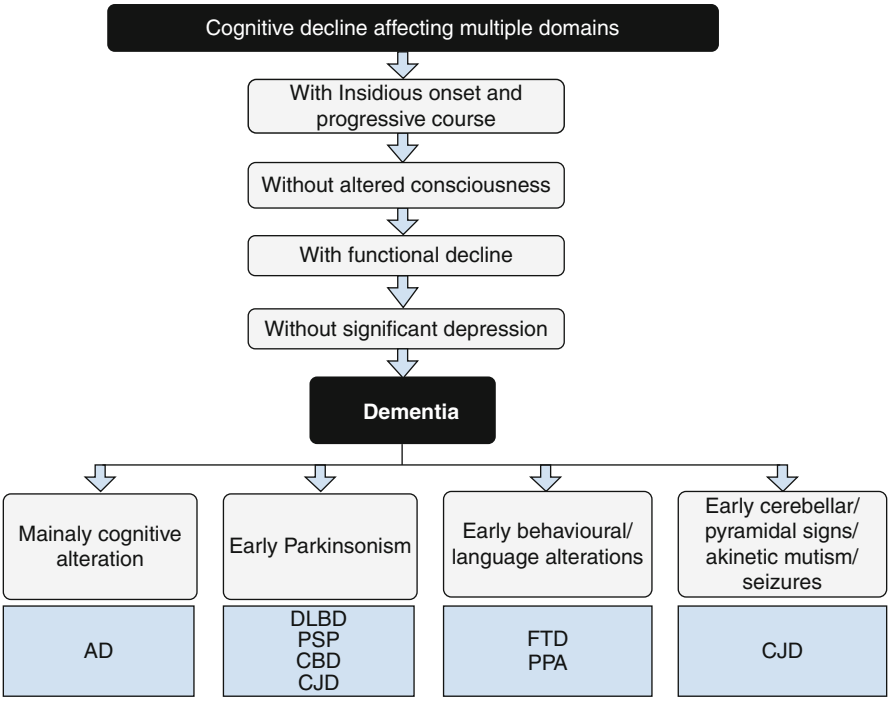

Fig. 1.2 Clinical algorithm for dementias

Molecular Classification

Recognition of a common mechanistic theme shared by many neurodegenerative disorders began to emerge in the last two decades. Many of these disorders are characterized neuropathologically by intracellular and/or extracellular aggregates of proteinaceous fibrils implicated in progressive brain degeneration. Thus, despite differences in the molecular composition of these filamentous lesions, growing evidence suggests that similar pathological mechanisms may underlie all these disorders.

Onset and progression of brain degeneration in neurodegenerative disorders may be linked to abnormal interactions between brain proteins, leading to their assembly into filaments, and aggregation of these filaments within brain cells or in the extracellular space. Originally, the majority of neurodegenerative disorders were classified into two major molecular groups: tauopathies (AD, PiD, argyrophilic grain disease (Saito et al. 2004; Goedert 2001a, b), PSP, corticobasal degeneration, and FTDP-17) and the synucleinopathies, (PD, DLB, and multiple system atrophy) (Goedert 2001a, b). However, a substantial number of cases lack both α-synuclein-immunoreactive inclusions and tau filaments. Furthermore, presence of amyloid beyond the accepted limits of normal aging strongly supports the hypothesis of its role in neurodegeneration. Imbalance between production and clearance, as well as aggregation of peptides, causes Aβ to accumulate, and this excess may be the initiating factor in Alzheimer's disease. However, Aβ has also been increasingly found in PD, DLBD, and other neurodegenerative disorders (Kotzbauer et al. 2012; Jellinger and Attems 2008) (Table 1.4).

β-Amyloid (Aβ): Amyloidopathies

β-Amyloid derives from the amyloid precursor protein (APP). APP undergoes proteolytic cleavages by β- and γ-secretases to generate β-amyloid (Kayed et al. 2003). Since secretases are linked to presenilin genes, presenilins are implicated in the proteolytic

Table 1.4 Molecular classification of neurodegenerative disorders

Amyloidopathies
Tauopathies
RNA–DNA binding proteins: TDP-43 and FUSpathies
Neuronal intermediate filament inclusion disorders
Synucleinopathies
Non-Lewy body synucleinopathies
Non-synucleinopathies with Lewy bodies
Polyglutamine disorders
Prion diseases
Neurodegeneration with brain iron accumulation and neuroferritinopathies
Mixed disorders

cleavage of APP. APP fragments may undergo degradation or oligomerization and extracellular plaque formation, which is a characteristic feature of the neuropathology of Alzheimer's disease (AD). In addition, 1–40 and 1–42, carboxy-terminally truncated Aβ peptides (1–37, 1–38, 1–39) may be found. As there is evidence that Aβ42 is toxic to cells (Selkoe 2001; Tanzi and Bertram 2005), it has been implicated in AD pathogenesis (Hardy 2006), known as the AD "amyloid hypothesis."

Amyloid has also been implicated in the genesis of inherited disorders such as in British and Danish familiar dementia. Elongated proteolytic processes resulting from mutation in the ITM2B gene lead to release of amyloidogenic peptides ABRI (Familiar British dementia) and ADAN (Familiar Danish dementia), which cause cerebral angiopathy and deposition of extracellular protein aggregates in combination with neurofibrillar degeneration (Holton et al. 2001, 2002).

Tau: Tauopathies

Tau is a microtubule-associated protein (MAP) that stabilized them and promotes their assembly. Six different isoforms of tau are expressed in the adult human brain. Neurofibrillary inclusions of tau protein are present not only in AD accompanying amyloid pathology but also in a wide range of neurodegenerative disorders. Even initially they were considered a nonspecific response of neurons to diverse noxa, discovery of mutations in the tau gene (MAPT) in frontotemporal dementia linked to chromosome 17 (FTDP-17) (Hutton 2001) highlighted its role in neurodegeneration. As a result, a long list of disorders displaying tau filaments have been grouped together under the name of tauopathies, which includes Pick disease, corticobasal degeneration, and progressive supranuclear palsy, among others (Ludolph et al. 2009; Galpern and Lang 2006).

RNA–DNA Binding Proteins: TDP-43 and FUSpathies

The major proteins, but not the only ones, that accumulate in the most common forms of FTD and ALS are RNA–DNA binding proteins and mutations in the TDP-43 gene, found in both disorders (Neumann et al. 2006). Another member of the family, the FUS-TLP, has been found mutated and accumulated in neuronal inclusions in rare forms of FTD and ALS (Mackenzie and Rademakers 2007).

Neuronal Intermediate Filament Inclusion Disorders

Neuronal intermediate filament inclusion disorders (NIFID) is a relatively new term referring to a heterogenic phenotype, in which patients present a range of symptoms

starting with dementia, progressing to movement disorders and ending in motoneuron disease. The disorder is characterized by neuronal and glial inclusions of FUS, plus spheroid cytoplasmatic and axonal inclusions conformed by intermediate filament (IF) (Mackenzie et al. 2010).

α-Synuclein: Synucleinopathies

Since α-synuclein was identified as the major structural component of Lewy bodies, Parkinson's disease was raised to the level of major class disease.*α-Synuclein is a phosphoprotein*. The physiological function of α-*synuclein* is not known; it is a lipid-binding protein located in neurons at the synapse level, where it is involved in vesicle traffic and neurotransmission (Goedert 2001a, b; Abeliovich et al. 2000). Other functions such as chaperone protein, inhibitor of phospholipase D2, and participation in oxidative stress have also been described. Lewy bodies are intracytoplasmic inclusions containing α-synuclein aggregations and the hallmark pathological signature of Parkinson's disease and diffuse Lewy body disease. However, they are also present in 7–37 % of normal aging individuals (Zaccai et al. 2008) and most notably in cases of Alzheimer's disease (Hansen et al. 1990).

Non-Lewy Body α-Synucleinopathies

In certain circumstances, α-synuclein pathological aggregates may not form Lewy bodies but α-synuclein-immunoreactive oligodendroglial inclusions, known as glial cytoplasmatic inclusions, as in the case of multiple system atrophy (Papp et al. 1989).

Lewy Bodies in Disorders Other than Synucleinopathies

Aside from being present in normal aging, Lewy bodies have been described in conditions other than α-synuclein disorders such as AD, PSP, Guam disease, FTD, and Down syndrome (Ozawa et al. 2004; Uchikado et al. 2006; Dickson et al. 2002; Jellinger 2008; Yamazaki et al. 2000; Gregory et al. 2009). Less commonly, they have also been found in *Niemann–Pick type* C, a sphingolipid storage disorder which results from autosomal recessive inherited deficiencies of lysosomal and intracellular lipids, trafficking proteins (Carstea et al. 1997). *Acid β-glycosidase-associated neurodegeneration* is an inherited disorder in which an enzyme known as β-glycosidase loses its capacity to catalyze glucosylceramide breakdown to ceramide causing Gaucher disease types I, II, and III (Clark et al. 2009; Sidransky

et al. 2009) and *PLA2G6-associated disorders*. PLA2G6 mutations which encode phospholipase A2 include a series of disorders from infantile neuroaxonal dystrophy to juvenile onset dystonia parkinsonism (Morgan et al. 2006; Paisan-Ruiz et al. 2009).

Polyglutamine Disorders

Huntington's disease is the pathognomonic disorder in which a genetic mutation encoding abnormal expansions of preexisting tandem repetition of bases (from triplets to quintuplets) present in different genes leads to molecular changes resulting in polyglutamine aggregation and further neurodegeneration. Besides HD (Ross and Tabrizi 2011), abnormal tandem of bases expansions are responsible for Friedreich ataxia (Patel and Isaya 2001), spinal bulbar atrophy (Katsuno et al. 2012), dentatorubropallidoluysian atrophy (Koide et al. 1994), and the full range of spinocerebellar ataxias (SCA) (Durr 2010).

Prion Diseases

Abnormal conformers of normal cellular proteins with increased tendency to aggregate and be transmissible from cell to cell carrying infective properties (Lee et al. 2010) have been named prions and are unequivocally implicated in hereditary and sporadic neurodegenerative disorders, including Creutzfeldt–Jakob. Genetic predisposition has been found in a polymorphism of the prion protein gene (PRNP) present even in sporadic cases (Mead et al. 2009).

Neurodegeneration with Brain Iron Accumulation

NBIA corresponds to a group of disorders characterized by brain iron accumulation, axonal swelling, and presence of spheroids. NBIA type I is a neurodegenerative disorder characterized by dementia, parkinsonism dystonia, and choreoathetosis caused by a mutation of the pantothenase kinase gene (PANK2) (Zhou et al. 2001). Although suggested, it remains to be proven whether cases with brain iron accumulation and neurodegeneration due to mutation of the PANK2 gene are associated with Lewy body pathology (Gregory et al. 2009). NBIA type II represents a more heterogeneous group of disorders including infantile neuroaxonal dystrophy, a condition which produces psychomotor retardation, hypotonia leading to tetraparesis, areflexia, cerebellar signs, rigidity, deafness, blindness, and mental deterioration, caused in general by a mutation in the PLA2G6 gene (Khateeb et al. 2006).

Neuroferritinopathies

Recent genetic and molecular data have led to considerable changes in the classification and nomenclature of tauopathies (Williams 2006; Hasegawa 2006; van Slegtenhorst et al. 2000). Original simplistic molecular classifications have become considerably more complex, mainly as a result of studies performed in FTD group cases. In light of the described complexity, discrimination between different disease entities is often only possible after describing the location of "hallmark molecular inclusions." These may be in the cytoplasm (neuronal cytoplasmatic inclusions NCI), in the nuclei (neuronal intranuclear inclusions NII), or in glial cells (glial inclusions GI). The latter may in turn be glial cytoplasmic inclusions (GCI) or astrocytic "plaques" (Neumann et al. 2006).

Conclusion

Neurodegenerative diseases encompass several entities characterized by variable clinical features. Clinical presentation, anatomical regions affected, neuropathology, or molecular aspects of this group of diseases overlap frequently, rendering the "perfect" classification an almost impossible mission in many cases despite presence of the hallmark molecular findings. The accepted fact that distinct diseases exist as unique entities is jeopardized in many cases by the fact that distinct diseases exist but exhibit overlapping features. The concept that distinct diseases do not exist and neurodegenerative diseases represent a "continuum" in which there is progressive variation in clinical/pathological features from one case to another, allowing them to be lumped together, is hard to reconcile with current knowledge, unless neurodegenerative disease were considered as points of a multidimensional continuum. The fact remains that none of the current classification are free from arbitrary definitions and all are plagued by conjectures.

References

Aarsland D, Karlsen K. Neuropsychiatric aspects of Parkinson's disease. Curr Psychiatry Rep. 1999;1(1):61–8.

Abeliovich A, Schmitz Y, Fariñas I, et al. Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. Neuron. 2000;25:239–52.

Armstrong RA. The interface between Alzheimer's disease, normal aging and related disorders. Curr Aging Sci. 2008;1:122–32.

Armstrong RA, Lantos PL, Cairns NJ. Overlap between neurodegenerative disorders. Neuropathology. 2005;25:111–24.

Armstrong R. On the 'classification' of neurodegenerative disorders: discrete entities, overlap or continuum? Folia Neuropathol. 2012;50(3):201–18.

Borges JL. John Wilkins' analytical language. In: Weinberger E et al., editors and trans. The total library: non-fiction 1922–86. London: Penguin Books; 2001. p. 229–32.

Brown RG, Marsden CD. 'Subcortical dementia': the neuropsychological evidence. Neuroscience. 1988;25(2):363–87.
Braga-Neto P, Felicio AC, Hoexter MQ, et al. Cognitive and olfactory deficits in Machado-Joseph disease: a dopamine transporter study. Parkinsonism Relat Disord. 2012;18(7):854–8.
Burn DJ, Jaros E. Multiple system atrophy: cellular and molecular pathology. Mol Pathol. 2001;54:419–26.
Carstea ED, Morris JA, Coleman KG, et al. Niemann-Pick C1 disease gene: homology to mediators of cholesterol homeostasis. Science. 1997;277:228–31.
Clark LN, Kartsaklis LA, Wolf Gilbert R, et al. Association of glucocerebrosidase mutations with dementia with Lewy bodies. Arch Neurol. 2009;66:578–83.
Cummings CJ, Zoghbi HY. Trinucleotide repeats: mechanisms and pathophysiology. Annu Rev Genomics Hum Genet. 2000;1:281–328.
Cummings JL. Subcortical dementia. Neuropsychology, neuropsychiatry, and pathophysiology. Br J Psychiatry. 1986;149:682–97.
Darvesh S, Freedman M. Subcortical dementia: a neurobehavioral approach. Brain Cogn. 1996;31(2):230–49.
Dickson DW, Bergeron C, Chin SS, et al. Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. J Neuropathol Exp Neurol. 2002;61:935–46.
Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. Mov Disord. 2007;22(16): 2314–24.
Duckett S, Stern J. Origins of the Creutzfeldt and Jakob concept. J Hist Neurosci. 1999;8:21–34.
Durr A. Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. Lancet Neurol. 2010;9(9):885–94.
Espay AJ, Litvan I. Parkinsonism and frontotemporal dementia: the clinical overlap. J Mol Neurosci. 2011;45(3):343–9.
Fahn S, Jankovic J, Hallett M. Principles and practice of movement disorders. 2nd ed. Philadelphia: Elsevier; 2011.
Feany MB, Dickson DW. Neurodegenerative disorders with ex-tensive tau pathology: a comparative study and review. Ann Neurol. 1996;40:139–48.
Förstl H. The Lewy body variant of Alzheimer's disease: clinical, pathophysiological and conceptual issues. Eur Arch Psych Clin Neurol. 1999;249:64–7.
Galvin JE, Lee VM, Trojanowski JQ. Synucleinopathies: clinical and pathological implications. Arch Neurol. 2001;58:186–90.
Galpern WR, Lang AE. Interface between tauopathies and synucleinopathies: a tale of two proteins. Ann Neurol. 2006;59(3):449–58.
Goedert M, Spillantini MG. Tau gene mutations and neurodegeneration. Biochem Soc Symp. 2001;67:59–71.
Goedert M. The significance of tau and α-synuclein inclusions in neurodegenerative disease. Curr Opin Genet Dev. 2001a;11(3):343–51.
Goedert M. Alpha-synuclein and neurodegenerative diseases. Nat Rev Neurosci. 2001b;2:492–501.
Goldstein LH, Abrahams S. Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment. Lancet Neurol. 2013;12(4):368–80.
Graeber MB, Kosel S, Egensperger R, Banati RB, Muller U, Bise K, Hoff P, Moller HJ, Fujisawa K, Mehraein P. Rediscovery of the case described by Alois Alzheimer in 1911: historical, histological and molecular genetic analysis. Neurogenetics. 1997;1:73–80.
Gregory A, Polster BJ, Hayflick SJ. Clinical and genetic delineation of neurodegeneration with brain iron accumulation. J Med Genet. 2009;46:73–80.
Hainfellner JA, Wanschitz J, Jellinger K, Liberski PP, Gullotta F, Budka H. Coexistence of Alzheimer-type neuropathology in Creutzfeldt-Jakob disease. Acta Neuropathol. 1998;96:116–22.
Hansen L, Salmon D, Galasko D, Masliah E, Katzman R, DeTeresa R, Thal L, Pay MM, Hofstetter R, Klauber M, et al. The Lewy body variant of Alzheimer's disease: a clinical and pathologic entity. Neurology. 1990;40(1):1–8.

Hardy J. Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. J Alzheimers Dis. 2006;9(3 Suppl):151–3.

Hasegawa M. Biochemistry and molecular biology of tauopathies. Neuropathology. 2006; 26(5):484–90.

Holton JL, Ghiso J, Lashley T, et al. Regional distribution of amyloid-Bri deposition and its association with neurofibrillary degeneration in familial British dementia. Am J Pathol. 2001;158:515–26.

Holton JL, Lashley T, Ghiso J, et al. Familial Danish dementia: a novel form of cerebral amyloidosis associated with deposition of both amyloid-Dan and amyloid-beta. J Neuropathol Exp Neurol. 2002;61:254–67.

Hughes T, Ross H, Madeley P, Finlayson G, Mindham RH, Biggins CA. Subcortical dementia. BMJ. 1993;307(6902):503.

Hutton M. Missense and splice site mutations in tau associated with FTDP-17: multiple pathogenic mechanisms. Neurology. 2001;56(11 Suppl 4):S21–5.

Jellinger KA. Neuropathological aspects of Alzheimer disease, Parkinson disease and frontotemporal dementia. Neurodegener Dis. 2008;5:118–21.

Jellinger KA, Attems J. Prevalence and impact of vascular and Alzheimer pathologies in Lewy body disease. Acta Neuropathol. 2008;115(4):427–36.

Katsuno M, Banno H, Suzuki K, Adachi H, Tanaka F, Sobue G. Molecular pathophysiology and disease-modifying therapies or spinal and bulbar muscular atrophy. Arch Neurol. 2012;69(4):436–40.

Kayed R, Head E, Thompson JL, et al. Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science. 2003;300:486–9.

Khateeb S, Flusser H, Ofir R, Shelef I, Narkis G, Vardi G, Shorer Z, Levy R, Galil A, Elbedour K, Birk OS. PLA2G6 mutation underlies infantile neuroaxonal dystrophy. Am J Hum Genet. 2006;79(5):942–8.

Koeppen AH, Mazurkiewicz JE. Friedreich ataxia: neuropathology revised. J Neuropathol Exp Neurol. 2013;72(2):78–90.

Koide R, Ikeuchi T, Onodera O, et al. Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). Nat Genet. 1994;6:9–13.

Kotzbauer PT, Cairns NJ, Campbell MC, Willis AW, Racette BA, Tabbal SD, Perlmutter JS. Pathologic accumulation of α-synuclein and Aβ in Parkinson disease patients with dementia. Arch Neurol. 2012;69(10):1326–31.

Kremen SA, Mendez MF, Tsai PH, Teng E. Extrapyramidal signs in the primary progressive aphasias. Am J Alzheimers Dis Other Demen. 2011;26(1):72–7.

Lee S, Antony L, Hartmann R, Knaus KJ, Surewicz K, Surewicz WK, Yee VC. Conformational diversity in prion protein variants influences intermolecular beta-sheet formation. EMBO J. 2010;29(1):251–62.

Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Davoisen RC, Goetz CG, Golbe LI, Grafman J, Growden JH, Hallett M, Jankovic J, Quinn NP, Tolisa E, Zee DS, Chase TW, FitzGibbon EJ, Hall Z, Juncos J, Nelson KB, Oliver E, Pramstaller P, Reich SG, Verny M. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP International Workshop. Neurology. 1996;47: 1–9.

Ludolph AC, Kassubek J, Landwehrmeyer BG, et al. Tauopathies with parkinsonism: clinical spectrum, neuropathologic basis, biological markers, and treatment options. Eur J Neurol. 2009;16(3):297–309.

Luheshi LM, Dobson CM. Bridging the gap: from protein misfolding to protein misfolding diseases. FEBS Lett. 2009;583:2581–6.

Mackenzie IR, Rademakers R. The molecular genetics and neuropathology of frontotemporal lobar degeneration: recent developments. Neurogenetics. 2007;8:237–48.

Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol. 2010;119(1): 1–4.

Maltête D, Guyant-Maréchal L, Mihout B, Hannequi D. Movement disorders and Creutzfeldt-Jakob disease: a review. Parkinsonism Relat Disord. 2006;12(2):65–71.
Mead S, Poulter M, Uphill J. Genetic risk factors for variant Creutzfeldt-Jakob disease: a genome-wide association study. Lancet Neurol. 2009;8(1):57–66.
Mesulam MM. A plasticity-based theory of the pathogenesis of Alzheimer's disease. Ann N Y Acad Sci. 2000;924:42–52.
Morgan NV, Westaway SK, Morton JE, et al. PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. Nat Genet. 2006;38:752–4.
Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. 2006;6(314):130–3.
Niwa A, Matsuo K, Shindo A, Yata K, Shiraishi T, Tomimoto H. Clinical and neuropathological findings in a patient with familial Alzheimer disease showing a mutation in the PSEN1 gene. Neuropathology. 2013;33(2):199–203.
Ott A, Breteler MM, van Harskamp F, Claus JJ, van der Cammen TJ, Grobbee DE, Hofman A. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. BMJ. 1995;310(6985):970–3.
Ozawa T, Paviour D, Quinn NP. The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations. Brain. 2004;127:2657–71.
Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). J Neurol Sci. 1989;94:79–100.
Paulsen JS. Cognitive impairment in Huntington disease: diagnosis and treatment. Curr Neurol Neurosci Rep. 2011;11(5):474–83.
Pillon B, Deweer B, Agid Y, Dubois B. Explicit memory in Alzheimer's, Huntington's, and Parkinson's diseases. Arch Neurol. 1993;50(4):374–9.
Paisan-Ruiz C, Bhatia KP, Li A, et al. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann Neurol. 2009;65:19–23.
Patel PI, Isaya G. Friedreich ataxia: from GAA triplet-repeat expansion to frataxin deficiency. Am J Hum Genet. 2001;69(1):15–24.
Prusiner SB. Prions. Proc Natl Acad Sci U S A. 1998;95:13363–83.
Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol. 2011;10(1):83–98.
Rüb U, Brunt ER, Deller T. New insights into the pathoanatomy of spinocerebellar ataxia type 3 (Machado-Joseph disease). Curr Opin Neurol. 2008;21(2):111–6.
Saito Y, Ruberu NN, Sawabe M, Arai T, Tanaka N, Kakuta Y, Yama -nouchi H, Marayama S. Staging of argyrophilic grains: an age-associated tauopathy. J Neuropathol Exp Neurol. 2004;63:911–8.
Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev. 2001;81:741–66.
Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. 2009;361:1651–61.
Tanzi RE, Bertram L. Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. Cell. 2005;120:545–55.
Tierney M, Fisher R, Lewis A, Zorzitto M, Snow W, Reid D, Nieuwstraten P. The NINCDS-ADRDA work group criteria for the clinical diagnosis of probable Alzheimer's disease. Neurology. 1988;38:359–64.
Uchikado H, DelleDonne A, Ahmed Z, et al. Lewy bodies in progressive supranuclear palsy represent an independent disease process. J Neuropathol Exp Neurol. 2006;65:387–95.
Uchikado H, Tsuchiya K, Tominaga I, Togo T, Oshima K, Akiyama H, Ikeda K, Oda T, Hirayasu Y. Argyrophilic grain disease clinically mimicking Parkinson's disease with dementia: report of an autopsy case. No To Shinkei. 2004;56(9):785–8.
Valis M, Masopust J, Bažant J, et al. Cognitive changes in spinocerebellar ataxia type 2. Neuro Endocrinol Lett. 2011;32(3):354–9.
van Slegtenhorst M, Lewis J, Hutton M. The molecular genetics of the tauopathies. Exp Gerontol. 2000;35(4):461–71.

Williams DR. Tauopathies: classification and clinical update on neurodegenerative diseases associated with microtubule-associated protein tau. Intern Med J. 2006;36(10):652–60.

Yamazaki M, Arai Y, Baba M, et al. Alpha-synuclein inclusions in amygdala in the brains of patients with the parkinsonism-dementia complex of Guam. J Neuropathol Exp Neurol. 2000;59:585–91.

Zaccai J, Brayne C, McKeith I, Matthews F, Ince PG, MRC Cognitive Function, Ageing Neuropathology Study. Patterns and stages of alpha-synucleinopathy: relevance in a population-based cohort. Neurology. 2008;70(13):1042–8.

Zhou B, Westaway SK, Levinson B, Johnson MA, Gitschier J, Hayflick SJ. A novel pantothenate kinase gene (PANK2) is defective in Hallervorden-Spatz syndrome. Nat Genet. 2001;28(4):345–9.

Chapter 2
Gait Disorders in Patients with Cognitive Impairment or Dementia

Moran Dorfman, Anat Mirelman, Jeffrey M. Hausdorff, and Nir Giladi

Abstract Cognitive impairment and dementia are common in aging. In recent years, there is a growing body of evidence that suggests that gait is reliant on cognitive function and that gait impairments and falls are affected by a wide spectrum of age-associated changes in cognitive function. Several studies have suggested that gait abnormalities can already be present in the early stages of cognitive decline, even before dementia has been diagnosed. In this chapter, we describe the relationship between gait and cognition as a function of the severity of cognitive decline. We begin with a review of the current understanding of age-associated changes in both cognition and motor function and the interrelation between these domains in older adults. We then review reports on gait changes in mild cognitive impairment, dementia, and Alzheimer's disease dementia, as well as alterations of motor function throughout the course of cognitive decline. Finally, we summarize information on therapeutic interventions designed to improve gait and reduce fall risk based on the interactions between gait and cognitive function.

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Introduction

Understanding the relationship between age-associated decline in cognitive function and mobility has been evolving. These common geriatric symptoms have long been viewed as distinct and separate domains. For example, gait impairments and fall risk in older adults were typically considered to be unrelated to age-associated changes in cognitive function, despite the higher risk of falls in people with dementia. There is now evidence to support the notion that the relationship between cognitive function and falls is not one of "all or none" (Montero-Odasso et al. 2012c). Instead, it appears that gait impairments and falls are both affected by a wide spectrum of age-associated changes in cognitive function (Chen et al. 2012; Segev-Jacubovski et al. 2011). Recent findings suggest that safe ambulation among older adults is more than a motor process and that it involves cognitive function as well. As such, it is important to consider gait impairments in the context of cognitive decline, and vice versa. In this chapter, we describe the relationship between gait and cognition as a function of the severity of cognitive decline. We first review the current understanding of age-associated changes in the relationship between cognition and gait in older adults. We then describe gait changes that occur in mild cognitive impairment as an early precursor of dementia and the alterations occurring with disease progression among patients with dementia. Finally, we briefly review emerging brain imaging evidence on the understanding of gait disturbances and falls among patients with dementia and summarize the growing number of therapeutic interventions designed to improve gait and reduce fall risk that have been based on the interactions between gait and cognitive function.

Age-Associated Changes in Gait

There is no clear definition of "normal aging," making it a challenge to identify which consequences of aging should be considered as being abnormal (Elble et al. 1994). Indeed, there is a wide spectrum of functional decline among older adults. Some abnormalities of posture and movement are more common with advanced age, but clear cutoffs and thresholds have not been defined, and certainly not at the individual level. Walking disability increases with age: while gait dysfunction is uncommon in persons under 65 years of age, the prevalence increases to 14 % in the next decade and affects almost 50 % of persons over the age of 85 years (Odenheimer et al. 1994). At least 20 % of noninstitutionalized older adults have some difficulties in walking or require the assistance of another person or assistive equipment (Montero-Odasso et al. 2012c; Ostchega et al. 2000). The locomotor capacity of older people also generally decreases. This deterioration results from multiple

aspects of functional decline of the nervous and the musculoskeletal systems; however, the extent to which these can be attributed to normal aging is not clear (Alexander 1996; Hausdorff 2007).

Many studies have quantitatively examined the kinematics of walking in older people in order to define normal walking. Most of these studies have found that during aging, gait velocity decreases, stride length becomes shorter, the base of support widens to increase stability, and double-limb support and stride-to-stride variability increase (Giladi et al. 2005; Maki 1997; Verghese and Xue 2011). The magnitude of these changes depends, to a large degree, on the inclusion and exclusion criteria applied. Among older adults with very "successful aging," these changes in gait may be small and nonsignificant (Odenheimer et al. 1994), whereas gait dysfunction can become debilitating in others. Imaging studies have been used to better understand the origin and impact of clinical changes in gait among older adults. For example, the volume of white matter hyperintensities (WMH) and/or periventricular high signals and ventricular volumes have been associated with mobility problems and falls among older adults (Holtzer et al. 2006; Maki 1997; Odenheimer et al. 1994; Yogev-Seligmann et al. 2008). The source of these subclinical changes and the impact of microvascular alterations on gait among older adults remain to be more fully delineated. Nonetheless, despite the heterogeneity in function and the existence of a subgroup of individuals among whom gait appears to be no different from that of younger adults, there is some decline in gait that can generally be observed in older adults that is partially related to aging.

Gait and Cognition

Gait disorders are common among subjects with cognitive impairments (Chen et al. 2012; Holtzer et al. 2006; Yogev-Seligmann et al. 2008). Gait is a complex task that requires cognitive input from multiple systems to maintain upright posture, in addition to the reliance on the motor control system (Hausdorff et al. 2005; Montero-Odasso et al. 2012c; Woollacott and Shumway-Cook 2002; Yogev-Seligmann et al. 2008). Walking in the real world is not an automatic motor task since it integrates high-level cognitive functions, such as attention, obstacle negotiation, and set shifting, in order to successfully ambulate in complex environments while carrying out multiple tasks (Yogev-Seligmann et al. 2008). Given these requirements of everyday walking, it is not surprising that emerging evidence suggests that early disturbances in cognitive abilities are associated with slower gait and gait instability during both single- and dual-task walking (Montero-Odasso et al. 2009a).

Risk of Falls

Falls are a serious health problem in the elderly population (Ganz et al. 2007). Falls contribute to functional decline and loss of mobility and independence, and

recurrent falls reflect frailty, immobility, and acute and chronic health impairments. The impact of falls is a major concern since about one-third of older adults living in the community over the age of 65 years experience falls every year (Hausdorff et al. 2001; Tinetti 1994), with the figure reaching as high as 50 % among adults over the age of 85 years (Blake et al. 1988). Cognitive impairment and dementia are known risk factors for falls (Harlein et al. 2009), and the incidence of falls in older people with cognitive impairment is approximately three times higher than that of cognitively intact adults, ranging from 1.1 to 6.4 (Asada et al. 1996; de Carle and Kohn 2001; Kallin et al. 2004; Shaw 2007; Tinetti et al. 1988; van Doorn et al. 2003). The higher risk of falls among people with dementia increases the risk for serious injuries, morbidity, and institutionalization (Kallin et al. 2004; Tinetti 1994; van Dijk et al. 1993). Furthermore, the population of fallers with cognitive decline is approximately five times more likely to be admitted to institutional care compared to people with cognitive problems who do not fall (Morris et al. 1987). Cognitive decline apparently exacerbates both the risk of falls and the impact of falls on function and health-related quality of life.

Until recently, falls and dementia had been studied and assessed as separate geriatric disorders. These two events are now considered as being intertwined, and so studying their interconnection paves the way to better understanding of motor–cognitive interactions (Montero-Odasso et al. 2012c; Sheridan and Hausdorff 2007) (see Fig. 2.1). In general, most falls among older adults occur during weight shifting while walking particularly while attention is directed to another task (Nevitt and Cummings 1993). There is interplay between gait variability, cognition, a particular executive function (EF), attention, and the risk of falls (Sheridan and Hausdorff 2007). Falls can be described as a complex, multifactorial phenomenon which is caused by several risk factors (Ganz et al. 2007). Eight categories of risk factors were identified in a review by Harlein et al. (Harlein et al. 2009). According to those authors, the type and severity of dementia, motor impairments, vision impairments, behavioral disturbances, functional impairments, fall history, neuroleptics, and low bone mineral density play an important role as factors that can lead to falls among people with cognitive decline. The association between type of dementia and falls was examined by Ballard et al. (1999) who noted that people with dementia with Lewy bodies were found to be more likely to fall and that the incidence of multiple falls was extremely high in this population (five or more falls in 3 months) (Ballard et al. 1999). Nakamura et al. assessed the influence of the severity of dementia on falls and found that the number of fallers was higher in the intermediate stage of the disease compared with the milder stage (Nakamura et al. 1996). Their findings, however, were not confirmed by other studies (Asada et al. 1996; Buchner and Larson 1987). The discrepancy in the findings can be explained by the use of different methods assessing severity.

Motor impairments, particularly gait disturbances, are considered one of the most consistent predictor of falls among older adults with cognitive decline (Ganz et al. 2007). Impaired gait, reduced muscular strength, and impaired balance (Harlein et al. 2009) as well as impairments in activity level and mobility

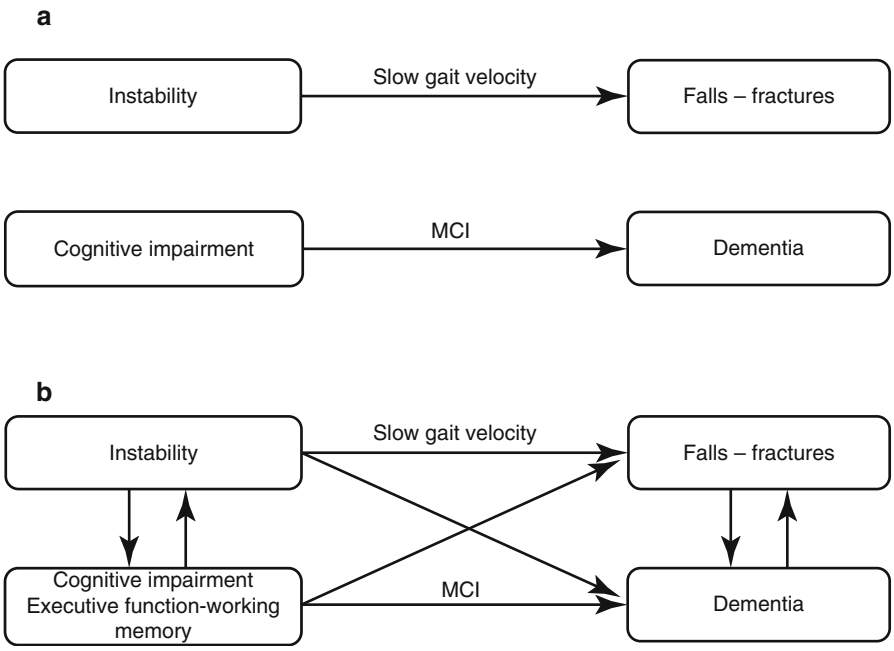

Fig. 2.1 Parallel decline in gait and cognitive function with aging. (**a**) Traditional view. Gait performance and cognitive function deteriorate with aging, yielding two geriatric entities: falls and dementia. (**b**) Alternative view. Cognition predicts mobility decline and falls, and mobility decline and slow gait predict cognitive deterioration. These phenomena occur concurrently. *MCI* mild cognitive impairment (Reprinted with permission from *Journal of the American Geriatrics Society* (Montero-Odasso et al. 2012c))

measures (Suttanon et al. 2013) contribute to fall risk in this population. Other measures of disability, such as peripheral neuropathy, musculoskeletal problems, and impaired tandem gait as a marker for ataxia, have also been shown to increase the risk of falls in patients with Alzheimer's disease (AD) (Buchner and Larson 1987). In a prospective study on 135 Japanese older adults (Suzuki et al. 2012), Suzuki et al. proposed a model of 11 fall-related behaviors that may be effective indicators to predict falls. The indicators consisted of intrinsic motor and behavioral aspects, such as being agitated and wandering, inability to maintain seated balance in a wheelchair, and impairments in judgment, such as immediate desire to urinate or defecate. Interestingly, according to this model, behaviors such as delirium, awareness of self, symptoms of Parkinson's disease, and wandering were not related to falls (Suzuki et al. 2012). In addition to intrinsic factors, psychotropic medications were found to also increase the risk of falls by causing sedation and postural hypotension (Ensrud et al. 2002; Husted et al. 2000; Thapa et al. 1995). These reports suggest that falls and risk of falls in older adults and specifically those with cognitive deficits or dementia are multifactorial in nature.

Gait Variability and Risk of Falls

Gait variability is a measure of gait consistency and reflects the stride-to-stride fluctuations in walking. Gait variability offers a complementary way of quantifying locomotion and its changes with aging and disease, and it is considered a reliable measure of fall risk as well (Hausdorff 2005). The variability of several spatiotemporal gait parameters has been widely studied, among them stride time, stance time, stride length, and step width (Brach et al. 2005, 2008; Richardson et al. 2004). Stride time variability reflects one of the final pathways of the outcomes that the central nervous system regulates (Hausdorff 2005). The general assumption is that there is an inverse association between stride time variability and gait stability (Montero-Odasso et al. 2012c). Gait variability tends to be higher in people with AD compared to age-matched controls, and it has been associated with a higher risk of falls among these individuals (Nakamura et al. 1996; Visser 1983). Cognitive deterioration, especially EF, is associated with increased gait variability and thus independently associated with future falls (Beauchet et al. 2008; Buracchio et al. 2011; Chen et al. 2012; Herman et al. 2010; Yogev-Seligmann et al. 2008).

Dual Task

Dual-task paradigms are used by clinicians to assess cognitive involvement during gait in older adults by measuring the interaction between cognition and mobility (Hausdorff et al. 2008; Yogev-Seligmann et al. 2008). Assessment of dual-task abilities may provide important information on gait, such as its automaticity and the risk for falls that might not be apparent during a routine examination. The use of a dual-task paradigm is a sensitive method to identify gait problems when cognitive reserve is limited (Beauchet et al. 2009). Gait changes while performing a dual task were found to be significantly associated with an increased fall risk in older adults (Beauchet et al. 2009; Herman et al. 2010; Montero-Odasso et al. 2012c; Segev-Jacubovski et al. 2011; Springer et al. 2006). Dual-task-related gait changes partly depend on the capacity to allocate attention between two tasks performed simultaneously and are mainly related to executive dysfunction. EF refers to a variety of higher cognitive processes that modulate and use information from the posterior cortical sensory systems to produce behavior (Perry and Hodges 1999). Deficits in EF probably reduce the ability to recruit compensatory mechanisms to counter age-associated changes in gait and balance and thus increase the risk of falls (Yogev-Seligmann et al. 2008). A systematic review and meta-analysis of 27 prospective cohort studies revealed an association between cognition and serious fall-related injury. Montero-Odasso et al. reported that dual-task load increased gait variability in people with mild cognitive impairment (MCI) compared with healthy controls (Montero-Odasso et al. 2012b). Individuals with AD who have greater deterioration in EF compared to healthy controls have greater dual-task cost than cognitively normal adults (Sheridan et al. 2003). The difficulty in the performance of dual tasking may represent impaired brain capacity and difficulty in sharing cognitive

resources between walking and cognitive tasks. Several studies showed that subjects with dementia exhibited greater gait changes compared to normal age-matched controls during the execution of dual tasks (Allali et al. 2008; Camicioli et al. 1997a, b; Woollacott and Shumway-Cook 2002), particularly in stride time and stride-to-stride variability. Interestingly, the magnitude of the effect of the secondary task on gait stability is reportedly in direct relationship with the complexity of the given dual task (Montero-Odasso et al. 2012b) and to the individual's cognitive capacity, with the greatest deterioration of gait performance observed in patients with cognitive impairments (Muir et al. 2012). These findings may help to explain the greater risk of falls and injuries among older adults with cognitive impairment or dementia.

Gait Changes in Mild Cognitive Impairment (MCI)

MCI is defined as a transition state between normal cognition and dementia in older adults (Petersen 2007). It has been recently established that cognitive decline is accompanied by early motoric decline, manifesting either as two separate biological processes or as a cascading intertwined process (Aggarwal et al. 2006; Boyle et al. 2005, 2007; Kluger et al. 1999; Louis et al. 2005; Verghese et al. 2002, 2007). Table 2.1 summarizes some of the key findings on gait changes in MCI.

Older people are often defined as having MCI based on impairments in memory (amnestic) or non-memory (non-amnestic) domains (Moretti et al. 2013). Both MCI subtypes have poorer performance on most gait variables, such as gait velocity, stride length, gait variability, cadence, swing time, and double support time, than age-matched healthy controls (Verghese et al. 2008). Conversely, the two MCI subtypes differ in certain gait domains. Subjects with amnestic MCI have poorer swing time, stride time variability, and stride length variability than those with non-amnestic MCI, suggesting that individuals with amnestic MCI tend to have more variability and a decreased rhythmical pattern of gait and control than individuals with non-amnestic MCI (Verghese et al. 2008). Serious gait alterations, such as hemiparetic gait and frontal or parkinsonian gait, are also more frequent in amnestic MCI than non-amnestic MCI (Verghese et al. 2008). MCI patients with two or more vascular factors were shown to have greater frontal–subcortical dysfunction (Montero-Odasso et al. 2012a). An interaction was found between a high vascular burden (two or more vascular factors) and the triad of executive dysfunction, gait disorders, and depressive symptoms among MCI patients (Montero-Odasso et al. 2012a). A magnetic resonance spectroscopy and volumetric imaging study exhibited an association between lower metabolite ratios and volume of the primary motor cortex and poor gait performance in both single- and dual-task conditions in mild cognitive impairment. These findings point to a possible involvement of decreased neuronal function in the primary motor cortex causing gait disorders (Annweiler et al. 2013), although other pathways are also likely to be involved.

Table 2.1 Gait and falls in mild cognitive impairment (MCI)

Reference	Participants	Outcome measures	Summary of findings
Cross-sectional studies			
Louis et al. (2005)	2,230 participants (mean age 77.2 ± 6.6 years): 608 participants with MCI including 255 participants with amnestic MCI (mean age 78.1 ± 7.0 years) and 353 with non-amnestic MCI (mean age 77.1 ± 6.6 years) and 1,622 participants cognitively intact	Neurologic assessment, including a modified motor portion of the Unified Parkinson's Disease Rating Scale	Mild parkinsonian signs, especially rigidity, are associated with amnestic MCI Amnestic MCI vs no MCI was 51 % higher in participants with mild Parkinson's signs compared to those with no mild Parkinson's signs
Boyle et al. (2005)	598 participants cognitively intact (mean age 79.6 ± 6.8 years) and 237 participants with MCI (mean age 82.8 ± 6.9 years)	Clinical evaluations, including assessments of parkinsonian signs and cognitive function	Parkinsonism signs, especially gait disturbance, bradykinesia, and rigidity, were more common in MCI subjects compared to cognitively intact subjects Lower levels of cognitive function, particularly in perceptual speed, were associated with higher levels of parkinsonism among individuals with MCI Participants with non-amnestic MCI showed more gait disturbances compared to participants with amnestic MCI
Verghese et al. (2008)	295 participants cognitively intact (mean age 79.3 ± 4.7 years), 54 participants with amnestic MCI (mean age 82.6 ± 5.7 years), and 62 participants with non-amnestic MCI (mean age 81.8 ± 6.2 years)	Clinical and quantitative gait performance	Neurologically impaired gaits were more common in amnestic MCI than in non-amnestic MCI and controls. Quantitative gait in multiple parameters was worse in both MCI types than in controls. Factor analysis revealed three independent factors representing pace, rhythm, and variability. Subjects with amnestic MCI had worse rhythm and variability scores than those with non-amnestic MCI and controls. Subjects with non-amnestic MCI had worse performance in the pace domain than the other two groups. Subjects with MCI and gait abnormalities had higher disability scores than subjects with MCI without gait abnormalities

Muir et al. (2012)	22 participants cognitively intact (mean age 71.0 ± 5.0 years), 29 participants with MCI (mean age 73.6 ± 6.2 years), and 23 participants with AD (mean age 77.5 ± 5.0 years)	Evaluation of gait performance while performing single and dual tasks	Gait velocity and stride time variability were not significantly under the single-task condition In contrast, gait velocity decreased and strides time and stride time variability increased under the dual-task condition in people with MCI and AD The greatest deterioration of gait performance occurred under complex motor task tests
Montero-Odasso et al. (2012a)	35 participants with MCI (mean age 75.5 ± 1.1 years)	Assessment to determine whether community-dwelling older adults with MCI and a high vascular burden were more likely to exhibit the frontal–subcortical triad of executive dysfunction, gait disorders, and depressive symptoms than those with a low vascular burden	Participants with two or more vascular factors had greater frontal–subcortical dysfunction There was an interaction between a high vascular burden, two or more vascular factors, and the three components of the triad The number of vascular factors was directly associated with the number of frontal–subcortical dysfunctions The vascular burden was associated with the number of frontal–subcortical dysfunctions
Montero-Odasso et al. (2012b, c)	25 participants cognitively intact (mean age 71.5 ± 4.1 years) and 53 participants with MCI (mean age 75.1 ± 6.3 years)	Gait assessment under single (usual walking) and dual tasking (naming animals and subtracting serial 7 s)	There was a significant difference within and between groups of increasing gait variability as dual-task complexity increased Gait velocity decreased within groups as dual-task complexity increased
Annweiler et al. (2013)	20 participants with MCI (mean age 76 ± 11 years)	Gait velocity and stride time variability while performing single and dual tasking Ratios of N-acetylaspartate to creatine and choline to creatine and cortical volume were calculated in the primary motor cortex	The neurochemistry and volume of the primary motor cortex were associated with gait performance while carrying out single and dual tasking. Cortical volume correlated with faster gait velocity during single ($P = 0.029$) and dual tasking ($P = 0.037$) and with decreased stride time variability during single tasking

(continued)

Table 2.1 (continued)

Reference	Participants	Outcome measures	Summary of findings
Prospective studies			
Asada et al. (1996)	86 community-dwelling elderly with dementia (mean age 77.5±8.1 years) and 98 community-dwelling elderly without dementia (mean age 73.7±7.3 years) (1-year follow-up)	Fall-related injury by self-report	Significant factors associated with fall-related injury were falls in the past (OR 3.6; 95 % CI 1.3–9.9), better physical function (OR 1.04; 95 % CI 1.00–1.08), and Assessment of Basic Care for the Demented (ABCD) scale (OR 0.7; 95 % CI 0.6–0.8)
Nakamura et al. (1996)	97 participants with AD (2-year follow-up)	Association of fall-related injuries and gait function in relation to severity of dementia	Gait speed decreased as the illness progressed, stride length shortened, grip strength (as an index of muscular strength) weakened, and stride length variability increased. Only stride length variability was a significant predictor of fall-related injuries The number of fallers was higher in the medium stage of the disease compared with the milder stage
Ballard et al. (1999)	30 participants with Lewy bodies dementia (mean age 76 years) and 35 participants with Alzheimer's disease (mean age 80 years) (3-month follow-up)	Falls according to definition of the Kellogg International Work Group	Significant factors associated with fall-related injury were falls in the past (OR 16.0; 95 % CI 4.4–58.0), dementia with Lewy bodies (OR 3.8; 95 % CI 1.3–10.8), and parkinsonism ($P=0.003$)
Aggarwal et al. (2006)	558 participants cognitively intact (mean age 74.6±6.7 years), 198 participants with MCI (mean age 78.7±7.0 years), and 60 participants with AD (mean age 81.9±6.7 years) (longitudinal, yearly repeat tests up to 10 years)	Motor assessment using performance-based measures of upper and lower extremity function and a modified version of the motor section of the Unified Parkinson's Disease Rating Scale	At baseline, participants with MCI had impaired motor function vs cognitively intact participants and superior motor function vs those with dementia Baseline levels of lower extremity motor performance, parkinsonian gait, and bradykinesia in MCI participants were inversely related to risk of AD

A MEDLINE literature search was conducted using the terms "gait," "gait disorder," "gait disorders," "falls," "walking," "Alzheimer's disease," "dementia," or "mild cognitive impairment" to identify potential papers. After review of the abstracts and cross-references, the relevant papers were studied and categorized into the entries shown in the tables. A formal meta-analysis process was not employed

AD Alzheimer-type dementia

Gait Changes as an Early Indicator of Dementia

The prevalence of dementia-associated gait disturbances depends on the type of dementia and the severity of cognitive impairment. Gait disturbances in vascular dementia (VaD) are more common in the early stages of the disease, while AD patients usually do not begin to demonstrate gait changes until later stages of the disease (Verghese et al. 2002). Several studies have shown that slow gait speed predicts cognitive decline (Camicioli et al. 1998; Inzitari et al. 2007; Taniguchi et al. 2012) and dementia (Verghese et al. 2002, 2013; Waite et al. 2005). A longitudinal cohort study found significant differences in gait speed and finger tapping speed between people who developed MCI and those who remained cognitively intact (Buracchio et al. 2010). In addition, a change-point analysis for MCI converters was used in an effort to determine the approximate time at which decline in motor function developed (Buracchio et al. 2010). The findings showed that a decrease in gait speed accelerated by 0.02 m/s per year in subjects with MCI, that this change began 12.1 years prior to the onset of MCI, and that it appeared earlier in men than women (Buracchio et al. 2010). Alternatively, it has also been hypothesized that cognitive changes precede or occur concomitantly with slowing gait because gait requires intact, complex, and integrated cognitive processes (Atkinson et al. 2010; Heuninckx et al. 2005; Njegovan et al. 2001; Soumare et al. 2009; Tabbarah et al. 2002; Watson and Leverenz 2010). The Sydney Older Persons Study examined 6-year outcomes of 630 community-dwelling participants aged 75 years or more at recruitment. The people with cognitive impairment in combination with gait and motor slowing were the most likely to deteriorate into dementia over the 6-year study period and most likely to die sooner (Waite et al. 2005).

Baseline gait status was found to influence the cumulative risk to develop any dementia and the cumulative risk to develop VaD, but not the cumulative risk to develop Alzheimer's disease (Aggarwal et al. 2006; Boyle et al. 2005, 2007; Kluger et al. 1999; Louis et al. 2005; Verghese et al. 2002, 2007). Executive dysfunction may impair gait, and gait impairments reduce the capacity to walk (Della et al. 2004). In an interesting prospective study of 422 community-residing older adults, subjects with neurologic gait abnormalities at baseline had a greater risk of developing dementia. These subjects had an increased risk of non-AD, but not of AD. Of non-Alzheimer's dementias, abnormal gait, such as unsteady gait, frontal gait, and hemiparetic gait, predicted the development of VaD. The predictive capability of early gait abnormalities in elderly people without dementia (Verghese et al. 2002) suggests that gait abnormalities may be considered as biomarkers for the future development of dementia, possibly reflecting an early preclinical underlying cerebrovascular and/or neurodegenerative disease (see Fig. 2.2).

Gait Changes in Dementia

Table 2.2 summarizes some of the key findings on gait changes in dementia. The prevalence of vascular dementia and other non-AD is 30–50 % of all dementias in older adults (Chui et al. 2000; Roman 2004; Verghese et al. 2002). Gait disorders

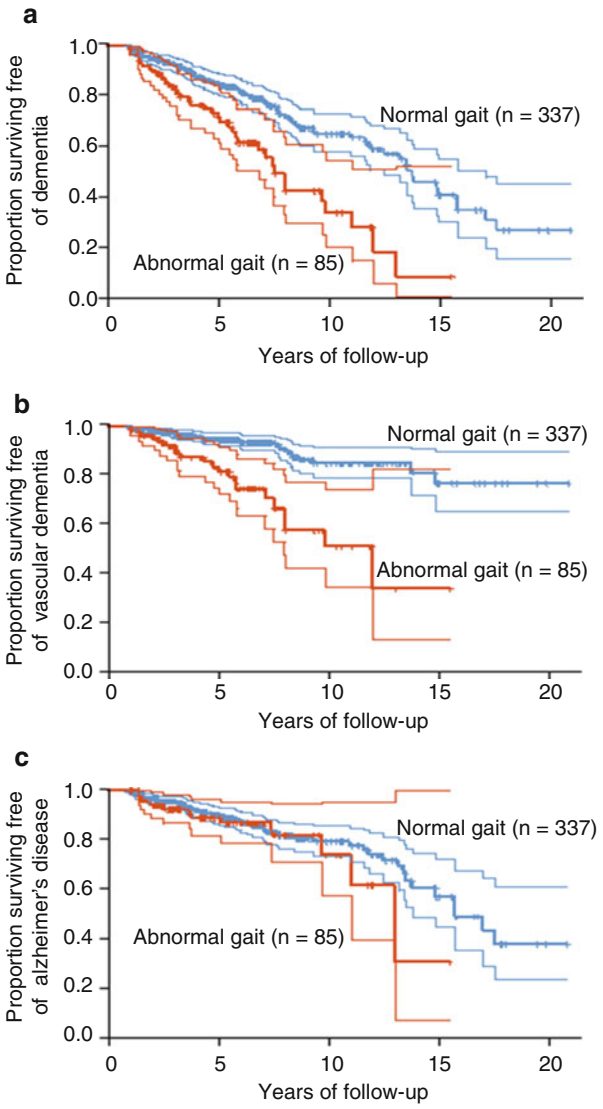

Fig. 2.2 Kaplan–Meier curves for the cumulative risk of (**a**) any dementia, (**b**) vascular dementia, and (**c**) Alzheimer's disease dementia according to gait status at enrollment. *Dotted lines* represent 95 % confidence intervals (From *New England Journal of Medicine*, Verghese et al. (2002). Copyright © 2002 Massachusetts Medical Society, Reprinted with permission from Massachusetts Medical Society)

occur late in the progression of Alzheimer's disease, while they present earlier or even precede vascular dementia (McKhann et al. 1984; Roman et al. 1993). Patients with AD present with a decrease in gait velocity and stride length as well as an increase in double support and stride length variability than healthy older adults (Alexander et al. 1995; Nakamura et al. 1996; Tanaka et al. 1995; Visser 1983). These changes could be considered as reflecting a more exaggerated impact of "aging." These gait features decline further as the disease continues to progress (van Iersel et al. 2004). Furthermore, individuals with VaD exhibit even slower walking

Table 2.2 Gait and falls in dementia

Reference	Study design	Participants	Outcome measures	Summary of findings
Studies reporting on gait changes as an early indicator of cognitive decline				
Verghese et al. (2002)	Prospective cohort with 6.6 years of follow-up	422 subjects without dementia at baseline: 337 subjects with normal gait (mean age 78.93 ± 3.03 years) and 85 subjects with abnormal gait (mean age 79.97 ± 3.11 years)	Association between neurologic gait status at baseline and the development of dementia	Subjects with neurologic gait abnormalities had a greater risk of developing dementia. These subjects had an increased risk of non-AD but not of AD Abnormal gait predicted the development of VaD in non-AD. Among the types of abnormal gait, unsteady gait, frontal gait, and hemiparetic gait predicted VaD
Waite et al. (2005)	Prospective 6-year study	630 community-dwelling participants aged ≥75 years at recruitment	Motor and cognitive assessment	Participants with cognitive impairment in combination with gait and motor slowing were the most likely to experience dementia over the 6-year study period and also the most likely to die
Buracchio et al. (2010)	Prospective cohort study with a 20-year follow-up	204 participants cognitively intact at baseline: 109 remained cognitively intact (mean age 79 ± 8.85 years) and 95 converted to MCI (mean age 83.5 ± 7.0 years)	Annual medical histories, neurologic examinations, and neuropsychological testing	Gait speed predicts MCI 12.1 years in advance An acceleration of gait speed decline occurred earlier in men than women For finger tapping speed, the change point occurred after the onset of MCI
Gait changes in dementia				
Visser et al. (1983)	Cross-sectional	11 AD patients (mean age 78.8 years) and 11 matched controls (mean age 78.3 years)	Gait and balance evaluation	AD patients had significantly shorter step length, lower gait speed, lower stepping frequency, greater step-to-step variability, greater double support ratio, and greater sway path compared to the control group

(continued)

Table 2.2 (continued)

Reference	Study design	Participants	Outcome measures	Summary of findings
Alexander et al. (1995)	Cross-sectional	17 patients with probable AD and 39 healthy older adults	Participants walked 6 m at a comfortable speed registration with LEDs and cameras	AD patients had decrease in gait speed compared to the controls While clearing obstacles, the AD patients exhibited slow crossing speed and landed closer to the obstacle. The percent of trials in which a subject made contact with an obstacle was significantly higher in AD patients
Tanaka et al. (1995)	Cross-sectional	15 participants with AD, 15 participants with VaD, and 15 controls	Participants walked 10 m at preferred speed	AD patients showed significantly slower velocity and shorter step length than healthy controls, and VaD patients exhibited a reduction on these two variables compared to AD patients
Nakamura et al. (1996)	Prospective cohort study with a 2-year follow-up	97 patients with AD	Participants walked 10 m three times at preferred speed	The number of fallers was significantly higher in moderate-stage AD patients than in the mild-stage AD patients Walking speed and stride length were significantly lower and the stride length variability was significantly higher in the moderate-stage AD patients compared to the mild-stage AD patients

Nakamura et al. (1997)	Cross-sectional	45 AD patients and 15 control subjects	Gait and posture evaluation and examination of rCBF in different clinical stages	Mild-stage AD participants increased postural sway associated with a reduced mean value of rCBF in the cortex Reduced mean rCBF values in the cortex and in the frontal lobe of moderate-stage AD participants were associated with increased postural sway and stride length variability and with decreased stride length Reduced rCBF in the basal ganglia and in the frontal lobe was also associated with increased postural sway, double support time, and stride length variability and with decreased walking speed and stride length in severe-stage participants
Van Iersel et al. (2006)	Cross-sectional	63 participants with dementia (mean age 79.8 ± 7.4 years) and 62 participants without dementia (mean age 74.7 ± 6.5 years)	Participants walked twice at preferred speed and twice while counting backwards (dual task)	After adjustment for parkinsonism and walking aids, participants with dementia walked faster than participants without dementia

AD Alzheimer-type dementia, *VaD* vascular dementia, *rCBF* regional cerebral blood flow

velocities compared to patients with AD (van Iersel et al. 2004). Another common gait feature in people with dementia is a relatively shorter step length, which correlates to decreased gait velocity and disease progression (Alexander et al. 1995; Nakamura et al. 1997; Tanaka et al. 1995; Visser 1983). Patients with AD exhibit significantly slower gait velocity and shorter step length compared to healthy controls, and patients with VaD exhibit an even greater reduction in gait speed and stride length relative to patients with AD (Tanaka et al. 1995). The short step length and decreased velocity also contribute to an increase in double support time and increase in stride length variability which, in turn, can increase unsteadiness and the risk of falls (Alexander et al. 1995; van Iersel et al. 2004).

The authors of a prospective study of the relationship between falls and stride length variability in 96 Japanese patients with AD observed a significant increase in fall incidence among moderate-stage AD patients compared to mild-stage AD patients, as well as a significant decrease in gait parameters, such as gait speed and stride length (Nakamura et al. 1996). In addition, stride length variability was significantly higher (worse) in patients with more severe AD than in patients with mild AD. Furthermore, there was a significant difference only in stride length variability when gait measures of fallers and non-fallers were compared according to the severity of dementia (Nakamura et al. 1996). The results of that study highlight the important relationship between specific aspects of gait and falls in patients with dementia. In contrast to those findings, however, only van Iersel et al.'s study demonstrated that patients with dementia walked faster than patients without dementia, and those authors considered that frontal lobe disinhibition and lack of insight might be responsible for this phenomenon (van Iersel et al. 2006).

"Cautious gait" is characterized by a decrease in gait velocity, step length, and static and dynamic balance, a widened base of support, hesitation and freezing, and a reduction in postural responses (Scherder et al. 2007). Cautious gait is likely to appear in the early stages of AD (O'Keeffe and Lavan 1996; Prehogan and Cohen 2004), while a "frontal gait disorder" is more common in more advanced stages of AD and it is characterized by pseudoparkinsonian symptoms, such as shuffling, and start and turn hesitation (O'Keeffe and Lavan 1996). The number of patients exhibiting parkinsonian symptoms increases during the course of evolving dementia. These symptoms reflect extrapyramidal signs, such as bradykinesia, cogwheel rigidity, rest tremor, and parkinsonian gait (Burns et al. 2005). Burns et al. suggest that extrapyramidal signs are related to basal ganglia pathologies that may account for the increasing prevalence of extrapyramidal signs as AD progresses (Burns et al. 2005).

Gait disorders in AD could be explained by a high burden of age-related subcortical hyperintensities on the frontal–subcortical circuits together with hippocampal degeneration (Annweiler et al. 2013). Increasing lines of evidence from clinical practice, epidemiological studies, and neuroimaging studies show that the vascular burden plays a key role in the onset and progression of AD (van Norden et al. 2012). Therefore, it is not surprising that the vascular component of AD appears to be involved in gait disorders among patients with AD. Gait velocity, stride length, and step width are the gait parameters most commonly affected in the presence of WMH

(Annweiler et al. 2012). In their review, Annweiler et al. (2012) suggested that quantitative parameters of gait, such as slower gait velocity and shorter stride length in AD-related gait disorders, are associated with WMH specifically in the frontal area and the basal ganglia, which are both part of the frontal–subcortical circuits. These findings could also account for the correlation between the lower hippocampal volume and function and qualitative gait disorders, such as higher stride length variability. Interestingly, the nigrostriatal dopamine system was found to remain unaffected. Zimmerman et al. reported that higher stride length variability in AD was associated with lower metabolism in the hippocampal cortex (Zimmerman et al. 2009) which has been suggested as the first cortical region damaged in AD (van Norden et al. 2012).

Interventions to Improve Gait in Dementia

For many years, dementia was not treated due to the notion that further deterioration was unavoidable once it had been diagnosed. In contrast to normal aging, only a limited number of studies have examined therapeutic methods to enhance gait and motor performance in patients with dementia. These few studies generally target cognition and behavior. It has been reported that improvement in cognition, particularly EF, may influence gait (Tanaka et al. 1995; Yogev-Seligmann et al. 2008), but only a few studies have directly assessed the effect of interventions on gait, balance, or falls in dementia. Table 2.3 summarizes interventions aimed at enhancing motor performance in dementia. These interventions can be divided into non-pharmacologic and pharmacologic types. The former includes cognitive training (Schwenk et al. 2010) which is based on the notion that dual-task deficits have been linked to functional decline and falls (Camicioli et al. 1997a; Yogev-Seligmann et al. 2008). Studies among patients with dementia have shown that music therapy may improve behavioral and psychological symptoms as well as cognitive functions and that it may also have a potential positive cardiovascular effect (Raglio et al. 2012). Unfortunately, only one study focused on the benefit of music therapy on motor performances (Clair and O'Konski 2006). There is some evidence that physical activity delays the onset of dementia in healthy older adults and slows down cognitive decline. A physical exercise program appears to be a promising non-pharmacologic strategy for slowing down cognitive decline (Balsamo et al. 2013). In addition to having a positive influence on cognition, several studies demonstrated that intensive dementia-specific motor training also increased the level of physical activity in this population (Hageman and Thomas 2002; Hauer et al. 2012; Rolland et al. 2007; Schwenk et al. 2010; Toulotte et al. 2003; Venturelli et al. 2011; Zieschang et al. 2013), with evidence of retention of gains even at 9 months after the end of training (Zieschang et al. 2013).

Pharmacologic interventions to improve cognition, particularly EF, have also been shown to influence motor abilities and gait performance (Auriel et al. 2006; Ben-Itzhak et al. 2008). Initial findings in older adults suggested that

Table 2.3 Interventions for improving gait in dementia

Reference	Study design	Participants	Type of intervention	Duration of intervention	Outcome measures	Summary of findings
Non-pharmacologic treatment of gait disturbances in patients with dementia or cognitive decline						
Hageman and Thomas (2002)	Pre–posttest design	26 elderly demented patients (mean age 79.9 ± 5.5 years)	Moderate physical activity, progressive resistance, and lower extremity exercise using Thera-Band	2–3 times/week for 6 weeks	Comfortable and fast gait velocity over a 6-m distance and the TUG	Improvement was observed on all gait measures, but the only significant change was in fast gait time
Toulotte et al. (2003)	RCT	20 elderly demented patients with a history of falling (mean age 81.4 ± 4.7 years)	The intervention group received physical activity training: strength exercise, proprioception, static and dynamic balance, and flexibility. No exercise for controls	Once/week for 45 min, 16 weeks	Get up and go test, sit on chair and reach test, 10-m walk test, and posturography	Gait speed, flexibility, and static balance improved. The intervention group did not fall while the control subjects fell 6 times during the 16 weeks. The intervention group started to fall again after the end of training
Clair et al. (2006)	Pre–posttest design	28 patients with advanced dementia	Comparison of gait parameters in three conditions of music therapy	16 weeks	Speed, cadence, and stride length	No significant differences in gait were observed, but caregiver burden apparently benefited from the use of acoustic stimuli
Rolland et al. (2007)	RCT	Intervention group of 67 patients with AD (mean age 82.8 ± 7.8 years) and control group of 67 patients with AD (mean age 83.1 ± 7.0 years)	The intervention group had a program of combined walking, exercise, muscle strength, balance, and flexibility tasks. The control group received routine medical care	1 h twice weekly during 12 months	Katz ADL score, ADL score measures of physical performance, nutritional status, behavioral disturbance, and depression	Improvement in the intervention group was observed on the 6WTt, but there was no effect on cognitive responses

Schwenk et al. (2010)	RCT	Intervention group of 20 patients with mild to moderate dementia (mean age 80.4 ± 7.1 years) and control group of 29 patients with mild to moderate dementia (mean age 82.3 ± 7.9 years)	Intervention subjects received cognitive training of progressively dual-task training. Controls received low-intensity exercise	2 h twice weekly, 12 weeks	Improvement in dual-task performance compared to baseline single tasks	Specific training improved performance on a challenging dual-task condition (e.g., serial three subtractions while walking), but not under less challenging dual-task conditions
Venturelli et al. (2011)	RCT	Intervention group of 11 patients (mean age 83 ± 6 years) and control group of 10 patients (mean age 85 ± 5 years) with advanced AD	The intervention group performed simple aerobic activities. The control group carried out daily organized activities (e.g., bingo, patchwork sewing, and music therapy)	Minimum 30 min of moderate exercise, 4 times a week during 24 weeks	A 6WT, the Barthel index of ADL, and MMSE	Improvement in the intervention group was observed on the 6WT and ADLs. Both groups had a decline in MMSE, but the intervention group's was slower
Hauer et al. (2012)	RCT	Intervention group of 62 patients with mild to moderate dementia (mean age 82.3 ± 6.6 years) and control group of 60 patients with mild to moderate dementia (mean age 82.9 ± 7.0 years)	Intervention subjects received progressive resistance and functional training. Controls received a low-intensity motor placebo activity	3-month intervention and 3-month follow-up	Strength, physical function, and physical activity	Intensive, dementia-adjusted training was feasible and substantially improved motor performance

(continued)

Table 2.3 (continued)

Reference	Study design	Participants	Type of intervention	Duration of intervention	Outcome measures	Summary of findings
Zieschang et al. (2013)	RCT	91 participants with mild to moderate dementia	The intervention group received a progressive resistance and functional training. The control group received a low-intensity motor placebo activity	=====	Strength and function were measured before the start of the training (T1), directly after training ceased (T2), 3 months after training ceased (T3), and 9 months after training ceased (T4)	Intensive dementia-specific motor training sustainably improved functional performance 9 months after the end of training
Pharmacologic treatment of gait disturbances in patients with dementia or cognitive decline						
Gurevich et al. (2006)	Pre–posttest design	26 patients with PD and dementia (mean age 75.2±4.9 years)	Patients received rivastigmine mean dose of 8.0 mg/day	12 weeks	Tremor and cognition	Rivastigmine caused only slight worsening of tremor in demented PD patients, while improving cognition
Litvineko et al. (2008)	Open control trial	Intervention group of 21 PD patients with dementia (mean age 68.6±9.3 years) and control group of 20 PD patients with dementia (mean age 72.6±8.6 years)	Intervention group received galantamine 4 mg twice daily for the first 4 weeks and then 8 mg twice daily to the end of the 24-week trial period. Controls continued taking	52 weeks	Cognitive, neuropsychiatric, and motor symptoms	The intervention group had better cognitive score and significant improvements in gait, freezing of gait, and falls compared to the controls

Assal et al. (2008)	Pre–posttest design	Intervention group of nine subjects with mild to moderate AD (mean age 77.9 ± 2.1 years) and 18 controls without dementia (mean age 78.1 ± 1.0 years)	Intervention group received galantamine treatment at a mean dose of 17.8 ± 3.5 mg/day according to standard criteria	24 weeks	Stride time before and after 6 months of galantamine treatment during single and dual tasking while walking	Stride time was shorter under dual task after treatment. There was no change in controls
Montero-Odasso et al. (2009b)	Open-label design	6 mild AD subjects (mean age 79.9 ± 4.0 years) and 8 no-treatment MCI control subjects (mean age 75.6 ± 6.2 years)	6 AD patients received donepezil during 1 month with 5 mg/day of donepezil and 3 months with 10 mg/day of donepezil. 8 MCI patients received no treatment during 4 months	4 months	Gait velocity and gait variability	Gait speed and gait variability improved under both single- and dual-task walking in the intervention group compared to control group. The increases in gait speed were sustained and continued to improve after 4 months, while MCI patients had decreased mean gait velocity and increased gait variability
Beauchet et al. (2011)	Pre–posttest design	Intervention group of 17 AD patients (mean age 83.8 ± 5.8 years) and 32 AD controls who did not take any anti-dementia drug (mean age 80.0 ± 6.6 years)	Intervention group received memantine 20 mg once daily in the morning (titrated in 5-mg increments over 4 weeks)	211 ± 78.2 days	Mean and CV of stride time were determined before and after 4 weeks of memantine treatment	Stride CV improved in the intervention group. There was no other significant difference between groups

TUG Timed Up and Go test, *RCT* randomized controlled trial, *PD* Parkinson's disease, *MCI* mild cognitive impairment, *CV* coefficient of variation, *MMSE* Mini-Mental State Examination, *ADL* activities of daily living, *6WT* 6-min walking test

methylphenidate (MPH) can enhance cognitive and motor function and that it may have a role as a therapeutic option for reducing fall risk (Auriel et al. 2006; Ben-Itzhak et al. 2008; Shorer et al. 2013). However, there is no study specific to people with dementia. The use of MPH (i.e., Ritalin) is well known in treating children with attention deficit hyperactivity disorder, but much less is known about its potential to improve motor function and gait among elderly people.

Acetylcholinesterase (AChE) inhibitors (e.g., donepezil, galantamine, and rivastigmine) are the most useful symptomatic treatment for AD and VaD (Seltzer et al. 2004). It has been suggested that AChE inhibitors may improve gait performance (Assal and van der Meulen 2009) by enhancing attentional resource allocation. The effects of donepezil and galantamine were evaluated in a few small studies and noted that patients treated with donepezil and galantamine had better motor performances (Assal et al. 2008; Drever et al. 2011; Litvinenko et al. 2008; Montero-Odasso et al. 2009b). However, one should keep in mind that AChE inhibitors may provoke parkinsonian symptoms in AD (Trabace et al. 2000), although Gurevich et al. found that rivastigmine caused only slight worsening of tremor without deleteriously affecting other PD symptoms while improving cognition among demented PD patients (Gurevich et al. 2006). Memantine is another symptomatic treatment for AD, and it reportedly has a beneficial effect on global cognitive function (McShane et al. 2006). Memantine-related decrease in stride time variability among people with AD has also been reported (Beauchet et al. 2011). It has been suggested that the combination of memantine plus vitamin D may be more protective than memantine alone against the neuronal loss and the subsequent declines in cognitive and gait performance in AD (Annweiler et al. 2012; Annweiler and Beauchet 2011). Overall, the findings of both the pharmacologic and non-pharmacologic studies for improving gait and reducing falls in the presence of dementia need to be replicated and investigated in large-scale, prospective, randomized, and controlled trials.

Summary and Future Directions

Cognitive alterations are the dominant symptom in dementia, but falls and gait disturbances are ubiquitous among affected individuals. A growing body of literature demonstrates that gait abnormalities can also be present in the early stage of the disease, even before dementia has been diagnosed. These gait abnormalities may serve as a biomarker and assist in the prediction of dementia. The results of the studies mentioned in this review emphasize the importance of routinely including gait assessment—specifically, gait speed and gait variability—in the examination of patients with cognitive decline (Hausdorff and Buchman 2013). Questions about the underlying mechanisms linking motor and cognitive function still remain unanswered. It is hoped that improvement in our ability to quantify and understand microvascular changes will lead to better understanding of the interactions between aging, gait alterations, and cognitive impairment and provide better targeted treatment to combat the functional deterioration in older adults with cognitive impairments and dementia.

References

Aggarwal NT, Wilson RS, Beck TL, et al. Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer disease. Arch Neurol. 2006;63(12):1763–9.

Alexander NB. Gait disorders in older adults. J Am Geriatr Soc. 1996;44(4):434–51.

Alexander NB, Mollo JM, Giordani B, et al. Maintenance of balance, gait patterns, and obstacle clearance in Alzheimer's disease. Neurology. 1995;45(5):908–14.

Allali G, Assal F, Kressig RW, et al. Impact of impaired executive function on gait stability. Dement Geriatr Cogn Disord. 2008;26(4):364–9.

Annweiler C, Beauchet O. Vitamin D-mentia: randomized clinical trials should be the next step. Neuroepidemiology. 2011;37(3–4):249–58.

Annweiler C, Beauchet O, Celle S, et al. Contribution of brain imaging to the understanding of gait disorders in Alzheimer's disease: a systematic review. Am J Alzheimers Dis Other Demen. 2012;27(6):371–80.

Annweiler C, Beauchet O, Bartha R, et al. Motor cortex and gait in mild cognitive impairment: a magnetic resonance spectroscopy and volumetric imaging study. Brain. 2013;136(Pt 3):859–71.

Asada T, Kariya T, Kinoshita T, et al. Predictors of fall-related injuries among community-dwelling elderly people with dementia. Age Ageing. 1996;25(1):22–8.

Assal F, van der Meulen M. Pharmacological interventions in primary care: hopes and illusions. Front Neurol Neurosci. 2009;24:54–65.

Assal F, Allali G, Kressig RW, et al. Galantamine improves gait performance in patients with Alzheimer's disease. J Am Geriatr Soc. 2008;56(5):946–7.

Atkinson HH, Rapp SR, Williamson JD, et al. The relationship between cognitive function and physical performance in older women: results from the women's health initiative memory study. J Gerontol A Biol Sci Med Sci. 2010;65(3):300–6.

Auriel E, Hausdorff JM, Herman T, et al. Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. Clin Neuropharmacol. 2006;29(1):15–7.

Ballard CG, Shaw F, Lowery K, et al. The prevalence, assessment and associations of falls in dementia with Lewy bodies and Alzheimer's disease. Dement Geriatr Cogn Disord. 1999;10(2):97–103.

Balsamo S, Willardson JM, Frederico SS, et al. Effectiveness of exercise on cognitive impairment and Alzheimer's disease. Int J Gen Med. 2013;6:387–91.

Beauchet O, Annweiler C, Allali G, et al. Recurrent falls and dual task-related decrease in walking speed: is there a relationship? J Am Geriatr Soc. 2008;56(7):1265–9.

Beauchet O, Annweiler C, Dubost V, et al. Stops walking when talking: a predictor of falls in older adults? Eur J Neurol. 2009;16(7):786–95.

Beauchet O, Allali G, Thiery S, et al. Association between high variability of gait speed and mild cognitive impairment: a cross-sectional pilot study. J Am Geriatr Soc. 2011;59(10):1973–4.

Ben-Itzhak R, Giladi N, Gruendlinger L, et al. Can methylphenidate reduce fall risk in community-living older adults? A double-blind, single-dose cross-over study. J Am Geriatr Soc. 2008;4(56):695–700.

Blake AJ, Morgan K, Bendall MJ, et al. Falls by elderly people at home: prevalence and associated factors. Age Ageing. 1988;17(6):365–72.

Boyle PA, Wilson RS, Aggarwal NT, et al. Parkinsonian signs in subjects with mild cognitive impairment. Neurology. 2005;65(12):1901–6.

Boyle PA, Wilson RS, Buchman AS, et al. Lower extremity motor function and disability in mild cognitive impairment. Exp Aging Res. 2007;33(3):355–71.

Brach JS, Berlin JE, VanSwearingen JM, et al. Too much or too little step width variability is associated with a fall history in older persons who walk at or near normal gait speed. J Neuroeng Rehabil. 2005;2:21.

Brach JS, Studenski S, Perera S, et al. Stance time and step width variability have unique contributing impairments in older persons. Gait Posture. 2008;27(3):431–9.

Buchner DM, Larson EB. Falls and fractures in patients with Alzheimer-type dementia. JAMA. 1987;257(11):1492–5.
Buracchio T, Dodge HH, Howieson D, et al. The trajectory of gait speed preceding mild cognitive impairment. Arch Neurol. 2010;67(8):980–6.
Buracchio TJ, Mattek NC, Dodge HH, et al. Executive function predicts risk of falls in older adults without balance impairment. BMC Geriatr. 2011;11:74.
Burns JM, Galvin JE, Roe CM, et al. The pathology of the substantia nigra in Alzheimer disease with extrapyramidal signs. Neurology. 2005;64(8):1397–403.
Camicioli R, Howieson D, Lehman S, et al. Talking while walking: the effect of a dual task in aging and Alzheimer's disease. Neurology. 1997a;48(4):955–8.
Camicioli R, Panzer VP, Kaye J. Balance in the healthy elderly: posturography and clinical assessment. Arch Neurol. 1997b;54(8):976–81.
Camicioli R, Oken BS, Sexton G, et al. Verbal fluency task affects gait in Parkinson's disease with motor freezing. J Geriatr Psychiatry Neurol. 1998;11(4):181–5.
Chen TY, Peronto CL, Edwards JD. Cognitive function as a prospective predictor of falls. J Gerontol B Psychol Sci Soc Sci. 2012;67(6):720–8.
Chui HC, Mack W, Jackson JE, et al. Clinical criteria for the diagnosis of vascular dementia: a multicenter study of comparability and interrater reliability. Arch Neurol. 2000;57(2):191–6.
Clair AA, O'Konski M. The effect of rhythmic auditory stimulation (RAS) on gait characteristics of cadence, velocity, and stride length in persons with late stage dementia. J Music Ther. 2006;43(2):154–63.
de Carle AJ, Kohn R. Risk factors for falling in a psychogeriatric unit. Int J Geriatr Psychiatry. 2001;16(8):762–7.
Della SS, Spinnler H, Venneri A. Walking difficulties in patients with Alzheimer's disease might originate from gait apraxia. J Neurol Neurosurg Psychiatry. 2004;75(2):196–201.
Drever BD, Riedel G, Platt B. The cholinergic system and hippocampal plasticity. Behav Brain Res. 2011;221(2):505–14.
Elble RJ, Moody C, Leffler K, et al. The initiation of normal walking. Mov Disord. 1994;9(2):139–46.
Ensrud KE, Blackwell TL, Mangione CM, et al. Central nervous system-active medications and risk for falls in older women. J Am Geriatr Soc. 2002;50(10):1629–37.
Ganz DA, Bao Y, Shekelle PG, et al. Will my patient fall? JAMA. 2007;297(1):77–86.
Giladi N, Herman T, Reider-Groswasser II, et al. Clinical characteristics of elderly patients with a cautious gait of unknown origin. J Neurol. 2005;252(3):300–6.
Gurevich TY, Shabtai H, Korczyn AD, et al. Effect of rivastigmine on tremor in patients with Parkinson's disease and dementia. Mov Disord. 2006;21(10):1663–6.
Hageman PA, Thomas VS. Gait performance in dementia: the effects of a 6-week resistance training program in an adult day-care setting. Int J Geriatr Psychiatry. 2002;17(4):329–34.
Harlein J, Dassen T, Halfens RJ, et al. Fall risk factors in older people with dementia or cognitive impairment: a systematic review. J Adv Nurs. 2009;65(5):922–33.
Hauer K, Schwenk M, Zieschang T, et al. Physical training improves motor performance in people with dementia: a randomized controlled trial. J Am Geriatr Soc. 2012;60(1):8–15.
Hausdorff JM. Gait variability: methods, modeling and meaning. J Neuroeng Rehabil. 2005;2:19.
Hausdorff JM. Gait dynamics, fractals and falls: finding meaning in the stride-to-stride fluctuations of human walking. Hum Mov Sci. 2007;26(4):555–89.
Hausdorff JM, Buchman AS. What links gait speed and MCI with dementia? A fresh look at the association between motor and cognitive function. J Gerontol A Biol Sci Med Sci. 2013;68(4):409–11.
Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. Arch Phys Med Rehabil. 2001;82(8):1050–6.
Hausdorff JM, Yogev G, Springer S, et al. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. Exp Rain Res. 2005;164(4):541–8.
Hausdorff JM, Schweiger A, Herman T, et al. Dual-task decrements in gait: contributing factors among healthy older adults. J Gerontol A Biol Sci Med Sci. 2008;63(12):1335–43.

Herman T, Mirelman A, Giladi N, et al. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. J Gerontol A Biol Sci Med Sci. 2010;65(10):1086–92.

Heuninckx S, Wenderoth N, Debaere F, et al. Neural basis of aging: the penetration of cognition into action control. J Neurosci. 2005;25(29):6787–96.

Holtzer R, Verghese J, Xue X, et al. Cognitive processes related to gait velocity: results from the Einstein Aging Study. Neuropsychology. 2006;20(2):215–23.

Husted JA, Cook RJ, Farewell VT, et al. Methods for assessing responsiveness: a critical review and recommendations. J Clin Epidemiol. 2000;53(5):459–68.

Inzitari M, Baldereschi M, Di CA, et al. Impaired attention predicts motor performance decline in older community-dwellers with normal baseline mobility: results from the Italian Longitudinal Study on Aging (ILSA). J Gerontol A Biol Sci Med Sci. 2007;62(8):837–43.

Kallin K, Gustafson Y, Sandman PO, et al. Drugs and falls in older people in geriatric care settings. Aging Clin Exp Res. 2004;16(4):270–6.

Kluger A, Ferris SH, Golomb J, et al. Neuropsychological prediction of decline to dementia in nondemented elderly. J Geriatr Psychiatry Neurol. 1999;12(4):168–79.

Litvinenko IV, Odinak MM, Mogil'naia VI, et al. Memantine (akatinol) therapy of cognitive impairment in Parkinson's disease complicated by dementia. Zh Nevrol Psikhiatr Im S S Korsakova. 2008;108(10):37–42.

Louis ED, Schupf N, Manly J, et al. Association between mild parkinsonian signs and mild cognitive impairment in a community. Neurology. 2005;64(7):1157–61.

Maki BE. Gait changes in older adults: predictors of falls or indicators of fear. J Am Geriatr Soc. 1997;45(3):313–20.

McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939–44.

McShane, R, Areosa, SA, Minakaran, N. Memantine for dementia. Cochrane Database Syst Rev. 2006;2:CD003154.

Montero-Odasso M, Bergman H, Phillips NA, et al. Dual-tasking and gait in people with mild cognitive impairment. The effect of working memory. BMC Geriatr. 2009a;9:41.

Montero-Odasso M, Wells J, Borrie M. Can cognitive enhancers reduce the risk of falls in people with dementia? An open-label study with controls. J Am Geriatr Soc. 2009b;57(2):359–60.

Montero-Odasso M, Annweiler C, Hachinski V, et al. Vascular burden predicts gait, mood, and executive function disturbances in older adults with mild cognitive impairment: results from the gait and brain study. J Am Geriatr Soc. 2012a;60(10):1988–90.

Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. Arch Phys Med Rehabil. 2012b;93(2):293–9.

Montero-Odasso M, Verghese J, Beauchet O, et al. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. J Am Geriatr Soc. 2012c;60(11): 2127–36.

Moretti F, De RD, Palmer K, et al. Prevalence and characteristics of mild cognitive impairment in the general population. Data from an Italian population-based study: The Faenza Project. Aging Ment Health. 2013;17(3):267–75.

Morris JC, Rubin EH, Morris EJ, et al. Senile dementia of the Alzheimer's type: an important risk factor for serious falls. J Gerontol. 1987;42(4):412–7.

Muir SW, Speechley M, Wells J, et al. Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. Gait Posture. 2012;35(1):96–100.

Nakamura T, Meguro K, Sasaki H. Relationship between falls and stride length variability in senile dementia of the Alzheimer type. Gerontology. 1996;42(2):108–13.

Nakamura T, Meguro K, Yamazaki H, et al. Postural and gait disturbance correlated with decreased frontal cerebral blood flow in Alzheimer disease. Alzheimer Dis Assoc Disord. 1997; 11(3):132–9.

Nevitt MC, Cummings SR. Type of fall and risk of hip and wrist fractures: the study of osteoporotic fractures. The Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 1993;41(11):1226–34.

Njegovan V, Hing MM, Mitchell SL, et al. The hierarchy of functional loss associated with cognitive decline in older persons. J Gerontol A Biol Sci Med Sci. 2001;56(10):M638–43.

O'Keeffe ST, Lavan JN. Predicting delirium in elderly patients: development and validation of a risk-stratification model. Age Ageing. 1996;25(4):317–21.

Odenheimer G, Funkenstein HH, Beckett L, et al. Comparison of neurologic changes in 'successfully aging' persons vs the total aging population. Arch Neurol. 1994;51(6):573–80.

Ostchega Y, Harris TB, Hirsch R, et al. The prevalence of functional limitations and disability in older persons in the US: data from the National Health and Nutrition Examination Survey III. J Am Geriatr Soc. 2000;48(9):1132–5.

Perry RJ, Hodges JR. Attention and executive deficits in Alzheimer's disease. A critical review. Brain. 1999;122(Pt 3):383–404.

Petersen RC. Mild cognitive impairment: current research and clinical implications. Semin Neurol. 2007;27(1):22–31.

Prehogan A, Cohen CI. Motor dysfunction in dementias. Geriatrics. 2004;59(11):53–60.

Raglio A, Bellelli G, Mazzola P, et al. Music, music therapy and dementia: a review of literature and the recommendations of the Italian Psychogeriatric Association. Maturitas. 2012;72(4):305–10.

Richardson JK, Thies SB, DeMott TK, et al. Interventions improve gait regularity in patients with peripheral neuropathy while walking on an irregular surface under low light. J Am Geriatr Soc. 2004;52(4):510–5.

Rolland Y, Pillard F, Klapouszczak A, et al. Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. J Am Geriatr Soc. 2007;55(2):158–65.

Roman GC. Vascular dementia. Advances in nosology, diagnosis, treatment and prevention. Panminerva Med. 2004;46(4):207–15.

Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43(2):250–60.

Scherder E, Eggermont L, Swaab D, et al. Gait in ageing and associated dementias, its relationship with cognition. Neurosci Biobehav Rev. 2007;31(4):485–97.

Schwenk M, Zieschang T, Oster P, et al. Dual-task performances can be improved in patients with dementia: a randomized controlled trial. Neurology. 2010;74(24):1961–8.

Segev-Jacubovski O, Herman T, Yogev-Seligmann G, et al. The interplay between gait, falls and cognition: can cognitive therapy reduce fall risk? Expert Rev Neurother. 2011;11(7):1057–75.

Seltzer B, Zolnouni P, Nunez M, et al. Efficacy of donepezil in early-stage Alzheimer disease: a randomized placebo-controlled trial. Arch Neurol. 2004;61(12):1852–6.

Shaw FE. Prevention of falls in older people with dementia. J Neural Transm. 2007;114(10):1259–64.

Sheridan PL, Hausdorff JM. The role of higher-level cognitive function in gait: executive dysfunction contributes to fall risk in Alzheimer's disease. Dement Geriatr Cogn Disord. 2007;2(24):125–37.

Sheridan PL, Solomont J, Kowall N, et al. Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease. J Am Geriatr Soc. 2003;51(11):1633–7.

Shorer Z, Yaakov B, Guy T, et al. Effect of single dose methylphenidate on walking and postural stability under single- and dual-task conditions in older adults–a double-blind randomized control trial. J Gerontol A Biol Sci Med Sci. 2013;68(10):1271–80.

Soumare A, Tavernier B, Alperovitch A, et al. A cross-sectional and longitudinal study of the relationship between walking speed and cognitive function in community-dwelling elderly people. J Gerontol A Biol Sci Med Sci. 2009;64(10):1058–65.

Springer S, Giladi N, Peretz C, et al. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. Mov Disord. 2006;21(7):950–7.

Suttanon P, Hill KD, Said CM, et al. A longitudinal study of change in falls risk and balance and mobility in healthy older people and people with Alzheimer disease. Am J Phys Med Rehabil. 2013;92(8):676–85.
Suzuki M, Kurata S, Yamamoto E, et al. Impact of fall-related behaviors as risk factors for falls among the elderly patients with dementia in a geriatric facility in Japan. Am J Alzheimers Dis Other Demen. 2012;27(6):439–46.
Tabbarah M, Crimmins EM, Seeman TE. The relationship between cognitive and physical performance: MacArthur Studies of Successful Aging. J Gerontol A Biol Sci Med Sci. 2002;57(4):M228–35.
Tanaka A, Okuzumi H, Kobayashi I, et al. Gait disturbance of patients with vascular and Alzheimer-type dementias. Percept Mot Skills. 1995;80(3 Pt 1):735–8.
Taniguchi Y, Yoshida H, Fujiwara Y, et al. A prospective study of gait performance and subsequent cognitive decline in a general population of older Japanese. J Gerontol A Biol Sci Med Sci. 2012;67(7):796–803.
Thapa PB, Gideon P, Fought RL, et al. Psychotropic drugs and risk of recurrent falls in ambulatory nursing home residents. Am J Epidemiol. 1995;142(2):202–11.
Tinetti ME. Prevention of falls and fall injuries in elderly persons: a research agenda. Prev Med. 1994;23(5):756–62.
Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med. 1988;26(319):1701–7.
Toulotte C, Fabre C, Dangremont B, et al. Effects of physical training on the physical capacity of frail, demented patients with a history of falling: a randomised controlled trial. Age Ageing. 2003;32(1):67–73.
Trabace L, Cassano T, Steardo L, et al. Biochemical and neurobehavioral profile of CHF2819, a novel, orally active acetylcholinesterase inhibitor for Alzheimer's disease. J Pharmacol Exp Ther. 2000;294(1):187–94.
van Dijk PT, Meulenberg OG, van de Sande HJ, et al. Falls in dementia patients. Gerontologist. 1993;33(2):200–4.
van Doorn C, Gruber-Baldini AL, Zimmerman S, et al. Dementia as a risk factor for falls and fall injuries among nursing home residents. J Am Geriatr Soc. 2003;51(9):1213–8.
van Iersel MB, Hoefsloot W, Munneke M, et al. Systematic review of quantitative clinical gait analysis in patients with dementia. Z Gerontol Geriatr. 2004;37(1):27–32.
van Iersel MB, Verbeek AL, Bloem BR, et al. Frail elderly patients with dementia go too fast. J Neurol Neurosurg Psychiatry. 2006;77(7):874–6.
van Norden AG, van Dijk EJ, de Laat KF, et al. Dementia: Alzheimer pathology and vascular factors: from mutually exclusive to interaction. Biochim Biophys Acta. 2012;1822(3):340–9.
Venturelli M, Scarsini R, Schena F. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. Am J Alzheimers Dis Other Demen. 2011;26(5):381–8.
Verghese J, Xue X. Predisability gait patterns in older adults. Gait Posture. 2011;33(1):98–101.
Verghese J, Lipton RB, Hall CB, et al. Abnormality of gait as a predictor of non-Alzheimer's dementia. N Engl J Med. 2002;347(22):1761–8.
Verghese J, Kuslansky G, Holtzer R, et al. Walking while talking: effect of task prioritization in the elderly. Arch Phys Med Rehabil. 2007;88(1):50–3.
Verghese J, Robbins M, Holtzer R, et al. Gait dysfunction in mild cognitive impairment syndromes. J Am Geriatr Soc. 2008;56(7):1244–51.
Verghese J, Wang C, Lipton RB, et al. Motoric cognitive risk syndrome and the risk of dementia. J Gerontol A Biol Sci Med Sci. 2013;68(4):412–8.
Visser H. Gait balance in senile dementia of Alzheimer's type. Age Ageing. 1983;12(4):296–301.
Waite LM, Grayson DA, Piguet O, et al. Gait slowing as a predictor of incident dementia: 6-year longitudinal data from the Sydney Older Persons Study. J Neurol Sci. 2005;229–230:89–93.
Watson GS, Leverenz JB. Profile of cognitive impairment in Parkinson's disease. Brain Pathol. 2010;20(3):640–5.

Woollacott M, Shumway-Cook A. Attention the control of posture and gait: a review of an emerging area of research. Gait Posture. 2002;16(1):1–14.
Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. Mov Disord. 2008;23(3):329–42.
Zieschang T, Schwenk M, Oster P, et al. Sustainability of motor training effects in older people with dementia. J Alzheimers Dis. 2013;34(1):191–202.
Zimmerman ME, Pan JW, Hetherington HP, et al. Hippocampal correlates of pain in healthy elderly adults: a pilot study. Neurology. 2009;73(19):1567–70.

Chapter 3
Falls in Patients with Dementia

Lynn Rochester, Sue Lord, Alison J. Yarnall, and David J. Burn

Abstract Falls are a major problem in dementia with an annual reported incidence of about 70–80 %, double that of older adults without cognitive impairment. Remaining mobile and free from falls is a priority, and understanding falls in dementia is of critical importance to mitigate the burden caused not only to the patient but also the carer. Despite this, there is currently no convincing evidence to mitigate falls risk in dementia. Gait and balance impairments are important falls risk factors as are cognitive impairment, and more recently the interdependency between these features has been recognized and is influencing assessment and the development of novel therapeutic strategies. This chapter covers four relevant and important key areas: (1) prevalence, incidence, and risk of falls with respect to different types of dementia including a focus on disorders in gait and balance which are important contributors and medication; (2) emerging evidence for contributory mechanisms; (3) evolving concepts relating to the interrelationship between gait, balance, cognition, and falls; and finally (4) approaches to mitigate falls risk and implications for clinical practice.

Keywords Dementia • Falls • Gait • Balance • Cognitive impairment • Risk factors

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Introduction

The increased worldwide prevalence of neurodegenerative disease means that by 2020 an estimated 42 million people will have a diagnosis of dementia (Ferri et al. 2005). Falls are a major problem in dementia with an annual reported incidence of about 70–80 % (Allan et al. 2009; Shaw 2002), double that of older adults without cognitive impairment (Tinetti et al. 1988). The consequence of falls in older adults with dementia makes sober reading and includes an increased risk of serious injury (Tinetti et al. 1988; Kallin et al. 2005), institutionalization (Morris et al. 1987), and mortality (Morrison and Siu 2000). Remaining mobile and free from falls is a therapeutic priority in older adults and those with dementia, and understanding falls in dementia is of critical importance to mitigate the burden caused not only to the patient but also the carer (Lowery et al. 2000a). The most recent clinical practice guideline for prevention of falls in older persons (American Geriatric Society/ British Geriatric Society 2011) concluded that "There is insufficient evidence to recommend for or against multifactorial or single interventions to prevent falls in older persons with known dementia living in the community or in long-term care facilities," due in large part to lack of studies and poor quality of studies.

Gait and balance impairments are risk factors for falls as are cognitive impairment and dementia. More recently the interdependency between these features has been recognized and as a consequence is influencing assessment and the development of novel therapeutic strategies. This chapter addresses falls in patients with dementia and explores the relationship between disorders that arise in gait and balance in dementia subtypes and falls. We define a fall as an event whereby a person comes to lie on the ground or another lower level with or without loss of consciousness (World Health Organisation2013). The most common forms of dementia (Alzheimer's disease (AD), vascular dementia (VAD), dementia with Lewy bodies (DLB), and Parkinson's disease with dementia (PDD)) are the main focus, however, where relevant mild cognitive impairment is discussed as a precursor to dementia. Rather than carrying out an exhaustive review of the body of literature, we instead refer to the key studies to illustrate critical points. Studies are limited to mild to moderate dementia which mainly involves individuals dwelling in the community rather than as residents of nursing homes. Four key areas are covered: (1) prevalence, incidence, and risk of falls with respect to different types of dementia including a focus on disorders in gait and balance which are important contributors; (2) emerging evidence for contributory mechanisms; (3) evolving concepts relating to the interrelationship between gait, balance, cognition, and falls; and finally (4) approaches to mitigate falls risk and implications for clinical practice.

Epidemiology, Prevalence, Incidence, and Risk of Falls in Dementia

Falls are the fifth leading cause of death among older adults (World Health Organisation 2013) and as such constitute a major health concern. Approximately one third of people over the age of 65 fall each year, with an increase in prevalence

Table 3.1 Annual prevalence and incidence of falls (falls/1,000 persons) and prevalence of gait and balance disorders in different dementia subtypes

	Controls	AD	VAD	DLB	PDD	PD
Falls prevalence (%)	36	47	47	77	90	61
Falls incidence (falls/1,000 people)	1,023	2,486	3,135	9,087	19,000	4,617
Gait disorder *N* (%)	3/42 (7)	10/40 (25)	31/39 (79)	24/32 (75)	43/46 (93)	20/46 (43)

Taken from Allan et al. (2005, 2009)

in dementia. Broadly speaking, people with dementia are two to three times more likely to fall than age-matched healthy counterparts, with institutionalized adults also at a higher risk compared with community living (Kröpelin et al. 2013). Although estimates vary widely according to the method of data collection, type of dementia, and domestic environment, figures suggest a prevalence of around 40 % for community-dwelling adults (Allan et al. 2009; Salva et al. 2012) and 60 % for people living in residential care (Eriksson et al. 2008). Several reports indicate a higher prevalence in people with dementia associated with Parkinson's disease (PD) compared with dementia related to vascular disease – differences that are also reflected in incidence figures (Table 3.1). Annual incidence figures are consistent for prospective studies, with estimates as noted above between 70 and 85 %, twice that of healthy older adults (Shaw 2002). Incidence figures for retrospective studies are less consistent and produce much lower estimates (Shaw 2002). The prevalence and incidence of falls is set to increase given the aging population, which is estimated to triple from 600 million to 2 billion by 2050 (World Health Organisation 2009), a third of who will end their lives with dementia (Department of Health 2009).

Compared with demented older adults who do not fall, fallers have a higher risk of functional decline and are five times more likely to be institutionalized (Salva et al. 2012). Falls in dementia are also a common cause of hospitalization. In a longitudinal study of 682 people with AD, falls resulted in admission in just over a fifth of the 26.2 % hospitalized (Voisin et al. 2010). People with dementia constitute a significant proportion of the total population of elderly hip fracture patients in hospitals (about 30–50 %) (Stenvall et al. 2012). Other specific issues include increase risk of delirium, poor recovery, increased institutionalization, and increased mortality (Scandol et al. 2013).

An extensive body of research has identified risk factors for falls in people with cognitive impairment and dementia. The evidence is difficult to summarize because of inconsistencies in the classification and severity of cognitive impairment and the environment in which people are tested. Overall, the key factors include type of dementia, gait and postural impairment, medication, neurocardiovascular instability, and environment (Kröpelin et al. 2013; Shaw 2007; Harlein et al. 2009). Below we focus on three of the major risk factors for falls in patients with dementia – dementia subtype, gait and balance impairments, and medication.

(a) Type of Dementia. Dementia itself is a recognized risk factor for falls with recent studies reporting the annual prevalence of falls in people with dementia living in the community range from 35 to 90 % (Allan et al. 2009; Shaw 2002; Salva et al. 2012) and those in residential care between 40 and 62 % (Eriksson

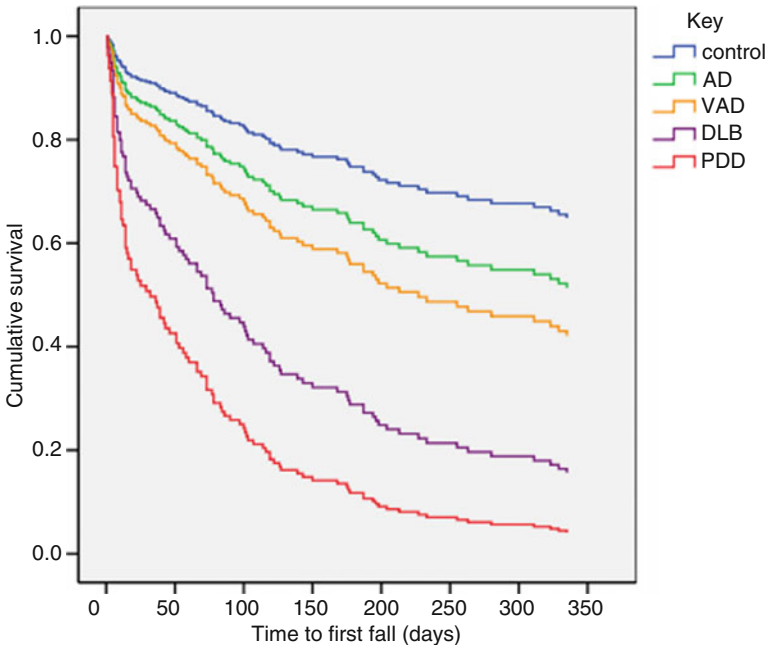

Fig. 3.1 Survival curve showing time to first fall by diagnosis (Reprinted from Allan et al. (2009))

et al. 2008). Cohorts are typically heterogeneous in nature and include dementias of mixed etiology and a broad range of severity. Understanding falls risk with respect to dementia subtype is highly relevant to a better understanding of the underlying mechanisms and to identify and target key at-risk groups for intervention. Allan et al. (2005) reported retrospective falls in dementia subtypes (AD, VAD, DLB, and PDD) and found that although people with dementia were more likely to report single or multiple falls in the previous year, the risk of falls was highly dependent upon subtype (see Table 3.1). A follow-on prospective study confirmed these findings and described the annual incidence of falls according to dementia and dementia subtype (Allan et al. 2009). Fall prevalence and rates with respect to dementia subtype are shown in Table 3.1, while Fig. 3.1 shows the time to first fall. It is clear that Lewy body dementias (DLB and PDD) have a far higher risk for falls than AD and VAD, a feature that also informs the diagnostic criteria for DLB (McKeith et al. 2000). It is also pertinent that fall-related injuries were greater in Lewy body dementias, while Lewy body disease and parkinsonism were identified as risk factors for falls in patients with dementia (Allan et al. 2009; Lowery et al. 2000b).

(b) Gait and Balance Impairment. Gait and balance disturbances are more common in older adults with a 35 % prevalence of gait disorders in older adults over the age of 70 (Verghese et al. 2006) and are important risk factors for falls (Ambrose et al. 2013). Classification schemes identify specific syndromes of gait such as hypokinetic-rigid gait, cautious gait, and higher-level gait disorders (Snijders et al. 2007) that include gait deficits such as slow, cautious gait; freezing of gait; start hesitation; balance impairment; and associated cognitive impairments.

These features are also associated with increased falls risk, for example, parkinsonism (slow gait with freezing) (Lim et al. 2008; Kerr et al. 2010; Latt et al. 2009) as well as mild cognitive impairment (Taylor et al. 2012; Camicioli and Majumdar 2010). The prevalence of gait and balance impairments is even greater in dementia (Ambrose et al. 2013; Taylor et al. 2012; van Iersel et al. 2004) accompanying the increased falls risk. The prevalence and severity of gait disorders are also dependent upon the dementia subtype (Allan et al. 2005) (see Table 3.1). The highest level of gait and balance impairments was also similar in pattern to falls rates with respect to dementia subtype being greatest in LBD, especially PDD, and the lowest in AD, although all groups had a higher prevalence of gait and balance impairment than controls. It is also worth noting, however, that the high incidence of falls in DLB could not be attributed purely to movement disorders such as parkinsonism as falls risk was found to be increased even in those without extrapyramidal signs (Imamura et al. 2000). What is evident is the added burden apparently placed by gait and balance disorders on falls risk in dementia, highlighting the complex relationship between gait, balance, cognition, and falls and will be discussed in section "The Complex Relationship Between Gait, Balance, Cognition, and Falls: Emerging Concepts."

(c) Medication. As discussed earlier, advanced age is the greatest risk factor for increased dementia risk. As age increases, so too does the number of medications prescribed, with polypharmacy itself a risk factor for falls in older adults (Neutel et al. 2002). In addition, patients with cognitive impairment and associated behavioral symptoms may be treated with psychotropic medications, which have long been associated with increased falls risk (Ensrud et al. 2002; Fick et al. 2007; Leipzig et al. 1999; Sheahan et al. 1995). Mechanisms through which falls occur in association with psychotropic medications may include fatigue/somnolence, decreased awareness of surroundings, confusion, orthostatic hypotension, or syncope. Benzodiazepines in particular, used to treat sleep disturbance in older adults and REM sleep behavior disorder in DLB and PDD, increase the risk of fall and subsequent hip fracture by at least 50 % (Cumming and Le Couteur 2003). More recently it has been recognized that antidepressants are associated with falls, with selective serotonin reuptake inhibitors associated with the highest adjusted hazard ratios for falls (1.66) (Coupland et al. 2011). Specific medications that may increase falls risk in patients with PDD include dopaminergic agents, which may precipitate falls through dyskinesias (Robinson et al. 2005). Therefore, it is prudent to consider rationalization of medications that may not be required or which may increase falls risk.

Common Mechanisms for Gait, Balance, and Cognitive Impairment: Contributors to Falls Risk?

A better understanding of the relationship between gait, balance, and cognitive decline is important to help explain the increased risk of falls in dementia. Potential candidates include the contribution of cholinergic dysfunction and small vessel cerebrovascular disease (CVD) to gait, balance, and cognitive impairment.

Cholinergic Dysfunction

In PD and PDD, falls are frequent and are closely related to cognition especially attention (Latt et al. 2009; Allcock et al. 2009; Burn et al. 2003; Burn et al. 2006), leading to an assumption that they may have a similar neurochemical mechanism, and therefore cognitive disturbance and falling may not be independent. Two major cholinergic projection systems in the brain could contribute and are shown in Fig. 3.2a. The pedunculopontine nucleus (PPN) in the brainstem contains cholinergic neurons that have a powerful influence on gait and postural control (Jenkinson et al. 2009; Karachi et al. 2010). Thalamic acetylcholinesterase (AChE) activity reflects cholinergic activity from neurons in the PPN (Bohnen and Albin 2011), which is reduced in early PD (Bohnen and Albin 2011; Gilman et al. 2010; Shimada et al. 2009) and more so in PD fallers (Bohnen et al. 2009a), suggesting a relationship with gait and postural dyscontrol. Cholinergic function (estimated using short-latency afferent inhibition) was also found to be highly associated to gait in PD (see Fig. 3.2b) even after adjusting for age and motor dysfunction (Rochester et al. 2012). Cholinergic neurons in the nucleus basalis of Meynert (nbM) play a role in attentional control and executive function (Yarnall et al. 2011) which also contribute to gait disturbance in PD (Lord et al. 2010, 2011a, b; Rochester et al. 2008; Yogev-Seligmann et al. 2005).

Small Vessel Cerebrovascular Disease

Leukoaraiosis or lesions of the white matter (WML) are seen as areas of increased signal intensity on brain scans and are common findings in older adults who are otherwise fit and well (LADIS study group et al. 2011). WML are associated with small vessel cerebrovascular disease (CVD) as a result of hypertension (an additional risk factor for falls in dementia) causing structural lesions in white matter tracts which can lead to changes in motor and cognitive function (LADIS study group et al. 2011). Structural changes can also occur in normal-appearing white matter and lead to motor and cognitive impairments (LADIS study group et al. 2011). In older adults without cognitive impairment, WML are associated with gait and balance disorders (Zheng et al. 2011; de Laat et al. 2011; Baezner et al. 2008; Rosano et al. 2006), in particular reduced speed and increased variability (Srikanth et al. 2009). They are also associated prospectively with increased falls risk (Srikanth et al. 2009; Blahak et al. 2008). Lesions in frontal-subcortical motor circuits were significantly associated with balance disturbances and increased falls risk (Blahak et al. 2008). In adults with high-level gait disorders (HLGD), a gait syndrome reflecting a more cautious hesitant gait, associated changes in white matter were found with diffusor tension imaging in pathways related to both motor and cognitive function (Kafri et al. 2013). The roles of WML and CVD are also increasingly recognized as contributory features to the pathophysiology of different dementia

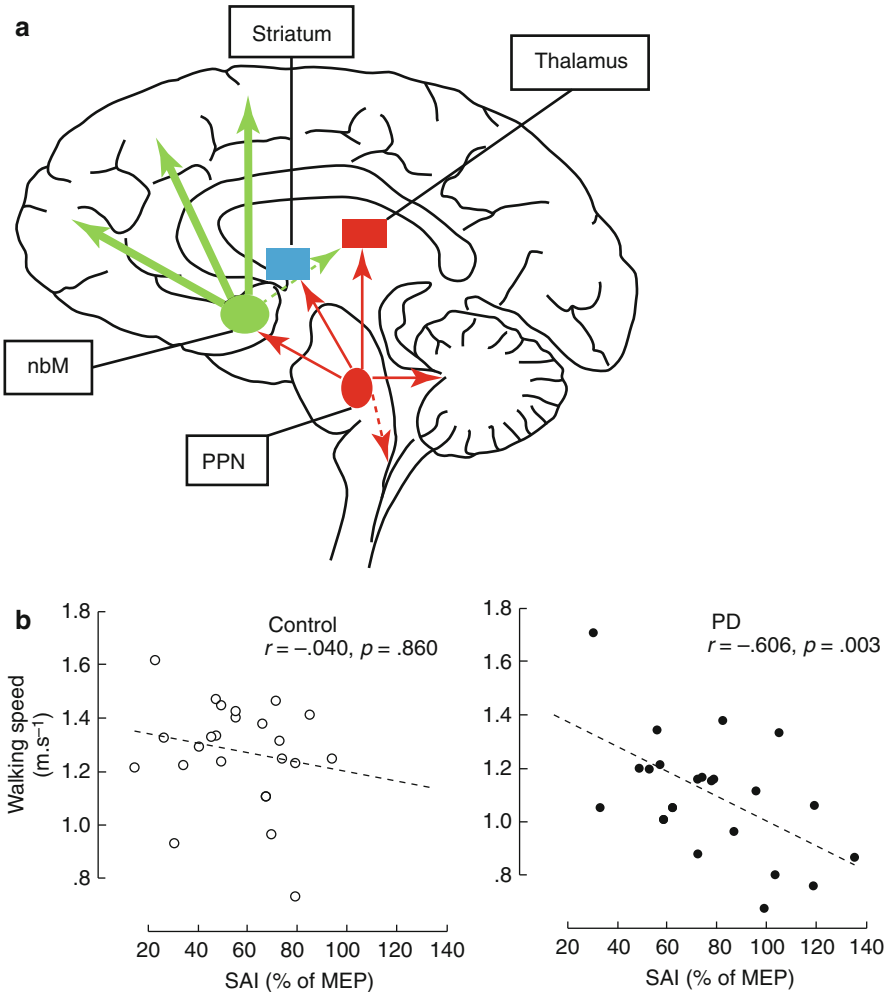

Fig. 3.2 (**a**) Schematic representation of cholinergic output in the cortex (Reprinted from Yarnall et al. (2011) with permission from John Wiley and Sons). Cholinergic interneurons in the striatum are shown in blue. The pedunculopontine nucleus (*PPN*; shown in *red*) provides the majority of cholinergic input to the thalamus, with other projections to the nucleus basalis of Meynert (*nbM*), striatum, substantia nigra, subthalamic nucleus, globus pallidus interna, cerebellum, and spinal cord. The nbM (shown in *green*) sends cholinergic projections to the cerebral cortex and also to thalamic nuclei. (**b**) Correlation of walking speed and short-latency afferent inhibition (*SAI*) in PD ($n = 22$) and control participants ($n = 22$) showing a significant association for PD only (Reprinted from Rochester et al. (2012), by permission of Oxford University Press)

subtypes leading to speculation that CVD and WML burden might be contributory pathological features in gait, balance, and cognitive impairment and therefore a common mechanism of falls in dementia. For example, AD is linked to CVD with evidence to suggest that CVD may accelerate the pathology and symptoms

associated with AD (Honjo et al. 2012). Furthermore, AD with cerebrovascular disease (CVD) has worse gait and balance than AD without cerebrovascular disease (Inzitari et al. 2013), and a systematic review found that in AD gait impairment was associated with a higher burden of WML with changes associated with frontal-subcortical lesions and atrophy and hypometabolism of the hippocampus (Annweiler et al. 2012). Comorbid WMD has also been reported to be a greater determinant of axial motor impairment than nigrostriatal dopaminergic denervation potentially contributing to balance impairment and falls risk in PD and possibly PDD (Bohnen et al. 2011). WML have also been shown to contribute to cortical cholinergic deafferentation (Bohnen et al. 2009b) and highlight the potential interactions between pathology and underlying mechanisms across pathology and dementias. These mechanisms are helpful to inform potential therapies to reduce falls risk in dementia.

The Complex Relationship Between Gait, Balance, Cognition, and Falls: Emerging Concepts

Until relatively recently, falls and dementia were treated as two relatively unrelated entities (Fig. 3.2a), with distinct pathways and causal features. This view is changing. A 2010 addition to American and British Geriatric Societies (American Geriatric Society/British Geriatric Society 2011) clinical practice guidelines for prevention of falls suggests that further to questioning patients about a fall, clinicians should also ask about the presence of any gait problems. This move reflects the wider, recent recognition of the complex interrelationship between gait, cognition, and falls, as depicted in Fig. 3.2b.

For the past decade, the link between cognition, gait, and falls has intensified. The notion that safe and effective gait (and by corollary, absence of falls) is due solely to an intact motor system has given way to a more complex model that reflects the cognitive control of balance and gait (Montero-Odasso et al. 2012). This "top-down" control is evident well before dementia states emerge. The cognitive "cost" of balance and walking is revealed when the motor system is stressed during assessment. The most common approach to producing "stress" is to use a dual-task testing paradigm, when the subject performs a simultaneous (usually cognitive) task during a balance task or during gait. For any adult, dual tasking is attention demanding but the effect is marked in people with cognitive impairment and dementia. In a seminal study in 1997, Lundin-Olsson (Lundin-Olsson et al. 1997) reported increased falls in institutionalized adults with dementia who were unable to continue walking when a conversation was initiated. This gave rise to the "stops walking when talking" test as a predictive measure of falls. Attention is a powerful modifier of gait and falls and may "drive" other cognitive features also involved. Allcock and colleagues (2009) demonstrated that power of attention and reaction time variability scores were significantly associated with falls, even when adjusted for motor severity. However, the relationship between dual task and falls is not

clear cut, given the wide range of response to dual task and protocols used in testing. The link between cognition, balance, and gait has focused attention on gait measurement and what it can reveal about future cognitive (and health) states. In longitudinal cohorts of community-dwelling older adults, gait impairment has been shown to predict mild cognitive decline and dementia (Verghese et al. 2007), along with falls (Ambrose et al. 2013) and adverse health outcomes (Abellan van Kan 2009).

The recent emphasis on cognitive control of gait and falls does not preclude the important contribution of sensorimotor function to balance, gait, and falls which is well established in the literature for non-demented fallers. For example, muscle strength and vision have been shown to be key determinants of balance, gait, and falls, and a comprehensive falls assessment includes these in a wider battery along with proprioceptive testing (Lord et al. 2003). The relative contribution of cognitive function to motor function is likely to be different in dementia, with cognitive function overriding other systems. This has not been studied in detail. However, knowledge of the role of cognition in pre-dementia states provides a basis for novel interventions, which are discussed below.

Mitigating Falls Risk in Dementias: Linking Traditional and Contemporary Approaches

As stated at the beginning of the chapter, the most recent clinical practice guideline for prevention of falls in older persons (American Geriatric Society/British Geriatric Society 2011) concluded that "There is insufficient evidence to recommend for or against multifactorial or single interventions to prevent falls in older persons with known dementia living in the community or in long-term care facilities," due in large part to lack of studies and poor quality of studies. Widely accepted falls reduction programs for older adults (e.g., FAME, Otago Falls Programme, Tai Chi) emerge from research that has excluded people with dementia or cognitive impairment (Gillespie et al. 2009). Exercise is feasible for people with dementia, but has focused on cardiovascular fitness rather than exercise to improve balance (Hill et al. 2009). Multicomponent interventions that target endurance, strength, and balance have been shown to improve physical functioning (Blankevoort et al. 2010), but the translation to falls is less convincing. Individualized, tailor-made programs may be more effective than generic interventions. A recent RCT reported beneficial outcomes for people with dementia who were exposed to an individualized, multidisciplinary medical and rehabilitation regime after hip fracture (Stenvall et al. 2012), and a recent pilot study reported a 32.6 % reduction in falls and decreased agitation in people with dementia living in a residential care home through the use of individualized therapies based on behavioral and cognitive profiles (Bharwani et al. 2012). Current evidence points to the need for targeted selection of participants, with consideration given to severity and type of dementia, presence of gait abnormalities and functional limitations, previous history of falls,

living environment, and age. The most critical of these is likely to be severity of dementia: above a certain threshold interventions will be ineffective (Shaw 2002). Physical activity is overall protective of cognitive decline and protective for first falls in dementia (Allan et al. 2009), but this may depend on the setting. Sherrington (Sherrington et al. 2008) reported that exercise alone had no benefit in reducing falls in people with dementia living in care homes, possibly because the exercises were mostly in sitting which does not sufficiently challenge postural mechanisms. Over time, interest in physical activity diminishes and mobility becomes more fragmented and related to less purposeful actions such as wandering during delirium. This trajectory of change needs to be considered when designing falls intervention program.

These studies do not tackle the complex interaction between cognitive impairment and gait and balance impairment which are common and related risk factors for falls in dementia as depicted in Fig. 3.3. Taking this contemporary view, new approaches are emerging that aim to address the role of cognition in control of gait and postural control using either pharmacological or non-pharmacological therapies (see Table 3.2 for examples) (see Montero-Odasso et al., for review (Montero-Odasso et al. 2012)) and are briefly considered below. This type of approach is typically aimed far earlier in the disease process targeting those with mild dementia or even earlier with mild cognitive impairment.

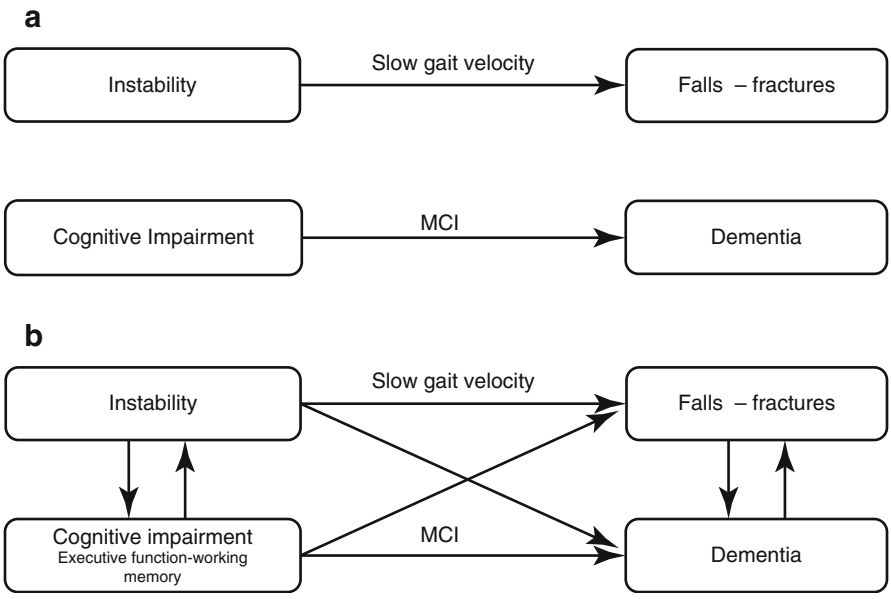

Fig. 3.3 Traditional and contemporary views of the decline in cognition and mobility and their relationship with falls. (**a**) Traditional view. (**b**) Alternative, emerging view (Reprinted from Montero-Odasso et al. (2012) with permission from John Wiley and Sons)

Table 3.2 Falls interventions in dementia: tradition and contemporary approaches with selected examples

Traditional	Contemporary
Single domain intervention approach (e.g., exercise) (Sherrington et al. 2008)	Pharmacological approaches targeting cognitive impairment – cholinergic dysfunction (Montero-Odasso et al. 2012; Chung et al. 2010)
Multifactorial intervention based on generic risk factors (Stenvall et al. 2012)	Exercise to reduce CVD as a potential risk factor
Multifactorial intervention based on risk factors specific to participants (e.g., residential setting, severity of dementia) (Oliver et al. 2007)	Tailor-made intervention, based on individual profile of, e.g., falls history, behavior, and cognitive impairment (Bharwani et al. 2012)
	Cognitive remediation using complex cognitive and motor skill training typically involving dual-task scenarios and decision making (Montero-Odasso et al. 2012; Schwenk et al. 2010)

Pharmacological Approaches

Some interesting preliminary pharmacological trials have reported the effects of cognitive enhancers on gait and falls. These approaches target the underlying common neurotransmitters involved in both cognition and motor control which act as a common mechanism as well as a potential therapeutic target. The cholinergic system (discussed earlier) is such an example. Cholinesterase inhibitors (ChEIs) (e.g., donepezil, galantamine, and rivastigmine) are used as symptomatic treatments to improve cognitive function (mainly attention) in AD, VAD, and also in PDD. There is also interest to see if they have a concurrent effect on gait and falls. The mechanism for action is unclear and may be mediated through improved attentional cognitive control of gait or directly through improved motor function. Early evidence in pilot trials in people with AD show improvements in gait function (Assal et al. 2008; Montero-Odasso et al. 2009) with some suggestions of reduced fall rates in PD (Chung et al. 2010) which is encouraging and is leading the way to larger clinical trials.

Non-pharmacological Approaches

Cognitive remediation therapies are also receiving interest and have been shown to improve executive function and attention in older adults with some emerging evidence in people with MCI and dementia (Montero-Odasso et al. 2012). These types of approaches involve complex cognitive and motor skill training typically involving dual-task scenarios and decision making. A recent study in people with dementia combining gait and cognitive exercise training (dual-task training) saw improved gait performance compared to simple exercises (Schwenk et al. 2010). Activity has been recognized as being protective against falls in dementia (Allan et al. 2009) and may be effective to target the risk factors for CVD and WML, providing a further potential therapeutic target for falls interventions (Srikanth et al. 2009).

Additional Considerations

Any fall, especially in older, frailer adults, is associated with risk of fracture. Fragility fractures are a major cause of morbidity and mortality, with 1-year mortality following fractured neck of femur up to 30 % (Wiles et al. 2011). Dementia is an independent risk factor for fracture in PD (Melton et al. 2006), where the risk of osteoporosis is increased due to reduced bone mineral density, vitamin D insufficiency, immobility, and reduced body mass index (Dobson et al. 2013; Ishizaki et al. 1993; Sato et al. 1997). In extrapyramidal disorders, hip fractures are more common than upper limb fractures, probably due to the mechanism of falling, with some evidence that this may also be true in AD (Williams et al. 2006). Therefore, bone health should be assessed in these patients, using tools such as the WHO FRAX tool (Kanis et al. 2008) or QFracture algorithm (Hippisley-Cox and Coupland 2012), with subsequent referral for dual energy X-ray absorptiometry (DXA) where appropriate. Investigation for secondary causes of osteoporosis (such as vitamin D levels and thyroid function tests) and attention to lifestyle factors (such as diet and smoking) should be initiated where necessary. The treatment of osteoporosis should follow locally agreed guidelines, with consideration to reduced mean life expectancy in older people with more advanced dementia: here quality of life and reduction in morbidity are important considerations. Lastly, occupational therapy home assessment and visual assessment and treatment may also reduce the rate of falling in community-dwelling older adults (Gillespie et al. 2009), although again the evidence in those with additional cognitive impairment is lacking.

Ultimately, earlier intervention may however be more appropriate when potential for compensation is greater. Targeting falls risk in mild cognitive impairment and treating this as a prodromal stage for dementia may ultimately yield the greatest benefits. Taking a combined approach to target multiple underlying mechanisms and behavioral remediation of gait and cognitive impairment may represent potentially exciting future developments to ameliorate falls risk in people with dementia.

Clinical Implications

- Gait and balance are useful biomarkers for falls risk in dementia and should be included in assessment.
- Currently, there is no clear evidence for effective interventions.
- Emerging approaches to mitigate risk should be considered.
- Early intervention may be more beneficial using MCI as a prodromal state for dementia when there is greater potential for compensation.
- Rationalization of medications, in particular with respect to centrally acting medications, should be considered at an early stage to limit potential iatrogenic harm.

References

Abellan van Kan G. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people. J Nutr Health Aging. 2009;13(10):881–9.

Allan LM, et al. Prevalence and severity of gait disorders in Alzheimer's and non-Alzheimer's dementias. J Am Geriatr Soc. 2005;53(10):1681–7.

Allan LM, et al. Incidence and prediction of falls in dementia: a prospective study in older people. PLoS One. 2009;4(5):e5521.

Allcock LM, et al. Impaired attention predicts falling in Parkinson's disease. Parkinsonism Relat Disord. 2009;15(2):110–5.

Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. Maturitas. 2013;75(1):51–61.

American Geriatric Society/British Geriatric Society. Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011;591(1):148–57.

Annweiler C, et al. Contribution of brain imaging to the understanding of gait disorders in Alzheimer's disease: a systematic review. Am J Alzheimers Dis Other Demen. 2012;27(6):371–80.

Assal F, et al. Galantamine improves gait performance in patients with Alzheimer's disease. J Am Geriatr Soc. 2008;56(5):946–7.

Baezner H, et al. Association of gait and balance disorders with age-related white matter changes: the LADIS study. Neurology. 2008;70(12):935–42.

Bharwani G, et al. Individualized behavior management program for Alzheimer's/dementia residents using behavior-based ergonomic therapies. Am J Alzheimers Dis Other Demen. 2012;27(3):188–95.

Blahak C, et al. Association of gait and balance disorders with age-related white mater changes: the LADIS study. Neurology. 2008;70:935–42.

Blankevoort CG, et al. Review of effects of physical activity on strength, balance, mobility and ADL performance in elderly subjects with dementia. Dement Geriatr Cogn Disord. 2010;30(5):392–402.

Bohnen NI, Albin RL. The cholinergic system and Parkinson disease. Behav Brain Res. 2011;221(2):564–73.

Bohnen NI, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. Neurology. 2009a;73(20):1670–6.

Bohnen NI, et al. Age-associated leukoaraiosis and cortical cholinergic deafferentation. Neurology. 2009b;72(16):1411–6.

Bohnen NI, et al. Leucoaraiosis, nigrostriatal denervation and motor symptoms in Parkinson's disease. Brain. 2011;134(Pt 8):2358–65.

Burn DJ, et al. Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: a cross-sectional comparative study. Mov Disord. 2003;18(8):884–9.

Burn DJ, et al. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2006;77(5):585–9.

Camicioli R, Majumdar SR. Relationship between mild cognitive impairment and falls in older people with and without Parkinson's disease: 1-year Prospective Cohort Study. Gait Posture. 2010;32(1):87–91.

Chung KA, et al. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. Neurology. 2010;75(14):1263–9.

Coupland C, et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011;343:d4551–66.

Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people – a review of the evidence. CNS Drugs. 2003;17(11):825–37.
de Laat KF, et al. Loss of white matter integrity is associated with gait disorders in cerebral small vessel disease. Brain. 2011;134(Pt 1):73–83.
Department of Health. Improving care for people with dementia. 2013. https://www.gov.uk/government/policies/improving-care-for-people-with-dementia.
Dobson R, et al. Bone health in chronic neurological diseases: a focus on multiple sclerosis and Parkinsonian syndromes. Pract Neurol. 2013;13(2):70–9.
Ensrud KE, et al. Central nervous system-active medications and risk for falls in older women. J Am Geriatr Soc. 2002;50(10):1629–37.
Eriksson S, Gustafson Y, Lundin-Olsson L. Risk factors for falls in people with and without a diagnosis of dementia living in residential care facilities: a prospective study. Arch Gerontol Geriatr. 2008;46(3):293–306.
Ferri C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366:2112–7.
Fick D, Kolanowski A, Waller J. High prevalence of central nervous system medications in community-dwelling older adults with dementia over a three-year period. Aging Ment Health. 2007;11(5):588–95.
Gillespie LD, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2009;2, CD007146.
Gilman S, et al. Cerebral cortical and subcortical cholinergic deficits in Parkinsonian syndromes. Neurology. 2010;74(18):1416–23.
Harlein J, et al. Fall risk factors in older people with dementia or cognitive impairment: a systematic review. J Adv Nurs. 2009;65(5):922–33.
Hill KD, et al. Effectiveness of balance training exercise in people with mild to moderate severity Alzheimer's disease: protocol for a randomised trial. BMC Geriatr. 2009;9:29.
Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ. 2012;344:e3427–43.
Honjo K, Black SE, Verhoeff NP. Alzheimer's disease, cerebrovascular disease, and the beta-amyloid cascade. Can J Neurol Sci. 2012;39(6):712–28.
Imamura T, et al. Fall-related injuries in dementia with Lewy bodies (DLB) and Alzheimer's disease. Eur J Neurol. 2000;7(1):77–9.
Inzitari M, et al. Cerebrovascular disease and gait and balance impairment in mild to moderate Alzheimer's disease. J Nutr Health Aging. 2013;17(1):45–8.
Ishizaki F, et al. Relationship between osteopenia and clinical characteristics of Parkinson's disease. Mov Disord. 1993;8(4):507–11.
Jenkinson N, et al. Anatomy, physiology, and pathophysiology of the pedunculopontine nucleus. Mov Disord. 2009;24(3):319–28.
Kafri M, et al. High-level gait disorder: associations with specific white matter changes observed on advanced diffusion imaging. J Neuroimaging. 2013;23(1):39–46.
Kallin K, Gustafson Y, Lundin-Olsson L. Factors associated with falls among older, cognitively impaired people in geriatric care settings. Am J Geriatr Psychiatry. 2005;13:501–9.
Kanis JA, et al. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19(4):385–97.
Karachi C, et al. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J Clin Invest. 2010;120(8):2745–54.
Kerr G, et al. Predictors of future falls in Parkinson disease. Neurology. 2010;75(2):116–24.
Kröpelin TF, et al. Fall determinants in older long-term care residents with dementia: a systematic review. Int Psychogeriatr. 2013;25(04):549–63.
LADIS study group et al. 2001-2011: A decade of the LADIS (Leukoaraiosis and DISability) study: what have we learned about white matter changes and small-vessel disease? Cerebrovasc Dis. 2011;32(6):577–88.
Latt M, et al. Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. Mov Disord. 2009;24(9):1280–9.

Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. J Am Geriatr Soc. 1999;47(1):40–50.
Lim I, et al. Identifying fallers with Parkinson's disease using home-based tests: who is at risk? Mov Disord. 2008;23(16):2411–5.
Lord S, Menz H, Tiedemann A. A physiological profile approach to falls risk assessment and prevention. Phys Ther. 2003;83:237–52.
Lord S, et al. Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's disease. Gait Posture. 2010;31(2):169–74.
Lord S, et al. Gait variability in Parkinson's disease: an indicator of non-dopaminergic contributors to gait dysfunction? J Neurol. 2011a;258(4):566–72.
Lord S, et al. Attention rather than spatial memory predicts distinct characteristics of Parkinson's disease. Mov Disord. 2011b;26(Suppl2):S392–424.
Lowery K, et al. Depression in the carers of dementia sufferers: a comparison of the carers of patients suffering from dementia with Lewy bodies and the carers of patients with Alzheimer's disease. J Affect Disord. 2000a;59(1):61–5.
Lowery K, Buri H, Ballard C. What is the prevalence of environmental hazards in the homes of dementia sufferers and are they associated with falls. Int J Geriatr Psychiatry. 2000b;15(10):883–6.
Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. Lancet. 1997;349(9052):617.
McKeith I, et al. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology. 2000;54(5):1050–8.
Melton 3rd LJ, et al. Fracture risk after the diagnosis of Parkinson's disease: influence of concomitant dementia. Mov Disord. 2006;21(9):1361–7.
Montero-Odasso M, Wells J, Borrie M. Can cognitive enhancers reduce the risk of falls in people with dementia? An open-label study with controls. J Am Geriatr Soc. 2009;57(2):359–60.
Montero-Odasso M, et al. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. J Am Geriatr Soc. 2012;60(11):2127–36.
Morris J, et al. Senile dementia of the Alzheimer's type: an important risk factor for serious falls. J Gerontol. 1987;42:412–7.
Morrison R, Siu A. Mortality from pneumonia and hip fractures in patients with advanced dementia. JAMA. 2000;284(19):2447–8.
Neutel CI, Perry S, Maxwell C. Medication use and risk of falls. Pharmacoepidemiol Drug Saf. 2002;11(2):97–104.
Oliver D, et al. Strategies to prevent falls and fractures in hospitals and care homes and effect of cognitive impairment: systematic review and meta-analyses. BMJ. 2007;334(7584):82.
Robinson K, et al. Falling risk factors in Parkinson's disease. NeuroRehabilitation. 2005;20(3):169–82.
Rochester L, et al. Walking speed during single and dual tasks in Parkinson's disease: which characteristics are important? Mov Disord. 2008;23(16):2312–8.
Rochester L, et al. Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease. Brain. 2012;135(Pt 9):2779–88.
Rosano C, et al. Quantitative measures of gait characteristics indicate prevalence of underlying subclinical structural brain abnormalities in high-functioning older adults. Neuroepidemiology. 2006;26(1):52–60.
Salva A, et al. Falls and risk factors for falls in community-dwelling adults with dementia (NutriAlz trial). Alzheimer Dis Assoc Disord. 2012;26(1):74–80.
Sato Y, Kikuyama M, Oizumi K. High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease. Neurology. 1997;49(5):1273–8.
Scandol J, Toson B, Close J. Fall-related hip fracture hospitalisations and the prevalence of dementia within older people in New South Wales, Australia: an analysis of linked data. Injury. 2013;44(6):776–83.

Schwenk M, et al. Dual-task performances can be improved in patients with dementia: a randomized controlled trial. Neurology. 2010;74(24):1961–8.
Shaw FE. Falls in cognitive impairment and dementia. Clin Geriatr Med. 2002;18(2):159–73.
Shaw FE. Prevention of falls in older people with dementia. J Neural Transm. 2007; 114(10):1259–64.
Sheahan SL, et al. Psychoactive medication, alcohol-use, and falls among older adults. J Behav Med. 1995;18(2):127–40.
Sherrington C, et al. Effective exercise for the prevention of falls: a systematic review and meta-analysis. J Am Geriatr Soc. 2008;56(12):2234–43.
Shimada H, et al. Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET. Neurology. 2009;73(4):273–8.
Snijders AH, et al. Neurological gait disorders in elderly people: clinical approach and classification. Lancet Neurol. 2007;6(1):63–74.
Srikanth V, et al. Cerebral white matter lesions, gait, and the risk of incident falls: a prospective population-based study. Stroke. 2009;40(1):175–80.
Stenvall M, et al. A multidisciplinary intervention program improved the outcome after hip fracture for people with dementia–subgroup analyses of a randomized controlled trial. Arch Gerontol Geriatr. 2012;54(3):e284–9.
Taylor ME, et al. Gait impairment and falls in cognitively impaired older adults: an explanatory model of sensorimotor and neuropsychological mediators. Age Ageing. 2012;41(5):665–9.
Tinetti M, Speechley M, Ginter S. Risk factors for falls among elderly people living in the community. N Engl J Med. 1988;319:1701–7.
van Iersel MB, et al. Systematic review of quantitative clinical gait analysis in patients with dementia. Z Gerontol Geriatr. 2004;37(1):27–32.
Verghese J, et al. Epidemiology of gait disorders in community-residing older adults. J Am Geriatr Soc. 2006;54(2):255–61.
Verghese J, et al. Quantitative gait dysfunction and risk of cognitive decline and dementia. J Neurol Neurosurg Psychiatry. 2007;78(9):929–35.
Voisin T, et al. Predictive factors of hospitalizations in Alzheimer's disease: a two-year prospective study in 686 patients of the REAL.FR study. J Nutr Health Aging. 2010;14(4):288–91.
Wiles MD, et al. Nottingham Hip Fracture Score as a predictor of one year mortality in patients undergoing surgical repair of fractured neck of femur. Br J Anaesth. 2011;106(4):501–4.
Williams DR, Watt HC, Lees AJ. Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study. J Neurol Neurosurg Psychiatry. 2006;77(4):468–73.
World Health Organisation. Violence and injury prevention and disability-falls. 2013. http://www.who.int/violence_injury_prevention_other_injury/falls/en/.
World Health Organisation. Global Health and Ageing. 2011. http://who.int/ageing/publications/global_health/en/.
Yarnall A, Rochester L, Burn DJ. The interplay of cholinergic function, attention, and falls in Parkinson's disease. Mov Disord. 2011;26(14):2496–503.
Yogev-Seligmann G, et al. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects are attention demanding. Eur J Neurosci. 2005;22:124–1256.
Zheng JJ, et al. Impact of white matter lesions on physical functioning and fall risk in older people: a systematic review. Stroke. 2011;42(7):2086–90.

Chapter 4
Treatment of Parkinsonism in Patients with Non-Parkinson Dementia

Raja Mehanna and Hubert H. Fernandez

Abstract Parkinsonism and dementia can co-occur in patients without Parkinson's disease, and most of patients with neurodegenerative parkinsonism develop significant cognitive impairment. Parkinsonism–dementia syndromes notably include dementia with Lewy bodies, progressive supranuclear palsy, corticobasal syndrome, normal-pressure hydrocephalus, vascular parkinsonism and dementia, drug-induced parkinsonism and dementia, frontotemporal lobe dementia, and Alzheimer's disease. Therapeutic options for parkinsonism in these patients are limited, and data are scarce. In this chapter, we summarize the available information on this topic.

Keywords Parkinsonism • Dementia • Treatment • Dementia with Lewy bodies • Progressive supranuclear palsy • Corticobasal syndrome • Normal-pressure hydrocephalus • Frontotemporal lobe dementia • Alzheimer's disease

Introduction

Parkinsonism is a disorder characterized by the clinical tetrad of tremor at rest, rigidity, akinesia (or bradykinesia), and postural instability (Mehanna and Jankovic 2013a; Fernandez et al. 2007). It can be subcategorized based on etiology into the following: primary (i.e., idiopathic Parkinson's disease), secondary (e.g., drug-induced parkinsonism, vascular parkinsonism, parkinsonism due to normal-pressure

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Table 4.1 Dementia syndromes that can be associated with parkinsonism, other than PDD (Liepelt-Scarfone et al. 2012; Possin and Kaufer 2010)

Dementia with Lewy bodies
Progressive supranuclear palsy
Corticobasal syndrome
Normal-pressure hydrocephaly
Vascular parkinsonism and dementia
Drug-induced parkinsonism and dementia
Frontotemporal lobe dementia
Alzheimer's disease
Others:
Prion diseases including Gerstmann-Sträussler-Scheinker syndrome
Metabolic derangements that have a predilection for basal ganglia structures such as:
Wilson disease
Neurodegeneration with brain iron accumulation
Idiopathic basal ganglia calcification (Fahr disease)

hydrocephalus, etc.), and atypical parkinsonism (also referred to as Parkinson-plus syndromes). In contrast to PD patients, those with atypical parkinsonism usually lack rest tremor, tend to have a more rapid progression and poor response to levodopa, and have additional ("plus") features, such as significant dysautonomia (in multiple system atrophy [MSA]), early gait instability (in progressive supranuclear palsy), limb dystonia and myoclonus (in corticobasal syndromes), behavioral features (in frontotemporal lobe dementia), and early cognitive impairment (in most atypical parkinsonian syndromes) (Mehanna and Jankovic 2010; Fernandez et al. 2007). At some point, the majority of patients with neurodegenerative parkinsonism develop significant cognitive impairments that, in many cases, progress to frank dementia (Wurtman 2013) (Table 4.1). In addition, patients with neurodegenerative dementia are prone to developing parkinsonism. The description of these parkinsonism–dementia syndromes has been covered in other chapters of this book. In this chapter, we will focus on the treatment of parkinsonism in the most frequent parkinsonism–dementia syndromes other than Parkinson's disease dementia (Table 4.2).

Dementia with Lewy Bodies (DLB)

The treatment of parkinsonian in patients with DLB follows the same treatment principles of idiopathic PD, where dopamine replacement remains the cornerstone of treatment. There are, however, some differences (Poewe 2005). The main concern is that pro-dopaminergic agents used to treat parkinsonism more readily exacerbate or cause hallucinations in DLB (McKeith et al. 2003; Frank 2003; Zupancic et al. 2011) as compared to idiopathic PD.

Because of their greater hallucination-inducing potential, dopamine agonists are generally not considered first-line agents in DLB and in fact should be avoided (Rascol et al. 2000; Parkinson Study Group 2000; Drach 2011).

Table 4.2 Treatment of parkinsonism in non-idiopathic PD demented patients

Diagnosis	First line (efficacy)	Other options	Comments
DLB	Levodopa (50–55 %)	Zonisamide	Avoid dopamine agonists, anticholinergics, and selegiline
PSP	Levodopa (38–54 %)	Pramipexole, ropinirole, amantadine, zolpidem	Might need higher doses of levodopa than PD
CBS	Levodopa (26 %)	Amantadine, anticholinergics (for tremor), selegiline, anticonvulsants, pramipexole, ropinirole	
NPH	VPS (50–70 %)	Levodopa	
VPD	Levodopa (33 %)	Amantadine	Control vascular risk factors
DIPD	Levodopa (NA)		Stop the offending agent
FTLD	Levodopa (NA)	Dopamine agonists, selegiline	No empiric data
AD	Levodopa (NA)	Dopamine agonists, selegiline	No empiric data

DLB dementia with Lewy bodies, *PSP* progressive supranuclear palsy, *CBS* corticobasal syndrome, *NPH* normal-pressure hydrocephaly, *VPD* vascular parkinsonism and dementia, *DIPD* drug-induced parkinsonism and dementia, *FTLD* frontotemporal lobe dementia, *AD* Alzheimer's disease

The efficacy and safety of levodopa in DLB has been assessed only in small series of up to 20 patients (Molloy et al. 2005; Bonelli et al. 2004; Goldman et al. 2008). Clinically significant improvement of parkinsonism after an oral dose of levodopa has been reported in up to 50 % of patients with DLB (Bonelli et al. 2004), but this series did not report adverse events. However, in a series of 19 patients with DLB, Goldman et al. (2008) reported that only 22 % had improvement in their motor symptoms with levodopa without worsening of their hallucinations. In a more recent series comparing the effect of levodopa on 24 DLB and 21 PD patients, Lucetti et al. (2010) reported a positive response to an acute oral load of 250 mg of levodopa in 55 % of the DLB patients and 90 % of the PD patients. A positive response was defined as an improvement of at least 15 % in the tapping test and at least 25 % in the walking test and rigidity score or tremor score. Patients were then treated with up to 600 mg per day of levodopa and reassessed at 6 and 12 months. At both follow-up visits, DLB patients who responded to the initial acute levodopa dose showed a greater motor benefit compared to DLB who did not satisfactorily respond to the acute levodopa dose challenge. However, when compared to PD acute levodopa responders, the benefit observed in DLB acute levodopa responders was comparable at 6 months but was less at 12 months, implying a more rapid reduction of levodopa efficacy in DLB. In this series, 2 DLB (8.3 %) patients were excluded because of exacerbation of hallucination on levodopa and not included in the analysis. Moreover, 30 % of the DLB patients were on clozapine and 50 % were on acetylcholinesterase inhibitors, which could have prevented or masked potential worsening of hallucination from levodopa. Overall, parkinsonism tends to respond less well to levodopa in DLB than in PD

or PD with dementia (PDD) (McKeith et al. 1996, 2005; Molloy et al. 2005; Bonelli et al. 2004; Goldman et al. 2008; Drach 2011). Levodopa-induced dyskinesia were reported less frequently in DLB than in PD patients in one retrospective study of 25 DLB and 64 PD patients (Papapetropoulos et al. 2006), but this could not be confirmed in prospective series (Lucetti et al. 2010). Should this be true, it would be another indicator of decreased sensibility of DLB patient to dopamine replacement therapy. In a cross-sectional study comparing the motor phenotype in 43 PDD and 26 DLB cases to that of 38 patients with PD and no dementia (Burn et al. 2003), the postural instability/gait difficulty-phenotype was significantly overrepresented in DLB compared to the uncomplicated PD group (69 % versus 38 % of cases).

In the less frequent cases where tremor is the dominant symptom of parkinsonism, anticholinergic drugs should still be avoided as they can worsen the cognitive deficit and/or induce delirium (Drach 2011). Amantadine 150 mg/day was reported to partially improve parkinsonism in one patient with DLB (Sato et al. 2010), but it can also worsen psychosis (Drach 2011) and is usually not recommended (Possin and Kaufer 2010).

Although not routinely used in clinical practice, a daily dose of 25–100 mg of zonisamide in addition to levodopa was shown to decrease off time without worsening dyskinesia in a randomized, double-blinded, controlled trial on 347 PD patients (Murata et al. 2007). While no such trial exists for DLB patients, some cases have been reported. Sato et al. (2010) reported motor improvement in one DLB patient after 4 weeks of a daily dose of 25 mg of zonisamide, and with marked gait improvement. The dose was then increased progressively to 75 mg daily with additional improvement of aggression, apathy, and irritability. No side effects were reported. The patient was also on a stable dose of amantadine 150 mg per day and donepezil 5 mg per day. Odawara et al. (2010) reported three additional DLB patients in whom zonisamide was added to levodopa for motor symptom control. Two patients had mild to moderate motor improvement at 25 mg/day, with dizziness at 50 mg/day. The third patient had no motor improvement but experienced drowsiness at 100 mg per day. All side effects improved after decreasing the dose. Interestingly, the first two patients had previously responded to levodopa while the third one did not. The effects of zonisamide on parkinsonism can be mediated by an increase in dopamine synthesis at doses between 25 and 100 mg per day (Murata et al. 2007) as well as an increase in extracellular levels of dopamine and serotonin (Farooq et al. 2008; Murata et al. 2007).

In summary, and in an attempt to optimize motor control without worsening cognitive or psychotic symptoms, low doses of levodopa should be used, possibly in combination with zonisamide. Dopamine agonists, anticholinergics, and amantadine should be avoided, as well as selegiline (Possin and Kaufer 2010), and perhaps other monoamine oxidase B (MAO-B) inhibitors. Data on catechol-O-methyltransferase (COMT) inhibitors in the DLB population are wanting, although presumably they are less likely, but far from exempt, in precipitating hallucinations among demented parkinsonian patients.

Progressive Supranuclear Palsy (PSP)

Although the response to levodopa may be poor or transient (van Balken and Litvan 2006), and parkinsonism in PSP seem to be less responsive to levodopa than other Parkinson-plus syndromes (Birdi et al. 2002), patients with PSP more often still receive a trial of levodopa/carbidopa. At least two studies involving up to 170 PSP patients have demonstrated an improvement of motor symptoms with levodopa in 38–54 % of patients (Nieforth and Golbe 1993; Golbe et al. 1990). The amplitude and duration of this response were however not specified (Burn and Warren 2005). Another retrospective study of 12 PSP patients showed a more modest response but reported significant adverse effects such as worsening of parkinsonism and postural hypotension in more than half the patients (Kompoliti et al. 1998a). It should be noted that the minimum clinically beneficial levodopa dose may be higher in PSP than that in PD (Lubarsky and Juncos 2008) and may require up to 1 g of levodopa per day. However, the response remains modest and is often short lived (3–5 years). Over time, dopaminergic therapy can reversibly worsen most motor and behavioral symptoms of PSP, and the difficult decision to stop these medications may need to be taken. However, since this drug-induced worsening can be dose dependent, a gradual de-escalation of dopaminergic drugs will give the opportunity to look for a lower dose with a more favorable risk–benefit ratio (Lubarsky and Juncos 2008). Moreover, abrupt discontinuation of dopaminergic drugs should be avoided to prevent a withdrawal-induced neuroleptic malignant-like syndrome (Serrano-Duenas 2003; Yoshikawa et al. 1997). Finally, PSP patients are less likely to develop severe motor fluctuations, dyskinesias, or dopaminergic-induced visual hallucinations than PD patients (Aarsland et al. 2001), suggestive of a more dopamine-resistant pathology.

In patients who do not respond to levodopa, dopamine receptor agonists such as pramipexole or ropinirole may be considered. Indeed, unlike levodopa, these medications act directly at the postsynaptic terminal in the striatum, bypassing the substantia nigra that is commonly affected with severe neuronal loss in PSP (Rabinovici and Miller 2010). If used as a first-line treatment, the response to these agents is often comparable or inferior to that of levodopa (Burn and Warren 2005).

Amantadine has been reported to transiently improve parkinsonism in 15 % of PSP patients (Irene and Yves 1992).

Finally, based on decreased frontal cortical GABA receptors on brain imaging of PSP patients, a crossover trial of the GABA agonist zolpidem on 10 PSP patients was conducted (Daniele et al. 1999). A single 5 mg zolpidem dose was found to improve the motor subscale of the United Parkinson's Disease Rating Scale by more than 20 %, while a dose of 10 mg of zolpidem or 250 mg of levodopa failed to exert such a response. The main side effect of this drug was mild drowsiness in 50 % of the patients and moderate drowsiness in an additional 10 %. These results have not been duplicated.

Corticobasal Syndrome (CBS)

CBS is notoriously resistant to levodopa, even more so than PSP. However, although the response to levodopa may be poor or transient, patients often receive a trial of levodopa. In a retrospective review of 147 patients with CBS, Kompoliti et al. (1998b) reported carbidopa/levodopa use in 87 % of the patients with a median daily dose of 300 mg (range 100–2,000 mg) but with improvement in only 26 % of the patients exposed to the drug. Twenty-five percent were treated with pergolide or bromocriptine, of whom only 6 % improved. Selegiline was used in 20 % of the patients and produced motor benefits in only 10 % of patients. Amantadine was prescribed in 16 % and improved bradykinesia, rigidity, and gait in 13 % of patients. Anticholinergic agents were used in 27 % of the patients and improved parkinsonism in 10 %. Finally, anticonvulsants were given to 9 % of the patients and improved parkinsonism, especially tremor, in 23 % of them, a success rate second only to levodopa. However, the study did not report the magnitude and duration of observed improvements. Dyskinesias did not occur even at high doses of dopaminergic therapy.

Overall, the response of parkinsonism to therapy is limited, with levodopa being the most efficacious agent. In patients who do not respond to levodopa, dopamine receptor agonists such as pramipexole or ropinirole may be considered. Indeed, unlike levodopa, these medications act directly at the postsynaptic terminal in the striatum, bypassing the substantia nigra which, similar to PSP, is also affected with severe neuronal loss in CBS (Rabinovici and Miller 2010). Finally, anticonvulsants might be useful in tremulous CBS patients.

Normal-Pressure Hydrocephalus (NPH)

In addition to subcortical dementia and urinary incontinence, NPH is characterized by a wide-based gait with short steps, stiff legs, start hesitation, and freezing, the so-called magnetic gait (Possin and Kaufer 2010). Moreover, NPH patients frequently exhibit bradykinesia and flexed posture (Fahn et al. 2011). Ventriculoperitoneal shunt surgery is the only established treatment of normal-pressure hydrocephalus (Liepelt-Scarfone et al. 2012) and has the maximal benefits if performed when cognitive impairment is still mild and of recent origin, with gait improving the most after surgery. Substantial improvement can be seen in 50–70 % of patients (Vanneste 2000) with benefits sustained up to a mean of 6 years (Pujari et al. 2008). When present, bradykinesia also improves markedly after the shunting procedure (Akiguchi et al. 2008). While NPH is typically poorly responsive to levodopa (Morishita et al. 2010), parkinsonism in NPH and obstructive hydrocephalus have been reported that could be levodopa responsive (Jankovic et al. 1986; Clough 1987; Zeidler et al. 1998; Racette et al. 2004).

Vascular Parkinsonism and Dementia

Binswanger disease, or subcortical ischemic vascular dementia, is a heterogeneous syndrome associated with multiple subcortical infarcts and/or diffuse subcortical leukoaraiosis and can be associated with vascular parkinsonism (Possin and Kaufer 2010). Overall, only about a third of patients with vascular parkinsonism improve with levodopa (Mehanna and Jankovic 2013b) with patients with vascular lesions in or close to the nigrostriatal pathway and rare cases with abnormal DAT-SPECT imaging being more likely to respond. While levodopa can improve bradykinesia and rigidity, amantadine can be beneficial for apathy and bradyphrenia (Liepelt-Scarfone et al. 2012). The management should include, if not emphasize, physical and occupational therapy as well as detection and treatment of atherosclerosis, hypertension, diabetes mellitus, and other stroke risk factors (Mehanna and Jankovic 2013b).

Drug-Induced Parkinsonism and Dementia

Because it is readily treatable by discontinuing the offending agent, an iatrogenic cause of parkinsonism–dementia should always be considered, and a review of the patient's medication list is mandatory. This is even more critical as drug-induced parkinsonism can be clinically indistinguishable from idiopathic Parkinson's disease. The most frequently incriminated drugs are the typical or conventional neuroleptics. However, atypical neuroleptics, especially in the Parkinson-vulnerable elderly and cognitively impaired population, still carry a risk and represented 46 % of the 6.8 % cases of drug-induced parkinsonism in a retrospective review of 354 parkinsonian patients (Esper and Factor 2008). Other agents include antiemetic agents such as metoclopramide and promethazine, anticonvulsants such as valproic acid, and lithium (Esper and Factor 2008). In addition, parkinsonism can be induced in demented patients by antipsychotic drugs prescribed to control behavioral symptoms (Czarnecki et al. 2008). This is often seen in the management of Alzheimer's disease, especially in long-term care facilities.

Discontinuing the offending agent often leads to a resolution of the symptoms, but this might take up to 18 months (Fahn et al. 2011; Lim et al. 2013). Meanwhile, if symptoms are severe, low doses of levodopa can be used for symptomatic relief.

Frontotemporal Lobe Dementia (FTLD)

No empiric data exists for the treatment of parkinsonism in FTLD, but some expert opinions have been published on the subject. A trial of levodopa should be attempted in FTLD patients with parkinsonism, but the response to levodopa may be poor or transient

(Rabinovici and Miller 2010). Dopamine receptor agonists, such as pramipexole or ropinirole, should be considered in cases of levodopa failure (Rabinovici and Miller 2010).

Contrary to patients with DLB, FTLD patients are less prone to hallucinations; thus, dopaminergic medications can be used more liberally. While not specifically assessed for the treatment of parkinsonism in FTLD, the potential benefit of dopamine agonists on apathy, perseveration, and executive functioning (Imamura et al. 1998; Rahman et al. 2001; Allain et al. 2003) and of selegiline on neuropsychological symptoms (Moretti et al. 2002) should prompt the consideration of these antiparkinsonian treatments in FTLD patients with parkinsonism.

Parkinsonism associated with FTLD is usually of the non-tremulous type. If tremor is a major source of complaints, anticholinergic medications can be considered but should be used very sparingly as they may worsen the cognitive and neuropsychiatric symptoms.

Frontotemporal dementia with parkinsonism is an autosomal dominant syndrome linked to chromosome 17 than be caused by tenths of different mutations (Graff-Radford and Woodruff 2007). It can be subdivided in two clinical phenotypes (Reed et al. 2001), one with a dementia-predominant symptomatology and the other with a parkinsonism-predominant phenotype. Most patients respond poorly, if at all, to levodopa (Wszolek et al. 2006). FTLD can also overlap clinically and pathologically with PSP and/or CBD (Graff-Radford and Woodruff 2007). In these cases, the symptomatic treatment of parkinsonism would be as detailed in the section on PSP and CBD, respectively.

Alzheimer's Disease (AD)

Although parkinsonism develops in 15–45 % of patients with AD (Fahn et al. 2011) and its presence correlates with greater cognitive impairment and worse prognosis compared to AD patients without parkinsonism (Kurlan et al. 2000; Wilson et al. 2003), there are no data available regarding the treatment of parkinsonism in AD except for an old report of familial AD presenting with levodopa-responsive parkinsonism (Giménez-Roldán et al. 1987). Such treatment can be extrapolated from the medical management of parkinsonism in other types of dementia, with low-dose levodopa as the cornerstone, while dopamine agonists carry a higher risk of hallucinations. However, as reported in the section on FTLD, dopamine agonists and selegiline could, in theory, benefit motor and cognitive symptoms, although the data supporting this practice are wanting. Finally, a significant portion of AD patient can experience drug-induced parkinsonism when using atypical antipsychotic agents to control agitation and other behavioral manifestations.

Conclusion

Parkinsonism associated with dementia is overall less responsive to levodopa compared to idiopathic PD or even PDD. Nevertheless, a trial of levodopa should be considered for lack of a better treatment. However, levodopa can worsen

hallucinations in DLB as well as motor and behavioral symptoms in advanced PSP and other atypical parkinsonian disorders. Dopamine agonists may also be beneficial in Parkinson-plus syndromes that have a lesser likelihood of developing levodopa-induced psychosis, such as PSP, CBS, FTLD, and AD. Support for the use of other antiparkinsonian drugs is even more limited and therefore should be used more sparingly. Finally, in these Parkinson-vulnerable populations, even atypical antipsychotic agents should be used very cautiously, and vigilance to the possibility of drug-induced parkinsonism should always be exercised since parkinsonian symptoms are potentially reversible.

References

Akiguchi I, Ishii M, Watanabe Y, Watanabe T, Kawasaki T, Yagi H, Shiino A, Shirakashi Y, Kawamoto Y. Shunt-responsive parkinsonism and reversible white matter lesions in patients with idiopathic NPH. J Neurol. 2008;255(9):1392–9.

Allain H, Bentué-Ferrer D, Tribut O, Mérienne M, Belliard S. Drug therapy of frontotemporal dementia. Hum Psychopharmacol. 2003;18(3):221–5.

Aarsland D, Litvan I, Larsen JP. Neuropsychiatric symptoms of patients with progressive supranuclear palsy and Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2001;13:42–9.

Birdi S, Rajput AH, Fenton M, Donat JR, Rozdilsky B, Robinson C, et al. Progressive supranuclear palsy diagnosis and confounding features: report on 16 autopsied cases. Mov Disord. 2002;17:1255–64.

Bonelli SB, Ransmayr G, Steffelbauer M, Lukas T, Lampl C, Deibl M. L-dopa responsiveness in dementia with Lewy bodies, Parkinson disease with and without dementia. Neurology. 2004;63:376–8.

Burn DJ, Warren NM. Toward future therapies in progressive supranuclear palsy. Mov Disord. 2005;20 Suppl 12:S92–8.

Burn DJ, Rowan EN, Minett T, Sanders J, Myint P, Richardson J, et al. Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy-bodies: a cross-sectional comparative study. Mov Disord. 2003;18:884–9.

Clough CG. A case of normal pressure hydrocephalus presenting as levodopa responsive parkinsonism. J Neurol Neurosurg Psychiatry. 1987;50(2):234.

Czarnecki K, Kumar N, Josephs KA. Parkinsonism and tardive antecollis in frontotemporal dementia–increased sensitivity to newer antipsychotics? Eur J Neurol. 2008;15(2):199–201.

Daniele A, Moro E, Bentivoglio AR. Zolpidem in progressive supranuclear palsy. N Engl J Med. 1999;341:543–4; erratum in N Engl J Med. 1999;341:1632.

Drach LM. Drug treatment of dementia with Lewy bodies and Parkinson's disease dementia–common features and differences. Med Monatsschr Pharm. 2011;34(2):47–52.

Esper CD, Factor SA. Failure of recognition of drug-induced parkinsonism in the elderly. Mov Disord. 2008;23(3):401–4.

Fahn S, Jankovic J, Hallett M. Atypical parkinsonism, parkinsonism-plus syndromes, and secondary Parkinsonian disorders. In: Fahn S, Jankovic J, Hallett M, editors. Principles and practice of movement disorders. Philadelphia: Churchill Livingstone/Elsevier; 2011. p. 197–240.

Farooq MU, Moore PW, Bhatt A, Aburashed R, Kassab MY. Therapeutic role of zonisamide in neuropsychiatric disorders. Mini Rev Med Chem. 2008;8:968–75.

Fernandez HH, Rodriguez RL, Skidmore FM, Okun MS. A practical approach to any movement disorder: diagnosis, medical and surgical management. New York: Demos Publishing, Inc; 2007.

Frank C. Dementia with Lewy bodies. Review of diagnosis and pharmacologic management. Can Fam Physician. 2003;49:1304–11.

Giménez-Roldán S, Mateo D, Escalona-Zapata J. Familial Alzheimer's disease presenting as levodopa-responsive parkinsonism. Adv Neurol. 1987;45:431–6.

Golbe LI, Sage JI, Duvoisin RC. Drug treatment of 83 patients with progressive supranuclear palsy. Neurology. 1990;40:438.

Goldman JG, Goetz CG, Brandabur M, Sanfilippo M, Stebbins GT. Effects of dopaminergic medications on psychosis and motor function in dementia with Lewy bodies. Mov Disord. 2008;23(15):2248–50.

Graff-Radford NR, Woodruff BK. Frontotemporal dementia. Semin Neurol. 2007;27(1):48–57.

Imamura T, Takanashi M, Hattori N, et al. Bromocriptine treatment for perseveration in demented patients. Alzheimer Dis Assoc Disord. 1998;12:109–13.

Irene L, Yves A, editors. Progressive supranuclear palsy: clinical and research approaches. New York: Oxford University Press; 1992.

Jankovic J, Newmark M, Peter P. Parkinsonism and acquired hydrocephalus. Mov Disord. 1986;1:59–64.

Kompoliti K, Goetz CG, Litvan I, Jellinger K, Verny M. Pharmacological therapy in progressive supranuclear palsy. Arch Neurol. 1998a;55(8):1099–102.

Kompoliti K, Goetz CG, Boeve BF, Maraganore DM, Ahlskog JE, Marsden CD, et al. Clinical presentation and pharmacologic therapy in corticobasal degeneration. Arch Neurol. 1998b;55:957–61.

Kurlan R, Richard IH, Papka M, Marshall F. Movement disorders in Alzheimer's disease: more rigidity of definitions needed. Mov Disord. 2000;15:24–9.

Liepelt-Scarfone I, Jamour M, Maetzler W. Co-occurrence of parkinsonism and dementia in clinical practice: relevant differential diagnoses. Z Gerontol Geriatr. 2012;45(1):23–33.

Lim T, Ahmed A, Itin I, Gostkowski M, Rudolph J, Cooper S, Fernandez HH. Is 6 months of neuroleptic withdrawal sufficient to distinguish drug-induced parkinsonism from Parkinson's disease? Int J Neurosci. 2013;123(3):170–4.

Lubarsky M, Juncos JL. Progressive supranuclear palsy: a current review. Neurologist. 2008;14(2):79–88.

Lucetti C, Logi C, Del Dotto P, Berti C, Ceravolo R, Baldacci F, Dolciotti C, Gambaccini G, Rossi G, Bonuccelli U. Levodopa response in dementia with Lewy bodies: a 1-year follow-up study. Parkinsonism Relat Disord. 2010;16(8):522–6.

Mehanna R, Jankovic J. Respiratory problems in neurologic movement disorders. Parkinsonism Relat Disord. 2010;16(10):628–38.

Mehanna R, Jankovic J. Movement disorders in multiple sclerosis and other demyelinating diseases. J Neurol Sci. 2013a;328(1–2):1–8.

Mehanna R, Jankovic J. Movement disorders in cerebrovascular disease. Lancet Neurol. 2013b;12(6):597–608.

Morishita T, Foote KD, Okun MS. INPH and Parkinson disease: differentiation by levodopa response. Nat Rev Neurol. 2010;6(1):52–6.

McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology. 1996;47(5):1113–24.

McKeith IG, Burn DJ, Ballard CG, Collerton D, Jaros E, Morris CM, et al. Dementia with Lewy bodies. Semin Clin Neuropsychiatry. 2003;8(1):46–57.

McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al., Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005;65(12):1863–72.

Molloy S, McKeith IG, O'Brien JT, Burn DJ. The role of levodopa in the management of dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2005;76(9):1200–3.

Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Effects of selegiline on frontotemporal dementia: a neuropsychological evaluation. Int J Geriatr Psychiatry. 2002;17:391–2.

Murata M, Hasegawa K, Kanazawa I, The Japanese Zonisamide on PD Study Group. Zonisamide improves motor function in Parkinson disease: a randomized, doubleblind study. Neurology. 2007;68:45–50.

Nieforth KA, Golbe LI. Retrospective study of drug response in 87 patients with progressive supranuclear palsy. Clin Neuropharmacol. 1993;16:338–46.

Odawara T, Shiozaki K, Togo T, Hirayasu Y. Administration of zonisamide in three cases of dementia with Lewy bodies. Psychiatry Clin Neurosci. 2010;64(3):327–9.

Papapetropoulos S, Lieberman A, Gonzalez J, Singer C, Laufer DZ, Mash DC. Family history of dementia: dementia with Lewy bodies and dementia in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2006;18(1):113–6.

Parkinson Study Group. Pramipexole vs. levodopa as initial treatment for Parkinson disease. A randomized controlled trial. JAMA. 2000;84:1931–8.

Possin KL, Kaufer DI. Parkinsonian dementias. Continuum. 2010;16(2 Dementia):57–79.

Poewe W. Treatment of dementia with Lewy bodies and Parkinson's disease dementia. Mov Disord. 2005;20 Suppl 12:S77–82.

Pujari S, Kharkar S, Metellus P, Shuck J, Williams MA, Rigamonti D. Normal pressure hydrocephalus: long-term outcome after shunt surgery. J Neurol Neurosurg Psychiatry. 2008;79(11):1282–6.

Racette BA, Esper GJ, Antenor J, Black KJ, Burkey A, Moerlein SM, et al. Pathophysiology of parkinsonism due to hydrocephalus. J Neurol Neurosurg Psychiatry. 2004;75:1617–9.

Rahman S, Robbins TW, Sahakian BJ. Comparative cognitive neuropsychological studies of frontal lobe function: implications for therapeutic strategies in frontal variant frontotemporal dementia. Dement Geriatr Cogn Disord. 2001;10 Suppl 1:15–28.

Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med. 2000;18(342):1481–91.

Rabinovici GD, Miller BL. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. CNS Drugs. 2010;24(5):375–98.

Reed LA, Wszolek ZK, Hutton M. Phenotypic correlations in FTDP-17. Neurobiol Aging. 2001;22:89–107.

Sato S, Mizukami K, Asada T. Successful treatment of extrapyramidal and psychotic symptoms with zonisamide in a patient with dementia with Lewy bodies. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(6):1130–1.

Serrano-Duenas M. Neuroleptic malignant syndrome-like, or—dopaminergic malignant syndrome—due to levodopa therapy withdrawal. Clinical features in 11 patients. Parkinsonism Relat Disord. 2003;9:175–8.

van Balken I, Litvan I. Current and future treatments in progressive supranuclear palsy. Curr Treat Options Neurol. 2006;8:211–23.

Vanneste JA. Diagnosis and management of normal-pressure hydrocephalus. J Neurol. 2000;247:5–14.

Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Parkinsonian like signs and risk of incident Alzheimer disease in older persons. Arch Neurol. 2003;60:539–44.

Wurtman RJ. Personalized medicine strategies for managing patients with parkinsonism and cognitive deficits. Metabolism. 2013;62 Suppl 1:S27–9.

Wszolek ZK, Tsuboi Y, Ghetti B, Pickering-Brown S, Baba Y, Cheshire WP. Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Orphanet J Rare Dis. 2006;1:30.

Yoshikawa H, Oda Y, Sakajiri K, Takamori M, Nakanishi I, Makifuchi T, et al. Pure akinesia manifested neuroleptic malignant syndrome: a clinical variant of progressive Supranuclear palsy. Acta Neuropathol. 1997;93:306–9.

Zeidler M, Dorman PJ, Ferguson IT, Bateman DE. Parkinsonism associated with obstructive hydrocephalus due to idiopathic aqueductal stenosis. J Neurol Neurosurg Psychiatry. 1998;64(5):657–9.

Zupancic M, Mahajan A, Handa K. Dementia with Lewy bodies: diagnosis and management for primary care providers. Prim Care Companion CNS Disord. 2011;13(5). pii: PCC.11r01190. doi: 10.4088/PCC.11r01190. PMID:22295275.

Chapter 5
Psychiatric Complications of Alzheimer's Disease Overlapping with Parkinsonism: Depression, Apathy, Catatonia, and Psychosis

Sergio E. Starkstein and Jaime Pahissa

Abstract Depression is a frequent comorbid condition in Alzheimer's disease (AD) and is associated with the presence of parkinsonism. Apathy in AD was reported to predict more severe parkinsonism, suggesting that apathy may be an early manifestation of a more aggressive AD phenotype characterized by loss of motivation, increasing parkinsonism, a faster cognitive and functional decline, and more severe depression.

Catatonia may be found in a small proportion of patients with AD, but rates are higher in hospitalized patients. Catatonia is significantly associated with more severe parkinsonism and depression and older age. Psychotic symptoms are relatively frequent in the late stages of AD. Current treatment with atypical antipsychotics has a concomitant risk of increased parkinsonism.

Keywords Depression • Apathy • Catatonia • Psychosis • Parkinsonism • Alzheimer's disease

Introduction

Psychiatric conditions, such as depression, apathy, and psychosis, are frequent comorbid conditions in Alzheimer's disease (AD). One of the major clinical challenges is to address the overlap between motor and psychiatric comorbidities in AD.

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For instance, depression and apathy may mimic the bradykinesia and bradyphrenia of AD patients with parkinsonism; catatonia may mimic rigidity and blunted expression, and side effects of psychotropic drugs may produce not only parkinsonism but also "positive" motor disorders such as akathisia and dyskinesia.

This chapter will review the phenomenology, frequency and treatment of depression, and apathy and catatonia in AD, with special emphasis on their motor manifestations in AD. We will conclude by examining the motor side effects on antipsychotic medication frequently used in dementia.

Depression in Alzheimer's Disease and Parkinsonism

AD and Depression: Diagnostic Issues

A major challenge in diagnosing depression in AD is how to identify those symptoms that pertain to depression from similar symptoms in AD. For instance, loss of interest in AD may be due to the patients' limitations with their daily activities; loss of pleasure may be related to the patients' diminished capacity to participate in their usual hobbies and leisure activities; loss of concentration is a common symptom in both depression and AD; and sleep problems are a well-known independent comorbid condition in dementia (Cohen-Cole and Stoudemire 1987).

The diagnostic dilemma becomes even more problematic when dealing with AD patients and comorbid parkinsonism, given that these patients show bradyphrenia, bradykinesia, and a high prevalence of REM sleep behavioral disturbance, which may be confused with the psychomotor retardation and sleep disturbance typical of depression.

Four strategies have been used to diagnose depression among patients with neurologic conditions. "The inclusive approach" diagnoses depression considering all the symptoms present, regardless of the medical condition (Cohen-Cole and Stoudemire 1987). The "exclusive approach," on the other hand, does not include for diagnosis those symptoms considered to be related to the physical illness (Gallo et al. 1999). The "substitutive approach" replaces overlapping symptoms of depression with psychological symptoms (Olin et al. 2002a). Finally, the "specific symptom approach" only considers for diagnosis those symptoms that were identified as belonging to a specific "depressive cluster" using specific statistical techniques, such as latent class analysis (Starkstein et al. 2011).

The American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) (APA 1994) criteria for major depression includes nine symptoms, five of which must be present and at least one of the five must be "depressed mood" or "loss of interest or pleasure." All must be judged to be significant in terms of severity, duration, distress, and impairment. The recently published DSM-V (APA 2013) does not include major changes to these criteria. Given the symptom overlap, the question arises as to the validity of the DSM-IV/V criteria for major depression in AD.

Lyketsos et al. suggested that the individual symptom approach in AD may ignore the high overlap of symptoms and should not be used for diagnostic purposes. Using latent class analysis, they identified a group with affective symptoms of depression as well as symptoms of anxiety and apathy. They proposed a specific set of diagnostic criteria for "AD-associated neuropsychiatric disturbance" (Lyketsos et al. 2001).

The National Institute of Mental Health (NIMH) conveyed a work group that proposed standardized diagnostic criteria for depression in AD (Olin et al. 2002b). These criteria are similar to the DSM-IV criteria for major depression but with the addition of irritability and social isolation and the replacement of loss of interest with loss of pleasure in response to social contact. Other modifications included the requirement of three rather than five symptoms for the diagnosis of depression and that symptoms do not have to be present nearly every day (Olin et al. 2002b).

Starkstein et al. examined the validity of the construct of major depression in a large series of patients with AD using LCA and found that all nine DSM-IV diagnostic criteria for major depression identified a cluster with high statistical significance. A second cluster included patients with an intermediate frequency of depressive symptoms, most of whom met DSM-IV criteria for minor depression, whereas a third cluster included patients with a very low frequency of depressive symptoms. Interestingly, anxiety and apathy were found to be significant predictors of depression in AD, whereas irritability was not. The authors concluded that the DSM-IV diagnostic criteria for major depression may be used without modifications in AD (Starkstein et al. 2011).

Frequency of Depression in AD

The frequency of depression in AD has been reported to range from 10 to 80 % (Migliorelli et al. 1995). This wide variation may be explained by relevant confounders, such as differences in psychiatric assessment techniques and diagnostic criteria, and sources of patients (e.g., patients screened from psychiatric clinics, neurologic clinics, or patients recruited from more representative community samples).

Migliorelli et al. examined 103 patients with probable AD with a structured psychiatric interview and standardized diagnostic criteria. They found that 51 % of the patients had depression (28 % had dysthymia and 23 % major depression). Women had a significantly higher prevalence of both major depression and dysthymia than men. Patients with major depression had an earlier onset of depression, and the prevalence of major depression was similar across the different stages of the illness (Migliorelli et al. 1995).

Starkstein et al. examined the frequency of major and minor depression in a series of 670 AD patients attending a memory clinic using the Structured Clinical Interview for DSM-IV. The main finding was that 26 % of the patients had major depression and another 26 % had minor depression (Starkstein et al. 2005a).

Richard et al. examined the association of late-life depression with dementia in a multiethnic community cohort study that included 2,160 community-dwelling Medicare recipients aged 65 years or older. Depression was assessed using the 10-item version of the Center for Epidemiologic Studies Depression Scale (CES-D), and depression was defined by a CES-D score of 4 or more. Their results showed that dementia was diagnosed at baseline in 217 participants and that participants with dementia were depressed twice as often as were those without dementia (odds ratio = 2.2; 95 % CI = 1.6–3.1) (Richard et al. 2013).

Management of Depression in AD

Studies of antidepressants for depression in AD produced inconclusive results, but the consensus based on recent randomized-controlled trials (RCT) is that antidepressants may not confer benefit over placebo.

A large RCT using the SSRI sertraline was conducted by Rosenberg et al. who enrolled 131 AD patients with mild–moderate AD meeting the NIMH criteria for depression in AD. The main finding was that neither remission rate nor scores on the Cornell Scale for Depression in Dementia (CSDD) were significantly different between sertraline and placebo groups after 12 weeks of treatment. Regardless of type of treatment, depression severity improved by an average of 50 %, and 40 % of the participants were judged to be either "better" or "much better" in their mood at treatment completion (Rosenberg et al. 2010). A 24-week study extension also failed to show a significant benefit of sertraline over placebo (Weintraub et al. 2010). Parkinsonism or other motor problems were not listed as a significant side effect of sertraline.

A recent multicenter RCT recruited 326 AD patients diagnosed with depression based on CSDD scores of 8 or more. Participants were allocated to receive sertraline (target dose 150 mg/day), mirtazapine (target dose 45 mg/day), or placebo. After 13 weeks of follow-up, there were no significant differences between the two active treatment and placebo groups on depression outcome. Parkinsonism was not listed as a prominent side effect of either sertraline or mirtazapine (Banerjee et al. 2011).

A Cochrane review of antidepressant efficacy for depression in dementia which examined the efficacy of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors included four studies with a total of 137 participants. Evidence offered weak support for the effectiveness of psychoactive drugs for depression in AD (Bains et al. 2002). Parkinsonism or other motor disorders were not found to be common side effects of these drugs, although the anticholinergic effect of TCAs was associated with postural hypotension and increased risk of falls.

A meta-analysis by Thompson et al. included 5 studies, which involved 82 subjects treated with antidepressants and 83 subjects who received placebo treatment. The authors reported a significantly higher efficacy for antidepressants over placebo in terms of both treatment response and remission of depression, and parkinsonism was not reported as a significant side effect (Thompson et al. 2007).

A recent meta-analysis that included 299 patients (Nelson and Devanand 2011) found that response and remission rates did not significantly differ between placebo

and active treatment. Parkinsonism was not reported a significant side effect of the active compounds (Nelson and Devanand 2011).

Enache et al. identified 11 RCTs for depression in AD or other types of dementia, with a total of 1,514 patients included. Of these, five studies reported that the antidepressant (sertraline, clomipramine, maprotiline, moclobemide, or citalopram) was more effective than placebo, whereas six studies using sertraline, mirtazapine, venlafaxine, imipramine, fluoxetine, or estrogen replacement therapy were negative. No parkinsonism was significantly associated with any of these medications (Enache et al. 2011).

The impact of discontinuing antidepressants among individuals with dementia was examined in a RCT that included 128 patients with dementia who had been prescribed escitalopram, citalopram, sertraline, or paroxetine for 3 months or more. The main finding was that patients who discontinued antidepressant treatment had significantly higher depression scores after 25 weeks as compared to the continuation group. Parkinsonism or other motor problems were not reported as relevant side effects of any of the psychotropic compounds (Bergh et al. 2012).

In conclusion, the efficacy of antidepressants in AD remains unclear. Two large RCTs demonstrated lack of efficacy for sertraline as compared to placebo, and one of them also showed lack of efficacy for mirtazapine. On the other hand, discontinuation of antidepressants was found to lead to a significant relapse of depression. Parkinsonism or other motor problems were not reported as significant side effects in any of the major RCTs or meta-analyses. One limitation of these studies is that the method used to asses for parkinsonism was not clearly specified.

Depression in AD and Parkinsonism

The question arises as to whether AD patients with parkinsonism may have a higher frequency of depression as compared to AD patients without parkinsonism. Choi et al. (2013) assessed parkinsonism in a series of 2,614 neuroleptic-free AD patients using a structured neurologic evaluation. After controlling for demographic, clinical, and cognitive variables, they found that parkinsonism in AD was significantly associated with higher depression scores, as measured with the Geriatric Depression Scale-15 (GDS-15) (Choi et al. 2013). Starkstein et al. (1996a) compared 33 patients with AD and 33 patients with PD matched for age, gender, and MMSE score. Major depression was significantly more frequent among PD patients (30 %) as compared to AD patients (6 %) ($P < 0.05$).

Apathy and Parkinsonism

Diagnostic Issues

Apathy is defined as a psychiatric syndrome characterized by deficits in goal-directed behavior as manifested by the simultaneous diminution in the cognitive and

Table 5.1 Diagnostic criteria for apathy

(A) Lack of motivation relative to the patient's previous level of functioning or the standards of his or her age and culture as indicated by either subjective account or observation by others
(B) Presence for at least 4 weeks during most of the day, of at least one symptom belonging to each of the following three domains:
Diminished goal-directed behavior
1. Lack of effort or energy to perform everyday activities
2. Dependency on prompts from others to structure everyday activities
Diminished goal-directed cognition
3. Lack of interest in learning new things or in new experiences
4. Lack of concern about one's personal problems
Diminished concomitants of goal-directed behavior
5. Unchanging or flat affect
6. Lack of emotional responsivity to positive or negative events
(C) The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
(D) The symptoms are not due to diminished level of consciousness or the direct physiological effects of a substance

emotional concomitants of goal-directed behavior (Marin 1991). Starkstein et al. (2001) validated a set of standardized criteria for the diagnosis of apathy in AD. They assessed a series of 319 patients with AD using the apathy scale (a severity rating scale) and found that 37 % of the sample met ad hoc criteria for apathy. These criteria include lack of motivation relative to the previous level of functioning and the presence during most of the day for at least 4 weeks of diminished goal-directed behavior, diminished goal-directed cognition, and blunted affect and emotion. An important finding of the study was a significant overlap between depression and apathy in AD: while 13 % of the AD sample had apathy and no depression, 24 % had both depression and apathy.

To our knowledge, there is a single structured interview for apathy validated for use in AD. Starkstein and coworkers developed the Structured Clinical Interview for Apathy (SCIA) to screen for symptoms and diagnose apathy based on the diagnostic criteria described above (Starkstein et al. 2005b). The SCIA includes a series of questions assessing the domains of motivation, effort, dependency on others, interest and concern, and affect and emotion. Based on responses to these questions, a diagnosis of apathy may be made using the Starkstein's and Leentjens' diagnostic criteria (Starkstein and Leentjens 2008) (Table 5.1).

Frequency of Apathy in AD

Starkstein et al. (2001) examined the prevalence of apathy in a study that included a consecutive series of 319 patients with AD, 117 patients with depression but no dementia, and 36 age-comparable healthy individuals (Starkstein et al. 2001). Based on apathy scale scores, apathy was diagnosed in 37 % of the AD patients, as

compared to 32 % among depressed patients without dementia, and in none of the healthy controls. About two-thirds of the AD patients with apathy were also depressed. Mulin et al. (2011) examined the frequency of apathy in a series of 306 patients with AD in a cross-sectional, multicenter study. Apathy was assessed with the Neuropsychiatric Inventory (NPI) and diagnoses carried out using the European Psychiatric Association Task Force on Apathy European diagnostic criteria for apathy (Mulin et al. 2011). Apathy was diagnosed in 55 % of the sample (Mullin et al. 2011). Finally, a recent study by Vilalta-Franch et al. (2013) assessed the 1-year prevalence of incidence of apathy in a sample of 491 patients with AD. They reported a prevalence of apathy of 21 % and an incidence of 11 % (Vilalta-Franch et al. 2013).

Treatment of Apathy in AD

There are no RCTs specifically designed to assess the efficacy of psychotropic compound to treat apathy in AD, and most of the literature is based on small case series or RCTs with apathy as a secondary outcome measure.

In a study of a series of 40 AD patients treated with the anticholinesterase inhibitor tacrine, Kaufer and colleagues (1998) reported a significant reduction of apathy in the group with moderate dementia (Kaufer et al. 1998), without significant motor side effects. Mega and coworkers (2005) examined changes in the severity of apathy in 19 patients with mild to moderate AD examined before and after treatment with the cholinesterase inhibitor galantamine. There was no significant change in clinical outcomes (Mega et al. 2005), but no parkinsonism was reported. A recent 6-week RCT that included 67 AD patients with apathy treated with methylphenidate (Rosenberg et al. 2013) failed to show significant benefits of the active compound as compared to placebo.

Psychostimulants have been used to treat apathy in AD in small series of patients, but no formal RCTs have been carried out. Galynker et al. (1997) reported a reduction in negative symptoms, as measured with the Scale for the Assessment of Negative Symptoms (SANS) in 12 patients with AD treated with methylphenidate. Parkinsonism was not reported to be a side effect of treatment (Galynker et al. 1997).

Siddique et al. (2009) assessed the efficacy of the SSRI citalopram (mean dose = 30 mg/day) on apathy NPI scores in a sample of 44 patients with AD previously treated with placebo in the context of a RCT (Siddique et al. 2009). While patients on citalopram showed a reduction of 60 % on the NPI apathy scale as compared to placebo treatment, this difference was not statistically significant (Siddique et al. 2009).

Apathy in AD and Parkinsonism

Parkinsonian signs are frequent in AD (see chapter by Starkstein and Merello) and are associated with a faster cognitive decline, worse quality of life, and early

nursing home admission. Cross-sectional studies in AD reported a significant association between parkinsonism and apathy (Starkstein et al. 2001). In a recent longitudinal study, Starkstein et al. (2006) examined the predictive validity and longitudinal progression and correlates of apathy in AD. The first study included a series of 354 patients that were followed for 1–4 years. At baseline, apathy was significantly associated with older age and depression. The frequency of apathy increased from 14 % in the stage of very mild AD to 61 % in the stage of severe AD. At follow-up, patients with apathy at baseline or patients who developed apathy during follow-up had a significant increase in depression scores and greater functional and cognitive decline.

A second study specifically examined the longitudinal association between apathy and parkinsonism in AD (Starkstein et al. 2010). The study included 169 patients with AD who were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) both at baseline and 1–4 years later. The main finding was that patients with apathy at baseline or those who developed apathy during follow-up had a significant increase in parkinsonism as compared with patients with no apathy at both assessments. The association between apathy and increasing parkinsonism was unrelated to age, gender, the severity of cognitive deficits, the presence of depression, or use of psychotropic medications. On the other hand, neither the presence of parkinsonism nor depression at baseline was significantly associated with more severe apathy at follow-up. The authors concluded that apathy may be an early manifestation of a more aggressive AD phenotype characterized by loss of motivation, increasing parkinsonism, a faster cognitive and functional decline, and more severe depression.

Catatonia

Before Kahlbaum described catatonia in 1874 (Kahlbaum 1874), a syndrome of catalepsy had been described as muscular rigidity, fixed posturing, and insensitivity to pain (Fink et al. 2010). Kahlbaum added the symptoms of echophenomena, grimacing, mannerisms, mutism, perseveration, posturing, negativism, rigidity, stereotypies, and staring. Catatonia is a motor and mood dysregulation syndrome that is found among men and women of all ages. Some of the catatonic symptoms are similar to parkinsonism, and it is therefore important to make an early diagnosis given that prompt treatment of catatonia is usually followed by good therapeutic results.

Diagnosis of Catatonia

The onset of catatonia is often acute, manifested by repetitive behaviors; stupor, sometimes alternating with agitated behaviors; and delirium. Some rare forms may be malignant, leading to death (Stauder 1934). While catatonia is often associated

with psychiatric disorders, such as schizophrenia, mood disorders, neuroleptic malignant syndrome (NMS), and serotonergic malignant syndrome, it can also be observed in a variety of neurologic and other medical conditions.

The DSM-IV included the category of "catatonia secondary to a medical disorder," while the DSM-5 criteria also include the category of "Unspecified Catatonia" for presentations with typical catatonic symptoms but without meeting the full criteria. The DSM-5 criteria for "Catatonic Disorder Due to Another Medical Condition" is met in the presence of three or more of the following symptoms: (1) stupor, (2) catalepsy, (3) waxy flexibility, (4) mutism, (5) negativism, (6) posturing, (7) mannerisms, (8) stereotypy, (9) agitation, (10) grimacing, (11) echolalia, and (12) echopraxia (American Psychiatric Association 2013).

There are currently several scales to measure the severity of catatonia. Northoff and coworkers (1999) designed the Northoff Catatonia Scale (NCS), based on the phenomenological description of catatonia by Kahlbaum (Northoff et al. 1999). The NCS distinguishes the categories of motor, affective, and behavioral catatonia, and it also includes motor phenomena not included in the DSM-5, such as festination (uncoordinated, inappropriate, jerky-like, and hasty movements which cannot be voluntarily controlled by the patient), athetotic movements (choreatic-like movements with a screw-shaped character); dyskinesias (involuntary fast movements, which cannot be voluntarily controlled by the patient, disturbing the normal patterns of movements), gegenhalten or paratonia (the resistance to passive movements with proportional strength to the increase of muscle tone), rigidity (muscular hypertonus which might be even and steady or cogwheel-like). muscular hypotonus (lose of active movement with an apparently decreased muscle tone in passive movements), sudden muscular tone alterations (rapid switches between muscular normotonus, hypotonus, and hypertonus), and akinesia (absence and paucity of movements for at least a half hour).

Francis and coworkers developed the Bush-Francis Catatonia Rating Scale (BFCRS), a 23-item rating scale that operationally defines each catatonic sign, rates its severity, and provides a standardized schema for clinical examination (Bush et al. 1996). These authors (Bush et al. 1996) suggested that two or more signs of catatonia present during 1 h or more or that can be reproduced in two or more occasions are sufficient for diagnosis (Bush et al. 1996). In clinical settings, the presence of even one catatonic sign should raise the suspicion of catatonia, and a full clinical examination should be undertaken, including assessment of brain structural abnormalities using CT or MRI scans and EEG to rule out nonconvulsive status epilepticus and encephalopathic states (Fink et al. 2010).

Frequency of Catatonia in AD

A recent study examined for the presence of catatonia all those patients referred to a consultation liaison service in a general hospital. Using the BFCS, the authors diagnosed catatonia in 9 % of the consults (Jaimes-Albornoz and Serra Mestres

2013). Rates of catatonia may be higher among hospitalized medical patients given that withdrawn patients (such those with a hypokinetic delirious) may not be recognized as catatonic (Zarr and Nowak 1990; Carroll et al. 2000; Cottencin et al. 2007).

Treatment of Catatonia

The treatment of catatonia is usually effective, with complete resolution in most cases (Francis 2010).

Treatment should be started with lorazepam, 2–6 mg/day by any route of administration, although some patients may require titration to higher doses (12–16 mg/day) (Jaimes-Albornoz and Serra-Mestres 2012). A recent open-label study in 20 catatonic patients showed that zolpidem (single oral dose of 10 mg) may be a useful treatment option for catatonia (Francis 2010). Finally, electroconvulsive therapy (ECT) has demonstrated great efficacy to treat catatonia even after pharmacologic treatment failed (Francis 2010).

Catatonia in AD and Parkinsonism

Starkstein et al. (1996b) reported that 20 % of 79 older adults with major depression referred to a psychiatric service met DSM-IV criteria for catatonia. A regression analysis demonstrated that UPDRS scores, HAM-D scores, and older age contributed significantly to catatonia scores. When patients with catatonia were matched with non-catatonic patients with PD based on UPDRS scores, catatonic patients had significantly higher scores on the DSM-IV clusters of stupor, excessive motor activity, extreme negativism, and posturing. Furthermore, apomorphine did not improve catatonic symptoms (Starkstein et al. 1996b).

Movement Disorder Due to Antipsychotic Medication in AD

Alzheimer's disease (AD), the most common cause of dementia in the elderly, is often associated with psychotic symptoms. The prevalence of psychosis in AD was recently estimated to be 7 %, with a 2-year cumulative incidence of 15 % (Vilalta-Franch et al. 2012). Psychotic symptoms persisted for 1 year or more in 69 % of patients with psychosis at baseline (Vilalta-Franch et al. 2012).

De Deyn et al. (2013) examined the efficacy of aripiprazole in a RCT that included 208 AD patients with psychosis. Aripiprazole was started at 2 mg/day and titrated upward up to 15 mg/day) depending on efficacy (mean dose = 10 mg/day).

Efficacy was similar for both active drug and placebo groups, and there were no between-group differences on the frequency of parkinsonism (De Deyn et al. 2013).

Schneider et al. (2006) evaluated the effectiveness of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in AD. This RCT included 421 outpatients with AD and psychosis, aggression, or agitation who were randomly assigned to receive olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks. The main outcomes were the time from initial treatment to the discontinuation of treatment for any reason and the number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks. Overall, 24 % of patients who received olanzapine, 18 % of patients who received risperidone, 16 % of patients who received quetiapine, and 5 % of patients who received placebo discontinued their assigned treatment owing to intolerability ($P<0.01$). No significant differences were noted on the CGIC scale by the end of the follow-up. Behavioral improvement was observed in 32 % of patients assigned to olanzapine, 29 % of patients assigned to risperidone, 26 % of patients assigned to quetiapine, and 21 % of patients assigned to placebo ($P=0.22$) (Schneider et al. 2006). Parkinsonism was significantly more frequent in patients on olanzapine (12 %) or risperidone (12 %) as compared to quetiapine (2 %) or the placebo groups (1 %).

Devanand and coworkers (2012) examined the risk of a recurrence of psychotic symptoms after discontinuation of risperidone (mean dose = 0.97 mg daily) in patients with AD for 4–8 months. The severity of psychosis and agitation were reduced with risperidone, although there was a mild increase in parkinsonism, and discontinuation of risperidone was associated with an increased risk of relapse. During the first 16-week period, there were no significant differences in adverse events as defined by increases above prespecified thresholds on scales measuring parkinsonism between patients receiving risperidone and those receiving placebo. Moreover, there were no significant differences between patients who received risperidone continuously for 32 weeks and those who received placebo with respect to parkinsonism and other movement disorders (Devanand et al. 2012).

Rocca et al. (2007) reported findings on a retrospective, naturalistic study on the effects of 6 months' treatment with risperidone, olanzapine, or quetiapine on behavioral disturbances in outpatients with mild to moderate AD. All three drugs produced significant improvements in behavioral disturbances, and medications were well tolerated with no significant differences emerging among treatments (Rocca et al. 2007).

Chiabrando et al. (2010) studied the prescriptive profile of antipsychotic drugs in 392 patients with dementia (49 % with AD) in terms of the choice of active substance and the clinical characteristics of patients. Hallucinations were present in 50 % of the cases and aggression in 53 %. There was an increased consumption of quetiapine and a parallel decrease in the use of risperidone and olanzapine during the study period. Neuroleptic doses were on average much lower than those used for treating non-AD psychoses. The most frequently observed adverse events were tremors (Chiabrando et al. 2010).

Conclusion

Parkinsonism is a frequent finding in AD, and several psychiatric disorders may mimic this movement disorder. Depression is highly prevalent in AD, and these patients may present with psychomotor retardation akin to bradyphrenia and bradykinesia. Apathy is another frequent behavioral comorbid condition in AD, and loss of motivation may lead to hypokinetic states. Catatonia is a relatively rare finding in AD, but many symptoms overlap with parkinsonism, making the differential diagnosis difficult. Finally, it is important to note that due to the high prevalence of psychotic symptoms in AD, a large proportion of AD patients are on neuroleptic medication, with a concomitant risk of increased parkinsonism.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Press; 1994.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.

Bains J, Birks JS, Dening TR. The efficacy of antidepressants in the treatment of depression in dementia. Cochrane Database Syst Rev. 2002;(4):CD003944.

Banerjee S, Hellier J, Dewey M, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. Lancet. 2011;378:403–11.

Bergh S, Selbæk G, Engedal K. Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial. BMJ. 2012;344:e1566.

Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. I. Rating scale and standardized examination. Acta Psychiatr Scand. 1996;93(2):129–36.

Carroll BT, Kennedy JC, Goforth HW. Catatonic signs in medical and psychiatric catatonias. CNS Spectr. 2000;5:66–9.

Chiabrando G, Bianchi S, Poluzzi E, Montanaro N, Scanavacca P. Profile of atypical-antipsychotics use in patients affected by dementia in the University Hospital of Ferrara. Eur J Clin Pharmacol. 2010;66(7):661–9.

Choi J, Myung W, Chung JW, et al. Association between functional impairment, depression, and extrapyramidal signs in neuroleptic-free patients with Alzheimer disease. J Geriatr Psychiatry Neurol. 2013;26(3):144–50.

Cohen-Cole SA, Stoudemire A. Major depression and physical illness. Psychiatr Clin North Am. 1987;10:1–17.

Cottencin O, Warembourg F, de Chouly de Lenclave M, et al. Catatonia and consultation-liaison psychiatry study of 12 cases. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:1170–6.

De Deyn PP, Drenth AF, Kremer BP, Oude Voshaar RC, Van Dam D. Aripiprazole in the treatment of Alzheimer's disease. Expert Opin Pharmacother. 2013;14(4):459–74.

Devanand DP, Mintzer J, Schultz SK, et al. Relapse risk after discontinuation of risperidone in Alzheimer's disease. N Engl J Med. 2012;367(16):1497–507.

Enache D, Winblad B, Aarsland D. Depression in dementia: epidemiology, mechanisms, and treatment. Curr Opin Psychiatry. 2011;24(6):461–72.

Fink M, Shorter E, Taylor MA. Catatonia is not Schizophrenia: Kraepelin's error and the need to recognize catatonia as an independent syndrome in medical nomenclature. Schizophr Bull. 2010;36:314–20.

Francis A. Catatonia: diagnosis, classification, and treatment. Curr Psychiatry Rep. 2010;12: 180–5.

Gallo JJ, Rabins PV, Anthony JC. Sadness in older persons: 13-year follow-up of a community sample in Baltimore, Maryland. Psychol Med. 1999;29:341–50.

Galynker I, Ieronimo C, Miner C, Rosenblum J, Vilkas N, Rosenthal R. Methylphenidate treatment of negative symptoms in patients with dementia. J Neuropsychiatry Clin Neurosci. 1997;9(2):231–9.

Jaimes-Albornoz W, Serra-Mestres J. Catatonia in the emergency department. Emerg Med J. 2012;29:863–7.

Jaimes-Albornoz W, Serra-Mestres J. Prevalence and clinical correlations of catatonia in older adults referred to a liaison psychiatry service in a general hospital. Gen Hosp Psychiatry. 2013;35:512–6.

Kahlbaum KL. Die Katatonie oder das Sannungsirreiseins. Berlin: Hirschwald; 1874.

Kaufer D, Cummings JL, Christine D. Differential neuropsychiatric symptom responses to tacrine in Alzheimer's disease: relationship to dementia severity. J Neuropsychiatry Clin Neurosci. 1998;10(1):55–63.

Lyketsos CG, Breitner JC, Rabins PV. An evidence-based proposal for the classification of neuropsychiatric disturbance in Alzheimer's disease. Int J Geriatr Psychiatry. 2001;11:1037–42.

Marin RS. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci. 1991;3:243–54.

Mega MS, Dinov ID, Porter V, et al. Metabolic patterns associated with the clinical response to galantamine therapy: a fludeoxyglucose f 18 positron emission tomographic study. Arch Neurol. 2005;62(5):721–8.

Migliorelli R, Teson A, Sabe L, Petrachi M, Leiguarda R, Starkstein SE. Prevalence and correlates of dysthymia and major depression among patients with Alzheimer's disease. Am J Psychiatry. 1995;152:37–44.

Mulin E, Leone E, Dujardin K, et al. Diagnostic criteria for apathy in clinical practice. Int J Geriatr Psychiatry. 2011;26(2):158–65. doi:10.1002/gps.2508.

Nelson JC, Devanand DP. A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. J Am Geriatr Soc. 2011;59:577–85.

Northoff G, Koch A, Wenke J, et al. Catatonia as a psychomotor syndrome: a rating scale and extrapyramidal motor symptoms. Mov Disord. 1999;14:404–16.

Olin JT, Katz IR, Meyers BS, Schneider LS, Lebowitz BD. Provisional diagnostic criteria for depression of Alzheimer disease: rationale and background. Am J Geriatr Psychiatry. 2002a;10(2):129–41.

Olin JT, Schneider LS, Katz IR, et al. Provisional diagnostic criteria for depression of Alzheimer disease. Am J Geriatr Psychiatry. 2002b;10(2):125–8.

Richard E, Reitz C, Honig LH, et al. Late-life depression, mild cognitive impairment, and dementia. JAMA Neurol. 2013;70(3):374–82.

Rocca P, Marino F, Montemagni C, et al. Risperidone, olanzapine and quetiapine in the treatment of behavioral and psychological symptoms in patients with Alzheimer's disease: preliminary findings from a naturalistic, retrospective study. Psychiatry Clin Neurosci. 2007;61(6):622–9.

Rosenberg PB, Drye LT, Martin BK, et al. Sertraline for the treatment of depression in Alzheimer disease. Am J Geriatr Psychiatry. 2010;18(2):136–45.

Rosenberg PB, Lanctôt KL, Drye LT, Herrmann N, Scherer RW, Bachman DL, Mintzer JE. Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: a randomized, placebo-controlled trial. J Clin Psychiatry. 2013;74:810–6.

Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med. 2006;355(15):1525–38.

Siddique H, Hynan LS, Weiner MF. Effect of a serotonin reuptake inhibitor on irritability, apathy, and psychotic symptoms in patients with Alzheimer's disease. J Clin Psychiatry. 2009;70:6.
Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. J Neurol Neurosurg Psychiatry. 2008;79:1088–92.
Starkstein SE, Petracca G, Teson A, et al. Catatonia in depression: prevalence, clinical correlates, and validation of a scale. J Neurol Neurosurg Psychiatry. 1996a;60:326–32.
Starkstein SE, Sabe L, Petracca G, et al. Neuropsychological and psychiatric differences between Alzheimer's disease and Parkinson's disease with dementia. J Neurol Neurosurg Psychiatry. 1996b;61:381–7.
Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. Am J Psychiatry. 2001;158(6):872–7.
Starkstein SE, Ingram L, Garau ML, Mizrahi R. On the overlap between apathy and depression in dementia. J Neurol Neurosurg Psychiatry. 2005a;76(8):1070–4.
Starkstein SE, Jorge R, Mizrahi R, Robinson RG. The construct of minor and major depression in Alzheimer's disease. Am J Psychiatry. 2005b;162(11):2086–93.
Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A prospective longitudinal study of apathy in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2006;77:8–11.
Starkstein SE, Brockman S, Bruce D, Petracca G. Anosognosia is a significant predictor for apathy in Alzheimer's disease. J Neuropsychiat Clin Neurosci 2010;22(2):378–83.
Starkstein SE, Dragovic M, Jorge R, Brockman S, Robinson RG. Diagnostic criteria for depression in Alzheimer disease: a study of symptom patterns using latent class analysis. Am J Geriatr Psychiatry. 2011;19(6):551–8.
Stauder K. Die totliche Katatonie. Archives fur Neurologie und Psychiatrie. 1934;23:614–32.
Thompson S, Herrmann N, Rapoport MJ, Lanctôt KL. Efficacy and safety of antidepressants for treatment of depression in Alzheimer's disease: a metaanalysis. Can J Psychiatry. 2007; 52(4):248–55.
Vilalta-Franch J, López-Pousa S, Calvó-Perxas L, Garre-Olmo J. Psychosis of Alzheimer disease: prevalence, incidence, persistence, risk factors, and mortality. Am J Geriatr Psychiatry. 2012;21(11):1135–43.
Vilalta-Franch J, Calvo-Perxas L, Garre-Olmo J, Turro Garriga O, Lopez-Pousa S. Apathy syndrome in Alzheimer's disease epidemiology: prevalence, incidence, persistence, and risk and mortality factors. J Alzheimers Dis. 2013;33:535–43.
Weintraub D, Rosenberg PB, Drye LT, et al. Sertraline for the treatment of depression in Alzheimer disease: week-24 outcomes. Am J Geriatr Psychiatry. 2010;18(4):332–40.
Zarr ML, Nowak T. Catatonia and burns. Burns. 1990;16:133–4.

Chapter 6
Drug-Induced Movement Disorders in Elderly Patients

Santiago Perez-Lloret, Jean-Louis Montastruc, and Olivier Rascol

Abstract Movement disorders such as dystonia, akathisia, parkinsonism, chorea, stereotypies, myoclonus, or tics can be observed during exposure to a large number of drugs commonly used for the treatment of diverse medical conditions. The most frequent drugs connected to movement disorders are antipsychotics, but they can also be observed with a variety of drugs, such as metoclopramide, prochlorperazine, cinnarizine, flunarizine, H1 antihistaminergic drugs, trimetazidine, or serotonin reuptake inhibitors. Clinical observation is crucial for differential diagnosis of drug-induced movement disorders. Neuroimaging by positron emission tomography (PET) or single photon emission computed tomography (SPECT) may be of help for diagnosing drug-induced parkinsonism or tardive dyskinesia. The first therapeutic measure is to withdraw the offending drug when possible. When needed, muscarine receptor blockers can be used to treat acute dystonia, propranolol or alprazolam for akathisia, and reserpine or methyldopa for life-threatening tardive syndromes.

Keywords Drug-induced movement disorders • Adverse drug reactions • Pharmacovigilance • Parkinsonism • Akathisia • Dystonia • Tremor • Chorea • Myoclonus • Tardive syndromes

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Movement Disorders in the Elderly

Movement disorders can occur in previously unaffected elderly patients or during the course of neuropsychiatric conditions (Haddad and Dursun 2008; Casey 1985). Such movement disorders need to be differentiated from those induced by drugs. In the following paragraphs, we will mention the most frequent movement disorders, and we will briefly discuss their prevalence in the elderly population.

Idiopathic Parkinson's disease (PD) is the most frequent movement disorder in the elderly (Poewe 2006) and affects over one million people in Europe and North America (Andlin-Sobocki et al. 2005; Lang and Lozano 1998). A systematic review of 25 incidence studies found incidence rates between 9 and 19 cases per 100,000 habitants per year, being the mean age of symptom onset was 60–65 years (Twelves et al. 2003). In some studies, incidence was as high as 263 per 1,000,000/year (Perez et al. 2010). Prevalence in subjects above 50 years old is between 2 and 5 % (de Rijk et al. 1997; Wenning et al. 2005).

Primary generalized dystonias are progressive, disabling disorders that typically begin in youth. Dystonia affects about 16 every 100,000 habitants of all ages (Steeves et al. 2012), but prevalence in subjects above 70 years is 131 per 100,000 (Das et al. 2007). Essential tremor is the most frequent cause of tremor besides drugs. Its overall prevalence in the elderly is between 2 and 14 % (Barbosa et al. 2013). The most frequent hyperkinetic movement disorder is Huntington's chorea with an incidence of 0.38 per 100,000 per year and a prevalence of 5.70 per 100,000 (Pringsheim et al. 2012). Other movement disorders are less frequent.

As mentioned earlier, a variety of movement disorders can occur in other neuropsychiatric symptoms. In Huntington's disease, for example, tardive dyskinesia (TD) resulting from exposure to antipsychotic drugs often prescribed for psychiatric symptoms of the disease has to be differentiated from chorea or dystonia. There are also a variety of complex repetitive hyperkinetic disorders presenting as mannerisms, stereotypies, and compulsions that may appear identical to certain movement disorders such as tics or dystonia, further complicating differential diagnosis. Lastly, hypokinetic conditions including bradyphrenia, catatonia, rigidity, catalepsy, negativism, and mutism are generally difficult to distinguish from various forms of drug-induced parkinsonism.

Drug-induced movement disorders (DIMD) were identified soon after antipsychotic marketing began in the 1950s. Initially, use of these drugs was linked to acute adverse extrapyramidal syndromes including acute dystonia, akathisia, and parkinsonism (Tarsy 1983). Later, TD was also recognized as an adverse drug reaction to antipsychotics. Since those years, many other drugs have been connected with DIMD including psychiatric or nonpsychiatric drugs such as serotonin-specific reuptake inhibitors, metoclopramide, or some calcium-channel blockers, among others (Bakheit 1997; Casey 1990; Mena and de Yebenes 2006; Orti-Pareja et al. 1999; van Harten et al. 1999).

Clinical Characteristics of Drug-Induced Movement Disorders in the Elderly

Symptoms and time to onset of DIMDs vary significantly and include parkinsonism as well as motor restlessness (akathisia), dystonia, and the entire spectrum of hyperkinesias (namely, chorea, stereotypies, myoclonus, dystonia, and tics) (Caligiuri et al. 2000). They can be categorized as acute (immediate), continuous (insidious), or persistent (tardive) (Table 6.1) (Rodnitzky 2002). Dystonia represents the most frequent acute drug reaction. Its development is fast, and in some cases it may be as severe as to require hospitalization. Continuous DIMDs persist only while the offending drug is being administered and remit after its discontinuation, either immediately or a variable period of time after discontinuation. They include akathisia, tremor, parkinsonism, chorea, and myoclonus. In case of parkinsonism, lack of remission after discontinuation could indicate that drug exposition unmasked a preexistent PD (Lopez-Sendon et al. 2013). Finally, tardive syndromes consist in a variety of DIMDs appearing long after beginning drug use. Typically, offending drug discontinuation will not relieve this kind of disorders (Rodnitzky 2002).

Table 6.1 Drug-induced movement disorders

DIMD	Main characteristics
Acute (*immediate*)	
Dystonia	Sustained involuntary muscular contractions or spasms resulting in abnormal postures or twisting and repetitive movements. Symptoms are associated with distress, with or without pain
Continuous (*insidious*)	
Akathisia	Subjective feeling of restlessness and need to move. Objective symptoms: walking in place, foot taping, rocking while seated
Parkinsonism	Tremor, rigidity, and slowness of movements affecting bilateral upper and lower extremities. Gait imbalance, masked facies, micrographia, and stooped posture may be present
Tremor	They can be postural, intentional, or action tremors. Their frequency can vary between 4 and 12 Hz
Chorea	Irregular, sudden-onset, explosive, purposeless movements
Myoclonus	Brief, involuntary, muscular jerks
Persistent (*tardive*)	
Dyskinesia Dystonia Akathisia Myoclonus Tics Tremor	Tardive dyskinesia: choreathetoid involuntary movements affecting the orofacial region and tongue. Lip smacking, chewing movements, and tongue protrusion are common. Symptoms are not painful but highly distressing

Acute Dystonia

Ninety-five percent of acute dystonic movements develop within 96 h of starting drug exposure. It is characterized by jerks or prolonged muscle spasms often involving the craniocervical region (eyes, mouth, throat, neck) or even oculogyric crises (van Harten et al. 1999; Casey 1992).

Involvement of trunk and limbs is less common than in idiopathic dystonia (van Harten et al. 1999; Casey 1992). Acute dystonic reactions can be dramatic and at times of enough severity to warrant lifesaving measures, such as involvement of laryngeal muscles causing acute respiratory distress. Principal risk factors are male gender, young age, previous episode of acute dystonia, recent cocaine use, hypocalcemia or hypoparathyroidism, and dehydration (van Harten et al. 1999; Casey 1992).

Main differential diagnosis are psychogenic dystonia, catatonia, or tardive dystonia. Psychogenic dystonia can be suspected in cases in which dystonia disappears whenever patients believe they are unobserved or other psychogenic movement disorders or nonorganic neurological features are present, or if symptoms of somatization disorder are present, or in the static form of dystonia. Catatonia is often accompanied by symptoms such as rigidity, akinesis, cerea flexibilitas, and mutism, which are not seen in acute dystonia nor related to drug treatment. The main difference between acute and tardive dystonia is that the latter occurs only after months or years of treatment with antipsychotics and does not improve rapidly after administration of muscarinic receptor blockers.

Acute Akathisia

Akathisia (Greek “not to sit”) consists in difficulty remaining still and a subjective sense of restlessness (Bakheit 1997; Akagi and Kumar 2002). It is a well-known adverse drug reaction of antipsychotics, antiemetics, and antidepressants, among others (Akagi and Kumar 2002). Difficult to detect reliably, it may present unexpectedly in a variety of clinical settings and be accompanied by unpleasant oral or genital paresthesia, burning, or lancinating pain not responding to conventional treatments. Principal risk factors are advanced age, presence of an affective disorder, cognitive impairment, female gender, and mental retardation.

Principal differential diagnoses are restless legs syndrome (RLS), mania (in bipolar patients), and dyskinesias (Bakheit 1997). RLS is characterized by muscle discomfort, pain and restlessness, or crawling sensations relieved by walking. Unlike akathisia, which ceases during sleep, RLS occurs mostly at night. Hyperactivity associated with anxiety states is often indistinguishable from akathisia, especially in psychotic patients on neuroleptics. However, sympathetic overactivity, for example, excessive sweating, palpitations, hyperventilation, tremulousness, and dilated pupils, characteristic of anxiety and panic attacks, is not seen in patients

with akathisia. In bipolar affective disorders, akathisia can be confused with spontaneous mania, although usually milder and short-lived. In addition, spontaneous mania is usually accompanied by delusions, hallucinations, and bizarre behavior.

Dyskinesia, in contrast to akathisia, is often unilateral or if bilateral tends to be more pronounced in the more severely affected arm and leg. As a rule, it increases in severity approximately 1–2 h after each levodopa and/or dopamine agonist dose, although not always.

Parkinsonism

DIP is the second most common cause of parkinsonian syndrome (Mena and de Yebenes 2006). The diversity of drugs involved in the production of DIP and the wide range of clinical disorders in which they are used poses a tough diagnostic challenge (Esper and Factor 2008). Several population-based studies suggest a prevalence between 1.7 and 2.7 % (Barbosa et al. 2006; Benito-Leon et al. 2004; Seijo-Martinez et al. 2011).

DIP is characterized by its symmetrical presentation with bradykinesia dominating the overall clinical picture (Mena and de Yebenes 2006; Gershanik 1994). Typical resting tremor is not frequently observed but when present is postural and of higher frequency than in idiopathic disease. It develops insidiously after the offending drug is introduced, taking weeks or months to manifest fully. Cognitive impairment is also frequently present (Kim et al. 2011). Main risk factors are older age, female gender, and cognitive impairment (Barbosa et al. 2006; Kim and Byun 2009).

The main differential diagnoses are idiopathic PD and the parkinsonian form of multiple system atrophy (Mena and de Yebenes 2006). DIP should be suspected in older patients, more prone to take different medications for underlying chronic conditions, including whenever symmetrical symptoms are present, disease onset is not compatible with idiopathic Parkinson's disease, or akinesia and postural tremor predominate over rigidity and rest tremor (Esper and Factor 2008; Gershanik 1994). Other drug-induced symptoms like akathisia or tardive dyskinesia can provide clues to potential parkinsonian syndrome origin.

Tremors, Chorea, and Myoclonus

Tremor is classified according to the behavior it is associated with (Morgan and Sethi 2005). Resting tremor is usually 4–6 Hz, occurs with the limb supported against gravity, and decreases with movement. Action or postural tremor varies widely in amplitude and frequency and occurs with maintained posture or movement. Finally, intentional tremor is terminal kinetic tremor (typically <5 Hz) with larger amplitude during final stages of target-directed movements.

Drug-induced tremors are generally dose-responsive and lack progression, unlike tremors in PD and essential tremor (Morgan and Sethi 2005). Main risk factors are older age, liver failure, CNS lesions, or anxiety.

Main differential diagnoses are chorea and myoclonus. Choreas are irregular, sudden-onset, explosive, purposeless movements (Montastruc and Durrieu 2004). They usually include facial, shoulder, or finger movements. They are facilitated by emotion and attention and inhibited by rest, calm, and sleep. They are infrequently caused by drugs, except for the well-known levodopa-induced dyskinesias in parkinsonian patients. Notwithstanding, contraceptives can cause choreas especially in the case of patients with antecedents of rheumatic fever. Antiepileptic can also be related to choreas.

Myoclonus is brief, involuntary, muscular jerks that can generate movement or not (Montastruc and Durrieu 2004). Penicillins are frequent causes of myoclonus. They can also occur with antiepileptic or antidepressant overdose, in the context of an encephalopathy.

Tardive Dyskinesia and Other Syndromes

Tardive syndromes often run a persistent course despite cessation of triggering drug therapy. In some instances, they may become permanent and irreversible. They should be considered in patients presenting abnormal involuntary movements after at least 3 months of total cumulative neuroleptic exposure, although they are more common after longer periods of exposure (1–2 years) (Casey 1990; Caligiuri et al. 2000). They can develop even after antipsychotics dose reduction (unmasked TD) or even after the causative drug has been withdrawn (covert or withdrawal TD).

TD consists of involuntary movements usually involving muscles of the tongue, lips, mouth, or face (i.e., the so-called buccolinguomasticatory syndrome) (Haddad and Dursun 2008; Casey 1990; Caligiuri et al. 2000; Paulson 2005). Upper facial muscles are less frequently affected by involuntary movements; however, it is possible to see increased blinking, blepharospasm, arching of the eyebrows, ocular torsion, and deviation.

Other parts of the body can be affected, though less frequently, and a wide range of movements can be observed including myoclonic jerks, tics, chorea, and dystonia. Gait can be abnormal, with a broad base, leg jerking, and repetitive irregular flexion and extension of the knees (Haddad and Dursun 2008; Tarsy 1983; Casey 1990). While standing in place, affected individuals tend to shift their weight from one leg to the other or exhibit pacing or marching in place. The diaphragm and accessory respiratory muscles are often involved causing a fast and irregular breathing pattern (respiratory dyskinesia). The movements are more pronounced when the patient is alert or excited and disappear during sleep. Patients can sometimes suppress the movements through intense voluntary effort. Main risk factors are older age and female gender, presence of affective disorders, alcoholism, diabetes mellitus, electroconvulsive treatment, iron deficiency, mental retardation, or organic brain disorder.

Most important differential diagnosis is chorea (Haddad and Dursun 2008). Movements in TD tend to be more patterned, repetitive, and stereotypic than in chorea.

Dystonic phenomena account in up to 20 % of tardive syndromes found in psychiatric inpatients and are similar to acute dystonia (Orti-Pareja et al. 1999; Burke et al. 1982). Motor and vocal tics following chronic neuroleptic treatment can occasionally be seen as part of the tardive syndrome. This type of clinical presentation has been described and referred as tardive tourettism (Jankovic 1995). In a small number of cases, myoclonus can be the predominant feature of TD. Tardive tremor has been also added to the clinical spectrum of TD (Jankovic 1995).

Diagnostic Work-Up

During the course of any drug treatment, movement disorders not necessarily related to intake may occur. Nonetheless, prescription drugs should always be considered a differential diagnosis for any movement disorder, especially if the patient is on an agent known to induce them. It should be kept in mind that subjects may not readily recall all the medications they receive.

Causality assessment is indispensable but many times difficult. The following aspects of the event should be considered (Rehan et al. 2009; Edwards and Aronson 2000; Montastruc et al. 2006):

- Timing in relation to drug intake. When symptoms begin soon after drug exposure starts, diagnosis may be easy; however, connecting symptoms to long-term drug use may be difficult.
- Plausibility of the event. If the event result from a known pharmacodynamic property of the drug (i.e., D2-blockage properties of neuroleptics), it may be easier to connect to the drug. Nonetheless, in some cases DIMD pathophysiology may not be known.
- Exclusion of other causes. DIMD may be diagnosed only after exclusion of every other possible cause for the event observed.
- Dechallenge may be of aid when feasible. Disappearance of DIMD after drug discontinuation is indicative of a link to the drug. Nonetheless, some DIMDs such as TD do not disappear after drug discontinuation.
- Rechallenge, when possible, may lead to the reappearance of the movement disorder, thus reassuring its drug-induced nature.

Clinical observation is crucial for DIMD differential diagnosis. In the case of DIP, while motor symptoms may not allow proper differentiation with PD, the absence of non-motor symptoms favors the former (Kim et al. 2013a). DIP patients have normal olfactory function except when dopaminergic loss was present in patients (Bovi et al. 2010). Clinical laboratory is in general not helpful for the diagnosis of DIMDs. Nonetheless, increased serum hyperprolactinemia can be used as a marker of dopamine receptor blockage when antipsychotics are used (Kinon et al. 2003).

For DIP and TD however, some diagnostic tools are available. Firstly, acute dopaminergic challenge with either levodopa or apomorphine may represent a useful tool for differentiating PD from DIP (Merello et al. 2002). Schizophrenic patients with DIP show a noteworthy absence of response to levodopa or apomorphine during a levodopa acute challenge (Merello et al. 1996).

Assessment of dopaminergic nigrostriatal pathway integrity can also be useful distinguishing DIMD, in which they are intact, from Parkinson's disease, in which they are not. This can be accomplished by imaging with positron emission tomography (PET) or single photon emission computed tomography (SPECT) using ligands binding to dopaminergic nigrostriatal system markers (Tolosa et al. 2003). The presence of the dopamine transporter in the presynaptical buttons of the dopaminergic neurons located in the striate nuclei can be assessed by [^{123}I]FP-CIT SPECT (Tolosa et al. 2003). Death of dopaminergic neurons, for example, in PD, leads to a reduced number of dopamine transporter, which cause a reduction in the intensity of the signal that the striatal level in the SPECT. In the case of [^{18}F]-dopa-PET, what is evaluated is the integrity of presynaptical dopaminergic structures in charge of uptaking and processing DOPA to form dopamine. Results are interpreted in an analogous way to those of SPECT.

Nonetheless, these techniques may not be enough in schizophrenic patients, in whom D2-receptor blockade may coexist with a dopamine nigrostriatal terminal defect (Tinazzi et al. 2012). In doubtful cases, combination of techniques might be useful for differential diagnosis (Kim et al. 2013b; Lee et al. 2007). Assessment of cardiac sympathetic denervation by using ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy may also provide further clues about the origin of the parkinsonian syndrome (Kim et al. 2013b; Lee et al. 2007).

For TD diagnosis, neuroimaging studies may helpful, as anomalies in basal ganglia and other brain regions in schizophrenic patients with TD have been identified (Khiat et al. 2008). These anomalies include caudate nuclei, left lentiform nuclei, and temporal sulci volume differences as well as reduction in T2 relaxation time in the left caudate nuclei.

Offending Drugs

Many psychotropic and nonpsychotropic drugs have been related to DIMD (Tables 6.2 and 6.3). In this section, we will review the most important ones.

Antipsychotics

Centrally acting dopamine receptor blockers, such as haloperidol and phenothiazine, are the agents most commonly associated with DIMD (Haddad and Dursun 2008; Orti-Pareja et al. 1999). The proposed mechanism for these adverse drug

Table 6.2 Movement disorders induced by psychotropic drugs

Drug	Acute dystonia	Akathisia	Drug-induced parkinsonism	Tardive dyskinesias	Tremors	Myoclonus	Other choreas	Tic
Anesthetics/SNC depressors								
Propofol	x (Brooks 2008)	x (Brooks 2008)					x (Jimenez-Jimenez et al. 1997)	
Procaine			x (Montastruc et al. 1994)					
Ethanol			x (Montastruc et al. 1994)		xx (Morgan and Sethi 2005)			
Anticonvulsants								
Valproic acid		x (Jimenez-Jimenez et al. 1997)	x (Mena and de Yebenes 2006; Nguyen et al. 2004; Masmoudi et al. 2006)		xx (Morgan and Sethi 2005)	x (Montastruc and Durrieu 2004)	x (Jimenez-Jimenez et al. 1997)	
Carbamazepine	x (van Harten et al. 1999)			x (van Harten et al. 1999; Blayac et al. 2004)			x (Jimenez-Jimenez et al. 1997)	
Topiramate								
Phenytoin	x (van Harten et al. 1999)	x (Jimenez-Jimenez et al. 1997)	x (Mena and de Yebenes 2006; Nguyen et al. 2004)	x (Lang 1992)		xx (Montastruc and Durrieu 2004)	x (Rodnitzky 2002)	
Phenobarbital				x (Lang 1992)		x (Montastruc and Durrieu 2004)	x (Jimenez-Jimenez et al. 1997)	
Gabapentin	x (Reeves et al. 1996)				x (Morgan and Sethi 2005)	xx (Asconape et al. 2000)	x (Jimenez-Jimenez et al. 1997)	

(continued)

Table 6.2 (continued)

Drug	Acute dystonia	Akathisia	Drug-induced parkinsonism	Tardive dyskinesias	Tremors	Myoclonus	Other choreas	Tic
Lamotrigine		xx (Rodnitzky 2002)			x (Morgan and Sethi 2005)			
Tiagabine					x (Morgan and Sethi 2005)			
Oxcarbazepine					x (Morgan and Sethi 2005)			
Levetiracetam			x (Mena and de Yebenes 2006)					
Ethosuximide		x (Montastruc et al. 1994)					x (Jimenez-Jimenez et al. 1997)	
Pregabalin			x (Perez-Lloret et al. 2009)		x (Perez-Lloret et al. 2009)			
Antidepressants								
Tricyclics	x (Montastruc and Durrieu 2004)	x (Bakheit 1997)	x (Nguyen et al. 2004)	x (Orti-Pareja et al. 1999; Blayac et al. 2004)	xx (Morgan and Sethi 2005)	x (Montastruc and Durrieu 2004)	x (Rodnitzky 2002)	
SSRIs	xx (van Harten et al. 1999)	xx (Bakheit 1997)	x (Mena and de Yebenes 2006; Jimenez-Jimenez and Molina 2000; Nguyen et al. 2004; Jimenez-Jimenez et al. 1996)	xx (Jimenez-Jimenez and Molina 2000; Blayac et al. 2004)	xx (Morgan and Sethi 2005; Jimenez-Jimenez and Molina 2000)	x (Montastruc and Durrieu 2004; Jimenez-Jimenez and Molina 2000)	x (Rodnitzky 2002)	x (Jimenez-Jimenez and Molina 2000)
Trazodone			x (Montastruc et al. 1994)			x (Montastruc and Durrieu 2004)		

Bupropion			x (Montastruc et al. 1994)			x (Montastruc and Durrieu 2004)
Venlafaxine						x (Montastruc and Durrieu 2004)
Nefazodone						x (Montastruc and Durrieu 2004)
Mirtazapine						x (Montastruc and Durrieu 2004)
Antiemetics						
Metoclopramide	xx (van Harten et al. 1999)	xx (Jimenez-Jimenez et al. 1996)	xx (Mena and de Yebenes 2006; Jimenez-Jimenez et al. 1996)	xx (Orti-Pareja et al. 1999; Blayac et al. 2004; Jimenez-Jimenez et al. 1996)	xx (Morgan and Sethi 2005)	xx (Montastruc and Durrieu 2004)
Domperidone	x (Bonuccelli et al. 1991)					
Clebopride			x (Montagna et al. 1992)			

(continued)

Table 6.2 (continued)

Drug	Acute dystonia	Akathisia	Drug-induced parkinsonism	Tardive dyskinesias	Tremors	Myoclonus	Other choreas	Tic
Antipsychotics								
Typical	xx (van Harten et al. 1999)	xx (Bakheit 1997; Jimenez-Jimenez et al. 1996)	xx (Bakheit 1997; Jimenez-Jimenez et al. 1996)	xx (Bakheit 1997; Jimenez-Jimenez et al. 1996)	xx (Blayac et al. 2004)	xx (Montastruc and Durrieu 2004)		x (Montastruc and Durrieu 2004; Blayac et al. 2004)
Atypical	x (Bakheit 1997; Gareri et al. 2006)	x (Bakheit 1997; Gareri et al. 2006)	x (Bakheit 1997; Gareri et al. 2006)	x (Bakheit 1997; Gareri et al. 2006)	x (Bakheit 1997; Gareri et al. 2006)	x (Bakheit 1997; Montastruc and Durrieu 2004; Gareri et al. 2006)		
Anxiolytics								
Buspirone	x (LeWitt et al. 1993)	x (LeWitt et al. 1993)	x (LeWitt et al. 1993)	x (LeWitt et al. 1993)	x (Jimenez-Jimenez et al. 1997)	x (Montastruc and Durrieu 2004; LeWitt et al. 1993)		
Diazepam	x (Lang 1992)		x (Jimenez-Jimenez et al. 1997)			x (Montastruc and Durrieu 2004)		
Clonazepam						x (Montastruc and Durrieu 2004)		
Lorazepam			x (Jimenez-Jimenez et al. 1996)	x (Orti-Pareja et al. 1999)				

CNS stimulants							
Methamphetamine/ amphetamines			x (Morgan and Sethi 2005)		x (Morgan and Sethi 2005)	x (Rodnitzky 2002)	x (Montastruc and Durrieu 2004; Blayac et al. 2004)
Cocaine	x (van Harten et al. 1999)	x (Chung and Chiu 1996)	x (Morgan and Sethi 2005)	x (Weiner et al. 2001)	x (Morgan and Sethi 2005)	xx (Jimenez-Jimenez et al. 1997)	x (Montastruc and Durrieu 2004; Blayac et al. 2004)
Methylphenidate		x (Chung and Chiu 1996)				xx (Rodnitzky 2002)	x (Montastruc and Durrieu 2004; Blayac et al. 2004)
Drugs for cephalea							
Sumatriptan	x (Oterino and Pascual 1998)						
Methysergide		x (Jimenez-Jimenez et al. 1997)					
Drugs for dementia							
Donepezil			x (Mena and de Yebenes 2006)				
Rivastigmine			x (Mena and de Yebenes 2006)				

(continued)

Table 6.2 (continued)

Drug	Acute dystonia	Akathisia	Drug-induced parkinsonism	Tardive dyskinesias	Tremors	Myoclonus	Other choreas	Tic
Pyridostigmine			x (Nguyen et al. 2004)					
Bethanechol			x (Montastruc et al. 1994)					
Opiates								
Meperidine		x (Jimenez-Jimenez et al. 1997)	x (Nguyen et al. 2004)			x (van Harten et al. 1999; Gareri et al. 2006)		
Morphine						xx (Montastruc and Durrieu 2004)		
Oxycodone						x (Lang 1992)		
Methadone				x (Clark and Elliott 2001)		x (Lang 1992)	x (Jimenez-Jimenez et al. 1997)	
Fentanyl				x (Blayac et al. 2004)	x (Petzinger et al. 1995)			
Tramadol						x (Montastruc and Durrieu 2004)		

Other drugs						
Lithium	xx (Bakheit 1997)	xx (Mena and de Yebenes 2006; Nguyen et al. 2004; Jimenez-Jimenez et al. 1996)	x (Orti-Pareja et al. 1999; Blayac et al. 2004; Jimenez-Jimenez et al. 1996)	xx (Morgan and Sethi 2005)	x (Montastruc and Durrieu 2004)	x (Jimenez-Jimenez et al. 1997)
Tetrabenazine	x (Sachdev 1995)	xx (Mena and de Yebenes 2006)	x (Jimenez-Jimenez et al. 1997; Blayac et al. 2004)			
Trihexyphenidyl			x (Blayac et al. 2004)			x (Rodnitzky 2002)

x uncommon/single report, *xx* common (frequency >10 %)

Table 6.3 Movement disorders induced by nonpsychotropic drugs

Drug	Acute dystonia	Akathisia	Drug-induced parkinsonism	Tardive dyskinesias	Tremors	Myoclonus	Other choreas
Antibiotics							
Amphotericin B			(Mott et al. 1995)		x (Morgan and Sethi 2005)		
Penicillin						xx (Montastruc and Durrieu 2004)	
Cephalosporins						xx (Montastruc and Durrieu 2004)	
Chloroquine	x (van Harten et al. 1999)						
Acyclovir					x (Morgan and Sethi 2005)		x (Jimenez-Jimenez et al. 1997)
Vidarabine					xx (Morgan and Sethi 2005)		
Co-trimoxazole					x (Morgan and Sethi 2005)		
Foscarnet	x (Dubow et al. 2008)						
Asthma/allergies							
Chlorpheniramine		x (Montastruc et al. 1994)	xx (Nguyen et al. 2004)	x (Lang 1992)	x (Jimenez-Jimenez et al. 1997)		
Theophylline					x (Jimenez-Jimenez et al. 1997)		

B2-adrenergic agonists	xx (Rodnitzky 2002)			xx (Morgan and Sethi 2005)		
Antineoplastics						
Cytosine arabinoside		x (Nguyen et al. 2004)		x (Morgan and Sethi 2005)		
Vincristine		x (Nguyen et al. 2004)		x (Morgan and Sethi 2005)		
Methotrexate		x (Nguyen et al. 2004)				
5-Fluorouracil		x (Nguyen et al. 2004)				
Doxorubicin		x (Bower and Muenter 1995)				
Thalidomide				x (Morgan and Sethi 2005)		
Ifosfamide				x (Morgan and Sethi 2005)		
Interferon alfa				xx (Morgan and Sethi 2005)		x (Jimenez-Jimenez et al. 1997)
Cardiovascular disorders						
Amiodarone		xx (Mena and de Yebenes 2006; Nguyen et al. 2004)	x (Werner and Olanow 1989)	xx (Morgan and Sethi 2005; Montastruc and Durrieu 2004)	x (Werner and Olanow 1989)	
Procainamide				xx (Morgan and Sethi 2005)		

(continued)

Table 6.3 (continued)

Drug	Acute dystonia	Akathisia	Drug-induced parkinsonism	Tardive dyskinesias	Tremors	Myoclonus	Other choreas
Pindolol					x (Morgan and Sethi 2005)		
Diltiazem/verapamil		x (Dick and Barold 1989)	x (Mena and de Yebenes 2006; Nguyen et al. 2004; Jimenez-Jimenez et al. 1996; Dick and Barold 1989)				
Drugs for vertigo							
Prochlorperazine/ thiethylperazine			xx (Mena and de Yebenes 2006)				
Cinnarizine/ flunarizine	x (van Harten et al. 1999)	x (Orti-Pareja et al. 1999; Jimenez-Jimenez et al. 1996)	xx (Nguyen et al. 2004)	x (Orti-Pareja et al. 1999; Jimenez-Jimenez et al. 1996)			
Endocrine disorders							
Levothyroxine		xx (Rodnitzky 2002)			xx (Morgan and Sethi 2005; Jimenez-Jimenez et al. 1997)		
Calcitonin					x (Morgan and Sethi 2005)		

Contraceptives			x (Jimenez-Jimenez et al. 1997)	x (Shale and Tanner 1996)			x (Rodnitzky 2002)
Corticosteroids		xx (Rodnitzky 2002)					
Veralipride (menopause)	x (Nguyen et al. 2004)		x (De Leo et al. 2006)	x (De Leo et al. 2006)	x (De Leo et al. 2006)		x (De Leo et al. 2006)
Hypoglycemics			x (Ross 1990)		x (Jimenez-Jimenez et al. 1997)		
Anabolic steroids				x (Shale and Tanner 1996)			x (Jimenez-Jimenez et al. 1997)
Reflux/gastric ulcers							
Cimetidine			x (Lang 1992)		x (Morgan and Sethi 2005)		x (Rodnitzky 2002)
Ranitidine			x (Lang 1992)				x (Rodnitzky 2002)
Misoprostol					x (Morgan and Sethi 2005)		
Lansoprazole			x (Angles et al. 2002)				
Bismuth						xx (Rodnitzky 2002)	

(continued)

Table 6.3 (continued)

Drug	Acute dystonia	Akathisia	Drug-induced parkinsonism	Tardive dyskinesias	Tremors	Myoclonus	Other choreas
Other drugs							
Cyclosporine/ tacrolimus			x (Nguyen et al. 2004)		xx (Morgan and Sethi 2005; Montastruc and Durrieu 2004)		
Naproxen sodium			x (Montastruc et al. 1994)				

x uncommon/single report, *xx* common (frequency >10 %)

reactions is dopamine receptor blockage at the level of the striatum. DIMDs are less frequently associated with the atypical antipsychotics, but dose-related movement disorders occur with olanzapine, risperidone, and quetiapine at higher doses as well (Gareri et al. 2006). Nonetheless, a recent intention-to-treat, secondary analysis of data from an earlier randomized controlled trial failed to find the expected reductions of DIMD frequency for participants randomized to second-generation drugs (Peluso et al. 2012).

Mechanisms underlying DIMDs are complex and not fully understood. They are probably related to alterations within subcortical brain regions (e.g., basal ganglia and thalamus) and do not involve the corticospinal pyramidal motor system.

Incidence of *acute dystonia* in treated patients varies from 2 to 64 % according to different series, and pathogenesis remains unclear. All antipsychotics bind to D2 receptors; it has therefore been suggested that blockage of these receptors in the caudate, putamen, and globus pallidus is partly responsible for causing acute dystonia (Rupniak et al. 1986).

DIP is observed on average in about 4 % of patients taking neuroleptics (Noyes et al. 2006; Rochon et al. 2005). DIP is caused by several mechanisms interfering with the normal nigrostriatal dopamine neuron function. Generally, compounds responsible for DIP block striatal dopamine D2 receptors, requiring blockade to exceed 75 % in order to trigger DIP (Remington et al. 2006). Several recent reports suggest certain neuroleptics produce DIP not only related to excessive blockade of dopamine receptors but also mediated through direct and persistent toxic effects on nigrostriatal dopamine neurons (Ulrich et al. 2005).

Akathisia affects about 28 % of patients on antipsychotics (Peluso et al. 2012). The underlying pathophysiologic mechanism of *akathisia* is thought to be an imbalance between cortical and nigrostriatal dopaminergic innervation, favoring increased functional activity of the mesolimbic and nigrostriatal systems, in particular the nucleus accumbens (Bakheit 1997).

The annual incidence of *TD* is about 5 % overall, including transient (3 %) and persistent (2 %) TD (Tarsy and Baldessarini 2006). Risk of TD has proven to be lower with atypical antipsychotics compared to classic ones. A recent review of clinical trials on several modern antipsychotics vs. haloperidol in schizophrenia showed that risperidone, olanzapine, quetiapine, amisulpride, or ziprasidone induced TD in 2.1 % of cases, which is lower than the aforementioned annual TD rate for classic antipsychotics. Indeed, among patients under 50, risk of new-onset TD with haloperidol (5.4 %) was 6.8 times greater than atypical antipsychotics (Correll et al. 2004). Conversely, TD incidence with modern drugs among patients over 50 was similar to rates in younger individuals exposed to haloperidol, suggesting an important agent-age interaction (Correll et al. 2004). The incidence of TD varied remarkably little among modern agents except for increased risk with higher doses of risperidone.

The pathophysiologic basis of TD remains speculative, but various neurochemical hypotheses have been proposed, including striatal dopaminergic hypersensitivity, basal ganglia cholinergic deficiency, dysfunctions of striatonigral γ-aminobutyric acid (GABA)-mediated neurons, glutamate-induced excitotoxicity, and oxidative

stress (Casey 2004; Galili et al. 2000; Silvestri et al. 2000). It has been proposed that antipsychotics result in increased dopamine turnover, followed by excess free radical production and subsequent damage to striatal GABAergic fibers, with reduced inhibitory activity on motor circuits (Casey 2004; Galili et al. 2000; Silvestri et al. 2000). Concurrently, chronic blockade of dopamine receptors results in excessive glutamate activity and resultant excitotoxicity. Likewise, chronic dopamine receptor blockade results in receptor supersensitivity and persistent changes within basal ganglia motor circuit.

Antidepressants

Traditional, tricyclic antidepressants, such as amitriptyline and imipramine, rarely produce movement disorders except for high-frequency, postural tremors that have been linked to their serotonergic properties (Morgan and Sethi 2005). Conversely, serotonin reuptake inhibitors produce a variety of hypokinetic and hyperkinetic movement disorders, including tremor, dystonia, bruxism, myoclonus, and other hyperkinesias with higher frequency (Jimenez-Jimenez and Molina 2000). Recent reports showed that akathisia is the most frequent serotonin reuptake inhibitor-related movement disorder, followed by dystonia, parkinsonism, and dyskinesia (Jimenez-Jimenez and Molina 2000). Interestingly, some serotonin receptor agonists used in PD, such as sarizotan, can worsen parkinsonism (Olanow et al. 2004).

The most plausible hypotheses for the induction of movement disorders by serotonin reuptake inhibitors are related to the interaction between the serotonergic and dopaminergic systems (Davies and Tongroach 1978; Dray et al. 1978; Di Mascio et al. 1998). Serotonin reuptake inhibitors would induce a 5HT2 receptor-mediated inhibition of nigral dopaminergic release in the striatum, thus causing the movement disorders.

Other Drugs

DIMDs can be associated with many other medications, including antiemetics which may block central dopamine receptors (droperidol, metoclopramide, or prochlorperazine), lithium, or calcium-channel blockers (cinnarizine, flunarizine), among others. Many of these drugs are widely prescribed and can be leading causes of DIMD. Metoclopramide, for example, has emerged as the most common cause of tardive dyskinesia in some movement disorder clinics (Kenney et al. 2008; Pasricha et al. 2006). H1 antihistaminergics are a frequent cause of DIP (Bondon-Guitton et al. 2011). This effect is explained by their chemical formula, as these drugs are phenothiazine derivatives and are thus D2-receptor blockers.

Tremor commonly occurs with lithium treatment and occasionally chorea (Montastruc and Durrieu 2004; Jimenez-Jimenez et al. 1997). The antiepileptic

drug valproate is commonly associated with tremor (Nouzeilles et al. 1999). Pregabalin has been shown to cause parkinsonism (Perez-Lloret et al. 2009). Interference with substance P neurotransmission in the basal ganglia is the proposed mechanism. For many years, chorea has been recognized as a complication of estrogen- and progesterone-containing products (Vela et al. 2004).

Parkinsonism induced by cinnarizine or flunarizine is still a serious medical problem in some countries due to the wide use of these products in the elderly, of whom up to one-third may suffer from an irreversible deficit (Garcia-Ruiz et al. 1992). The pathophysiologic mechanisms underlying calcium-channel blocker-induced movement disorders remain uncertain but are most likely due to D2-receptor block resulting from piperazine core (Chouza et al. 1986). Another drug with the same structure, trimetazidine, frequently causes parkinsonism (Masmoudi et al. 2012).

Management

The first therapeutic measure is to withdraw the offending drug when possible. This sole measure will probably suffice for most patients. Nonetheless, in some instances, extra measures will need to be taken. A summary of such measures is offered in Table 6.4.

In most instances, *acute dystonia* presents spontaneous resolution shortly after drug withdrawal. Nonetheless, if treatment is needed, such as in the case of stridor, antihistamines and/or benzodiazepines can be of help (van Harten et al. 1999; Povlsen and Pakkenberg 1990). Intramuscular or intravenous administration of muscarinic receptor blockers (biperiden 5 mg or procyclidine 5 mg) or antihistamines (promethazine 50 mg) is usually effective within 20 min. Occasionally, second or third injections are necessary. After resolution, treatment with anticholinergics should be continued for at least 24–48 h to prevent recurrence.

Anticholinergics have been commonly prescribed as a preventive treatment of *DIP* in patients treated with antipsychotics without strong evidence to support this use. Preliminary unconfirmed evidence supporting the use of vitamin E as a neuroprotective has been published (Mena and de Yebenes 2006). Once DIP is diagnosed, the best possible treatment is discontinuation of the causative drug (Mena and de Yebenes 2006). In the majority of cases, however, it subsides gradually over a period

Table 6.4 Therapeutic intervention for some drug-induced movement disorders

Movement disorder	Recommended measure/s
Acute dystonia	Biperiden 5 mg, procyclidine 5 mg, or promethazine 50 mg i.v.
Acute akathisia	Propranolol, alprazolam, mianserin (akathisia related to lithium)
Parkinsonism	Levodopa, dopamine agonists (poor response)
Tardive syndromes	Prevention: use the lowest possible dose of antipsychotics. Reserpine, methyldopa (reserved for debilitating or life-threatening syndrome). Tetrabenazine

of weeks or months, but in some cases it may persist as long as a year or more (Mena and de Yebenes 2006). Patients show global improvement soon after drug withdrawal, and cognitive and mood disturbances subside more slowly, while tremor may persist 18 months after drug discontinuation in a significant number of patients. In those patients in whom parkinsonism becomes persistent and irreversible after drug withdrawal, diagnosis of latent idiopathic parkinsonism should be considered. Hyposmia and dopaminergic loss as observed by neuroimaging techniques are indicative of such subclinical disease (Kim et al. 2013b).

Propranolol, alprazolam, or antiserotonergic drugs have been reported to be effective in the treatment of *akathisia* (Bakheit 1997; Amsterdam et al. 1994). Lithium-induced akathisia was claimed to be particularly responsive to mianserin, a noradrenaline and serotonin reuptake inhibitor. Although low serum iron is commonly associated with neuroleptic-induced tardive akathisia, the value of iron supplements is doubtful and may even be harmful.

The best treatment for *TD* is prevention. To accomplish this, the lowest effective dose of antipsychotics should be identified for each patient and regularly rechecked. After TD develops, drug withdrawal is followed by improvement from 0 to 92 % of patients, depending on the study (Casey 1990). This wide range is due to multiple factors including patient variables (e.g., age), treatment variables (drug dose and cumulative exposure), and temporal aspects (early diagnosis, duration of treatment, and duration of TD follow-up). Age is consistently correlated with TD improvement, with younger patients more likely to improve. It may take up to 5 years for complete remission to occur. Shorter neuroleptic exposure and age under 60 after onset of TD are correlated with greater likelihood of remission. Dyskinesias, however, may reappear when antipsychotics are reinstituted. In a significant number of patients, they may become irreversible despite antipsychotics cessation.

Treating TD is a clinical challenge. Unfortunately, no drugs are uniformly safe and effective over extended treatment periods. Reducing dopaminergic function is the most effective way of suppressing (masking) TD (Jeste and Wyatt 1982). This strategy is justified only in those rare cases when TD is severe, debilitating, or life-threatening. Functional reduction of dopamine can be achieved with presynaptical depletion (reserpine) or by false transmission (methyldopa). Tetrabenazine has been successfully used for tardive dyskinesia, tardive tremor, and tardive tourettism treatment (Jankovic 2009). Botulinum toxin can be used to treat tardive dystonia (Jankovic 2009). Muscarinic receptor blockers should not be used as they may lower the threshold for the appearance of tardive syndrome (Klawans and Rubovits 1974).

Conclusion

Movement disorders are common adverse drug reactions. They should be envisioned when treatment with possible offending drugs is initiated. Off-label use of movement disorder-inducing drugs or use beyond recommended doses should be

discouraged. If a patient must receive a movement disorder-inducing drug, minimal doses should be prescribed and careful follow-up is recommended.

In this chapter, we provided an extensive albeit not exhausting list of potential offending agents. Nonetheless, clinicians should remain alert, as DIMD may be encountered either with innovative, insufficiently studied drugs or with well-known drugs but used in new or wider populations or under new therapeutic regimens. Future research should also focus on identifying new treatments for DIMD, which at present are sorely lacking.

References

Akagi H, Kumar TM. Lesson of the week: akathisia: overlooked at a cost. BMJ. 2002;324: 1506–7.

Amsterdam JD, Hornig-Rohan M, Maislin G. Efficacy of alprazolam in reducing fluoxetine-induced jitteriness in patients with major depression. J Clin Psychiatry. 1994;55:394–400.

Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J. Cost of disorders of the brain in Europe. Eur J Neurol. 2005;12 Suppl 1:1–27.

Angles A, Bagheri H, Saivin S, Montastruc JL. Interaction between lansoprazole and bromocriptine in a patient with Parkinson's disease. Therapie. 2002;57:408–10.

Asconape J, Diedrich A, DellaBadia J. Myoclonus associated with the use of gabapentin. Epilepsia. 2000;41:479–81.

Bakheit A. The syndrome of motor restlessness–a treatable but under-recognised disorder. Postgrad Med J. 1997;73:529–30.

Barbosa MT, Caramelli P, Maia DP, et al. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambui study). Mov Disord. 2006;21:800–8.

Barbosa MT, Caramelli P, Cunningham MC, et al. Prevalence and clinical classification of tremor in elderly-A community-based survey in Brazil. Mov Disord. 2013;28(5):640–6.

Benito-Leon J, Bermejo-Pareja F, Morales-Gonzalez JM, et al. Incidence of Parkinson disease and parkinsonism in three elderly populations of central Spain. Neurology. 2004;62:734–41.

Blayac JP, Pinzani V, Peyriere H, Hillaire-Buys D. Drug-induced movement disorders: tardive syndromes. Therapie. 2004;59:113–9.

Bondon-Guitton E, Perez-Lloret S, Bagheri H, et al. Drug-induced parkinsonism: a review of 17 years' experience in a regional pharmacovigilance center in France. Mov Disord. 2011;26: 2226–31.

Bonuccelli U, Nocchiero A, Napolitano A, et al. Domperidone-induced acute dystonia and polycystic ovary syndrome. Mov Disord. 1991;6:79–81.

Bovi T, Antonini A, Ottaviani S, et al. The status of olfactory function and the striatal dopaminergic system in drug-induced parkinsonism. J Neurol. 2010;257:1882–9.

Bower JH, Muenter MD. Temporary worsening of parkinsonism in a patient with Parkinson's disease after treatment with paclitaxel for a metastatic grade IV adenocarcinoma. Mov Disord. 1995;10:681–2.

Brooks DE. Propofol-induced movement disorders. Ann Emerg Med. 2008;51:111–2.

Burke RE, Fahn S, Jankovic J, et al. Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. Neurology. 1982;32:1335–46.

Caligiuri MR, Jeste DV, Lacro JP. Antipsychotic-induced movement disorders in the elderly: epidemiology and treatment recommendations. Drugs Aging. 2000;17:363–84.

Casey DE. Spontaneous and tardive dyskinesias: clinical and laboratory studies. J Clin Psychiatry. 1985;46:42–7.

Casey DE. Tardive dyskinesia. West J Med. 1990;153:535–41.

Casey DE. Neuroleptic-induced acute dystonia. In: Lang AE, Weiner WJ, editors. Drug-induced movement disorders. 1st ed. Mount Kisco: Futura; 1992. p. 21–40.
Casey DE. Pathophysiology of antipsychotic drug-induced movement disorders. J Clin Psychiatry. 2004;65 Suppl 9:25–8.
Chouza C, Scaramelli A, Caamano JL, et al. Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. Lancet. 1986;1:1303–4.
Chung WS, Chiu HP. Drug-induced akathisia revisited. Br J Clin Pract. 1996;50:270–8.
Clark JD, Elliott J. A case of a methadone-induced movement disorder. Clin J Pain. 2001;17:375–7.
Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry. 2004; 161:414–25.
Das SK, Banerjee TK, Biswas A, et al. Community survey of primary dystonia in the city of Kolkata, India. Mov Disord. 2007;22:2031–6.
Davies J, Tongroach P. Neuropharmacological studies on the nigro-striatal and raphe-striatal system in the rat. Eur J Pharmacol. 1978;51:91–100.
De Leo V, Morgante G, Musacchio MC, et al. The safety of veralipride. Expert Opin Drug Saf. 2006;5:695–701.
de Rijk MC, Tzourio C, Breteler MM, et al. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry. 1997;62:10–5.
Di Mascio M, Di Giovanni G, Di Matteo V, et al. Selective serotonin reuptake inhibitors reduce the spontaneous activity of dopaminergic neurons in the ventral tegmental area. Brain Res Bull. 1998;46:547–54.
Dick RS, Barold SS. Diltiazem-induced parkinsonism. Am J Med. 1989;87:95–6.
Dray A, Davies J, Oakley NR, et al. The dorsal and medial raphe projections to the substantia nigra in the rat: electrophysiological, biochemical and behavioural observations. Brain Res. 1978;151:431–42.
Dubow JS, Panush SR, Rezak M, Leikin J. Acute dystonic reaction associated with foscarnet administration. Am J Ther. 2008;15:184–6.
Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356:1255–9.
Esper CD, Factor SA. Failure of recognition of drug-induced parkinsonism in the elderly. Mov Disord. 2008;23:401–4.
Galili R, Mosberg, Gil-Ad I, et al. Haloperidol-induced neurotoxicity – possible implications for tardive dyskinesia. J Neural Transm. 2000;107:479–90.
Garcia-Ruiz PJ, de Garcia YJ, Jimenez-Jimenez FJ, et al. Parkinsonism associated with calcium channel blockers: a prospective follow-up study. Clin Neuropharmacol. 1992;15:19–26.
Gareri P, De Fazio P, De Fazio S, et al. Adverse effects of atypical antipsychotics in the elderly: a review. Drugs Aging. 2006;23:937–56.
Gershanik OS. Drug-induced parkinsonism in the aged. Recognition and prevention. Drugs Aging. 1994;5:127–32.
Haddad PM, Dursun SM. Neurological complications of psychiatric drugs: clinical features and management. Hum Psychopharmacol. 2008;23 Suppl 1:15–26.
Jankovic J. Tardive syndromes and other drug-induced movement disorders. Clin Neuropharmacol. 1995;18:197–214.
Jankovic J. Treatment of hyperkinetic movement disorders. Lancet Neurol. 2009;8:844–56.
Jeste DV, Wyatt RJ. Therapeutic strategies against tardive dyskinesia. Two decades of experience. Arch Gen Psychiatry. 1982;39:803–16.
Jimenez-Jimenez FJ, Molina JA. Extrapyramidal symptoms associated with Selective Serotonin Reuptake Inhibitors. CNS Drugs. 2000;14:367–79.
Jimenez-Jimenez FJ, Orti-Pareja M, Yuso-Peralta L, et al. Drug-induced parkinsonism in a movement disorders unit: a four-year survey. Parkinsonism Relat Disord. 1996;2:145–9.

Jimenez-Jimenez FJ, Garcia-Ruiz PJ, Molina JA. Drug-induced movement disorders. Drug Saf. 1997;16:180–204.
Kenney C, Hunter C, Davidson A, Jankovic J. Metoclopramide, an increasingly recognized cause of tardive dyskinesia. J Clin Pharmacol. 2008;48:379–84.
Khiat A, Kuznetsov Y, Blanchet PJ, Boulanger Y. Diffusion-weighted imaging and magnetization transfer imaging of tardive and edentulous orodyskinesia. Mov Disord. 2008;23:1281–5.
Kim JH, Byun HJ. Non-motor cognitive-perceptual dysfunction associated with drug-induced parkinsonism. Hum Psychopharmacol. 2009;24:129–33.
Kim YD, Kim JS, Chung SW, et al. Cognitive dysfunction in drug induced parkinsonism (DIP). Arch Gerontol Geriatr. 2011;53:e222–6.
Kim JS, Youn J, Shin H, Cho JW. Nonmotor symptoms in drug-induced parkinsonism and drug-naive Parkinson disease. Can J Neurol Sci. 2013a;40:36–41.
Kim JS, Oh YS, Kim YI, et al. Combined use of (1)(2)(3)I-metaiodobenzylguanidine (MIBG) scintigraphy and dopamine transporter (DAT) positron emission tomography (PET) predicts prognosis in drug-induced Parkinsonism (DIP): a 2-year follow-up study. Arch Gerontol Geriatr. 2013b;56:124–8.
Kinon BJ, Gilmore JA, Liu H, Halbreich UM. Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. Psychoneuroendocrinology. 2003;28 Suppl 2:55–68.
Klawans HL, Rubovits R. Effect of cholinergic and anticholinergic agents on tardive dyskinesia. J Neurol Neurosurg Psychiatry. 1974;37:941–7.
Lang AE. Miscellaneous drug-induced, movement disorders. In: Lang AE, Weiner WJ, editors. Drug-induced movement disorders. 1st ed. New York: Futura Publishing; 1992. p. 339–81.
Lang AE, Lozano AM. Parkinson's disease. First of two parts. N Engl J Med. 1998;339:1044–53.
Lee PH, Yeo SH, Yong SW, Kim YJ. Odour identification test and its relation to cardiac 123I-metaiodobenzylguanidine in patients with drug induced parkinsonism. J Neurol Neurosurg Psychiatry. 2007;78:1250–2.
LeWitt PA, Walters A, Hening W, McHale D. Persistent movement disorders induced by buspirone. Mov Disord. 1993;8:331–4.
Lopez-Sendon J, Mena MA, de Yebenes JG. Drug-induced parkinsonism. Expert Opin Drug Saf. 2013;12(4):487–96.
Masmoudi K, Gras-Champel V, Masson H, Andrejak M. Parkinsonism and/or cognitive impairment with valproic acid therapy: a report of ten cases. Pharmacopsychiatry. 2006; 39:9–12.
Masmoudi K, Masson H, Gras V, Andrejak M. Extrapyramidal adverse drug reactions associated with trimetazidine: a series of 21 cases. Fundam Clin Pharmacol. 2012;26:198–203.
Mena MA, de Yebenes JG. Drug-induced parkinsonism. Expert Opin Drug Saf. 2006;5:759–71.
Merello M, Starkstein S, Petracca G, et al. Drug-induced parkinsonism in schizophrenic patients: motor response and psychiatric changes after acute challenge with L-Dopa and apomorphine. Clin Neuropharmacol. 1996;19:439–43.
Merello M, Nouzeilles MI, Arce GP, Leiguarda R. Accuracy of acute levodopa challenge for clinical prediction of sustained long-term levodopa response as a major criterion for idiopathic Parkinson's disease diagnosis. Mov Disord. 2002;17:795–8.
Montagna P, Gabellini AS, Monari L, Lugaresi E. Parkinsonian syndrome after long-term treatment with clebopride. Mov Disord. 1992;7:89–90.
Montastruc JL, Durrieu G. Drug-induced tremor and acute movement disorders. Therapie. 2004;59:97–103.
Montastruc JL, Llau ME, Rascol O, Senard JM. Drug-induced parkinsonism: a review. Fundam Clin Pharmacol. 1994;8:293–306.
Montastruc JL, Sommet A, Lacroix I, et al. Pharmacovigilance for evaluating adverse drug reactions: value, organization, and methods. Joint Bone Spine. 2006;73:629–32.
Morgan JC, Sethi KD. Drug-induced tremors. Lancet Neurol. 2005;4:866–76.

Mott SH, Packer RJ, Vezina LG, et al. Encephalopathy with parkinsonian features in children following bone marrow transplantations and high-dose amphotericin B. Ann Neurol. 1995;37:810–4.
Nguyen N, Pradel V, Micallef J, et al. Drug-induced parkinson syndromes. Therapie. 2004; 59:105–12.
Nouzeilles M, Garcia M, Rabinowicz A, Merello M. Prospective evaluation of parkinsonism and tremor in patients treated with valproate. Parkinsonism Relat Disord. 1999;5:67–8.
Noyes K, Liu H, Holloway RG. What is the risk of developing parkinsonism following neuroleptic use? Neurology. 2006;66:941–3.
Olanow CW, Damier P, Goetz CG, et al. Multicenter, open-label, trial of sarizotan in Parkinson disease patients with levodopa-induced dyskinesias (the SPLENDID Study). Clin Neuropharmacol. 2004;27:58–62.
Orti-Pareja M, Jimenez-Jimenez FJ, Vazquez A, et al. Drug-induced tardive syndromes. Parkinsonism Relat Disord. 1999;5:59–65.
Oterino A, Pascual J. Sumatriptan-induced axial dystonia in a patient with cluster headache. Cephalalgia. 1998;18:360–1.
Pasricha PJ, Pehlivanov N, Sugumar A, Jankovic J. Drug insight: from disturbed motility to disordered movement–a review of the clinical benefits and medicolegal risks of metoclopramide. Nat Clin Pract Gastroenterol Hepatol. 2006;3:138–48.
Paulson GW. Historical comments on tardive dyskinesia: a neurologist's perspective. J Clin Psychiatry. 2005;66:260–4.
Peluso MJ, Lewis SW, Barnes TR, Jones PB. Extrapyramidal motor side-effects of first- and second-generation antipsychotic drugs. Br J Psychiatry. 2012;200:387–92.
Perez F, Helmer C, Dartigues JF, et al. A 15-year population-based cohort study of the incidence of Parkinson's disease and dementia with Lewy bodies in an elderly French cohort. J Neurol Neurosurg Psychiatry. 2010;81:742–6.
Perez-Lloret S, Amaya M, Merello M. Pregabalin-induced parkinsonism: a case report. Clin Neuropharmacol. 2009;32(6):353–4.
Petzinger G, Mayer SA, Przedborski S. Fentanyl-induced dyskinesias. Mov Disord. 1995;10:679–80.
Poewe W. The natural history of Parkinson's disease. J Neurol. 2006;253 Suppl 7:VII2–6.
Povlsen UJ, Pakkenberg H. Effect of intravenous injection of biperiden and clonazepam in dystonia. Mov Disord. 1990;5:27–31.
Pringsheim T, Wiltshire K, Day L, et al. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. Mov Disord. 2012;27:1083–91.
Reeves AL, So EL, Sharbrough FW, Krahn LE. Movement disorders associated with the use of gabapentin. Epilepsia. 1996;37:988–90.
Rehan HS, Chopra D, Kakkar AK. Physician's guide to pharmacovigilance: terminology and causality assessment. Eur J Intern Med. 2009;20:3–8.
Remington G, Mamo D, Labelle A, et al. A PET study evaluating dopamine D2 receptor occupancy for long-acting injectable risperidone. Am J Psychiatry. 2006;163:396–401.
Rochon PA, Stukel TA, Sykora K, et al. Atypical antipsychotics and parkinsonism. Arch Intern Med. 2005;165:1882–8.
Rodnitzky RL. Drug-induced movement disorders. Clin Neuropharmacol. 2002;25:142–52.
Ross RT. Drug-induced parkinsonism and other movement disorders. Can J Neurol Sci. 1990;17:155–62.
Rupniak NM, Jenner P, Marsden CD. Acute dystonia induced by neuroleptic drugs. Psychopharmacology (Berl). 1986;88:403–19.
Sachdev P. The epidemiology of drug-induced akathisia: part I. Acute akathisia. Schizophr Bull. 1995;21:431–49.
Seijo-Martinez M, del Castro RM, Rodriguez AJ, et al. Prevalence of parkinsonism and Parkinson's disease in the Arosa Island (Spain): a community-based door-to-door survey. J Neurol Sci. 2011;304:49–54.

Shale H, Tanner C. Pharmacological options for the management of dyskinesias. Drugs. 1996;52:849–60.
Silvestri S, Seeman MV, Negrete JC, et al. Increased dopamine D2 receptor binding after long-term treatment with antipsychotics in humans: a clinical PET study. Psychopharmacology (Berl). 2000;152:174–80.
Steeves TD, Day L, Dykeman J, et al. The prevalence of primary dystonia: a systematic review and meta-analysis. Mov Disord. 2012;27:1789–96.
Tarsy D. History and definition of tardive dyskinesia. Clin Neuropharmacol. 1983;6:91–9.
Tarsy D, Baldessarini RJ. Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? Mov Disord. 2006;21:589–98.
Tinazzi M, Cipriani A, Matinella A, et al. [(1)(2)(3)I]FP-CIT single photon emission computed tomography findings in drug-induced Parkinsonism. Schizophr Res. 2012;139:40–5.
Tolosa E, Coelho M, Gallardo M. DAT imaging in drug-induced and psychogenic parkinsonism. Mov Disord. 2003;18 Suppl 7:S28–33.
Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. Mov Disord. 2003;18:19–31.
Ulrich S, Sandmann U, Genz A. Serum concentrations of haloperidol pyridinium metabolites and the relationship with tardive dyskinesia and parkinsonism: a cross-section study in psychiatric patients. Pharmacopsychiatry. 2005;38:171–7.
van Harten PN, Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. BMJ. 1999;319:623–6.
Vela L, Sfakianakis GN, Heros D, et al. Chorea and contraceptives: case report with pet study and review of the literature. Mov Disord. 2004;19:349–52.
Weiner WJ, Rabinstein A, Levin B, et al. Cocaine-induced persistent dyskinesias. Neurology. 2001;56:964–5.
Wenning GK, Kiechl S, Seppi K, et al. Prevalence of movement disorders in men and women aged 50–89 years (Bruneck Study cohort): a population-based study. Lancet Neurol. 2005;4:815–20.
Werner EG, Olanow CW. Parkinsonism and amiodarone therapy. Ann Neurol. 1989;25:630–2.

Chapter 7
Scales for Measuring Parkinsonism in Demented Patients

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Abstract The term "parkinsonism" refers to a syndrome combining motor symptoms such as bradykinesia, rigidity, tremor, and other clinical signs characteristic of Parkinson's disease. A large range of these disorders can simultaneously express parkinsonism and dementia, although with variable occurrence particularly related to the onset of disease and expression of clinical symptoms. Therefore, motor and cognitive assessment in these conditions are relevant, for both clinical research and practice. Most of the rating scales applied in this situation are measures coming from the realm of the movement disorders, used for evaluation of Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, etc. Also, there are generic scales designed for assessment of motor state that may be useful in the appropriate context. Some of the most frequently used scales are reviewed in this chapter, with particular attention to their description and basic clinimetric properties.

Keywords Rating scales • Assessment • Parkinsonism • Parkinson's disease • Progressive supranuclear palsy • Multiple system atrophy • Dementia • Dementia with Lewy bodies • Dementia associated with Parkinson's disease • Alzheimer's disease

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Abbreviations

AD	Alzheimer's disease
DLB	Dementia with Lewy bodies
ESRS	Extrapyramidal Symptom Rating Scale
FAST	Functional Assessment Staging
ICARS	International Cerebellar Ataxia Rating Scale
MDS-UPDRS	Movement Disorder Society-sponsored version of the UPDRS
MSA	Multiple system atrophy
NNIPPS-PPS	Natural History and Neuroprotection in Parkinson Plus Syndromes – Parkinson Plus Scale
PD	Parkinson's disease
PDD	Dementia associated with Parkinson's disease
PEPS	Pyramidal and Extrapyramidal Scale
PIGD	Postural instability gait difficulty
POS-PP	Palliative Care Outcome Scale-Parkinsonism Plus
PSP	Progressive supranuclear palsy
PSPRS	Progressive Supranuclear Palsy Rating Scale
RSGE-CD	Rating Scale for Gait Evaluation in Cognitive Deterioration
SCOPA	Scales for Outcomes in Parkinson's Disease
UMSARS	Unified Multiple System Atrophy Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale

Dementia and Parkinsonism

Parkinsonism is considered to be an umbrella term which includes a combination of motor signs such as bradykinesia, rigidity, postural instability, and impaired gait, manifestations characterizing Parkinson's disease (PD) but shared by several conditions that express other "red flags" signs simultaneously. In terms of neurodegenerative disorders causing dementia and parkinsonism, the most common are Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and PD. Dementia and parkinsonism may coexist in varying patterns. For instance, appearance of parkinsonian features in patients with AD is usually a late and not an inevitable occurrence, while the development of dementia in patients with a clinical diagnosis of DLB is thought to be an early event. In Parkinson's disease, dementia associated with Parkinson's disease (PDD) reflects another spectrum where signs of executive dysfunction may be present in a very early state, whereas frank PDD is usually a late feature.

In relation to PD, the prevalence of dementia increases with the age and the progression of PD (Dubois et al. 1990; Hughes et al. 2000; Aarsland et al. 2007). As a consequence, dementia will be present in a large number of PD patients usually beyond 20 years disease duration (Hely et al. 2008). Indeed, the cumulative incidence of dementia in PD patients may be as high as 80 % (Aarsland et al. 2003, 2005; Buter et al. 2008). However, cognitive decline is present in approximately one third of the

Table 7.1 Examples of conditions that can associate simultaneously dementia and parkinsonism

Neurodegenerative	Other
Parkinson's disease	Cerebrovascular disease
Dementia with Lewy bodies	Normal-pressure hydrocephalus
Corticobasal degeneration	Creutzfeldt-Jakob disease
Multiple system atrophy	HIV-associated dementia
Progressive supranuclear palsy	Traumatic brain injury
Huntington's disease	Alcoholic dementia
Alzheimer's disease	
Frontotemporal dementia	

PD patients at an early stage of disease (Reid et al. 1989; Foltynie et al. 2004), and it has been suggested that the possible onset of PDD might be predictable by measuring if PD patients suffer from early cognitive impairment (Pedersen et al. 2013). PD patients with postural instability gait difficulty (PIGD) are at higher risk to get dementia and also have a faster rate of cognitive decline (Burn et al. 2006; Alves et al. 2006). Furthermore, a study by McKeith et al. (2006) showed that extrapyramidal motor symptoms are more impaired (McKeith et al. 2006) and are associated to more rapid noncognitive disease progression (Williams et al. 2006) in DLB than in AD.

In addition, it has been reported that in patients with AD and parkinsonism, psychosis appears more frequently than in patients without AD and parkinsonism (Zubenko et al. 1991; Mayeux et al. 1985). By analyzing the parkinsonian signs in AD, it may be possible to predict the risk to develop a psychosis (Caligiuri et al. 2003).

In Table 7.1, we list the common conditions that can be associated with dementia and parkinsonism. This list is not exhaustive as many rare metabolic and genetic conditions can cause dementia with a degree of parkinsonism, but in this chapter we will not be able to cover these conditions.

We have attempted to subdivide these conditions to neurodegenerative and other disorders (see Table 7.1).

Scales to Measure Parkinsonism in Dementia

Scales and questionnaires are commonly used to determine the type of manifestations of the underlying condition, to measure their severity and frequency, and to establish their relationships with demographic, historical, functional, and psychosocial factors. They are needed, for example, to determine the patients' current health state and its course over time, to compare groups of patients, to inform the outcomes of clinical practices and trials, to file and share information, to assign resources, and to make decisions in Health Policy. For multicenter and international collaborations, it is important to harmonize measurements in order to obtain homogeneous results. A survey by Ramirez Diaz et al. (2005), for example, emphasized the need of unified tools and evaluation criteria in order to get robust data collection.

In general, scales can be divided into generic, which means that they are usable in any condition, or specific, meaning that they can just be used for one condition in particular. Furthermore, scales can be classified in several ways: self-completed or rater-completed; single-item, multi-item, or composite; unidimensional or multidimensional; and disease-centered and patient-centered measures. Only a few of the above conditions (Table 7.1) have validated scales including specific assessment of parkinsonism.

In order to review scales for selection of the most appropriate, for a research study or clinical practice, for instance, some aspects have to be considered. The most relevant are shown in the Table 7.2 that includes the most commonly considered and relevant points for description and clinimetric information of a scale. For example, the systematic reviews on scales performed by the Movement Disorder Society Task Force have been based on a similar scheme (www.movementdisorders.org/publications/ebm_reviews/).

Concerning patients with dementia, it has to be considered that they are usually not fully capable to adequately complete self-assessments or respond to interviews. That is the reason why, in the setting of dementia, this kind of evaluations needing the patients' inference cannot be used or have to be completed by a proxy (caregiver, health professional), a situation challenging the reliability and validity of the assessment. However, the rating scales used for evaluation of parkinsonism are rater based and completed by a health professional who performs the motor examination. Patient's collaboration for doing some maneuvers (e.g., tapping fingers or hand, rapid alternative movements, walking a distance, etc.) is necessary, but usually there is a response option (e.g., unable to do, cannot perform the task, unable to test, etc.) adequate for the situation lacking of patient's collaboration. Therefore, data quality is usually satisfactory for this kind of assessment.

A brief review of the scales useful to evaluate parkinsonism in patients with dementia ensues.

Unified Parkinson's Disease Rating Scale (UPDRS)

In 1987 (Fahn and Elton 1987) the Unified Parkinson's Disease Rating Scale (UPDRS) was introduced, which has now become one of the most used scales in Parkinson's disease (Ramaker et al. 2002). This scale takes about 10–20 min to complete and is available from the original publications. It is a public domain scale that evaluates impairment and disability for basic activities of daily life (Movement Disorder Society Task Force 2003). It contains 42 items, which are separated into four domains: (1) mentation, behavior, and mood; (2) activities of daily living; (3) motor items, which are relevant in the context of the present chapter; and (4) complications. In addition, it covers a modified Hoehn and Yahr Staging (1967) and the Schwab and England Scale. Besides the importance for this chapter, section of the "UPDRS" is completed by a health professional and focused on the clinical examination of motor impairment characteristic of parkinsonism, needing not the input of patients themselves. Concerning the psychometric properties in PD,

Table 7.2 Elements for description and evaluation of a scale

1. *Description of the scale*	
Scale name	
Descriptive aspects	Construct to be measured
	Components: number of items and subscales
	Answer options and type of scoring
	Time frame
	Application (interview, observation, by phone, etc.)
	Time to complete the scale
	Rater (patient, proxy, professional, etc.)
	Generic/specific
	For generic scales: is the scale validated in the specific condition in which will be used?
	Copyright? Public domain?
	How to obtain the scale (and manual for users)
2. *Attributes of the scale*	
Feasibility	Appropriateness of questions for the target population?
Acceptability	Floor and ceiling effects?
	Score distribution
Scaling assumptions	Appropriate location of items in the subscales
Dimensionality	Factors (concordant with subscales?)
Reliability	Internal consistency
	Inter-rater reliability
	Test-retest reliability
Validity	Face validity
	Content validity
	Criterion-related validity
	Hypotheses testing (convergent, known-groups, structural, internal validity)
Responsiveness and interpretability	Sensitive to changes in the construct?
	Minimally clinical important difference (or similar) determined?
	Cumulative distribution function?
	Other: correlation with other measures?
Cross-cultural adaptations and others	Translations/adaptations
	Alternative modes of administration
Overall impression	Advantages and disadvantages

internal consistency, inter-rater and test-retest reliability, and construct validity are satisfactory as a whole (Martinez-Martin and Forjaz 2006), and the scale is sensitive to changes. The scale has been translated to several languages and has been widely used in different studies and settings (Movement Disorder Society Task Force 2003). However, some ambiguities in the written text, as well as lack of adequate instructions for the raters and the missing of many non-motor aspects, promoted the revision of the scale to a new version (MDS-UPDRS) free of these shortcomings (Movement Disorders Society Task Force 2003).

Cubo et al. (2000) and Kroonenberg et al. (2006) have reported that the motor examination of the UPDRS can also be used for patients with progressive

supranuclear palsy (PSP). Section III, motor examination, has been used to assess the motor impairment in multiple system atrophy (MSA) (Seppi et al. 2005) showing similar clinimetric properties in MSA than in PD (Tison et al. 2002a) and a high correlation with the International Cerebellar Ataxia Rating Scale (ICARS) in MSA patients (Tison et al. 2002b). UPDRS motor scores have been used to assess extrapyramidal symptoms in AD (Ellis et al. 1996; Caligiuri et al. 2003) and to distinguish between these DLB patients and AD patients (Kaur et al. 2013) and are sensitive to changes due to treatment with cholinesterase inhibitors in PDD (Rolinski et al. 2012).

Modified versions of the UPDRS motor section have been used to characterize AD patients (Wilson et al. 2000; Park et al. 2006) and to predict the risk of developing dementia in older people (Louis et al. 2010).

Movement Disorder Society-Sponsored Version of the UPDRS (MDS-UPDRS)

The Movement Disorder Society-sponsored version of the UPDRS (MDS-UPDRS) is a revised form of the UPDRS specifically addressed to overcome the problems identified in the latter scale (Movement Disorders Society Task Force 2003) to achieve a scale more comprehensive, including a wide range of non-motor symptoms, more understandable through the fewer use of medical jargon, and also more applicable for patients with different levels of disability (Goetz et al. 2007). It also has standardized translation and teaching programs (Goetz et al. 2010, 2012). To fulfill the entire scale takes about 30 min; however, to complete the motor section, the patients only need 10 min. Studied psychometric attributes are adequate (Goetz et al. 2008; Martinez-Martin et al. 2013), although the inter-rater reliability as well as the content validity have not been tested yet. The test-retest reliability has only been addressed in the Spanish validation study (Martinez-Martin et al. 2013). The scale is available in several languages (www.movementdisorders.org/publications/rating_scales) and more translations and local validations will follow in the near future. By comparing the MDS-UPDRS to the UPDRS scale, in particular, the motor domains of these two scales correlated significantly (Goetz et al. 2008; Merello et al. 2011). An association between the MDS-UPDRS motor scores and cognitive impairment has been described in LRRK2- associated PD patients (Ben Sassi et al. 2012) and is a promising tool to assess bradykinesia in parkinsonian syndromes (Pal and Goetz 2013). Müller et al. (2013) have demonstrated that the PIGD motor phenotype as assessed by the MDS-UPDRS motor section is a risk factor for the development of dementia associated to PD. In PSP, MDS-UPDRS scores correlated with degeneration of white matter tracts detected using diffusion tensor imaging (Whitwell et al. 2011). To date, the MDS-UPDRS performance has not been tested in other patients with dementia.

Unified Multiple System Atrophy Rating Scale (UMSARS)

The multidimensional Unified Multiple System Atrophy Rating Scale (UMSARS) (Wenning et al. 2004) is a disease-specific scale, which is useful in order to detect the disease severity and progression as well as several important aspects of MSA (Geser et al. 2006).

The scale, which takes about 30–45 min, has to be completed by a health professional. The UMSARS is divided into 4 different domains: (1) historical review in order to detect disease-related impairments (12 items), (2) motor examination (14 items), (3) autonomic examination, and 4) global disability. The items in the four domains can be rated from 0 (no impairment) to 4 (severe impairment).

The inter-rater reliability for the first and second domain has been shown to be at least substantial, in some cases even excellent (Wenning et al. 2004). Except for ocular motor dysfunction, these results have been confirmed by Krismer et al. (2012). Furthermore, for the first and second domain of the scale, the internal consistency was reported to be high (Wenning et al. 2004). According to the study by Wenning et al. (2013), even relatively unexperienced health professionals can reliably complete the UMSARS as long as they underwent clear training instructions. Regarding the second domain, which captures motor impairment, it is correlated significantly with the motor domain of the UPDRS, which likely results from the fact that it is based on this. The UMSARS is sensitive to changes due to disease progression (Wenning et al. 2013) and to treatment (Novak et al. 2012), and it can be used as an outcome measure in clinical trials.

Progressive Supranuclear Palsy Rating Scale (PSPRS)

The Progressive Supranuclear Palsy Rating Scale (PSPRS) (Golbe and Ohman-Strickland 2007) is a useful and practical tool that can be used as a routine measurement for assessment of PSP patients' disability and disease progression and also may be used as variable for clinical trials and indicator of prognosis. It takes about 10 min to fulfill the 28 items divided into 6 main groups. These groups contain daily activities (by history), behavior, bulbar, ocular motor, limb motor, and gait/midline. Whereas 6 of the total of 28 items are rated on a 3-point scale (0–2), the missing 22 items are rated on a 5-point scale (0–4). A maximum of 100 points can be obtained. The scale has an excellent overall reliability, moderate convergent validity, and predictive validity in relation to subsequent survival (Golbe and Ohman-Strickland 2007).

Pyramidal and Extrapyramidal Scale (PEPS)

The Pyramidal and Extrapyramidal Scale (PEPS) especially detects motor symptoms in patients with dementia or mild cognitive impairment because of the small vessel disease and has been developed and validated by Kim et al. (2011a). The

scale can be particularly used to follow the disease process. The scale consists of 34 items, which are subdivided into five domains: (1) corticospinal (6/60), (2) corticobulbar (9/60) tract symptoms and signs, (3) extrapyramidal symptoms/signs (30/60), (4) gait abnormalities (9/60), and (5) gait severity (6/60). The patient can reach a maximum of 60 points.

The test-retest and the inter-rater reliability coefficients were satisfactory. In addition, the motor signs scores as measured by the UPDRS were significantly correlated with the total and extrapyramidal signs scores from the PEPS (Kim et al. 2011a). Moreover, the motor deficits as assessed by the PEPS correlated with supra- and infratentorial lesions identified by magnetic resonance imaging (Kim et al. 2011b). The scale has not been used beyond the original authors.

Extrapyramidal Symptom Rating Scale (ESRS)

The Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese 2005) addresses particularly drug-induced movement disorders. It is a clinician-rated tool composed by 62 items that are scored in a 7-point scale for frequency and movement amplitude. Six factors have been identified: (1) hypokinetic parkinsonism, (2) orofacial dyskinesia, (3) trunk/limb dyskinesia, (4) akathisia, (5) tremor, and (6) tardive dystonia. Psychometric properties are adequate (Knol et al. 2010) in terms of inter-rater reliability, convergent validity, and sensitivity to change. It is a widely used scale for assessing adverse effects of pharmacologic treatment in behavioral and psychological symptoms in dementia (De Deyn and Wirshing 2001).

Natural History and Neuroprotection in Parkinson Plus Syndromes: Parkinson Plus Scale (NNIPPS-PPS)

This scale has been especially developed to measure disease severity and progression in MSA and PSP in order to predict the survival and as a sensitive instrument for clinical trials (Payan et al. 2011). The scale comprises 83 items, summarized into 15 dimensional sub-scores and a total score with a maximum of 309 points. This scale shows a very appropriate content as well as a good convergent validity. Furthermore, the internal consistency of the total score and the inter-rater reliability have been found excellent (Payan et al. 2011). The scale is able to predict survival and is responsive to changes, although PSP patients show higher progression rates than MSA patients. Nonetheless, the scale has not been tested beyond the original validation study.

Other Scales

Other PD rating scales that have been used to assess extrapyramidal motor signs in dementia patients (Ellis et al. 1996) are the *Webster scale* (Webster 1968) and the *Columbia University Parkinson's Disease Rating Scale* (Yahr et al. 1969). However,

there is a lack of data of these scales' performance and psychometric attributes in dementia patients. Similarly, *Scales for Outcomes in Parkinson's Disease* (*SCOPA*)-*Motor* includes a 10-item "clinical examination" section useful to assess the motor impairment in Parkinson's disease (Marinus et al. 2004; Martinez-Martin et al. 2005).

On the other hand, the *Functional Assessment Staging* (*FAST*) scale (Reisberg 1988), a tool specifically designed to assess functional decline in AD, has been also used to characterize cognitive impairment and dementia in PD patients on the basis of specific deficits in functional capacity (Sabbagh et al. 2009). In MSA and PSP patients, the *Palliative Care Outcome Scale-Parkinsonism Plus* (*POS-PP*) (Higginson et al. 2012), a modified version of the POS-Symptoms (POS-S) (Hearn and Higginson 1999) with items on Parkinson's related symptoms, has been applied in a longitudinal study to identify predictors of change. A *Rating Scale for Gait Evaluation in Cognitive Deterioration* (*RSGE-CD*), that contains parkinsonian components, has been recently validated (Martinez-Martin et al. 2012).

Conclusion

There is a variety of scales assessing the signs that characterize the parkinsonian syndrome. Most of these scales have been designed to evaluate disorders in which the motor aspects are relevant and frequently the most typical aspect of the disease and have not been properly validated in populations experiencing dementia as predominant feature. However, management and clinical assessment of parkinsonism is important for a complete evaluation of a patient with dementia and parkinsonism. As such, development of specific scales which can be reliably and reproducibly applied to demented parkinsonian patients remains a key unmet need. Further large-scale studies are required to develop these tools in an international framework.

References

Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. 2003;60:387–92.

Aarsland D, Zaccai J, Brayne C. A systematic review of prevalence studies of dementia in Parkinson's disease. Mov Disord. 2005;20:1255–63.

Aarsland D, Kvaløy JT, Andersen K, Larsen JP, Tang MX, Lolk A, Kragh-Sørensen P, Marder K. The effect of age of onset of PD on risk of dementia. J Neurol. 2007;254:38–45.

Alves G, Larsen JP, Emre M, Wentzel-Larsen T, Aarsland D. Changes in motor subtype and risk for incident dementia in Parkinson's disease. Mov Disord. 2006;21:1123–30.

Ben Sassi S, Nabli F, Hentati E, Nahdi H, Trabelsi M, Ben Ayed H, et al. Cognitive dysfunction in Tunisian LRRK2 associated Parkinson's disease. Parkinsonism Relat Disord. 2012;18:243–6.

Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, McKeith IG. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2006;77:585–9.

Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D. Dementia and survival in Parkinson disease: a 12-year population study. Neurology. 2008;70:1017–22.

Caligiuri MP, Peavy G, Salmon DP, Galasko DR, Thal LJ. Neuromotor abnormalities and risk for psychosis in Alzheimer's disease. Neurology. 2003;61:954–8.
Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophr Res. 2005;76:247–65.
Cubo E, Stebbins GT, Golbe LI, Nieves AV, Leurgans S, Goetz CG, et al. Application of the unified Parkinson's disease rating scale in progressive supranuclear palsy: factor analysis of the motor scale. Mov Disord. 2000;15:276–9.
De Deyn PP, Wirshing WC. Scales to assess efficacy and safety of pharmacologic agents in the treatment of behavioral and psychological symptoms of dementia. J Clin Psychiatry. 2001;62 Suppl 21:19–22.
Dubois B, Pillon B, Sternic N, Lhermitte F, Agid Y. Age induced cognitive disturbances in Parkinson's disease. Neurology. 1990;40:38–41.
Ellis RJ, Caligiuri M, Galasko D, Thal LJ. Extrapyramidal motor signs in clinically diagnosed Alzheimer disease. Alzheimer Dis Assoc Disord. 1996;10:103–14.
Fahn S, Elton RL. UPDRS program members. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent developments in Parkinson's disease, vol. 2. Florham Park: Macmillan Healthcare Information; 1987. p. 153–64.
Foltynie T, Brayne CEG, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain. 2004;127:550–60.
Geser F, Wenning GK, Seppi K, Stampfer-Kountchev M, Scherfler C, Sawires M, et al. Progression of multiple system atrophy (MSA): a prospective natural history study by the european MSA Study Group (EMSA SG). Mov Disord. 2006;21:179–86.
Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): process, format, and clinimetric testing plan. Mov Disord. 2007;22:41–7.
Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-Sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23:2129–70.
Goetz CG, Stebbins GT, Chmura TA, Fahn S, Poewe W, Tanner CM. Teaching program for the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale: (MDS-UPDRS). Mov Disord. 2010;25:1190–4.
Goetz CG, Stebbins GT, LaPelle N, Huang J, Tilley BC. MDS-UPDRS non-English translation program. Mov Disord. 2012;27 Suppl 1:S96.
Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain. 2007;130:1552–65.
Hearn J, Higginson IJ. Development and validation of a core outcome measure for palliative care: the palliative care outcome scale. Palliative Care Core Audit Project Advisory Group. Qual Health Care. 1999;8:219–27.
Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2008;23:837–44.
Higginson IJ, Gao W, Saleem TZ, Chaudhuri KR, Burman R, McCrone P, et al. Symptoms and quality of life in late stage Parkinson syndromes: a longitudinal community study of predictive factors. PLoS One. 2012;7:e46327.
Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967;17:427–42.
Hughes TA, Ross HF, Musa S, Bhattacherjee S, Nathan RN, Mindham RHS, et al. A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. Neurology. 2000;54:1596–602.
Kaur B, Harvey DJ, Decarli CS, Zhang L, Sabbagh MN, Olichney JM. Extrapyramidal signs by dementia severity in Alzheimer disease and dementia with Lewy bodies. Alzheimer Dis Assoc Disord. 2013;27(3):226–32. doi:10.1097/WAD.0b013e31826f040d.
Kim SH, Seo SW, Go SM, Chin J, Lee BH, Lee JH, et al. Pyramidal and extrapyramidal scale (PEPS): a new scale for the assessment of motor impairment in vascular cognitive impairment associated with small vessel disease. Nab Clin Neurol Neurosurg. 2011a;113:181–7.

Kim SH, Park JS, Ahn HJ, Seo SW, Lee JM, Kim ST, et al. Voxel-based analysis of diffusion tensor imaging in patients with subcortical vascular cognitive impairment: correlates with cognitive and motor deficits. J Neuroimaging. 2011b;21:317–24.

Knol W, Keijsers CJ, Jansen PA, van Marum RJ. Systematic evaluation of rating scales for drug-induced parkinsonism and recommendations for future research. J Clin Psychopharmacol. 2010;30:57–63.

Krismer F, Seppi K, Tison F, Sampaio C, Zangerl A, Peralta C, et al. The unified multiple system atrophy rating scale: intrarater reliability. Mov Disord. 2012;27:1683–5.

Kroonenberg PM, Oort FJ, Stebbins GT, Leurgans SE, Cubo E, Goetz CG. Motor function in Parkinson's disease and supranuclear palsy: simultaneous factor analysis of a clinical scale in several populations. BMC Med Res Methodol. 2006;6:26.

Louis ED, Tang MX, Schupf N. Mild parkinsonian signs are associated with increased risk of dementia in a prospective, population-based study of elders. Mov Disord. 2010;25:172–8.

Marinus J, Visser M, Stiggelbout AM, Martin Rabey J, Martinez-Martin P, Bonuccelli U, et al. A short scale for the assessment of motor impairments and disabilities in Parkinson's disease: the SPES/SCOPA. J Neurol Neurosurg Psychiatry. 2004;75:388–95.

Martinez-Martin P, Forjaz MJ. Metric attributes of the unified Parkinson's disease rating scale 3.0 battery: part I, feasibility, scaling assumptions, reliability, and precision. Mov Disord. 2006;21:1182–8.

Martinez-Martin P, Benito-Leon J, Burguera JA, Castro A, Linazasoro G, Martinez-Castrillo JC, et al. The SCOPA-motor scale for assessment of Parkinson's disease is a consistent and valid measure. J Clin Epidemiol. 2005;58:674–9.

Martinez-Martin P, Osa Ruiz E, Gómez-Conesa A, Olazarán J, The RSGE-CD Validation Group. A Rating Scale for Gait Evaluation in Cognitive Deterioration (RSGE-CD): validation study. J Alzheimers Dis. 2012;31:543–53.

Martinez-Martin P, Rodriguez-Blazquez C, Alvarez-Sanchez M, Arakaki T, Bergareche-Yarza A, Chade A, et al. Expanded and independent validation of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). J Neurol. 2013;260:228–36.

Mayeux R, Stern Y, Spanton S. Heterogeneity in dementia of the Alzheimer type: evidence of subgroups. Neurology. 1985;35:453–61.

McKeith IG, Rowan E, Askew K, Naidu A, Allan L, Barnett N, et al. More severe functional impairment in dementia with Lewy bodies than Alzheimer disease is related to extrapyramidal motor dysfunction. Am J Geriatr Psychiatry. 2006;14:582–8.

Merello M, Gerschcovich ER, Ballesteros D, Cerquetti D. Correlation between the Movement Disorders Society Unified Parkinson's Disease rating scale (MDS-UPDRS) and the Unified Parkinson's Disease rating scale (UPDRS) during l-dopa acute challenge. Parkinsonism Relat Disord. 2011;17:705–7.

Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov Disord. 2003;18:738–50.

Müller ML, Frey KA, Petrou M, Kotagal V, Koeppe RA, Albin RL, et al. β-amyloid and postural instability and gait difficulty in Parkinson's disease at risk for dementia. Mov Disord. 2013;28:296–301.

Novak P, Williams A, Ravin P, Zurkiya O, Abduljalil A, Novak V. Treatment of multiple system atrophy using intravenous immunoglobulin. BMC Neurol. 2012;12:131.

Pal G, Goetz CG. Assessing bradykinesia in Parkinsonian disorders. Front Neurol. 2013;4:54.

Park M, Comella CL, Leurgans SE, Fan W, Wilson RS, Bennett DA. Association of daytime napping and Parkinsonian signs in Alzheimer's disease. Sleep Med. 2006;7:614–8.

Payan CA, Viallet F, Landwehrmeyer BG, Bonnet AM, Borg M, Durif F, et al. Disease severity and progression in progressive supranuclear palsy and multiple system atrophy: validation of the NNIPPS-Parkinson Plus Scale. PLoS One. 2011;6:e22293.

Pedersen KF, Larsen JP, Tysnes OB, Alves G. Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. JAMA Neurol. 2013;70:580–6.

Ramaker C, Marinus J, Stiggelbout AM, van Hilten BJ. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Mov Disord. 2002;17:867–76.

Ramirez Diaz SP, Gil Gregorio P, Ribera Casado JM, Reynish E, Ousset PJ, Vellas B, et al. The need for a consensus in the use of assessment tools for Alzheimer's disease: the Feasibility Study (assessment tools for dementia in Alzheimer Centres across Europe), a European Alzheimer's Disease Consortium's (EADC) survey. Int J Geriatr Psychiatry. 2005;20:744–8.

Reid WGJ, Broe GA, Hely MA, Morris JG, Williamson PM, O'Sullivan DJ, et al. The neuropsychology of de novo patients with idiopathic Parkinson's disease: the effects of age of onset. Int J Neurosci. 1989;48:205–17.

Reisberg B. Functional assessment staging (FAST). Psychopharmacol Bull. 1988;24(4):653–9.

Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies. Parkinson's disease dementia and cognitive impairment in Parkinson's disease. Cochrane Database Syst Rev. 2012;3, CD006504.

Sabbagh MN, Adler CH, Lahti TJ, Connor DJ, Vedders L, Peterson LK, et al. Parkinson disease with dementia: comparing patients with and without Alzheimer pathology. Alzheimer Dis Assoc Disord. 2009;23:295–7.

Seppi K, Yekhlef F, Diem A, Luginger Wolf E, Mueller J, Tison F, et al. Progression of parkinsonism in multiple system atrophy. J Neurol. 2005;252:91–6.

Tison F, Yekhlef F, Chrysostome V, Balestre E, Quinn NP, Poewe W, et al. Parkinsonism in multiple system atrophy: natural history, severity (UPDRS-III), and disability assessment compared with Parkinson's disease. Mov Disord. 2002a;17:701–9.

Tison F, Yekhlef F, Balestre E, Chrysostome V, Quinn N, Wenning GK, et al. Application of the international cooperative ataxia scale rating in multiple system atrophy. Mov Disord. 2002b;17:1248–54.

Webster DD. Critical analysis of the disability in Parkinson's disease. Mod Treat. 1968;5:257–82.

Wenning GK, Tison F, Seppi K, Sampaio C, Diem A, Yekhlef F, et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord. 2004;19:1391–402.

Wenning GK, Geser F, Krismer F, Seppi K, Duerr S, Boesch S, et al. The natural history of multiple system atrophy: a prospective European cohort study. Lancet Neurol. 2013;12:264–74.

Whitwell JL, Master AV, Avula R, Kantarci K, Eggers SD, Edmonson HA, Jack Jr CR, Josephs KA. Clinical correlates of white matter tract degeneration in progressive supranuclear palsy. Arch Neurol. 2011;68:753–60.

Williams MM, Xiong C, Morris JC, Galvin JE. Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. Neurology. 2006;67:1935–41.

Wilson RS, Bennett DA, Gilley DW, Beckett LA, Schneider JA, Evans DA. Progression of parkinsonian signs in Alzheimer's disease. Neurology. 2000;54:1284–9.

Yahr MD, Duvoisin RC, Schear MJ, Barrett RE, Hoehn MM. Treatment of parkinsonism with levodopa. Arch Neurol. 1969;21:343–54.

Zubenko GS, Moossy J, Martinez AJ, et al. Neuropathologic and neurochemical correlates of psychosis in primary dementia. Arch Neurol. 1991;48:619–24.

Chapter 8
Movement Disorders in Alzheimer's Disease

Sergio E. Starkstein and Marcelo Merello

Abstract Movement disorders are a frequent finding in AD and an important issue for differential diagnosis especially with diffuse Lewy body dementia and Creutzfeldt–Jakob disease. Temporal occurrence through the evolution of the disease and severity are crucial for differential diagnosis. In addition, psychiatric complications of AD either itself or due to the use of neuroleptics represent another source of motor symptoms. In this chapter, we will review mainly those movement disorders resulting from the neurodegenerative process.

Keywords Alzheimer's disease • Parkinsonism • Dystonia • Corticobasal syndrome • Paratonia

Alzheimer's Disease

Alzheimer's disease (AD) is the most common type of dementia, affecting more than five million people in the USA (Bateman et al. 2012). AD accounts for over 70 % of dementia cases among individuals over the age of 70 years (Tarawneh and Holtzman 2012), and its incidence increases exponentially with age (Kukull et al. 2002). Without successful treatment, AD will affect about 200 million individuals by the year 2050 (Thies and Bleiler 2011). Neuropathological changes are known to start several decades before the first clinical symptoms (Jack et al. 2010; Price and

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Morris 1999; Braak and Braak 1997), especially among those with autosomal dominant AD. Brain changes compatible with dementia are present in about 65 % of 80-year-olds (Villegmane et al. 2011; Rowe et al. 2010).

Diagnosis of AD

Since 2007, two sets of diagnostic criteria have been introduced in clinical practice. Dubois and coworkers proposed the International Work Group (IWG) criteria for the diagnosis of AD (Cummings et al. 2013). The novelty of these criteria is that they require a clinical phenotype characterized by anterograde amnesia; supportive evidence of biomarkers, such as positron emission tomography (PET) brain amyloid scans and brain metabolic activity and structural analysis using PET and magnetic resonance imaging, respectively; and genetic and cerebrospinal fluid (CSF) analysis. Thus, the IWG criteria integrate the assessment of biomarkers to clinical criteria, providing a more biological approach to diagnosis. The IWG criteria for probable AD include the core diagnostic criteria for a gradual and progressive impairment of episodic memory over more than 6 months. The recall deficit does not improve with cueing or recognition, and the memory deficit may be an isolated finding or be associated with other cognitive deficits. Additionally, one or more of the following supportive features are referred for a diagnosis of probable AD: (1) medial temporal lobe atrophy, (2) low 1–42 beta amyloid or increased total tau in the CSF, (3) hypometabolism in bilateral temporoparietal regions, or (4) a proven AD autosomal dominant mutation (Dubois et al. 2010). This strategy also allows classifying groups into those with prodromal AD (memory deficits, one or more positive biomarkers, and no impairments on activities of daily living (ADLs)) and AD dementia, when deficits in ADLs are present. Finally, the use of biomarkers identifies four diagnostic groups: (1) asymptomatic at-risk state with positive biomarkers, (2) preclinical AD with an autosomal dominant mutation, (3) prodromal AD with memory deficits and a biomarker for AD, and (4) AD dementia.

The second set of criteria were recently proposed by McKhann and coworkers (2011). The authors proposed core clinical criteria for AD which include the presence of cognitive and neuropsychiatric symptoms that produce impairments in ADLs representing a clear decline from previous levels of functioning. Cognitive impairment is diagnosed based on a clinical history assessed with the patient and an informant, as well as an objective cognitive impairment. The diagnosis of probable AD also requires anterograde amnesia, poor judgment, impaired visuospatial abilities, impaired language, and personality changes such as apathy and disinhibited behaviors. For a diagnosis of probable AD, patients not only have to meet the above criteria but also must have an insidious onset, history of worsening, and initial and prominent cognitive deficits characterized by anterograde memory deficits, word-finding deficits, or impaired reasoning.

The above set of criteria also include the major biomarkers for AD, such as a brain beta amyloid deposition (e.g., low CSF A-beta 42, positive PET amyloid imaging), or biomarkers of neural degeneration (increased CSF tau, hypometabolism

in temporoparietal cortices, and atrophy in medial temporoparietal regions). Nevertheless, the authors suggested that AD biomarkers should not be used in the routine assessment of patients. The authors finally suggested a category of "possible" dementia for those individuals who meet clinical criteria for a non-AD dementia (e.g., frontotemporal dementia, vascular dementia), but also have positive biomarkers for AD, or positive AD neuropathology.

Future studies will need to validate the above diagnostic criteria. In this context, it is important to stress that the accuracy for the "old" NINCDS-ADRDA criteria was reported to range from 68 to 88 % (Risse et al. 1990; Boller et al. 1989; Gilleard et al. 1992; Burns et al. 1990). A recent study that used different sets of neuropathological criteria for the diagnosis of AD demonstrated that only 50 % of 411 patients with a clinical diagnosis of AD had the neuropathology of AD (Shim et al. 2013), with most of the remaining patients having the neuropathology of AD combined with the pathology for dementia of Lewy bodies, vascular dementia, or both.

A recent study (Lowe et al. 2013) examined the concordance of the NIAA-AD criteria and findings in the ADNI study. The main finding was that 95 % of patients meeting criteria for probable AD had the typical AD pattern of brain hypometabolism and a positive amyloid scan. On the other hand, 30 % of individuals with amyloid positive scans had no typical AD hypometabolism. Moreover, conflicting evidence was also found between hippocampal atrophy as measured with magnetic resonance imaging (MRI) and PET brain hypometabolism. Therefore, biomarker findings were substantially inconsistent at the individual level. The problem of conflicting biomarker results will have to be examined in future studies. It should also be examined whether specific biomarkers are significantly related with movement disorders, as explained below. We will now review the most common movement disorders among patients with AD as diagnosed with NINCDS-ADRDA criteria. Whether the new diagnostic criteria identify subgroups with increased risk of movement disorders should be the focus of future studies.

Parkinsonism

Rigidity and postural instability develop in roughly 30 % of patients with Alzheimer's disease, whereas a similar percentage of patients with Parkinson's disease eventually have dementia due to Alzheimer's disease or other causes (Richards et al. 1993). Parkinsonism in dementia represents a challenge and can be associated with greater functional impairment, particularly with walking and continence (Richards et al. 2002). Many factors contribute to the variability in reported parkinsonism in AD. Some of the inconsistencies derive from variability in the definitions of parkinsonism, the use of unstructured clinical evaluation rather than standardized scales, inconsistent consideration of treatments with neuroleptics, and moreover inclusion of subjects at varying noncomparable stages of disease. In addition, small sample size and variable levels of participation at follow-up result in limited power. Also, many studies considered motor signs globally, and only a few reports have focused on individual domains of motor signs. In addition, most previous studies considered

motor signs only at a single point during the course of AD, typically at the baseline visit or less frequently at any point during the disease course, but patients' lack of follow-up and evolution of motor signs during disease progression or even its association with different outcomes are difficult to describe.

In one early attempt to describe parkinsonism in AD, we used the motor section of the UPDRS to divide patients into two groups: (a) Alzheimer's disease–parkinsonism: patients included in this group had rigidity, bradykinesia, and resting tremor; rigidity plus bradykinesia only; or resting tremor only. Bradykinesia was defined as a score >1 on the finger tapping, rapid hand movements, and alternating movements of the hands sections of the UPDRS. Rigidity was defined as a score >1 in the UPDRS (only cogwheel rigidity was considered). (b) Alzheimer's disease–extrapyramidal signs: patients included in this group had extrapyramidal signs other than bradykinesia, rigidity, or resting tremor (flexed posture, gait disorders, masked facies). In our cross-sectional study of 78 patients, we found that 23 % of the patients showed parkinsonism, 56 % showed isolated extrapyramidal signs, and only 21 % had no extrapyramidal signs. Whereas the frequency of parkinsonism was significantly higher than in age-comparable normal controls, the prevalence of isolated extrapyramidal signs was not significantly different. Secondly, parkinsonism in Alzheimer's disease failed to improve after the apomorphine test. Thirdly, patients with Alzheimer's disease–parkinsonism had significantly more severe deficits on neuropsychological tasks assessing abstract reasoning, set-shifting abilities, and executive functions than patients with Alzheimer's disease but no extrapyramidal signs, whereas patients with Alzheimer's disease and isolated extrapyramidal signs had scores in between both groups. Lastly, patients with Alzheimer's disease–parkinsonism showed a significantly higher frequency of both major depression and dysthymia than patients with Alzheimer's disease and no extrapyramidal signs (Merello et al. 1994). The relationship between parkinsonism and psychiatric symptoms in AD was later confirmed in a larger study on 169 patients meeting diagnostic criteria for AD followed between 1 and 4 years after the baseline evaluation. Patients with apathy at baseline or those who developed apathy during follow-up had a significant increase in parkinsonism at follow-up when compared with patients with no apathy at both assessments. The association between apathy and increasing parkinsonism was unrelated to age, gender, the severity of cognitive deficits, the presence of depression, or use of psychotropic medications. On the other hand, neither the presence of parkinsonism nor depression at baseline was significantly associated with more severe apathy at follow-up (Starkstein et al. 2009). In addition Park et al. described that the risk of sleepiness was 2.37 times greater in AD participants with parkinsonian features when compared to the AD participants without parkinsonism (Park et al. 2011).

There is little published information on patterns of progression of parkinsonism in AD. Several studies have shown that the probability of meeting criteria for parkinsonism increases with time (Morris et al. 1989; Stern et al. 1996; Chen et al. 1991). Wilson et al. (2000) reported an average of 4.5 % of annual increases in bradykinesia, 6.1 % on rigidity, and 8.9 % on gait and posture. While large cohort studies reported an average annual increase of 1.5 % on UPDRS scores on people with PD, Wilson et al. reported that in persons with AD, parkinsonism progressed

more than twice as fast (Wilson et al. 2000). The same authors interestingly reported that there was an average annual increase of 1.39 units in postural tremor (95 % CI, 0.76–2.02), whereas little change was evident in resting tremor (mean, 0.33 units; 95 % CI, 0.12–0.54).

Motor signs in AD are important because they may predict cognitive and functional decline, institutionalization, and death, and as compared to patients with AD without motor signs, patients with AD with motor signs have higher annual total cost of care (Murman et al. 2003; Morris et al. 1989; Soininen et al. 1992; Haan et al. 2002). Scarmeas et al. even found certain selectivity of each motor sign to determine specific outcome. In that way, presence of tremor was associated with increased risk for cognitive decline, presence of bradykinesia with increased risk for functional decline, and presence of postural–gait impairments with increased risk for institutionalization and death (Scarmeas et al. 2005).

The modification of parkinsonism in AD after dopaminergic therapy presents an important clinical as well psychopathological implicancies. We have not found clinical improvements after the apomorphine injection in 11 Alzheimer's disease patients with parkinsonism suggesting that parkinsonism in AD is not related to presynaptic nigrostriatal dysfunction (Merello et al. 1994). This may be in agreement with DaTscan studies which showed indemnity of nigrostriatal pathway in AD patients with parkinsonism (Vaamonde-Gamo et al. 2005). On the other hand, we have examined the presence of significant regional cerebral blood flow (rCBF) differences between AD patients with and without parkinsonism. Nine patients with AD and parkinsonism showed significantly lower rCBF in the superior frontal, superior temporal, and parietal regions of the left hemisphere than AD patients without parkinsonism. Rigidity and bradykinesia independently accounted for the decreased rCBF in these areas. These findings suggest that the presence of EPS in AD may result from dysfunction in specific brain regions other than basal ganglia (Starkstein et al. 1995).

Parkinsonism in AD Versus Parkinsonism in DLBD or Creutzfeldt–Jakob Disease

AD subjects had some degree of measurable parkinsonism, which worsened with the cognitive severity of the disease. Up to 50 % of patients with DLB are reported to have extrapyramidal motor symptoms at diagnosis and 75 % at some stage during the illness (McKeith et al. 1992). Besides the well-known "1-year rule" which clearly discriminates the temporal relationship between parkinsonism and dementia in AD and DLBD patients (Fig. 8.1), those subjects with a late-stage AD (MMSE 0–10) had a similar degree of parkinsonism to those with early-stage LBV (MMSE 26–30) but had significantly less parkinsonism compared with those subjects with early-stage DLB (MMSE 26–30) (Kaur et al. 2013). By studying 9 different parkinsonian features in AD and DLBD patients (masked facies 4.2 %/48 %, hypophonia 3.4/30.8 %, rigidity 9.8 %/44 %, gait disturbance 14 %/43 %, bradykinesia

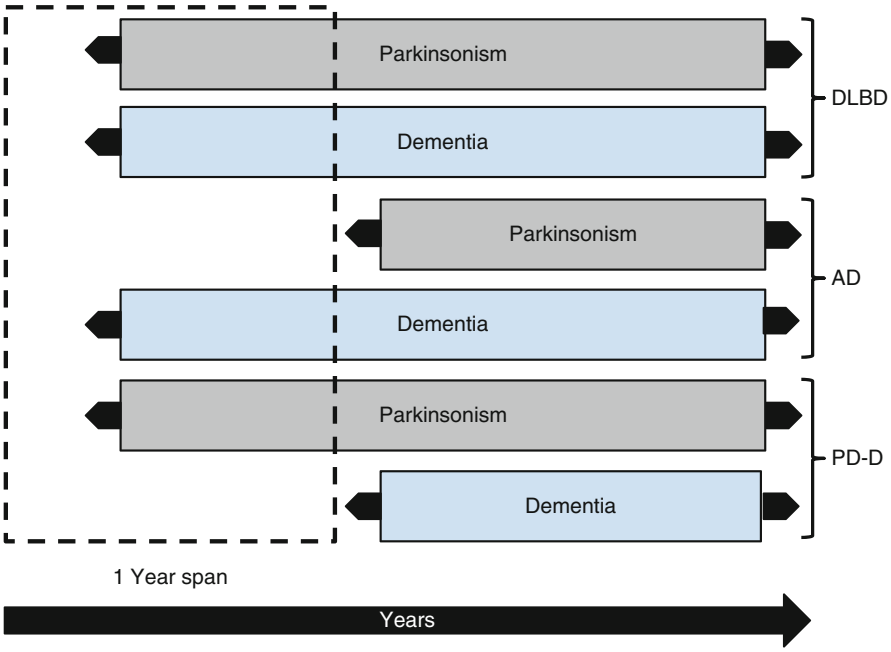

Fig. 8.1 Temporal relationship between parkinsonism and disease evolution in Parkinson's disease-related dementia, diffuse Lewy body dementia, and Alzheimer's disease

19 %/55 %, impaired chair rise 15 %/29 %, rest tremor 3 %/13 %, postural instability 12 %/26 %, and postural tremor 6 %/12 %), logistic regression models consistently demonstrate that all 9 EPSs differentiate DLB from AD, regardless of age, sex, education, or MMSE, and being masked facies the one that best differentiated AD from Lewy body (odds ratio, 6.5; $P<0.001$; 95 % confidence interval, 3.8–11.1), Kaur et al. (2013) findings were in agreement with those of Ballard et al. and Galasko et al. (Ballard et al. 1997; Galasko et al. 1996), which demonstrate that rest tremor, action tremor, bradykinesia, facial expression, and rigidity subscales of the UPDRS were helpful in differentiating DLB from AD. Patients with DLB experience a greater level of functional impairment than subjects with AD of similar cognitive ability largely attributable to parkinsonism (Chap. 10). The loss of dopaminergic neurons in DLB can be confirmed in vivo with a presynaptic dopamine transporter marker DaTscan, whereas there are no changes in DaTscan in AD compared with controls (Piggott et al. 1999).

In patients with rapidly progressive dementia and motor signs, Creutzfeldt–Jakob disease (CJD) should be the first suspected diagnosis. However, the presence of dementia, myoclonus, and rigidity with a longer course of disease may suggest AD or even DLBD. In an elegant study, Tschampa et al. (2001) described that myoclonus and extrapyramidal signs were especially common in patients with CJD and patients with DLB and in more than 50 % of patients with AD. Extrapyramidal signs in patients with

AD and with DLB were restricted to limb rigidity (>50 % respectively) and parkinsonism (58 % in patients with DLB, 8 % in CJD, and 11 % in AD). Patients with CJD additionally showed hyperkinetic signs (40 %). Nearly all patients with CJD and 37 % of patients with AD had cerebellar signs, not noted in DLB. Regarding hyperkinetic movement disturbances, dystonia and athetosis were seen exclusively in CJD patients (Edler et al. 2009). In other comparative studies, dystonia and athetosis were also seen in CJD patients only, but dystonia has also been reported to be present at a low frequency of 6 % in DLB patients (Louis et al. 1997; Burkhardt et al. 1988) (Fig. 8.2).

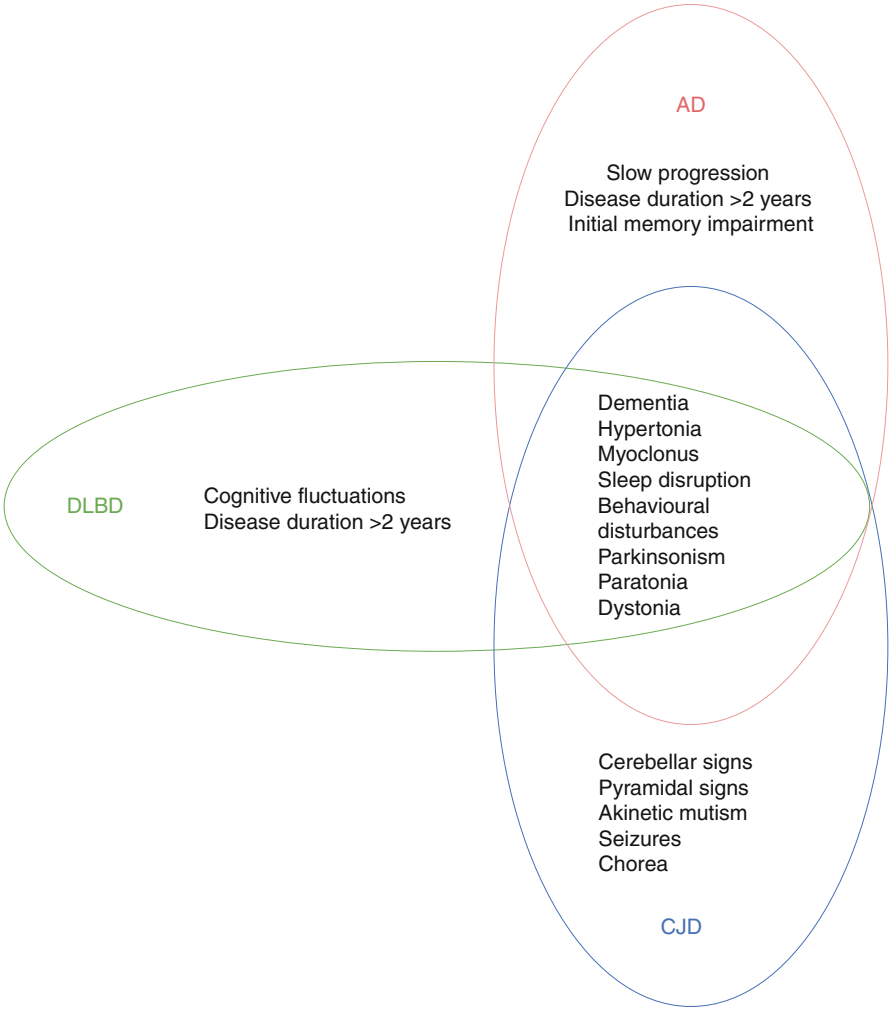

Fig. 8.2 Movement disorders occurring in Alzheimer's disease, diffuse Lewy body disease, and Creutzfeldt–Jakob disease

Corticobasal Syndrome

Corticobasal syndrome, with asymmetric parkinsonism, dystonia, and apraxia, is increasingly recognized as a presentation of sporadic cases of AD (Duker et al. 2012; Chand et al. 2006). There are only a few reports of AD clinically presenting with the corticobasal syndrome. All 7 cases presented with typical clinical features and fulfilled the proposed research criteria of corticobasal syndrome, but pathologically, all cases had SP and NFT consistent with AD (Doran et al. 2003; Lleo et al. 2002; Boeve et al. 1999; Chand et al. 2006). On the other hand, alien limb phenomenon has been scantly reported in AD (Ball et al. 1993). NFTs found in the striatum, substantia nigra, dorsal raphe, and even the midbrain tectum are known to occur in advanced AD and are likely to contribute to the clinical signs of dystonia, parkinsonism, and even myoclonus. In addition, descriptions of families with mutations in the presenilin 1 (PS1) gene (the most common cause of autosomal dominant early-onset AD) (Sherrington et al. 1995) have revealed a heterogeneous clinical phenotype, including pyramidalism, spastic paraparesia, ataxia, myoclonus seizures, or also corticobasal syndrome with dystonic features (Zekanowski et al. 2003; Anheim et al. 2007; Kauwe et al. 2008; Wisniewski et al. 1998).

Myoclonus

The prevalence of myoclonus increases during disease progression, and up to 50 % of AD patients eventually develop myoclonus. Although myoclonus develops in the latter stages of the illness, an earlier age of AD onset, faster progression (Gauthier et al. 2006), and familial causes of AD are associated with a higher incidence of myoclonus appearance at earlier stages of the disease (Caviness 2003). Myoclonus in AD is considered to be of cortical origin with electrophysiological characteristic of cortical reflex myoclonus.

Pisa Syndrome

Pisa syndrome was originally coined to describe a rare form of tardive dystonia or acute dystonia associated with the use of neuroleptics. The typical clinical picture is the tonic lateral flexion of the trunk associated with a mild backward rotation and not related to musculoskeletal sustained fixed abnormalities. There is a current debate whether it corresponds to the same entity of persistent lateral deviation and whether it is associated with camptocormia. It has been described in a Parkinson's disease patient, and the sign has been included as supportive criterion for multiple system atrophy. EMG showed abnormal tonic hyperactivity on the side of the deviation in the paravertebral thoracic muscles and in the abdominal oblique muscles (Tassorelli et al. 2012). It has been suggested that Pisa syndrome corresponded to a

dystonia of the trunk probably associated with a dopaminergic–cholinergic imbalance or serotoninergic or noradrenergic dysfunction. This is further supported by its recently reported improvement after PPN DBS (Shih et al. 2013). Anticholinergic drugs may be effective in treating Pisa syndrome in about 40 % of patients. On the other hand, four Pisa syndrome cases have been reported among patients with AD treated with cholinesterase inhibitors in which problem resolved in 1–4 weeks after the discontinuation of cholinesterase inhibitors, and after rechallenge of ChEIs, three patients presented again Pisa syndrome within 1–7 weeks (Miyaoka et al. 2001; Villarejo et al. 2003). Further three cases were reported in pharmacovigilance ChEIs studies (Vanacore et al. 2005) arguing the relationship between ChEIs use and Pisa syndrome.

Paratonia

Paratonia is one of the associated movement disorders characteristic of dementia. Paratonic rigidity consists of a resistance to passive movement of a limb whereby the degree of resistance varies depending on the speed of movement. Resistance increases when the limb is moved more rapidly and decreases or even disappears when it is moved more slowly. Paratonia has been also called "gegenhalten." It has been suggested that AD patients who develop paratonia represent a subtype of patients with a more rapid decline (Gladstone and Black 2002) and that the presence of paratonia might represent executive and planning impairments (Bennett et al. 2002). In a series of 86 patients with advanced dementia composed of 52.3 % ($n=45$) AD, 25.6 % ($n=22$) vascular dementia, 17.4 % ($n=15$) AD plus vascular dementia, and 2.3 % ($n=2$) DLBD, Hobbelen et al. found paratonia in 77–82 % of the patients (Hobbelen et al. 2008). Other study found that paratonia was present in 48, 70, and 83 % of persons in GDS stages 4, 5, and 6, respectively, and there was a significant correlation between the presence of paratonia and cognition (MMSE), illness stage (GDS), depression (HAM-D), and the number of frontal lobe release signs (Vahia et al. 2007). There is a potential utility of paratonia as an independent marker of disease stage in AD. Besides, failure to precisely characterize paratonia in dementia has important implicancies as it can lead to improper use of antiparkinsonian medication and may be confused with parkinsonian rigidity.

Dystonia

Dystonia in AD patients has been described in the context of a corticobasal syndrome as an unusual presentation form either in older patients or in early-onset cases associated with progranulin mutations (Spina et al. 2007). Dystonia in AD patients secondary to mirtazapine (van den Bosch et al. 2006), neuroleptics (Magnuson et al. 2000), and rivastigmine (Pavlis et al. 2007) has been also described.

References

Anheim M, Hannequin D, Boulay C, et al. Ataxic variant of Alzheimer's disease caused by Pro117Ala PS1 mutation. J Neurol Neurosurg Psychiatry. 2007;78:1414–5.

Ball JA, Lantos PL, Jackson M, et al. Alien hand sign in association with Alzheimer's histopathology. J Neurol Neurosurg Psychiatry. 1993;56:1020–3.

Ballard C, McKeith I, Burn D, et al. The UPDRS scale as a means of identifying extrapyramidal signs in patients suffering from dementia with Lewy bodies. Acta Neurol Scand. 1997;96:366–71.

Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med. 2012;367:795–804.

Bennett HP, Corbett AJ, Gaden S, et al. Subcortical vascular disease and functional decline: a 6-year predictor study. J Am Geriatr Soc. 2002;50:1969–77.

Boeve BF, Maraganore DM, Parisi JE, et al. Pathologic heterogeneity in clinically diagnosed corticobasal degeneration. Neurology. 1999;53:795–800.

Boller F, Lopez OL, Moossy J. Diagnosis of dementia: clinicopathologic correlations. Neurology. 1989;39:76–9.

Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging. 1997;18:351–7.

Burkhardt CR, Filley CM, Kleinschmidt-DeMasters BK, et al. Diffuse Lewy body disease and progressive dementia. Neurology. 1988;38:1520–8.

Burns A, Luthert P, Levy R, et al. Accuracy of clinical diagnosis of Alzheimer's disease. BMJ. 1990;301:1026.

Caviness JN. Myoclonus and neurodegenerative disease—what's in a name? Parkinsonism Relat Disord. 2003;9:185–92.

Chand P, Grafman J, Dickson D, et al. Alzheimer's disease presenting as corticobasal syndrome. Mov Disord. 2006;21:2018–22.

Chen J-Y, Stern Y, Sano M, Mayeux R. Cumulative risks of developing extrapyramidal signs, psychosis, or myoclonus in the course of Alzheimer's disease. Arch Neurol. 1991;48:1141–3.

Cummings JL, Dubois B, Molinuevo JL, Scheltens P. International Work Group criteria for the diagnosis of Alzheimer disease. Med Clin North Am. 2013;97:363–8.

Doran M, du Plessis DG, Enevoldson TP, et al. Pathological heterogeneity of clinically diagnosed corticobasal degeneration. J Neurol Sci. 2003;216:127–34.

Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol. 2010;9:1118–27.

Duker AP, Espay AJ, Wszolek ZK, et al. Atypical motor and behavioral presentations of Alzheimer disease: a case-based approach. Neurologist. 2012;18:266–72.

Edler J, Mollenhauer B, Heinemann U, et al. Movement disturbances in the differential diagnosis of Creutzfeldt-Jakob disease. Mov Disord. 2009;24:350–6.

Galasko D, Katzman R, Salmon DP, et al. Clinical and neuropathological findings in Lewy body dementias. Brain Cogn. 1996;31:166–75.

Gauthier S, Vellas B, Farlow M, et al. Aggressive course of disease in dementia. Alzheimers Dement. 2006;2:210–7.

Gilleard CJ, Kellett JM, Coles JA, et al. The St. George's dementia bed investigation study: a comparison of clinical and pathological diagnosis. Acta Psychiatr Scand. 1992;85:264–9.

Gladstone DJ, Black SE. The neurological examination in aging, dementia and cerebrovascular disease. Part 2: motor examination. Geriatr Aging. 2002;5:44–9.

Haan MN, Jagust WJ, Galasko D, Kaye J. Effect of extrapyramidal signs and Lewy bodies on survival in patients with Alzheimer disease. Arch Neurol. 2002;59:588–93.

Hobbelen JS, Koopmans RT, Verhey FR, et al. Diagnosing paratonia in the demented elderly: reliability and validity of the Paratonia Assessment Instrument (PAI). Int Psychogeriatr. 2008;20:840–52.

Jack Jr CR, Knopman DS, Jaqust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9:119–28.
Kaur B, Harvey DJ, Decarli CS, et al. Extrapyramidal signs by dementia severity in Alzheimer disease and dementia with Lewy bodies. Alzheimer Dis Assoc Disord. 2013;27(3):226–32.
Kauwe JS, Wang J, Chakraverty S, et al. Novel presenilin 1 variant (P117A) causing Alzheimer's disease in the fourth decade of life. Neurosci Lett. 2008;438:257–9.
Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. Arch Neurol. 2002;59:1737–46.
Lleo A, Rey MJ, Castellvi M, et al. Asymmetric myoclonic parietal syndrome in a patient with Alzheimer's disease mimicking corticobasal degeneration. Neurologia. 2002;17:223–6.
Louis ED, Klatka LA, Liu Y, Fahn S. Comparison of extrapyramidal features in 31 pathologically confirmed cases of diffuse Lewy body disease and 34 pathologically confirmed cases of Parkinson's disease. Neurology. 1997;48:376–80.
Lowe VJ, Peller PJ, Weigand SD, et al. Application of the National Institute on Aging-Alzheimer's Association AD criteria to ADNI. Neurology. 2013;80:2130–7.
Magnuson TM, Roccaforte WH, Wengel SP, Burke WJ. Medication-induced dystonias in nine patients with dementia. J Neuropsychiatry Clin Neurosci. 2000;12:219–25.
McKeith IG, Perry RH, Fairbairn AF, et al. Operational criteria for senile dementia of Lewy body type (SDLT). Psychol Med. 1992;22:911–22.
McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:263–9.
Merello M, Sabe L, Teson A, et al. Extrapyramidalism in Alzheimer's disease: prevalence, psychiatric, and neuropsychological correlates. J Neurol Neurosurg Psychiatry. 1994;57:1503–9.
Miyaoka T, Seno H, Yamamori C, et al. Pisa syndrome due to a cholinesterase inhibitor (donepezil): a case report. J Clin Psychiatry. 2001;62:573–4.
Morris JC, Drazner M, Fulling K, et al. Clinical and pathological aspects of parkinsonism in Alzheimer's disease. Arch Neurol. 1989;46:651–7.
Murman DL, Kuo SB, Powell MC, Colenda CC. The impact of parkinsonism on costs of care in patients with AD and dementia with Lewy bodies. Neurology. 2003;61:944–9.
Park M, Shah RC, Fogg LF, Wyatt JK. Daytime sleepiness in mild Alzheimer's disease with and without parkinsonian features. Sleep Med. 2011;12:397–402.
Pavlis CJ, Kutscher EC, Carnahan RM, et al. Rivastigmine-induced dystonia. Am J Health Syst Pharm. 2007;64:2468–70.
Piggott MA, Marshall EF, Thomas N, et al. Striatal dopaminergic markers in dementia with Lewy bodies, Alzheimer's and Parkinson's diseases: rostrocaudal distribution. Brain. 1999;122:1449–68.
Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol. 1999;45:358–68.
Richards M, Stern Y, Marder K, et al. Relationships between extrapyramidal signs and cognitive function in a community-dwelling cohort of patients with Parkinson's disease and normal elderly individuals. Ann Neurol. 1993;33:267–74.
Richards M, Touchon J, Ledesert B, et al. Mild extrapyramidal signs and functional impairment in ageing. Int J Geriatr Psychiatry. 2002;17:150–3.
Risse SC, Raskind MA, Nochlin D, et al. Neuropathological findings in patients with clinical diagnoses of probable Alzheimer's disease. Am J Psychiatry. 1990;147:168–72.
Rowe CC, Ellis KA, Rimajowa M, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Neurobiol Aging. 2010;31:1275–83.
Scarmeas N, Albert M, Brandt J, et al. Motor signs predict poor outcomes in Alzheimer disease. Neurology. 2005;64:1696–703.
Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature. 1995;375:754–60.

Shih LC, Vanderhorst VG, Lozano AM, et al. Improvement of pisa syndrome with contralateral pedunculopontine stimulation. Mov Disord. 2013;28:555–6.
Shim YS, Roe CM, Buckles VD, Morris JC. Clinicopathologic study of Alzheimer's disease: Alzheimer mimics. J Alzheimers Dis. 2013;35:799–811.
Soininen H, Laulumaa V, Helkala EL, et al. Extrapyramidal signs in Alzheimer's disease: a 3-year follow-up study. J Neural Transm Park Dis Dement Sect. 1992;4:107–19.
Spina S, Murrell JR, Huey ED, et al. Corticobasal syndrome associated with the A9D Progranulin mutation. J Neuropathol Exp Neurol. 2007;66:892–900.
Starkstein SE, Vazquez S, Merello M, et al. SPECT study of parkinsonism in Alzheimer's disease. J Neuropsychiatry Clin Neurosci. 1995;7:308–13.
Starkstein SE, Merello M, Brockman S, et al. Apathy predicts more severe parkinsonism in Alzheimer's disease. Am J Geriatr Psychiatry. 2009;17:291–8.
Stern Y, Liu X, Albert M, et al. Modeling the influence of extrapyramidal signs on the progression of Alzheimer's disease. Arch Neurol. 1996;53:1121–6.
Tarawneh R, Holtzman DM. The clinical problem of symptomatic Alzheimer disease and mild cognitive impairment. Cold Spring Harb Perspect Med. 2012;2:1–16.
Tassorelli C, Furnari A, Buscone S, et al. Pisa syndrome in Parkinson's disease: clinical, electromyographic, and radiological characterization. Mov Disord. 2012;27:227–35.
Thies W, Bleiler L. 2011 Alzheimer's disease facts and figures. Alzheimers Dement. 2011;7:208–44.
Tschampa HJ, Neumann M, Zerr I, et al. Patients with Alzheimer's disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry. 2001;71:33–9.
Vaamonde-Gamo J, Flores-Barragan JM, Ibañez R, et al. DaT-SCAN SPECT in the differential diagnosis of dementia with Lewy bodies and Alzheimer's disease. Rev Neurol. 2005;41:276–9.
Vahia I, Cohen CI, Prehogan A, Memon Z. Prevalence and impact of paratonia in Alzheimer disease in a multiracial sample. Am J Geriatr Psychiatry. 2007;15:351–3.
van den Bosch S, Bouckaert F, Peuskens J. Mirtazapine-induced dystonia in a patient with Alzheimer's disease. Tijdschr Psychiatr. 2006;48:153–7. Dutch.
Vanacore N, Suzzareddu G, Maggini M, et al. Pisa syndrome in a cohort of Alzheimer's disease patients. Acta Neurol Scand. 2005;111:199–201.
Villarejo A, Camacho A, Garcia-Ramos R, et al. Cholinergic-dopaminergic imbalance in Pisa syndrome. Clin Neuropharmacol. 2003;26:119–21.
Villegmane VL, Pike KE, Chételat G, et al. Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease. Ann Neurol. 2011;69:181–92.e.
Wilson RS, Bennett DA, Gilley DW, et al. Progression of Parkinsonian signs in Alzheimer's disease. Neurology. 2000;54:1284–9.
Wisniewski T, Dowjat WK, Buxbaum JD, et al. A novel Polish presenilin-1 mutation (P117L) is associated with familial Alzheimer's disease and leads to death as early as the age of 28 years. Neuroreport. 1998;9:217–21.
Zekanowski C, Styczynska M, Peplonska B, et al. Mutations in presenilin 1, presenilin 2 and amyloid precursor protein genes in patients with early-onset alzheimer's disease in Poland. Exp Neurol. 2003;184:991–6.

Chapter 9
Movement Disorders in Frontotemporal Dementia

Emma Devenney and John Hodges

Abstract Our understanding of frontotemporal dementia (FTD) and its related syndromes has advanced significantly in recent years. One of the most prominent areas of progress is in the overlap syndromes of FTD and movement disorders, at a clinicopathological and genetic level. The aim of this chapter is to discuss the clinical, pathological, and genetic complexities of disorders of movement typically seen in FTD.

Keywords Frontotemporal dementia • Movement disorder • Parkinsonism • Apraxia • Dystonia • Myoclonus • Amyotrophic lateral sclerosis

Abbreviations

ALS	Amyotrophic lateral sclerosis
bvFTD	Behavioral variant frontotemporal dementia
CBS	Corticobasal syndrome
DLB	Dementia with Lewy bodies
FTD	Frontotemporal dementia
PNFA	Progressive nonfluent aphasia
PSP	Progressive supranuclear palsy
SD	Semantic dementia
VBM	Voxel-based morphometry

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Background

Frontotemporal dementia is an umbrella term which encompasses a heterogeneous group of syndromes with a variety of overlapping clinical, imaging, and pathological features. Patients typically present below the age of 65 years, and the prevalence rates in this age group are only marginally less than in Alzheimer's disease (AD) (Ratnavalli et al. 2002). Arnold Pick first described the constellation of symptoms including aphasia, apraxia, and behavioral changes, at the turn of the last century, associated with frontal and temporal atrophy. The pathology associated with this syndrome was described later with the identification of round, silver staining inclusions, also known as "Pick's bodies" (Onari 1926) which led to controversy concerning the term Pick's disease which was applied by some to the clinical entity and by others to a distinctive pathological appearance which is present in a minority of cases with the clinical syndrome (Hodges et al. 2004). In 1994, the Lund and Manchester groups coined the phrase frontotemporal lobar dementia (FTLD) (Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups 1994) which led to an upsurge in interest culminating in the development of international consensus criteria in 1998 when the preferred term frontotemporal dementia (FTD) was adopted (Neary et al. 1998). A number of clinically recognized subtypes of FTD have emerged: a subtype defined by behavioral and executive deficits known as behavioral variant FTD (bvFTD) and two language variants – semantic dementia (SD) and progressive nonfluent aphasia (PNFA). Very recently more detailed and specific diagnostic criteria for both the behavioral syndrome (Rascovsky et al. 2011) and the aphasic variants (Gorno-Tempini et al. 2011) have been published by international consensus groups. Of relevance to this chapter, these syndromes are considered to be on a spectrum with extrapyramidal disorders, notably corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP), as well as amyotrophic lateral sclerosis (ALS) (Boeve 2007).

The pathology in FTD is characterized by severe focal atrophy of frontal and temporal regions, subcortical gliosis, and neuronal loss. The classification of subtypes depends upon the presence of intraneuronal protein inclusions which are typically either phosphorylated tau protein or ubiquitinated TAR-DNA binding protein (TDP-43). These two account for over 90 % of cases, while fused in sarcoma (FUS)-positive pathology and ubiquitin proteasome system pathology due to *CHMP2B* mutations FTD-3, are present in a small proportion of cases. Up to 40 % of patients report a family history of dementia although this is often a single relative with late-onset dementia. In 10–20 % of all cases, there is a history suggestive of an autosomal dominant gene mutation (Goldman et al. 2005). Mutations in microtubule-associated protein tau (*MAPT*), progranulin (*GRN*) or the recently discovered hexanucleotide repeat expansion in the noncoding region of chromosome 9 (*C9ORF72*) accounts for the majority of familial cases with the latter appearing to be the most common occurring in up to one-third of cases of familial FTD as well as familial ALS (DeJesus-Hernandez et al. 2011; Renton et al. 2011).

The behavioral variant of FTD is the most common subtype of FTD and is characterized by an alteration in personality and social conduct into which patients

have little or no insight but is a cause of considerable distress for carers (Mioshi et al. 2009). The diagnosis hinges on a detailed carer interview to elicit key behavioral features, notably apathy, alterations in social conduct and inhibitory control, loss of empathy, mental rigidity, stereotypic speech and motor behaviors, and a change in eating habits toward sweet cravings and a lack of satiety. In addition, patients may exhibit prominent executive deficits. It has been suggested that memory is spared in FTD, however recent studies have demonstrated poor performance of tests of episodic memory (Hornberger et al. 2010). In contrast to Alzheimer's disease, orientation is well preserved. In parallel, patients typically have neuroimaging evidence of atrophy in the orbitofrontal cortex, insula, and medial thalamus on MRI or hypoperfusion in these areas on functional imaging (Schroeter et al. 2008). Unlike some of the other FTD syndromes, it is difficult to predict pathology; approximately 50 % of cases have FTLD-tau pathology, while the other 50 % have FTLD-TDP deposition. Of all variants, bvFTD appears to be most likely associated with ALS, particularly in those patients harboring the *C9ORF72* genetic mutation.

Semantic dementia is characterized by progressive anomia and impaired word comprehension secondary to dissolution of semantic networks in the anterior temporal lobe (Hodges et al. 1992). The loss of vocabulary affects mainly nouns in the early stages and shows a marked familiarity effect, in that even advanced cases can recognize high-frequency words. In contrast, phonology and syntax are relatively preserved, and speech remains fluent although simplified with use of higher-frequency substitutions and filler words such as "thing" and "that place." Patients initially function very well at home; however as the disease progresses, object knowledge and use becomes impaired, and this parallels the language deficits with lower-frequency objects initially compromised. The anterior temporal lobe atrophy is usually asymmetrical and predominantly left sided in most cases (Hodges et al. 1992). Deficit in person recognition (prosopagnosia) is the key feature of the right predominant syndrome, which progresses to a cross-modal loss of face, name, and voice recognition (Evans et al. 1995). Behavioral features, similar to those found in bvFTD, are common in patients with SD and particularly in those with the right temporal variant. Pathologically SD is relatively homogenous with the majority of cases showing TDP-43 pathology, and of all FTD variants, it is most likely to be sporadic.

In contrast to SD, PNFA patient's speech is strikingly nonfluent with speech distortion, pauses, groping, and agrammatism (Gorno-Tempini et al. 2011). The distortion of speech is due to breakdown in motor planning, referred to as speech apraxia, causing impairment of rhythm and the normal stress patterns of speech. These deficits occur in the presence of spared word comprehension. Sentence comprehension however can be impaired due to problems understanding the grammatical elements of sentences. Word repetition is often impaired due to articulatory errors. FTLD-tau is most frequently present in these cases. Patients with PNFA commonly develop Parkinsonism and apraxia which may lead to a change in syndromic diagnosis to corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP) (Kertesz et al. 2005). In a large longitudinal clinicopathological study Kertesz and colleagues (Kertesz et al. 2005) identified evolution to CBS or PSP in almost half of 22 cases of PNFA.

Frontotemporal Dementia with Parkinsonism

Prevalence and Clinical Features

Of the movement disorders, Parkinsonism is the only one commonly described in patients with FTD although the exact prevalence is unclear largely due to differences in what is meant by Parkinsonism. The majority of information comes from large clinicopathological studies of FTD, as there have been few cohort studies dedicated solely to the characterization of parkinsonian features in FTD. One such cohort study objectively evaluated extrapyramidal features according to the Unified Parkinson's Disease Rating Scale-III (UPDRS-III) in 75 bvFTD patients. Almost a quarter of patients satisfied criteria for Parkinsonism, most commonly due to bradykinesia and rigidity, with tremor in only 29 % of cases (Padovani et al. 2007). A positive correlation was found between parkinsonian features and delusions and hallucinations implicating dopaminergic dysfunction and striatal pathology, although the study lacked pathological confirmation of this hypothesis. The recently described *C9ORF72* mutation commonly presents with prominent psychotic features (Snowden et al. 2012) and Parkinsonism can also develop suggesting that cases with the *C9ORF72* mutation may have been included in these earlier studies. In another cohort study, 80 % of bvFTD patients presented with at least a single feature of Parkinsonism (Diehl-Schmid et al. 2007). In contrast to the previous study, the UPDRS was modified to a dichotomous variation, and patients were considered to have Parkinsonism if they showed evidence of any one of (1) resting tremor, (2) rigidity, (3) akinesia, or (4) parkinsonian gait/posture. Again akinesia was the most common feature present in 84 %, followed by parkinsonian gait/posture in 71 % and rigidity in 36 %. Tremor was even less frequent, being present in only 7 % of patients. The exclusion of patients taking antipsychotic medications is a major strength of these studies, thus excluding the confounding factor of drug-induced Parkinsonism.

Several clinicopathological series have also reported the prevalence of Parkinsonism in FTD patient populations which have the benefit of longitudinal follow-up as well as pathological confirmation of the clinical diagnosis. A large clinicopathological study in Cambridge in 2004 studied extrapyramidal features in FTD patients: 1/8 PNFA patients, 5/26 bvFTD patients, and 3/9 FTD-ALS patients had evidence of parkinsonian features at presentation with no evidence of parkinsonian features in 9 SD patients (Hodges et al. 2004). Parkinsonism tends to evolve with disease progression as evidenced by reports from a large clinicopathological study at the University of Pennsylvania (Forman et al. 2006): extrapyramidal signs at presentation were present in almost half of the cohort, while 82 % of FTD patients had such signs at last examination.

In contrast to PNFA and bvFTD, semantic dementia rarely, if ever, manifests with Parkinsonism (Davies et al. 2005). Although Parkinsonism has been considered to be a particular feature of familial FTD, there is no clear evidence that it is more or less common than in sporadic disease (Piguet et al. 2004).

Pathology and Neural Correlates

The neural basis of parkinsonian features in FTD remains unclear. A degree of atrophy of the basal ganglia and histopathological changes in the striatum have been reported (Mann et al. 1993). Another study found a significant inverse correlation between the degree of severity of parkinsonian symptoms and the degree of uptake of a dopamine transporter ligand, suggesting that striatal dysfunction is a factor in these conditions (Rinne et al. 2002). This idea was corroborated in a case series of six patients who satisfied criteria for both dementia with Lewy bodies (DLB) and FTD at presentation: two cases came to autopsy, pathological study of these cases revealed gliosis and neuronal loss in the basal ganglia and substantia nigra with pigment loss in the latter (Claassen et al. 2008). While Parkinsonism in FTD has been linked to underlying tau pathology (Hodges et al. 2004), TDP-43 pathology was actually present in each of these cases.

Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17 (FTDP-17)

As CBS and PSP are discussed in detail in another chapter, the remainder of this chapter will focus on the inherited forms of FTD.

Background

Parkinsonism in FTD has been reported in the literature since the turn of the century but was initially overlooked in favor of the prominent behavioral and language features. In 1998 a dementia and Parkinsonism syndrome was linked to chromosome 17q21-22 in an Irish kindred which sparked considerable interest in this area (Lendon et al. 1998). The first frontotemporal dementia and Parkinsonism consensus consortium met in Ann Arbor in 1996 to discuss the clinical and neuropathological features of this and 12 other kindreds with FTDP-17, as it then became known (Foster et al. 1997). Despite clinical heterogeneity within and between families, a severe behavioral disorder characteristic of FTD and Parkinsonism without resting tremor was common to all. Neuropathologically, there was atrophy of the frontal and temporal cortices, as well as the basal ganglia and depigmentation of the substantia nigra. A defect in the microtubule-associated protein tau (*MAPT*) gene on chromosome 17 was discovered 2 years later in a proportion of FTDP-17 families (Hutton et al. 1998), but it was almost another decade before a mutation in the progranulin gene (*GRN*) was discovered to account for the remaining FTDP-17 families (Gass et al. 2006).

Over 40 mutations in the *MAPT* gene have now been described, all of which have underlying tau pathology, and account for approximately 30 % of all familial FTD (Houlden et al. 1999; Poorkaj et al. 2001; Rosso et al. 2003; Stanford et al. 2004). Over 50 mutations of the *GRN* gene have been described; these *GRN*

Table 9.1 Comparison of features: FTDP-17 *MAPT* vs. FTDP-17 *GRN*

Characteristic	*MAPT*	*GRN*
Age at onset	25–65 years, usually in 40s	>50 years
Disease duration	3–10 years, mean 5 years	1–15 years, mean 7 years
Penetrance	>95 %	90 % by 70 years
Clinical feature		
Parkinsonism	Infrequent	Frequent
Apraxia	Very rare	Infrequent
ALS features	Very rare	Never
Psychosis	Infrequent	Frequent
Imaging		
Symmetry	Symmetrical	Asymmetrical
Distribution of atrophy	Anteromedial temporal lobe and orbitofrontal cortex	Inferior fontal, inferior temporal, and inferior parietal lobes

carriers exclusively exhibit TDP-43 pathology and this mutation is reportedly present in 6–25 % of familial FTD (Baker et al. 2006; Cruts et al. 2006).

Clinical Features

At a clinical level, FTDP-17 associated with *MAPT* and *GRN* mutations has common and contrasting features (Table 9.1). Both show an autosomal dominant pattern of inheritance (Foster et al. 1997). *MAPT* mutation carriers can present initially with either a predominant parkinsonian syndrome or a dementia (Baba et al. 2005; Tsuboi et al. 2002), with the precise mutation determining the clinical phenotype; the *N279K* mutation has a predominant parkinsonian presentation (Wszolek et al. 2000), personality and behavioral changes characterize the *P301L* and *10 +16 mutation* (Kodama et al. 2000; Janssen et al. 2002), and the S305S mutation does not appear to favor either (Stanford et al. 2000; Reed et al. 2001).

Although the reported age of onset ranges from 25 to 65 years in *MAPT* carriers, the majority of patients first exhibit signs in their 40s and live for 3–10 years with the disease (Boeve and Hutton 2008; Espay and Litvan 2011). An exception to this is the *R406W* mutation carriers who have a much longer disease duration with reports of patient surviving into their 70s (Van Swieten et al. 1999). *GRN* mutations tend to present later than *MAPT*, with most patients developing symptoms after 50 years of age with a mean disease duration of 5 years (3–22 years) and a shorter disease duration in late-onset disease (Van Swieten and Heutink 2008). The *MAPT* mutation is almost fully penetrant, although there are reports of asymptomatic individuals living into old age (Hutton et al. 1998). In contrast, *GRN* carriers exhibit incomplete penetrance with 10 % of carriers remaining asymptomatic at 70 years (Gass et al. 2006; Boeve and Hutton 2008). Parkinsonism has been reported in approximately 40 % of *GRN* cases (Le Ber et al. 2007). In common with *MAPT* mutation carriers, the Parkinsonism is generally symmetrical with bradykinesia, rigidity, and rarely resting tremor and with modest or little response to levodopa (Tsuboi et al. 2002). Features typically associated with PSP, including supranuclear gaze palsy, eyelid apraxia, myoclonus, dysphagia,

dysarthria, and pyramidal features, have all been reported in *MAPT* mutation carriers (Stanford et al. 2000), while dystonia is infrequent in all mutation carriers.

TDP-43 pathology is common to both patients with FTD in association with *GRN* mutations and patients with ALS. Despite this commonality, features of ALS are not found in *GRN* carriers which suggests a distinct pathogenetic mechanism in *GRN* carriers. ALS features are also rarely found in *MAPT* carriers. (Seelaar et al. 2007; Pickering-Brown et al. 2008; Tsuboi 2006). By contrast although apraxia is rare in *MAPT* carriers, it can be a feature of *GRN* carriers. Severe behavioral disorders are found in the majority of carriers of both mutations, in addition to frontal dysexecutive cognitive deficits (Boeve and Hutton 2008; Le Ber et al. 2007). In one published *GRN* case, the patient developed features of Kluver-Bucy syndrome with prominent hypersexuality, hyperphagia, and psychotic features (Boeve et al. 2006). In general, psychotic features have been reported in up to a quarter of *GRN* carriers and include hallucinations and/or delusions which in some cases has led to misdiagnoses of schizophrenia. Hallucinations include visual (animals and people) reported in 25 % in one series and tactile (insects crawling over the skin) in another series (Le Ber et al. 2007; Beck et al. 2008). Psychotic features are also reported in *MAPT* carriers but appear to be less common (Saito et al. 2002; Spina et al. 2007). Nonfluent aphasia often accompanies the behavioral and personality deficits in *GRN* carriers but is rarely the predominant feature, and semantic dementia is very rare (Pickering-Brown et al. 2008). A dynamic aphasia has also been documented in a number of patients, characterized by a decreased output of speech without evidence of a motor speech disorder or agrammatism, resulting in mutism in a selection of patients (Beck et al. 2008).

Imaging in FTLD-17

Gray and white matter atrophy patterns can aid in the distinction between the genetic causes of FTLD-17 and may offer insight into the neural basis of symptomatology in these diseases. In brief, voxel-based morphometry (VBM) analyses have determined significant variations in the neuroimaging signatures of *GRN* and *MAPT* mutations. *GRN* mutation carriers have smaller brain volumes and tend to atrophy faster than *MAPT* carriers. The most striking difference is in the hemispheric asymmetry seen in *GRN* carriers compared to relatively symmetrical atrophy in *MAPT* carriers. As might be expected given the high prevalence of apraxia, *GRN* carriers tend to have an atrophy pattern involving the inferior parietal lobe as well as inferior frontal and temporal lobes. In contrast, *MAPT* carriers exhibit a symmetrical anteromedial temporal lobe and orbitofrontal atrophy with involvement of the fornix. Involvement of the long intrahemispheric association tracts has also been documented in those with *GRN* mutations (Rohrer et al. 2010a; Whitwell et al. 2012).

ALS, FTD, and Parkinsonism: *C9ORF72*

It is now clear that ALS overlaps considerably at a clinical, pathological, and genetic level with FTD to such an extent that the two disorders are considered to form a

continuum with pure ALS at one end of the spectrum and pure FTD (without ALS) at the other (Lillo and Hodges 2009), although most cases appear to fall somewhere in the middle with around 20 % of ALS cases also meeting criteria for FTD and a much greater proportion having subtle behavioral and/or cognitive changes (Strong 2008). The recent discovery of the *C9ORF72* genetic mutation has consolidated this concept (DeJesus-Hernandez et al. 2011; Renton et al. 2011) and extended this overlap to involve Parkinsonism. Parkinsonism has been reported in up to 30 % of patients with this mutation, although reports have varied between studies (Snowden et al. 2012; Boeve et al. 2012; Sha et al. 2012). The Parkinsonism mirrors that found in other inherited and sporadic cases of FTD with bilateral rigidity and bradykinesia without tremor. It has been proposed that intermediate numbers of repeat copies of the mutation confer a significant risk of developing Parkinson's disease (Nuytemans et al. 2013). The imaging finding in *C9ORF72* carriers are variable. A proportion present with frontal and temporal atrophy typically found in patients with FTD, while others have relatively normal MRI imaging. Atrophy of subcortical structures including the thalamus and cerebellum are emerging as a diagnostic marker of the *C9ORF72* mutation (Whitwell et al. 2012). A higher burden of TDP-43 pathology and neuronal cell death in the substantia nigra of mutation carriers compared to noncarriers may explain the increased incidence of parkinsonian features in this cohort (Cooper-Knock et al. 2013).

Perry Syndrome

Perry syndrome is a rare genetic disorder due to a *G71R* mutation in the *DCTN1* gene, characterized by Parkinsonism, hypoventilation, weight loss, depression, or psychiatric disease. In one published case, the patient exhibited slowing of vertical saccades and a marked behavioral disorder typical of bvFTD but without focal atrophy on MRI or convincing executive cognitive deficits (Newsway et al. 2010). This rare disorder is also linked to FTD, as TDP-43 pathology is common to both.

Dystonia and Myoclonus

Dystonia has been rarely reported in FTD, aside from a handful of instances where it has been linked with mutations in the *MAPT* and *GRN* gene. It has, however, been described in FTD patients treated with antipsychotic medications. All three patients in a case series of FTD patients treated with antipsychotic medications developed a tardive dystonia which manifested as an antecollis (Czarnecki et al. 2008). In another case series, up to 30 % of FTD patients developed extrapyramidal features when treated with antipsychotic medications (Pijnenburg et al. 2003). The dangers of such medication have been well documented in DLB and linked to dopaminergic dysfunction (Piggott et al. 1998). It seems logical then that a similar danger exists in FTD cohorts and accords well with the evidence for striatal dysfunction in FTD patients.

Similar to dystonia, myoclonus has been reported rarely and exclusively in cases of FTDP-17. In these cases, the myoclonus involved the upper extremities and was described as small, subtle, and action induced, without detectable activation with rest stimuli (Caviness and Wszolek 2002).

Apraxia

This section considers the literature on apraxia in FTD particularly in PNFA which, of the FTD syndromes, shows the greatest overlap with CBS at both a clinical and pathological level (Kertesz et al. 2005). Apraxia is a core component of CBS which must be present to make the diagnosis, and is common in PSP (Soliveri et al. 2005; Mathew et al. 2012). Patients with CBS also exhibit features of PNFA and/or behavioral abnormalities. This can make it very difficult to disentangle the literature on apraxia in FTD since many mixed cases are labeled as CBS rather than PNFA with apraxia (Sha et al. 2006).

While apraxia is considered common in PNFA, it has not been well characterized. Variations in the definition of apraxia and a lack of consensus regarding the underlying cortical circuitry involved have probably contributed to the dearth of studies on this topic. Up until 2003 case reports and case series described the presence of apraxia in PNFA (Kertesz et al. 1994; Karbe et al. 1993). Others reported an absence of apraxia in PNFA cases (Béland and Ska 1992; Craenhals et al. 1990). The first prospective case–control study documented some form of apraxia in 90 % of all PNFA subjects (Joshi et al. 2003): apraxia was present in 70 % for both pantomime and imitation gestures, while 20 % showed apraxia for imitation only. Unfortunately, this study had limitations: firstly, it is unclear how patients reaching criteria for CBS or PSP were excluded. Moreover, evaluation of orofacial apraxia and apraxia of speech (AOS) was not considered.

A comprehensive review of apraxia in 16 PNFA patients, using a standardized Apraxia Battery and incorporating VBM analyses, was reported by Rohrer et al. (2010b): three patients also had CBS and two PSP. Using a surrogate measure for AOS, they found that all patients had evidence of AOS. More recently it has been suggested that AOS can be the presenting sign of neurodegenerative disease in the absence of aphasia referred to as primary progressive AOS (PPAOS) (Josephs et al. 2012). Longitudinal studies are needed to determine if such cases evolve into a PNFA syndrome. In the Rohrer et al. cohort, orofacial apraxia was often associated with AOS and the neural basis for both localized to the left inferior frontal gyrus. Even after excluding patients with CBS and PSP over a quarter of PNFA, patients exhibited features of limb apraxia.

In *GRN* mutation carriers, estimates of the rate of apraxia range from 16 to 71 % in the bvFTD phenotype and 25–60 % in PNFA (Le Ber et al. 2007; Beck et al. 2008). Approximately 6 % of *GRN* carriers satisfy criteria for CBS with apraxia, asymmetric Parkinsonism, and rigidity (Le Ber et al. 2007; Pickering-Brown et al. 2008; Beck et al. 2008), while apraxia alone or in combination with CBS features is present in up to 50 %

of carriers. This likely reflects the parietal involvement seen in these cases. Apraxia is not a common feature of the *MAPT* or the *C9ORF72* mutation.

Future Directions

In summary, there has been great progress in our understanding of neurodegenerative diseases over recent years on clinical, genetic, and pathological levels. Overwhelming evidence for the overlap between FTD and movement disorders has been consistently noted. However, this brings a level of increasing complexity to diagnoses and raises questions regarding underlying pathological mechanisms in individual patients. As such, there remains much work to be done to determine biomarkers which accurately delineate the underlying pathology in individual patients and which in turn will inform future pharmacological interventions.

References

Baba Y, Tsuboi Y, Baker MC, Uitti RJ, Hutton ML, Dickson DW, et al. The effect of tau genotype on clinical features in FTDP-17. Parkinsonism Relat Disord. 2005;11(4):205–8.

Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature. 2006;442(7105):916–9.

Beck J, Rohrer JD, Campbell T, Isaacs A, Morrison KE, Goodall EF, et al. A distinct clinical, neuropsychological and radiological phenotype is associated with progranulin gene mutations in a large UK series. Brain. 2008;131(3):706–20.

Béland R, Ska B. Interaction between verbal and gestural language in progressive aphasia: a longitudinal case study. Brain Lang. 1992;43(3):355–85.

Boeve BF. Links between frontotemporal lobar degeneration, corticobasal degeneration, progressive supranuclear palsy, and amyotrophic lateral sclerosis. Alzheimer Dis Assoc Disord. 2007;21(4):S31–8. Epub 2007/12/20.

Boeve BF, Hutton M. Refining frontotemporal dementia with parkinsonism linked to chromosome 17: introducing FTDP-17 (MAPT) and FTDP-17 (PGRN). Arch Neurol. 2008;65(4):460–4. Epub 2008/04/17.

Boeve BF, Baker M, Dickson DW, Parisi JE, Giannini C, Josephs KA, et al. Frontotemporal dementia and parkinsonism associated with the IVS1+ 1G→A mutation in progranulin: a clinicopathologic study. Brain. 2006;129(11):3103–14.

Boeve BF, Boylan KB, Graff-Radford NR, DeJesus-Hernandez M, Knopman DS, Pedraza O, et al. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. Brain. 2012;135(Pt 3):765–83. Epub 2012/03/01.

Caviness JN, Wszolek ZK. Myoclonus in pallido-ponto-nigral degeneration. Adv Neurol. 2002;89:35–9.

Claassen DO, Parisi JE, Giannini C, Boeve BF, Dickson DW, Josephs KA. Frontotemporal dementia mimicking dementia with Lewy bodies. Cogn Behav Neurol. 2008;21(3):157–63.

Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. J Neurol Neurosurg Psychiatry. 1994;57(4):416–8.

Cooper-Knock J, Frolov A, Highley JR, Charlesworth G, Kirby J, Milano A, et al. C9ORF72 expansions, parkinsonism, and Parkinson disease: a clinicopathologic study. Neurology. 2013;81(9):808–11. Epub 2013/07/26.

Craenhals A, Raison-Van Ruymbeke A, Rectem D, Seron X, Laterre E. Is slowly progressive aphasia actually a new clinical entity? Aphasiology. 1990;4(5):485–509.
Cruts M, Gijselinck I, van der Zee J, Engelborghs S, Wils H, Pirici D, et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature. 2006;442(7105):920–4.
Czarnecki K, Kumar N, Josephs K. Parkinsonism and tardive antecollis in frontotemporal dementia–increased sensitivity to newer antipsychotics? Eur J Neurol. 2008;15(2):199–201.
Davies RR, Hodges JR, Kril JJ, Patterson K, Halliday GM, Xuereb JH. The pathological basis of semantic dementia. Brain. 2005;128(Pt 9):1984–95. Epub 2005/07/08.
DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011;72(2):245–56.
Diehl-Schmid J, Schulte-Overberg J, Hartmann J, Forstl H, Kurz A, Haussermann P. Extrapyramidal signs, primitive reflexes and incontinence in fronto-temporal dementia. Eur J Neurol. 2007; 14(8):860–4.
Espay AJ, Litvan I. Parkinsonism and frontotemporal dementia: the clinical overlap. J Mol Neurosci. 2011;45(3):343–9. Epub 2011/09/06.
Evans JJ, Heggs AJ, Antoun N, Hodges JR. Progressive prosopagnosia associated with selective right temporal lobe atrophy. A new syndrome? Brain. 1995;118(Pt 1):1–13.
Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, et al. Frontotemporal dementia: clinicopathological correlations. Ann Neurol. 2006;59(6):952–62.
Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ, Gilman S. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Conference participants. Ann Neurol. 1997;41(6):706–15.
Gass J, Cannon A, Mackenzie IR, Boeve B, Baker M, Adamson J, et al. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. Hum Mol Genet. 2006;15(20):2988–3001.
Goldman JS, Farmer JM, Wood EM, Johnson JK, Boxer A, Neuhaus J, et al. Comparison of family histories in FTLD subtypes and related tauopathies. Neurology. 2005;65(11):1817–9.
Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76(11):1006–14. Epub 2011/02/18.
Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain. 1992;115(Pt 6):1783–806.
Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, et al. Clinicopathological correlates in frontotemporal dementia. Ann Neurol. 2004;56(3):399–406.
Hornberger M, Piguet O, Graham AJ, Nestor PJ, Hodges JR. How preserved is episodic memory in behavioral variant frontotemporal dementia? Neurology. 2010;74(6):472–9. Epub 2010/02/10.
Houlden H, Baker M, Adamson J, Grover A, Waring S, Dickson D, et al. Frequency of tau mutations in three series of non-Alzheimer's degenerative dementia. Annals of neurology. 1999;46(2):243–8.
Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, et al. Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. Nature. 1998;393(6686):702–5. Epub 1998/06/26.
Janssen JC, Warrington EK, Morris HR, Lantos P, Brown J, Revesz T, et al. Clinical features of frontotemporal dementia due to the intronic tau 10(+16) mutation. Neurology. 2002;58(8):1161–8. Epub 2002/04/24.
Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, Master AV, et al. Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech. Brain. 2012;135(5):1522–36.
Joshi A, Roy EA, Black SE, Barbour K. Patterns of limb apraxia in primary progressive aphasia. Brain Cogn. 2003;53(2):403–7.
Karbe H, Kertesz A, Polk M. Profiles of language impairment in primary progressive aphasia. Arch Neurol. 1993;50(2):193.
Kertesz A, Hudson L, Mackenzie IR, Munoz DG. The pathology and nosology of primary progressive aphasia. Neurology. 1994;44(11):2065.

Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. Brain. 2005;128(Pt 9):1996–2005.

Kodama K, Okada S, Iseki E, Kowalska A, Tabira T, Hosoi N, et al. Familial frontotemporal dementia with a P301L tau mutation in Japan. J Neurol Sci. 2000;176(1):57–64. Epub 2000/06/24.

Le Ber I, Van Der Zee J, Hannequin D, Gijselinck I, Campion D, Puel M, et al. Progranulin null mutations in both sporadic and familial frontotemporal dementia. Hum Mutat. 2007;28(9):846–55.

Lendon CL, Lynch T, Norton J, McKeel Jr DW, Busfield F, Craddock N, et al. Hereditary dysphasic disinhibition dementia: a frontotemporal dementia linked to 17q21-22. Neurology. 1998;50(6):1546–55.

Lillo P, Hodges JR. Frontotemporal dementia and motor neurone disease: overlapping clinicopathological disorders. J Clin Neurosci. 2009;16(9):1131–5.

Mann DM, South PW, Snowden JS, Neary D. Dementia of frontal lobe type: neuropathology and immunohistochemistry. J Neurol Neurosurg Psychiatry. 1993;56(6):605–14.

Mathew R, Bak TH, Hodges JR. Diagnostic criteria for corticobasal syndrome: a comparative study. J Neurol Neurosurg Psychiatry. 2012;83(4):405–10.

Mioshi E, Bristow M, Cook R, Hodges JR. Factors underlying caregiver stress in frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord. 2009;27(1):76–81. Epub 2009/01/22.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 1998;51(6):1546–54.

Newsway V, Fish M, Rohrer JD, Majounie E, Williams N, Hack M, et al. Perry syndrome due to the DCTN1 G71R mutation: a distinctive levodopa responsive disorder with behavioral syndrome, vertical gaze palsy, and respiratory failure. Mov Disord. 2010;25(6):767–70.

Nuytemans K, Bademci G, Kohli MM, Beecham GW, Wang L, Young JI, et al. C9ORF72 intermediate repeat copies are a significant risk factor for Parkinson disease. Ann Hum Genet. 2013;77(5):351–63.

Onari KSH. Anatomishe Beitrage zur Lehre von der Pickschen umschriebenen Grosshirnrinden-Atrophie ('Picksche Krankheit'). Z Gesamte Neurol Psych. 1926;101:470–511.

Padovani A, Agosti C, Premi E, Bellelli G, Borroni B. Extrapyramidal symptoms in frontotemporal dementia: prevalence and clinical correlations. Neurosci Lett. 2007;422(1):39–42.

Pickering-Brown SM, Rollinson S, Du Plessis D, Morrison KE, Varma A, Richardson AM, et al. Frequency and clinical characteristics of progranulin mutation carriers in the Manchester frontotemporal lobar degeneration cohort: comparison with patients with MAPT and no known mutations. Brain. 2008;131(Pt 3):721–31.

Piggott MA, Perry EK, Marshall EF, McKeith IG, Johnson M, Melrose HL, et al. Nigrostriatal dopaminergic activities in dementia with Lewy bodies in relation to neuroleptic sensitivity: comparisons with Parkinson's disease. Biol Psychiatry. 1998;44(8):765–74.

Piguet O, Brooks WS, Halliday GM, Schofield PR, Stanford PM, Kwok JB, et al. Similar early clinical presentations in familial and non-familial frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2004;75(12):1743–5. Epub 2004/11/19.

Pijnenburg Y, Sampson E, Harvey R, Fox N, Rossor M. Vulnerability to neuroleptic side effects in frontotemporal lobar degeneration. Int J Geriatr Psychiatry. 2003;18(1):67–72.

Poorkaj P, Grossman M, Steinbart E, Payami H, Sadovnick A, Nochlin D, et al. Frequency of tau gene mutations in familial and sporadic cases of non-Alzheimer dementia. Arch Neurol. 2001;58(3):383–7.

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134(Pt 9):2456–77. Epub 2011/08/04.

Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. Neurology. 2002;58(11):1615–21. Epub 2002/06/12.

Reed LA, Wszolek ZK, Hutton M. Phenotypic correlations in FTDP-17. Neurobiol Aging. 2001;22(1):89–107. Epub 2001/02/13.

Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011;72(2):257–68.

Rinne JO, Laine M, Kaasinen V, Norvasuo-Heila MK, Nagren K, Helenius H. Striatal dopamine transporter and extrapyramidal symptoms in frontotemporal dementia. Neurology. 2002;58(10): 1489–93.

Rohrer JD, Ridgway GR, Modat M, Ourselin S, Mead S, Fox NC, et al. Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by progranulin and tau mutations. Neuroimage. 2010a;53(3):1070–6.

Rohrer JD, Rossor MN, Warren JD. Apraxia in progressive nonfluent aphasia. J Neurol. 2010b; 257(4):569–74.

Rosso SM, Donker Kaat L, Baks T, Joosse M, de Koning I, Pijnenburg Y, et al. Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. Brain. 2003;126(Pt 9):2016–22.

Saito Y, Geyer A, Sasaki R, Kuzuhara S, Nanba E, Miyasaka T, et al. Early-onset, rapidly progressive familial tauopathy with R406W mutation. Neurology. 2002;58(5):811–3.

Schroeter ML, Raczka K, Neumann J, von Cramon DY. Neural networks in frontotemporal dementia–a meta-analysis. Neurobiol Aging. 2008;29(3):418–26.

Seelaar H, Schelhaas HJ, Azmani A, Küsters B, Rosso S, Majoor-Krakauer D, et al. TDP-43 pathology in familial frontotemporal dementia and motor neuron disease without progranulin mutations. Brain. 2007;130(5):1375–85.

Sha S, Hou C, Viskontas IV, Miller BL. Are frontotemporal lobar degeneration, progressive supranuclear palsy and corticobasal degeneration distinct diseases? Nat Clin Pract Neurol. 2006;2(12):658–65. Epub 2006/11/23.

Sha SJ, Takada LT, Rankin KP, Yokoyama JS, Rutherford NJ, Fong JC, et al. Frontotemporal dementia due to C9ORF72 mutations: clinical and imaging features. Neurology. 2012;79(10): 1002–11. Epub 2012/08/10.

Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, et al. Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. Brain. 2012;135(Pt 3):693–708. Epub 2012/02/04.

Soliveri P, Piacentini S, Girotti F. Limb apraxia in corticobasal degeneration and progressive supranuclear palsy. Neurology. 2005;64(3):448–53.

Spina S, Murrell JR, Yoshida H, Ghetti B, Bermingham N, Sweeney B, et al. The novel Tau mutation G335S: clinical, neuropathological and molecular characterization. Acta Neuropathol. 2007;113(4):461–70.

Stanford PM, Halliday GM, Brooks WS, Kwok JB, Storey CE, Creasey H, et al. Progressive supranuclear palsy pathology caused by a novel silent mutation in exon 10 of the tau gene: expansion of the disease phenotype caused by tau gene mutations. Brain. 2000;123(Pt 5):880–93. Epub 2000/04/25.

Stanford PM, Brooks WS, Teber ET, Hallupp M, McLean C, Halliday GM, et al. Frequency of tau mutations in familial and sporadic frontotemporal dementia and other tauopathies. J Neurol. 2004;251(9):1098–104.

Strong MJ. The syndromes of frontotemporal dysfunction in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2008;9(6):323–38.

Tsuboi Y. Neuropathology of familial tauopathy. Neuropathology. 2006;26(5):471–4. Epub 2006/11/04.

Tsuboi Y, Baker M, Hutton ML, Uitti RJ, Rascol O, Delisle MB, et al. Clinical and genetic studies of families with the tau N279K mutation (FTDP-17). Neurology. 2002;59(11):1791–3. Epub 2002/12/11.

Van Swieten JC, Heutink P. Mutations in progranulin (GRN) within the spectrum of clinical and pathological phenotypes of frontotemporal dementia. Lancet Neurol. 2008;7(10):965–74.

Van Swieten J, Stevens M, Rosso S, Rizzu P, Joosse M, De Koning I, et al. Phenotypic variation in hereditary frontotemporal dementia with tau mutations. Ann Neurol. 1999;46(4):617–26.

Whitwell JL, Weigand SD, Boeve BF, Senjem ML, Gunter JL, DeJesus-Hernandez M, et al. Neuroimaging signatures of frontotemporal dementia genetics: C9ORF72, tau, progranulin and sporadics. Brain. 2012;135(Pt 3):794–806. Epub 2012/03/01.

Wszolek ZK, Uitti RJ, Hutton M. A mutation in the microtubule-associated protein tau in pallido-nigro-luysian degeneration. Neurology. 2000;54(10):2028–30. Epub 2000/05/24.

Chapter 10
Dementia with Lewy Bodies

Anne-Catherine Vijverman, Carmela Tartaglia, and Susan Fox

Abstract DLB is a progressive multisystem neurodegenerative disorder with widespread alpha-synuclein (αSyn) deposits in the central and peripheral nervous system as well as within the autonomic nervous system. In addition to dementia, its distinctive clinical features are visual hallucinations, parkinsonism, cognitive fluctuations, dysautonomia, sleep disorders, and neuroleptic sensitivity. The disease has an insidious onset and progresses to death with variable disease duration of on average 6.4 years. "Dementia with Lewy bodies" (DLB) is the clinical syndrome and "Lewy body disease" (LBD) refers to the pathological disease. The neuropathological hallmark of LBD is the presence of αSyn-positive neuronal inclusions in the form of Lewy bodies and Lewy neuritis. Neurochemically, DLB is associated with alterations in several neurotransmitter systems, the main changes occurring in the cholinergic, dopaminergic, and serotoninergic systems.

Currently no disease-modifying therapy is available, and management is therefore focused on symptomatic relief, but the combination of extrapyramidal symptoms, neuropsychiatric symptoms, and neuroleptic sensitivity makes the pharmacological treatment of DLB challenging. The mainstay of treatment includes levodopa for the parkinsonism and cholinesterase inhibitors for the cognitive deficits. Non-pharmacological, behavioral strategies aimed at modifying stressors in the environment should be employed whenever possible.

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Abbreviations

5-HT	Serotonin (5-hydroxytryptamine)
AD	Alzheimer's disease
ApoE4	Apolipoprotein E ε 4 allele
$A\beta_{42}$	Amyloid β
CSF	Cerebrospinal fluid
DaTSCAN	Dopamine transporter SPECT
DLB	Dementia with Lewy bodies
EEG	Electroencephalography
EPS	Extrapyramidal signs
GBA1	Glucocerebrosidase gene
LB	Lewy bodies
LBD	Lewy body disease
LN	Lewy neurites
MIBG	^{123}*I-meta*-iodobenzylguanidine
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
NFT	Neurofibrillary tangle
PD	Parkinson's disease
PDD	Parkinson's disease with dementia
PET	Positron-emission tomography
PIB-PET	^{11}C-Pittsburgh compound B-PET
PIGD	Postural instability and gait difficulties
RBD	REM sleep behavior disorder
REM	Rapid eye movement
sCJD	Sporadic Creutzfeldt-Jakob disease
SP	Senile Plaque
SPECT	Single photon emission computerized tomography
SSRI's	Selective serotonin reuptake inhibitors
TD	Tremor dominant
VH	Visual hallucinations
αSyn	alpha-synuclein
τ	Total tau

Introduction

Dementia with Lewy bodies (DLB) is a clinical syndrome characterized by slowly progressive cognitive, neuropsychiatric, and motor decline. Frederick Lewy was the first to report abnormal intracytoplasmic protein deposits in a patient with Parkinson's disease

(PD) in 1912, later called "Lewy body inclusions." The relationship between the neuropathological finding of cortical Lewy bodies (LBs) and dementia was described almost 40 years later by Okazaki et al. (1961), while it was not until 1984 that Kosaka et al. first used the term "diffuse Lewy body disease" to describe a new disease entity consisting of presenile dementia with presence of cortical LBs (Huang and Halliday 2013). Since then, confusion has arisen as many different names have been used to describe this disorder, including diffuse Lewy body disease, Lewy body dementia, senile dementia of Lewy body type, dementia with Lewy bodies, Lewy body variant of Alzheimer's disease, dementia associated with cortical Lewy bodies, and Lewy body disease. In this chapter, we will use the term "dementia with Lewy bodies" when describing the clinical syndrome and "Lewy body disease" (LBD) when referring to the pathological disease. This is in agreement with the 1996 consortium workshop on DLB that published the first clinical and pathological diagnostic criteria (McKeith et al. 1996). The criteria were revised in 1999 and 2005, with further clinicopathological correlation studies demonstrating a need for refinement due to a low sensitivity – though high specificity – of the previous diagnostic consensus criteria (McKeith et al. 2005). Following the criteria of 2005, a definite diagnosis is reserved for cases with pathological confirmation, whereas possible and probable DLB are diagnosed in vivo.

DLB shows significant clinical and pathological overlap with other neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease with dementia (PDD). In particular, DLB and PDD are likely the same disorder but with variable clinical presentation. Many patients with DLB and PDD will have Alzheimer pathological changes at postmortem, thus adding to the clinicopathological confusion.

Epidemiology

An estimate of 26 % of dementia in the elderly (>75 years) is caused by DLB, thereby making it the second leading cause of neurodegenerative dementia in the elderly after AD (77 %) (Costa et al. 2003; Zaccai et al. 2005; Parkkinen et al. 2001; Barker et al. 2002) and more prevalent than vascular dementia (18 %) and frontotemporal dementia (5 %) (Barker et al. 2002). The frequency of postmortem diagnosis of LBD is 28 % in patients <60 years of age and only 18 % in 80+ patients (Barker et al. 2002). There is a greater frequency of LBD among males <70 years of age (38 % versus 24 %) but not among older subjects (Barker et al. 2002). The disease has an insidious onset with a more rapid progression than idiopathic PD, the mean disease course from symptom onset until death is 5–8 years (average 6.4 years) (Williams et al. 2006). Rarely it can present with a more rapid progression, death occurring less than 2 years after the first symptom, thereby mimicking other dementias such as sporadic Creutzfeldt-Jakob disease (sCJD) (Haik et al. 2000; Tartaglia et al. 2012).

Clinical Features

DLB is a progressive multisystem neurodegenerative disorder with central, peripheral, and autonomic nervous system involvement. According to the revised

Table 10.1 Clinical consensus criteria for the diagnosis of dementia with Lewy bodies (McKeith et al. 2005)

Clinical features
Central feature: dementia
Core features
Spontaneous parkinsonian motor signs
Visual hallucinations
Fluctuations with pronounced variations in attention and alertness
Suggestive features
REM sleep behavior disorder
Severe neuroleptic sensitivity
Low dopamine transporter uptake in basal ganglia on SPECT/PET imaging
Supportive features
Repeated falls and syncope
Transient, unexplained loss of consciousness
Severe autonomic dysfunction (orthostatic hypotension, urinary incontinence)
Hallucinations in other modalities
Systematized delusions
Depression
Relative preservation of medial temporal lobe structures on CT/MRI scan
Generalized low uptake and reduced occipital activity on SPECT/PET
Abnormal (low uptake) MIBG myocardial scintigraphy
Prominent slow wave activity and temporal lobe transient sharp waves on EEG
Clinical Diagnosis
Definite DLB: neuropathological confirmation of LBD
Probable DLB
Dementia + 2/3 core features
or
Dementia + 1 core feature + 1 suggestive feature
Possible DLB
Dementia + 1 core feature
or
Dementia + ≥1 suggestive feature

REM rapid eye movements, *SPECT* single-photon emission computerized tomography, *PET* positron-emission tomography, *MRI* magnetic resonance imaging, *CT* computerized tomography, *MIBG* ^{123}I-metaiodobenzylguanidine, *EEG* electroencephalography, *DLB* dementia with Lewy bodies, *LBD* Lewy body disease

diagnostic criteria (McKeith et al. 2005) (Table 10.1), the key feature of DLB is dementia, defined by a cognitive decline substantial enough to interfere with activities of daily living. The core features of DLB are cognitive fluctuations, visual hallucinations, and spontaneous parkinsonism. Supportive features are REM sleep behavior disorders (RBD), severe neuroleptic sensitivity, and low dopamine transporter uptake in basal ganglia on single-photon emission computerized tomography (SPECT) or on positron-emission tomography (PET). Additional suggestive symptoms are frequently associated with DLB, although aspecific, and are therefore not part of the diagnostic criteria.

Motor Manifestations

Spontaneous parkinsonism that is not drug induced is a core feature in the clinical diagnosis of DLB. Symptoms occur with ~50 % loss of nigrostriatal dopaminergic neurons (Fearnley and Lees 1991) and are described in up to 50 % of patients with DLB at diagnosis (McKeith et al. 2004). The parkinsonian features in DLB (Table 10.2) are more symmetric at onset when compared to the unilateral onset seen in idiopathic PD (Gnanalingham et al. 1997; Del Ser et al. 2000). The axial bradykinetic-rigid subtype, with postural instability and gait difficulties (PIGD), is encountered more frequently than the tremor-dominant (TD) subtype (McKeith et al. 1996; Galasko et al. 1996; Jankovic et al. 1990). Burn et al. found in a cross-sectional study of 107 patients that 69 % of DLB patients present the PIGD subtype as opposed to 38 % in PD, where the tremor-dominant (TD) subtype is much more prevalent (Burn et al. 2003).

Extrapyramidal signs and symptoms (EPS) may also occur in later stages of AD (Lopez et al. 1997). Although not clinicopathologically correlated, Kaur et al. analyzed data from the US National Alzheimer's Coordinating Center (Kaur et al. 2013) of 1,826 patients with AD and 130 patients with DLB, characterizing EPS in both diseases (Table 10.2). Hypomimia and hypophonia occurred in 4.2 % of the AD group as opposed to more than 48 % in DLB. Likewise, bradykinesia, rigidity, impaired posture, and postural instability were significantly more prevalent in DLB when compared to AD (55 % versus 19.3 %). The prevalence of tremor was also significantly higher in DLB than in AD, 13.9 % versus 3.2 % respectively for resting tremor in DLB and AD and 12.3 % versus 6.2 % for action/postural tremor.

Myoclonus is a common sign of many dementias. Up to 35 % of patients with DLB will develop myoclonus (Tartaglia et al. 2012), predominantly occurring in upper limbs, induced by action and posture but seldom observed in the resting position (Weiner and Tolosa 2011). It has clinical and electrophysiological characteristics of cortical myoclonus (Weiner and Tolosa 2011). When associated with rapid cognitive decline and hallucinations, the Heidenhain variant of sCJD may need to be considered. Distinguishing diagnostic features in DLB are absence of cortical ribonning on brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) 14-3-3 negativity, and less common periodic electroencephalographic (EEG) changes (Tartaglia et al. 2012).

Non-motor Manifestations

Cognitive Manifestations

The key clinical feature of DLB is cognitive impairment sufficient to be defined as dementia. Dementia in DLB is characterized by more severe visuospatial, attentional, and executive dysfunctions compared to relative preservation of memory (Mosimann et al. 2004). The visuospatial and visuoconstructive decline in DLB are

Table 10.2 Clinical differential diagnosis of DLB, AD, PD, and PDD

	DLB	AD	PD	PDD
Extrapyramidal symptoms	Often more symmetric	Rare, usually mild in late stages	Initially often asymmetric	Initially often asymmetric
PIGD subtype[a]	69 %	–	38 %	88 %
TD subtype[a]	31 %	–	62 %	12 %
Hypomimia[b]	48.5 %	4.2 %		
Hypophonia[b]	30.8 %	3.4 %		
Rigidity[b]	44.6 %	9.8 %		
Impaired posture/gait[b]	43.1 %	14.2 %		
Bradykinesia[b]	55.4 %	19.3 %		
Impaired chair rise[b]	28.9 %	15.4 %		
Postural instability[b]	26.2 %	12.5 %		
Resting tremor[b]	13.9 %	3.2 %		
Action/postural tremor[b]	12.3 %	6.2 %		
Cognitive impairment	Early disturbances in attention and visuoperceptive functions	Early impairment of declarative memory and attention	Impaired executive and visuoperceptive functions	Impaired executive and visuoperceptive functions
Fluctuations in cognition	Prominent, early second to hourly variations	Moderate day to day variations	Mild day to day variations	Mild day to day variations
Neuropsychiatric symptoms				
Visual hallucinations	Typical, early, and persistent	Sometimes, late course	Often present with anticholinergic dopaminergic drugs	Often present with anticholinergic dopaminergic drugs
Delusions	Typical	Usually present	Present	Present
Depression	Usually present	Usually present	Usually present	Usually present

DLB Dementia with Lewy bodies, *AD* Alzheimer's Disease, *PD* Parkinson's Disease, *PDD* Parkinson's Disease with dementia, *PIGD* Postural instability and gait difficulties, *TD* tremor dominant

[a]Prevalence in cross-sectional study of Burn et al. (2003)

[b]Prevalence in cross-sectional study of Kaur et al. (2013)

striking, so that even with mild cognitive impairment patients seem to be unable to draw a clock, to copy overlocking pentagons, or to navigate (Cormack et al. 2004). This neuropsychological finding sometimes allows discrimination with AD, certainly in the early stages (Yoshizawa et al. 2013). Language is relatively preserved, although dysprosody is often seen. Dementia characteristics of DLB and PDD are very similar, and the distinction is mainly made based on the arbitrary 1-year rule (McKeith et al. 1996). By definition, patients developing dementia prior to parkinsonism or during the first year of disease are diagnosed with DLB. In PDD, the onset of motor symptoms precedes dementia by at least 1 year, generally occurring only later in the disease course, but encountered in up to 80 % of all PD patients during the course of their disease (Aarsland et al. 2003).

Fluctuations in attention and alertness are considered part of DLB's core features according to the diagnostic consensus criteria (McKeith et al. 2005). As opposed to AD, the transient fluctuating episodes last seconds to hours and may consist of staring spells, confusion, episodes of decreased attention, or disorganized speech with sometimes a confabulatory or delusional quality. The level of cognition returns to near normal after those spontaneous fluctuations in awareness that are generally not triggered by discernible environmental factors. EEG shows variability in theta rhythm during the spells (Yamamoto and Imai 1988; Doran and Larner 2004). There can also be a loss of alpha activity and occurrence of slow wave transient activity in the temporal lobes (Briel et al. 1999). In AD, fluctuations also are a common feature, although less prevalent, and they consist of more daily variations.

Neuropsychiatric Manifestations

Visual hallucinations (VH), misperceptions, and mood alterations are some of the frequently encountered neuropsychiatric manifestations of DLB. Spontaneous VH are a core feature of DLB, often present early in the disease, recurring daily and lasting minutes at a time (Mosimann et al. 2006). The phenomenology of the VH is typically of 3-dimensional, detailed mute animate subjects in the central field of vision, similar as in PDD, although dopaminergic medications are frequently the trigger in the latter. Auditory and tactile hallucinations are much less common but can occur. In both DLB and PDD, medical causes of delirium should always be excluded as a trigger. The VH in DLB might be related to alterations in cortical acetylcholine together with abnormalities in brainstem and visual systems (Collerton et al. 2005). This is corroborated by the reduction of visual hallucinations that occurs in DLB when cholinesterase inhibitors (AChI) are started (Barber et al. 2000; Burn et al. 2006). It remains unclear if there is a relationship between the occurrence of visual hallucinations and the occipital hypometabolism found in DLB (Imamura et al. 1999).

Misperceptions, characterized by seeing existing objects as animate subjects, are frequently encountered as well. Other psychotic symptoms may occur in DLB, including paranoid delusions, often of spouse infidelity and fear of strangers in the

home. Common mood alterations in DLB include depression and anxiety, although not specific for DLB (Borroni et al. 2008).

Hypersensitivity to Neuroleptics

Neuroleptics are often used in behavioral and psychological symptoms of dementia. However, due to their dopamine-blocking character, these agents cause or worsen motor complications and sedation. Increased rigidity, postural falls, immobility, confusion, pronounced sedation (with rare coma or death), and a three-fold increased mortality risk are reported side effects from neuroleptics in DLB, even when used in very small amounts (McKeith et al. 1992; Byrne et al. 1992). Such side effects occur more commonly with so-called typical neuroleptics (McKeith et al. 1992; Byrne et al. 1992) but are also seen with atypical neuroleptics. About 50 % of patients treated with neuroleptics will develop severe side effects. If absolutely required, atypical neuroleptics should be used, although increased sensitivity to these newer drugs has also been seen (Friedman and Fernandez 2002). Neuroleptic sensitivity might be due to a failure of upregulation of dopamine D2 receptors in the striatum (Piggott et al. 1998) and to dopaminergic hypoactivity in DLB (Nishijima and Ishiguro 1989; Sechi et al. 1996).

Autonomic Manifestations

Autonomic postganglionic neurons are probably one of the earliest regions affected by LB pathology, but autonomic failure doesn't occur within the first year of disease (Wenning et al. 1999). Urinary incontinence and orthostatic hypotension are the most common symptoms, but adrenergic dysfunction (an impaired pressor response to acute sympathetic stimulation in physical stress), distal anhidrosis, and urinary urgency or retention are also frequently seen. Dopaminergic agents can exacerbate signs and symptoms of postural hypotension and should be stopped unless providing a significant benefit.

Sleep

As in other synucleinopathies, REM sleep behavior disorders (RBD) are a frequent finding in DLB. In RBD, muscle atonia during the REM phase of sleep is lost, resulting in complex motor activity that makes patients act out their dreams during sleep (Schenck et al. 1986). The underling mechanism appears to be early Lewy body pathology in the pedunculopontine nucleus and locus coeruleus together with resulting cholinergic (and less important noradrenergic) deficits (Boeve et al. 2004). Presence of RBD can precede neurodegenerative disease manifestations by up to 20 years (Schenck et al. 1986; Tan et al. 1996; Ferman et al. 1999; Postuma et al. 2013), with up to 50 % of RBD patients developing one of the neurodegenerative synucleinopathies (Boeve et al. 2007).

Etiology and Genetics

Although DLB is generally considered a sporadic disease, Mendelian inheritance has been shown in families presenting with variable degrees of dementia and parkinsonism (Bogaerts et al. 2007). PD is associated with several genetic mutations following an either autosomal dominant or autosomal recessive inheritance pattern. Many such individuals with monogenic parkinsonism may develop dementia, and some genetic mutations appear to have a higher prevalence of dementia as part of the phenotype, in particular αSyn. Genetic links to DLB are less well described, but as with idiopathic PD, both environmental and genetic factors are likely playing a role in the pathogenesis of this disease, since monozygotic twins do not present the same incidence of DLB (Wang et al. 2009).

Duplications (Chartier-Harlin et al. 2004) and triplications (Singleton et al. 2003) of the αSyn gene are associated with rare kindreds of DLB families, but there is clinical heterogeneity within the families, ranging from DLB to PD or PDD (Bogaerts et al. 2007). A genetic defect at the 2q35-q36 locus on chromosome 2 was identified in two families with autosomal dominant inheritance, but the gene linked to this locus is not yet found (Bogaerts et al. 2007), and the mutation is most likely more complex than in monogenic disorders (Meeus et al. 2012).

Mutations in amyloid precursor proteins, presenilin 1 and presenilin 2, were linked to monogenic Alzheimer's dementia with variable degree of concomitant amyloid and LB pathology, the phenotype varying along the spectrum of AD and DLB (Meeus et al. 2012).

Genetic risk factors have been found to increase DLB susceptibility. Mutations in the glucocerebrosidase gene (GBA1) appear to be associated with synucleinopathies, with the highest prevalence of these mutations in DLB, followed by PD and multiple system atrophy (MSA), but not seen in normal controls (Mata et al. 2008; Nalls et al. 2013). Several hypotheses have been proposed to explain the link between GBA1 and synucleinopathies, but the association still remains incompletely understood. One of the possible underlying mechanisms is impairment of lysosomal degradation of αSyn due to deficient or mutant glucocerebrosidase (Sidransky and Lopez 2012). Earlier disease onset, more associated cognitive changes and a higher disease severity were noted in both DLB and PD GBA1 mutation carriers compared to noncarriers with parkinsonism (Nalls et al. 2013; Sidransky and Lopez 2012).

Apolipoprotein E ε4 allele (ApoE4), a well-known risk factor for AD (Schellenberg et al. 1987), has also been associated with DLB, including in pure DLB, where there are little or no Alzheimer's disease-like pathological changes in the brain. This suggests that the neurodegeneration associated with ApoE4 is related to a different process than the previously thought beta-amyloid processing (Tsuang et al. 2013).

Pathophysiology

The pathophysiology of DLB involves progressive structural and neurochemical changes in various parts of the nervous system.

Structural Neuropathological Changes

The neuropathological hallmark of LBD is the presence of αSyn-positive neuronal inclusions in the form of Lewy bodies and Lewy neuritis (LN). They consist of pathological presynaptic αSyn aggregates caused by altered αSyn processing, but they are not specific to synucleinopathies. Up to 10 % of normally aging elderly present αSyn pathology at autopsy (Bennett et al. 2006). Also, in 20 % of the dementia population, LBs are found in limbic or cortical regions. Even though there is a (weak) direct relation between the quantity of LBs and likelihood of developing DLB, it is the pattern of LB involvement that is most important in the pathological diagnosis of DLB (McKeith et al. 2005). With brainstem-dominant LBD, there is a low likelihood of developing the clinical DLB syndrome, whereas the likelihood is much higher with neocortical and limbic Lewy pathology (McKeith et al. 2005), since neocortical LBs are not seen in normal aging brains (Perry et al. 1990a).

In early DLB, αSyn-positive inclusions are already found in both brainstem and cortex, whereas in PD there is an ascending progression, from medullary and olfactory nuclei initially to the cortex in later stages. Braak's six-stage system for PD (Braak et al. 2003) divided this caudo-rostral progression into six stages with clinical correlate: stage 1 and 2 correspond to premotor PD, stage 3 and 4 are clinically linked to motor signs in PD, and the last stages are related to combined motor and cognitive impairment (Braak et al. 2003).

The microscopic identification of LBs is now easier due to more sensitive neuropathological detection tools, αSyn-staining allowing the most reliable detection (McKeith et al. 2005). Hematoxylin and eosin staining are only capable of adequately identifying brainstem LBs, often underappreciating cortical LBs and missing LNs (McKeith et al. 2005). Ubiquitin immunohistochemistry has a higher sensitivity for LBs and LNs but is not very specific, since neurofibrillary tangles (NFTs) also contain ubiquitin.

LBs are localized in the neuronal cytoplasm and have a spherical eosinophilic appearance. Although the primary constituent is αSyn in both brainstem and cortical LBs, brainstem LBs have a different microscopic appearance than cortical LBs, the former being intensely eosinophilic and surrounded by a clear halo and the latter being less eosinophilic and lacking the halo (McKeith et al. 2005).

Simultaneous with Lewy body pathology, autopsy of DLB patients reveals a considerable amount of coexisting AD pathology, namely, amyloid-containing senile plaques (SPs) and NFTs. A lower AD pathology burden is associated with a higher diagnostic accuracy for DLB: a high neocortical neurofibrillary tangle burden mitigates against the diagnosis of DLB, even in the presence of cortical LBs (McKeith et al. 2005). Again the pattern of amyloid involvement is the most important in distinguishing DLB from AD, with less hippocampal involvement and more paralimbic involvement in DLB compared to AD (McKeith et al. 2005).

Coexisting vascular pathology may also contribute to cognitive impairment in patients with any type of dementia, including DLB. The pathological characterization of DLB versus PDD has been confusing due to variability in pathological series

published to date. Such differences arise from variable referral bases, e.g., nursing homes versus community-based referrals. Thus, there still remains controversy around the pathological phenotype of dementias in parkinsonian syndromes.

Neurochemical Changes

DLB is associated with alterations in several neurotransmitter systems including cholinergic, dopaminergic, and serotoninergic, accounting for many of the clinical features that can occur in the absence of significant brain atrophy.

Striatal dopamine transporter deficiencies contribute to the EPS in DLB (McKeith et al. 2005), but in contrast with PD, there is simultaneous reduction in striatal D2 receptors (Duda 2004). Also, the PIGD subtype, encountered more frequently in DLB, is thought to be rather a non-dopaminergic motor manifestation linked to cholinergic deficits, as opposed to the TD subtype that is mainly of dopaminergic origin (Jankovic et al. 1990). That is why the overall response to levodopa treatment is lower in DLB compared to PD (Jankovic et al. 1990).

Acetylcholinergic deficits in DLB (Perry et al. 1990a, b, 1994; Shiozaki et al. 1999), resulting in cognitive and neuropsychiatric symptoms, are due to a reduction in activity of choline acetyltransferase and to a loss of cholinergic neurons (Perry et al. 1994; Francis and Perry 2007) with preservation of muscarinic receptor activity (Shiozaki et al. 1999). This cholinergic deficit is more pronounced in DLB compared to AD (Perry et al. 1990b), explaining greater benefits from cholinergic pharmacological therapy in DLB (Querfurth et al. 2000; Samuel et al. 2000; McKeith et al. 2000). An imbalance in cholinergic and dopaminergic activity may exacerbate or precipitate hallucinations (Duda 2004).

Serotonin (5-HT) has long been recognized to play a central role in neuropsychiatric symptoms like depression and psychosis (Puzynski and Jakomow 1975). A reduction of 5-HT levels in the striatum, neocortex, and frontal cortex (Scatton et al. 1983) was reported together with a loss of 5-HT neurons (Halliday et al. 1990) in the dorsal raphe nucleus. There is also an increase in inhibitory 5-HT1a receptors on pyramidal neurons of the cortex (Francis and Perry 2007).

Diagnostic Tests

There are no objective diagnostic tests available to confirm the clinical diagnosis of DLB. Currently, the diagnosis is based on clinical assessment and examination in vivo. Some imaging modalities may assist in the differentiation from other dementia or parkinsonian syndromes.

Brain MRI, for example, does not show any DLB-specific structural findings, but the degree of medial temporal lobe atrophy and hippocampal atrophy is less pronounced than in AD on volumetric MRI measures (Barber et al. 2000). Also, MRI

is useful in excluding any significant structural changes, such as hydrocephalus or space-occupying lesions.

Functional imaging of the brain, and the nigrostriatal pathways more specifically, can be obtained by PET or SPECT. However, in many centers, such studies are only available as research tools. Brain SPECT and ^{18}*F-2-deoxy-2*-fluoro-D-glucose PET show occipital lobe hypoperfusion and hypometabolism, respectively, in the absence of structural occipital changes on MRI (Lobotesis et al. 2001; Minoshima et al. 2001). This is seen in DLB and PDD but is not encountered in AD (Lobotesis et al. 2001; Minoshima et al. 2001; Colloby and O'Brien 2004).

Dopamine transporter SPECT (DaTSCAN) in DLB shows, as in PD, low striatal dopamine transporter activity, reflecting damage to the integrity of the nigrostriatal system in vivo (Hu et al. 2000). An abnormal DaTSCAN is a suggestive feature and can be present years before the full clinical syndrome of DLB develops (McKeith et al. 2005) and may assist in differentiating AD from DLB, since dopaminergic reuptake is normal in AD (Walker et al. 2002). However, some patients fulfilling the clinical criteria of probable DLB have a normal DaTSCAN, and therefore DLB cannot be excluded on the basis of a normal DaTSCAN. Papathanasiou et al. proposed neocortical predominant LB pathology as a possible explanation for false negativity, sparing the brainstem in the early stages (Papathanasiou et al. 2012), but Siepel et al. reported no such association (Siepel et al. 2013).

In vivo estimation of amyloid deposition by means of the amyloid-binding tracer, ^{11}C-Pittsburgh compound B (PIB)-PET, was suggested as a promising biomarker in differentiating DLB from PDD, PD, and other neurodegenerative disorders. PIB-PET detects amyloid-β deposition without any binding to the αSyn-containing cortical LBs (Ye et al. 2008; Fodero-Tavoletti et al. 2007). However, as amyloid burden increases with age, one third of the normal aging population also has a positive PIB-PET (Klunk et al. 2006). In addition, PIB-PET can be negative in DLB and can be positive in PDD. The latter is generally seen in later stages of PDD, probably accounting for the delay in onset of cognitive impairment (Gomperts et al. 2012). Thus, due to the high sensitivity but low specificity, PIB-PET is not yet considered a valid diagnostic tool in differentiating DLB from other parkinsonian diseases (Gomperts et al. 2012).

Although in vivo detection of αSyn would be of great value, the intracellular location of the LBs limits the development of such a tool. However, just as CSF concentration changes of amyloid β ($A\beta_{42}$), total tau (τ) and hyperphosphorylized tau are used to diagnose AD, a reduction of αSyn CSF concentration is found in synucleinopathies as opposed to AD patients, but the quantification of CSF-αSyn does not allow differentiation among the different synucleinopathies (Tateno et al. 2012). Concomitant amyloid pathology explains why, similarly to AD, CSF-$A\beta_{42}$ is reduced in DLB and a likewise increase of CSF values of τ and hyperphosphorylized τ is observed (Mollenhauer et al. 2011).

^{123}*I-meta*iodobenzylguanidine (MIBG) myocardial scintigraphy is a semiquantitative technique that estimates postganglionic sympathetic cardiac innervation (Taki et al. 2004), because MIBG is a physiological norepinephrine analogue. There is evidence suggesting that the autonomic postganglionic neurons are one of the

earliest regions affected by LB pathology. LB degeneration of the autonomic nervous system causes postganglionic sympathetic nerves to degenerate (Orimo et al. 2005), resulting in a reduced uptake of MIBG. Thus, there is increasing interest in the potential diagnostic value of this finding in early detection of DLB. ^{123}I-metaiodobenzylguanidine (MIBG) cardiac scintigraphy estimates myocardial sympathetic nerves, with a reduced uptake in DLB (Suzuki et al. 2006). This allows discrimination with AD, where this feature is not found (Taki et al. 2004). Similar MIBG findings are seen in PD (Taki et al. 2004) but not in MSA (Chung et al. 2009), and this technique can therefore not be used to differentiate DLB from other synucleinopathies.

Neuropsychological examination aids in the differentiation of AD, PDD, and DLB by means of the pattern of cognitive deficits, but overlap exists so that it is not completely reliable for diagnostic accuracy.

Management

Currently, no disease-modifying therapy is available and management is therefore focused on symptomatic relief by pharmacological and non-pharmacological measures (Table 10.3). The combination of EPS, neuropsychiatric symptoms, and neuroleptic sensitivity makes the pharmacological treatment of DLB challenging. Many drugs are contraindicated in DLB. Behavioral strategies aimed at modifying stressors in the environment should be employed whenever possible. In general, whenever required, medications should be started low, increased slowly, and stopped if no apparent benefit occurs. Also, when a patient with DLB needs surgery, minimizing length and strength of general anesthetics may be beneficial in preventing postoperative delirium.

Pharmacological

Parkinsonism

Rigidity and bradykinesia respond less to levodopa therapy in DLB than in idiopathic PD (Molloy et al. 2005; Bonelli et al. 2004), with a benefit in only one third (Molloy et al. 2005; Bonelli et al. 2004). Moreover, DLB patients are more sensitive to the side effects of dopaminergic agents, especially dopamine agonists, and can cause or worsen neuropsychiatric side effects (Molloy et al. 2005). Strategies for decreasing the incidence of adverse events include starting levodopa at lower doses and increasing more slowly than in PD. The trial should be longer if well tolerated as often drugs take several weeks to take effect. Given the predisposition to side effects and the sensitivity to interactions, the treatment should be stopped if no obvious clinical response has been observed.

Table 10.3 Therapeutic strategies in dementia with Lewy bodies

Treatment options			
Symptoms	Treatment options	Details	Comments
Parkinsonism	Non-pharmacological	Physiotherapy and physical exercise	Balance, gait, arm swing
	Pharmacological		
	Levodopa	Start very slow (50 mg BID or TID), increase slowly per ½ tablets	Continue several weeks if well tolerated; stop if no apparent benefit (30 % responders).
			Side effects: (transient) gastrointestinal upset, visual hallucinations, delusions, orthostatic hypotension
	Dopamine agonists		Relatively contraindicated because of risk of worsening behavioral problems
	Anticholinergics		*Strictly* contraindicated because of high risk of increased cognitive and neuropsychiatric symptoms
Cognitive impairment	Non-pharmacological	Modifying stressors in the environment.	–
		Physiotherapy	
		Active social interactions	
	Pharmacological		
	Cholinesterase inhibitors		
	Rivastigmine	Start 1.5 mg BID, increase by 1.5 mg every 2–4 weeks, maximum 6 mg BID	Side effects: worsening parkinsonism (in 10 %: tremor), (transient) gastrointestinal upset, cardiac arrhythmia
	Donepezil	Start 5 mg OD for 4 weeks, then increase to 10 mg OD	Side effects: gastrointestinal (less with slow increase), (transient) gastrointestinal upset, cardiac arrhythmia
	Galantamine	8 mg OD, increase slowly to max 24 mg OD	Effective and well tolerated in a 24-week open-label study, but no RCTs
	Memantine	Start at 5 mg OD and increase to 10 mg BID	Well tolerated

Neuropsychiatric symptoms			
Visual hallucinations	Non-pharmacological	No treatment if not harmful or disturbing	–
	Pharmacological		
	Atypical neuroleptics		
	Quetiapine	Start at 12.5 mg OD, increase slowly if necessary	Sedation
	Clozapine	Start at 12.5 mg OD, increase per 12.5 mg if necessary, max 50 mg OD	Sedation
	Typical neuroleptics	–	*Strictly* contraindicated
Depression	Non-pharmacological	Modifying stressors in the environment	–
	Pharmacological		
	SSRIs	Drug dependent	Drug dependent
	TCA	–	Strictly contraindicated
Autonomic impairment			
Orthostatic hypotension	Non-pharmacological	Increased fluid intake	–
		30° inclination of bed's head end	–
		Slow rising from lying/seated position	–
		Wearing compression stockings	–
		Eating small meals	–
	Pharmacological		
	Fludrocortisone	Start at 0.1 mg QHS, increase slowly to maximum 0.3 mg QHS if necessary	Fluid retention, edema
	Midodrine	Start at 5 mg TID, increase slowly to max 10 mg TID	–
Sleep disturbances			
EDS	Non-pharmacological	Physiotherapy and active social interactions to improve nighttime sleep	–
		Rule out/treat disturbed sleeping pattern, mood disturbances, and drug side effects	–
	Pharmacological		
	Melatonin	Start 3 mg QHS, slowly increase per 3 mg to maximum 12 mg QHS	–
	Psychostimulants	Safety?	No prior RCTs

(continued)

Table 10.3 (continued)

Treatment options			
Symptoms	Treatment options	Details	Comments
RBD	Non-pharmacological	No treatment if not harmful or disturbing	–
	Pharmacological		
	Clonazepam	Start 0.25 mg QHS, increase per 0.25 mg to maximum 1 mg QHS	Side effects: sedation
	Melatonin	Start 3 mg QHS, slowly increase per 3 mg to maximum 12 mg QHS	–
Treatment strategy			
Start pharmacological treatment only if symptoms are harmful or disturbing and if non-pharmacological strategies are insufficient			
Start low, go slow			
Stop treatment if no apparent benefit			
Anticholinergics, TCA, and typical neuroleptics are strictly contraindicated			
Avoid general anesthesia (Surgery necessary? Possible locoregional anesthesia?) or reduce length and strength of general anesthesia			

SSRI selective serotonin reuptake inhibitors, *TCA* tricyclic antidepressant, *EDS* excessive daytime sleepiness, *RBD* REM sleep behavior disorder, *RCT* randomized controlled trial

Unlike in idiopathic PD, dopamine agonists are relatively contraindicated and anticholinergics are strictly contraindicated because they often worsen the clinical picture by inducing behavioral problems. Overall many individuals with DLB are not taking any dopaminergic agents as the motor symptoms are often relatively mild in contrast to the cognitive issues and because reduced tolerability and side effects limit their use.

Cognitive Impairment and Neuropsychiatric Symptoms

Cholinesterase inhibitors such as rivastigmine and donepezil may improve cognitive function and behavioral symptoms in DLB (McKeith et al. 2000). A placebo-controlled study of a 20-week treatment with rivastigmine (6–12 mg) showed significant improvement of cognitive symptoms in DLB by ameliorating concentration and simultaneously reducing fluctuations, apathy, anxiety, visual hallucinations, and delusions (McKeith et al. 2000; Emre et al. 2004; Rolinski et al. 2012). Compared to donepezil, adverse events are more common with rivastigmine (Rolinski et al. 2012). Worsening of parkinsonism is reported with rivastigmine, although occurrence rates differ (McKeith et al. 2000; Emre et al. 2004). Worsening of tremor was reported in up to 10 % (Emre et al. 2004; Rolinski et al. 2012). Similar to AD, the most common reason for discontinuation is gastrointestinal upset.

Changes in glutamatergic activity have been identified in DLB (Dalfo et al. 2004). The *N-methyl*-D-aspartate receptor antagonist memantine, used in AD (Reisberg et al. 2003), has also shown benefit in DLB (Aarsland et al. 2009) with improvement of the clinical global impression of change scores after 24 weeks, compared to a placebo group. No effects were seen on motor or psychiatric symptoms (Aarsland et al. 2009), although previous case reports had shown worsening of cognition (Menendez-Gonzalez et al. 2005) and psychosis (Ridha et al. 2005).

Visual hallucinations should not be treated unless they are harmful or disturbing to the patient, taking into account the profound neuroleptic sensitivity these individuals experience. Other medical causes (acute infection, general anesthesia, etc.) can cause delirium and trigger or worsen VH and should be ruled out. Typical neuroleptics are strictly contraindicated in DLB, due to risk of worsening parkinsonism (Piggott et al. 1994) as well as the risk of sudden coma or death. Atypical neuroleptics of choice are quetiapine and clozapine, since they seem to have less side effects when treating psychotic symptoms in DLB (Morgante et al. 2004). Patients typically need very low doses, such as 25–50 mg/day of quetiapine to effectively reduce VH.

Lastly, as severe cholinergic deficits form the basis of neuropsychiatric symptoms in DLB, any drug with anticholinergic properties should be avoided. Therefore, tricyclic antidepressant should not be used in the treatment of depression in DLB (Spina and Scordo 2002) as opposed to selective serotonin reuptake inhibitors (SSRIs) that are a much better choice (Nyth and Gottfries 1990).

Autonomic Impairment

Orthostatic hypotension should first be addressed by conservative measures including increased fluid intake, 30° inclination of the bed's head end, slow rising, wearing compression stockings, eating small meals, etc. If insufficient, fludrocortisone or midodrine may improve the orthostatic blood pressure drop.

Urinary incontinence should not be treated with anticholinergic agents, certainly in the presence of orthostatic hypotension.

Sleep

Different types of sleep disruption occur, requiring recognition and management. If left untreated, such sleep issues may aggravate excessive daytime sleepiness (EDS) and fluctuations, which can lead to an increase of psychiatric symptoms and reduced quality of life of the patient and caregivers.

RBD may respond to low dosages of clonazepam, rarely needing up to 1 mg QHS, but can cause sedation. Melatonin and quetiapine may also be successful (Boeve et al. 2003). Psychostimulants have been reported to improve EDS (Boeve et al. 2004) when arising independently from a disturbed sleeping pattern, mood disturbances, or drug side effects, but no randomized controlled trials exist to confirm their safety and tolerability (Dolder et al. 2010).

Non-pharmacological

Although there are no randomized controlled trials or cohort studies evaluating the benefit of non-pharmacological measures in DLB, such approaches may benefit cognitive and physical skills. The patient should be encouraged to take part in social activities to maintain active social interactions, stimulating the patient's arousal and improving nighttime sleep. On the other hand, as in PD, physical activity is highly recommended (Goodwin et al. 2008; Keus et al. 2007). Since DLB generally shows more axial than appendicular EPS, exercises of balance, walking, and arm swing helps mobility and prolongs independency. Often physiotherapy is needed to help in mobilizing the patients and teaching them easy exercises to perform on a daily basis.

References

Aarsland D, et al. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. 2003;60(3):387–92.

Aarsland D, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. Lancet Neurol. 2009;8(7):613–8.

Barber R, et al. MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia. Neurology. 2000;54(6):1304–9.
Barker WW, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord. 2002;16(4):203–12.
Bennett DA, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006;66(12):1837–44.
Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med. 2003;4(4):281–4.
Boeve BF, Silber MH, Ferman TJ. REM sleep behavior disorder in Parkinson's disease and dementia with Lewy bodies. J Geriatr Psychiatry Neurol. 2004;17(3):146–57.
Boeve BF, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain. 2007;130(Pt 11):2770–88.
Bogaerts V, et al. A novel locus for dementia with Lewy bodies: a clinically and genetically heterogeneous disorder. Brain. 2007;130(Pt 9):2277–91.
Bonelli SB, et al. L-dopa responsiveness in dementia with Lewy bodies, Parkinson disease with and without dementia. Neurology. 2004;63(2):376–8.
Borroni B, Agosti C, Padovani A. Behavioral and psychological symptoms in dementia with Lewy-bodies (DLB): frequency and relationship with disease severity and motor impairment. Arch Gerontol Geriatr. 2008;46(1):101–6.
Braak H, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197–211.
Briel RC, et al. EEG findings in dementia with Lewy bodies and Alzheimer's disease. J Neurol Neurosurg Psychiatry. 1999;66(3):401–3.
Burn DJ, et al. Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: a cross-sectional comparative study. Mov Disord. 2003;18(8):884–9.
Burn D, et al. Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. Mov Disord. 2006;21(11):1899–907.
Byrne EJ, Burns A, Waite J. Neuroleptic sensitivity in dementia with cortical Lewy bodies. BMJ. 1992;305(6862):1158–9.
Chartier-Harlin MC, et al. Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. Lancet. 2004;364(9440):1167–9.
Chung EJ, et al. MIBG scintigraphy for differentiating Parkinson's disease with autonomic dysfunction from Parkinsonism-predominant multiple system atrophy. Mov Disord. 2009;24(11):1650–5.
Collerton D, Perry E, McKeith I. Why people see things that are not there: a novel Perception and Attention Deficit model for recurrent complex visual hallucinations. Behav Brain Sci. 2005;28(6):737–57; discussion 757–94.
Colloby S, O'Brien J. Functional imaging in Parkinson's disease and dementia with Lewy bodies. J Geriatr Psychiatry Neurol. 2004;17(3):158–63.
Cormack F, et al. Pentagon drawing and neuropsychological performance in Dementia with Lewy Bodies, Alzheimer's disease, Parkinson's disease and Parkinson's disease with dementia. Int J Geriatr Psychiatry. 2004;19(4):371–7.
Costa DC, et al. Dementia with Lewy bodies versus Alzheimer's disease: role of dopamine transporter imaging. Mov Disord. 2003;18 Suppl 7:S34–8.
Dalfo E, et al. Abnormal metabotropic glutamate receptor expression and signaling in the cerebral cortex in diffuse Lewy body disease is associated with irregular alpha-synuclein/phospholipase C (PLCbeta1) interactions. Brain Pathol. 2004;14(4):388–98.
Del Ser T, et al. Dementia with Lewy bodies: findings from an international multicentre study. Int J Geriatr Psychiatry. 2000;15(11):1034–45.
Dolder CR, Davis LN, McKinsey J. Use of psychostimulants in patients with dementia. Ann Pharmacother. 2010;44(10):1624–32.
Doran M, Larner AJ. EEG findings in dementia with Lewy bodies causing diagnostic confusion with sporadic Creutzfeldt-Jakob disease. Eur J Neurol. 2004;11(12):838–41.

Duda JE. Pathology and neurotransmitter abnormalities of dementia with Lewy bodies. Dement Geriatr Cogn Disord. 2004;17 Suppl 1:3–14.
Emre M, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med. 2004;351(24):2509–18.
Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain. 1991;114(Pt 5):2283–301.
Ferman TJ, et al. REM sleep behavior disorder and dementia: cognitive differences when compared with AD. Neurology. 1999;52(5):951–7.
Fodero-Tavoletti MT, et al. In vitro characterization of Pittsburgh compound-B binding to Lewy bodies. J Neurosci. 2007;27(39):10365–71.
Francis PT, Perry EK. Cholinergic and other neurotransmitter mechanisms in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies. Mov Disord. 2007;22 Suppl 17:S351–7.
Friedman JH, Fernandez HH. Atypical antipsychotics in Parkinson-sensitive populations. J Geriatr Psychiatry Neurol. 2002;15(3):156–70.
Galasko D, et al. Clinical and neuropathological findings in Lewy body dementias. Brain Cogn. 1996;31(2):166–75.
Gnanalingham KK, et al. Motor and cognitive function in Lewy body dementia: comparison with Alzheimer's and Parkinson's diseases. J Neurol Neurosurg Psychiatry. 1997;62(3):243–52.
Gomperts SN, et al. Brain amyloid and cognition in Lewy body diseases. Mov Disord. 2012;27(8):965–73.
Goodwin VA, et al. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2008;23(5):631–40.
Haik S, et al. Dementia with Lewy bodies in a neuropathologic series of suspected Creutzfeldt-Jakob disease. Neurology. 2000;55(9):1401–4.
Halliday GM, et al. Neuropathology of immunohistochemically identified brainstem neurons in Parkinson's disease. Ann Neurol. 1990;27(4):373–85.
Hu XS, et al. 18 F-fluorodopa PET study of striatal dopamine uptake in the diagnosis of dementia with Lewy bodies. Neurology. 2000;55(10):1575–7.
Huang Y, Halliday G. Can we clinically diagnose dementia with Lewy bodies yet? Transl Neurodegener. 2013;2(1):4.
Imamura T, et al. Visual hallucinations and regional cerebral metabolism in dementia with Lewy bodies (DLB). Neuroreport. 1999;10(9):1903–7.
Jankovic J, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology. 1990;40(10):1529–34.
Kaur B, et al. Extrapyramidal signs by dementia severity in Alzheimer disease and dementia with Lewy bodies. Alzheimer Dis Assoc Disord. 2013;27:226–32.
Keus SH, et al. Evidence-based analysis of physical therapy in Parkinson's disease with recommendations for practice and research. Mov Disord. 2007;22(4):451–60; quiz 600.
Klunk WE, et al. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain. 2006;129(Pt 11):2805–7.
Lobotesis K, et al. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. Neurology. 2001;56(5):643–9.
Lopez OL, et al. Extrapyramidal signs in patients with probable Alzheimer disease. Arch Neurol. 1997;54(8):969–75.
Mata IF, et al. Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. Arch Neurol. 2008;65(3):379–82.
McKeith I, et al. Neuroleptic sensitivity in patients with senile dementia of Lewy body type. BMJ. 1992;305(6855):673–8.
McKeith IG, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology. 1996;47(5):1113–24.
McKeith I, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet. 2000;356(9247):2031–6.

McKeith I, et al. Dementia with Lewy bodies. Lancet Neurol. 2004;3(1):19–28.
McKeith IG, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005;65(12):1863–72.
Meeus B, Theuns J, Van Broeckhoven C. The genetics of dementia with Lewy bodies: what are we missing? Arch Neurol. 2012;69(9):1113–8.
Menendez-Gonzalez M, Calatayud MT, Blazquez-Menes B. Exacerbation of Lewy bodies dementia due to memantine. J Alzheimers Dis. 2005;8(3):289–91.
Minoshima S, et al. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. Ann Neurol. 2001;50(3):358–65.
Mollenhauer B, et al. Alpha-synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study. Lancet Neurol. 2011;10(3):230–40.
Molloy S, et al. The role of levodopa in the management of dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2005;76(9):1200–3.
Morgante L, et al. Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. Clin Neuropharmacol. 2004;27(4):153–6.
Mosimann UP, et al. Visual perception in Parkinson disease dementia and dementia with Lewy bodies. Neurology. 2004;63(11):2091–6.
Mosimann UP, et al. Characteristics of visual hallucinations in Parkinson disease dementia and dementia with Lewy bodies. Am J Geriatr Psychiatry. 2006;14(2):153–60.
Nalls MA, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol. 2013;70:727–35.
Nishijima K, Ishiguro T. Clinical course and CSF monoamine metabolism in neuroleptic malignant syndrome–a study of nine typical cases and five mild cases. Seishin Shinkeigaku Zasshi. 1989;91(6):429–56.
Nyth AL, Gottfries CG. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multicentre study. Br J Psychiatry. 1990;157:894–901.
Okazaki H, Lipkin LE, Aronson SM. Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriparesis in flexion. J Neuropathol Exp Neurol. 1961;20:237–44.
Orimo S, et al. Cardiac sympathetic denervation precedes neuronal loss in the sympathetic ganglia in Lewy body disease. Acta Neuropathol. 2005;109(6):583–8.
Papathanasiou ND, et al. Diagnostic accuracy of (1)(2)(3)I-FP-CIT (DaTSCAN) in dementia with Lewy bodies: a meta-analysis of published studies. Parkinsonism Relat Disord. 2012;18(3):225–9.
Parkkinen L, et al. Alpha-synuclein pathology is highly dependent on the case selection. Neuropathol Appl Neurobiol. 2001;27(4):314–25.
Perry EK, et al. Cholinergic and dopaminergic activities in senile dementia of Lewy body type. Alzheimer Dis Assoc Disord. 1990a;4(2):87–95.
Perry EK, et al. Evidence of a monoaminergic-cholinergic imbalance related to visual hallucinations in Lewy body dementia. J Neurochem. 1990b;55(4):1454–6.
Perry EK, et al. Neocortical cholinergic activities differentiate Lewy body dementia from classical Alzheimer's disease. Neuroreport. 1994;5(7):747–9.
Piggott MA, et al. Dopamine D2 receptors in demented patients with severe neuroleptic sensitivity. Lancet. 1994;343(8904):1044–5.
Piggott MA, et al. Nigrostriatal dopaminergic activities in dementia with Lewy bodies in relation to neuroleptic sensitivity: comparisons with Parkinson's disease. Biol Psychiatry. 1998;44(8):765–74.
Postuma RB, et al. Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies. Mov Disord. 2013;28(5):597–604.
Puzynski S, Jakomow B. Disturbances in tryptophan and serotonin metabolism in affective psychoses and schizophrenia. Pol J Pharmacol Pharm. 1975;27(Suppl):47–60.
Querfurth HW, et al. Acetylcholinesterase inhibition in dementia with Lewy bodies: results of a prospective pilot trial. Dement Geriatr Cogn Disord. 2000;11(6):314–21.
Reisberg B, et al. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003;348(14):1333–41.

Ridha BH, Josephs KA, Rossor MN. Delusions and hallucinations in dementia with Lewy bodies: worsening with memantine. Neurology. 2005;65(3):481–2.
Rolinski M, et al. Cholinesterase inhibitors for dementia with Lewy bodies. Parkinson's disease dementia and cognitive impairment in Parkinson's disease. Cochrane Database Syst Rev. 2012;3, CD006504.
Samuel W, et al. Better cognitive and psychopathologic response to donepezil in patients prospectively diagnosed as dementia with Lewy bodies: a preliminary study. Int J Geriatr Psychiatry. 2000;15(9):794–802.
Scatton B, et al. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res. 1983;275(2):321–8.
Schellenberg GD, et al. Association of an apolipoprotein CII allele with familial dementia of the Alzheimer type. J Neurogenet. 1987;4(2–3):97–108.
Schenck CH, et al. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. 1986, classical article. Sleep. 2002;25(2):293–308.
Sechi G, et al. Acute hyponatremia and neuroleptic malignant syndrome in Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry. 1996;20(3):533–42.
Shiozaki K, et al. Alterations of muscarinic acetylcholine receptor subtypes in diffuse Lewy body disease: relation to Alzheimer's disease. J Neurol Neurosurg Psychiatry. 1999;67(2):209–13.
Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. Lancet Neurol. 2012;11(11):986–98.
Siepel FJ, et al. (123I)FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study. BMJ Open. 2013;3(4). pii: e002642. doi: 10.1136/bmjopen-2013-002642.
Singleton AB, et al. Alpha-synuclein locus triplication causes Parkinson's disease. Science. 2003;302(5646):841.
Spina E, Scordo MG. Clinically significant drug interactions with antidepressants in the elderly. Drugs Aging. 2002;19(4):299–320.
Suzuki M, et al. Impaired myocardial 123I-metaiodobenzylguanidine uptake in Lewy body disease: comparison between dementia with Lewy bodies and Parkinson's disease. J Neurol Sci. 2006;240(1–2):15–9.
Taki J, et al. Significance of 123I-MIBG scintigraphy as a pathophysiological indicator in the assessment of Parkinson's disease and related disorders: it can be a specific marker for Lewy body disease. Ann Nucl Med. 2004;18(6):453–61.
Tan A, Salgado M, Fahn S. Rapid eye movement sleep behavior disorder preceding Parkinson's disease with therapeutic response to levodopa. Mov Disord. 1996;11(2):214–6.
Tartaglia MC, et al. Clinical overlap between Jakob-Creutzfeldt disease and Lewy body disease. Can J Neurol Sci. 2012;39(3):304–10.
Tateno F, et al. Alpha-synuclein in the cerebrospinal fluid differentiates synucleinopathies (Parkinson Disease, dementia with Lewy bodies, multiple system atrophy) from Alzheimer disease. Alzheimer Dis Assoc Disord. 2012;26(3):213–6.
Tsuang D, et al. APOE epsilon4 increases risk for dementia in pure synucleinopathies. JAMA Neurol. 2013;70(2):223–8.
Walker Z, et al. Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. J Neurol Neurosurg Psychiatry. 2002;73(2):134–40.
Wang CS, et al. Twin pairs discordant for neuropathologically confirmed Lewy body dementia. J Neurol Neurosurg Psychiatry. 2009;80(5):562–5.
Weiner WJ, Tolosa E. Hyperkinetic movement disorders. Preface. Handb Clin Neurol. 2011;100:ix.
Wenning GK, et al. Time course of symptomatic orthostatic hypotension and urinary incontinence in patients with postmortem confirmed parkinsonian syndromes: a clinicopathological study. J Neurol Neurosurg Psychiatry. 1999;67(5):620–3.
Williams MM, et al. Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. Neurology. 2006;67(11):1935–41.
Yamamoto T, Imai T. A case of diffuse Lewy body and Alzheimer's diseases with periodic synchronous discharges. J Neuropathol Exp Neurol. 1988;47(5):536–48.

Ye L, et al. In vitro high affinity alpha-synuclein binding sites for the amyloid imaging agent PIB are not matched by binding to Lewy bodies in postmortem human brain. J Neurochem. 2008;105(4):1428–37.

Yoshizawa H, Vonsattel JP, Honig LS. Early neuropsychological discriminants for Lewy body disease: an autopsy series. J Neurol Neurosurg Psychiatry. 2013;84:1326–30.

Zaccai J, McCracken C, Brayne C. A systematic review of prevalence and incidcence studies of dementia with Lewy bodies. Age Ageing. 2005;34(6):561–6.

Chapter 11
Dementia in Parkinson's Disease and Atypical Parkinsonism

Maria Stamelou and Kailash Bhatia

Abstract Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease. The prevalence of Parkinson's disease dementia (PDD) is roughly estimated to be around 30 %, while PDD will occur in over 80 % of patients after 20 years of disease, conferring an important impact on patient management and prognosis. The main clinical syndrome of PDD is that of a frontal-subcortical dysexecutive visuospatial impairment, as well as neuropsychiatric features such as hallucinations and delusions and thus quite similar to that of dementia with Lewy bodies (DLB). The etiopathogenesis is unknown, but α-synuclein pathology spreading from the brainstem to the neocortex is involved, and it seems that concomitant Alzheimer's disease pathology, in particular Aβ plaques, is crucially implicated. Moreover, genetic factors have been recently highlighted as important pathogenetic factors. The diagnosis is based on clinical diagnostic criteria for PDD and mild cognitive impairment. There is no neuroprotective or disease-modifying treatment for PDD. The best evidence for symptomatic treatment exists for the acetylcholinesterase inhibitor, rivastigmine.

With regard to dementia in atypical parkinsonism, much less is known. The prevalence of dementia in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) is high and impairs quality of life in these patients. The cognitive profile reflects that of a frontal-subcortical dysfunction in PSP and additionally parietal dysfunction in CBD, while memory is in both conditions relatively preserved. Apathy, depression, and disinhibition are the most common neuropsychiatric

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features, while hallucinations and delusions occur extremely rarely. Tau pathology in the cortex and subcortical structures seems to correlate with these cognitive phenotypes; however, the understanding of the pathophysiology as well as treatment options is limited. In contrast, dementia in multiple system atrophy (MSA) still counts as one of the exclusion criteria for its diagnosis. Recent studies have highlighted that executive dysfunction does occur in MSA, but etiopathogenesis and treatments are still to be researched.

Keywords Dementia • Parkinson's disease • Mild cognitive impairment • α-synuclein • Progressive supranuclear palsy • Subcortical dementia • Corticobasal degeneration

Dementia in Parkinson's Disease

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease. The typical clinical motor syndrome of PD is associated with neurodegeneration and neuronal loss in the substantia nigra and the presence of inclusions that contain the protein α-synuclein (α-syn) known as Lewy bodies. However, although the clinical phenotype is predominated by motor features, it is now well established that a variety of non-motor features belong to the disease. In particular with regard to cognition, the prevalence of Parkinson's disease dementia (PDD) is roughly estimated to be around 30 %, while PDD will occur in over 80 % of patients after 20 years of disease (Hely et al. 2008). Moreover, mild cognitive impairment (MCI) may be present in up to 36 % of newly diagnosed cases of PD (Foltynie et al. 2004; Bronnick et al. 2006; Buter et al. 2008; Litvan et al. 2012; Burn and Barker 2013; Duncan et al. 2013; Yarnall et al. 2013).

PDD can exacerbate the disabilities caused by motor symptoms in PD, and the presence of cognitive impairment or dementia in patients with PD is associated with a loss of independence, a lower quality of life, and a shorter survival time than PD patients without dementia (Rosenthal et al. 2010). The course of decline in PDD is progressive over time with periods of rapid worsening (Emre et al. 2007a). Therefore, PDD has an important impact on patient management and prognosis, which makes the understanding of its pathophysiology crucial for future therapeutic research.

Clinical Features of PDD

Clinical Risk Factors to Develop PDD

Age is the most prominent risk factor for PDD (Kempster et al. 2010; Levy et al. 2002; Williams-Gray et al. 2009) independently from the age of PD onset. PDD also correlates with the severity of motor disability, and the aging factor may be

additive to the severity of the motor dysfunction (Levy et al. 2000, 2002). Other factors such as visual hallucinations, and the PD phenotype (e.g., prominent axial rigidity and bradykinesia as opposed to tremor), confer risk for the development of PDD (Emre et al. 2007a; Jankovic and Poewe 2012; Galvin et al. 2006). Mild cognitive impairment (MCI) has also been associated with an increased risk of developing PDD (Litvan et al. 2012; Levy et al. 2002).

Cognitive Deficits

The most common cognitive deficits in PDD include those in attention, executive functioning, and visuospatial processing. Attentional performance may fluctuate, leading to a variable level of function and a major impact upon activities of daily living (Bronnick et al. 2006). In tests such as the letter cancelation test and others, PDD patients are slower, tend to fluctuate more, and incur on a higher number of errors than Alzheimer's dementia (AD) patients, whereas the profile of PDD seems to be similar to that seen in dementia with Lewy bodies (DLB). Executive dysfunction has been widely recognized in PDD and the most used tests have been verbal fluency, digit span backward, Wisconsin Card Sorting Test, Stroop Test, and Trail Making Test (Kudlicka et al. 2011). Studies assessing visuospatial function have shown greater deficits in PDD than AD patients (Jeannerod and Jacob 2005). It has been shown that visual perception, space-motion perception, and object-form perception are globally more impaired in PDD patients than non-demented PD patients, and AD patients (Mosimann et al. 2004).

In PDD, short-term memory is impaired, both for initial learning and immediate recall. Traditionally, amnesic deficits in PD have been considered to be mainly of retrieval, rather than encoding and storage. However, memory loss in PDD has been associated more with a frontally mediated retrieval deficit thus again a deficit in executive functioning, than to an intrinsic defect (Emre et al. 2007a). A large meta-analysis has shown that verbal fluency impairment is more pronounced than that seen in PD non-demented patients; also, semantic fluency seems to be more compromised than phonemic fluency (Henry and Crawford 2004). Significant language deficits are not typically seen in PDD and occur much less frequently than in AD (Pillon et al. 1993). When present, language deficits in PDD are more likely associated to executive dysfunction-related problems in sentence processing rather than an intrinsic core language deficit (Grossman et al. 2012).

Neuropsychiatric Features

Neuropsychiatric symptoms, including hallucinations and delusions, depression, anxiety, and apathy, are well reported in PD. Hallucinations tend to be more common in DLB than in PDD and in the latter more frequent than in AD (Aarsland et al. 2000). Delusions seem to be less frequent than hallucinations in PDD but more common than in AD and less than in DLB (Aarsland et al. 2005). Dysphoria and

depression occur with approximately the same frequency in PDD and AD (40–58 %) patients (Aarsland et al. 2001). Anxiety occurs at a similar frequency (30–49 %) as depressed mood, and these symptoms may frequently coexist in the same patient (Bronnick et al. 2007). Irritable mood, anger, and aggression are common in AD, but uncommon in PDD (Engelborghs et al. 2005). Prominent apathy may occur in PDD but also in other forms of dementia, including frontotemporal dementia, progressive supranuclear palsy, AD, and DLB. Furthermore, some individuals may exhibit an impulse control disorder that is characterized by compulsive gambling, eating, purchasing, sexual behavior, and/or a dopamine dysregulation syndrome (Weintraub 2008). The etiology of impulse control disorders in PD is thought to be due to stimulation of hypersensitive ventral striatal-frontal connections by dopaminergic therapy rather than a direct consequence of the neurodegenerative process that is specific to PD and PDD (Weintraub 2008; Weintraub et al. 2013).

Etiopathogenesis of PDD

Neuropathology

Several lines of evidence from studies using α-syn immunohistochemistry in *post-mortem* brains implicate cortical α-syn pathology as the strongest correlate of dementia in PDD demonstrating higher levels of cortical α-syn pathology than do cases of PD without dementia (Jellinger 2007; Compta et al. 2011; Irwin et al. 2012, 2013; Duda et al. 2002; Hurtig et al. 2000). The Braak hypothesis states that Lewy body pathology progresses in a sequence from the pons and brainstem via the forebrain and limbic system to the neocortex. These stages might progress in parallel with cognitive decline (Braak et al. 2005). Indeed, many studies have found that the level of global cortical and limbic α-syn pathology or the levels of α-syn pathology in specific brain regions, such as the parahippocampal or anterior cingulate gyrus, can discriminate between PD without dementia and PDD and are the strongest correlate to PDD when compared with other possible factors such as genetic (Irwin et al. 2012, 2013; Kovari et al. 2003). Neurochemically, cholinergic deficits occur in patients with PDD, attributed to neuronal loss in basal forebrain cholinergic nuclei, and are associated with the transition of α-syn pathology into limbic and neocortical regions (Ballard et al. 2006; Perry et al. 1985; Whitehouse et al. 1983; Yarnall et al. 2011; Shimada et al. 2009).

However, despite the crucial role of a-syn in PDD, the hallmark pathologies of AD, that is, mainly the levels of Aβ plaques and less the tau neurofibrillary tangles (NFTs), have been found to inversely correlate with the cognitive status in a subset of PDD patients (Jellinger 2007; Compta et al. 2011; Kovari et al. 2003; Jellinger et al. 2002). Cortical α-syn, tau, and Aβ pathologies together have been shown to more accurately predict dementia than any single marker alone (Compta et al. 2011; Irwin et al. 2012, 2013; Tsuboi et al. 2005; Kotzbauer et al. 2012). Thus, AD pathology (and in particular Aβ plaque pathology) may have an important role in the

pathogenesis of PDD and a possible synergy with α-syn pathology (Masliah et al. 2001; Clinton et al. 2010). Indeed, clinically, patients with PDD and AD pathology have shorter disease duration, older age at onset of motor symptoms, and shortened survival times compared to PDD patients without concomitant AD pathology (Compta et al. 2009, 2011; Irwin et al. 2012, 2013; Halliday and McCann 2010; Halliday et al. 2008).

In summary, the progression of Lewy body and neurite pathology from subcortical areas into limbic and cortical structures seems to be the major determinant of the development of dementia in most individuals with PDD; however, other pathologies such as that of AD may be implicated in the underlying neuropathology of PDD.

Genetics

Genetic factors may also play an important role in the development of cognitive impairment in PDD. Some monogenic forms of PD have been associated with dementia such as those resulting from pathogenic mutations of the α-synuclein gene (*SNCA*), whereas others such as mutations in leucine-rich repeat kinase 2 (*LRRK2*) or the *parkin* gene do not seem to be as strongly linked to PDD and DLB (Poulopoulos et al. 2012; Sidransky et al. 2009). Heterozygous mutations in the b-glucocerebrosidase (*GBA*) gene are associated with an increased risk of PD or DLB, and GBA-linked PD is associated with a higher risk and an earlier age of onset of dementia, as well as higher levels of cortical and limbic α-syn pathology than noncarrier patients with PD (Sidransky et al. 2009; Alcalay et al. 2012; Clark et al. 2009; Nalls et al. 2013; Neumann et al. 2009; Tsuang et al. 2012). Moreover, polymorphisms of *DYRK1A*, which encodes a kinase that phosphorylates proteins such as α-synuclein and amyloid precursor protein, have been associated with PDD and DLB (Jones et al. 2012).

The APOE ε4 allele has been established as a risk factor for AD and may also confer an increased risk of dementia in PD, but further studies are needed (Morley et al. 2012; Tsuang et al. 2013; Wider et al. 2012). The H1/H1 haplotype of the *MAPT* gene, encoding for protein tau, has been associated with an increased risk of some tauopathies, for example, progressive supranuclear palsy (Hoglinger et al. 2011). Interestingly, this variation in *MAPT* has been associated with PD as well; however, the risk for PDD as associated with the H1/H1 haplotype in PD has been less well studied (Neumann et al. 2009; Tsuang et al. 2013; Wider et al. 2012; Hoglinger et al. 2011). Other possible associations such as the BDNF (Met/Met) homozygote genotype need further confirmation (Guerini et al. 2009).

Diagnosis of PDD

At the outset it should be clarified that frank dementia in the initial stages of PD is not considered a typical feature of the disease (Massano and Bhatia 2012). This is particularly relevant in the differential diagnosis with DLB, in which the cognitive

features are similar to PDD. According to the research criteria for DLB, patients should have an onset of dementia within 1 year after the onset of motor symptoms, while in PDD dementia, this occurs at least 1 year after PD onset (McKeith 2006). Similarly, cognitive dysfunction at early stages should alert the clinician for other differential diagnoses in particular when other atypical features are present such as progressive supranuclear palsy (Litvan et al. 1996). Moreover, clinicians should always search for possible secondary causes if cognitive impairment in Parkinson's disease is noted, such as side effects from dopaminergic treatment.

The identification of patients with PDD but even more so of PD patients with MCI, and thus patients at high risk to develop dementia, is crucial for management and prognostic reasons but also for future therapeutic research. Clinical criteria for PDD have recently been proposed, which however lack clinicopathological validation (Tables 11.1 and 11.2) (Emre et al. 2007a). Identification of a dementia syndrome, defined as impairment in at least two of the four core cognitive domains (e.g., attention, executive functioning, visuospatial functioning, and free recall memory), is needed for diagnosis. Impairment should be severe enough to affect daily social, occupational, or personal care independent of the effects of motor or autonomic symptoms. Behavioral symptoms such as apathy, depressed or anxious mood, hallucinations, delusions, or excessive daytime sleepiness support the diagnosis of cognitive impairment. The criteria are highly specific when all eight items are met, but their sensitivity is low (Martinez-Martin et al. 2011; Dujardin et al. 2010; Barton et al. 2012). However, the criteria are more sensitive for PDD diagnosis than is the fourth edition of the diagnostic and statistical manual of mental disorders (DSM-4) (Emre et al. 2007a). Moreover, diagnostic criteria for MCI in PD have been proposed recently (Table 11.3) (Litvan et al. 2012). Possible biomarkers for MCI are currently under research (Duncan et al. 2013; Yarnall et al. 2013).

Treatment of PDD

The current pharmacological strategy is symptomatic and there is no neuroprotective or disease-modifying treatment available. Treatment of PDD includes acetylcholinesterase inhibitors that have been shown to improve cognition and the ability to perform activities of daily living in PDD, with the largest body of evidence for rivastigmine (Barone et al. 2008; Burn et al. 2006; Emre et al. 2007b; McKeith et al. 2000; Oertel et al. 2008; Poewe et al. 2006; Schmitt et al. 2010; Seppi et al. 2011; Wesnes et al. 2005). No established clinical or biological markers can predict which patients will improve, but it is suggested that those with visual hallucinations and hyperhomocysteinemia respond particularly well (Barone et al. 2008; Burn et al. 2006). Evidence is less robust for the other cholinesterase inhibitors such as donepezil. It is however important to point out that these drugs may worsen motor symptoms, while dopamine agonists used to treat motor symptoms may worsen cognition, complicating therapeutic options in PDD. Acetylcholinesterase

Table 11.1 Features of dementia associated with Parkinson's disease (Emre et al. 2007a)

I. Core features	1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria (Gibb and Lees 1988)
	2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
	Impairment in more than one cognitive domain
	Representing a decline from premorbid level
	Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms
II. Associated clinical features	1. Cognitive features:
	Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
	Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting, or set maintenance; impaired mental speed (bradyphrenia)
	Visuospatial functions: Impaired. Impairment in tasks requiring visuospatial orientation, perception, or construction
	Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, and recognition is usually better than free recall
	Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
	2. Behavioral features:
	Apathy: Decreased spontaneity, loss of motivation, interest, and effortful behavior
	Changes in personality and mood including depressive features and anxiety
	Hallucinations: Mostly visual, usually complex, formed visions of people, animals, or objects
	Delusions: Usually paranoid, such as infidelity or phantom boarder (unwelcome guests living in the home) delusions
	Excessive daytime sleepiness
III. Features which do not exclude PDD, but make the diagnosis uncertain	Coexistence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g., presence of relevant vascular disease in imaging
	Time interval between the development of motor and cognitive symptoms not known
IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present, make it impossible to reliably diagnose PDD	Cognitive and behavioral symptoms appearing solely in the context of other conditions such as the following:
	Acute confusion due to either systemic diseases or abnormalities or drug intoxication, major depression according to DSM IV
	Features compatible with "probable vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging and a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Table 11.2 Criteria for the diagnosis of probable and possible PDD (Emre et al. 2007a)

Probable PDD	(A) Core features: Both must be present
	(B) Associated clinical features:
	Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuospatial functions, and impaired free recall memory which usually improves with cueing)
	The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of probable PDD; lack of behavioral symptoms, however, does not exclude the diagnosis
	(C) None of the group III features present
	(D) None of the group IV features present
Possible PDD	(A) Core features: Both must be present
	(B) Associated clinical features:
	Atypical profile of cognitive impairment in one or more domains, such as prominent- or receptive-type (fluent) aphasia or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
	Behavioral symptoms may or may not be present
	or
	(C) One or more of the group III features present
	(D) None of the group IV features present

inhibitors might affect concurrent plaque pathological changes in patients with DLB (Ballard et al. 2007). There is inconsistent evidence for the glutaminergic agent memantine having a beneficial effect in PDD (Seppi et al. 2011; Aarsland et al. 2009; Emre et al. 2010; Larsson et al. 2011; Leroi et al. 2009; Ondo et al. 2011; Svenningsson et al. 2012).

In 2011, the Movement Disorder Society taskforce on evidence-based medicine published a revised review of treatments for non-motor symptoms of PD and concluded that rivastigmine is effective and clinically useful in the treatment of dementia; evidence for donepezil, galantamine, and memantine was insufficient. All drugs had acceptable risks without the need for specialized monitoring. Evidence from placebo-controlled studies supported the use of clozapine for psychosis (Seppi et al. 2011).

Histamine H3 receptor antagonists are being developed mainly for fatigue and sleep disturbances in PD but are also thought of as procognitive drugs in AD (Chazot 2010). Effects on cognition in PD have not yet been reported. Cognitive intervention programs are useful in AD and MCI (Jean et al. 2010). They might be particularly relevant in PD because increased dopamine release has been noted after cognitive training (Backman et al. 2011). Preliminary reports were positive, and results of the first randomized trial showed that intensive cognitive training led to improvement in various cognitive tasks compared with the control group immediately after the intervention (Paris et al. 2011). Novel pharmacological treatments, cell-based therapies, gene transfer, antibodies blocking amyloid or α-synuclein aggregation, and trophic factor approaches are under development.

Table 11.3 Criteria for the diagnosis of PD-MCI (Litvan et al. 2012)

I. Inclusion criteria
Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria (Gibb and Lees 1988)
Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant *or* observed by the clinician
Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities (detailed in section III)
Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present
II. Exclusion criteria
Diagnosis of PD dementia based on MDS Task Force proposed criteria (Emre et al. 2007a)
Other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)
Other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing
III. Specific guidelines for PD-MCI level I and level II categories
(A) Level I (abbreviated assessment)
Impairment on a scale of global cognitive abilities validated for use in PD *or*
Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less than five cognitive domains are assessed)
(B) Level II (comprehensive assessment)
Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial)
Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains
Impairment on neuropsychological tests may be demonstrated by:
Performance approximately 1–2 SDs below appropriate norms *or*
Significant decline demonstrated on serial cognitive testing *or*
Significant decline from estimated premorbid levels
IV. Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed and is strongly suggested for research purposes)
PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired *or*
PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains)

Dementia in Atypical Parkinsonism

The term "atypical parkinsonism" usually refers to disorders that present with parkinsonism and some features which are atypical for PD such as, for example, symmetric parkinsonism, symptoms unresponsive to dopaminergic treatment, and additional signs (e.g., among others alien limb phenomenon, vertical gaze palsy, early falls). Classically, disorders that belong to the atypical parkinsonian disorders are progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), and DLB (which has been discussed in PDD), which

are distinct pathological entities. Of those, PSP and CBD belong neuropathologically to the family of tauopathies, whereas MSA and DLB belong to the α-synucleinopathies.

Dementia in Progressive Supranuclear Palsy and Corticobasal Degeneration

Introduction

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are two distinct pathological entities (Litvan et al. 1996; Armstrong et al. 2013). The classical PSP phenotype is characterized by postural instability and early falls, early cognitive dysfunction, and abnormalities of vertical gaze and is referred to as Richardson's syndrome (RS) (Williams et al. 2005). The classical CBD phenotype consists of asymmetric parkinsonism, cortical signs (e.g., apraxia, cortical sensory loss, alien limb), and possibly other signs such as dystonia and myoclonus and is referred to as corticobasal syndrome (CBS). However, patients with PSP and CBD may present with phenotypes other than the classical ones: patients with PSP pathology may present as PSP-parkinsonism, CBS, pure akinesia with gait freezing, progressive nonfluent aphasia, and others; (Lee et al. 2011; Ling et al. 2010; Stamelou et al. 2012; Williams and Lees 2009a, b) patients with CBD pathology may present with RS, a frontotemporal dementia (FTD) phenotype, and others (Armstrong et al. 2013; Ling et al. 2010; Stamelou et al. 2012; Kouri et al. 2011). Thus, patients with PSP and CBD may present with overlapping clinical features including cognitive ones and also with phenotypes of other dementia syndromes mainly FTD.

In contrast to PD, cognitive and neuropsychiatric features may be the presenting symptom of PSP and CBD (Donker Kaat et al. 2007). Dementia is evident in both disorders in clinical practice; however, well-designed, prospective prevalence studies of dementia in these patients are lacking. From a report of 67 patients, 85 % showed evidence of cognitive impairment, although dementia criteria were not applied (Donker Kaat et al. 2007). Similarly, "cognitive problems" were reported as the initial presenting complaint in 15 % of a prevalent sample of 187 cases (Nath et al. 2003). Cognitive and neuropsychiatric features have an important impact on QoL in PSP and CBD (Winter et al. 2011).

Clinical Features of Dementia in PSP and CBD

Clinical Risk Factors for Dementia in PSP and CBD

In contrast to PDD described above, clinical risk factors to develop dementia in these disorders are not well studied. For PSP, certain phenotypes such as PSP with parkinsonism seem to develop dementia later than the classical phenotype RS, (Williams

et al. 2005) but large prospective studies are missing. The time of onset of the symptoms and the duration of disease do not seem to influence the course of dementia in these disorders, which however may correlate with age and clinical motor disability scores (Brown et al. 2010). The evolution of cognitive impairment in relation to the motor symptoms varies greatly not only for the different phenotypes of PSP and CBD but also within the classical phenotypes RS and CBS (Brown et al. 2010).

Cognitive Features of PSP and CBD

Given the rarity of these disorders, most research refers to clinically diagnosed rather than pathology-confirmed PSP and CBD patients. No prospective longitudinal studies with pathological confirmation are available.

In PSP, prominent deficits are described on tests of attention and executive function, with verbal fluency being particularly severely affected, as well as deficits in both verbal and nonverbal memory with a relative preservation of recognition. PSP patients have impairments in processing speed and cognitive flexibility (Dubois et al. 1988). In one study, the neurocognitive performance of 200 patients with RS revealed primary executive dysfunction (e.g., 74 % impaired on the Frontal Assessment Battery, 55 % impaired on Initiation/Perseveration subscale of the Dementia Rating Scale), with milder difficulties in memory, construction, and naming (Gerstenecker et al. 2013; Mimura et al. 1997).

These deficits have been confirmed also in larger clinical studies (Brown et al. 2010).

Patients with CBD typically demonstrate difficulties that reflect impairment of frontal-subcortical and posterior cortical visuospatial association areas, with executive problem solving and pre-motor coordination of praxis tasks that are not typically observed in patients with PSP or AD (Pillon et al. 1995) (Massman et al. 1996). Executive dysfunction and language difficulties characterize the cognitive profile, while memory is generally preserved. Difficulty with limb apraxias and relatively intact memory was found when compared to AD patients (Massman et al. 1996). Language difficulties including verbal fluency and anomia are common in CBD.

Neuropsychiatric Features of PSP and CBD

The most commonly described neuropsychiatric symptoms observed in PSP patients include apathy and anhedonia, disinhibition, depression, and bulbar affect, while hallucinations and delusions are rare (Williams and Lees 2009a). Apathy can be a consequence of depression; however, in PSP apathy seems to be independent of depression, the latter being rare (Litvan et al. 1996, 1997; Litvan 1994). From 22 probable PSP and 50 probable AD patients, 91 % PSP patients reported apathy which was continuously present in the Neuropsychiatric Inventory (NPI), as opposed to 72 % of AD patients (Litvan et al. 1996; Cummings et al. 1994). The next most commonly reported symptom is disinhibition (around 36 %), while

hallucinations and delusions are not observed in PSP in contrast to AD patients (Litvan et al. 1996, 1997; Litvan 1994). Comparing PSP with PD using the NPI and taking into account confounding factors such as dopaminergic medication showed that the clinical syndrome in PSP is predominated by apathy and disinhibition, while PD patients predominantly complained of hallucinations and delusions rather than apathy or depression (Aarsland et al. 2001).

The most common symptoms in CBD include depression, apathy, agitation, personality changes, and irritability. In contrast, delusions and hallucinations are, as in PSP, exceedingly rare. In a clinical series of 15 CBS, 73 % of CBS patients had depression, 40 % apathy, and 20 % agitation on the NPI and none had delusions or hallucinations (Litvan et al. 1997; Wenning et al. 1998). Twenty-two percent of 36 pathology confirmed CBD patients reported neuropsychiatric symptoms mainly depression, compulsive behaviors, and frontal lobe release signs in a retrospective study of pathology confirmed CBD, in which none reported hallucinations (Geda et al. 2007).

Etiopathogenesis of Dementia in PSP and CBD

Neuropathology

Microscopically, tau pathology in PSP is specifically concentrated in the globus pallidus, subthalamic nuclei, and substantia nigra, and thus dementia is typically considered a "subcortical dementia." There are some lesions in the motor cortex, basal ganglia, cerebellum, and certain brainstem nuclei. In the brainstem, the periaqueductal grey of midbrain as well as the superior colliculus and many nuclei involved in vertical gaze and alertness show the greatest pathology. The cellular changes in PSP include argyrophilic neurofibrillary tangles and positive tau immunohistochemistry in the globus pallidus and the characteristic tufted astrocytes (as opposed to the astrocytic plaques in CBD) primarily identified in the striatum and motor cortex. Gross evaluation of PSP brain tissue usually reveals mild frontal lobe atrophy and marked midbrain atrophy with enlarged cerebral aqueduct. The substantia nigra is affected and expresses less pigment in the midbrain. There is also pronounced atrophy of the subthalamic nucleus and superior cerebellar peduncles (Dickson et al. 2007). The distribution of tau pathology in frontal-subcortical structures seems to reflect the clinical dementia phenotype in these patients, and it has been shown that phenotypes of PSP with less cognitive impairment like PSP-parkinsonism have a lower cortical tau burden in pathology, albeit in small numbers of patients (Williams and Lees 2009a).

The histopathological criteria for CBD require the abnormal deposition of hyperphosphorylated tau protein as a distinct type of intracellular inclusions known as astrocytic plaques. There are ballooned achromatic neurons and inclusions referred to as "corticobasal bodies" in both grey and white matter in the cerebral cortex and subcortical areas including the basal ganglia, while hippocampi and temporal cortices are usually unaffected (Dickson et al. 2002). Gross pathology of brains from CBD patients reveals asymmetric atrophy of the superior parietal and frontal lobes contralateral to the symptomatic limb apraxia (Dickson et al. 2002).

To which extent concomitant pathologies may be implicated in the natural history of dementia in these disorders, such as AD pathology, is unknown, as large studies are missing.

Diagnosis of Dementia in PSP and CBD

In contrast to PDD, there are no formal criteria for the diagnosis of dementia in PSP and CBD. Clinical diagnosis of PSP relies on widely accepted criteria, which, however, are based on retrospective studies and lack prospective validation. In the current criteria for clinical diagnosis of PSP, cognitive dysfunction is mentioned as a supportive criterion only (Litvan et al. 1996). In the recently published clinical criteria of CBD, several cognitive and neuropsychiatric domains are taken into account, to diagnose possible or probable CBD (Armstrong et al. 2013).

In terms of useful cognitive tests, a recent meta-analysis of 141 cognitive tests used in parkinsonian disorders showed that only 16 were found to be highly useful. Inferior performance on phonemic and semantic verbal fluency, the Trail Making Test, and the Wisconsin Card Sorting Test was moderately to very useful in separating PSP from PD and MSA. Cognitive testing could not differentiate CBS from other parkinsonian disorders, although sequential orobuccal apraxia was very useful. Obviously, these tests must be interpreted in conjunction with other clinical characteristics to be helpful diagnostically (Lee et al. 2012).

Treatment of Dementia in PSP and CBD

Therapeutic trials to enhance cognitive function in PSP and CBD are rare and usually included a few number of patients, in an open-label fashion. A double-blinded placebo-controlled trial of donepezil (an acetylcholinesterase inhibitor) showed mild cognitive benefits and deleterious side effects, which exacerbated the parkinsonian features of PSP and dramatically worsened the functional status (Litvan et al. 2001). A small study on five PSP patients with rivastigmine showed a possible mild benefit (Liepelt et al. 2010). Thus, there are currently no evidence-based treatments for dementia in PSP and CBD, and more research on the pathophysiology underlying PSP and CBD is required to find safe and tolerable pharmacological alternatives. In terms of possible disease-modifying or neuroprotective treatments, two large double-blind studies using the GSK-3b inhibitor tideglusib, and the microtubule stabilizer davunetide, showed no clinical improvement after 1 year, in none of the outcome measures including cognitive ones (Höglinger et al. 2013).

Dementia in Multiple System Atrophy

Multiple system atrophy (MSA) is a sporadic, adult-onset, neurodegenerative disease, clinically characterized by a variable combination of parkinsonism, cerebellar ataxia,

and/or autonomic dysfunction (Gilman et al. 2008). According to the predominant feature at onset, it is subclassified to MSA with parkinsonism (MSA-P) and MSA with cerebellar signs (MSA-C). MSA belongs to the α-synucleinopathies and is characterized by the presence of abnormal α-synuclein-positive cytoplasmic inclusions in oligodendrocytes, termed glial cytoplasmic inclusions (Wenning and Jellinger 2005).

Currently, cognitive dysfunction is an exclusion criterion for the diagnosis of MSA according to validated, widely accepted clinical criteria (Gilman et al. 2008). Indeed, as for PD, frank dementia at onset or initial stages in a patient with parkinsonism should prompt to investigate for other causes than MSA, such as DLB, PSP, or CBD. However, sparse evidence exists for some cognitive deficits in MSA. In a retrospective study on pathologically confirmed cases, dementia has been reported from 14 % in up to 15.7 %; however, in none was dementia reported within the first 5 years from onset (Gilman et al. 2008). In a large study on over 300 MSA patients, global cognitive impairment was found in 11–32 % of these patients, which correlated with age, severity of motor symptoms, and lower level of education (Brown et al. 2010). The etiopathogenesis and possible treatments are currently under research (Kim et al. 2013).

References

Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc. 2000;48(8):938–42.

Aarsland D, Cummings JL, Larsen JP. Neuropsychiatric differences between Parkinson's disease with dementia and Alzheimer's disease. Int J Geriatr Psychiatry. 2001;16(2):184–91.

Aarsland D, Zaccai J, Brayne C. A systematic review of prevalence studies of dementia in Parkinson's disease. Mov Disord. 2005;20(10):1255–63.

Aarsland D, Ballard C, Walker Z, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. Lancet Neurol. 2009;8(7):613–8.

Alcalay RN, Caccappolo E, Mejia-Santana H, et al. Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. Neurology. 2012;78(18):1434–40.

Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013;80(5):496–503.

Backman L, Nyberg L, Soveri A, et al. Effects of working-memory training on striatal dopamine release. Science (New York, NY). 2011;333(6043):718.

Ballard C, Ziabreva I, Perry R, et al. Differences in neuropathologic characteristics across the Lewy body dementia spectrum. Neurology. 2006;67(11):1931–4.

Ballard CG, Chalmers KA, Todd C, et al. Cholinesterase inhibitors reduce cortical Abeta in dementia with Lewy bodies. Neurology. 2007;68(20):1726–9.

Barone P, Burn DJ, van Laar T, Hsu C, Poewe W, Lane RM. Rivastigmine versus placebo in hyperhomocysteinemic Parkinson's disease dementia patients. Mov Disord. 2008;23(11):1532–40.

Barton B, Grabli D, Bernard B, et al. Clinical validation of Movement Disorder Society-recommended diagnostic criteria for Parkinson's disease with dementia. Mov Disord. 2012; 27(2):248–53.

Braak H, Rub U, Jansen Steur EN, Del Tredici K, de Vos RA. Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology. 2005;64(8):1404–10.

Bronnick K, Ehrt U, Emre M, et al. Attentional deficits affect activities of daily living in dementia-associated with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006;77:1136–42.

Bronnick K, Emre M, Lane R, Tekin S, Aarsland D. Profile of cognitive impairment in dementia associated with Parkinson's disease compared with Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2007;78(10):1064–8.

Brown RG, Lacomblez L, Landwehrmeyer BG, et al. Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy. Brain. 2010;133:2382–93.

Burn DJ, Barker RA. Mild cognitive impairment in Parkinson's disease: millstone or milestone? Pract Neurol. 2013;13(2):68–9.

Burn D, Emre M, McKeith I, et al. Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. Mov Disord. 2006;21(11): 1899–907.

Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D. Dementia and survival in Parkinson disease: a 12-year population study. Neurology. 2008;70:1017–22.

Chazot PL. Therapeutic potential of histamine H3 receptor antagonists in dementias. Drug News Perspect. 2010;23(2):99–103.

Clark LN, Kartsaklis LA, Wolf Gilbert R, et al. Association of glucocerebrosidase mutations with dementia with lewy bodies. Arch Neurol. 2009;66(5):578–83.

Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM. Synergistic interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. J Neurosci. 2010;30:7281–9.

Compta Y, Marti MJ, Ibarretxe-Bilbao N, et al. Cerebrospinal tau, phospho-tau, and beta-amyloid and neuropsychological functions in Parkinson's disease. Mov Disord. 2009;24(15):2203–10.

Compta Y, Parkkinen L, O'Sullivan SS, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain. 2011;134:1493–505.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308–14.

Dickson DW, Bergeron C, Chin SS, et al. Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. J Neuropathol Exp Neurol. 2002;61(11):935–46.

Dickson DW, Rademakers R, Hutton ML. Progressive supranuclear palsy: pathology and genetics. Brain Pathol (Zurich, Switzerland). 2007;17(1):74–82.

Donker Kaat L, Boon AJ, Kamphorst W, Ravid R, Duivenvoorden HJ, van Swieten JC. Frontal presentation in progressive supranuclear palsy. Neurology. 2007;69(8):723–9.

Dubois B, Pillon B, Legault F, Agid Y, Lhermitte F. Slowing of cognitive processing in progressive supranuclear palsy. A comparison with Parkinson's disease. Arch Neurol. 1988; 45(11):1194–9.

Duda JE, Giasson BI, Mabon ME, Lee VM, Trojanowski JQ. Novel antibodies to synuclein show abundant striatal pathology in Lewy body diseases. Ann Neurol. 2002;52(2):205–10.

Dujardin K, Dubois B, Tison F, et al. Parkinson's disease dementia can be easily detected in routine clinical practice. Mov Disord. 2010;25(16):2769–76.

Duncan GW, Firbank MJ, O'Brien JT, Burn DJ. Magnetic resonance imaging: a biomarker for cognitive impairment in Parkinson's disease? Mov Disord. 2013;28(4):425–38.

Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord. 2007a;22(12):1689–707; quiz 1837.

Emre M, Cummings JL, Lane RM. Rivastigmine in dementia associated with Parkinson's disease and Alzheimer's disease: similarities and differences. J Alzheimers Dis. 2007b;11(4):509–19.

Emre M, Tsolaki M, Bonuccelli U, et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010;9(10):969–77.

Engelborghs S, Maertens K, Nagels G, et al. Neuropsychiatric symptoms of dementia: cross-sectional analysis from a prospective, longitudinal Belgian study. Int J Geriatr Psychiatry. 2005;20(11):1028–37.

Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain. 2004;127(Pt 3):550–60.

Galvin JE, Pollack J, Morris JC. Clinical phenotype of Parkinson disease dementia. Neurology. 2006;67(9):1605–11.

Geda YE, Boeve BF, Negash S, et al. Neuropsychiatric features in 36 pathologically confirmed cases of corticobasal degeneration. J Neuropsychiatry Clin Neurosci. 2007;19(1):77–80.
Gerstenecker A, Mast B, Duff K, Ferman TJ, Litvan I. Executive dysfunction is the primary cognitive impairment in progressive supranuclear palsy. Arch Clin Neuropsychol. 2013;28(2):104–13.
Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry. 1988;51(6):745–52.
Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008;71(9):670–6.
Grossman M, Gross RG, Moore P, et al. Difficulty processing temporary syntactic ambiguities in Lewy body spectrum disorder. Brain Lang. 2012;120(1):52–60.
Guerini FR, Beghi E, Riboldazzi G, et al. BDNF Val66Met polymorphism is associated with cognitive impairment in Italian patients with Parkinson's disease. Eur J Neurol. 2009;16(11):1240–5.
Halliday GM, McCann H. The progression of pathology in Parkinson's disease. Ann N Y Acad Sci. 2010;1184:188–95.
Halliday G, Hely M, Reid W, Morris J. The progression of pathology in longitudinally followed patients with Parkinson's disease. Acta Neuropathol. 2008;115(4):409–15.
Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2008;23:837–44.
Henry JD, Crawford JR. Verbal fluency deficits in Parkinson's disease: a meta-analysis. J Int Neuropsychol Soc. 2004;10(4):608–22.
Hoglinger GU, Melhem NM, Dickson DW, et al. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet. 2011;43(7):699–705.
Höglinger GU, Huppertz HJ, Wagenpfeil S, et al. Del Ser T; for the TAUROS MRI Investigators. Tideglusib reduces progression of brain atrophy in progressive supranuclear palsy in a randomized trial. Mov Disord. 2014. doi:10.1002/mds.25815.
Hurtig HI, Trojanowski JQ, Galvin J, et al. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology. 2000;54(10):1916–21.
Irwin DJ, White MT, Toledo JB, et al. Neuropathologic substrates of Parkinson disease dementia. Ann Neurol. 2012;72:587–98.
Irwin DJ, Lee VM, Trojanowski JQ. Parkinson's disease dementia: convergence of alpha-synuclein, tau and amyloid-beta pathologies. Nat Rev Neurosci. 2013;14(9):626–36.
Jankovic J, Poewe W. Therapies in Parkinson's disease. Curr Opin Neurol. 2012;25(4):433–47.
Jean L, Bergeron ME, Thivierge S, Simard M. Cognitive intervention programs for individuals with mild cognitive impairment: systematic review of the literature. Am J Geriatr Psychiatry. 2010;18(4):281–96.
Jeannerod M, Jacob P. Visual cognition: a new look at the two-visual systems model. Neuropsychologia. 2005;43(2):301–12.
Jellinger KA. Morphological substrates of parkinsonism with and without dementia: a retrospective clinico-pathological study. J Neural Transm Suppl. 2007;72:91–104.
Jellinger KA, Seppi K, Wenning GK, Poewe W. Impact of coexistent Alzheimer pathology on the natural history of Parkinson's disease. J Neural Transm (Vienna, Austria : 1996). 2002;109(3):329–39.
Jones EL, Aarsland D, Londos E, Ballard C. A pilot study examining associations between DYRK1A and alpha-synuclein dementias. Neurodegener Dis. 2012;10(1–4):229–31.
Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain. 2010;133(Pt 6):1755–62.
Kim HJ, Jeon BS, Kim YE, et al. Clinical and imaging characteristics of dementia in multiple system atrophy. Parkinsonism Relat Disord. 2013;19(6):617–21.
Kotzbauer PT, Cairns NJ, Campbell MC, et al. Pathologic accumulation of alpha-synuclein and Abeta in Parkinson disease patients with dementia. Arch Neurol. 2012;69(10):1326–31.

Kouri N, Murray ME, Hassan A, et al. Neuropathological features of corticobasal degeneration presenting as corticobasal syndrome or Richardson syndrome. Brain. 2011;134(Pt 11): 3264–75.
Kovari E, Gold G, Herrmann FR, et al. Lewy body densities in the entorhinal and anterior cingulate cortex predict cognitive deficits in Parkinson's disease. Acta Neuropathol. 2003;106(1):83–8.
Kudlicka A, Clare L, Hindle JV. Executive functions in Parkinson's disease: systematic review and meta-analysis. Mov Disord. 2011;26(13):2305–15.
Larsson V, Engedal K, Aarsland D, Wattmo C, Minthon L, Londos E. Quality of life and the effect of memantine in dementia with lewy bodies and Parkinson's disease dementia. Dement Geriatr Cogn Disord. 2011;32(4):227–34.
Lee SE, Rabinovici GD, Mayo MC, et al. Clinicopathological correlations in corticobasal degeneration. Ann Neurol. 2011;70(2):327–40.
Lee W, Williams DR, Storey E. Cognitive testing in the diagnosis of parkinsonian disorders: a critical appraisal of the literature. Mov Disord. 2012;27(10):1243–54.
Leroi I, Overshott R, Byrne EJ, Daniel E, Burns A. Randomized controlled trial of memantine in dementia associated with Parkinson's disease. Mov Disord. 2009;24(8):1217–21.
Levy G, Tang MX, Cote LJ, et al. Motor impairment in PD: relationship to incident dementia and age. Neurology. 2000;55(4):539–44.
Levy G, Schupf N, Tang MX, et al. Combined effect of age and severity on the risk of dementia in Parkinson's disease. Ann Neurol. 2002;51(6):722–9.
Liepelt I, Gaenslen A, Godau J, et al. Rivastigmine for the treatment of dementia in patients with progressive supranuclear palsy: clinical observations as a basis for power calculations and safety analysis. Alzheimers Dement. 2010;6(1):70–4.
Ling H, O'Sullivan SS, Holton JL, et al. Does corticobasal degeneration exist? A clinicopathological re-evaluation. Brain. 2010;133(Pt 7):2045–57.
Litvan I. Cognitive disturbances in progressive supranuclear palsy. J Neural Transm Suppl. 1994;42:69–78.
Litvan I, Mangone CA, McKee A, et al. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. J Neurol Neurosurg Psychiatry. 1996;60(6):615–20.
Litvan I, Campbell G, Mangone CA, et al. Which clinical features differentiate progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) from related disorders? A clinicopathological study. Brain. 1997;120(Pt 1):65–74.
Litvan I, Phipps M, Pharr VL, Hallett M, Grafman J, Salazar A. Randomized placebo-controlled trial of donepezil in patients with progressive supranuclear palsy. Neurology. 2001;57(3): 467–73.
Litvan I, Goldman JG, Tröster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord. 2012;27(3):349–56.
Martinez-Martin P, Falup-Pecurariu C, Rodriguez-Blazquez C, et al. Dementia associated with Parkinson's disease: applying the Movement Disorder Society Task Force criteria. Parkinsonism Relat Disord. 2011;17(8):621–4.
Masliah E, Rockenstein E, Veinbergs I, et al. b-amyloid peptides enhance a-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease. Proc Natl Acad Sci U S A. 2001;98:12245–50.
Massano J, Bhatia KP. Clinical approach to Parkinson's disease: features, diagnosis, and principles of management. Cold Spring Harb Perspect Med. 2012;2(6):a008870.
Massman PJ, Kreiter KT, Jankovic J, Doody RS. Neuropsychological functioning in cortical-basal ganglionic degeneration: differentiation from Alzheimer's disease. Neurology. 1996;46(3): 720–6.
McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. J Alzheimers Dis. 2006;9(3 Suppl):417–23.

McKeith I, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet. 2000;356(9247): 2031–6.

Mimura M, White RF, Albert ML. Corticobasal degeneration: neuropsychological and clinical correlates. J Neuropsychiatry Clin Neurosci. 1997;9(1):94–8.

Morley JF, Xie SX, Hurtig HI, et al. Genetic influences on cognitive decline in Parkinson's disease. Mov Disord. 2012;27(4):512–8.

Mosimann UP, Mather G, Wesnes KA, O'Brien JT, Burn DJ, McKeith IG. Visual perception in Parkinson disease dementia and dementia with Lewy bodies. Neurology. 2004;63(11): 2091–6.

Nalls MA, Duran R, Lopez G, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol. 2013;70(6):727–35.

Nath U, Ben-Shlomo Y, Thomson RG, Lees AJ, Burn DJ. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. Neurology. 2003;60(6):910–6.

Neumann J, Bras J, Deas E, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain. 2009;132(Pt 7):1783–94.

Oertel W, Poewe W, Wolters E, et al. Effects of rivastigmine on tremor and other motor symptoms in patients with Parkinson's disease dementia: a retrospective analysis of a double-blind trial and an open-label extension. Drug Saf. 2008;31(1):79–94.

Ondo WG, Shinawi L, Davidson A, Lai D. Memantine for non-motor features of Parkinson's disease: a double-blind placebo controlled exploratory pilot trial. Parkinsonism Relat Disord. 2011;17(3):156–9.

Paris AP, Saleta HG, de la Cruz Crespo Maraver M, et al. Blind randomized controlled study of the efficacy of cognitive training in Parkinson's disease. Mov Disord. 2011;26(7):1251–8.

Perry EK, Curtis M, Dick DJ, et al. Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. J Neurol Neurosurg Psychiatry. 1985;48(5): 413–21.

Pillon B, Deweer B, Agid Y, Dubois B. Explicit memory in Alzheimer's, Huntington's, and Parkinson's diseases. Arch Neurol. 1993;50(4):374–9.

Pillon B, Blin J, Vidailhet M, et al. The neuropsychological pattern of corticobasal degeneration: comparison with progressive supranuclear palsy and Alzheimer's disease. Neurology. 1995; 45(8):1477–83.

Poewe W, Wolters E, Emre M, et al. Long-term benefits of rivastigmine in dementia associated with Parkinson's disease: an active treatment extension study. Mov Disord. 2006;21(4): 456–61.

Poulopoulos M, Levy OA, Alcalay RN. The neuropathology of genetic Parkinson's disease. Mov Disord. 2012;27(7):831–42.

Rosenthal E, Brennan L, Xie S, et al. Association between cognition and function in patients with Parkinson disease with and without dementia. Mov Disord. 2010;25(9):1170–6.

Schmitt FA, Farlow MR, Meng X, Tekin S, Olin JT. Efficacy of rivastigmine on executive function in patients with Parkinson's disease dementia. CNS Neurosci Ther. 2010;16(6):330–6.

Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: treatments for the non-motor symptoms of Parkinson's disease. Mov Disord. 2011;26 Suppl 3:S42–80.

Shimada H, Hirano S, Shinotoh H, et al. Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET. Neurology. 2009;73:273–8.

Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. 2009;361(17):1651–61.

Stamelou M, Alonso-Canovas A, Bhatia KP. Dystonia in corticobasal degeneration: a review of the literature on 404 pathologically proven cases. Mov Disord. 2012;27(6):696–702.

Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. Lancet Neurol. 2012;11(8): 697–707.

Tsuang D, Leverenz JB, Lopez OL, et al. GBA mutations increase risk for Lewy body disease with and without Alzheimer disease pathology. Neurology. 2012;79(19):1944–50.
Tsuang D, Leverenz JB, Lopez OL, et al. APOE epsilon4 increases risk for dementia in pure synucleinopathies. JAMA Neurol. 2013;70(2):223–8.
Tsuboi Y, Josephs KA, Boeve BF, et al. Increased tau burden in the cortices of progressive supranuclear palsy presenting with corticobasal syndrome. Mov Disord. 2005;20(8):982–8.
Weintraub D. Dopamine and impulse control disorders in Parkinson's disease. Ann Neurol. 2008;64 Suppl 2:S93–100.
Weintraub D, Papay K, Siderowf A. Screening for impulse control symptoms in patients with de novo Parkinson disease: a case-control study. Neurology. 2013;80(2):176–80.
Wenning GK, Jellinger KA. The role of alpha-synuclein in the pathogenesis of multiple system atrophy. Acta Neuropathol. 2005;109(2):129–40.
Wenning GK, Litvan I, Jankovic J, et al. Natural history and survival of 14 patients with corticobasal degeneration confirmed at postmortem examination. J Neurol Neurosurg Psychiatry. 1998;64(2):184–9.
Wesnes KA, McKeith I, Edgar C, Emre M, Lane R. Benefits of rivastigmine on attention in dementia associated with Parkinson disease. Neurology. 2005;65(10):1654–6.
Whitehouse PJ, Hedreen JC, White 3rd CL, Price DL. Basal forebrain neurons in the dementia of Parkinson disease. Ann Neurol. 1983;13(3):243–8.
Wider C, Ross OA, Nishioka K, et al. An evaluation of the impact of MAPT, SNCA and APOE on the burden of Alzheimer's and Lewy body pathology. J Neurol Neurosurg Psychiatry. 2012; 83:424–9.
Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. Lancet Neurol. 2009a;8(3):270–9.
Williams DR, Lees AJ. How do patients with parkinsonism present? A clinicopathological study. Intern Med J. 2009b;39(1):7–12.
Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain. 2005;128(Pt 6):1247–58.
Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. 2009;132:2958–69.
Winter Y, Spottke AE, Stamelou M, et al. Health-related quality of life in multiple system atrophy and progressive supranuclear palsy. Neurodegener Dis. 2011;8(6):438–46.
Yarnall A, Rochester L, Burn DJ. The interplay of cholinergic function, attention, and falls in Parkinson's disease. Mov Disord. 2011;26:2496–503.
Yarnall AJ, Rochester L, Baker MR, et al. Short latency afferent inhibition: a biomarker for mild cognitive impairment in Parkinson's disease? Mov Disord. 2013;28(9):1285–8.

Chapter 12
Vascular Dementia and Parkinsonism

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Abstract Cerebrovascular disease is a leading cause of mortality and morbidity worldwide. Its clinical manifestations vary from acute neurological deficit to stepwise or slowly progressive chronic deficits. Although originally described as separate entities, vascular dementia and vascular parkinsonism are overlapping spectrums of cognitive and extrapyramidal manifestations associated with subcortical vascular damage. In this chapter, we discuss the main concepts underlying the historical concepts of Binswanger encephalopathy and lower-body parkinsonism, present the main features of vascular dementia and vascular parkinsonism, summarize recommendations for clinical management, and close with suggestions for future research in these prevalent and often neglected conditions.

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Cerebrovascular Disease

Cerebrovascular disease (CVD) is a leading public health problem and a major cause of adult and elderly disability. Although acute stroke is associated with a high mortality, chronic progressive vascular damage accounts for a significant proportion of the neurological decline associated with ageing and with slowly progressive forms of neurological disability, including so-called vascular dementia and vascular parkinsonism.

CVD might be caused by intracerebral micro- or macrobleed or by neuronal death due to ischemia. The latter one is caused by primary vasculopathies, procoagulant hematological conditions, or embolic causes of stroke, mainly heart disease. The most common cause of chronic ischemic cerebrovascular disease presents in the elderly and stems from progressive atherosclerotic damage to large, medium, and small vessels caused by a combination of various risk factors. The main risk factors are ageing, hypertension, smoking, diabetes mellitus, dyslipidemia, and obesity. In addition, non-atherosclerotic vasculopathies, which are individually rare, make up a significant proportion of the cerebrovascular disease observed in the young adult population and include alcohol consumption, drug misuse, vasculitis, collagen disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial disease, fibromuscular dysplasia, syphilis, HIV, and idiopathic or traumatic arterial dissection, among others. Hematological causes of stroke include sickle cell disease, polycythemia or thrombocythemia of various origins, antiphospholipid antibody syndrome, malignancies (including myeloma, leukemia, and solid tumors), and the more rare thrombotic thrombocytopenic purpura, paroxysmal nocturnal hemoglobinuria, and genetic thrombophilias. Cardiac causes of CVD include atrial fibrillation, vascular heart disease, bacterial and marantic endocarditis, and less frequently myocardial infarction and chronic cardiomyopathy.

All of these contributing factors for CVD can happen concomitantly, and therefore patients will often present mixed forms of CVD, including large, medium, and small artery disease, and often watershed syndromes and chronic encephalopathy (see Table 12.1). Large artery disease usually evolves chronically in the elderly, and carotid or vertebral artery occlusions are often preceded by the chronic development of a network of collateral circulation many times limiting the extensive brain damage that could be caused by acute occlusion of an otherwise healthy artery, even with the physiological anastomosis of the circle of Willis. Classic examples of medium artery disease include the middle cerebral artery syndrome and the basilar artery syndromes. The first can cause hemiplegia and hemisensory loss in the milder cases up to obtundation and life-threatening cerebral edema in the most severe case. The latter can cause various forms of motor deficits, cranial nerve syndromes, and the dramatic locked-in syndrome.

Table 12.1 Mechanisms of cerebrovascular disease

Mechanism	Example of causative condition	Example of clinical syndrome
Large artery occlusion	Atherosclerosis, idiopathic or traumatic arterial dissection	Internal carotid artery syndrome
Medium-sized artery occlusion	Atherosclerosis, vasculitis	Middle cerebral artery syndrome
Small artery disease	Arteriolosclerosis	Lacunar pure complete hemiparesis
Watershed	Hypoxic or hypovolemic state	Postanoxic ischemic encephalopathy after cardiac arrest

The classic acute manifestation of small artery disease is the lacunar stroke: a sudden neurological deficit caused by the occlusion of a small artery, generating a small subcortical or brainstem stroke which is between 1 and 15 mm in size. The most common lacunar syndromes include pure motor hemiplegia, pure hemisensory deficit or pure sensorimotor hemisyndrome (all of which can be complete, incomplete, or alternate, depending on the location of the stroke), ataxia hemiparesis, and also dysarthria and clumsy hand syndrome (often associated with thalamic infarction). The so-called silent small vessel disease will often go unnoticed and asymptomatic even under neurological scrutiny. Nevertheless, small vessel occlusion might lead to cumulative neuronal loss leading to progressive neurological deficit, including extrapyramidal features and cognitive decline.

The Evolving Concepts of Vascular Dementia (VaD) and Vascular Parkinsonism (VP)

Otto Ludwig Binswanger (October, 1852 to July, 1929) had a long-standing career in clinical neuroscience between receiving his medical degree in 1877 and being appointed rector of Jena University in 1911. During his career he worked in neurology, psychology, and psychiatry and contributed with more than 100 papers encompassing subjects from epilepsy to hysteria. It was through his work with neuropathology that he described eight patients suffering from progressive deterioration of their motor and cognitive capacities, including "aphasic disturbances(…), hemiamblyopia or hemianopia, hemiparesis with loss of the sense of pressure, position or touch(…) combined with the slow and relentless deterioration of intellectual performances." He called this syndrome "encephalitis subcorticalis chronica progressive" because at postmortem examination he found that these patients had "a pronounced atrophy of the hemispheric white matter, either restricted to one or more gyri in one brain area or of several hemispheric regions affected with variable severity; (…) these changes are most clearly found in the area of the occipital and temporal lobes, so that temporal and occipital horns are widened into bag-like

cavities, while the anterior portion of the lateral ventricle shows relatively little enlargement and the frontal white matter is almost unaffected by the disease process. (…) The cortex does not show any remarkable macroscopic change apart from a slight narrowing. Invariably, these cases show severe atheroma of the cerebral arteries it is very likely that the subcortical loss of fibres is caused by a deficiency of the blood supply resulting from arteriosclerosis."

The concept that vascular disease could cause progressive neurological disease was new, and it was Alzheimer who coined the term "Binswanger encephalitis" when characterizing this process further in patients of his own. Alzheimer described the microscopic pathology adding that "One can show in the white matter, the presence of more or less numerous foci which produce wide areas of secondary degeneration… Usually the foci are also to be found in the internal capsule, the lenticular nucleus, the thalamus, and particularly in the pons in the region of the pyramidal tract… caused by a particularly severe arteriosclerosis of the long vessels deep in the white matter with intense atrophy of the white matter" (Pearce 1997).

MacDonald Critchley (February, 1900 to October, 1997) was a neurology consultant and later dean at the Institute of Neurology in Queen Square and during his prolific academic life published extensively in the various fields of neurology. In 1929, he described what he called "arteriosclerotic parkinsonism" which he described as a "symptomatic variant of paralysis agitans." Unlike Binswanger's clinicopathological work, Critchley's was a clinical description of a series of patients which he saw critically in comparison with the sparse literature on vascular causes of parkinsonism (then including syphilis and larger strokes) and whose clinical features included short-stepping gait, rigidity, and masked faces, often associated with dementia, pseudobulbar palsy, pyramidal signs, and cerebellar and sphincter dysfunction (Critchley 1929). Due to the lack of pathological confirmation, and the difficulty in establishing diagnostic criteria, Critchley's proposal was heavily criticized although he bravely rejected the idea of a retraction. One of the main criticisms was that patients did not necessarily presented with classic bradykinesia, to which Critchley responded proposing that the syndrome could be better referred to as arteriosclerotic pseudoparkinsonism (Critchley 1981).

As with similar neurological conditions which were progressively differentiated over the twentieth century, the clinical and neuropathological substrates of the conditions described by Binswanger and MacDonald Critchley were further refined by advances in neuroimaging (especially the advent of CT and MRI imaging, largely available in the last decades) and neuropathology (including immunohistochemistry for the various proteins involved in neurodegeneration). Various names have been used to refer to parkinsonism caused by CVD, and more recently "vascular parkinsonism" seems to be the choice among various international centers (see Table 12.2 for historical evolution of the terms).

Although currently it is largely believed that atherosclerosis can cause progressive dementia, vascular parkinsonism remains a somewhat controversial subject; the differentiation between these two conditions among themselves and their symbiotic coexistence with other forms of neurodegeneration remains mysterious. Given that neurodegenerative conditions are most likely the end-spectrum clinical manifestations of widely prevalent neurodegenerative processes (including cell death associated with the deposition of characteristic proteins such as alpha-synuclein,

Table 12.2 Names used to describe parkinsonism caused by cerebrovascular disease

Name	Example of reference
Arteriosclerotic parkinsonism	Critchley (1929)
Arteriosclerotic pseudoparkinsonism	Critchley (1981)
Lower-body or lower-half parkinsonism	Fitzgerald and Jankovic (1989)
Vascular pseudoparkinsonism	Chang CM, Yu YL, Ng HK, Leung SY, Fong KY, et al. Vascular pseudoparkinsonism. Acta Neurol Scand. 1992;86:588–92.
Vascular parkinsonism	Jankovic J. Lower body (vascular) parkinsonism. Arch Neurol. 1990;47:728.
	Zijlmans JC, Thijssen HO, Vogels OJ, Kremer HP, Poels PJ, Schoonderwaldt HC, Merx JL, Van 'T Hof MA, Thien T, Horstink MW, et al. MRI in patients with suspected vascular parkinsonism. Neurology. 1995;45:2183–8.
	Yamanouchi H, Nagura H. Neurological signs and frontal white matter lesions in vascular parkinsonism. A clinicopathologic study. Stroke. 1997;28:965–9.
	Demirkiran et al. (2001)
	Zijlmans et al. (2004a)
	Rampello et al. (2005)

Adapted from from Glass (2012)

beta-amyloid, and tau) and that small vessel disease is almost ubiquitous in the elderly, the differentiation between vascular and primary neurodegeneration is very challenging both on the research and clinical settings (Gorelick and Pantoni 2013), and overall all processes contribute to neurological disability (Fig. 12.1). Overall, in individual cases one process might be grossly more abundant then the other. For example, in cases of clear-cut idiopathic Parkinson's disease (PD) fulfilling Queen Square Brain Bank criteria (Gibb and Lees 1988) and possibly with antemortem confirmation of nigrostriatal deficit (i.e., SPECT or PET scan), often there is some degree of small artery disease in the brain imaging by MRI or CT. Although CVD does not fully justify the entirety of symptoms, which are traditionally attributed to the neurodegenerative process, there is recent evidence that the neuronal damage caused by the vascular disease plays an important role contributing to disability, in particular when it comes to axial symptoms of PD (Bohnen et al. 2011).

Diagnosis of Vascular Dementia and Parkinsonism

The worldwide epidemiology of vascular dementia and vascular parkinsonism remains scatty at best (Vale et al. 2012). This is due to the difficult differentiation between vascular and neurodegenerative chronic conditions, the different diagnostic criteria used historically, and also the frequency of CVD being affected by age, ethnicity, and socioeconomic factors. As a rule of thumb, vascular dementia might account for up to 15–20 % of dementia cases (Bradley et al. 2008) and be classified into various types (see Table 12.3). Vascular parkinsonism may only account for less than 10 % of parkinsonism cases (Glass 2012).

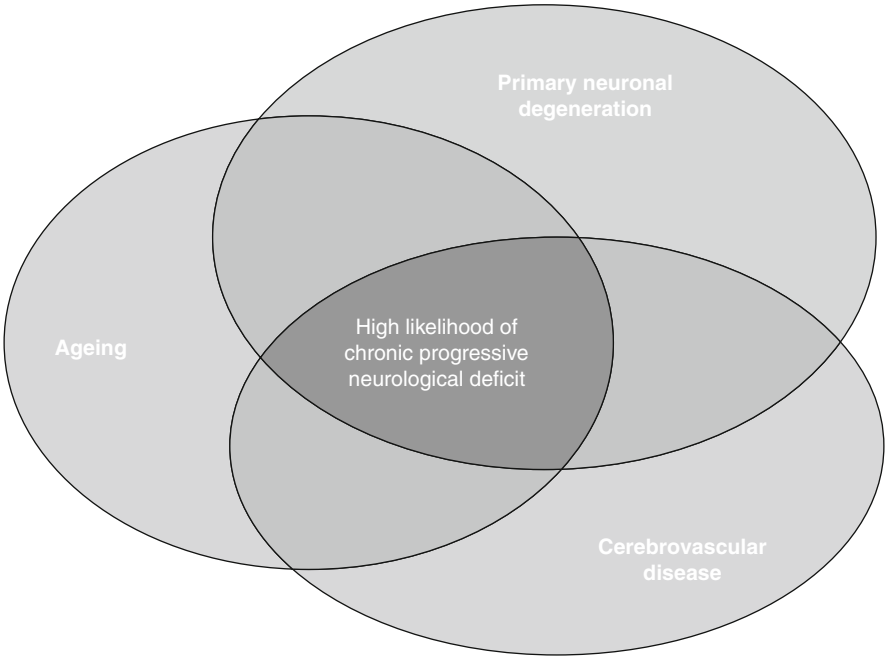

Fig. 12.1 Contributing factors for chronic neurological deficit. The interplay of natural mechanisms of ageing (cell apoptosis, decreased neuronal plasticity, etc.) and cumulative neurodegenerative processes (such as the intracellular deposition of abnormal proteins, cell death, glial dysfunction, etc.) and cerebrovascular disease of the various types contributes to the development of chronic neurological deficit

Table 12.3 Main types of cognitive impairment associated with cerebrovascular disease

Name	Main features
Subcortical ischemic vascular dementia	Chronically progressive cognitive loss associated with a cumulative effect of various small ischemic foci caused by small vessel disease. Also known as small vessel dementia, lacunar state, Binswanger disease, Binswanger encephalopathy
Multi-infarct dementia	Cognitive decline associated with various successive cortical strokes
Strategic infarct dementia	Cognitive decline arising from stroke affecting cognitive area (e.g., angular gyrus, thalamus, basal forebrain, etc.)
Mixed dementia	Combination of significant cerebrovascular disease associated with underlying neurodegeneration, often Alzheimer's disease or TPD43 proteinopathy
Vascular mild cognitive impairment	Cognitive decline not fulfilling clinical criteria for dementia which is associated with significant cerebrovascular disease on brain imaging
Others	Includes specific vascular diseases with associated cognitive decline including CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

Infarcts can be ischemic or hemorrhagic strokes

Table 12.4 Features supporting vascular dementia by NINDS-AIREN criteria

Criteria	Details
Dementia	Cognitive decline from a previous higher level
	Impairment of memory and of two or more domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis)
	Documentation by neurological examination or neuropsychological evaluation
	Enough to interfere with activities of daily living and not due to physical effects of stroke alone
Cerebrovascular disease (CVD)	Focal signs on neurologic examination consistent with stroke (with or without history of stroke)
	And evidence of relevant CVD by brain imaging (CT or MRI)
A relationship between the above two disorders	One or more of the following:
	(a) Onset of dementia within 3 months following a recognized stroke
	(b) Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits

Summarized from Román et al. (1993)
The presence of ALL these features makes vascular dementia "probable"

Despite various limitations (Tang et al. 2004; Román 2004; Ballard et al. 2004), the NINDS-AIREN (Román et al. 1993) remains largely used to diagnose vascular dementia. The NINDS-AIREN criteria classify subjects into definite, probable, and possible vascular dementia based on main features demonstrating (a) dementia, (b) cerebrovascular disease, and (c) a link between these two, which are summarized in Table 12.4. In addition, exclusion criteria and features which make VaD more or less likely are also provided (Table 12.5). The presence of all features supporting VaD and no exclusion makes vascular dementia "probable." Less concrete evidence might still justify a diagnosis of "possible" vascular dementia, while postmortem confirmation of significant cerebrovascular disease without evidence of significant neurodegeneration (i.e., tau and beta-amyloid pathology) closes a diagnosis of "definite" VaD.

In addition to the NINDS-AIREN criteria, the Hachinski ischemic score (Hachinski and Lassen 1974) seen in Table 12.6 might be useful in clinical practice as a rough guide to estimate the likelihood of VaD in a patient with cognitive deficit (Brewster et al. 2012). A meta-analysis of pathologically confirmed cases showed that using a cutoff of ≤ 4 for AD and ≥ 7 for VaD, as originally proposed, yielded a sensitivity of 89.0 % a and a specificity of 89.3 % to differentiate VaD from AD (Moroney et al. 1997).

The clinical diagnosis of vascular parkinsonism remains controversial, although progressive evidence shows that it is a separate clinical entity from neurodegenerative parkinsonism and that it has its own natural history (see Fig. 12.2). It affects older subjects than neurodegenerative parkinsonism in general, with a tendency to start on the eighth decade of life, and, in comparison with Parkinson's disease, patients present with gait difficulties and cognitive decline quicker after disease onset. In addition, gait problems in PD are usually indicative of advanced disease, coinciding with

Table 12.5 Additional criteria for vascular dementia (VaD) by NINDS-AIREN criteria

Criteria	Details
Exclusion criteria	(a) Factors precluding neuropsychological testing: disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment
	(b) Systemic disorders or other brain diseases that could account for deficits
Features which make VaD uncertain or unlikely	(a) Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging
	(b) Absence of focal neurologic signs, other than cognitive disturbance
	(c) Absence of cerebrovascular lesions on brain CT or MRI
Features consistent with probable VaD	(a) Early presence of a gait disturbance (small-step gait or marche à petits pas, or magnetic, apraxic-ataxic, or parkinsonian gait)
	(b) History of unsteadiness and frequent, unprovoked falls
	(c) Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease
	(d) Pseudobulbar palsy
	(e) Personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function

Summarized from Román et al. (1993)

Table 12.6 Hachinski ischemic score

Criteria	Score
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2

Summarized from Hachinski et al. (1975)

admittance to nursing home, which is one of the most important prognostic markers in parkinsonism. In VP, gait disturbance and cognitive decline tend to present earlier in the disease (on average, halfway through the disease course), and patients are only admitted to nursing home much later and closer to the end of the disease course. Multiple system atrophy and progressive supranuclear palsy, which are important differential diagnoses, present much earlier in life and progress faster than VP.

In a clinicopathological study, the clinical features at presentation varied according to the speed of onset and the underlying vascular pathological state, i.e., the presence of strategic (lacunar) infarction and diffuse subcortical ischemic vascular

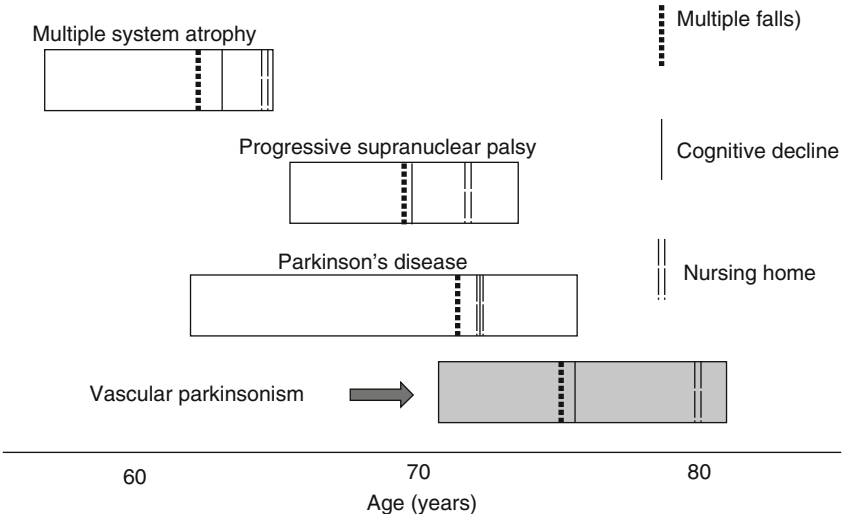

Fig. 12.2 Natural history of vascular parkinsonism. Milestones of disease progression in pathologically proven parkinsonian syndromes. *Bars* represent the time between average disease onset and average age at death (average disease duration). The *vertical lines* indicate the average time to reach each milestone (Adapted from Glass et al. (2012))

disease (Zijlmans et al. 2004a). Certain clinical features are common in VP, including bilateral or acute onset and the presence of an early shuffling gait, falls, cognitive impairment, urinary incontinence, and corticospinal or pseudobulbar signs or symptoms. Zijlmans et al. (2004a) proposed the first criteria for the clinical diagnosis of VP based on a systematic clinicopathological investigation and emphasized that these criteria would need to be evaluated both prospectively and retrospectively against patients with pathologically established other forms of parkinsonism to analyze sensitivity, specificity, and positive and negative predictor values (see Table 12.7). Testing olfactory function may be helpful in differentiating vascular parkinsonism from Parkinson's disease, since in contrast to Parkinson's disease, olfactory function may be preserved (Katzenschlager et al. 2004). Likewise, the presence of a rather symmetrical FP-CIT uptake reduction in the basal ganglia may help to distinguish VP from PD (Zijlmans et al. 2007).

Clinical Management of Vascular Dementia and Vascular Parkinsonism

The main approach to the management of VaD or VP regards the risk factors for progression of vascular disease. These follow the guidelines for cerebrovascular disease in general and should target the main form of CVD present in each specific patient. Pharmacotherapy allied with lifestyles changes can be successful in reducing the rate of progression of the underlying CVD, and might be neuroprotective. Although isolated studies have shown that individual antihypertensive drugs might

Table 12.7 Proposed clinical criteria for the diagnosis of vascular parkinsonism

Criteria	Details
Parkinsonism	Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions in either upper limb or lower limb, including the presence of reduced step length)
	and at least 1 of the following:
	Rest tremor
	Muscular rigidity
	Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Cerebrovascular disease	Evidence of relevant cerebrovascular disease by brain imaging (CT or MRI)
	The presence of focal signs or symptoms that are consistent with stroke
A relationship between these 2 disorders	An acute or delayed progressive onset with infarcts in or near areas that can increase the basal ganglia motor output (GPe [globus pallidus pars externa] or SNc [substantia nigra pars compacta]) or decrease the thalamocortical drive directly (VL [ventral lateral] nuclei of the thalamus, large frontal lobe infarct). At onset, parkinsonism consists of a contralateral bradykinetic rigid syndrome or shuffling gait within 1 year after a stroke (VPa)
In practice:	An insidious onset of parkinsonism with extensive subcortical white matter lesions, bilateral symptoms at onset, and the presence of early shuffling gait or early cognitive dysfunction (VPi); the "classical clinical type"
Exclusion criteria	History of repeated head injury
	Encephalitis
	Neuroleptic treatment at onset of symptoms
	The presence of cerebral tumor or communicating hydrocephalus
	Other alternative explanations for Parkinson syndrome

Summarized from Zijlmans et al. (2004a)

decrease cognitive decline associated with CVD (Peters et al. 2008), it is likely this is a class effect rather than specific. Although dyslipidemia has been strongly associated with cognitive decline, there is not yet enough evidence that statins can reduce cognitive decline per se (McGuiness et al. 2010). While experimental evidence suggests it might decrease amyloidogenesis, clinical trials to date failed to show a neuroprotective effect (Sabbagh and Sparks 2012). There is some evidence that the use of nonsteroidal anti-inflammatory drugs might decrease the risk of both dementia and parkinsonism (Noyce et al. 2012), but not nearly enough to recommend its use. There is not enough evidence for the use of either antiplatelets, anticoagulants, or surgical vascular treatment (Witt et al. 2007) to prevent incidence or progression of VaD or VP, but the normal recommendations for these treatments in the context of CVD do apply.

There is only sparse evidence to support the use of symptomatic treatment in VP and VaD, and a case-by-case consideration is the usual route. The response of the parkinsonian symptoms to levodopa is controversial. Most works on VP

show a limited and only occasional good response to levodopa, sometimes in very high doses (FitzGerald and Jankovic 1989; Winikates and Jankovic 1999; Demirkiran et al. 2001; Rampello et al. 2005; Santangelo et al. 2010; Jellinger 2002). However, a good response has been seen in the majority of the cases with postmortem-confirmed diagnosis of VP collected at the Queen Square Brain Bank (Zijlmans et al. 2004b; Glass et al. 2012), but the fact that this institution targets specifically cases that had an in vivo diagnosis of PD might be responsible for this bias. Taking the literature on VP into consideration and the fact that in clinical practice the differentiation between VP and PD might be quite difficult, a trial of l-dopa is recommended in all cases.

Likewise, other medications for PD might be tried. The controversy regarding the clinical criteria for VaD, the wide array of assorted cognitive testing, and the frequent association of VaD with neurodegeneration make the results of clinical trials on symptomatic drugs for VaD heterogeneous and difficult to interpret. There is no class I evidence for the symptomatic treatment of VaD. Various drugs have been used empirically in clinical practice with inconclusive results in clinical trials, including Ginkgo biloba, piracetam, nicergoline, vinpocetine, pentoxifylline, citicoline, and cerebrolysin. Selective serotonin reuptake inhibitors and environmental modifications might be helpful in behavioral disturbances, agitation, depression, and psychosis (Seitz et al. 2011).

Cholinesterase inhibitors have been shown to be useful for mild to moderate VaD in placebo-controlled clinical trials (Erkinjuntti et al. 2004), including donepezil (Black et al. 2003), galantamine (Erkinjuntti et al. 2002), and rivastigmine (Ballard et al. 2008), particularly in cases of subcortical ischemic VaD, probably due to a greater cholinergic deficit seen in such patients, and in more elderly patients, probably due to concomitant Alzheimer's pathology. Memantine might be useful for moderate to severe VaD as well (Wilcock et al. 2002; Kavirajan and Schneider 2007; McShane et al. 2011). However, although controlled trials did confirm statistically significant improvements in cognitive function by standardized measurements, the clinical significance of the findings and the cost-benefit of such treatments are still uncertain, and for this reason these drugs have not been approved for this therapeutic clinical indication by the drug agencies.

Conclusion

VaD and VP are part of a spectrum of clinical manifestations of rather common neuropathological mechanisms which cause cell death through ischemia/hemorrhage and neurodegeneration. The synergistic combination of underlying pathology, the decrease of cognitive reserve, and other predisposing factors unified culminates with the clinical manifestations observed in these two conditions which often overlap in clinical practice.

References

Ballard CG, Burton EJ, Barber R, Stephens S, Kenny RA, Kalaria RN, O'brien JT. NINDS AIREN neuroimaging criteria do not distinguish stroke patients with and without dementia. Neurology. 2004;63(6):983–8.

Ballard C, Sauter M, Scheltens P, He Y, Barkhof F, van Straaten EC, van der Flier WM, Hsu C, Wu S, Lane R. Efficacy, safety and tolerability of rivastigmine capsules in patients with probable vascular dementia: the VantagE study. Curr Med Res Opin. 2008;24(9):2561–74.

Black S, Román GC, Geldmacher DS, Salloway S, Hecker J, Burns A, Perdomo C, Kumar D, Pratt R, Donepezil 307 Vascular Dementia Study Group. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. Stroke. 2003;34(10):2323–30.

Bohnen NI, Muller ML, Zarzhevsky N, Koeppe RA, Bogan CW, Kilbourn MR, et al. Leucoaraiosis, nigrostriatal denervation and motor symptoms in Parkinson's disease. Brain. 2011;134(Pt 8): 2358–65.

Bradley WG, Daroff RB, Fenichel G, Jankovic J. Neurology in clinical practice. Philadelphia: Butterworth-Heinemann/Elsevier Saunders; 2008.

Brewster PW, Mcdowell I, Moineddin R, Tierney MC. Differential prediction of vascular dementia and Alzheimer's disease in nondemented older adults within 5 years of initial testing. Alzheimers Dement. 2012;8(6):528–35.

Critchley M. Arteriosclerotic parkinsonism. Brain. 1929;52:23–83.

Critchley M. Arteriosclerotic pseudo-parkinsonism. Tunbridge Wells: Pitman Medical; 1981.

Demirkiran M, Bozdemir H, Sarica Y. Vascular parkinsonism: a distinct, heterogeneous clinical entity. Acta Neurol Scand. 2001;104:63–7.

Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomized trial. Lancet. 2002;359:1283–90.

Erkinjuntti T, Roman G, Gauthier S. Treatment of vascular dementia–evidence from clinical trials with cholinesterase inhibitors. J Neurol Sci. 2004;226:63–6.

Fitzgerald PM, Jankovic J. Lower body parkinsonism: evidence for vascular etiology. Mov Disord. 1989;4:249–60.

Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry. 1988;51:745–52.

Glass P. Clinical features of vascular parkinsonism in pathologically confirmed cases. MSc thesis, UCL Institute of Neurology. London, 2012.

Glass PG, Lees AJ, Bacellar A, Zijlmans J, Katzenschlager R, Silveira-Moriyama L. The clinical features of pathologically confirmed vascular parkinsonism. J Neurol Neurosurg Psychiatry. 2012;83(10):1027–9.

Gorelick PB, Pantoni L. Advances in vascular cognitive impairment. Stroke. 2013;44(2):307–8.

Hachinski VC, Lassen NA. Multi-infarct dementia: a cause of mental deterioration in the elderly. Lancet. 1974;2:207–10.

Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. Arch Neurol. 1975;32: 632–7.

Jellinger KA. Vascular parkinsonism-neuropathological findings. Acta Neurol Scand. 2002;105: 414–5.

Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomized controlled trials. Lancet Neurol. 2007;6:782–92.

Katzenschlager R, Zijlmans J, Evans A, Watt H, Lees AJ. Olfactory function distinguishes vascular parkinsonism from Parkinson's disease. J Neurol Neurosurg Psychiatry. 2004;75:1749–52.

Mcshane R, Areosa AS, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. 2011;(3):CD003154.pub1.

Mcguiness B, Ohare J, Craig D, et al. Statins for the treatment of dementia. Cochrane Database Syst Rev. 2010;(8):CD007514.
Moroney JT, Bagiella F, Desmond DW, et al. Meta-analysis of the Hachinski Ischemic Score in pathologically verified dementias. Neurology. 1997;49:1096–105.
Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, Schrag A. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol. 2012;72(6):893–901.
Pearce JMS. Binswanger's "encephalitis subcorticalis chronica progressiva". J Neurol Neurosurg Psychiatry. 1997;63:308. doi:10.1136/jnnp.63.3.308.
Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008;7:683–9.
Rampello L, Alvano A, Battaglia G, Raffaele R, Vecchio I, Malaguarnera M. Different clinical and evolutional patterns in late idiopathic and vascular parkinsonism. J Neurol. 2005;252:1045–9.
Román CG, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINCDS-AIREN International Workshop. Neurology. 1993;43:250–60.
Román GC. Facts, myths, and controversies in vascular dementia. J Neurol Sci. 2004;226(1–2): 49–52.
Sabbagh MN, Sparks DL. Statins to treat Alzheimer's disease: an incomplete story. Expert Rev Neurother. 2012;12(1):27–30. doi:10.1586/ern.11.171.
Santangelo G, Vitale C, Trojano L, de Gaspari D, Bilo L, Antonini A, Barone P. Differential neuropsychological profiles in Parkinsonian patients with or without vascular lesions. Mov Disord. 2010;25:50–6.
Seitz DP, Adunuri N, Gill SS, Gruneir A, Herrmann N, Rochon P. Antidepressants for agitation and psychosis in dementia. Cochrane Database Syst Rev. 2011;(2):CD008191.
Tang WK, Chan SS, Chiu HF, Ungvari GS, Wong KS, Kwok TC, Mok V, Wong KT, Richards PS, Ahuja AT. Impact of applying NINDS-AIREN criteria of probable vascular dementia to clinical and radiological characteristics of a stroke cohort with dementia. Cerebrovasc Dis. 2004;18(2):98–103.
Vale TC, Barbosa MT, Caramelli P, Cardoso F. Vascular parkinsonism and cognitive impairment. Dement Neuropsychol. 2012;6(3):137–44.
Wilcock G, Möbius HJ, Stöffler A, MMM 500 group. A double-blind, placebo-controlled, multicentre study of memantine in mild to moderate vascular dementia (MMM 500). Int Clin Psychopharmacol. 2002;17:197–305.
Winikates J, Jankovic J. Clinical correlates of vascular parkinsonism. Arch Neurol. 1999;56: 98–102.
Witt K, Borsch K, Daniels C, et al. Neuropsychological consequences of endarterectomy and endovascular angioplasty with stent placement for treatment of symptomatic carotid stenosis. A prospective randomized study. J Neurol. 2007;254:1524–32.
Zijlmans JC, Daniel SE, Hughes AJ, Revesz T, Lees AJ. Clinicopathological investigation of vascular parkinsonism, including clinical criteria for diagnosis. Mov Disord. 2004a;19:630–40.
Zijlmans JC, Katzenschlager R, Daniel SE, Lees AJ. The L-dopa response in vascular parkinsonism. J Neurol Neurosurg Psychiatry. 2004b;75:545–7.
Zijlmans J, Evans A, Fontes F, et al. [123I] FP-CIT spect study in vascular parkinsonism and Parkinson's disease. Mov Disord. 2007;22:1278–85.

Chapter 13
Progressive Apraxia of Speech and Primary Progressive Aphasias

Keith A. Josephs and Jennifer L. Whitwell

Abstract Apraxia of speech (AOS) is a motor disorder that occurs as a result of impairment in the planning or programming of movements for speech production. It is typically associated with cerebrovascular events, although it can also occur in the context of neurodegeneration where its importance has typically been deemphasized to "just a component of a presenting syndrome." Primary progressive aphasia (PPA) is such a syndrome in which AOS coexists with other linguistic deficits, typically agrammatic aphasia. Recently, however, AOS has been demonstrated to occur in a pure or isolated form, known as primary progressive apraxia of speech (PPAOS), reaffirming the importance of neurodegenerative AOS. Furthermore, anatomic and pathologic associations differ between AOS-dominant syndromes and PPA variants. Understanding the relationship between AOS-dominant variants, including PPAOS and PPA, and their relationship to movement disorders including corticobasal degeneration and progressive supranuclear palsy, is important and will be the focus of this chapter.

Keywords Apraxia of speech • Primary progressive aphasia • Tau • Progressive supranuclear palsy • Corticobasal degeneration • Agrammatic aphasia

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Part I Clinical

Apraxia of Speech

Apraxia of speech (AOS) is a type of motor speech disorder that occurs as a result of a defect in the planning and programming of speech production (Darley et al. 1975). Apraxia of speech has characteristics that are distinct from dysarthria, another type of motor speech disorder. Dysarthria, unlike AOS, reflects a defect of neuromuscular function (Darley et al. 1969). The salient features of AOS are sound production errors that may include any combination of distorted sound substitutions, additions, prolongations, and truncations. Articulation is effortful and is associated with groping and uncoordinated movements of buccolingual structures.

Apraxia of speech has been most commonly associated with cerebrovascular events in which the onset is acute and severity maximum. More recently, however, there has been increased interest in AOS that is progressive in nature (Duffy 2006, 2013). Progressive AOS (PAOS), unlike AOS due to cerebrovascular events, is characterized by a general worsening of AOS features; errors in speech production become more frequent and more severe over time (Table 13.1). As a result, verbal communication becomes more problematic. Ultimately, patients with PAOS become anarthric and are no longer able to verbally communicate.

Progressive Apraxia of Speech

Progressive AOS is one of the cardinal features of a neurodegenerative disorder and should be viewed in the same light as progressive memory loss or progressive gait impairment. Progressive AOS can co-occur with other cognitive and motor features and hence be a component of a neurodegenerative syndrome. In fact, it may be the most prominent component of the syndrome. Recently, it has been demonstrated that PAOS can be an isolated feature at presentation and hence can exist in a pure form in the absence of other cognitive and motor features (Josephs et al. 2012). When PAOS occurs in isolation, we used the term primary progressive apraxia of speech (PPAOS) (Duffy 2006; Josephs et al. 2012) (Table 13.1). Patients with PPAOS or PAOS, in which AOS is the most salient feature, will decline over time, and sometimes other cognitive and motor deficits will develop, resulting in the emergence of a variety of progressive clinical syndromes (Fig. 13.1). Most commonly, it appears that patients with PAOS or PPAOS later develop difficulty with balance and gait, aphasia, limb praxis, Parkinsonism, and eye movement abnormalities (Broussolle et al. 1992; Josephs et al. 2006a). In fact, it has been observed that some patients that initially presented with PAOS later develop features of progressive supranuclear palsy syndrome (PSPS) or corticobasal syndrome (CBS) (Josephs et al. 2006a; Josephs and Duffy 2008). Such patients tend to have limb coordination problems, may begin to fall, and may ultimately become wheel chair bound. Another subset

Table 13.1 Clinical definitions and demographics based on a cohort of 100 subjects

Clinical syndrome	Definition	Mean age at onset	Gender dominance
Primary progressive apraxia of speech (PPAOS)	Apraxia of speech is the only feature present and is characterized by distorted sound production	69	Female
Progressive apraxia of speech (PAOS)	Apraxia of speech is the most prominent feature. Additional motor, cognitive, or language features are present but are less prominent	67	Male
Agrammatic variant of primary progressive aphasia (agPPA)	Agrammatic aphasia is the only feature present or the most prominent feature. Apraxia of speech may be present but is less prominent	66	Equal
Semantic variant of primary progressive aphasia (svPPA)	Syndrome characterized by poor naming and loss of word meaning.	64	Equal
Logopenic variant of primary progressive aphasia (lvPPA)	Syndrome characterized by poor naming without loss of word meaning, poor sentence repetition, and phonological errors	63	Equal
Corticobasal syndrome (CBS)	Syndrome characterized by asymmetric ideomotor apraxia, dystonia, parkinsonism, and cortical sensory loss. Apraxia of speech and agrammatic aphasia may be present.	N/A	N/A
Syndrome + motor neuron disease	Features of apraxia of speech or agrammatic aphasia are accompanied by features of motor neuron disease, such as spastic and flaccid dysarthria, tongue and limb fasciculation, weakness, hyperreflexia, and Babinski sign	N/A	N/A

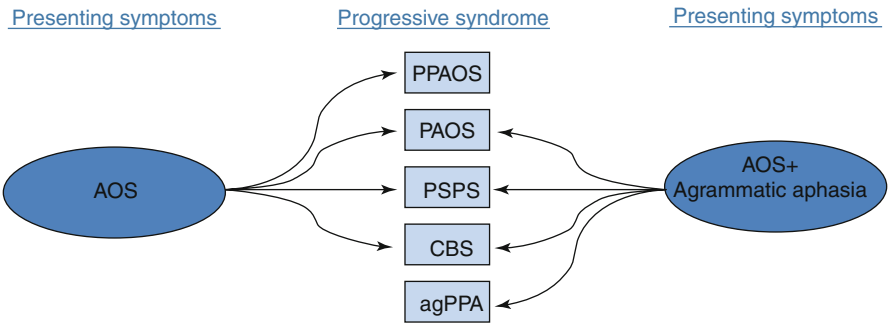

Fig. 13.1 demonstrates how patients presenting with apraxia of speech variants progress over time. *AOS* apraxia of speech, *agPPA* agrammatic variant of primary progressive aphasia, *PAOS* progressive apraxia of speech (i.e., AOS >>other cognitive and motor features), *PPAOS* primary progressive apraxia of speech (AOS only), *CBS* corticobasal syndrome, *PSPS* progressive supranuclear palsy syndrome

of patients with dominant AOS or PPAOS develops agrammatic aphasia in written and spoken form (Josephs et al. 2006a). In such instances, the AOS remains more prominent than the aphasia.

Syndromes Associated with Progressive Apraxia of Speech

Progressive apraxia of speech may coexist with other cognitive and motor deficits. In some instances, the PAOS is the most prominent feature of the presenting syndrome. In such instances, the chief complaint is usually that of speech problems; other presenting features are more subtle and at times may only have been identified during the neurological and/or speech and language evaluation. In other instances, when AOS coexists with other cognitive and/or motor deficits, the other features of the syndrome overshadow the AOS. Typically, when this occurs, the chief complaint is related to one of the other symptoms and the AOS tends to be mild. Two syndromes that are worth discussing in detail in which PAOS commonly occurs early in the disease course are primary progressive aphasia (PPA) and CBS.

Primary Progressive Aphasia

The term primary progressive aphasia (PPA) is used in situations in which there is a progressive disorder characterized by impairment of specific aspects of language function (Mesulam 1982, 2001). These include grammar, naming, single word comprehension, sentence comprehension, and repetition. Three subtypes of PPA are now recognized (Table 13.1).

Agrammatic Variant of PPA

The first subtype of PPA is the agrammatic variant (agPPA) (Gorno-Tempini et al. 2011). Agrammatic PPA is a syndrome in which the most salient feature is that of agrammatism in language production. This may be observed in spoken or written form. In agrammatic PPA, function words and articles may be conspicuously absent, e.g., “Man fishing with wife on dock. Boat goes by she waves to them.” Importantly, patients with agPPA commonly also exhibit PAOS (Ogar et al. 2005). Hence, agPPA is typically characterized by the presence of agrammatic aphasia of greater severity than the accompanying PAOS (Josephs et al. 2013a). Examination shows little deficits in naming and in sentence repetition for content words, as well as difficulty understanding complex sentence structures, e.g., “put the brown newspaper under the blue book in the middle drawer.” Importantly, given that PPA is a disorder of language, a diagnosis of PPA should only be made when language impairment, not AOS, is the most prominent feature of the syndrome (Mesulam 2003).

Semantic Variant of PPA

The second subtype of PPA is the semantic variant (svPPA) (Gorno-Tempini et al. 2011; Warrington 1975). In svPPA, the speech output is fluent and may even be excessively verbose. However, with more careful attention to what is actually being said, it becomes apparent that the patient is being circumloquacious in order to avoid certain words that no longer has specific meaning to the patient. Therefore, specific words may be absent in general conversation and replaced with more general words for the item or object being described, e.g., the patient may say animal instead of hyena or flower instead of hibiscus. There may also be reference to the fact that the patient no longer understands the meaning of certain words; the patient may no longer know what the word lapel means and hence will not be able to tell how a lapel is different from a collar. Examination shows poor naming and loss of single word meaning and comprehension (Hodges and Patterson 2007). Unlike in agPPA, AOS rarely, if ever, coexists with svPPA.

Logopenic Variant of PPA

The third subtype of PPA is the logopenic variant (lvPPA) (Gorno-Tempini et al. 2004, 2011). In lvPPA, the speech output may be fluent, but it may also be characterized by hesitancy as the patient pauses and searches for words. However, unlike in svPPA, patients with lvPPA can easily recognize the item when the name is provided by the examiner, and hence the patient has *not* lost word meaning. Memory loss is also often a common complaint in patients with lvPPA. Like in svPPA, patients with lvPPA perform poorly on naming tasks but there is no loss of word meaning. Examination also reveals poor repetition of sentences with loss of words or replacement of exact content words. One additional feature of lvPPA is the production of sound errors known as phonological or phonemic errors. With phonological errors, one sound is produced for another, e.g., sesipic instead of specific. Importantly, unlike in AOS, the sounds are not distorted. It can be difficult at times to distinguish AOS errors from phonological errors, resulting in patients with lvPPA being misdiagnosed as having PAOS and vice versa. Apraxia of speech rarely occurs in lvPPA.

Corticobasal Syndrome

Apraxia of speech and agrammatic aphasia, occurring together or separately, can be early features of corticobasal syndrome (CBS) (Josephs et al. 2006a; Josephs and Duffy 2008; Assal et al. 2012; Kertesz et al. 2005). As described in the CBS chapter, CBS is diagnosed in a patient presenting with asymmetric signs and symptoms indicative of cortical and basal ganglia dysfunction. Patients with CBS may present with asymmetric ideomotor apraxia, cogwheel or gegenhalten rigidity, bradykinesia, action myoclonus, dystonia, astereognosis, and agraphesthesia (Armstrong et al. 2013).

Patients with CBS, who also have AOS, are more likely to show right limb asymmetry, i.e., the right side is the more affected side, and often also have agrammatic aphasia. In CBS in which AOS or agrammatic aphasia are present, the presenting complaint is usually that of limb dysfunction, as opposed to speech difficulties, although both may be mentioned as being experienced by the patient.

Overlap with Motor Neuron Disease

Although we have described these syndromes as being relatively pure, it needs to be recognized that these clinical syndromes can also be associated with motor neuron disease (MND) (Caselli et al. 1993; Coon et al. 2011; Czell et al. 2013; da Rocha et al. 2007) (Table 13.1). However, in such instances, the syndrome is also characterized by the presence of flaccid and spastic dysarthria. In fact, it is the dysarthrias that are most likely to be the dominant feature on examination, not the AOS nor the aphasia. Therefore, in the absence of flaccid and spastic, or just flaccid dysarthria, MND is unlikely to be identified. One large series identified patients with AOS that had MND (Duffy et al. 2007). However, all of the patients had coexisting spastic and flaccid dysarthria (Duffy et al. 2007). Motor neuron disease almost never coexists with lvPPA and only very rarely coexists with svPPA. In the latter case, a rare association of svPPA and pure upper MND, i.e., no anterior horn cell disease, has been described (Josephs et al. 2013b).

Movement Disorders Associated with Apraxia of Speech and Primary Progressive Aphasia

Apraxia of speech can be associated with movement disorders, although the movement disorder identified tends to be a syndrome as opposed to being an isolated feature. We previously discussed the association of AOS and CBS at presentation; patients with AOS may also show features of CBS and PSPS with disease progression. When this occurs, the patient is usually 5 years out from onset. It is rare, however, for the classic syndrome of PSPS to co-occur with AOS at presentation (Whitwell et al. 2013a). When PSPS features develop in patients that originally present with PPAOS or PAOS, they tend to be milder than what is typically observed in PSPS that starts off with balance problems and eye movement abnormalities. However, slowing of vertical eye movements, balance problems, and falls become more prevalent and severe over time in patients presenting with PPAOS or PAOS. Similarly, patients with PPAOS or PAOS may show the emergence of ideomotor apraxia after many years (Josephs et al. 2006a, 2012). Of the three PPA syndromes, agPPA is the one most likely to also develop features of CBS and PSPS over time (Kertesz et al. 2005). In fact, ideomotor apraxia has been shown to be more common in agPPA than lvPPA (Adeli et al. 2013). Parkinsonian features such as rigidity and

bradykinesia are relatively common later on in the disease course in PPAOS and PAOS. In PPA, almost 30 % of patients present with at least one parkinsonian sign, such as bradykinesia, rigidity, tremor, postural instability, or gait disturbance (Kremen et al. 2011). Parkinsonian features are more common in agPPA than lvPPA and are almost absent in svPPA (Graff-Radford et al. 2012; Kremen et al. 2011). Dystonia is much less common but may also be observed later on in the disease course. Hyperkinetic movements can also occur, although resting tremor is rare. Asymmetric limb myoclonus can occur later on in the disease course in patients who later develop the CBS. Stereotypies and ticks have not been emphasized in PPA, PPAOS, or PAOS.

Part II Anatomy

Anatomy of Progressive Apraxia of Speech

Routine clinical studies in patients with PAOS have not been very helpful in identifying the anatomic correlate of PAOS. However, studies using research-based imaging techniques performed using groups of patients have demonstrated that PAOS is associated with the premotor cortex. Structural magnetic resonance imaging (MRI) studies using voxel-level techniques, such as voxel-based morphometry, in patients with PPAOS have shown focal patterns of grey matter atrophy involving the superior premotor and supplemental motor cortices (Josephs et al. 2012; Whitwell et al. 2013a). White matter atrophy is also observed in the premotor cortex, underlying regions of grey matter loss, but tends to also involve inferior premotor regions. Detailed analysis of white matter tracts using diffusion tensor imaging (DTI) has shown that PPAOS is associated with degeneration of premotor aspects of the superior longitudinal fasciculus and the body of the corpus callosum (Josephs et al. 2012). Hypometabolism on 18-F fluorodeoxyglucose positron emission tomography (FDG-PET) scans is also observed in the superior premotor cortices in patients with PPAOS (Fig. 13.2a), although hypometabolism on FDG-PET can be very mild, or even absent, in some patients (Josephs et al. 2012).

Imaging findings in patients with PPAOS overlap to some degree with those associated with PSPS, with both syndromes showing atrophy and hypometabolism in the premotor cortex and degeneration of the superior longitudinal fasciculus and body of the corpus callosum (Whitwell et al. 2011, 2013a; Knake et al. 2010; Josephs et al. 2008). However, in contrast to PPAOS, patients with PSPS typically show greater involvement of the prefrontal cortex and striking atrophy in the midbrain (Whitwell et al. 2013a). Mild midbrain atrophy has however been observed in patients with PPAOS, likely reflecting the fact that these patients often develop clinical features of PSPS (Whitwell et al. 2013a). In patients with both PAOS and agrammatic aphasia, where the AOS is the more dominant feature, VBM and FDG-PET studies show involvement of the superior premotor cortex extending into the middle and inferior premotor regions (Fig. 13.2b) (Josephs et al. 2013a). This finding suggests that the

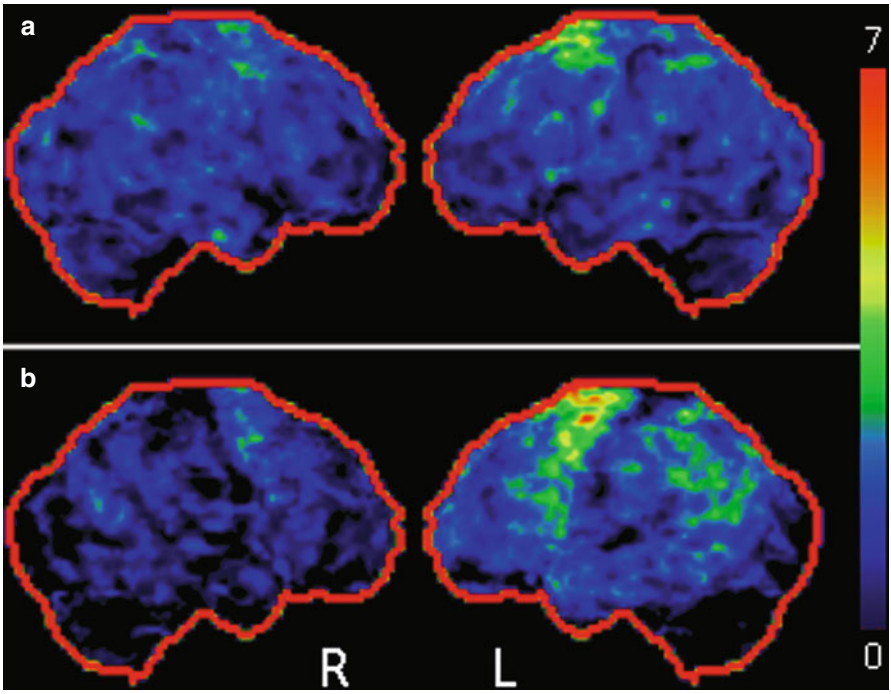

Fig. 13.2 demonstrates focal hypometabolism of the left superior premotor cortex in a patient with PPAOS (**a**) with extension of the hypometabolism into middle and inferior premotor cortices in a patient with PAOS (AOS > agrammatic aphasia) (**b**)

agrammatic aphasia component is associated with involvement of the inferior premotor cortex. Indeed, correlations have been observed between volume and metabolism in the inferior premotor cortex, particularly the pars triangularis which forms part of Broca's area, and the severity of agrammatic aphasia (Whitwell et al. 2013b). In contrast, the severity of AOS has been shown to correlate to volume of the superior premotor cortex (Whitwell et al. 2013b). These findings show that AOS and agrammatic aphasia have distinct neuroanatomical underpinnings.

Anatomy of Primary Progressive Aphasia

Each of the three variants of PPA shows distinct regional abnormalities within the frontotemporal and parietal cortices. In agPPA, routine brain MRI scans reveal atrophy of the left inferior frontal lobe with widening of the left perisylvian fissure (Fig. 13.3a). Research studies demonstrate atrophy and hypometabolism on FDG-PET throughout the left premotor cortex (Fig. 13.3b) but also with involvement of the left insula, striatum, lateral temporal lobes, and often other regions in the left frontal and parietal lobes (Josephs et al. 2006a, 2010; Gorno-Tempini et al. 2004;

Grossman et al. 2004; Rohrer et al. 2009). Patterns observed in patients with agPPA are typically more widespread than those observed in patients with PAOS. Relatively widespread patterns of white matter tract degeneration have also been observed in agPPA, involving the superior longitudinal fasciculus, corpus callosum, anterior cingulate, inferior frontal-occipital fasciculus, and temporal lobe tracts such as the

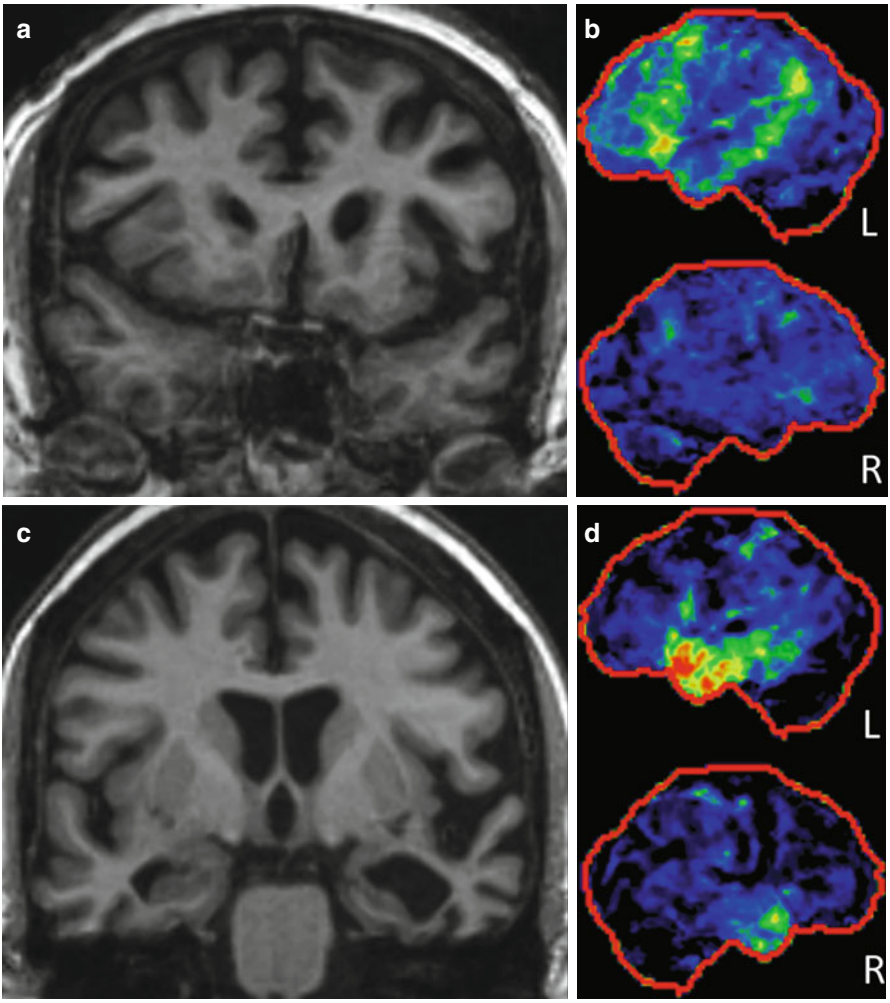

Fig. 13.3 demonstrates the abnormalities that can be identified on MRI and FDG-PET in patients with the different variants of PPA. In (**a**), a patient with agPPA shows widening of the left perisylvian area, while in (**b**), FDG-PET shows premotor cortical hypometabolism, as well as hypometabolism in left temporal and even parietal cortices. On MRI (**c**) there is left > right anterior medial temporal lobe atrophy which is also seen on the FDG-PET scan (**d**) in a patient with svPPA. A patient with the lvPPA variant shows left parietal atrophy on MRI (**e**), while FDG-PET shows left temporal and parietal hypometabolism (**f**)

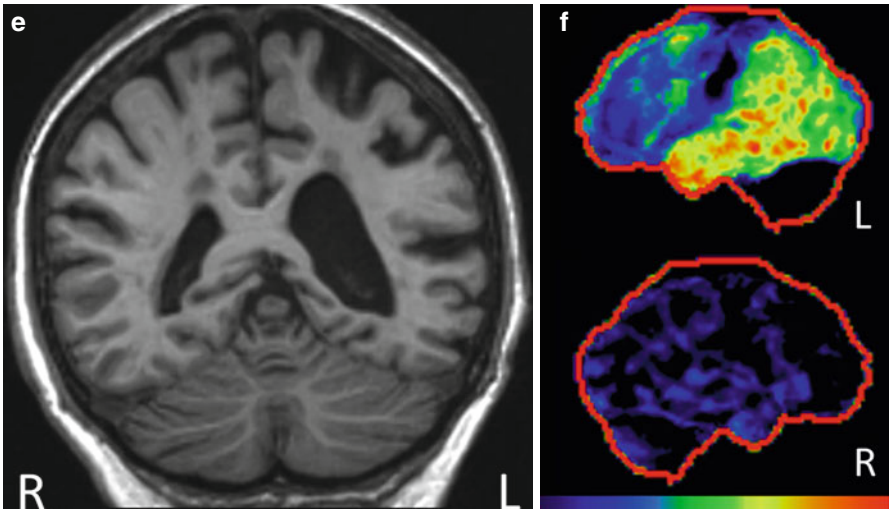

Fig. 13.3 (continued)

uncinate fasciculus and inferior longitudinal fasciculus (Galantucci et al. 2011; Schwindt et al. 2013; Whitwell et al. 2010a; Grossman et al. 2013). White matter tract degeneration is typically asymmetric, with greater involvement of the left hemisphere. Patients with agPPA and parkinsonism can also show glucose hypometabolism in the bilateral dorsal and left ventral midbrain (Roh et al. 2010).

In svPPA, there is a distinct pattern of anterior medial temporal lobe atrophy that is easily detected with routine MRI scans (Fig. 13.3c). Atrophy typically targets the fusiform and inferior temporal gyri, although atrophy is also observed in the hippocampus, amygdala, entorhinal cortex, and middle temporal gyrus (Chan et al. 2001; Galton et al. 2001; Mummery et al. 2000). This pattern of abnormality is also observed on FDG-PET scans (Fig. 13.3d). White matter tract degeneration on DTI predominantly involves temporal lobe tracts, particularly the uncinate fasciculus and anterior regions of the inferior longitudinal fasciculus (Schwindt et al. 2013; Whitwell et al. 2010a; Acosta-Cabronero et al. 2012; Agosta et al. 2010; Zhang et al. 2009; Mahoney et al. 2013). The inferior longitudinal fasciculus has been shown to be involved to a greater degree in svPPA than both agPPA and lvPPA (Hodges and Patterson 2007; Assal et al. 2012). The left temporal lobe is usually affected more than the right (Chan et al. 2001; Galton et al. 2001; Mummery et al. 2000), although equal involvement of left and right temporal lobes can be observed, particularly later in the disease course when the right side has "caught up with" the left side. Patients with right greater than left sided atrophy and hypometabolism typically present with behavioral dyscontrol and loss of facial recognition (Chan et al. 2009; Edwards-Lee et al. 1997; Thompson et al. 2003; Josephs et al. 2009a), instead of PPA. Patients often also show atrophy and hypometabolism in the orbitofrontal cortices.

Patients with lvPPA also have distinct and characteristic patterns of atrophy, with routine head MRI showing atrophy of the left lateral temporal and parietal

lobes (Fig. 13.3e). Group MRI studies and FDG-PET (Fig. 13.3f) show striking involvement of the left lateral temporal and parietal lobes but can also show involvement of the precuneus, frontal lobes, and even the occipital lobes (Gorno-Tempini et al. 2004; Josephs et al. 2010; Madhavan et al. 2013; Ridgway et al. 2012). The medial temporal lobe is usually relatively spared. The right temporal and parietal lobes may be abnormal but are nearly always less affected than the left. White matter tract degeneration can be observed on DTI affecting temporal and parietal tracts, including the left inferior longitudinal fasciculus, uncinate fasciculus, and superior longitudinal fasciculus (Armstrong et al. 2013; Graff-Radford et al. 2012).

Anatomy of Corticobasal Syndrome with Apraxia of Speech

The pattern of atrophy or hypometabolism observed in patients presenting with CBS and AOS is similar to the pattern observed in patients presenting with CBS without AOS. The same is true regardless of whether agrammatic aphasia is present. In both instances, i.e., AOS is absent or present, patients show involvement of the premotor cortex, often with extension into the prefrontal cortex and sometimes into the superior parietal lobe (Josephs et al. 2008; Grossman et al. 2004; Boxer et al. 2006; Huey et al. 2009; Whitwell et al. 2010b; Groschel et al. 2004). The striatum can also be heavily affected. Atrophy and hypometabolism are often asymmetric, involving the hemisphere contralateral to the side of the greatest affected limb (Whitwell et al. 2010b; Koyama et al. 2007; Soliveri et al. 1999). White matter tract degeneration is also asymmetric and involves frontoparietal association fibers as well as the body and splenium of the corpus callosum (Borroni et al. 2008). Therefore, patients presenting with CBS with AOS will show greater abnormalities, especially in prefrontal regions, compared to patients with PPAOS or PAOS that later develop features of CBS, at least earlier in the disease course.

Part III Pathology

Pathological Overview

Over the last decade, many investigators interested in AOS and PPA have assessed the pathological processes associated with these different syndromes (Josephs et al. 2005, 2006a, b; Mesulam 2001; Kertesz et al. 1994, 2005; Davies et al. 2005; Galton et al. 2000; Graff-Radford et al. 1990; Greene et al. 1996; Hodges et al. 2004; Knibb et al. 2006; Knopman et al. 1990; Lang 1992; Lippa et al. 1991; Wechsler et al. 1982). Unfortunately, it is very difficult to interpret some of these older studies since subjects were not separated by phenotype or syndrome and instead were all lumped as PPA, including those with PAOS and PPAOS. Regardless, these older

studies demonstrated that the pathological processes associated with PPA were not homogeneous. Taken together, these studies demonstrated that many different pathologies, including Alzheimer's disease (Kertesz et al. 2005; Galton et al. 2000; Greene et al. 1996; Knibb et al. 2006), accounted for PPA. Another problem with older studies was the fact that modern immunohistochemistry techniques were not performed, and even if they were performed, they were incomplete, at least compared to more recent studies.

With the advent of immunohistochemistry, and recent discoveries of different proteins that are associated with dementia in general, pathologists have a better grasp on the biochemistry and the pathological processes that are associated with these syndromes. Therefore, current classification first separates Alzheimer's disease from non-Alzheimer's disease pathologies. Non-Alzheimer's disease pathologies are then further separated under the broad categories of synucleinopathies, tauopathies, and TDP-43 proteinopathies (Dickson 2003). Synucleinopathies are not discussed in this chapter but include multiple system atrophy and Lewy body diseases (Dickson 2003); Lewy bodies are rarely found in PPA patients (Caselli et al. 2002). Further subclassification of the tauopathies exists and includes diseases in which tau is the predominant abnormal protein identified histologically (Josephs et al. 2011). Therefore, tauopathies include progressive supranuclear palsy (PSP) (Hauw et al. 1994), corticobasal degeneration (CBD) (Dickson et al. 2002), Pick's disease with Pick's bodies (PiD) (Dickson 2001), and frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) (Ghetti et al. 2003). Similarly the TDP-43 proteinopathies are subclassified in types A–D (Mackenzie et al. 2011). For both tauopathies and TDP-43 proteinopathies, subclassification is based on the distribution of the inclusions, as well as the morphological appearances of the inclusions.

Clinicopathological Associations

There is no one-to-one relationship between the clinical syndromes described in this chapter and the pathologies discussed here. However, there are strong associations (Josephs et al. 2011) (Table 13.2). The clinical syndrome of PPAOS, for example, is strongly associated with tauopathies (Josephs et al. 2006a, 2011; Deramecourt et al. 2010). Although published studies are lacking, clinical evidence suggests that of the tauopathies that can be associated with PAOS and PPA, PPAOS is most strongly associated with PSP pathology, less so CBD and PiD (Josephs et al. 2006a). Similar to PPAOS, PAOS is also associated with tauopathies. However, PAOS may be more strongly associated with CBD pathology than PSP pathology (Josephs et al. 2006a). The three variants of PPA appear to also have a strong association with certain pathologies. The svPPA is strongly associated with TDP-43 proteinopathies and is almost always associated with type C pathology (Josephs et al. 2009b; Mackenzie et al. 2006; Snowden et al. 2007). The lvPPA is strongly associated with Alzheimer's disease pathology (Mesulam et al. 2008). In fact, some investigators have argued not to include lvPPA in the discussion of AOS and PPA since the other

Table 13.2 Clinicopathological associations

Clinical syndrome	Most likely pathology	Other pathologies
Primary progressive apraxia of speech (PPAOS)	Progressive supranuclear palsy	Corticobasal degeneration and Pick's disease
Progressive apraxia of speech (PAOS)	Corticobasal degeneration	Progressive supranuclear palsy and Pick's disease
Agrammatic variant of primary progressive aphasia (agPPA)	TDP type A	Progressive supranuclear palsy and corticobasal degeneration
Semantic variant of primary progressive aphasia (svPPA)	TDP type C	TDP type A, Alzheimer's disease
Logopenic variant of primary progressive aphasia (lvPPA)	Alzheimer's disease	TDP type A
Syndrome + motor neuron disease	TDP type B	TDP type A

variants are associated with non-Alzheimer's disease pathologies, while lvPPA is associated with Alzheimer's disease. Unfortunately, not all lvPPA patients have Alzheimer's disease pathology (Mesulam et al. 2008) which is the counterargument to include lvPPA in such discussions. There is a small subset of lvPPA patients that shows TDP-43 proteinopathy, similar to svPPA (Mesulam et al. 2008). However, unlike svPPA that is associated with TDP-43 type C pathology, lvPPA when associated with TDP-43 pathology is associated with TDP-43 type A pathology (Josephs et al. 2009b). The most complicated syndromic pathologic association to explain is that of agPPA. Currently, it is unclear whether agPPA, as defined in this chapter, is strongly associated with any one pathology. In most cases, agPPA includes patients with and without AOS, and in such instances both tau and TDP-43 pathologies have been identified (Snowden et al. 2007; Mesulam et al. 2008). Weak evidence suggests that agPPA in which AOS is present may be more strongly associated with tauopathies, particularly CBD, while agPPA in which AOS is absent is more strongly associated with TDP-43 proteinopathy, especially TDP-43 type A. It is also worth mentioning that if any of the syndromes described in this chapter are associated with features of MND, then the underlying pathology is most likely to be that of TDP-43 type B (Josephs et al. 2009b, 2011; Mackenzie et al. 2006; Snowden et al. 2007). Therefore, in the presence of flaccid and spastic dysarthria, TDP type B pathology must be strongly suspected. Future studies are also necessary to assess clinicopathological associations in those PPA patients with parkinsonism.

Part IV Genetics

There are no genetic abnormalities that completely account for any one of the syndromes discussed in this chapter. However, there have been reports of patients with a genetic abnormality, namely, a mutation in the progranulin gene on chromosome 17, that have presented with PPA (Mesulam et al. 2007; Mukherjee et al. 2006; Rohrer et al. 2010; Kelley et al. 2009). Most of these reports did not further classify the PPA into one of the three variants. However, patients with progranulin gene

mutations are almost always fluent and hence have features that overlap with svPPA and lvPPA. To our knowledge, there are no definitive, well-characterized patients with PPAOS or PAOS that have had a mutation in the progranulin gene. Recently, there have also been a handful of patients with PPA that have been found to have a repeat expansion in the *C9ORF72* gene (Simon-Sanchez et al. 2012; Snowden et al. 2006, 2012; Mahoney et al. 2012). Other investigators with large cohorts of patients with *C9ORF72* repeat expansions, however, have not identified patients with PPA (Boeve et al. 2012). There are no reports of the repeat expansion accounting for the PPAOS or PAOS phenotypes. Most patients with FTDP-17, i.e., with a mutation in the microtubule associated protein tau gene, have not commonly presented with any of the clinical syndromes discussed in this chapter. There are a few reports of patients presenting as svPPA, although it is unclear whether these patients were truly svPPA or whether they had a behavioral presentation in which naming was also affected as part of the behavioral syndrome (Pickering-Brown et al. 2008).

Summary

There are many different clinical syndromes in which a motor speech disorder or aphasia is the defining feature. In some instances, the motor speech disorders and aphasia co-occur. However, it is important not to lump all these features under the heading of PPA. In fact, the presence of AOS is strongly predictive of tau pathologies, the presence of flaccid and spastic dysarthrias of MND and TDP type B pathology, svPPA of TDP type C pathology, and lvPPA of Alzheimer's disease. Understanding how to separate these clinical features and syndromes will have important prognostic value and future therapeutic benefit. Parkinsonism is frequent in agPPA and lvPPA, and further imaging and pathological studies are necessary to better characterize this feature.

References

Acosta-Cabronero J, Patterson K, Fryer TD, Hodges JR, Pengas G, et al. Atrophy, hypometabolism and white matter abnormalities in semantic dementia tell a coherent story. Brain. 2012;134:2025–35.

Adeli A, Whitwell JL, Duffy JR, Strand EA, Josephs KA. Ideomotor apraxia in agrammatic and logopenic variants of primary progressive aphasia. J Neurol. 2013;260:1594–600.

Agosta F, Henry RG, Migliaccio R, Neuhaus J, Miller BL, et al. Language networks in semantic dementia. Brain. 2010;133:286–99.

Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013;80:496–503.

Assal F, Laganaro M, Remund CD, Ragno Paquier C. Progressive crossed-apraxia of speech as a first manifestation of a probable corticobasal degeneration. Behav Neurol. 2012;25:285–9.

Boeve BF, Boylan KB, Graff-Radford NR, DeJesus-Hernandez M, Knopman DS, et al. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. Brain. 2012;135:765–83.

Borroni B, Garibotto V, Agosti C, Brambati SM, Bellelli G, et al. White matter changes in corticobasal degeneration syndrome and correlation with limb apraxia. Arch Neurol. 2008;65: 796–801.

Boxer AL, Geschwind MD, Belfor N, Gorno-Tempini ML, Schauer GF, et al. Patterns of brain atrophy that differentiate corticobasal degeneration syndrome from progressive supranuclear palsy. Arch Neurol. 2006;63:81–6.

Broussolle E, Tommasi M, Mauguiere F, Chazot G. Progressive anarthria with secondary parkinsonism: a clinico-pathological case report. J Neurol Neurosurg Psychiatry. 1992;55:577–80.

Caselli RJ, Windebank AJ, Petersen RC, Komori T, Parisi JE, et al. Rapidly progressive aphasic dementia and motor neuron disease. Ann Neurol. 1993;33:200–7.

Caselli RJ, Beach TG, Sue LI, Connor DJ, Sabbagh MN. Dement Geriatr Cogn Disord. 2002; 14:55–8.

Chan D, Fox NC, Scahill RI, Crum WR, Whitwell JL, et al. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. Ann Neurol. 2001;49:433–42.

Chan D, Anderson V, Pijnenburg Y, Whitwell J, Barnes J, et al. The clinical profile of right temporal lobe atrophy. Brain. 2009;132:1287–98.

Coon EA, Sorenson EJ, Whitwell JL, Knopman DS, Josephs KA. Predicting survival in frontotemporal dementia with motor neuron disease. Neurology. 2011;76:1886–93.

Czell D, Andersen PM, Neuwirth C, Morita M, Weber M. Progressive aphasia as the presenting symptom in a patient with amyotrophic lateral sclerosis with a novel mutation in the OPTN gene. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14:138–40.

da Rocha AJ, Valerio BC, Buainain RP, Ferraz ME, da Silva CJ, et al. Motor neuron disease associated with non-fluent rapidly progressive aphasia: case report and review of the literature. Eur J Neurol. 2007;14:971–5.

Darley FL, Aronson AE, Brown JR. Differential diagnostic patterns of dysarthria. J Speech Hear Res. 1969;12:246–69.

Darley FL, Aronson AE, Brown JR. Motor speech disorders. Philadelphia: W.B. Saunders; 1975.

Davies RR, Hodges JR, Kril JJ, Patterson K, Halliday GM, et al. The pathological basis of semantic dementia. Brain. 2005;128:1984–95.

Deramecourt V, Lebert F, Debachy B, Mackowiak-Cordoliani MA, Bombois S, et al. Prediction of pathology in primary progressive language and speech disorders. Neurology. 2010;74:42–9.

Dickson DW. Neuropathology of Pick's disease. Neurology. 2001;56:S16–20.

Dickson DW. Neurodegeneration: the molecular pathology of dementia and movement disorders. Basel: ISN Neuropath Press; 2003.

Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, et al. Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. J Neuropathol Exp Neurol. 2002;61:935–46.

Duffy J. Apraxia of speech in degenerative neurologic disease. Aphasiology. 2006;20:511–27.

Duffy JR. Motor speech disorders: substrates, differential diagnosis, and management. St Louis: Mosby; 2013.

Duffy JR, Peach RK, Strand EA. Progressive apraxia of speech as a sign of motor neuron disease. Am J Speech Lang Pathol. 2007;16:198–208.

Edwards-Lee T, Miller BL, Benson DF, Cummings JL, Russell GL, et al. The temporal variant of frontotemporal dementia. Brain. 1997;120(Pt 6):1027–40.

Galantucci S, Tartaglia MC, Wilson SM, Henry ML, Filippi M, et al. White matter damage in primary progressive aphasias: a diffusion tensor tractography study. Brain. 2011;134:3011–29.

Galton CJ, Patterson K, Xuereb JH, Hodges JR. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. Brain. 2000;123(Pt 3):484–98.

Galton CJ, Patterson K, Graham K, Lambon-Ralph MA, Williams G, et al. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. Neurology. 2001;57:216–25.

Ghetti B, Hutton M, Wszolek Z. Frontotemporal dementia and parkinsonism linked to chromosome 17 associated with tau gene mutations (FTDP-17T). In: Dickson D, editor. Neurodegeneration: the molecular pathology of dementia and movement disorders. Basel: ISN Neuropath Press; 2003. p. 86–102.

Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, et al. Cognition and anatomy in three variants of primary progressive aphasia. Ann Neurol. 2004;55:335–46.
Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76:1006–14.
Graff-Radford NR, Damasio AR, Hyman BT, Hart MN, Tranel D, et al. Progressive aphasia in a patient with Pick's disease: a neuropsychological, radiologic, and anatomic study. Neurology. 1990;40:620–6.
Graff-Radford J, Duffy JR, Strand EA, Josephs KA. Parkinsonian motor features distinguish the agrammatic from logopenic variant of primary progressive aphasia. Parkinsonism Relat Disord. 2012;18:890–2.
Greene JD, Patterson K, Xuereb J, Hodges JR. Alzheimer disease and nonfluent progressive aphasia. Arch Neurol. 1996;53:1072–8.
Groschel K, Hauser TK, Luft A, Patronas N, Dichgans J, et al. Magnetic resonance imaging-based volumetry differentiates progressive supranuclear palsy from corticobasal degeneration. Neuroimage. 2004;21:714–24.
Grossman M, McMillan C, Moore P, Ding L, Glosser G, et al. What's in a name: voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. Brain. 2004;127:628–49.
Grossman M, Powers J, Ash S, McMillan C, Burkholder L, et al. Disruption of large-scale neural networks in non-fluent/agrammatic variant primary progressive aphasia associated with frontotemporal degeneration pathology. Brain Lang. 2013;127:106–20.
Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology. 1994;44:2015–9.
Hodges JR, Patterson K. Semantic dementia: a unique clinicopathological syndrome. Lancet Neurol. 2007;6:1004–14.
Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, et al. Clinicopathological correlates in frontotemporal dementia. Ann Neurol. 2004;56:399–406.
Huey ED, Pardini M, Cavanagh A, Wassermann EM, Kapogiannis D, et al. Association of ideomotor apraxia with frontal gray matter volume loss in corticobasal syndrome. Arch Neurol. 2009;66:1274–80.
Josephs KA, Duffy JR. Apraxia of speech and nonfluent aphasia: a new clinical marker for corticobasal degeneration and progressive supranuclear palsy. Curr Opin Neurol. 2008;21:688–92.
Josephs KA, Boeve BF, Duffy JR, Smith GE, Knopman DS, et al. Atypical progressive supranuclear palsy underlying progressive apraxia of speech and nonfluent aphasia. Neurocase. 2005;11:283–96.
Josephs KA, Duffy JR, Strand EA, Whitwell JL, Layton KF, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain. 2006a;129:1385–98.
Josephs KA, Petersen RC, Knopman DS, Boeve BF, Whitwell JL, et al. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology. 2006b;66:41–8.
Josephs KA, Whitwell JL, Dickson DW, Boeve BF, Knopman DS, et al. Voxel-based morphometry in autopsy proven PSP and CBD. Neurobiol Aging. 2008;29:280–9.
Josephs KA, Whitwell JL, Knopman DS, Boeve BF, Vemuri P, et al. Two distinct subtypes of right temporal variant frontotemporal dementia. Neurology. 2009a;73:1443–50.
Josephs KA, Stroh A, Dugger B, Dickson DW. Evaluation of subcortical pathology and clinical correlations in FTLD-U subtypes. Acta Neuropathol. 2009b;118:349–58.
Josephs KA, Duffy JR, Fossett TR, Strand EA, Claassen DO, et al. Fluorodeoxyglucose F18 positron emission tomography in progressive apraxia of speech and primary progressive aphasia variants. Arch Neurol. 2010;67:596–605.
Josephs KA, Hodges JR, Snowden JS, Mackenzie IR, Neumann M, et al. Neuropathological background of phenotypical variability in frontotemporal dementia. Acta Neuropathol. 2011;122:137–53.
Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, et al. Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech. Brain. 2012;135:1522–36.

Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, et al. Syndromes dominated by apraxia of speech show distinct characteristics from agrammatic PPA. Neurology. 2013a;81:337–45.

Josephs KA, Whitwell JL, Murray ME, Parisi JE, Graff-Radford NR, et al. Corticospinal tract degeneration associated with TDP-43 type C pathology and semantic dementia. Brain. 2013b;136:455–70.

Kelley BJ, Haidar W, Boeve BF, Baker M, Graff-Radford NR, et al. Prominent phenotypic variability associated with mutations in Progranulin. Neurobiol Aging. 2009;30:739–51.

Kertesz A, Hudson L, Mackenzie IR, Munoz DG. The pathology and nosology of primary progressive aphasia. Neurology. 1994;44:2065–72.

Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. Brain. 2005;128:1996–2005.

Knake S, Belke M, Menzler K, Pilatus U, Eggert KM, et al. In vivo demonstration of microstructural brain pathology in progressive supranuclear palsy: a DTI study using TBSS. Mov Disord. 2010;25:1232–8.

Knibb JA, Xuereb JH, Patterson K, Hodges JR. Clinical and pathological characterization of progressive aphasia. Ann Neurol. 2006;59:156–65.

Knopman DS, Mastri AR, Frey 2nd WH, Sung JH, Rustan T. Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. Neurology. 1990;40:251–6.

Koyama M, Yagishita A, Nakata Y, Hayashi M, Bandoh M, et al. Imaging of corticobasal degeneration syndrome. Neuroradiology. 2007;49:905–12.

Kremen SA, Mendez MF, Tsai P, Teng E. Extrapyramidal signs in the primary progressive aphasias. Am J Alzheimers Dis Other Demen. 2011;26:72–7.

Lang AE. Cortical basal ganglionic degeneration presenting with "progressive loss of speech output and orofacial dyspraxia". J Neurol Neurosurg Psychiatry. 1992;55:1101.

Lippa CF, Cohen R, Smith TW, Drachman DA. Primary progressive aphasia with focal neuronal achromasia. Neurology. 1991;41:882–6.

Mackenzie IR, Baborie A, Pickering-Brown S, Du Plessis D, Jaros E, et al. Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype. Acta Neuropathol (Berl). 2006;112:539–49.

Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Du Plessis D, et al. A harmonized classification system for FTLD-TDP pathology. Acta Neuropathol. 2011;122:111–3.

Madhavan A, Whitwell JL, Weigand SD, Duffy JR, Strand EA, et al. FDG PET and MRI in logopenic primary progressive aphasia versus dementia of the Alzheimer's type. PLoS One. 2013;8:e62471.

Mahoney CJ, Beck J, Rohrer JD, Lashley T, Mok K, et al. Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. Brain. 2012;135:736–50.

Mahoney CJ, Malone IB, Ridgway GR, Buckley AH, Downey LE, et al. White matter tract signatures of the progressive aphasias. Neurobiol Aging. 2013;34:1687–99.

Mesulam MM. Slowly progressive aphasia without generalized dementia. Ann Neurol. 1982;11:592–8.

Mesulam MM. Primary progressive aphasia. Ann Neurol. 2001;49:425–32.

Mesulam MM. Primary progressive aphasia–a language-based dementia. N Engl J Med. 2003;349:1535–42.

Mesulam M, Johnson N, Krefft TA, Gass JM, Cannon AD, et al. Progranulin mutations in primary progressive aphasia: the PPA1 and PPA3 families. Arch Neurol. 2007;64:43–7.

Mesulam M, Wicklund A, Johnson N, Rogalski E, Leger GC, et al. Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. Ann Neurol. 2008;63:709–19.

Mukherjee O, Pastor P, Cairns NJ, Chakraverty S, Kauwe JS, et al. HDDD2 is a familial frontotemporal lobar degeneration with ubiquitin-positive, tau-negative inclusions caused by a missense mutation in the signal peptide of progranulin. Ann Neurol. 2006;60:314–22.

Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RS, et al. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. Ann Neurol. 2000;47:36–45.

Ogar J, Slama H, Dronkers N, Amici S, Gorno-Tempini ML. Apraxia of speech: an overview. Neurocase. 2005;11:427–32.

Pickering-Brown SM, Rollinson S, Du Plessis D, Morrison KE, Varma A, et al. Frequency and clinical characteristics of progranulin mutation carriers in the Manchester frontotemporal lobar degeneration cohort: comparison with patients with MAPT and no known mutations. Brain. 2008;131:721–31.

Ridgway GR, Lehmann M, Barnes J, Rohrer JD, Warren JD, et al. Early-onset alzheimer disease clinical variants: multivariate analyses of cortical thickness. Neurology. 2012;79:80–4.

Roh JH, Suh MK, Kim EJ, Go SM, Na DL, Seo SW. Glucose metabolism in progressive nonfluent aphasia with and without parkinsonism. Neurology. 2010;75:1022–4.

Rohrer JD, Warren JD, Modat M, Ridgway GR, Douiri A, et al. Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. Neurology. 2009;72:1562–9.

Rohrer JD, Crutch SJ, Warrington EK, Warren JD. Progranulin-associated primary progressive aphasia: a distinct phenotype? Neuropsychologia. 2010;48:288–97.

Schwindt GC, Graham NL, Rochon E, Tang-Wai DF, Lobaugh NJ, et al. Whole-brain white matter disruption in semantic and nonfluent variants of primary progressive aphasia. Hum Brain Mapp. 2013;34:973–84.

Simon-Sanchez J, Dopper EG, Cohn-Hokke PE, Hukema RK, Nicolaou N, et al. The clinical and pathological phenotype of C9ORF72 hexanucleotide repeat expansions. Brain. 2012;135:723–35.

Snowden JS, Pickering-Brown SM, Mackenzie IR, Richardson AM, Varma A, et al. Progranulin gene mutations associated with frontotemporal dementia and progressive non-fluent aphasia. Brain. 2006;129:3091–102.

Snowden J, Neary D, Mann D. Frontotemporal lobar degeneration: clinical and pathological relationships. Acta Neuropathol. 2007;114:31–8.

Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, et al. Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. Brain. 2012;135:693–708.

Soliveri P, Monza D, Paridi D, Radice D, Grisoli M, et al. Cognitive and magnetic resonance imaging aspects of corticobasal degeneration and progressive supranuclear palsy. Neurology. 1999;53:502–7.

Thompson SA, Patterson K, Hodges JR. Left/right asymmetry of atrophy in semantic dementia: behavioral-cognitive implications. Neurology. 2003;61:1196–203.

Warrington E. Selective impairment of semantic memory. Q J Exp Psychol. 1975;27:635–57.

Wechsler AF, Verity MA, Rosenschein S, Fried I, Scheibel AB. Pick's disease. A clinical, computed tomographic, and histologic study with golgi impregnation observations. Arch Neurol. 1982;39:287–90.

Whitwell JL, Avula R, Senjem ML, Kantarci K, Weigand SD, et al. Gray and white matter water diffusion in the syndromic variants of frontotemporal dementia. Neurology. 2010a;74:1279–87.

Whitwell JL, Jack Jr CR, Boeve BF, Parisi JE, Ahlskog JE, et al. Imaging correlates of pathology in corticobasal syndrome. Neurology. 2010b;75:1879–87.

Whitwell JL, Master AV, Avula R, Kantarci K, Eggers SD, et al. Clinical correlates of white matter tract degeneration in progressive supranuclear palsy. Arch Neurol. 2011;68:753–60.

Whitwell JL, Duffy JR, Strand EA, Machulda MM, Senjem ML, et al. Neuroimaging comparison of primary progressive apraxia of speech and progressive supranuclear palsy. Eur J Neurol. 2013a;20:629–37.

Whitwell JL, Duffy JR, Strand EA, Xia R, Mandrekar J, et al. Distinct regional anatomic and functional correlates of neurodegenerative apraxia of speech and aphasia: an MRI and FDG-PET study. Brain Lang. 2013b;125:245–52.

Zhang Y, Schuff N, Du AT, Rosen HJ, Kramer JH, et al. White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. Brain. 2009;132:2579–92.

Chapter 14
Normal Pressure Hydrocephalus

Paolo Missori, Antonio Daniele, and Carlo Colosimo

Abstract Although it has been nearly 50 years since its first description of clinical and radiological, there is considerable uncertainty about the diagnosis of normal pressure hydrocephalus because it shares the semiotics with the group of dementias. Hakim's triad (impaired gait, initially type clumsiness of the lower limbs followed over time by inability to ambulate or maintain an erect posture; cognitive impairment, initially limited to worsening deficits in memory fixation and execution of complex actions; the urinary disorder, initially type "urgent urination" and then complete urinary incontinence) characterizes the progressive course of the adult chronic hydrocephalus. The clinical onset is typically nonspecific, subtle, and most often monosymptomatic. The first diagnostic procedure is a head CT scan and/or brain MRI, which shows an abnormal dilatation of the lateral ventricles and the third ventricle, associated to variable brain atrophy. Not all subjects will develop a set of symptoms, since the altered cerebrospinal fluid dynamics can remain stable for many years or get progressively worse until the appearance of the clinical triad of normal pressure hydrocephalus. The test of intrathecal infusion (Katzman test) carried out at constant speed with the introduction of saline solution into the lumbar subarachnoid space and the concomitant detection of cerebrospinal fluid pressure establishes that patients with outflow resistance ranging from 12 to 19 mmHg/ml/min can improve clinically after surgery. This method requires extensive and prolonged experience of the center of application and the use of computer systems. The withdrawal of lumbar cerebrospinal fluid provides for the evacuation of 30–50 cc of

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cerebrospinal fluid by lumbar puncture under local anesthesia, preceded and followed by gait assessment and neuropsychological tests. It also uses the continuous withdrawal of CSF with an intrathecal catheter placed for 3 days, in order to drain approximately 135 ml/24 h and the aim of reducing false negatives. After surgery, the patient is usually able to regain a good quality of life, with independence in daily living activities. The duration of such postsurgical improvement is variable, but patients may improve again readjusting the opening pressure of the programmable valve, although a high comorbidity index is strictly related to a poor outcome.

Keywords Cerebrospinal fluid • Dementia • Gait abnormalities • Hydrocephalus • Idiopathic • Normal pressure • Programmable valve • Shunt • Urinary incontinence • Ventricle

Historical Remarks

In ancient times, hydrocephalus was associated to children with progressive enlargement of the head. Tapping the subcutaneous tissue of the frontal skin was the therapeutic procedure adopted for more than 2,000 years (Missori et al. 2010). Fabrizio d'Acquapendente was the first physician to perform a ventricular drainage in a child through insertion of a cannula in the frontal ventricle (Missori et al. 2011). The occurrence of hydrocephalus in adults, without increase of the head size, was a late clinical discovery. Pathological descriptions in the eighteenth and nineteenth centuries reported increase of "humor" in the ventricular system (Missori et al. 2010), but diagnosis in adults during life was impossible. The introduction of the withdrawal of cerebrospinal fluid (CSF) from the lumbar space in meningitic disease allowed the first therapeutic approach in adults affected by hydrocephalus (Wynter 1891). Hugo Wilhelm von Ziemssen considered the "spinal paracentesis" "an effective mean of reducing intracranial pressure in … hydrocephalus, … sometimes improvement in the subjective troubles and in the condition of the sensorium was striking and of long duration" (von Ziemssen 1893). Since then, withdrawal of CSF in patients with chronic hydrocephalus or increased intracranial pressure was extensively performed (Albert 1918; Browning 1897; Greenfield 1935; MacCordick 1922; Rhodes 1903). The introduction of the ventriculography by Dandy (Dandy 1918) allowed the radiological diagnosis of pediatric hydrocephalus (Dandy 1918), and later Evans introduced a ratio to differentiate normal from hydrocephalic children (Evans 1942). In 1949, the first cerebrospinal pediatric shunt was applied by Matson, Nulsen, and Spitz (Matson 1949; Nulsen and Spitz 1951). In that time, the diagnosis of secondary hydrocephalus in adults was limited to patients with brain tumors and post-traumatic or post-meningitic hydrocephalus. In the mid-1960s, Adams and Hakim demonstrated in three adults with hydrocephalus (primary in one and post-traumatic in two) associated to typical neurological features that withdrawal of 15–20 ml of CSF determined a marked clinical improvement (Adams et al. 1965). The subsequent surgical ventriculoatrial shunt allowed a definite clinical improvement. Since then

the pressure of the CSF was in the normal range, the disease was named "normal pressure" hydrocephalus (NPH). For some years, the term was unchanged, but due to the unknown origin of the disease, the term "idiopathic" NPH was added (Black 1980; Greenberg et al. 1977; Shenkin et al. 1975). During the second half of the twentieth century, the diagnostic and therapeutic procedures of withdrawal of CSF became more common after the introduction of spinal catheters and continuous CSF drainage (Aitken and Drake 1964; Matera and Althabe 1962; Vourc'h 1963; Vourc'h and Rougerie 1960). The advent of computed tomography represented a milestone of the radiological diagnosis (Gunasekera and Richardson 1977; Jacobs and Kinkel 1976), with a transposition of the Evans' index values for hydrocephalus' diagnosis from the pneumoencephalography (Gawler et al. 1976; Synek et al. 1976). A further progress came with the "Charles Miller Fisher test," in which clinical improvement persisted many months after a single 20–30 ml CSF tap in patients with NPH (Fisher 1978). This procedure was considered more effective if extended to more days (Di Lauro et al. 1986). Katzman was the first to suggest an infusion of physiologic solution into the lumbar subarachnoid space, with monitoring of CSF pressure (Katzman and Hussey 1970). After infusion of physiologic solution into the lumbar subarachnoid space and monitoring CSF pressure, the capacity to absorb additional physiologic solution was reduced in patients with NPH and the CSF pressure quickly increased. The last remark in this history is the guidelines for the diagnosis and management of idiopathic normal pressure hydrocephalus which came to light from an international group of researchers in 2005 (Marmarou et al. 2005b). In a five-step document, all the solved and unsolved questions were addressed, to offer an essential reference from which prospective randomized studies could originate.

Introduction

The CSF is produced by the choroid plexuses of the lateral and fourth ventricles and from the capillary ultrafiltrate of the Virchow-Robin spaces, at a rate varying between 0.2 and 0.6 ml per minute or 600 and 700 ml per day (Wright 1978). This amount of fluid is reabsorbed through three main systems: the arachnoid villi into the cerebral venous sinuses, the subarachnoid space along thoracic and lumbosacral spinal rootlets, and the olfactory pathway (Edsbagge et al. 2004; Johnston 2003; Luedemann et al. 2002; Mollanji et al. 2002). The equilibrium between production and reabsorption allows normal ventricle size during life, and every pathological condition which alters this CSF balance can produce progressive ventricular enlargement, up to hydrocephalus. This simple concept is challenged by some brain degenerative disorders (i.e., Alzheimer's disease, progressive supranuclear palsy, frontotemporal dementia, vascular dementia, dementia with Lewy bodies, Parkinson's disease), in which a progressive tissue loss is replaced by CSF. In these patients, the atrophy of the brain is the primary event and the increase of the amount of CSF results from neuronal loss. The characteristic secondary ventricular enlargement resembles moderate hydrocephalus, but the clinical picture must be carefully

Table 14.1a Prevalence of adult chronic idiopathic hydrocephalus in the literature

	Prevalence (%)	Sample	Criteria for the diagnosis of NPH
Fisher (1982)	4	Dementia	Clinical
Casmiro et al. (1989)	0.5	2 out of 396 subjects over 65 years	Clinical
Trenkwalder et al. (1995)	0.5	4 out of 982 patients with Parkinson's disease	Clinical
Bech-Azeddine et al. (2001)	3.5	14 out of 400 patients of a memory clinic	Clinical
Clarfield (2003)	1	50 out of 5,000 patients with dementia	Clinical
Marmarou et al. (2007)	11.56	17 out of 147 dementia	Clinical-radiological
Brean and Eide (2008)	0.022	21.9 per 100,000 adults	Clinical-radiological
Hiraoka et al. (2008)	7.6	13 out of 170 adults over 65 years	Radiological
Tanaka et al. (2009)	1.4	7 out of 7,497 adults over 65 years	Clinical-radiological

evaluated together with neurological examination and brain imaging, since the correct diagnosis of NPH is promoted by additional tests. Other conditions which may resemble the clinical picture of NPH (either in early stages or later in the course of the primary disease) include secondary post-traumatic or posthemorragic hydrocephalus, systemic lupus erythematosus, and rarely neurosarcoidosis (Honda et al. 2004; Westhout and Linskey 2008; Wikkelsø et al. 1982). In these conditions, the clinical course is characterized by faster progression, unlike in NPH patients. Other rare conditions in which an NPH can occur are myotonic dystrophy and Paget's disease (Christensen 1988; Delavallée and Raftopoulos 2006; Martin et al. 1985; Moiyadi et al. 2006; Riggs et al. 1985; Roohi et al. 2005).

Epidemiology

Currently, the prevalence and incidence of NPH cannot be determined precisely, although probably it is a common disease and its prevalence increases with age (Conn 2011; Marmarou et al. 2005b). It is assumed that NPH roams to about 4 % of all dementias (Fisher 1982). The results of various studies providing data about prevalence and incidence of NPH are reported in Tables 14.1a and 14.1b. The diagnosis is also strongly influenced by the criteria used to establish the diagnosis of NPH.

A study carried out in San Marino in a population of 396 people over 65 identified two patients with NPH, with a prevalence of 0.5 % (Casmiro et al. 1989). Similarly, a German door-to-door investigation on motor disorders in parkinsonism detected four patients with NPH out of 982 subjects (Trenkwalder et al. 1995). According to a census of 2000 in the USA reporting about 35 million people over 65, a 0.5 %

Table 14.1b Incidence of adult chronic idiopathic hydrocephalus in the literature

	Incidence		Criteria for the diagnosis of NPH
Vanneste et al. (1993)	0.13–0.22	100,000/year	Clinical
Krauss and Halve (2004)	1.8	100,000/year	Clinical-radiological
Tisell et al. (2005)	1–3	100,000/year	Clinical-radiological
Brean and Eide (2008)	5.5	100,000/year	Clinical-radiological

prevalence of NPH would result in a number of approximately 175,000 patients affected by NPH (Suzuchi et al. 2000), while a 12 % prevalence of Alzheimer's disease would result in 4.5 million of patients. A study conducted in a sample of 400 patients of a memory clinic (Gunasekera and Richardson 1977) detected 14 patients (3.5 %) suffering from IICA (Bech-Azeddine et al. 2001). In a meta-analysis of 37 studies on dementia, the prevalence of adult chronic idiopathic NPH in 5,000 patients is about 1 % (Clarfield 2003). Accordingly, among patients with dementia in the USA (between four and six million), the number of patients with NPH may range between 40,000 and 60,000 (Hebert et al. 2003). These estimates may increase by four times (160,000–240,000 patients) if we refer to a prevalence of 4 % of NPH reported by other studies (Relkin et al. 2005). A recent investigation, performed in the USA on a population of 147 patients, reported a prevalence of 11.56 % of patients suffering from NPH (Marmarou et al. 2007). Recent studies performed on healthy population showed a sharp increase in the prevalence of the NPH. In Norway, a study of 100,000 people identified 21.9 cases (Brean and Eide 2008), while a Japanese work detected an incidence ranging from 2.9 (clinical and radiological diagnosis) to 7.6 % (radiological diagnosis only) in the healthy population of over 65 years (Hiraoka et al. 2008). In Italy, according to a survey carried out in November 2006, people over 65 years accounts for about 20 % of the population (about 11 million out of a total of 56 million) (Colitti et al. 2006). Accordingly, the estimated number of NPH patients may be about 55,000. A retrospective study performed in the USA showed that in 2000 the number of NPH patients treated by drainage was only 5,547 per year, suggesting that a limited number of patients are diagnosed and then treated, as compared to the potential number of subjects to be treated (Patwardhan and Nanda 2005). Vanneste has estimated that the incidence of patients with NPH in the Netherlands might be between 1.3 and 2.2 per million per year (Vanneste et al. 1993). Krauss in Germany calculated an incidence of 1.8 per 100,000 per year (Krauss and Halve 2004). Finally, a Swedish study reported that the use of derivative systems for patients with NPH is around 30 % of all shunt surgery, which is between only 3 and 6 per 100,000 people (Tisell et al. 2005). In Norway, however, a recent study in 2008 reported an incidence of 5.5 patients with NPH per 100,000 per year (Brean and Eide 2008). Since histological studies show lesions consistent with Alzheimer's disease in brain biopsies of patients with NPH, the coexistence of two diseases leads to underestimate the right number of patients with NPH (Chakravarty 2004; Silverberg et al. 2003). Thus, it might be speculated that NPH may occur in 15–20 % of demented patients (Relkin et al. 2005). In Italy, the prevalence of patients with NPH might be around 836,000 (7 % of the Italian

population over 65 years). As in the next decades an overall aging of population is expected (in 2050, 33 % of the Italian population will be over 65 years), this will result in a progressive increase in the number of patients with NPH.

Familial Normal Pressure Hydrocephalus

Few studies reported a possible familial association in NPH (Portenoy et al. 1984). The description of a large family with four members showing a late-onset primary NPH across three generations suggests the opportunity to search for underdiagnosed and asymptomatic NPH in adult family members of patients with NPH (Takahashi et al. 2011). An autosomal dominant transmission has been hypothesized. Another study reported two sisters with clinical and radiological features of NPH, who underwent shunt placement with clinical improvement (Cusimano et al. 2011). In both sisters, an epsilon3-epsilon3 genotype of the apolipoprotein E (ApoE) on chromosome 19 was detected. Familial aggregation of NPH among first-degree relatives is suggested by an incidence of 7.1 and 0.7 % among control relatives (McGirr and Cusimano 2012).

Clinical Picture

The most characteristic picture in patients with NPH is the Hakim's triad: gait disturbance, urinary incontinence, and cognitive decline (Adams et al. 1965). Gait disturbances may occur as the first symptom and vary in the course. In early phases, the patient may complain of a slow, wide-based walking with small steps and sudden drops, charged to the shoes or uneven floor (McHugh 1964; Missori et al. 2010; Roger et al. 1950). In later stages, a cane or wheeled walker may be needed. In late stages, due to tendency to fall, the patient is completely unable to walk. Differentiating between Parkinson's disease and NPH can be challenging for the practicing clinician; in NPH usually the motor impairment is mainly confined in the lower limbs (*lower-body parkinsonism*) and the response to levodopa is poor or absent, but in some cases, the differential diagnosis may not be so straightforward (Table 14.2). Dopamine transporter brain imaging (*DaTSCAN*) using single-photon emission tomography (SPECT) may be useful, since it shows an abnormal picture in all cases of PD, while the uptake is usually normal in NPH. Disturbances of micturition usually appear in association with other symptoms of NPH. In early stages NPH patients often complain daily need to urinate more often than usual, sometimes with urgency. When the disease worsens, occasional incontinence happens. This symptom is very harmful to patients and relatives, and in males the attention is often focused on prostatic function and sometimes surgery is even carried out to treat urinary symptoms. In patients with NPH SPECT, studies showed that urinary dysfunction may be closely related with right frontal cerebral hypoperfusion, the most common urodynamic abnormality being detrusor overactivity (Sakakibara et al. 2008, 2012).

Table 14.2 Differences between normal pressure hydrocephalus and Parkinson's disease gait

Features	Normal pressure hydrocephalus	Parkinson's disease
Early stages	May occur as the first symptom Clumsiness of the lower limbs	Usually not the first symptom Subtle, if present Loss of unilateral arm swing
Middle stages	Wide-based walking	Normal or narrow-based walking
	Small steps	Small steps
	Stooped stance	Stooped stance
	Sudden drops	Sometimes, festination and freezing
	Charged to the shoes or uneven floor	
	Outward rotated feet and a diminished height of the steps	
	Frequent freezing	
Late stages	Tendency to fall	Tendency to fall
	Inability to ambulate or maintain an erect posture	Inability to ambulate or maintain an erect posture
	Frequent freezing	Frequent festination and freezing
Speed	Slow	Slow
Stride length	Reduced	Reduced
Rhythmicity	Reduced	Reduced
Symmetry	Reduced	Reduced
Improvement with external clues	Mild	Moderate
Response to levodopa	None or mild	Moderate

Cognitive and behavioral symptoms are key clinical features of NPH and may appear in early disease stages (Hashimoto et al. 2010). In individual patients with NPH, however, the cognitive impairment may vary largely, ranging from a mild cognitive decline to a moderate or severe dementia in other patients.

Various neuropsychological studies have supported the view suggesting that patients with NPH may frequently show a "subcortical" pattern of cognitive impairment (Cummings and Benson 1984; Devito et al. 2005), which is often seen in pathologies affecting various subcortical structures and is mainly characterized by the occurrence of mental slowness, deficits of attention and frontal executive functions (planning, problem-solving, set-shifting), relatively mild deficits of long-term memory, and behavioral changes (apathy most frequently, depressive symptoms in some patients). Since deficits of executive functions frequently arise from a dysfunction of the frontal lobes, which are abundantly connected to various subcortical structures (Alexander et al. 1986), the term "frontal-subcortical" cognitive impairment/dementia has also been proposed. Such most frequently reported "frontal-subcortical" pattern of cognitive impairment observed in patients with NPH does usually not include aphasic, apraxic, or agnostic deficits, which are by contrast common in patients with "cortical" dementias (*in primis*, Alzheimer's disease). As to long-term memory deficits, it has been shown that patients with NPH

in early disease stages have usually a relatively preserved ability to store information in long-term memory systems (at variance with patients with Alzheimer's disease since early disease stages), but are usually impaired mostly in the retrieval of stored information from long-term memory systems and therefore may benefit from external cues aimed at facilitating such retrieval (Iddon et al. 1999). This pattern of memory impairment of NPH patients may be shared by other conditions with a "frontal-subcortical" pattern of cognitive impairment, such as Parkinson's disease (Taylor et al. 1986). In addition, deficits of spatial long-term memory (Iddon et al. 1999), constructional praxic abilities (Goodman and Meyer 2001), and psychomotor speed (Kaye et al. 1990) have been detected in patients affected by NPH.

In a recent study (Saito et al. 2011) aimed at further investigating cognitive functioning in patients affected by idiopathic NPH, 32 patients with NPH who significantly improved after surgery were recruited and underwent a quite extensive neuropsychological assessment before ($n=32$) and 1 year ($n=26$) after CSF shunt surgery. Moreover, a group of patients with Alzheimer's disease ($n=32$) matched to the NPH group as for several clinical and demographic variables (including overall cognitive functioning as measured by performance on the mini-mental state examination, MMSE) and a group of healthy controls (HCs) ($n=30$) were recruited. The results of such study show that patients with NPH showed a significantly worse performance as compared to healthy controls on most cognitive tasks (MMSE, tasks of verbal and spatial short-term memory, phonological and semantic verbal fluency, episodic verbal memory, several tasks assessing visual discrimination, and the Frontal Assessment Battery (FAB) assessing executive functions), while no significant difference was found between the NPH and HCs on a task of object naming. Moreover, the NPH group performed significantly worse than the AD group on some cognitive tasks (spatial short-term memory, phonological verbal fluency, FAB, some tasks assessing visual discrimination), while the AD group was more impaired than the NPH group on specific cognitive variables assessing episodic verbal memory. Although deficits of frontal cognitive functions (including executive functions) were the most prominent in the NPH group, this study pointed out that memory deficits and visuoperceptual and visuospatial deficits may also occur in patients with NPH. This recent study (Saito et al. 2011) suggests that, although deficits of frontal cognitive functions (including executive functions) due to a disruption of frontal-subcortical circuits are the most prominent in patients with NPH, memory deficits and visuoperceptual and visuospatial deficits (due to a disruption of neural circuits involving more "posterior" cortical and subcortical structures) may also occur in patients with NPH.

As to other behavioral symptoms (Bloom and Kraft 1998; Kito et al. 2009; Koch et al. 2009), besides apathy and depression, it has been less commonly reported that patients with NPH may show manic and psychotic symptoms (Kwentus and Hart 1987; Rice and Gendelman 1973), including aggressivity, hypersexuality, and delusional jealousy (Yusim et al. 2008).

A distinguishing feature of NPH is the relatively slow but progressive clinical evolution (12–24 months), as the patient becomes unable to carry out everyday activities and to look after himself. However, some patients may show a slower

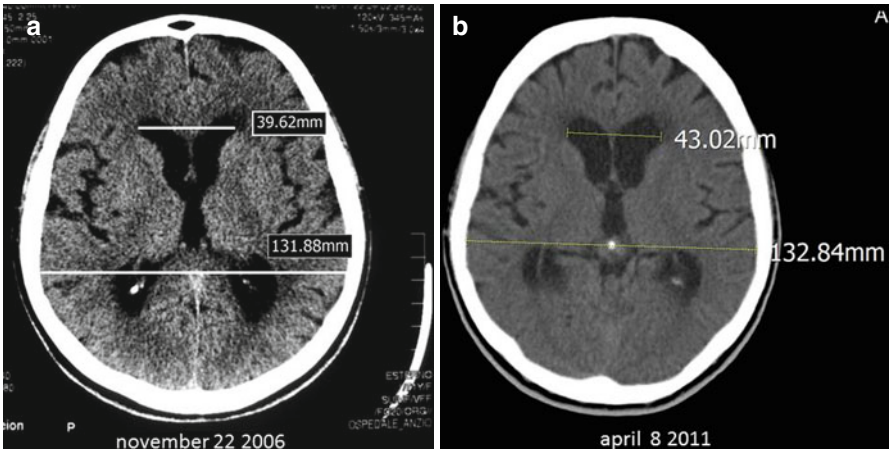

Fig. 14.1 (**a**) A 72-year-old female with gait instability. CT scan shows Evans' index of 39.62 mm/131.88 mm = 0.30. (**b**) The same patient after 55 months complaining short memory impairment, recurrent falls, and urgent urination. On control CT scan the frontal horns appear more enlarged with Evans' index increase: 43.02 mm/132.84 mm = 0.32

clinical progression both for very mild symptoms and for misdiagnosis. In these patients, neuroimaging commonly shows a ventriculomegaly. When acute or subacute symptoms of intracranial pressure (headache, alteration of consciousness, cranial nerve deficits, vomiting, dizziness) occur in a short period of time (1–2 weeks) associated to brain scan of ventricular enlargement, a secondary hydrocephalus other than NPH or a cerebrovascular disease should be considered as the causative condition. In the cases in which a previous neuroradiological imaging is available, a comparison of the Evans' index between the old and new examination allows a more secure and reliable assessment of the ventricular progression and of clinical diagnosis (Figs. 14.1 and 14.2).

Scales for Grading of Severity

Various grading scales have been reported for assessment of patients with NPH. The use of functional scales based on the degree of disability or stroke rehabilitation scales have been proposed, but these scales were not devised to assess changes in the severity of main symptoms of NPH (Klinge et al. 2005). The need to develop assessment scales to be largely shared in the clinical evaluation of patients with NPH prompted the proposal of two new grading scales (Hellström et al. 2012; Kubo et al. 2008). A major advantage of both scales is the possibility to compare the neurological conditions before and after each diagnostic or therapeutic procedure. Cognitive, gait, and urinary symptoms are assessed in both scales (Hellström et al. 2012; Kubo et al. 2008), while the examination of balance only in one (Hellström et al. 2012). In the Swedish scale (Hellström et al. 2012), three different professionals evaluate

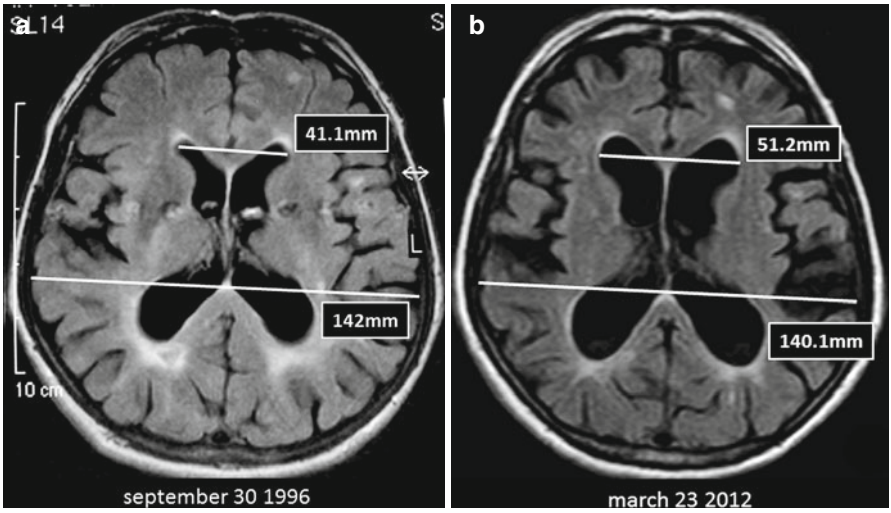

Fig. 14.2 (**a**) A 61-year-old female with short-term memory deficit. MRI shows Evans' index of 41.1 mm/142 mm = 0.28. (**b**) The same patient after 16 years with mild cognitive impairment, progressive gait disturbance, and occasional urinary incontinence: Evans' index of 51.2 mm/140.1 mm = 0.36. Note the secondary brain atrophy with widening of the Sylvian cisterns

separately the three main groups (cognitive, gait, urinary) of symptoms, and scores may range from 0 to 100, where 100 is the performance of an age-matched healthy population. Such scale discriminates well between levels of severity. Following surgery, a patient is considered improved if a >5-point increment can be detected on the scale. In the Japanese scale (Kubo et al. 2008), the clinical assessment is performed by two independent physicians. Patients with NPH were assessed with this scale after a CSF tap test and after shunt surgery. For the triad of symptoms, scores may range from 0 to 4, with higher scores indicating more severe symptoms. Patients who obtain an improvement in at least 1 of the 3 domains are judged to have a clinically significant improvement. Reliability and validity in predicting shunt responsiveness were assessed for this scale.

Neuroradiological Evaluation

On computed tomography (CT) or magnetic resonance imaging (MRI), the radiological finding of ventricular enlargement is a necessary landmark of NPH, but it is not sufficient to determine if patients are suffering from NPH. In neurodegenerative diseases, cerebral atrophy causes secondary ventricular enlargement and a radiological differential diagnosis with NPH can be problematic. The first step in the evaluation of an image must be the computation of the Evans' index, by dividing the maximum width of the frontal horns by the maximum width of the inner table of

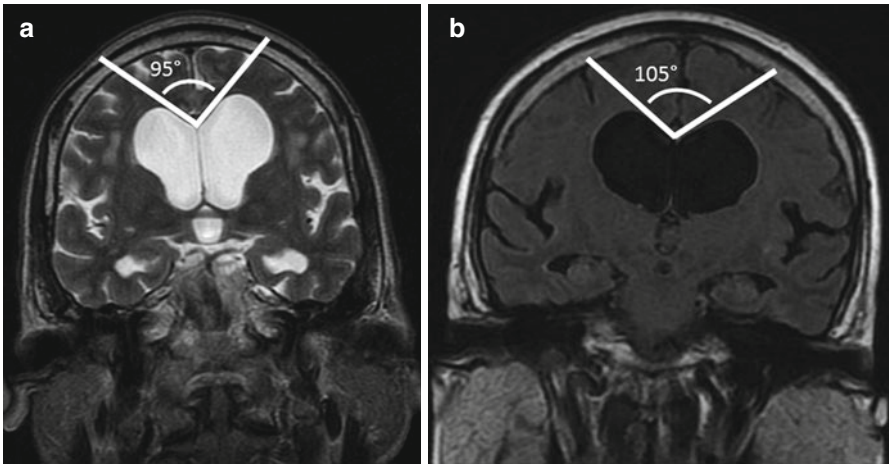

Fig. 14.3 (**a**) A 67-year-old male with slight cognitive impairment, progressive gait disturbance, and occasional urinary incontinence. Neuroradiological examinations from July 1993 show progressive ventricular enlargement. In the last MRI (June 2012), the Evans' index is 59.4 mm/137.60 mm = 0.43, and on T2 coronal image at the level of the posterior commissure, the callosal angle is more than 90°. After a positive tap test, a programmable shunt was inserted. Ten months after surgery the patient has a lasting clinical benefit on gait disturbance and urinary incontinence. (**b**) A 64-year-old female with gait instability and urinary incontinence. On MRI the Evans' index shows 47.4 mm/127.1 mm = 0.37. On coronal T1 image at the level of the posterior commissure, the callosal angle is more than 90°. Two years after surgery the patient is asymptomatic. The callosal angle must be interpreted in association to the clinical symptoms and all the neuroradiological findings

the cranium at the level of the Monro's foramens in the frontal horns (Evans 1942). A value equal or more than 0.3 support the diagnosis of probable NPH (Ishikawa et al. 2008; Marmarou et al. 2005b), but a lower value cannot exclude this diagnosis (Naruse and Matsuoka 2013). After shunt for NPH, the majority of the patients assessed by the Evans' index showed no ventricular changes, despite a satisfactory clinical improvement (Meier et al. 2003). Since remarkable differences were found in the Evans' index calculated at different planes on CT scans, its value has been questioned and not considered an ideal tool for diagnosis of NPH (Ambarki et al. 2010; Toma et al. 2011a). Other simple criteria which support a radiological diagnosis of NPH include a tight high-convexity and medial subarachnoid spaces, enlarged Sylvian fissures, a small callosal angle (under 90°) on the coronal section of MRI, and periventricular signal changes (Fig. 14.3) (Hashimoto et al. 2010; Ishii et al. 2008; Kitagaki et al. 1998; Sasaki et al. 2008). The aqueductal CSF stroke volume, which is the mean volume of CSF passing through the Sylvian aqueduct during cardiac systole and diastole, is a valuable tool in the preoperative evaluation of NPH patients. Higher aqueductal stroke volume in patients with short clinical history may be associated to a post-shunt improvement of clinical symptoms (Bradley et al. 1996; El Sankari et al. 2012; Scollato et al. 2009). The assessment of the ventricular size and volume may show very variable changes and may not easily correlate with

clinical improvement after CSF withdrawal (Anderson et al. 2002; Lenfeldt et al. 2012; McConnell et al. 2004; Palm et al. 2006). However, if the ventricular and brain volumes are assessed with a specific software, after prolonged external lumbar drainage, the brain volume may increase and the ventricular volume may decrease, more markedly than after a single tap withdrawal (Singer et al. 2012). A study with functional MRI in NPH patients showed a bilateral increased activation in the supplementary motor area after CSF removal (Lenfeldt et al. 2008b). Moreover, proton magnetic resonance spectroscopy revealed normalization of N-acetyl-aspartate in the frontal white matter after a 3-day lumbar drainage (Lenfeldt et al. 2008a).

The Supplemental Tests

The lack of a confident radiological diagnosis of NPH prompted the investigation of other diagnostic tools. Three diagnostic procedures are widely carried out: the withdrawal of lumbar CSF (30–50 ml), the external lumbar drainage (a 3-day drainage of approximately 135 ml/24 h), and the infusion test (lumbar infusion bolus technique: 4 ml, 1 ml/s). The choice among such options seems to be fundamentally related to the experience of each single center or clinician, more than to evidence-based studies, since these tools can be used for selecting patients for shunt surgery, but not for excluding patients from treatment (Wikkelsø et al. 2013). Comparisons among these procedures have been carefully investigated in various studies, highlighting advantages and disadvantages (Marmarou et al. 2005a). It should be pointed out that when the clinical and radiological diagnosis of NPH is highly probable, shunt surgery may be recommended also in the absence of supplemental tests, with a degree of certainty ranging from 50 to 61 % (Klinge et al. 2012; Marmarou et al. 2005a). However, it is recommended that all patients with probable or possible NPH should perform one of these tests, in order to obtain a probability measure of a successful response to shunt surgery, beyond such 50–61 % degree of certainty. The tap test has a higher positive predictive value (100 %) for a good response to surgical shunt, but a low sensitivity (from 21 to 61 %). A negative tap test cannot exclude patients from surgical treatment. The removal of CSF may improve gait or cognitive performance neuropsychological tests. The external lumbar drainage shows high sensitivity (50–100 %) and high positive predictive value (80–100 %). This procedure requires a hospitalization for some days, but in some patients may be complicated by replacement of escaped lumbar drain and, rarely, by secondary meningitis. Changes in walking pattern or neuropsychological tests are important variables to be assessed before and after CSF removal. In particular, an improvement of gait (speed, number of steps, stride length) is considered that may predict a good postsurgical outcome, suggesting the opportunity of a surgical treatment (Matousek et al. 1995; Damasceno et al. 1997; Stolze et al. 2000; Virhammar et al. 2012; Wikkelsø et al. 1982). As compared with the tap test, the CSF resistance outflow test has a similar positive predictive value (75–92 %), but a higher sensitivity (57–100 %). To perform this test, the baseline cerebrospinal pressure must be recorded before and immediately after injection. Patients with a threshold of CSF

outflow resistance ranging from 12 to 19 mmHg/ml/min seem to improve clinically after surgery, but there is still disagreement about the exact value to be considered pathological (Czosnyka et al. 2003). This procedure can be performed to assess the failure of a third ventriculostomy or of a surgical shunt (Aquilina et al. 2012; Malm et al. 2004).

The Surgical Treatment

Clinical evidence supports the value of surgery in NPH patients, despite the lack of randomized controlled trials comprising surgical treatment versus no surgery (Esmonde and Cooke 2002; Toma et al. 2011b, 2012). The best surgical technique to treat NPH should be aimed at obtaining a diversion of flow of CSF and at favoring the impaired processes involved in CSF reabsorption. There are two surgical options to enable such events: the endoscopic third ventriculostomy and the placement of a CSF shunt from a cerebral ventricle into an absorbing cavity or the vascular system. The endoscopic third ventriculostomy is performed through a frontal burr hole. The endoscope is inserted in the brain to gain the Monro's foramen and the floor of the third ventricle. After the identification of landmarks (the mammillary bodies and tuber cinereum), a catheter pierces a chosen place to put CSF flow between the interpeduncular cistern and the third ventricle. A low complication rate, a low mortality rate, and good neurological improvement are reported (Bouras and Sgouros 2012; Fountas et al. 2012; Gangemi et al. 2004, 2008). Since in the long-term follow-up closure of the fenestration and recurrent symptoms after initial successful treatment occur, these patients should be monitored for some years (Amini and Schmidt 2005; Cage et al. 2011; Fabiano et al. 2010; Longatti et al. 2004). A randomized clinical trial comparing the endoscopic third ventriculostomy with the ventriculoperitoneal shunt (shunt into the abdominal cavity) shows that the shunt has a better neurological outcome 12 months after surgery (Pinto et al. 2013). Indeed the surgical shunt is the most widely performed procedure to treat the NPH. Over the past few decades, the rate of complications after surgical treatment has decreased considerably, due to the improvement of the techniques and valve systems (Black 1980; Farahmand et al. 2009; Greenberg et al. 1977; Larsson et al. 1991; Poca et al. 2004; Savitz and Bobroff 1999; Zemack and Romner 2008). The ventriculoperitoneal shunt is more widely performed as compared with the ventriculoatrial shunt, probably due to early reports indicating a less risk of serious complications and neurosurgeon's confidence for the abdominal insertion in pediatric patients (Keucher and Mealey 1979; Mazza et al. 1980; Olsen and Frykberg 1983; Vernet et al. 1993). This conclusion has been initially transferred to adult patients (Lam and Villemure 1997). More recent surgical series show no difference between ventriculoperitoneal and ventriculoatrial shunt in adult hydrocephalus, and in some cases ventriculoatrial shunt is carried out after a failure of the ventriculoperitoneal shunt (Farahmand et al. 2009; Murakami et al. 2010; Stranjalis et al. 2012; Zhang et al. 2009). An alternative surgical option in patients with NPH is the lumboperitoneal shunt (Bloch and McDermott 2012; Chang et al. 1999; Yadav et al. 2010). Since NPH is a communicating hydrocephalus, it is

possible to drain the lumbar CSF into the abdominal cavity, through an intrathecal spinal catheter, with a programmable valve. The technique is apparently simple, but the rate of complication is not low (Karabatsou et al. 2004; Wang et al. 2007). The ventriculopleural shunt (into the space between the visceral and parietal pleura of the lungs) is very rarely performed in patients with NPH and is indicated when other routes are not available (Megison and Benzel 1988). The introduction of programmable (flow-regulated) versus nonadjustable (differential-pressure) valves has changed the surgical view: the amount of CSF withdrawal can be varied according to the clinical changes which can occur in the early or late postoperative follow-up (Zemack and Romner 2000). Readjusting the opening pressure may decrease the incidence of clinical complications of underdrainage or overdrainage (Freimann and Sprung 2012). A low CSF pressure has been proven to have a better outcome, but it is plagued by overdrainage complications (Boon et al. 1998). Accordingly, the combination of programmable valve with a gravitational valve (which eliminates overdrainage by increasing resistance as patient moves upright) may improve the outcome (Lemcke and Meier 2010; Meier and Lemcke 2006). A recent trial showed that a gravitational valve (which switches between a low pressure mode in the supine position and a high pressure mode in the upright position) reduces the risk of overdrainage complications, as compared with a standard programmable valve (Lemcke et al. 2013).

Outcome

The most relevant feature of patients who undergo surgical treatment for NPH is the rapid neurological improvement in the early postoperative period. In the majority of cases, patients regain the ability to walk and control micturition but also, albeit less frequently, of cognitive and behavioral symptoms. Accordingly, NPH is included among the infrequent conditions of reversible dementia. In particular, it has been observed that deficits of episodic verbal memory (Gallassi et al. 1991), constructional praxic abilities (Goodman and Meyer 2001), and psychomotor speed (Kaye et al. 1990) may improve after shunt surgery, at least in subgroups of NPH patients. On the other hand, it has been reported that deficits of executive functions may not improve after surgery (Iddon et al. 1999). By contrast, in a more recent study (Saito et al. 2011), 1 year after CSF surgery, the NPH group showed a significant improvement on tasks assessing frontal functions (FAB), including executive functions.

In a recent neuropathological study (Cabral et al. 2011), a group of nine patients with a clinical diagnosis of NPH was examined, and it was observed that in eight out of such nine patients, there were neuropathological changes consistent with AD. This study on a small sample of patients with a clinical diagnosis of NPH suggests that AD may be a frequent pathological comorbidity in patients with NPH and such comorbidity may at least partially preclude cognitive improvement after surgery.

A study carried out in 36 patients with NPH (Chang et al. 2006) who underwent neuropsychological testing before and after ventriculoperitoneal shunt insertion reported that one third of patients showed good cognitive improvement (defined as improvement by at least 25 % on at least half of the cognitive tests administered).

The degree of cognitive improvement was found to be greater in women than in men, and there was a significant negative linear relationship between age and probability of good cognitive improvement. Younger age was found to be a better predictor of improvement on memory tests, while female sex was a better predictor of improvement on non-memory tests after shunt insertion (Chang et al. 2006).

In conclusion, an extensive neuropsychological assessment in patients with suspected NPH may show the pattern of cognitive impairment in each individual patient and could be a helpful tool in the differential diagnosis of NPH, in monitoring disease progression, and in assessing clinical response to surgery (Devito et al. 2005).

After surgery, the patient is usually able to regain a good quality of life, with independence in daily living activities. The duration of such postsurgical improvement is still difficult to be predicted. At least a 1-year post-shunt monitoring period may be necessary to evaluate the clinical effects of the surgical procedure (Klinge et al. 2005, 2012). However, some shunted NPH patients experience years after surgery a variable decline and recurrence of symptoms, but after readjusting the opening pressure of the programmable valve (increasing the outflow of CSF), patients may improve again (Aygok et al. 2005; Koivisto et al. 2013). Accordingly, a periodic clinical follow-up is mandatory to avoid delays in the valve adjustment. Several studies showed that comorbidities (mainly cardiovascular and cerebrovascular disorders) may affect significantly long-term outcome in shunted patients with NPH (Kiefer et al. 2006; Lemcke and Meier 2012; Malm et al. 2013; Meier and Lemcke 2008, 2010; Mirzayan et al. 2010), suggesting that a high comorbidity index is strictly related to a poor outcome (Lemcke and Meier 2012; Mirzayan et al. 2010).

References

Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WT. Symptomatic occult hydrocephalus with "normal" cerebrospinal fluid pressure: a treatable syndrome. N Engl J Med. 1965;273:117–26.

Aitken RR, Drake CG. Continuous spinal drainage in the treatment of postoperative cerebrospinal-fluid fistulae. J Neurosurg. 1964;21:275–7.

Albert F. Lumbar puncture as applied to craniocerebral surgery. Ann Surg. 1918;68:549–50.

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986;9:357–81.

Ambarki K, Israelsson H, Wåhlin A, Birgander R, Eklund A, Malm J. Brain ventricular size in healthy elderly: comparison between Evans index and volume measurement. Neurosurgery. 2010;67:94–9.

Amini A, Schmidt RH. Endoscopic third ventriculostomy in a series of 36 adult patients. Neurosurg Focus. 2005;19:E9.

Anderson RC, Grant JJ, de la Paz R, Frucht S, Goodman RR. Volumetric measurements in the detection of reduced ventricular volume in patients with normal-pressure hydrocephalus whose clinical condition improved after ventriculoperitoneal shunt placement. J Neurosurg. 2002;97:73–9.

Aquilina K, Pople IK, Sacree J, Carter MR, Edwards RJ. The constant flow ventricular infusion test: a simple and useful study in the diagnosis of third ventriculostomy failure. J Neurosurg. 2012;116:445–52.

Aygok G, Marmarou A, Young HF. Three-year outcome of shunted idiopathic NPH patients. Acta Neurochir Suppl. 2005;95:241–5.

Bech-Azeddine R, Waldemar G, Knudsen GM, Hogh P, Bruhn P, Wildschiodtz G, Gjerris F, Paulson OB, Juhler M. Idiopathic normal-pressure hydrocephalus: evaluation and findings in a multidisciplinary memory clinic. Eur J Neurol. 2001;8:601–11.

Black PM. Idiopathic normal-pressure hydrocephalus. Results of shunting in 62 patients. J Neurosurg. 1980;52:371–7.

Bloch O, McDermott MW. Lumboperitoneal shunts for the treatment of normal pressure hydrocephalus. J Clin Neurosci. 2012;19:1107–11.

Bloom KK, Kraft WA. Paranoia–an unusual presentation of hydrocephalus. Am J Phys Med Rehabil. 1998;77:157–9.

Boon AJ, Tans JT, Delwel EJ, Egeler-Peerdeman SM, Hanlo PW, Wurzer HA, Avezaat CJ, de Jong DA, Gooskens RH, Hermans J. Dutch Normal-Pressure Hydrocephalus Study: randomized comparison of low- and medium-pressure shunts. J Neurosurg. 1998;88:490–5.

Bouras T, Sgouros S. Complications of endoscopic third ventriculostomy: a systematic review. Acta Neurochir Suppl. 2012;113:149–53.

Bradley Jr WG, Scalzo D, Queralt J, Nitz WN, Atkinson DJ, Wong P. Normal pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging. Radiology. 1996;198:523–9.

Brean A, Eide PK. Prevalence of probable idiopathic normal pressure hydrocephalus in a Norwegian population. Acta Neurol Scand. 2008;118:48–53.

Browning W. Lumbar puncture for the removal of cerebro-spinal fluid. In: Browning W, editor. The normal and pathological circulation in the central nervous system. Philadelphia: J. B. Lippincott Company; 1897. p. 54–60.

Cabral D, Beach TG, Vedders L, Sue LI, Jacobson S, Myers K, Sabbagh MN. Frequency of Alzheimer's disease pathology at autopsy in patients with clinical normal pressure hydrocephalus. Alzheimers Dement. 2011;7:509–13.

Cage TA, Auguste KI, Wrensch M, Wu YW, Gupta N. Self-reported functional outcome after surgical intervention in patients with idiopathic normal pressure hydrocephalus. J Clin Neurosci. 2011;18:649–54.

Casmiro M, Benassi G, Cacciatore FM, D'Alessandro R. Frequency of idiopathic normal pressure hydrocephalus. Arch Neurol. 1989;46:608.

Chakravarty A. Unifying concept for Alzheimer's disease, vascular dementia and normal pressure hydrocephalus – a hypothesis. Med Hypotheses. 2004;63:827–33.

Chang CC, Kuwana N, Ito S. Management of patients with normal-pressure hydrocephalus by using lumboperitoneal shunt system with the Codman Hakim programmable valve. Neurosurg Focus. 1999;7:e8.

Chang S, Agarwal S, Williams MA, Rigamonti D, Hillis AE. Demographic factors influence cognitive recovery after shunt for normal-pressure hydrocephalus. Neurologist. 2006; 12:39–42.

Christensen PB. Normal pressure hydrocephalus in myotonic dystrophy. Eur Neurol. 1988;28:285–7.

Clarfield AM. The decreasing prevalence of reversible dementias: an updated meta-analysis. Arch Intern Med. 2003;163:2219–29.

Colitti MC, Casaccia V, Bella A, Perra A, Binkin N. VETUS a Orvieto un'indagine sulla qualità della vita delle persone con più di 64 anni nel comune di Orvieto. Not Ist Super Sanità. 2006;11:III–IV.

Conn HO. Normal pressure hydrocephalus (NPH): more about NPH by a physician who is the patient. Clin Med. 2011;11:162–5.

Cummings JL, Benson DF. Subcortical dementia. Review of an emerging concept. Arch Neurol. 1984;41:874–9.

Cusimano MD, Rewilak D, Stuss DT, Barrera-Martinez JC, Salehi F, Freedman M. Normal-pressure hydrocephalus: is there a genetic predisposition? Can J Neurol Sci. 2011;38:274–81.

Czosnyka M, Czosnyka Z, Momjian S, Schmidt E. Calculation of the resistance to CSF outflow. J Neurol Neurosurg Psychiatry. 2003;74:1354.

Damasceno BP, Carelli EF, Honorato DC, Facure JJ. The predictive value of cerebrospinal fluid tap-test in normal pressure hydrocephalus. Arq Neuropsiquiatr. 1997;55:179–85.

Dandy WE. Ventriculography following the injection of air into the cerebral ventricles. Ann Surg. 1918;68:5–11.
Delavallée M, Raftopoulos C. Normal pressure hydrocephalus in a patient with myotonic dystrophy: case report with a 10-year follow-up. Neurosurgery. 2006;58:E796.
Devito EE, Pickard JD, Salmond CH, Iddon JL, Loveday C, Sahakian BJ. The neuropsychology of normal pressure hydrocephalus (NPH). Br J Neurosurg. 2005;19:217–24.
Di Lauro L, Mearini M, Bollati A. The predictive value of 5 days CSF diversion for shunting in normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 1986;49:842–3.
Edsbagge M, Tisell M, Jacobsson L, Wikkelso C. Spinal CSF absorption in healthy individuals. Am J Physiol Regul Integr Comp Physiol. 2004;287:R1450–5.
El Sankari S, Fichten A, Gondry-Jouet C, Czosnyka M, Legars D, Deramond H, Balédent O. Correlation between tap test and CSF aqueductal stroke volume in idiopathic normal pressure hydrocephalus. Acta Neurochir Suppl. 2012;113:43–6.
Esmonde T, Cooke S. Shunting for normal pressure hydrocephalus (NPH). Cochrane Database Syst Rev. 2002;(3):CD003157.
Evans WA. An encephalographic ratio for estimating ventricular enlargement and cerebral atrophy. Arch Neurol Psychiatry. 1942;47:931–7.
Fabiano AJ, Doyle K, Grand W. Delayed stoma failure in adult communicating hydrocephalus after initial successful treatment by endoscopic third ventriculostomy: case report. Neurosurgery. 2010;66:E1210–1.
Farahmand D, Hilmarsson H, Högfeldt M, Tisell M. Perioperative risk factors for short term shunt revisions in adult hydrocephalus patients. J Neurol Neurosurg Psychiatry. 2009;80:1248–53.
Fisher CM. Communicating hydrocephalus. Lancet. 1978;1(8054):37.
Fisher CM. Hydrocephalus as a cause of disturbances of gait in the elderly. Neurology. 1982;32:1358–63.
Fountas KN, Kapsalaki EZ, Paterakis KN, Lee GP, Hadjigeorgiou GM. Role of endoscopic third ventriculostomy in treatment of selected patients with normal pressure hydrocephalus. Acta Neurochir Suppl. 2012;113:129–33.
Freimann FB, Sprung C. Shunting with gravitational valves–can adjustments end the era of revisions for overdrainage-related events?: clinical article. J Neurosurg. 2012;117:1197–204.
Gallassi R, Morreale A, Montagna P, Sacquegna T, Di Sarro R, Lugaresi E. Binswanger's disease and normal-pressure hydrocephalus. Clinical and neuropsychological comparison. Arch Neurol. 1991;48:1156–9.
Gangemi M, Maiuri F, Buonamassa S, Colella G, de Divitiis E. Endoscopic third ventriculostomy in idiopathic normal pressure hydrocephalus. Neurosurgery. 2004;55:129–34.
Gangemi M, Maiuri F, Naddeo M, Godano U, Mascari C, Broggi G, Ferroli P. Endoscopic third ventriculostomy in idiopathic normal pressure hydrocephalus: an Italian multicenter study. Neurosurgery. 2008;63:62–7.
Gawler J, Du Boulay GH, Bull JW, Marshall J. Computerized tomography (the EMI Scanner): a comparison with pneumoencephalography and ventriculography. J Neurol Neurosurg Psychiatry. 1976;39:203–11.
Goodman M, Meyer WJ. Dementia reversal in post-shunt normal pressure hydrocephalus predicted by neuropsychological assessment. J Am Geriatr Soc. 2001;49:685–6.
Greenberg JO, Shenkin HA, Adam R. Idiopathic normal pressure hydrocephalus– a report of 73 patients. J Neurol Neurosurg Psychiatry. 1977;40:336–41.
Greenfield JG. Lumbar puncture in diagnosis. Br Med J. 1935;2:1265–7.
Gunasekera L, Richardson AE. Computerized axial tomography in idiopathic hydrocephalus. Brain. 1977;100:749–54.
Hashimoto M, Ishikawa M, Mori E, Kuwana N, Study of INPH on neurological improvement (SINPHONI). Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res. 2010;7:18.
Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol. 2003;60:1119–22.
Hellström P, Klinge P, Tans J, Wikkelsø C. A new scale for assessment of severity and outcome in iNPH. Acta Neurol Scand. 2012;126:229–37.

Hiraoka K, Meguro K, Mori E. Prevalence of idiopathic normal-pressure hydrocephalus in the elderly population of a Japanese rural community. Neurol Med Chir. 2008;48:197–9.
Honda K, Matsumoto M, Kaneko T, Kamei I, Tatsumi H, Murai N, Mineharu Y, Oita J. Linear deposition of immunoglobulins and complement components on the dura in normal pressure hydrocephalus complicating systemic lupus erythematosus. J Clin Neurosci. 2004;11:561–3.
Iddon JL, Pickard JD, Cross JJ, Griffiths PD, Czosnyka M, Sahakian BJ. Specific patterns of cognitive impairment in patients with idiopathic normal pressure hydrocephalus and Alzheimer's disease: a pilot study. J Neurol Neurosurg Psychiatry. 1999;67:723–32.
Ishii K, Kanda T, Harada A, Miyamoto N, Kawaguchi T, Shimada K, Ohkawa S, Uemura T, Yoshikawa T, Mori E. Clinical impact of the callosal angle in the diagnosis of idiopathic normal pressure hydrocephalus. Eur Radiol. 2008;18:2678–83.
Ishikawa M, Hashimoto M, Kuwana N, Mori E, Miyake H, Wachi A, Takeuchi T, Kazui H, Koyama H. Guidelines for management of idiopathic normal pressure hydrocephalus. Neurol Med Chir (Tokyo). 2008;48(Suppl):S1–23.
Jacobs L, Kinkel W. Computerized axial transverse tomography in normal pressure hydrocephalus. Neurology. 1976;26(6 PT1):501–7.
Johnston M. The importance of lymphatics in cerebrospinal fluid transport. Lymphat Res Biol. 2003;1:41–4.
Karabatsou K, Quigley G, Buxton N, Foy P, Mallucci C. Lumboperitoneal shunts: are the complications acceptable? Acta Neurochir (Wien). 2004;146:1193–7.
Katzman R, Hussey F. A simple constant-infusion manometric test for measurement of CSF absorption. I. Rationale and method. Neurology. 1970;20:534–44.
Kaye JA, Grady CL, Haxby JV, Moore A, Friedland RP. Plasticity in the aging brain. Reversibility of anatomic, metabolic, and cognitive deficits in normal-pressure hydrocephalus following shunt surgery. Arch Neurol. 1990;47:1336–41.
Keucher TR, Mealey Jr J. Long-term results after ventriculoatrial and ventriculoperitoneal shunting for infantile hydrocephalus. J Neurosurg. 1979;50:179–86.
Kiefer M, Eymann R, Steudel WI. Outcome predictors for normal-pressure hydrocephalus. Acta Neurochir Suppl. 2006;96:364–7.
Kitagaki H, Mori E, Ishii K, Yamaji S, Hirono N, Imamura T. CSF spaces in idiopathic normal pressure hydrocephalus: morphology and volumetry. AJNR Am J Neuroradiol. 1998;19:1277–84.
Kito Y, Kazui H, Kubo Y, Yoshida T, Takaya M, Wada T, Nomura K, Hashimoto M, Ohkawa S, Miyake H, Ishikawa M, Takeda M. Neuropsychiatric symptoms in patients with idiopathic normal pressure hydrocephalus. Behav Neurol. 2009;21:165–74.
Klinge P, Marmarou A, Bergsneider M, Relkin N, Black PM. Outcome of shunting in idiopathic normal-pressure hydrocephalus and the value of outcome assessment in shunted patients. Neurosurgery. 2005;57(3 Suppl):S40–52.
Klinge P, Hellström P, Tans J, Wikkelsø C, European iNPH Multicentre Study Group. One-year outcome in the European multicentre study on iNPH. Acta Neurol Scand. 2012;126:145–53.
Koch HJ, Nanev D, Becker K. Acute behaviour disorder in a patient with X-linked hydrocephalus with normal pressure. Wien Med Wochenschr. 2009;159:62–4.
Koivisto AM, Alafuzoff I, Savolainen S, Sutela A, Rummukainen J, Kurki M, Jääskeläinen JE, Soininen H, Rinne J, Leinonen V. Poor cognitive outcome in shunt-responsive idiopathic normal pressure hydrocephalus. Neurosurgery. 2013;72:1–8.
Krauss JK, Halve B. Normal pressure hydrocephalus. survey on contemporary diagnostic algorithms and therapeutic decision-making in clinical practice. Acta Neurochir. 2004;146:379–88.
Kubo Y, Kazui H, Yoshida T, Kito Y, Kimura N, Tokunaga H, Ogino A, Miyake H, Ishikawa M, Takeda M. Validation of grading scale for evaluating symptoms of idiopathic normal-pressure hydrocephalus. Dement Geriatr Cogn Disord. 2008;25:37–45.
Kwentus JA, Hart RP. Normal pressure hydrocephalus presenting as mania. J Nerv Ment Dis. 1987;175:500–2.

Lam CH, Villemure JG. Comparison between ventriculoatrial and ventriculoperitoneal shunting in the adult population. Br J Neurosurg. 1997;11:43–8.
Larsson A, Wikkelsö C, Bilting M, Stephensen H. Clinical parameters in 74 consecutive patients shunt operated for normal pressure hydrocephalus. Acta Neurol Scand. 1991;84:475–82.
Lemcke J, Meier U. Improved outcome in shunted iNPH with a combination of a Codman Hakim programmable valve and an Aesculap-Miethke Shunt Assistant. Cent Eur Neurosurg. 2010;71: 113–6.
Lemcke J, Meier U. Idiopathic normal pressure hydrocephalus (iNPH) and co-morbidity: an outcome analysis of 134 patients. Acta Neurochir Suppl. 2012;114:255–9.
Lemcke J, Meier U, Müller C, Fritsch MJ, Kehler U, Langer N, Kiefer M, Eymann R, Schuhmann MU, Speil A, Weber F, Remenez V, Rohde V, Ludwig HC, Stengel D. Safety and efficacy of gravitational shunt valves in patients with idiopathic normal pressure hydrocephalus: a pragmatic, randomised, open label, multicentre trial (SVASONA). J Neurol Neurosurg Psychiatry. 2013;84:850–7.
Lenfeldt N, Hauksson J, Birgander R, Eklund A, Malm J. Improvement after cerebrospinal fluid drainage is related to levels of N-acetyl-aspartate in idiopathic normal pressure hydrocephalus. Neurosurgery. 2008a;62:135–41.
Lenfeldt N, Larsson A, Nyberg L, Andersson M, Birgander R, Eklund A, Malm J. Idiopathic normal pressure hydrocephalus: increased supplementary motor activity accounts for improvement after CSF drainage. Brain. 2008b;131:2904–12.
Lenfeldt N, Hansson W, Larsson A, Birgander R, Eklund A, Malm J. Three-day CSF drainage barely reduces ventricular size in normal pressure hydrocephalus. Neurology. 2012;79:237–42.
Longatti PL, Fiorindi A, Martinuzzi A. Failure of endoscopic third ventriculostomy in the treatment of idiopathic normal pressure hydrocephalus. Minim Invasive Neurosurg. 2004;47:342–5.
Luedemann W, Kondziella D, Tienken K, Klinge P, Brinker T, Berens von Rautenfeld D. Spinal cerebrospinal fluid pathways and their significance for the compensation of kaolin-hydrocephalus. Acta Neurochir Suppl. 2002;81:271–3.
MacCordick AH. Observations on the value of lumbar puncture. Can Med Assoc J. 1922;12:168–70.
Malm J, Lundkvist B, Eklund A, Koskinen LO, Kristensen B. CSF outflow resistance as predictor of shunt function. A long-term study. Acta Neurol Scand. 2004;110:154–60.
Malm J, Graff-Radford NR, Ishikawa M, Kristensen B, Leinonen V, Mori E, Owler BK, Tullberg M, Williams MA, Relkin NR. Influence of comorbidities in idiopathic normal pressure hydrocephalus – research and clinical care. A report of the ISHCSF task force on comorbidities in INPH. Fluids Barriers CNS. 2013;10:22.
Marmarou A, Bergsneider M, Klinge P, Relkin N, Black PM. The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus. Neurosurgery. 2005a;57(3 Suppl):S17–28.
Marmarou A, Bergsneider M, Relkin N, Klinge P, Black PM. Development of guidelines for idiopathic normal-pressure hydrocephalus: introduction. Neurosurgery. 2005b;57(3 Suppl):S1–3.
Marmarou A, Young HF, Aygok GA. Estimated incidence of normal pressure hydrocephalus and shunt outcome in patients residing in assisted-living and extended-care facilities. Neurosurg Focus. 2007;22:E1.
Martin BJ, Roberts MA, Turner JW. Normal pressure hydrocephalus and Paget's disease of bone. Gerontology. 1985;31:397–402.
Matera R, Althabe BM. Continuous lumbar drainage of the cerebrospinal fluid in neurosurgery. Sem Med. 1962;121:1083–7.
Matousek M, Wikkelsö C, Blomsterwall E, Johnels B, Steg G. Motor performance in normal pressure hydrocephalus assessed with an optoelectronic measurement technique. Acta Neurol Scand. 1995;91:500–5.
Matson DD. A new operation for the treatment of communicating hydrocephalus: report of a case secondary to generalized meningitis. J Neurosurg. 1949;6:238–47.
Mazza C, Pasqualin A, Da Pian R. Results of treatment with ventriculoatrial and ventriculoperitoneal shunt in infantile nontumoral hydrocephalus. Childs Brain. 1980;7:1–14.

McConnell KA, Zou KH, Chabrerie AV, Bailey NO, Black PM. Decreases in ventricular volume correlate with decreases in ventricular pressure in idiopathic normal pressure hydrocephalus patients who experienced clinical improvement after implantation with adjustable valve shunts. Neurosurgery. 2004;55:582–92.

McGirr A, Cusimano MD. Familial aggregation of idiopathic normal pressure hydrocephalus: novel familial case and a family study of the NPH triad in an iNPH patient cohort. J Neurol Sci. 2012;321:82–8.

McHugh PR. Occult hydrocephalus. Q J Med. 1964;33:297–308.

Megison DP, Benzel EC. Ventriculo-pleural shunting for adult hydrocephalus. Br J Neurosurg. 1988;2:503–5.

Meier U, Lemcke J. Clinical outcome of patients with idiopathic normal pressure hydrocephalus three years after shunt implantation. Acta Neurochir Suppl. 2006;96:377–80.

Meier U, Lemcke J. The influence of co-morbidity on the postoperative outcomes of patients with idiopathic normal pressure hydrocephalus (iNPH). Acta Neurochir Suppl. 2008;102:141–4.

Meier U, Lemcke J. Co-morbidity as a predictor of outcome in patients with idiopathic normal-pressure hydrocephalus. Acta Neurochir Suppl. 2010;106:127–30.

Meier U, Paris S, Gräwe A, Stockheim D, Hajdukova A, Mutze S. Is there a correlation between operative results and change in ventricular volume after shunt placement? A study of 60 cases of idiopathic normal-pressure hydrocephalus. Neuroradiology. 2003;45:377–80.

Mirzayan MJ, Luetjens G, Borremans JJ, Regel JP, Krauss JK. Extended long-term (> 5 years) outcome of cerebrospinal fluid shunting in idiopathic normal pressure hydrocephalus. Neurosurgery. 2010;67:295–301.

Missori P, Paolini S, Currà A. From congenital to idiopathic adult hydrocephalus: a historical research. Brain. 2010;133:1836–49.

Missori P, Paolini S, Domenicucci M. The origin of the cannula for ventriculostomy in pediatric hydrocephalus. J Neurosurg Pediatr. 2011;7:290–4.

Moiyadi AV, Praharaj SS, Pillai VS, Chandramouli BA. Hydrocephalus in Paget's disease. Acta Neurochir (Wien). 2006;148:1297–300.

Mollanji R, Bozanovic-Sosic R, Zakharov A, Makarian L, Johnston MG. Blocking cerebrospinal fluid absorption through the cribriform plate increases resting intracranial pressure. Am J Physiol Regul Integr Comp Physiol. 2002;282:R1593–9.

Murakami M, Morine M, Iwasa T, Takahashi Y, Miyamoto T, Hon PK, Nakagawa Y. Management of maternal hydrocephalus requires replacement of ventriculoperitoneal shunt with ventriculoatrial shunt: a case report. Arch Gynecol Obstet. 2010;282:339–42.

Naruse H, Matsuoka Y. Post-operative improvement of 14 cases who were considered iNPH despite Evans' index of 0.3 or less. No Shinkei Geka. 2013;41:25–30.

Nulsen F, Spitz EB. Treatment of hydrocephalus by direct shunt from ventricle to jugular vein. Surg Forum. 1951;2:399–409.

Olsen L, Frykberg T. Complications in the treatment of hydrocephalus in children. A comparison of ventriculoatrial and ventriculoperitoneal shunts in a 20-year material. Acta Paediatr Scand. 1983;72:385–90.

Palm WM, Walchenbach R, Bruinsma B, Admiraal-Behloul F, Middelkoop HA, Launer LJ, van der Grond J, van Buchem MA. Intracranial compartment volumes in normal pressure hydrocephalus: volumetric assessment versus outcome. AJNR Am J Neuroradiol. 2006;27:76–9.

Patwardhan RV, Nanda A. Implanted ventricular shunts in the United States: the billion-dollar-a-year cost of hydrocephalus treatment. Neurosurgery. 2005;56:139–44.

Pinto FC, Saad F, Oliveira MF, Pereira RM, Miranda FL, Tornai JB, Lopes MI, Ribas ES, Valinetti EA, Teixeira MJ. Role of endoscopic third ventriculostomy and ventriculoperitoneal shunt in idiopathic normal pressure hydrocephalus: preliminary results of a randomized clinical trial. Neurosurgery. 2013;72:845–54.

Poca MA, Mataró M, Del Mar Matarín M, Arikan F, Junqué C, Sahuquillo J. Is the placement of shunts in patients with idiopathic normal-pressure hydrocephalus worth the risk? Results of a study based on continuous monitoring of intracranial pressure. J Neurosurg. 2004; 100:855–66.

Portenoy RK, Berger A, Gross E. Familial occurrence of idiopathic normal-pressure hydrocephalus. Arch Neurol. 1984;41:335–7.
Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic normal-pressure hydrocephalus. Neurosurgery. 2005;57:S4–16.
Rhodes H. The value of lumbar puncture in general practice. Br Med J. 1903;2:73–4.
Rice E, Gendelman S. Psychiatric aspects of normal pressure hydrocephalus. JAMA. 1973;223:409–12.
Riggs JE, Rubenstein MN, Gutmann L. Myotonic dystrophy and normal-pressure hydrocephalus. Neurology. 1985;35:1535.
Roger H, Paillas J, Roger J, Tamalet J. Grande hydrocéphalie latente du vieillard chez une démente artérioscléreuse. Rev Neurol. 1950;82:437–8.
Roohi F, Mann D, Kula RW. Surgical management of hydrocephalic dementia in Paget's disease of bone: the 6-year outcome of ventriculo-peritoneal shunting. Clin Neurol Neurosurg. 2005;107:325–8.
Saito M, Nishio Y, Kanno S, Uchiyama M, Hayashi A, Takagi M, Kikuchi H, Yamasaki H, Shimomura T, Iizuka O, Mori E. Cognitive profile of idiopathic normal pressure hydrocephalus. Dement Geriatr Cogn Dis Extra. 2011;1:202–11.
Sakakibara R, Kanda T, Sekido T, Uchiyama T, Awa Y, Ito T, Liu Z, Yamamoto T, Yamanishi T, Yuasa T, Shirai K, Hattori T. Mechanism of bladder dysfunction in idiopathic normal pressure hydrocephalus. Neurourol Urodyn. 2008;27:507–10.
Sakakibara R, Uchida Y, Ishii K, Kazui H, Hashimoto M, Ishikawa M, Yuasa T, Kishi M, Ogawa E, Tateno F, Uchiyama T, Yamamoto T, Yamanishi T, Terada H. Correlation of right frontal hypoperfusion and urinary dysfunction in iNPH: a SPECT study. Neurourol Urodyn. 2012;31:50–5.
Sasaki M, Honda S, Yuasa T, Iwamura A, Shibata E, Ohba H. Narrow CSF space at high convexity and high midline areas in idiopathic normal pressure hydrocephalus detected by axial and coronal MRI. Neuroradiology. 2008;50:117–22.
Savitz MH, Bobroff LM. Low incidence of delayed intracerebral hemorrhage secondary to ventriculoperitoneal shunt insertion. J Neurosurg. 1999;91:32–4.
Scollato A, Gallina P, Gautam B, Pellicanò G, Cavallini C, Tenenbaum R, Di Lorenzo N. Changes in aqueductal CSF stroke volume in shunted patients with idiopathic normal-pressure hydrocephalus. AJNR Am J Neuroradiol. 2009;30:1580–6.
Shenkin HA, Greenberg JO, Grossman CB. Ventricular size after shunting for idiopathic normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 1975;38:833–7.
Silverberg GD, Mayo M, Saul T, Rubenstein E, McGuire D. Alzheimer's disease, normal-pressure hydrocephalus, and senescent changes in CSF circulatory physiology: a hypothesis. Lancet Neurol. 2003;2:506–11.
Singer OC, Melber J, Hattingen E, Jurcoane A, Keil F, Neumann-Haefelin T, Klein JC. MR volumetric changes after diagnostic CSF removal in normal pressure hydrocephalus. J Neurol. 2012;259:2440–6.
Stolze H, Kuhtz-Buschbeck JP, Drücke H, Jöhnk K, Diercks C, Palmié S, Mehdorn HM, Illert M, Deuschl G. Gait analysis in idiopathic normal pressure hydrocephalus–which parameters respond to the CSF tap test? Clin Neurophysiol. 2000;111:1678–86.
Stranjalis G, Kalamatianos T, Koutsarnakis C, Loufardaki M, Stavrinou L, Sakas DE. Twelve-year hospital outcomes in patients with idiopathic hydrocephalus. Acta Neurochir Suppl. 2012;113:115–7.
Suzuchi H, Matsubara T, Kanamaru K, Kojima T. Chronic hydrocephalus presenting with bilateral ptosis after minor head injury: case report. Neurosurgery. 2000;47:977–9.
Synek V, Reuben JR, Du Boulay GH. Comparing Evans' index and computerized axial tomography in assessing relationship of ventricular size to brain size. Neurology. 1976;26:231–3.
Takahashi Y, Kawanami T, Nagasawa H, Iseki C, Hanyu H, Kato T. Familial normal pressure hydrocephalus (NPH) with an autosomal-dominant inheritance: a novel subgroup of NPH. J Neurol Sci. 2011;308:149–51.
Tanaka N, Yamaguchi S, Ishikawa H, Ishii H, Meguro K. Prevalence of possible idiopathic normal-pressure hydrocephalus in Japan: the Osaki-Tajiri project. Neuroepidemiology. 2009;32:171–5.

Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. Brain. 1986;109:845–83.
Tisell M, Hoglund M, Wikkelso C. National and regional incidence of surgery for adult hydrocephalus in Sweden. Acta Neurol Scand. 2005;112:72–5.
Toma AK, Holl E, Kitchen ND, Watkins LD. Evans' index revisited: the need for an alternative in normal pressure hydrocephalus. Neurosurgery. 2011a;68:939–44.
Toma AK, Stapleton S, Papadopoulos MC, Kitchen ND, Watkins LD. Natural history of idiopathic normal-pressure hydrocephalus. Neurosurg Rev. 2011b;34:433–9.
Toma AK, Papadopoulos MC, Stapleton S, Kitchen ND, Watkins LD. Conservative versus surgical management of idiopathic normal pressure hydrocephalus: a prospective double-blind randomized controlled trial: study protocol. Acta Neurochir Suppl. 2012;113:21–3.
Trenkwalder C, Schwarz J, Gebhard J, Ruland D, Trenkwalder P, Hense HW, Oertel WH. Starnberg trial on epidemiology of Parkinsonism and hypertension in the elderly. Prevalence of Parkinson's disease and related disorders assessed by a door-to-door survey of inhabitants older than 65 years. Arch Neurol. 1995;52:1017–22.
Vanneste J, Augustijn P, Tan WF, Dirven C. Shunting normal pressure hydrocephalus: the predictive value of combined clinical and CT data. J Neurol Neurosurg Psychiatry. 1993;56:251–6.
Vernet O, Campiche R, de Tribolet N. Long-term results after ventriculoatrial shunting in children. Childs Nerv Syst. 1993;9:253–5.
Virhammar J, Cesarini KG, Laurell K. The CSF tap test in normal pressure hydrocephalus: evaluation time, reliability and the influence of pain. Eur J Neurol. 2012;19:271–6.
von Ziemssen HW. Paracentesis of the spinal dura. Epitome of current medical literature. Br Med J. 1893;1:81.
Vourc'h G. Continuous cerebrospinal fluid drainage by indwelling spinal catheter. Br J Anaesth. 1963;35:118–20.
Vourc'h G, Rougerie J. Continuous drainage of the cerebrospinal fluid. New method by the installation of a permanent spinal catheter. Its value in neurosurgery. Presse Med. 1960;68:1491–2.
Wang VY, Barbaro NM, Lawton MT, Pitts L, Kunwar S, Parsa AT, Gupta N, McDermott MW. Complications of lumboperitoneal shunts. Neurosurgery. 2007;60:1045–8.
Westhout FD, Linskey ME. Obstructive hydrocephalus and progressive psychosis: rare presentations of neurosarcoidosis. Surg Neurol. 2008;69:288–92.
Wikkelsø C, Andersson H, Blomstrand C, Lindqvist G. The clinical effect of lumbar puncture in normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 1982;45:64–9.
Wikkelsø C, Hellström P, Klinge PM, Tans JT. The European iNPH Multicentre Study on the predictive values of resistance to CSF outflow and the CSF Tap Test in patients with idiopathic normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 2013;84:562–8.
Wright EM. Transport processes in the formation of the cerebrospinal fluid. Rev Physiol Biochem Pharmacol. 1978;83:3–34.
Wynter WE. Four cases of tubercular meningitis in which paracentesis was performed for the relief of fluid pressure. Lancet. 1891;1:981–2.
Yadav YR, Parihar V, Sinha M. Lumbar peritoneal shunt. Neurol India. 2010;58:179–84.
Yusim A, Anbarasan D, Bernstein C, Boksay I, Dulchin M, Lindenmayer JP, Saavedra-Velez C, Shapiro M, Sadock B. Normal pressure hydrocephalus presenting as Othello syndrome: case presentation and review of the literature. Am J Psychiatry. 2008;165:1119–25.
Zemack G, Romner B. Seven years of clinical experience with the programmable Codman Hakim valve: a retrospective study of 583 patients. J Neurosurg. 2000;92:941–8.
Zemack G, Romner B. Adjustable valves in normal-pressure hydrocephalus: a retrospective study of 218 patients. Neurosurgery. 2008;62 Suppl 2:677–87.
Zhang J, Qu C, Wang Z, Wang C, Ding X, Pan S, Ji Y. Improved ventriculoatrial shunt for cerebrospinal fluid diversion after multiple ventriculoperitoneal shunt failures. Surg Neurol. 2009;72 Suppl 1:S29–33.

Chapter 15
Movement Disorders in Infectious Dementias

Francisco Cardoso and Paulo Caramelli

Abstract A myriad of infectious diseases may course with a combination of movement disorders and cognitive decline. The spectrum of movement disorder in these conditions is varied, ranging from parkinsonism to a multitude of hyperkinesias, including tremor, dystonia, chorea, and myoclonus. As to the profile of cognitive changes, the most commonly found abnormalities belong to the so-called subcortical dementia. Among viral infections, postencephalitic parkinsonism and HIV infection are examples of conditions combining cognitive and movement disorders. The former is just of historical importance since it vanished as mysteriously as it started. The majority of HIV+patients develop neurologic complications despite the advent of highly active antiretroviral therapy. A substantial proportion of these patients display the combination of movement disorder, particularly parkinsonism, and cognitive impairment. Neurosyphilis, a spirochetal infection, is also historically relevant, but it remains as an important cause of dementia although movement disorders are rare. Prion diseases are uncommon and their infectious forms are even rarer. Nevertheless, they should always be ruled out in patients with rapidly progressive dementia and myoclonus. Neurocysticercosis, the most common parasitic disease worldwide, is increasingly recognized as a cause of cognitive disorder although movement disorders are exceedingly rare in these subjects. Finally, although the incidence of Sydenham's chorea is in decline, it remains as the most common cause of acute chorea in children and not infrequently it is associated with a dysexecutive syndrome.

Keywords Infections • Prions • Postencephalitic parkinsonism • HIV • AIDS • Syphilis • Neurocysticercosis • Sydenham's chorea

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Introduction

The aim of this chapter is to describe the clinical features of movement disorders in conditions where dementia is caused by infectious agents. From a historical point of view, neurosyphilis is the prototypical infection that combines cognitive and movement disorders. Also with a historical interest is postencephalitic parkinsonism, a consequence of the encephalitis lethargica that plagued Europe in the first decades of the twentieth century. In the late twentieth century, many patients of the epidemics of HIV infection also displayed movement disorders in combination with dementia. The aim of this chapter is to provide a description of the clinical features, epidemiology, and guidelines of management of movement disorders present in the context of infectious dementing illnesses. Of note, although outside of the scope of this chapter, there is evidence suggesting that Parkinson's disease (PD) may be caused by an infectious proteinaceous particle that has a prion-like behavior (Olanow and Brundin 2013).

Neurosyphilis

Cognition

Different clinical syndromes emerge in neurosyphilis, such as meningitis, meningomyelitis, meningovascular syphilis, general paresis, tabes dorsalis, and optic atrophy. Cognitive impairment and behavioral disturbances are common manifestations, especially in late forms of the disease, such as meningovascular syphilis and general paresis. Memory decline, dysexecutive syndrome, and topographical disorientation, together with hallucinations, delusions, apathy, irritability, and aggression, are usual symptoms and signs found in these patients frequently leading to dementia (Carr 2003; Nitrini et al. 2010).

Although much less frequent than in the past century, neurosyphilis is still identified as the cause of dementia in some patients (Takada et al. 2003; Nitrini et al. 2010). For this reason, several guidelines for dementia diagnosis recommend serological tests for syphilis, as a routine procedure, especially in developing countries (Caramelli et al. 2011), or in cases at high risk or presenting suggestive clinical features, in developed nations (Sorbi et al. 2012).

Phenomenology of Movement Disorders

Pseudoathetosis as a result of sensory ataxia is the movement disorder classically described in association with tabes dorsalis, a clinical form of tertiary syphilis. There are, however, reports of rare individuals with neurosyphilis who presented with parkinsonism, corticobasal syndrome, chorea, and dystonia (Nitrini 2000; Benito-León et al. 2004; Spitz et al. 2008; Ozben et al. 2009; Chauhan and Pickens 2011; Tong et al. 2013)

Epidemiology

In the past century, there has been a significant decline of the prevalence of neurosyphilis. However, in the last years there is a resurgence of this condition, with clinicians seeing more patients (Kent and Romanelli 2008). Although coinfection with HIV is well recognized, this is not the main factor responsible for increase of the incidence of neurosyphilis (Zetola and Klausner 2007). Movement disorders are rarely seen in patients with the latter: in a recent series from China, they were seen in no more than seven of 169 subjects (Tong et al. 2013).

Treatment

Although treatment with penicillin is invariably effective in eliminating the *Treponema*, unfortunately most patients remain with their clinical features unchanged or only partially recovered, especially in the late forms of neurosyphilis (Nitrini 2008). Despite the lack of controlled trials, clinicians resort to symptomatic measures to ameliorate specific problems such as L-dopa for parkinsonism and neuroleptics for chorea.

Postencephalitic Parkinsonism

Cognition

Encephalitis may occasionally lead to parkinsonism, being usually caused by virus. Clinical presentation is characterized by reduced level of consciousness and *delirium*, with parkinsonian features developing few weeks after the beginning of the illness. Although mental changes are common, with impaired attention and slowness of thinking, there is no specific cognitive marker. Behavioral changes are also frequent in postencephalitic parkinsonism, such as psychosis, impulsivity, and obsessive-compulsive symptoms (Rail et al. 1981).

Phenomenology of Movement Disorders

Despite intensive effort, the etiology of the pandemic encephalitis lethargica that swept Europe in the beginning of the twentieth century was never determined. The possibility of influenza virus was ruled out, and there is a recent suggestion that it was caused by an enterovirus (Dourmashkin et al. 2012). There are occasional reports of patients who develop parkinsonism following other encephalitic illnesses: western equine encephalitis, Coxsackie B, measles, Epstein-Barr virus (Hsieh et al. 2002; Dimova et al. 2006; Roselli et al. 2006), chicken pox encephalitis, and Japanese encephalitis. The importance of the latter as cause of parkinsonism is shown by a

study of 52 patients, of whom 5 developed pure parkinsonian syndrome poorly responsive to levodopa, ophthalmoparesis, opsoclonus, as well as isolated lesions of the substantia nigra on MRI (Pradhan et al. 1999). A review of a large database of patients who developed PD or parkinsonism in the United Kingdom between 1994 and 2007 showed that there was an association between seasonal influenza and development of parkinsonism (OR = 3.03) but not PD (Toovey et al. 2011).

Constantin von Economo delineated three main clinical presentations of encephalitis lethargica, a condition that bears his name (von Economo 1931). The most common variety started with an influenza-like illness, followed by increasing drowsiness and confusion, with progression to continuous sleep, stupor, and finally coma. External ophthalmoplegia, often with pupillary involvement and oculogyric crises, were early features of the disease, and some patients developed basal ganglia, cerebellar, or upper motor neuron signs. A second group of patients presented with severe acute parkinsonism, often combined with catalepsy and mutism, whereas a third hyperkinetic group mimicked acute catatonic schizophrenia with extreme motor restlessness, impulsions, visual hallucinations, and dyskinesias. Some survivors of the pandemic were left with postencephalitic parkinsonism. Several features distinguished this parkinsonian disorder from PD: lack of or minimal deterioration over decades, presence of oculogyric crises in many patients, and extreme sensitivity to small doses of L-dopa, improving within a few days but developing severe complications including dyskinesias, behavioral disturbances, and motor fluctuations. A study of patients with pathologically proven postencephalitic parkinsonism has confirmed that vertical supranuclear gaze palsy and eyelid apraxia were common findings in this condition (Wenning et al. 1997). The following clinical features should be considered major criteria supporting the diagnosis of encephalitis lethargica; an acute or subacute encephalitic illness that as part of its clinical picture displays at least three of the following criteria: (1) signs of basal ganglia involvement, (2) oculogyric crises, (3) ophthalmoplegia, (4) severe obsessive-compulsive behavior, (5) akinetic mutism, (6) central respiratory irregularities, and (7) somnolence or sleep inversion. In fact, a clinicopathologic study confirmed that onset before middle age, symptom duration lasting more than 10 years, and the presence of oculogyric crisis, as well as history of encephalitis lethargica, were good predictors of the diagnosis of postencephalitic parkinsonism (Litvan et al. 1998).

Epidemiology

Postencephalitic parkinsonism, once epidemic, is currently rare, although no population-based data are available. Encephalitis lethargica has disappeared, but, as already mentioned, occasionally there are reports on conditions mimicking its clinical features. It remains unclear, however, whether these patients have the same condition as the one described by von Economo. Japanese encephalitis, on the other hand, is a major public health problem in Asia, where there are 300,000 new cases each year. Many of these patients eventually develop movement disorders (Pradhan et al. 1999; Kalita and Misra 2000).

Treatment

The treatment of postencephalitic parkinsonism, regardless of the underlying etiology, relies on the use of L-dopa replacement therapy. Most patients do respond to this medication, but the majority rapidly develops motor and non-motor complications such as fluctuations, dyskinesias, psychosis, and other behavioral disorders.

HIV Infection

Cognition

Cognitive impairment associated with HIV infection can be classified in three different categories, namely, asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia (Antinori et al. 2007). With the advent of highly active antiretroviral therapy almost two decades ago, a dramatic decline in the number of cases of moderate to severe dementia occurred. However, mild forms of cognitive impairment are still very frequent and cause significant morbidity for the patients (Kranick and Nath 2012).

Asymptomatic neurocognitive impairment is characterized by deficits on objective neuropsychological testing in two or more cognitive domains in patients with no cognitive complaints. Subsequent symptomatic decline is observed in many cases, although it is not predictable. Mild neurocognitive disorder is diagnosed in patients presenting mild functional decline, which is not explained by another condition, and performing at least one standard deviation below normative values on neuropsychological testing in two or more cognitive domains. HIV-associated dementia features cognitive deficits in at least two cognitive domains, falling below two standard deviations on neuropsychological tests and also by significant functional impairment (Kranick and Nath 2012).

The cognitive profile found in HIV infection includes deficits in information processing, working memory, prospective memory, decision making, and verbal fluency. This clinical picture resembles to the one found in subcortical dementias, such as Parkinson disease and Huntington disease, and reflects damage to frontostriatal structures (Ances and Ellis 2007).

Phenomenology of Movement Disorders

Movement disorders are not uncommon in patients with acquired immunodeficiency syndrome (AIDS) and have received much attention in the past (Brew 2001; Cardoso 2002b). They usually occur in subjects already known to be HIV+ as a result of opportunistic infections, HIV encephalopathy, or side effects of drugs. In

clinical practice, tremor is the most common movement disorder identified in HIV+ patients (Cardoso 2002b). However, hemichorea-hemiballismus is the most frequently reported dyskinesia in HIV+ subjects (Piccolo et al. 1999; Cardoso 2002a). Characteristically, this hyperkinesia is an acute complication of patients with established AIDS, but in a few instances, hemichorea-hemiballismus may be the presenting symptom of HIV infection (Pardo et al. 1998; Cardoso 2002b). Chorea as direct manifestation of HIV encephalopathy has been reported by some (Passarin et al. 2005; Sevigny et al. 2005). A French group described remission of chorea related to HIV encephalopathy after introduction of highly active antiretroviral therapy (Trocello et al. 2006).

Tremor is the second most commonly reported movement disorder in AIDS patients. As it is often caused by *Toxoplasma* abscesses located in the mesencephalon or thalamus, patients present with tremor of subacute onset with rest, postural, and kinetic components, known as Holmes tremor (Koppel and Daras 1990; Micheli et al. 1997). "Wing beating" tremor, related to middle cerebellar peduncle lesions, mild postural tremor associated with HIV encephalopathy, and isolated rest tremor induced by dopamine receptor blockers or trimethoprim-sulfamethoxazole have also been reported (Swenson et al. 1989; Singer et al. 1990; Manji et al. 1995; Cardoso 2002a). There are reports on the association of tremor with progressive multifocal leukoencephalopathy, a common opportunistic infection in HIV+ patients (Rieder and Ziomkowski 2005; Sporer et al. 2005).

Less often, HIV+ patients may develop other hyperkinesias, such as generalized or focal dystonia, Meige syndrome, myoclonus, painful legs and moving toes syndrome, akathisia, tics, stiff person syndrome, oculomasticatory myorhythmia associated with Whipple disease, and opsoclonus-myoclonus (Jankovic 1986; Nath et al. 1987; Tolge and Factor 1991; McDaniel and Summerville 1994; Lannuzel et al. 2002; Canafoglia et al. 2003; Factor et al. 2003; Shah and Chudgar 2005; Wicki et al. 2008; Wiersinga et al. 2012). Recently, there is a report of one patient with acute onset of myoclonus and other neurologic clinical features who was found to have West Nile virus infection in association with HIV (Josekutty et al. 2013). There is also one study describing the occurrence of paroxysmal hyperkinesia in six patients with advanced AIDS without underlying opportunistic infections (Mirsattari et al. 1999).

Parkinsonism as part of HIV encephalopathy and, less frequently, resulting from toxoplasmosis abscesses, parenchymatous tuberculosis granuloma, cryptococcal abscesses, and other opportunistic infections has also been reported in patients with AIDS (Carrazana et al. 1989; de la Fuente Aguado et al. 1996; Mirsattari et al. 1998; Bouffard et al. 2003). In one of these studies, the authors describe six patients with parkinsonism and ten others with "parkinsonian features." In one half of the subjects, the akinetic rigid syndrome was related to exposure to neuroleptics, whereas no cause was identified in the remaining ones. These patients, who accounted for 5.2 % of all subjects seen in a Neuro-AIDS clinic, did not present with rest tremor, and the majority of them also had additional clinical features such as dementia, seizures, vacuolar myelopathy, and peripheral neuropathy. The CD4 values were consistently low (mean of 14 cells/mm^3). There is also a description of

parkinsonism in an HIV+ patient secondary to interaction between ritonavir, an antiretroviral agent, and buspirone (Clay and Adams 2003). A Spanish group described an HIV+ woman with probable progressive multifocal leukoencephalopathy involving one putamen who presented with contralateral eating-induced myoclonus and dystonia of the face (Gaig et al. 2007). A recent report described the occurrence of PSP-like picture as an initial sign of HIV infection (Jang et al. 2012). There is also a study describing that the coexistence of HIV and Lyme neuroborreliosis may present with tremor (Bremell et al. 2011).

Epidemiology

There are no community-based studies of the prevalence of movement disorders in HIV infection. However, in a series of patients seen at tertiary referral centers, approximately 2–3 % of subjects with AIDS develop these complications. In one study, parkinsonian signs were identified in about 5 % of patients (Mirsattari et al. 1998; Cardoso 2002a).

The introduction of highly active antiretroviral therapy has led to a decrease in the frequency of HIV encephalopathy as well as of opportunistic neurologic complications in AIDS patients (Maschke et al. 2000). Although movement disorders have not been specifically studied in these investigations, based on the decline of reports on this issue as well as the reduced number of HIV+ patients seen in movement disorders clinic, one may speculate that their incidence has also decreased.

Treatment

The symptomatic management of chorea-hemiballismus in AIDS patients can be done with the use of dopamine receptor blockers. As these patients have a dopaminergic deficit induced by the HIV, they are susceptible to development of tremor and parkinsonism when exposed to dopamine receptor blockers. Fortunately, hemichorea-hemiballismus has a tendency for spontaneous improvement after a few weeks when it becomes possible to discontinue the neuroleptics.

Parkinsonism associated with HIV encephalopathy is rarely a clinical problem important enough to deserve symptomatic treatment. Unfortunately, in the rare instances when it is clinically problematic, patients do not respond to levodopa, although a few reports suggest that children do improve on this medication (Mirsattari et al. 1998; Cardoso 2002a). Because of the potential of medications to induce motor side effects in HIV+ patients, it is extremely important to attempt to discontinue offending drugs, such as neuroleptics. In case there is a recognized associated opportunistic infection, patients must also receive specific therapy. Finally, although its role in the treatment and prevention of motor complications is

not clearly established, initial evidence suggests that highly active antiretroviral therapy has a positive impact on these problems (Maschke et al. 2000; Sacktor et al. 2000; Brew 2001; Hersh et al. 2001; Cardoso 2002b).

Prions

Cognition

From a population point of view, Creutzfeldt-Jakob disease (CJD) is an uncommon condition. However, it is the most common form of prion disease, presenting with dementia in all cases. More often the disease is sporadic (85 % of cases), but it can be familial in about 10–15 % of patients, iatrogenic in 1 %, and there is also the variant CJD, limited to the United Kingdom and France (Johnson 2005).

Sporadic CJD manifests initially with cognitive (39 % of cases) or behavioral (20 % of cases) abnormalities according to one large study (Geschwind et al. 2007). It is a form of rapidly progressive dementia, with 90 % of patients dying less than 1 year after the onset of symptoms (Johnson 2005).

Familial CJD usually has a longer clinical course than the sporadic form. The clinical phenotype, including the profile of cognitive and behavioral changes, may be similar to the one found in sporadic cases, but different presentations may occur, including features resembling frontotemporal dementia (Nitrini et al. 2001).

Phenomenology of Movement Disorders

Typically, the onset of sporadic CJD is in the sixth and seventh decades of life with a clinical picture characterized by a rapidly progressive dementia and other behavioral disorders. In most cases, death ensues in less than a year (Brown et al. 1994; Paterson et al. 2012; Puoti et al. 2012). The age at onset of iatrogenic forms is more variable, with the latency ranging from a few months to 10–15 years. Shorter latencies are usually observed in surgical cases, whereas patients exposed to contaminated hormones developed CJD after a much longer period (Cardoso 2002a).

Movement disorders were identified in 91 % of patients, of whom 81 % had multifocal cortical myoclonus, of a series of 300 subjects with pathologically verified sporadic CJD (Brown et al. 1994). Although not always clearly described in the literature, other movement disorders found in these patients are tremor, rigidity, parkinsonism, dystonia, and chorea (Brown et al. 1994; Cardoso 2002a, b). Ataxia is the clinical hallmark of kuru and Gerstmann-Sträussler-Scheinker disease (Cardoso 2002a; Liberski et al. 2012). Variant Creutzfeldt-Jakob disease (vCJD) is a novel human prion disease caused by the bovine spongiform encephalopathy agent (Ironside 2012). In addition to myoclonus, these patients often have ataxia and chorea (Will et al. 1996; Bowen et al. 2000; Ironside 2012).

Epidemiology

Sporadic prion diseases are rare with the incidence of CJD estimated to be one case per million population per year (Brown et al. 1987; Puoti et al. 2012). Infectious prion diseases are even rarer. In the past kuru was common among subjects of the Fore tribe of the highlands of New Guinea, but it has been eliminated with the disappearance of individuals at genetic risk (those homozygous for the 129 Met allele of the PRNP gene encoding for prion protein) and cannibalism (Gajdusek 1977; Liberski et al. 2012).

There are less than 100 published cases of iatrogenic CJD related to corneal and dura mater transplants, inadequately sterilized neurosurgical instruments, and contaminated growth hormone or gonadotrophins prepared from cadaveric pituitary tissue (Brown et al. 1992).

Most cases of vCJD have occurred in the United Kingdom, with smaller numbers in 11 other countries (Ironside 2012). There are also recent reports describing individuals who acquired vCJD by transfusion of blood-derived products of asymptomatic patients (Gregori et al. 2011; Ironside 2012; Millar and Makris 2012).

Treatment

Movement disorders are a relatively minor finding in the clinical picture of patients with prion diseases. Nevertheless, if they cause disability, symptomatic treatment for movement disorders can be used following guidelines similar to those used for patients without prion diseases. Unfortunately, the prognosis of these conditions is ominous not existing any measure effective in halting their relentless and fatal progression.

Neurocysticercosis

Cognition

Cognitive impairment is a common clinical manifestation of neurocysticercosis (NC), and its frequency and severity varies according to the disease phase (active and calcified forms).

In a recent cross-sectional study, 80 treatment-naive patients with NC (40 with active and 40 with calcified disease) were submitted to a comprehensive neuropsychological and functional evaluation and were compared to a group of matched healthy controls. Cognitive impairment was identified in 25 % of patients with calcified NC, none of them fulfilling diagnostic criteria for dementia. On the other hand, 40 % of patients with active disease were cognitively impaired, with dementia

being identified in 12.5 % of all cases (Rodrigues et al. 2012). Importantly, cognitive impairment or dementia could not be explained by the use of antiepileptic drugs use, seizures, or depression (Ciampi de Andrade et al. 2010).

Hence, NC leads to a spectrum of cognitive changes from mild impairment in a single domain to multiple cognitive deficits without functional decline and, sometimes, to dementia. These features are more prominent during the active phase of the disease, with attenuation in the calcified stage.

Phenomenology of Movement Disorders

NC, infestation of the central nervous system by encapsulated larvae of *Taenia solium*, is the most common neurologic parasitic disease worldwide (Davis and Kornfeld 1991; Del Brutto et al. 1996; Cardoso 2002a; Del Brutto 2013). Epilepsy and intracranial hypertension due to hydrocephalus are present in up to 92 % of NC patients (Bianchin et al. 2012; Del Brutto 2013; Singh et al. 2013). The clinical manifestations are, however, protean, including focal deficits, cognitive and behavioral changes, meningitis, optic neuropathy, stroke, and others (Davis and Kornfeld 1991; Croker et al. 2012; Del Brutto et al. 1996; Del Brutto 2013). Interestingly, despite the high frequency of basal ganglia cysts, movement disorders are rarely reported in NC (Cosentino et al. 2002). One possible explanation for such an observation is the slow growth of the cysts that gradually displace the basal ganglia structures without lesioning them. The rare reports of movement disorders in NC encompass the occurrence of parkinsonism, either related to intraparenchymal lesions or hydrocephalus (Cardoso 2002a; Sá et al. 2005; Prashantha et al. 2008), or hemichorea-hemiballismus (Cardoso 2002a; Cosentino et al. 2006; Karnik et al. 2011).

Epidemiology

NC remains as a major public health problem in Latin American and India (Del Brutto 2013). It is, however, becoming increasingly common in regions with high rates of immigration from endemic areas, such as the South as well as the East Coast of the United States (Scharf 1988; Croker et al. 2012).

Treatment

Patients with NC and parkinsonism may improve with L-dopa therapy, but the majority of reported cases just respond to treatment of the intraparenchymal lesions or the causative underlying hydrocephalus (Cardoso 2002a; Sá et al. 2005; Prashantha et al. 2008). Subjects who present with hemichorea-hemiballismus are usually responsive to neuroleptics or tetrabenazine.

The specific treatment of NC remains a highly controversial subject with unsolved issues, including when to use anticysticercal therapy, the role of steroids, and indications of surgical therapy (Takayanagui et al. 2011; Baird et al. 2013; Del Brutto 2013). Nevertheless, most authorities believe that the use of cysticidal drugs improve clinical findings and is associated with a more favorable long-term prognosis. A recent evidence-based guideline of the treatment of parenchymal NC issued by the American Academy of Neurology concluded that albendazole plus either dexamethasone or prednisolone should be considered for adults and children with NC, both to decrease the number of active lesions on brain imaging studies (Level B) and to reduce long-term seizure frequency (Level B) (Baird et al. 2013).

Sydenham's Chorea

Cognition

Cognitive functioning has been object of only few studies in Sydenham's chorea (SC). Executive dysfunction has been reported in adult patients even when chorea was in remission (Beato et al. 2010). Simple and brief cognitive tests, sensitive to evaluation of prefrontal functions, such as phonemic verbal fluency, are able to detect significant changes; thus, they may be used in clinical practice (Cunningham et al. 2006).

Phenomenology of Movement Disorders

SC is the most common movement disorder associated with bacterial infection. Typically, patients develop this disease 4–8 weeks after an episode of streptococcal pharyngitis. In most series, there is a female preponderance. The usual age at onset of SC is 8–9 years of age, although there are reports of patients developing chorea in the third decade of life (Cardoso et al. 1997). Chorea rapidly spreads, becoming generalized, but 20 % of patients remain with hemichorea (Nausieda et al. 1980; Cardoso et al. 1997). The random and continuous flow of contractions typical of chorea produces motor impersistence, particularly noticeable during tongue protrusion and ocular fixation. The muscle tone is usually decreased, and in severe and rare cases (8 % of all patients) is so pronounced that the patient may become bedridden (chorea paralytica).

Patients often display other neurologic and nonneurologic symptoms and signs. Although the distinction between chorea and motor tics may be difficult, the latter, as well as simple vocal tics, are frequently reported to occur in SC. In a cohort of 108 SC patients carefully followed up at our unit, we have identified vocalizations in just 8 % of subjects. We have avoided the term "tic" because there was no premonitory sign or complex sound, and, conversely, the vocalizations were associated with severe cranial chorea. These findings suggest that involuntary sounds present

in a few patients with SC result from choreic contractions of the upper respiratory tract muscles rather than true tics (Teixeira et al. 2009).

Dysarthria is common, and patients with more severe forms of this condition may present a remarkably decreased verbal output. There is evidence that many patients with active chorea have hypometric saccades, and a few also show oculogyric crisis. In the older literature, there are also references to papilledema, central retinal artery occlusion, and seizures in some patients with SC. Migraine is more common in children with SC than in controls. In a cohort of 55 patients with this movement disorder, 21.8 % were found to have migraine, whereas this type of headache was seen in no more than 8 % of 110 matched controls (Teixeira et al. 2005a).

Attention has been drawn to behavioral abnormalities associated with this condition. We investigated the behavior of 56 patients with SC, 50 subjects with rheumatic fever without chorea, and 50 healthy matched controls. Obsessive-compulsive disorder was diagnosed in 23 % of the patients with chorea, whereas just 6 and 4 % of the rheumatic fever group and healthy controls met criteria for this condition (Maia et al. 2005). Other studies have confirmed that obsessions and compulsions are commonly seen in patients with SC (Asbahr et al. 1998; Mercadante et al. 2000; Hounie et al. 2004). We saw one patient with paranoid psychosis with onset in parallel with SC and also found that another patient with SC developed trichotillomania (Kummer et al. 2007; Teixeira et al. 2007). These findings and the observation that hyperactivity, learning disorders, and other behavioral problems are common in patients with rheumatic fever and chorea contributed to establish the notion that SC is a model for childhood autoimmune neuropsychiatric disorders (Swedo 1994).

It must be kept in mind that SC is a major manifestation of rheumatic fever, although in approximately 20 % of patients, chorea is the sole finding. Nevertheless, up to 80 % of patients display cardiac involvement in SC, whereas the association with arthritis is less common, seen in 30 % of subjects (Cardoso et al. 1997). The current diagnostic criteria of SC are a modification of the Jones criteria: chorea with acute or subacute onset and lack of clinical and laboratory evidence of alternative cause are mandatory findings, and the diagnosis is further supported by the presence of additional major or minor manifestations of rheumatic fever (Special Writing Group of the Committee of Rheumatic Fever 1992; Cardoso et al. 1997, 1999).

Epidemiology

SC is the most common cause of acute chorea in children; however, its prevalence has decreased in conjunction with the reduction of rheumatic fever in North America and Western Europe. For instance, in Fairfax County, Virginia, the annual age-adjusted incidence rate of initial attacks of rheumatic fever per 100,000 children declined from 3.0 in 1970 to 0.5 in 1980 (Schwartz et al. 1983). Furthermore, Nausieda and colleagues demonstrated that SC accounted for 0.9 %

of children admitted to hospitals in Chicago before 1940, whereas this number dropped to 0.2 % between 1950 and 1980 (Nausieda et al. 1980). However, at least eight outbreaks of rheumatic fever with occurrence of chorea have been identified in the United States (Ayoub 1992). Even in areas where there has been a decline in the incidence of rheumatic fever, such as Pennsylvania in the United States, this illness account for almost all cases of acute chorea among children (Zomorrodi and Wald 2006).

Rheumatic fever has remained a significant public health problem in developing areas, particularly within the low income population. In the top end of the Northern Territory in Australia, an area predominantly inhabited by Aborigine people, the prevalence of rheumatic fever was 9.6 per 1,000 people aged 5–14 years in 1995 (Carapetis et al. 1996). SC occurs in about 26 % of patients with rheumatic fever (Cardoso et al. 1997). Clinical observation in our unit suggests that there is a decline of the frequency of SC in Brazil, an area where rheumatic fever used to be endemic.

Treatment

There are few controlled studies of symptomatic treatment of SC (Cardoso 2008). The first choice of the authors is valproic acid and just if the patient fails to respond to this medication, the next option is to prescribe neuroleptics. The latter can also be prescribed as a first-line treatment in patients who present with chorea paralytica. Risperidone, a relatively potent dopamine D2 receptor blocker, is usually effective in controlling the chorea. Dopamine D2 receptor blockers must be used with great caution in patients with SC. We performed a case–control study comparing the response to these drugs in patients with SC and Tourette syndrome. We demonstrated that 5 % of 100 patients with chorea developed extrapyramidal complications, whereas these findings were not observed among patients with tics matched for age and neuroleptics dosage (Teixeira et al. 2003).

Finally, the most important measure in the treatment of patients with SC is secondary prophylaxis with penicillin or, if there is allergy, with sulfa drugs up to 21 years of age. In case the onset occurs after this age, the recommendation is to maintain prophylaxis indefinitely (Cardoso 2002a).

Some controversy exists as to the role of immunosuppression in the management of SC. Despite mentions of the effectiveness of prednisone in suppressing chorea, this drug is only used when there is associated severe carditis. A placebo-controlled study showed that oral prednisone only accelerates the control of chorea; rates of remission and recurrence were not changed by the active treatment (Paz et al. 2006). Intravenous methylprednisolone is reserved for patients with persistent disabling chorea refractory to antichoreic agents (Cardoso et al. 2003; Barash et al. 2005; Teixeira et al. 2005b). Few reports describe the usefulness of plasma exchange or intravenous immunoglobulin in SC. Because of the efficacy of other therapeutic agents, potential complications, and the high cost of the latter treatment modalities, these options are not usually recommended.

Conclusions

In this chapter we reviewed a number of infectious diseases that course with a combination of movement disorders and cognitive decline. Historically, postencephalitic parkinsonism and neurosyphilis were the first infectious conditions combining these features to be studied. The former has vanished, but syphilis remains an important cause of dementia although movement disorders are rare. Prion diseases are uncommon and their infectious forms are even rarer. Nevertheless, they should always be ruled out in patients with rapidly progressive dementia and myoclonus. The majority of HIV + patients develop neurologic complications despite the advent of highly active antiretroviral therapy. A substantial proportion of these patients display the combination of movement disorder, particularly parkinsonism, and cognitive impairment. Neurocysticercosis, the most common parasitic disease worldwide, is increasingly recognized as a cause of cognitive disorder although movement disorders are exceedingly rare in these subjects. Finally, although the incidence of Sydenham's chorea is in decline, it remains as the most common cause of acute chorea in children and not infrequently it is associated with a dysexecutive syndrome.

References

Ances BM, Ellis RJ. Dementia and neurocognitive disorders due to HIV-1 infection. Semin Neurol. 2007;27:86–92.

Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007;69:1789–99.

Asbahr FR, Negrao AB, Gentil V, et al. Obsessive-compulsive and related symptoms in children and adolescents with rheumatic fever with and without chorea: a prospective 6-month study. Am J Psychiatry. 1998;155:1122–4.

Ayoub EM. Resurgence of rheumatic fever in the United States. The changing picture of a preventable illness. Postgrad Med. 1992;92:133–6.

Baird RA, Wiebe S, Zunt JR, Halperin JJ, Gronseth G, Roos KL. Evidence-based guideline: treatment of parenchymal neurocysticercosis: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013;80(15):1424–9.

Barash J, Margalith D, Matitiau A. Corticosteroid treatment in patients with Sydenham's chorea. Pediatr Neurol. 2005;32:205–7.

Beato R, Maia DP, Teixeira Jr AL, Cardoso F. Executive functioning in adult patients with Sydenham's chorea. Mov Disord. 2010;25:853–7.

Benito-León J, Alvarez-Linera J, Louis ED. Neurosyphilis masquerading as corticobasal degeneration. Mov Disord. 2004;19(11):1367–70.

Bianchin MM, Velasco TR, Santos AC, Sakamoto AC. On the relationship between neurocysticercosis and mesial temporal lobe epilepsy associated with hippocampal sclerosis: coincidence or a pathogenic relationship? Pathog Glob Health. 2012;106(5):280–5.

Bouffard JP, Mena H, Ripple M, Troncoso J. Mesencephalic cryptococcal abscesses presenting with parkinsonism as an initial manifestation of AIDS. Mov Disord. 2003;18:1354–7.

Bowen J, Mitchell T, Pearce R, Quinn N. Chorea in new variant Creutzfeldt-Jacob disease. Mov Disord. 2000;15(6):1284–5.

Bremell D, Säll C, Gisslén M, Hagberg L. Lyme neuroborreliosis in HIV-1 positive men successfully treated with oral doxycycline: a case series and literature review. J Med Case Reports. 2011;5:465.

Brew BJ. HIV neurology. New York: Oxford University Press; 2001.
Brown P, Cathala F, Raubertas RF, Gajdusek DC, Castaigne P. The epidemiology of Creutzfeldt-Jakob disease: conclusion of a 15-year investigation in France and review of the world literature. Neurology. 1987;37(6):895–904.
Brown P, Gibbs Jr CJ, Rodgers-Johnson P, Asher DM, Sulima MP, Bacote A, Goldfarb LG, Gajdusek DC. Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. Ann Neurol. 1994;35(5):513–29.
Brown P, Preece MA, Will RG. "Friendly fire" in medicine: hormones,homografts, and Creutzfeldt-Jakob disease. Lancet. 1992;340(8810):24–7.
Canafoglia L, Panzica F, Franceschetti S, et al. Rhythmic cortical myoclonus in a case of HIV-related encephalopathy. Mov Disord. 2003;18:1533–8.
Caramelli P, Teixeira AL, Buchpiguel CA, Lee HW, Livramento JA, Fernandez LL, Anghinah R. Diagnosis of Alzheimer's disease in Brazil: supplementary exams. Dement Neuropsychol. 2011;5:1–10.
Carapetis JR, Wolff DR, Currie BJ. Acute rheumatic fever and rheumatic heart disease in the top end of Australia's Northern Territory. Med J Aust. 1996;164:146–9.
Cardoso F. Infectious and transmissible movement disorders. In: Jankovic J, Tolosa E, editors. Parkinson's disease and movement disorders. 4th ed. Baltimore: Lippincott Williams & Wilkins; 2002a. p. 945–66.
Cardoso F. HIV-related movement disorders: epidemiology, pathogenesis and management. CNS Drugs. 2002b;16(10):663–8.
Cardoso F. Sydenham's chorea. Curr Treat Options Neurol. 2008;10(3):230–5.
Cardoso F, Silva CE, Mota CC. Sydenham's chorea in 50 consecutive patients with rheumatic fever. Mov Disord. 1997;12:701–3.
Cardoso F, Vargas AP, Oliveira LD, Guerra AA, Amaral SV. Persistent Sydenham's chorea. Mov Disord. 1999;14:805–7.
Cardoso F, Maia D, Cunningham MC, Valenca G. Treatment of Sydenham chorea with corticosteroids. Mov Disord. 2003;18(11):1374–7.
Carr J. Neurosyphilis. Pract Neurol. 2003;3:328–41.
Carrazana E, Rossitch E, Samuels MA. Parkinsonian symptoms in a patient with AIDS and cerebral toxoplasmosis. J Neurol Neurosurg Psychiatry. 1989;52:1445–6.
Chauhan VV, Pickens 4th AT. Opisthotonus in neurosyphilis: a case report. J Emerg Med. 2011;41:613–5.
Ciampi de Andrade D, Rodrigues CL, Abraham R, et al. Cognitive impairment and dementia in neurocysticercosis: a cross-sectional controlled study. Neurology. 2010;74:1288–95.
Clay PG, Adams MM. Pseudo-Parkinson disease secondary to ritonavir-buspirone interaction. Ann Pharmacother. 2003;37:202–5.
Cosentino C, Velez M, Torres L, Garcia HH, Cysticercosis Working Group in Perú. Cysticercosis lesions in basal ganglia are common but clinically silent. Clin Neurol Neurosurg. 2002;104(1):57–60.
Cosentino C, Vélez M, Torres L, Garcia HH. Neurocysticercosis-induced hemichorea. Mov Disord. 2006;21(2):286–7.
Croker C, Redelings M, Reporter R, Sorvillo F, Mascola L, Wilkins P. The impact of neurocysticercosis in California: a review of hospitalized cases. PLoS Negl Trop Dis. 2012;6(1):e1480.
Cunningham MC, Maia DP, Teixeira Jr AL, Cardoso F. Sydenham's chorea is associated with decreased verbal fluency. Parkinsonism Relat Disord. 2006;12:165–7.
Davis LE, Kornfeld M. Neurocysticercosis: neurologic, pathogenic, diagnostic and therapeutic aspects. Eur Neurol. 1991;31(4):229–40.
de la Fuente-Aguado J, Bordon J, Moreno JA, Sopena B, Rodriguez A, Martinez-Vasquez C. Parkinsonism in an HIV-infected patient with hypodense cerebral lesion. Tuber Lung Dis. 1996;77(2):191–2.
Del Brutto OH. Neurocysticercosis: new thoughts on controversial issues. Curr Opin Neurol. 2013;26(3):289–94.
Del Brutto OH, Wadia NH, Dumas M, Cruz M, Tsang VC, Schantz PM. Proposal of diagnostic criteria for human cysticercosis and neurocysticercosis. J Neurol Sci. 1996;142(1–2):1–6.

Dimova PS, Bojinova V, Georgiev D, Milanov I. Acute reversible parkinsonism in Epstein-Barr virus-related encephalitis lethargica-like illness. Mov Disord. 2006;21:564–6.
Dourmashkin RR, Dunn G, Castano V, McCall SA. Evidence for an enterovirus as the cause of encephalitis lethargica. BMC Infect Dis. 2012;12:136.
Factor SA, Troche-Panetto M, Weaver SA. Dystonia in AIDS: report of four cases. Mov Disord. 2003;18:1492–8.
Gaig C, Muñoz E, Valls-Solé J, Martí MJ, Tolosa E. Eating-induced facial myoclonic dystonia probably due to a putaminal lesion. Mov Disord. 2007;22:877–80.
Gajdusek DC. Unconventional viruses and the origin and disappearance of kuru. Science. 1977; 197:943–60.
Geschwind MD, Haman A, Miller BL. Rapidly progressive dementia. Neurol Clin. 2007;25: 783–807.
Gregori L, Yang H, Anderson S. Estimation of variant Creutzfeldt-Jakob disease infectivity titers in human blood. Transfusion. 2011;51(12):2596–602.
Hersh BP, Rajendran PR, Battinelli D. Parkinsonism as the presenting manifestation of HIV infection: improvement on HAART. Neurology. 2001;56(2):278–9.
Hounie AG, Pauls DL, Mercadante MT, et al. Obsessive-compulsive spectrum disorders in rheumatic fever with and without Sydenham's chorea. J Clin Psychiatry. 2004;65:994–9.
Hsieh JC, Lue KH, Lee YL. Parkinson-like syndrome as the major presenting symptom of Epstein-Barr virus encephalitis. Arch Dis Child. 2002;87:358.
Ironside JW. Variant Creutzfeldt-Jakob disease: an update. Folia Neuropathol. 2012;50(1):50–6.
Jang W, Kim JS, Ahn JY, Kim HT. Reversible progressive supranuclear palsy-like phenotype as an initial manifestation of HIV infection. Neurol Sci. 2012;33:1169–71.
Jankovic J. Whipple's disease of the central nervous system in AIDS. N Engl J Med. 1986;315: 1029–30.
Johnson RT. Prion diseases. Lancet Neurol. 2005;4:635–42.
Josekutty J, Yeh R, Mathew S, et al. Atypical presentation of West Nile Virus (WNV) in a newly diagnosed Human Immunodeficiency Virus (HIV) patient in New York City. J Clin Microbiol. 2013;51:1307–9.
Kalita J, Misra UK. Markedly severe dystonia in Japanese encephalitis. Mov Disord. 2000;15: 1168–72.
Karnik PS, Tullu MS, David JJ, Ghildiyal RG. Neurocysticercosis-induced hemiballismus in a child. J Child Neurol. 2011;26(7):904.
Kent ME, Romanelli F. Reexamining syphilis: an update on epidemiology, clinical manifestations, and management. Ann Pharmacother. 2008;42(2):226–36.
Koppel BS, Daras M. "Rubral" tremor due to midbrain Toxoplasma abscess. Mov Disord. 1990;5(3): 254–6.
Kranick SM, Nath A. Neurologic complications of HIV-1 infection and its treatment in the era of antiretroviral therapy. Continuum (Minneap Minn). 2012;18:1319–37.
Kummer A, Maia DP, Cardoso F, Teixeira AL. Trichotillomania in acute Sydenham's chorea. Aust N Z J Psychiatry. 2007;41:1013–4.
Lannuzel A, Hermann C, Yousry C, Lees A, Caparros-Lefebvre D. Encephalomyelitis with rigidity complicating human immunodeficiency virus infection. Mov Disord. 2002;17(1):202–4.
Liberski PP, Sikorska B, Lindenbaum S, Goldfarb LG, McLean C, Hainfellner JA, Brown P. Kuru: genes, cannibals and neuropathology. J Neuropathol Exp Neurol. 2012;71(2):92–103.
Litvan I, Jankovic J, Goetz CG, et al. Accuracy of the clinical diagnosis of postencephalitic parkinsonism: a clinicopathologic study. Eur J Neurol. 1998;5:451–7.
Maia DP, Teixeira Jr AL, Quintao Cunningham MC, Cardoso F. Obsessive compulsive behavior, hyperactivity, and attention deficit disorder in Sydenham chorea. Neurology. 2005;64(10):1799–801.
Manji H, Sweeney B, Connolly S, et al. Movement disorders in AIDS: infective, neoplastic and iatrogenic causes. Parkinsonism Relat Disord. 1995;1:13–9.
Maschke M, Kastrup O, Esser S, Ross B, Henge U, Hufnagel A. Incidence and prevalence of neurological disorders associated with HIV infection since the introduction of highly active antiretroviral therapy (HAART). J Neurol Neurosurg Psychiatry. 2000;69:376–80.

McDaniel JS, Summerville MB. Tic disorder associated with encephalopathy in advanced HIV disease. Gen Hosp Psychiatry. 1994;16:298–300.
Mercadante MT, Busatto GF, Lombroso PJ, et al. The psychiatric symptoms of rheumatic fever. Am J Psychiatry. 2000;157:2036–8.
Micheli F, Granana N, Scorticati MC, et al. Unilateral postural and action tremor resulting from thalamic toxoplasmosis in a patient with acquired immunodeficiency syndrome. Mov Disord. 1997;12:1096–8.
Millar CM, Makris M. Dealing with the uncertain risk of variant Creutzfeldt-Jakob disease transmission by coagulation replacement products. Br J Haematol. 2012;158(4):442–52.
Mirsattari SM, Berry ME, Holden JK, Ni W, Nath A, Power C. Paroxysmal dyskinesias in patients with HIV infection. Neurology. 1999;52:109–14.
Mirsattari SM, Power C, Nath A. Parkinsonism with HIV infection. Mov Disord. 1998;13:684–9.
Nath A, Jankovic J, Pettigrew LC. Movement disorders and AIDS. Neurology. 1987;37:37–41.
Nausieda PA, Grossman BJ, Koller WC, et al. Sydenham chorea: an update. Neurology. 1980;30: 331–4.
Nitrini R. The history of tabes dorsalis and the impact of observational studies in neurology. Arch Neurol. 2000;57:605–6.
Nitrini R. Clinical and therapeutic aspects of dementia in syphilis and Lyme disease. Handb Clin Neurol. 2008;89:819–23.
Nitrini R, Teixeira da Silva LS, Rosemberg S, et al. Prion disease resembling frontotemporal dementia and parkinsonism linked to chromosome 17. Arq Neuropsiquiatr. 2001;59:161–4.
Nitrini R, Paiva ARB, Takada LT, Brucki SMD. Did you rule out neurosyphilis? Dement Neuropsychol. 2010;4:338–45.
Olanow CW, Brundin P. Parkinson's disease and alpha synuclein: is Parkinson's disease a prion-like disorder? Mov Disord. 2013;28(1):31–40.
Ozben S, Erol C, Ozer F, Tiras R. Chorea as the presenting feature of neurosyphilis. Neurol India. 2009;57(3):347–9.
Pardo J, Marcos A, Bhathal H, Castro M, Varea de Seijas E. Chorea as a form of presentation of human immunodeficiency virus-associated dementia complex. Neurology. 1998;50:568–9.
Passarin MG, Alessandrini F, Nicolini GG, et al. Reversible choreoathetosis as the early onset of HIV-encephalopathy. Neurol Sci. 2005;26:55–6.
Paterson RW, Torres-Chae CC, Kuo AL, Ando T, Nguyen EA, Wong K, Dearmond SJ, Haman A, Garcia P, Johnson DY, Miller BL, Geschwind MD. Differential diagnosis of Jakob-Creutzfeldt disease. Arch Neurol. 2012;24:1–5.
Paz JA, Silva CA, Marques-Dias MJ. Randomized double-blind study with prednisone in Sydenham's chorea. Pediatr Neurol. 2006;34:264–9.
Piccolo I, Causarano R, Sterzi R, et al. Chorea in patients with AIDS. Acta Neurol Scand. 1999;100: 332–6.
Pradhan S, Pandey N, Shashank S, Gupta RK, Mathur A. Parkinsonism due to predominant involvement of substantia nigra in Japanese encephalitis. Neurology. 1999;53:1781–6.
Prashantha DK, Netravathi M, Ravishankar S, Panda S, Pal PK. Reversible parkinsonism following ventriculoperitoneal shunt in a patient with obstructive hydrocephalus secondary to intraventricular neurocysticercosis. Clin Neurol Neurosurg. 2008;110(7):718–21.
Puoti G, Bizzi A, Forloni G, Safar JG, Tagliavini F, Gambetti P. Sporadic human prion diseases: molecular insights and diagnosis. Lancet Neurol. 2012;11(7):618–28.
Rail D, Scholtz C, Swash M. Post-encephalitic parkinsonism: current experience. J Neurol Neurosurg Psychiatry. 1981;44:670–6.
Rieder CR, Ziomkowski SC. Head tremor and progressive multifocal leukoencephalopathy in AIDS patients: report of two cases. Arq Neuropsiquiatr. 2005;63:150–3.
Rodrigues CL, de Andrade DC, Livramento JA, et al. Spectrum of cognitive impairment in neurocysticercosis: differences according to disease phase. Neurology. 2012;78:861–6.
Roselli F, Russo I, Fraddosio A, et al. Reversible Parkinsonian syndrome associated with antineuronal antibodies in acute EBV encephalitis: a case report. Parkinsonism Relat Disord. 2006; 12:257–60.

Sá DS, Teive HA, Troiano AR, Werneck LC. Parkinsonism associated with neurocysticercosis. Parkinsonism Relat Disord. 2005;11(1):69–72.
Sacktor NC, Skolasky RL, Lyles RH, Esposito D, Selnes OA, McArthur JC. Improvement in HIV-associated motor slowing after antiretroviral therapy including protease inhibitors. J Neurovirol. 2000;6(1):84–8.
Scharf D. Neurocysticercosis. Two hundred thirty-eight cases from a California hospital. Arch Neurol. 1988;45(7):777–80.
Schwartz RH, Hepner SI, Ziai M. Incidence of acute rheumatic fever. A suburban community hospital experience during the 1970s. Clin Pediatr. 1983;22:798–801.
Sevigny JJ, Chin SS, Milewski Y, et al. HIV encephalitis simulating Huntington's disease. Mov Disord. 2005;20:610–3.
Shah I, Chudgar P. Progressive multifocal leukoencephalopathy (PML) presenting as intractable dystonia in an HIV-infected child. J Trop Pediatr. 2005;51(6):380–2.
Singer C, Sanchez-Ramos J, Rey G, et al. AIDS dementia complex presenting as an unusual unilateral hand tremor, clumsiness and posturing. Ann Neurol. 1990;28:301.
Singh G, Burneo JG, Sander JW. From seizures to epilepsy and its substrates: neurocysticercosis. Epilepsia. 2013;54(5):783–92.
Sorbi S, Hort J, Erkinjuntti T, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. Eur J Neurol. 2012;19:1159–79.
Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. JAMA. 1992;268(15):2069–73.
Spitz M, Maia FM, Gomes HR, Scaff M, Barbosa ER. Parkinsonism secondary to neurosyphilis. Mov Disord. 2008;23(13):1948–9.
Sporer B, Seelos K, Asmus F, et al. Posterior fossa tremor induced by HIV-associated progressive multifocal leukoencephalopathy. Eur Neurol. 2005;53:96–7.
Swedo SE. Sydenham's chorea. A model for childhood autoimmune neuropsychiatric disorders [clinical conference]. JAMA. 1994;272:1788–91.
Swenson JR, Erman M, Labelle J, Dimsdale JE. Extrapyramidal reactions. Neuropsychiatric mimics in patients with AIDS. Gen Hosp Psychiatry. 1989;11:248–53.
Takada LT, Caramelli P, Radanovic M, Anghinah R, Hartmann AP, Guariglia CC, Bahia VS, Nitrini R. Prevalence of potentially reversible dementias in a dementia outpatient clinic of a tertiary university-affiliated hospital in Brazil. Arq Neuropsiquiatr. 2003;61:925–9.
Takayanagui OM, Odashima NS, Bonato PS, Lima JE, Lanchote VL. Medical management of neurocysticercosis. Expert Opin Pharmacother. 2011;12(18):2845–56.
Teixeira AL, Cardoso F, Maia DP, Cunningham MC. Sydenham's chorea may be a risk factor for drug induced parkinsonism. J Neurol Neurosurg Psychiatry. 2003;74(9):1350–1.
Teixeira Jr AL, Cardoso F, Maia DP, et al. Frequency and significance of vocalizations in Sydenham's chorea. Parkinsonism Relat Disord. 2009;15:62–3.
Teixeira Jr AL, Maia DP, Cardoso F. Psychosis following acute Sydenham's chorea. Eur Child Adolesc Psychiatry. 2007;16(1):67–9.
Teixeira Jr AL, Meira FC, Maia DP, Cunningham MC, Cardoso F. Migraine headache in patients with Sydenham's chorea. Cephalalgia. 2005a;25:542–4.
Teixeira Jr AL, Maia DP, Cardoso F. Treatment of acute Sydenham's chorea with methylprednisolone pulse-therapy. Parkinsonism Relat Disord. 2005b;11(5):327–30.
Tolge CF, Factor SA. Focal dystonia secondary to cerebral toxoplasmosis in a patient with acquired immune deficiency syndrome. Mov Disord. 1991;6:69–72.
Tong ML, Lin LR, Zhang HL, Huang SJ, Liu GL, Zheng WH, Su YH, Wu JY, Dong J, Liu LL, Yang TC. Spectrum and characterization of movement disorders secondary to neurosyphilis. Parkinsonism Relat Disord. 2013;19(4):441–5.
Toovey S, Jick SS, Meier CR. Parkinson's disease or Parkinson symptoms following seasonal influenza. Influenza Other Respi Viruses. 2011;5:328–33.
Trocello JM, Blanchet A, Bourdain F, et al. Resolution of choreic movements associated with HIV encephalitis with anti-retroviral therapy. Rev Neurol (Paris). 2006;162:89–91.

von Economo C. Encephalitis lethargica: its sequelae and treatment (trans: Newman KO). New York: Oxford University Press; 1931.
Wenning GK, Jellinger K, Litvan I. Supranuclear gaze palsy and eyelid apraxia in postencephalitic parkinsonism. J Neural Transm. 1997;104(8–9):845–65.
Wicki J, Germanier Y, Sztajzel R, Burkhard PR. Brueghel syndrome as a new manifestation of HIV encephalopathy. Eur Neurol. 2008;60:107–8.
Wiersinga WJ, Prins JM, van de Beek D. Therapy-resistant opsoclonus-myoclonus syndrome secondary to HIV-1 infection. Clin Infect Dis. 2012;54:447–8.
Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, Poser S, Pocchiari M, Hofman A, Smith PG. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet. 1996;347(9006):921–5.
Zetola NM, Klausner JD. Syphilis and HIV infection: an update. Clin Infect Dis. 2007;44(9):1222–8.
Zomorrodi A, Wald ER. Sydenham's chorea in western Pennsylvania. Pediatrics. 2006;117:e675–9.

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