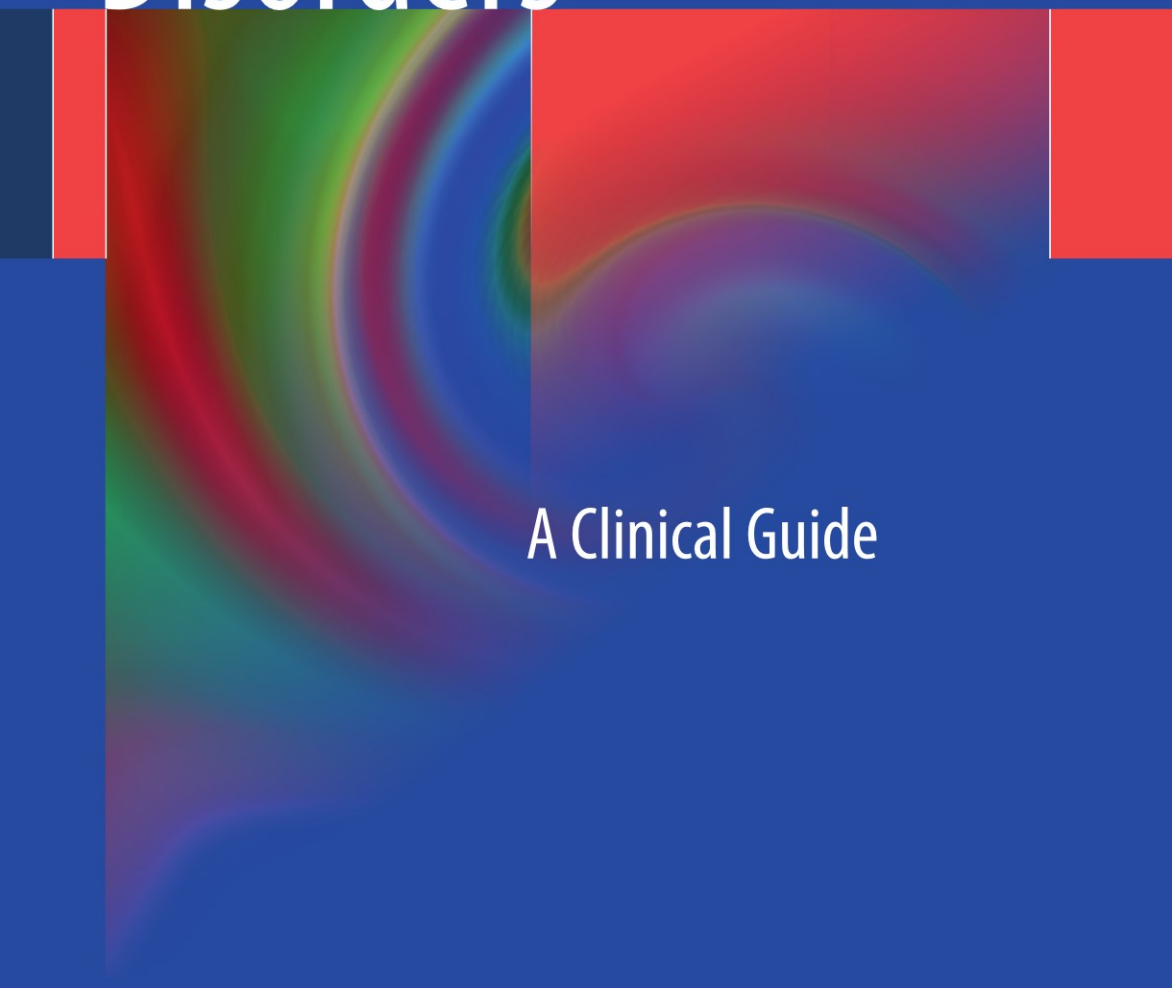
Orla Hardiman
Colin P. Doherty *Editors*

Neurodegenerative Disorders



A Clinical Guide

Springer

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Orla Hardiman • Colin P. Doherty
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Foreword

Neurodegeneration has never been a very attractive way to describe a group of diseases. It says nothing about causes and lumps together a vast array of very different conditions. It also arises from an era which was completely devoid of any notion of cause or any hope of treatment. I remember being told by one of my most distinguished mentors in neurology that there had not been a single good idea about ALS since it was clearly described by Charcot in the nineteenth century. As recently as the latter quarter of the twentieth century, people who decided to work on one of these so-called degenerative conditions were felt to have descended into a hopeless morass, out of which there was no academic escape.

The first crack in the icicle came with the discovery of L-dopa to treat Parkinson disease. From that point an entire field of neuropharmacology arose, turning some of the degenerative conditions into manageable, albeit not curable, chronic illnesses. Then came molecular biology, genetics, and modern neuroimaging. Neurodegeneration finally came out of the closet. New ideas were generated regarding the possible causes of some of the toughest nuts to crack: namely, Alzheimer disease, motor neuron diseases, Parkinson disease, Huntington disease, the familial peripheral neuropathies, and the spinocerebellar degenerations. More recently, possible treatments (some of which even work a little) are being considered, including stereotactic brain surgery with more precise deep brain stimulation, magnetic and direct current brain stimulation, strategies aimed at neuronal protection from excitatory neurotransmitters or free radicals and methods aimed at unfolding abnormal proteins (e.g., amyloid, prions, synuclein, tau) or reducing their accumulation in the brain. Large scale automated methods have come into being which allow screening of enormous numbers of small molecules which might interfere with the newly illuminated causes of some of the neurodegenerative conditions. Finally, diseases which were thought to fit into another category altogether, such as the presumed inflammatory multiple sclerosis, were repatriated into the newly acceptable category of neurodegeneration.

Clearly it was time for a monograph on the clinical aspects of the new neurodegenerative diseases, and Orla Hardiman and Colin Doherty of Dublin have delivered it. The book begins with a treatise on the common themes in neurodegeneration, bringing the reader up to date on modern theories that have replaced the simplistic abiotrophy (premature ageing) of the past. The second chapter characterizes the various advances in neurodiagnostics that have opened Pandora's box and can allow the sophisticated clinician to better characterize the nature, prognosis and potential treatment of the neurodegenerations. The next eight chapters cover the major categories of neurodegenerative diseases: Alzheimer disease, vascular dementias, Parkinson disease, fronto-temporal dementia,

amyotrophic lateral sclerosis, Huntington disease, Parkinsonian syndromes, including progressive supranuclear palsy, corticobasal degeneration, strionigral degeneration, multisystem atrophy and a potpourri of others, and prion diseases. The book ends with two special chapters the subjects of which span all of the major categories of disease; one on the management of neuropsychiatric symptoms and a second on palliative care.

Doctors Hardiman and Doherty are international authorities on the subject and have used their considerable influence to assemble an impressive group of authors. Anyone who is seriously interested in neurology will find this volume a must read.

Boston, MA, USA Martin A. Samuels, MD, DSc(hon), FRCP, MACP, FAAN

Preface

The main purpose of this book is to provide a manageable account of the common neurodegenerative conditions. We have aimed to provide a portable resource that outlines the main clinical features, treatment options, and outcomes of most common conditions encountered in clinical practice.

As the population ages, there will be an inevitable rise in the incidence and prevalence of neurodegenerative diseases. In the absence of disease-modifying therapies, this impending expansion in late onset disability will lead to an increased burden on health services and on society in general. At present we continue to rely on symptomatic therapies and quality-of-life-enhancing interventions, aimed at alleviating the suffering experienced by those affected and their extended families.

There is an urgent need to develop therapeutic strategies for the neurodegenerative disease. This imperative poses a great challenge for clinicians and scientists committed to treatment. And while this challenge cannot be underestimated, the advances – particularly in the last two decades – of molecular genetics, diagnostics, biomarker development, and high throughput therapeutics have brought us to the brink of true disease-modifying treatments.

This handbook is an attempt to draw together what is currently known and understood about neurodegeneration for an audience of clinicians and healthcare workers who may not be specialists in the area.

We have gathered a group of internationally respected authors to translate the myriad clinical descriptions, investigative techniques, and potential therapeutic developments into an exciting story of true scientific and clinical triumph over the last 100 years.

We have begun and ended the book with a series of overview chapters. The first two chapters deal with general principles that underlie degeneration, and the contribution of established and new diagnostics techniques. We have selected the most common neurodegenerative conditions as topics for the ensuing chapters. We have included a chapter on vascular dementias, although some would argue that these are not truly neurodegenerative in nature. However, we believe that the increasing recognition of overlaps between what are considered traditional neurodegenerative processes and the effects of chronic ischemic disease justifies this chapter.

The final chapters were designed to provide broad treatment outlines for the practicing clinician. Managing the neuropsychiatric consequences of neurodegeneration can be challenging and we have aimed to provide a concise and evidence-based account of the current thinking in this area.

The last chapter deals with issues around end of life and seeks to integrate the role of palliative care into the mainstream management of neurodegeneration.

In the interests of size and portability, we have asked each author to provide a list of key references at the end of each chapter, rather than referencing throughout the text.

We have excluded a number of important conditions that might be considered neurodegenerative. Notably, we decided at the conceptual phase of the book not to include childhood onset neurodegenerative conditions. We have also excluded the spinocerebellar ataxias as onset is usually, although not exclusively, in the first two decades of life. We have also decided to exclude multiple sclerosis, as despite the secondary degenerative phase of this condition, we have considered a primary neuroinflammatory condition to be outside the scope of the book.

We thank all the contributors, their sources, and inspirations. Each contributor is a practicing clinician, and we acknowledge the demands of precious time that each contribution has generated.

We also thank our publishers, and in particular Barbara Lopez-Lucio who has patiently worked with us for over a year, and whose assiduous pursuit of the final drafts from tardy editors has made this book possible. And finally, we acknowledge the support of our respective families, who provided us with the time and space to complete this work.

Orla Hardiman
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Common Themes in the Pathogenesis of Neurodegeneration

1

Susan C. Byrne, Lewis P. Rowland, Jean Paul G. Vonsattel, Alfred T. Welzel, Dominic M. Walsh, and Orla Hardiman

Abstract Neurodegenerative diseases share a number of common features with respect to clinical course, pathology, and molecular mechanisms. This chapter outlines the common themes of neurodegeneration, including the concept of selective neuronal vulnerability, genetic susceptibility, aberrant protein structures, disruption in mitochondrial function, altered axonal transport, oxidative stress, and neuroinflammation. A greater understanding of the shared pathophysiologic processes for neurodegenerative diseases will help to develop therapeutic agents that may be beneficial to a range of different clinical phenotypes.

Keywords Selective vulnerability • Neuropathology • Protein aggregation • Oxidative stress

Introduction

As the population increases in size and life expectancies continue to rise, so do the number of people diagnosed with neurodegenerative diseases. This term refers to age-dependent progressive diseases, caused by degeneration of the central nervous system (CNS). Traditionally, these conditions were characterized clinically, but with advances in imaging, it has become possible to attribute specific clinical manifestations of disease to degeneration in specific anatomical regions of the CNS. Histopathological analysis, genetic studies, and proteomic interrogation have further refined the diagnosis of neurodegenerative diseases.

Neurodegenerative diseases share certain common features including histopathology, clinical course, and molecular mechanisms of pathogenesis. Comparing two different diseases, there may be both overlap with regard to some features and divergence of other aspects. As new categories of disease emerge, some are seen to share common pathogenic features and genetic origins.

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The aim of this chapter is to describe the common themes that underlie the major neurodegenerative diseases, and to draw biochemical, histopathological, and molecular genetic parallels across the different disease categories that are outlined in the remainder of this book.

Common Clinical Features of Neurodegenerative Diseases

In 2003, Przedborski and colleagues recognized the clinical and pathological manifestations of neurodegenerative diseases, which:

- Affect "specific subsets of neurons"
- Arise without clear explanation and could be either inherited or acquired
- "Progress relentlessly"
- Are often age-related, increasing in frequency with advancing age
- Are often accompanied by microscopic signs of four stages of disorder:
  - Neuronal pathology
  - Neuronal cell death
  - Disappearance of neuronal cell bodies
  - Glial proliferation

The following may serve as a brief overview of common clinical features of neurodegenerative diseases:

- The chronic clinical course is relentlessly progressive until death.
- The disorder is not reversible by any known therapy although drug therapy or gene therapy may give marginal and temporary improvement.
- Phenotypic variability is commonly seen.
- Cognitive impairment and dementia are common manifestations in neurodegenerative disorders but are not seen in all forms. The diagnosis of dementia has been formalized so that cognitive changes in frontotemporal dementia (FTD) and Alzheimer disease can generally be differentiated by formal neuropsychological tests.
- The major risk factor is advancing age. The term *age-related neurodegenerative diseases* is commonly used.
- The condition appears to be heritable in a small percentage of cases.
- In the familial form of the disease, the onset occurs up to a decade before onset of the sporadic form of the disease.
- Several different neurodegenerative diseases may appear together within a family.
- Different clinical manifestations are mediated by dysfunction of different anatomical regions of degeneration.
- Features of more than one neurodegenerative diseases may appear to coexist in one patient. There is clinical overlap between amyotrophic lateral sclerosis (ALS) and FTD, indeed the two conditions are believed by some to represent a spectrum rather than separate diseases. In the ALS–parkinsonism–dementia complex of Guam, patients have evidence of two motor diseases as well as dementia.

- Advances in genetics of neurodegenerative diseases have demonstrated that diverse clinical phenotypes may share similar genotypes, and that clinically similar phenotypes may be associated with a wide variety of genotypes.

Classification of Neurodegenerative Diseases

Neurodegenerative diseases are diagnosed primarily on the basis of history and clinical examination (Fig. 1.1). Diagnostic criteria, based primarily on clinical findings, have been generated for most of the common neurodegenerative diseases. The suspected diagnosis is then confirmed by carrying out directed tests in the fields of neurophysiology, neuropsychology, neuroimaging, or genetic analysis. Often, the best diagnostic tool is the observation of the patient over the course of time; antemortem tissue analysis usually does not play a role in diagnosis.

Eponymous classifications (e.g., Alzheimer disease, Parkinson disease, and Huntington disease) remain useful in a clinical setting, as the diagnosis generates a framework for clinical discussion, prognostication, and disease management. However, it is increasingly recognized that neurodegenerative diseases can also be subdivided into categories based on pathological or genetic characteristics, as outlined in Fig 1.1, and as the field advances, diagnostic categories for some diseases will accordingly require some adjustment.

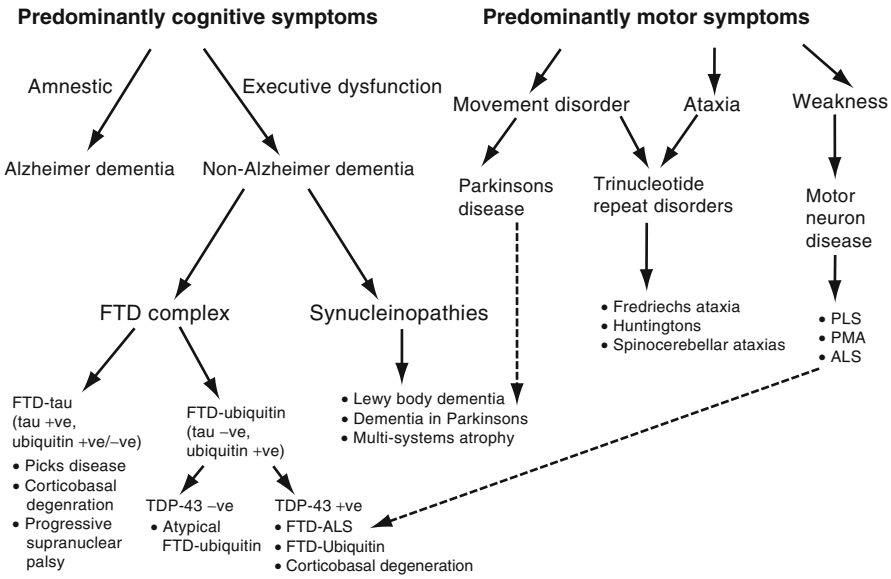

Fig. 1.1 Clinical classification of neurodegenerative diseases

A number of common themes have emerged in the pathogenesis of various neurodegenerative diseases. Whether these commonalities are simply secondary processes, which reflect the fact that neurons have a limited repertoire by which to die, or whether they reveal important initiating upstream mechanisms remains unclear.

In the following section, some putative common pathogenic molecular mechanisms will be discussed, but it is worth bearing in mind that it is not currently possible to distinguish between mechanisms that initiate disease and those that contribute to disease progression. Both may yield targets suitable for therapeutic intervention, but only the former can yield knowledge that will lead to disease prevention.

Common Themes in Genetics

Familial aggregation of specific neurodegenerative diseases is well recognized. Excepting the trinucleotide repeat disorders, which exhibit Mendelian inheritance with full penetrance and anticipation, neurodegenerative disorders have a small percentage of familial cases and a large percentage of apparently sporadic cases. Sporadic and familial cases are usually phenotypically and histologically indistinguishable, although the onset of familial cases tends be earlier. This suggests that genetic mutations accelerate the molecular processes that lead to late-onset sporadic disease.

A number of causative genes have been discovered for specific neurodegenerative diseases. An understanding of gene function has helped to elaborate mechanisms of disease, as well as providing a platform for research into similar mechanisms in other neurodegenerative diseases. For example, mutations in APP, Presenilin 1, and Presenilin 2, which occur in early onset Alzheimer disease (AD), cause altered protein production and increased aggregation of β-amyloid protein (Aβ). Similarly, PARK 1, the first gene to be identified in Parkinson disease (PD), alters the production of the protein α-synuclein. Mutations in genes associated with oxidative stress pathways, SOD1 and DJ1, have been implicated in familial amyotrophic lateral sclerosis (ALS) and PD, respectively. The discovery of TAR-DP and FUS in ALS and frontotemporal dementia (FTD)-ALS has pointed to the likely role of altered RNA regulation in some neurodegenerative diseases.

Genome-wide association studies and high-throughput sequencing have identified susceptibility genes in many neurodegenerative conditions. Moreover, overlap between susceptibility genes has been reported. APOE4 is well established as a risk factor for late-onset AD. However, meta-analysis has shown that presence of the allele is also linked to PD and FTD. Although the incidence of APOE4 is the same in patients with ALS as the general population, the presence of the APOE4 allele is associated with earlier age of disease onset.

Common Themes in Neuropathology

Thorough pathological diagnosis depends on the pathologist having access to accurate clinical information as well as tissue analysis. Pathological diagnostic criteria presume that phenomena involved in degeneration tend to occur together, but invariably they are evident

at different time points during the disease. Thus, interpretation of the neuropathological data must take into account when in the clinical course of the disease the pathological assessment has been performed.

Both gross and microscopic tissue examination can help to identify pathological processes and can also differentiate features that are purely degenerative, and those that emerge from the innate responses to protect and repair. Finding the site of the earliest visible alteration helps in establishing the diagnosis. Degeneration in the hippocampal and frontal lobe pyramidal neurons is associated with AD, in the dopaminergic neurons of the substantia nigra with PD, in the upper and lower motor neurons of the pyramidal system with ALS and in the medium-sized spiny GABAergic neurons of the striatum with HD.

Dementia coupled with mainly limbic atrophy suggests Alzheimer disease (AD), while mild atrophy implies Lewy body disease. Moderate cognition decline in the setting of asymmetric, motor and sensory impairment, with reduced metabolic activities, and atrophy prevailing around the central sulcus is indicative of corticobasal degeneration. However, if these changes involve the lateral half of the putamen, caudal to the mammillary body, multiple system atrophy (MSA) is the most likely diagnosis. Despite the topographical differences in neurodegenerative diseases, gross histopathological findings are similar – there is regional atrophy with gliosis and neuronal loss as well as abnormal accumulation of protein.

A large subset of neurodegenerative diseases display protein aggregates. Ubiquitinated neuronal nuclear inclusions occur in polyglutaminopathies including Huntington disease (HD). Either parenchymal or vascular accumulation of Aβ occurs with aging, as well as in the occurrence of AD in children with Down syndrome. Neostriatal large neurons are rather resistant compared to medium size neurons in HD, but they degenerate in progressive supranuclear palsy and in AD. Loss of spinal motor neurons is typical in amyotrophic lateral sclerosis (ALS), whereas glial cells degenerate in MSA. Lewy bodies are a hallmark of Parkinson disease with or without dementia and involve many classes of neurons.

In summary, the three practical steps that are useful while appraising the pathologic phenotypes of neurodegenerative diseases are:

1. Identifying the sites or systems where the brunt of the tissue loss occurs, which might be revealed on neuroimaging at some time points during the disease, or eventually on postmortem examination.
2. Cataloging the cells undergoing degeneration.
3. Identifying the abnormal aggregates, their cellular (neuronal vs. glial cells) and topographic propensities (extracellular, cytoplasmic, or nuclear).

General experience confirms that these steps are crucial for assigning the most appropriate diagnosis to most of the currently classifiable neurodegenerative diseases.

Selective Vulnerabilities

Cells are constantly placed under stress because of intrinsic metabolic processes and also because of a number of extrinsic factors. Neurons are even more vulnerable as they facilitate neurotransmission and maintain the metabolic needs required for long axonal

Table 1.1 Neurologic diseases and selectively vulnerable cells

Disease	Vulnerable neuron
Parkinson disease	Dopaminergic neurons
Alzheimer disease	Cholinergic neurons
Amyotrophic lateral sclerosis	Upper and lower motor neurons
Frontotemporal dementia	Frontotemporal cortical neurons
Huntington disease	GABAinergic neurons

projections. Larger neurons with myelinated axons extending long distances appear to be most vulnerable. These neurons have high energy requirements, are especially reliant on axonal transport, and have a larger surface area for exposure to environmental toxins. Coupled with the fact that once damaged they cannot regenerate, neurons in general represent a vulnerable group of cells.

So why then are certain subgroups of neurons more susceptible than others? A number of hypotheses have been proposed to account for specific selective susceptibility of certain neurons to specific pathological processes (Table 1.1). Neuroblasts arise from the neuroectoderm at 8 weeks of fetal life and then proceed to differentiate into highly specialized neurons. Even though all neurons of an individual have the same genes, it is the gene expression profile that determines the highly specialized function of a specific neuron. This degree of specialization is thought to render individual neurons more susceptible to anoxia and oxidative stress, and factors that lead to selective vulnerability include the type of neuron and the neuronal microenvironment.

The dopaminergic neurons located in the substantia nigra in PD are particularly prone to reactive oxygen species (ROS)-induced injury. This selective vulnerability is believed to derive from the fact that neurons in the substantia nigra have very high levels of iron and copper, both of which are capable of catalyzing ROS formation. Additional evidence suggests that the substantia nigra may have low stores of antioxidant molecules such as glutathione, thereby increasing neuronal susceptibility to the damaging effects of ROS. However, this does not explain the vulnerability of neurons associated with PD in other regions of the brain such as autonomic ganglia, brainstem, and spinal cord.

In ALS, motor neurons are affected primarily, although it is now recognized that non-motor neurons are involved in cognitive dysfunction. Motor neurons are large cells and often have long axonal fibers. In lower motor neurons, these fibers may stretch over a meter in order to supply distal muscles. They require a strong cytoskeleton, neurofilament network, and efficient axonal transport system. Motor neurons are highly metabolic and exquisitely sensitive to energy demands. Any one or a multitude of these factors makes motor neurons vulnerable. As is the case in the substantia nigra, deficiencies of protective agents such as glutathione and cytosolic calcium-binding proteins can add to neuronal stress.

The different phenotypic characteristics of individual diseases remain difficult to explain. In Mendelian diseases, differences can be evident within families with the same mutation. For example, a proband with familial ALS may present with flail arm and slow progression, while another family member may present with rapidly

progressive bulbar onset disease. Similarly, some patients with AD may have executive or visuospatial deficits, while others have an amnestic syndrome. In kindreds with triplication of APP, the clinical disease segregates into two distinct phenotypes: those with classical AD indistinguishable from idiopathic AD and those with vascular dementia and a stroke-like syndrome. The causes of these phenotypic variations remain to be determined.

Aberrant Protein Structure

The formation of aberrant structures by more than 20 different proteins appears to underlie a large disease group, many of which afflict the CNS (Table 1.2). Indeed, deposits of protein aggregates are histological hallmarks of many neurodegenerative diseases and consequently, the proteins involved and the mechanism of their aggregation is under intense scrutiny.

Table 1.2 Neurologic diseases associated with aberrant protein structure

Disease	Protein deposited	Site of deposition
Parkinson disease	α-synuclein	Intracellular (Lewy neuritis and Lewy bodies)
Multiple systems atrophy	α-synuclein	Intracellular argyrophilic inclusions in both oligodendroglia and neurons
Hereditary cerebral amyloid angiopathy	Cystatin C	Extracellular
Congophilic amyloid angiopathy	β-amyloid	Extracellular
Alzheimer disease	β-amyloid	Extracellular (amyloid plaques)
Alzheimer disease	Tau	Intracellular (paired helical filaments)
Frontotemporal dementia	Tau	Intracellular inclusions (paired helical filaments and Pick bodies)
Familial British dementia	ABri	Extracellular (amyloid plaques)
Familial British dementia	ADan	Extracellular (amyloid plaques)
Transmissible spongiform encephalopathies	Prion protein	Extracellular amyloid plaques and/or diffuse deposits
Amyotrophic lateral sclerosis	TDP43-ubiqitin	Cytoplasmic inclusions and ubiquitin-positive neuronal threads
Huntington disease	Mutant huntingtin	Nuclear and cytoplasmic inclusions
Inherited spinocerebellar ataxias	Various proteins with polyglutamine expansions	Nuclear and cytoplasmic inclusions

The mechanism by which the attainment of an aberrant protein structure causes disease is still unclear and may involve both the loss of a vital physiological function, and the acquisition of toxic properties. While loss of function can be harmful, toxic gain of function is invariably pathogenic. Toxicity may be direct or indirect. For instance, an aberrant protein structure might bind to a specific receptor directly, causing an inappropriate activation of a cascade that initiates cellular changes, which in turn lead to compromise of cellular function. Alternatively, aberrant structures might acquire properties that allow them to interact with and destabilize cellular membranes or other proteins, thus causing a secondary toxicity. Moreover, accumulation of aberrant proteins may strain the normal mechanisms responsible for controlling protein folding and degradation, resulting in a generalized loss of protein homeostasis and consequent toxicity.

Oligomerization or polymerization of aberrantly folded proteins is concentration dependent. Changes in production, degradation, or clearance of native protein are hypothesized to underlie the assembly of aberrantly folded protein. Once formed, such structures are thought to be the primary event driving pathogenesis (Fig. 1.2). Consequently, many of the therapies under development are designed either to: (1) decrease the quantity of soluble native protein, or (2) remove aberrant protein.

It has been suggested that a threshold of abnormal aggregation must be reached before clinical signs appear, but it is as yet unclear whether deposited protein aggregates or other smaller protein assemblies are the principle mediators of disease. Evidence against deposits of protein aggregates as mediators of disease comes from the finding that many aggregated proteins are found in brains of elderly individuals who die without clinical signs of disease.

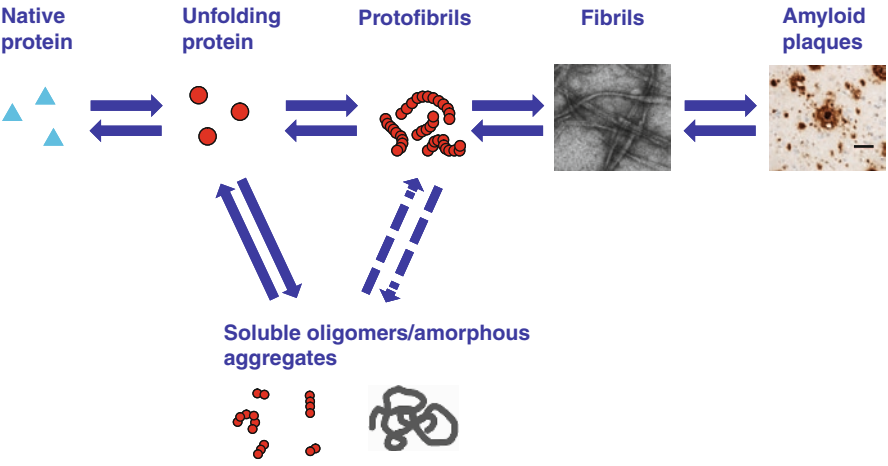

Fig. 1.2 Pathways to aberrant protein structure and aggregation in amyloid related diseases: The process is initiated by denaturation, unfolding, or misfolding (indicated by the transition from *blue triangle* to *red circle*). Proteins can form oligomers or amorphous aggregates or small, structured polymers known as protofibrils. Protofibrils mature into amyloid fibrils and then into aggregates of amyloid fibrils. Current data indicate that all aberrant protein structures (i.e., all structures shown other than the native monomer) are toxic

Inclusion Bodies

Inclusion bodies are relatively large electron-dense structures that contain membrane-limited protein aggregates. Such deposits often contain ubiquitin-positive material, which is believed to accumulate due to impairment of the ubiquitin-proteasome system (UPS). Under normal conditions, cytoplasmic proteins are tagged for destruction by the enzymatic addition of four or more ubiquitin molecules, but buildup of substrate, decreased efficiency of ubiquitin conjugation, or impaired degradation of ubiquitinated protein can trigger accumulation of partially ubiquitinated protein aggregates. For instance, it is believed that impaired ubiquitination of α-synuclein may explain how mutations in the PRKN gene cause early onset PD. PRKN encodes an E3 ubiquitin ligase (Parkin), which when mutated appears less efficient at ubiquitinating α-synuclein and aggregates of partially ubiquitinated α- accumulate in cytoplasmic structures known as Lewy bodies.

Pathological inclusion bodies are also seen in ALS, FTD, and HD. However, it is not clear if inclusions are purely pathogenic since Marinesco bodies and Hirano bodies are also found in aged asymptomatic individuals. Moreover, several studies have documented the detection of inclusions in functional neurons, implying that these structures may be protective rather than pathogenic.

Altered RNA Metabolism

There is increasing interest in the role of aberrant RNA processing in the pathogenesis of neurodegenerative disease. Mutations in two important genes, FUS and TDP-43, identified in a small percentage of familial ALS and FTD cases, are associated with altered RNA processing. Similarly, loss of function mutations in another RNA regulator, progranulin, has been linked with FTD, which, in turn, may be associated with motor neuron disease in some families. The protein products of TDP-43 and FUS/TLS (FUsed in Sarcoma, Translocated in LipoSarcoma) are both structurally similar to heterogeneous ribonucleoproteins (hnRNP), which are involved in multiple aspects of RNA processing. Mutations in the TAR DNA binding protein, TDP-43, and the protein, FUS/TLS have widespread downstream effects on multiple differentially spliced mRNA species. Consequently, it is anticipated that quite diverse pathogenic pathways are triggered depending on the RNA binding protein and the type of neurons involved. The mutations in the TDP-43 gene are seen in some familial ALS cases, but cytoplasmic inclusions containing ubiquinated and hyperphosphorylated forms of wild-type TDP-43 may be found in cases of sporadic ALS. Inclusions containingTDP-43 are also seen in more than half of all FTD cases, and TDP-43 and FUS/TLS inclusions have been reported in other neurodegenerative conditions including: corticobasal degeneration, sporadic AD and familial AD, Down syndrome, hippocampal sclerosis dementia, familial British dementia, PD, ALS–parkinsonism–dementia complex of Guam and some myopathies.

It is not yet known if TDP-43 inclusions act as a primary neurotoxin or if they are a cellular by-product of some other toxic event. Similarly, FUS/TLS is a highly active

nuclear protein involved in many aspects of RNA metabolism and also plays an important role in mRNA transport along dendrites. Thus, loss of function mutations in FUS/TLS may lead to abnormal synapse function in the motor nerves and abnormal modulation of neuronal plasticity that is essential for proper activity.

Oxidative Stress

In all cells, but particularly highly metabolically active cells such as neurons, there is a constant production and elimination of reactive oxygen species (ROS). At any time, the balance is such that an unusual increase in ROS or loss of antioxidant protection can lead to accumulation of ROS and ensuing cellular damage. High levels of ROS can cause nuclear DNA oxidation and repairing such damage requires substantial expenditure of metabolic energy. If damaged DNA is not adequately repaired, this can lead to cellular dysfunction and apoptosis. Accumulated oxidatively damaged DNA has been observed in AD, PD, ALS, and vascular dementia (VD). Calcium plays an integral role in signaling within the cell and also in maintenance of cellular homeostasis. As part of the role in signaling, ROS activate calcium channels and deactivate calcium pumps. This leads to abnormally high intracellular levels of calcium, which in turn may lead to cell death. Mitochondrial ROS also cause increased uptake of calcium ions with increased membrane permeability, resulting in the release of cytochrome-C, which initiates the apoptotic cascade.

In vivo and in vitro studies have shown that nicotinamide adenine dinucleotide phosphate (NADPH) oxidase derived from microglia play an important role in the generation of ROS. In PD, microglia-specific NADPH oxidases are involved in the production of ROS, which may contribute to the death of dopaminergic neurons. A similar process is seen in ALS, whereby oxygen radicals produced by microglial NADPH oxidase are believed to injure motor neurons. Evidence from the mutant SOD1 mouse model of ALS indicates that genes encoding NADPH oxidase are upregulated in disease and this leads to an increased concentration of ROS in mouse spinal cord tissue.

Mitochondrial Dysfunction

Mitochondria play a crucial role in the production of cellular energy using the respiratory chain. Consequently, accumulated mitochondrial dysfunction is implicated in both normal aging and neurodegeneration. Proposed mechanisms of this effect include failure to meet the energy needs of the cell, calcium misregulation, leading to cell death, over production of ROS, and cytochrome C-induced apoptosis.

Well-documented incidents have shown that ingestion of certain neurotoxins can lead to the sudden onset of clinical syndromes identical to neurodegenerative diseases such as Parkinson disease or Huntington disease. Two such events led to the discovery that some neurotoxins are potent inhibitors of complexes within the mitochondrial respiratory chain. In 1982, seven young drug abusers injected intravenous forms of a synthetic

heroin derivative, 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), and developed the signs and symptoms of PD. This was because of the presence of a contaminant, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). When pure MPTP is injected into animals, it causes specific degenerative of dopaminergic neurons in the substantia nigra pars compacta and produces an irreversible and severe parkinsonism phenotype. After infusion, MPTP crosses the blood–brain barrier and is taken up by glia and serotonergic neurons and converted to MPDP+and then to MPP+. Thereafter, MPP+ is released and specifically taken up by dopaminergic neurons and concentrated in mitochondria where it acts as a potent inhibitor of mitochondrial complex I. Similarly, exposure to 3-nitropropionic acid (3NPA) leads to rapid onset of a Huntington-type syndrome. It is now known that 3NPA is an inhibitor of mitochondrial complex II. Discovery that exogenous neurotoxins can inhibit mitochondrial complexes leading to rapid onset of neurological symptoms suggests that mitochondrial dysfunction plays a central role in these diseases.

Excitotoxicity

Glutamate is an important excitatory neurotransmitter in the CNS and its misregulation has been implicated in the development of neurodegenerative diseases. Glutamate has essential roles in synaptic transmission and plasticity, which are important in learning and memory as well and sensory and motor functions. Transmission of glutamate is mediated through three major receptors – *N*-methyl-D-aspartate receptors (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptors, and kainite receptors. The glutamate excitotoxicity hypothesis postulates that excessive synaptic glutamate causes over-activation of the postsynaptic NMDA and AMPA receptors resulting in neuronal death. High glutamate levels, which continuously activate postsynaptic receptors, may lead to increased intracellular calcium and catabolic enzyme activity. Downstream effects can include depolarization of mitochondrial membrane, activation of the caspase system, and production of reactive oxidation species, all of which culminate in cell death (Fig. 1.3). Excessive synaptic glutamate may be potentiated because of a fault in the cellular glutamate reuptake system. Excitatory amino-acid transporter 2 (EAAT2) is a glutamate transporter involved in cerebral glutamate transport. It has been postulated that some patients with ALS have decreased expression of this protein. Similar studies carried out in patients with AD have also shown a reduction in EAAT 2 expression. It has been shown that GLUR2, an AMPA glutamate receptor subtype responsible for calcium permeability into the postsynaptic cell, is not expressed in motor neurons affected by ALS because of a defect in the editing process for messenger RNA encoding the GLUR2 receptor. Absence of a functional GLUR2 subunit allows calcium influx into the postsynaptic cell and results in cellular damage.

Parkin, which is the gene product of PARK2, has regulator effects on excitatory glutaminergic synapese. Abnormalities in parkin production can lead to enhanced synaptic activity and may even trigger an increase in the number of glutamate receptors. Excessive glutaminergic activity may be responsible for nigral excitotoxicity.

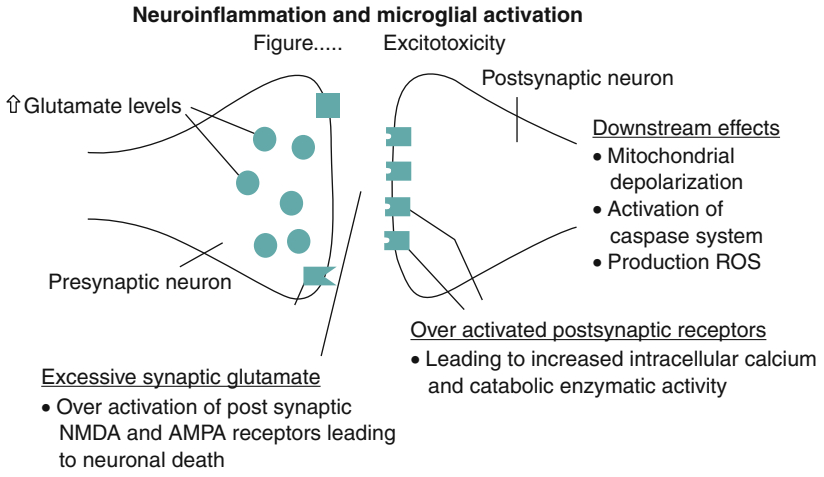

Fig. 1.3 Proposed mechanisms of glutamate-induced excitotoxicity

Given this evidence, it would seem beneficial to downregulate glutamate activity in patients affected by neurodegenerative disease. Riluzole has a direct and indirect blocking effect on glutamate receptor activation and is proven to slow the progression of ALS. Unfortunately, no other anti-glutamate agent has been successful in disease treatment.

Neuroinflammation and Microglial Activation

An epidemiological study carried out in 1980s was the first to postulate an association between inflammation and neurodegeneration. The study demonstrated that the incidence of AD was lower in patients with rheumatoid arthritis (RA) who had been on long-term anti-inflammatory treatment compared to those who had not. Since then, detailed descriptions of systemic and CNS specific proinflammatory cascades have fueled the hypothesis that neuroinflammation plays an active role in the process of neurodegeneration. Microglia are CNS-specific macrophages, derived from myeloid precursor cells, which enter the CNS during embryogenesis. The primary function of this subset of immune cells is to protect the brain from extrinsic pathogens and processes. Recently, a number of experiments have shown that activated microglia can cause irreversible damage to tissues of the CNS. Microglia in the deactivated or resting state are in surveillance mode. They constantly sample the surrounding milieu to detect signals associated with injured brain tissue. A number of factors have been identified that upregulate microglia to the activated state.

During the process of activation, microglia are highly plastic and differ in morphology and phenotype depending on the nature of the insult-causing activation. Microglia may remain in the activated state for prolonged periods. However, it is unlikely that microglial activation is the primary cause of any neurodegenerative process. It is more likely that an

initial challenge induces an inflammatory cascade, which in turn initiates maladaptive processes and positive feedback loops that cause further pathological inflammation.

Postmortem examination of brain tissue from PD patients has demonstrated activated microglia in the substantia nigra pars compacta. In AD, neuroinflammation is considered a downstream effect of abnormal protein production. Aβ causes upregulation and activation of microglia leading to an inflammatory cascade. This cascade sets out to respond to abnormal protein accumulation but causes damage as a by-product of activation.

An analogy on the macroscopic scale can be drawn to acute brain injury such as a stroke, where reparative attempts by the brain tissue can cause edema, which in turn leads to an increase in intracranial pressure and even death. In the same way, processes that set out to reverse neurodegeneration may actually contribute to secondary damage. Understanding the balance between protective and destructive capabilities of microglia has led to trials seeking to slow progression of neurodegenerative diseases by dampening down neuroinflammatory processes.

Disrupted Axonal Transport

In neurons, proteins and lipids are manufactured in the cell body and are transported along axonal projections, which can extend over a meter in length, to synaptic terminals. Conversely, neurotrophic factors transported from synaptic terminals help to regulate cellular function. This process is called fast axonal transport and is an essential part of cellular homeostasis.

Dysfunction in the axonal transport system was first studied in large motor neurons. A decreased level of kinesin-mediated anterograde transport and retrograde dynein-mediated transport was observed in patients with ALS. Since then, research has shown that SOD1 aggregates interact with the retrograde transport system in a way that may lead to axonal dysfunction (Fig. 1.4). A decrease in retrograde transport could lead to toxicity at synaptic terminals as well as a loss of positive feedback from factors that stimulate neuronal survival. Mitochondrial distribution could be affected, resulting in a mismatch in

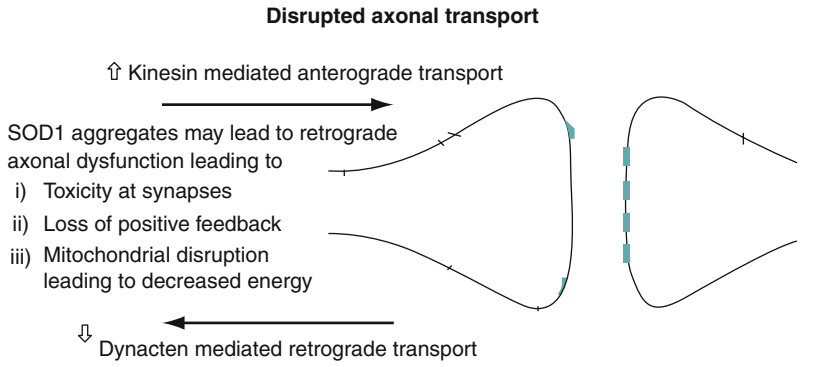

Fig. 1.4 Schematic model of how mutant SOD1 aggregates lead to altered axonal transport in ALS

energy provision. The accumulation of damaged mitochondria at synaptic terminals could cause increased terminal ROS production.

Conclusion

While arguments can be made regarding pathophysiological processes that make neurons vulnerable to degeneration, we still do not know fully why some people are physiologically more susceptible to specific neurodegenerative diseases, and why different neurodegenerative diseases cluster within some kindreds. It is clear that the common neurodegenerative conditions share similar processes. Increased understanding of the pathophysiologic processes for neurodegenerative diseases is likely to lead to disease-modifying therapeutic interventions that may be beneficial over a range of different clinical phenotypes.

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Advances in Diagnostics for Neurodegenerative Disorders

2

Arun L.W. Bokde, James F.M. Meaney, Niall P. Sheehy, Richard B. Reilly, Sharon Abrahams, and Colin P. Doherty

Abstract In this chapter, the established investigative techniques for aiding diagnosis in neurodegenerative disease are reviewed. Beginning with neuropsychological analysis, this review ranges though structural (anatomic), dynamic, and functional brain imaging using MRI and radio-nucleotide scanning to complex neurophysiological applications. In each section, the increasing likelihood of developing true noninvasive biomarkers is addressed. The future of multi-modality imaging and its contribution to, not only to diagnosis, but to classification, prognosis, and treatment outcome in neurodegeneration is considered.

Keywords Neuropsychology • MRI, fMRI, PET • Neurophysiology

Introduction

There is a constant need in clinical medicine to obtain objective measurements of physical and cognitive function as the basis for diagnosis and monitoring of health. The prevalence of neurodegenerative diseases, particularly those that affect older people, is predicted to increase rapidly in the coming decades. As the scope of degenerative diseases expands to include more and more named conditions, so also it contracts as common themes in pathological degeneration emerge. To keep pace with these rapid changes, a range of diagnostics tests have emerged, coupling quantifiable phenotypic traits using neuropsychological methods and techniques with cutting edge imaging and neurophysiological modalities. This chapter complements Chap. 1 with a review of the common utility of these methods in clinical practice as well as a review of future developments that will go hand in hand with new molecular genetic understanding and therapeutic promise.

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Clinical Neuropsychological Assessment

Why Undertake a Clinical Neuropsychological Assessment?

Clinical neuropsychological assessment is undertaken to define cognitive impairment in a patient and has particular relevance to the diagnosis and management of the cognitive and behavior changes associated with neurodegenerative disease.

A neuropsychological assessment:

- Informs the clinician of whether a cognitive impairment is present or not. This is of prime importance in the dissociation of changes in cognition due to healthy aging from cognitive impairment. This may be achieved through the use of cognitive screening tools, but such screening measures can be deceptive and hence a more in-depth investigation may be warranted.
- Primarily, aids in diagnosis by informing the clinician of potential reasons for the cognitive impairment, including the differentiation of organic causes, e.g., dementias, from nonorganic causes, such as affective disorder. Many neurodegenerative diseases have specific and often distinct profiles of cognitive and behavior change dependent on the pattern of cerebral dysfunction. Hence, assessment can be of great benefit in the diagnosis of the type of neurodegenerative disease and in informing treatment decisions.
- Provides information on the rate of change; deterioration of function over that expected from aging may indicate a degenerative process and is essential for diagnosis, or recovery of functioning either spontaneously, e.g., after stroke, or following treatment.
- Provides information on an individual's ability to make informed decisions and hence give recommendations on capacity issues (mental and legal).
- Can inform on the functional consequences of the disability in everyday life and provide targets for support and intervention and management.

When Is Cognitive Screening Not Sufficient?

An ideal cognitive screening tool approaches 100% sensitivity (no false negatives), thus rarely erroneously excluding an organic brain disease. However, by definition, a highly sensitive test tends to sacrifice specificity, thus often failing to reliably subclassify a neurodegenerative disorder. There are a number of sensitive cognitive screening tools available, which are currently being used by clinicians (Table 2.1). Within neurodegeneration, the Addenbrooke's Cognitive Examination-Revised (ACE-R) is particularly useful; a well-developed tool that incorporates the Mini-Mental State Examination (MMSE) but includes a more comprehensive assessment designed to be sensitive to non-Alzheimer type dementias. This screen can be useful in the initial detection of whether cognitive impairment is present, or in monitoring change over time. However, the ability of this screening test to inform on a specific diagnosis is limited. This is primarily due to the complexity involved in interpretation of impairment, and the simplicity of the screening measures. For example, a patient may perform poorly on learning and delayed recall of a name and address for reasons including attentional dysfunction, motivation, language impairment, semantic

Table 2.1 Neuropsychological tests commonly used in clinical neuropsychological evaluation

Screening measures • Addenbrooke's Cognitive Examination (ACE-R) • Frontal Assessment Battery (FAB)
Tests of premorbid functions • National Adult Reading Test • Wecshler Test of Adult Reading
Tests of intelligence/general ability • Wechsler Adult Intelligence Scale (WAIS-III and IV)
Tests of memory functions • Wechsler Memory Scale (WMS-III and IV) • Adult Memory and Information Processing Battery • Rivermead Behavioral Memory Test • Doors and People test • Rey Osterrieth Complex Figure • Recognition Memory Test (Words and Faces) • List Learning Tests (Rey Auditory Verbal Learning and California Verbal Learning test) • Autobiographical Memory Interview
Tests of executive functions and attention • Behavioral Assessment of Dysexecutive Syndrome (BADS) • Delis-Kaplan Executive Function System (D-KEFS) • Wisconsin Card Sorting Test • Trail Making Test • Stroop Test • Hayling and Brixton Tests • Verbal Fluency (semantic categories and FAS test) • Test of Everyday Attention
Tests of language functions • Confrontation Naming Tests (Boston or Graded Naming test) • Word-Picture MatchingPeabody Vocabulary Test • Pyramids and Palm Trees Test • Test for reception of grammar (TROG) • Token test • Boston Diagnostic Aphasia Examination (expression/comprehension sub-tests)
Tests of visuoperceptual/spatial functions • Visual and Object Space Perception Battery • Benton Line Orientation Test • Birmingham Object Recognition Battery • Behavioral Inattention Test

memory deficit, in addition to that of primary memory impairment. Moreover, it is only through the demonstration of a specific problem with retention of information over time, which indicates a typical amnestic profile as found in early Alzheimer's disease. This can only be delineated through more extensive neuropsychological investigation.

Screening scores can also be deceptive in cases where patients are estimated to have high or low premorbid functioning, where scores are either not sensitive or falsely exaggerate impairment, respectively. Moreover, cognitive screening tools may also be of little value in cases where physical disability is present, such as with difficulties in speech, writing, vision, or hearing, common in this patient population. In these cases, more expert testing is required to differentiate whether performance decrements are due to cognitive impairment.

What Is in a Clinical Neuropsychological Assessment?

An assessment can include a variety of methods but is primarily based on the use of standardized cognitive tests. The development of these have advanced rapidly over recent years and there is now available a huge range of individual tests and batteries (Table 2.1). Although the Wechsler Intelligence and Memory Scales remain widely used and have been recently revised and extended to produce the IV series, there are also a comprehensive range of batteries focused on specific cognitive domains. For example, the Delis Kaplan Executive Function System (D-KEFS) includes a large range of measures of executive functions, while visuoperceptual/constructional abilities can be assessed using the Visual and Object Space and Perception Battery (VOSP). Larger batteries have the advantage of extensive normative data across the age ranges and many subtests can be used individually. Moreover, individual well normed and researched tests are available, which are adept at measuring a particular function relevant to a specific disease, e.g., the Pyramids and Palm Trees test, which assesses semantic knowledge. There are also more informal, unstandardized tests, which reveal a wealth of qualitative information such as drawing objects like a clock face, more nonuniform figures from memory, or using a patient's personal possession in a memory test. Figure 2.1 illustrates varied configurations of a clock face drawn by patients with frontotemporal dementia (FTD), parkinsonism, and Alzheimer's disease.

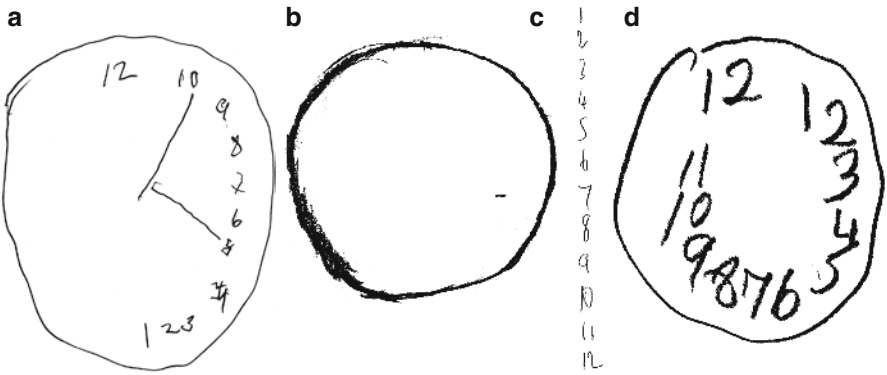

Fig. 2.1 (**a**) Clock drawing in patient with frontotemporal variant with parkinsonism. Backward sequencing suggests poor semantic/executive function with prominent frontal involvement. (**b**, **c**) Clock drawing in Alzheimer's disease. Patient could not be persuaded to put numbers inside the clock again, illustrating poor planning and rigid thinking as a result of frontal lobe involvement. (**d**) Clock drawing in frontotemporal dementia (FTD). Poor number placement indicates poor planning and executive function due to frontal lobe pathology

A comprehensive neuropsychological assessment includes information on premorbid functions, current intellectual functions, memory (e.g., visual, verbal, working memory, long-term memory, semantic memory, recall vs. recognition), executive functions (e.g., planning, strategy formation, monitoring, flexibility, attention, and speed of information processing), language including production and comprehension and visuoperceptual and spatial functions. Behavioral assessment is of vital importance, particularly in the context of some neurodegenerative diseases, e.g., FTD (see Chap. 6). This may be provided through direct observation, interviews with informant/carer, and self-report questionnaires. Assessment of mood and affective disturbance is also essential for differential diagnosis. Performance may be judged against normative data, estimate of premorbid or current intellectual functions, or a previous assessment.

Hence, the field has progressed rapidly and there are a plethora of assessment methods available to the neuropsychologist. Many neuropsychologists provide an idiosyncratic approach tailored to the patient. Best practice is hypothesis driven in which the neuropsychologist investigates profiles of impairment based on current knowledge of neurodegenerative illness and the demonstration of selective neuropsychological deficit.

What Types of Referral Should Be Made to Neuropsychology?

The referral question is of particular importance and a specific referral question will aid the neuropsychologist in defining the assessment and produce a more informative report. In terms of diagnostic issues, the relevance of the neuropsychological assessment will depend on the extent to which the cognitive and behavior symptoms form an integral part of the diagnostic criteria. The neuropsychologist working within neurodegeneration can inform on differential diagnosis on healthy aging vs. cognitive impairment and mild cognitive impairment vs. early dementia; here the neuropsychologist will be able to estimate whether there has been a decline in functioning from estimated premorbid functioning or from baseline and can indicate the number of domains that are impaired. This is of particular importance in diagnosis and in helping to determine suitability for treatment. Most notably, the neuropsychologist can aid in the differential diagnosis of the type of dementia, including Alzheimer's disease, vascular dementia, Lewy body dementia, and focal dementias (FTD – differentiation of all three variants and posterior cortical atrophy).

Specialized assessment is vital to demonstrate the focal nature of the impairment, which can be particularly difficult. For example, in frontal variant of FTD, behavioral change may be evident without overt cognitive dysfunction. The neuropsychologist can also aid in identifying cognitive impairment in those with subcortical and motor involvement including Parkinson's disease (PD), Huntington's disease (HD), progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBD), and amyotrophic lateral sclerosis/motor neuron disease (ALS/MND). Here, expertise lies in determining the specific neuropsychological profile and hence identifying whether the cognitive impairment is related to the disease, or comorbidity with another factor, and also in differentiating between the effects of physical disability and cognitive impairment. Factors that need to be considered in referral include the motivation of the patient to undertake an extensive assessment, appropriateness for testing including physical disability, and medication issues that may affect cognitive performance or psychiatric status.

Magnetic Resonance Imaging (Anatomic)

Introduction

The introduction of magnetic resonance imaging (MRI) into routine clinical practice in the last 25 years has served to illuminate many chronic neurological disorders. With the passage of time, powerful novel pulse sequences have been developed, which have allowed for both discrete qualitative and quantitative evaluation of brain cortex, white matter, deep nuclei, and blood vessels, all within a reasonable timeframe. The soft tissue discrimination offered by multi-sequence MRI is unrivalled by other neuroimaging modalities. The ability to accurately depict brain structures at high resolution with MRI has paved the way for accurate determination of segmental and whole brain volumes, which coupled with reproducible depiction of defined anatomical landmarks by automated feature detection at follow-up, ensures follow-up anatomical scans are positioned in the exact same plane as earlier. This allows optimal evaluation of subtle longitudinal changes in brain pathology. Apart from static anatomic imaging, a range of dynamic and functional techniques have emerged such as diffusion- and perfusion-weighted imaging (DWI and PWI) for the determination of acute regional cellular damage or cells at risk; diffusion tensor imaging (DTI), which maps white matter connectivity within the brain and frequently demonstrates interruption in brain pathways when other anatomical imaging appears normal; magnetic resonance spectroscopy (MRS), which gives regional metabolic information about cellular activity; and functional MRI (fMRI), which uses the paramagnetic properties of deoxygenated hemoglobin and volume of perfusion to isolate regional brain activity (fMRI and DTI are dealt with in more detail below).

MRI stands alone amongst competing modalities in that it is virtually devoid of side effects at the current most commonly available field strength, 1.5T. As a result, repeat acquisitions during an examination and multiple repeat longitudinal studies strength can be performed without harming the patient. Additionally, the substantial benefits at higher field strengths of 3T and 7T and beyond, which will offer significant additional improvements on both structural and functional imaging, can be exploited safely without risk to the patient and will likely shed further light on neurodegenerative disease processes.

The most common abnormality seen on structural imaging in degenerative disease is atrophy or loss of brain volume, which is manifest by decreases in gyral size and sulcal widening. In keeping with the common themes of neurodegeneration, atrophy is a combination of neuronal loss, decrease in synaptic density and cell shrinkage, and is common to most of the disorders under this rubric. Where they differ in, usually, is the location of greatest tissue loss, which often correlates with the initial and developing clinical manifestations of the disorder. A short discussion of findings in common neurodegenerative processes follows.

Normal Aging

Similar to the above discussion on neuropsychological testing, brain MRI is increasingly being used as a screening test for all forms of brain disorder. Although technical advances are rapid, the true sensitivity and specificity of MRI remains to be determined. Volumetric

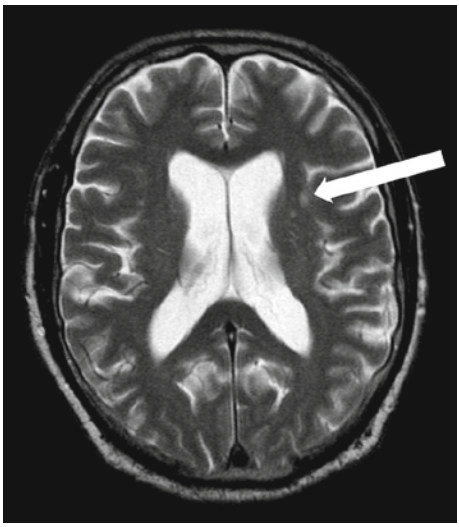

Fig. 2.2 Normal aging. Axial T2-weighted fast spin echo (FSE) sequence. Note mild generalized atrophy with occasional white matter hyperintensity (*arrow*) in this 70 year-old man who is cognitively normal and complaining of headaches

research from the 1990s has shown that once physiological growth is complete in adolescence, brain volume remains reasonably stable until the early 40s. Thereafter, there is a slow progressive decline in volume that is considered a normal part of aging. Distinguishing disease atrophy from normal shrinkage remains a constant challenge in normal clinical practice. Furthermore, the normal variation in structural integrity makes side-to-side comparisons with subtle morphological change hazardous. Finally, normal involutional age-related changes may show up in the white matter and appear to represent vascular pathology (Fig. 2.2). Given that the greatest risk factor for a neurodegenerative disease is age, and the most consistent abnormalities are atrophy and white matter disease, great care must be taken to avoid nominating the normally aged brain as diseased.

Alzheimer's Disease

The two main pathological entities that are diagnostic of AD, extracellular neuritic plaques and neurofibrillary tangles, are microscopic and beyond the resolution of MRI. However, MRI plays a very important role in suspected AD, first in excluding other causes such as vascular dementia, and second, in revealing structural abnormalities that correlate with AD and which can be serially followed.

The cardinal feature of MRI in AD is volume loss, which can be extensive and generalized in advanced disease. However, early on, preferential atrophy of the hippocampus and entorhinal cortex can be seen, which correlates with the classic amnestic presentation of typical AD. As the disease progresses, volume loss appears in parietal and superior temporal lobes as well as the cingulate gyrus. Pathologically, the white matter abnormalities associated with AD have been shown to be inhomogeneous and to selectively involve regions connected with association cortices (corpus callosum and frontal, parietal and temporal lobes), with relative sparing of white matter tracts that subserve motor (internal

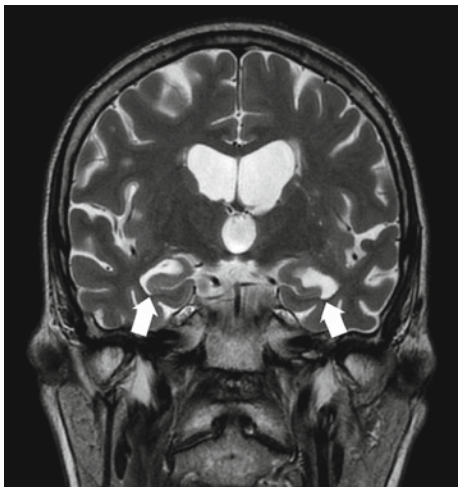

Fig. 2.3 Alzheimer's disease. Coronal T2-weighted fast spin echo (FSE) sequence. Note the pattern of generalized atrophy with preferential involvement of the medial temporal lobes (hippocampi) bilaterally (*arrows*). There is little or no white matter disease indicating reasonably a pure form of plaque and tangle disease

capsule) or visual (optic radiations) functions (Fig. 2.3). Longitudinal studies of brain volume usually reveal progressive volume loss in AD, which can be expressed as a percentage of initial brain volume.

Currently, volume loss detection in routine clinical evaluation is of limited value since patients are often significantly impaired by the time the imaging changes are appreciated. The challenge is to pick up changes in unimpaired, at-risk populations or in mild cognitive impairment. Brain morphometry has recently been facilitated by improvements in thresholding, edge detection, deformable surface detection, a-priori models, and, increasingly, hybrid models, which combine favorable inherent features of multiple models, which can be converted into a rate of atrophy in cubic centimeters per year. This will likely yield the earliest findings, thus constituting a biomarker for disease intervention. Determination of normal and pathological brain iron content is readily performed with MRI, as susceptibility-induced signal decrease in iron-containing structures can be measured directly, and tiny foci of iron deposition, a feature of amyloid angiopathy can be highlighted by gradient-echo and susceptibility-weighted imaging.

Vascular Dementia

Clinically established vascular dementia can be difficult to distinguish from moderate to severe AD. Both can involve memory and executive dysfunction to varying degrees. The presence of more cortical abnormalities such as aphasia and agnosia in AD compared to the stepwise deterioration seen in vascular dementia cannot be relied upon to readily distinguish.

MRI allows observation of the degree of brain atrophy. But it is the predominance of white matter disease, which is obvious on most T2-weighted sequences, which tends to favor vascular disease. In clinical practice, many clinical dementias are a mixture of vascular and Alzheimer pathology, which can usually be reliably discerned in good quality MRI (Fig. 2.4).

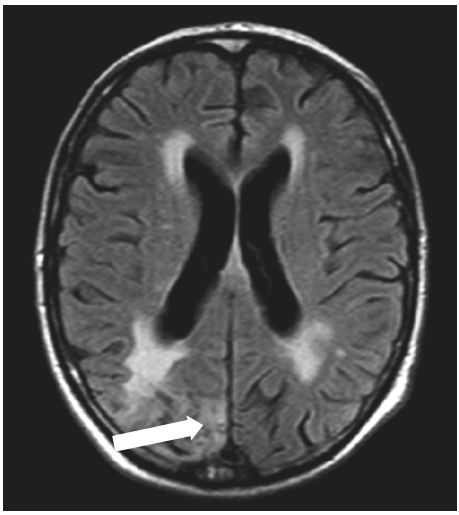

Fig. 2.4 Vascular dementia. Axial T2-weighted FLAIR (fluid attenuated inversion recovery) sequence. There is mild generalized atrophy with sulchal widening and ventricular dilation. The subcortical white matter shows a high signal around anterior and posterior horns of the lateral ventricles indicating ischemic damage. There is an established (probably embolic) infarct in the right occipital lobe (*arrow*)

Diffusion-weighted imaging allows accurate differentiation of acute vascular infarction from more longstanding brain disease. Sometimes, the stepwise progression can be reflected in a combination of acute, subacute, and established abnormalities.

Evaluation of the proximal intracranial arteries with time-of-flight MRA, coupled with high resolution of the aortic arch, carotid and vertebral arteries with contrast-enhanced MRA allows clear depicting of arterial disease in vascular dementia. Evaluation of segmental brain perfusion, which for a long time remained the domain of SPECT imaging and more recently PET, is rivaled by contrast-enhanced MR techniques and more recently challenged by methods such as arterial spin labeling. The latter rapidly labels and images arterial blood without the use of exogenous contrast agents and offers the potential for repeated evaluation of patients prior to and following pharmacological and other interventions.

Movement Disorders

Traditionally, brain imaging in Parkinson's disease and related diseases has been of limited value, the main role for MRI is to exclude vascular disease of the basal ganglia as a cause for the movement disorder. In clinical practice, a 'normal' aged MRI, in the right clinical scenario, still has a high predicative value for the diagnosis of Parkinson's disease (PD). In keeping with the overlapping pathologies in neurodegenerative diseases, atrophy of the brain is recognized as a common feature. Because the pathology in PD classically starts asymmetrically in the midline and deep grey nuclei, this atrophy is often difficult to appreciate qualitatively.

Other movement disorders that have more in common pathologically FTDs such as progressive supranuclear palsy (PSP) and CBD may have more focal atrophy allowing for better clinical correlation. In PSP, third ventricle dilation and midbrain atrophy with shortening of the anteroposterior length of the midbrain are reportedly characteristic (Fig. 2.5).

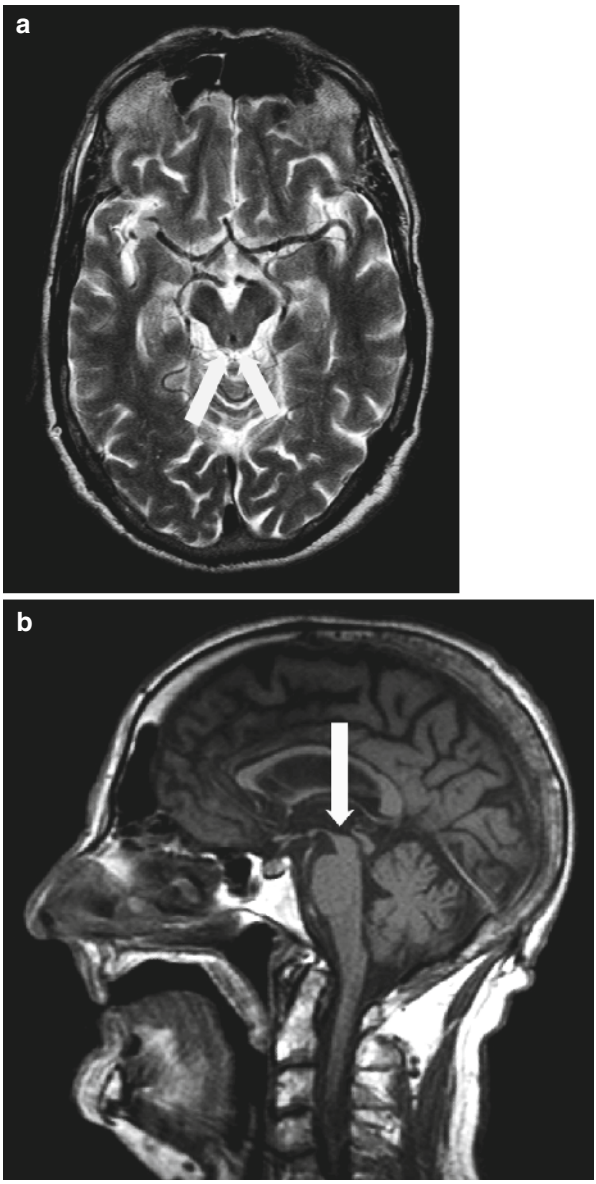

Fig. 2.5 (**a**) Progressive supranuclear palsy (PSP). Axial T2 FSE sequence. This image demonstrates the characteristic flattening and atrophy of the superior colliculii (*arrows*). (**b**) Progressive supranuclear palsy (PSP). Sagittal T1-weighted sequence. This images shows the characteristic flattening and concavity of the dorsal midbrain, the so-called humming bird sign

Frontotemporal Dementia and Amyotrophic Lateral Sclerosis

The term FTD encompasses an increasing number of complex phenotypic subtypes and an equally expanding list of distinct pathological entities. The molecular pathology is advancing so fast that brain imaging has yet to contribute significantly as a specific diagnostic modality. The most common clinical feature of these disorders tends to be varying amounts of involvement of cortical frontal and temporal regions, the amnesia of classical AD being

much less pronounced. Thus, brain imaging tends to reflect focal cortical atrophy with obvious left temporal atrophy of semantic dementia having the most predictive value (Fig. 2.6). The subtle bilateral frontal atrophy of behavioral variant (bv-FTD) is the least obvious qualitatively. MRI currently cannot reliably distinguish involvement of the motor system in ALS.

Creutzfeldt–Jakob Disease

Abnormal increased signal intensity within the caudate nuclei, putamen, and cerebral cortex bilaterally on T2- and FLAIR-weighted imaging have been well documented; however, as these changes occur late, they are not useful for diagnosis although serial evaluation of these abnormalities can be used to document progress. More recently, diffusion abnormalities within the same areas have been documented and as diffusion abnormalities usually predate the aforementioned MR findings, it is believed that abnormalities on diffusion-weighted imaging can point toward the diagnosis in the early stages (Fig. 2.7). However, DWI abnormalities are not entirely specific, and other causes such as Alzheimer's disease,

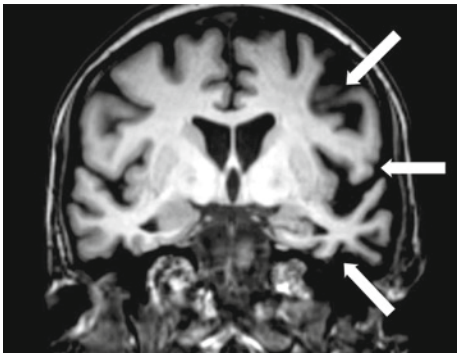

Fig. 2.6 Frontotemporal dementia (FTD). Coronal T1-weighted FSE sequence. This image shows generalized atrophy with additional focal atrophy of the left frontal and temporal regions (*arrows*)

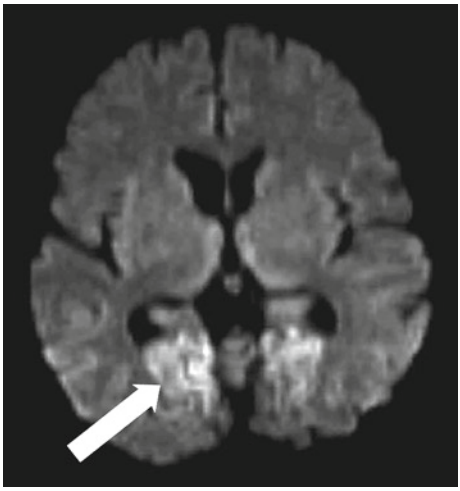

Fig. 2.7 Creutzfeldt–Jakob Disease (CJD). Diffusion-weighted imaging (DWI) B-Value = 1,000. This image shows a bright signal in the medial occipital regions (*arrow*) in a pathologically proven case of Heidenhain variant sporadic CJD

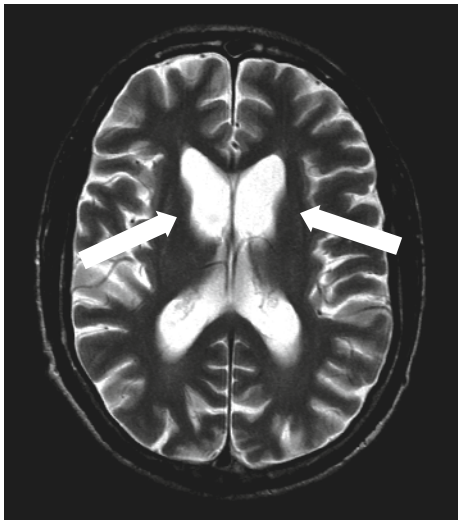

Fig. 2.8 Huntington's disease (HD). Axial FSE sequence showing caudate atrophy (*arrows*) with mild generalized atropy in remaining brain

vascular dementia, mitochondrial abnormalities (MELAS syndrome), CNS lymphoma (and occasionally, other CNS neoplasms), and viral encephalitides can mimic the changes seen in Creutzfeldt–Jakob disease (CJD). More recently, techniques have been developed to reduce bias in the selection of anatomic regions of interest and observer or operator dependency (e.g., voxel-based morphometry).

Diffusion-weighted imaging abnormalities have been observed in the temporal lobes, corpus callosum, hippocampi, and posterior centrum semi-ovale.

Huntington's Disease

Loss of volume of the caudate nucleus and putamen are a fundamental and marked feature and in many cases, point to the diagnosis (Fig. 2.8). Whole-brain volumes are also smaller in HD compared to matched controls. Abnormalities on diffusion-weighted MRI in the aforementioned areas are common along with nonspecific periventricular white matter abnormalities.

Advances in Functional MRI and Neurodegenerative Diseases

Understanding the normal functional performance of the brain requires two pathways of investigation:

- To understand the basic design of the macroscopic and microscopic circuitry of the brain.
- To discover the rules that govern the interactions among neurons and neuronal networks that give rise to overt and covert behaviors.

With neuroimaging tools such as magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and diffusion tensor imaging (DTI), one can measure the changes at the macroscopic level in brain structure and function. Structural brain MRI can measure grey and white volume and shape at the sub-millimeter level in the brain. Functional MRI measures the local hemodynamic response due to neuronal activation in a cognitive task and can map changes in activation typically at 2–3 mm spatial resolution. DTI data is based on measurement of the diffusion of water molecules in the myelin sheath and allows one to map the large-scale white matter structures in the brain.

The breakdown pattern in the neural networks can serve as candidate biomarkers for the diagnosis of neurodegenerative disorders. In a following section, the research efforts to integrate multiple imaging domains (such as fMRI and DTI data, or DTI with MRI) will be described, as it is believed that integration of multi-domain data will lead to more sensitive and specific biomarkers in discriminating between patient groups and healthy subjects. In addition, recent advances in multivariate statistical analysis methods that may help in quantifying the risk of individual subjects to developing a specific neurodegenerative disorder will be presented.

Resting Coherent Networks

The resting brain is not "at rest" – there are multiple low-frequency coherent networks that are active when the brain is not performing a goal-oriented task – for example, networks have been discovered in visual cortex, motor cortex, networks along the dorsal area of the brain (usually denoted as attentional networks), and the default mode network (DMN). It has been shown that the different low-frequency fluctuations reflect not only the structural architecture of the brain but also the functional organization of the brain. For example, it has been found that the spatial pattern of low-frequency coherent oscillations in the visual cortex overlaps the activation pattern measured using fMRI during performance of a saccadic eye movement task. This pattern of low-frequency oscillations in the visual cortex and of the saccadic eye movement matches the underlying anatomical circuitry. It has also been noted that the low-frequency fluctuations in subregions of the primary motor cortex are most strongly functionally linked to low-frequency fluctuation in regions in the contralateral hemisphere, with a similar spatial location along the contralateral primary motor cortex. Given our knowledge of the somatotopic organization of the primary motor network, these findings suggest that functional subregions of the motor network are one-on-one linked to their functional homolog in the contralateral hemisphere and organized in a somatotopic fashion.

These findings open a new approach to using neuroimaging for the investigation of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and frontotemporal dementia, by examining the possible alterations in the low-frequency coherent oscillations in the various networks that are present in the brain. A significant advantage of the low-frequency coherent oscillations of brain activity during rest is that it offers a simple way to measure brain activity in specific networks without the use of a cognitive paradigm. Without the use of a paradigm, there are no additional factors such as performance levels of individuals (both healthy subjects and patient groups), and it allows for

investigation of the connectivity among multiple networks. The resting coherent networks are measured by having the participants lie quietly in the scanner for typically 7–10 min with eyes open or closed.

One particular approach to using the low-frequency coherent fluctuations as possible biomarkers candidates for diagnosis is the focus on the DMN in Alzheimer's disease (AD). The DMN, composed of the posterior cingulate, medial temporal regions, lateral inferior parietal regions, and medial frontal cortex, is of particular interest in AD as the medial temporal regions and posterior cingulate have been shown to underpin memory function, and these two regions are the earliest ones affected in Alzheimer's disease. Thus, by investigating the magnitude of the DMN in the hippocampus and the posterior cingulate, one can obtain a marker for the integrity of these two structures. It has been shown that in patients with AD, the correlation of the activity in the posterior cingulate to the hippocampus is statistically significantly decreased compared to healthy subjects. Similar differences in the DMN have been found in subjects with mild cognitive impairment compared to healthy subjects and in healthy subjects that are carriers of the APOE e4 allele compared to non-carriers – with the APOE e4 allele being a risk factor for Alzheimer's disease. Thus, the DMN strength in the posterior cingulate and hippocampus could be a potential biomarker not only for diagnosis of Alzheimer's disease but also prediction of risk in developing Alzheimer's disease, and also for using to investigate the effectiveness of treatments. There are still significant issues to be addressed regarding the sensitivity of the low-frequency fluctuations to disease neuropathology, sensitivity compared to active cognitive paradigms, and the specificity of the changes that one sees.

Structural Connectivity in the Brain

Network connectivity also can be investigated using DTI, which provides a measure of the structural integrity of the white matter tracts connecting regions of the brain. The integration of fMRI with DTI to investigate changes across a neural network has the potential to be a very powerful tool to aid in the development of a marker for a range of neurodegenerative diseases. The combination of DTI and fiber tracking allowed for the in vivo assessment of fiber connections within the brain. This method has been shown to successfully reconstruct major fiber tracts and to be sensitive toward changes in the fiber's structural integrity. The limitations of standard DTI sequences are that the data cannot provide information on axonal connectivity, or discriminate between afferent and efferent pathways of axonal tracts.

Analogous to the connectivity studies with low-frequency fluctuations using fMRI, investigation of the structural network architecture of the brain using DTI allows one to characterize the architecture of the anatomical connectivity patterns in the human brain. This is crucial because it could increase our understanding of how functional brain states emerge from their underlying structural substrates and provide new insights into the association of brain function deficits with underlying structural disruption in brain disorders.

The framework in which the structural architecture of the brain can be examined is within a connectome, which refers to the detailed anatomical description of the network

with elements of the human brain in terms of network nodes (hubs) and bridges (structural connections between nodes). Nodes represent brain regions with coherent patterns of anatomical or functional connections. The bridges represent structural connections and may also represent the density and size of the connections between nodes. By having a description of a brain network in these terms, the effects of lesions on the network can be investigated and the characteristics of such lesions, such as location, size, type can be quantified.

Integration of Functional and Structural Connectivity

Only few studies have combined fMRI–DTI to relate the spatial distribution of brain activity to fiber tract pathways (Fig. 2.9). The microstructural alterations in white matter, as detectable by DTI, may underlie alterations in functional connectivity of brain activity associated with deficits in cognitive performance in neurodegenerative disorders such as Alzheimer's disease, and amyotrophic lateral sclerosis. It has been found in older healthy subjects that the strength of the DMN network activation was correlated to the magnitude of the fractional anisotropy values (a measure of white matter organization) in the white matter tracts connecting the regions of the DMN. Further investigation of the DMN revealed that the activation in the network reflected the integrity of the white matter tracts connecting the various regions of the DMN. The integrity of the DMN activation did not reflect a nonspecific change in brain structure but was a function of the structural integrity underpinning the DMN network.

Multivariate Analysis Techniques

Standard analysis approaches to differences in brain structure or brain activation between a patient group and healthy subjects have been utilized to detect significant structural or functional differences. However, not many statistical approaches have been developed to quantify the risk score for brain disease in an individual. Multivariate approaches provide a way to extract from thousands of voxels within an image the spatial pattern of voxels necessary to predict the presence of a neurodegenerative disorder. These techniques allow for deriving a single value representing the degree to which a disease-specific spatial pattern of alterations in brain structure or function is present in a single individual.

The application of these techniques is most advanced in the MRI domain. Potential clinical application has proved most promising in Alzheimer's disease, where, e.g., there is increased grey matter atrophy in hippocampus, lateral parietal regions, posterior cingulate in very mild Alzheimer's disease patients compared to age-matched healthy controls. One area of intense focus is the application of these techniques to subjects with mild cognitive impairment (MCI) to predict which subjects will convert to Alzheimer's disease within a 1–2 year period.

The challenge of quantifying the brain atrophy at the individual subject level is that the spatial pattern of brain atrophy in MCI is complex and highly variable, and it evolves in time as the disease progresses. Even when statistically significant differences are found

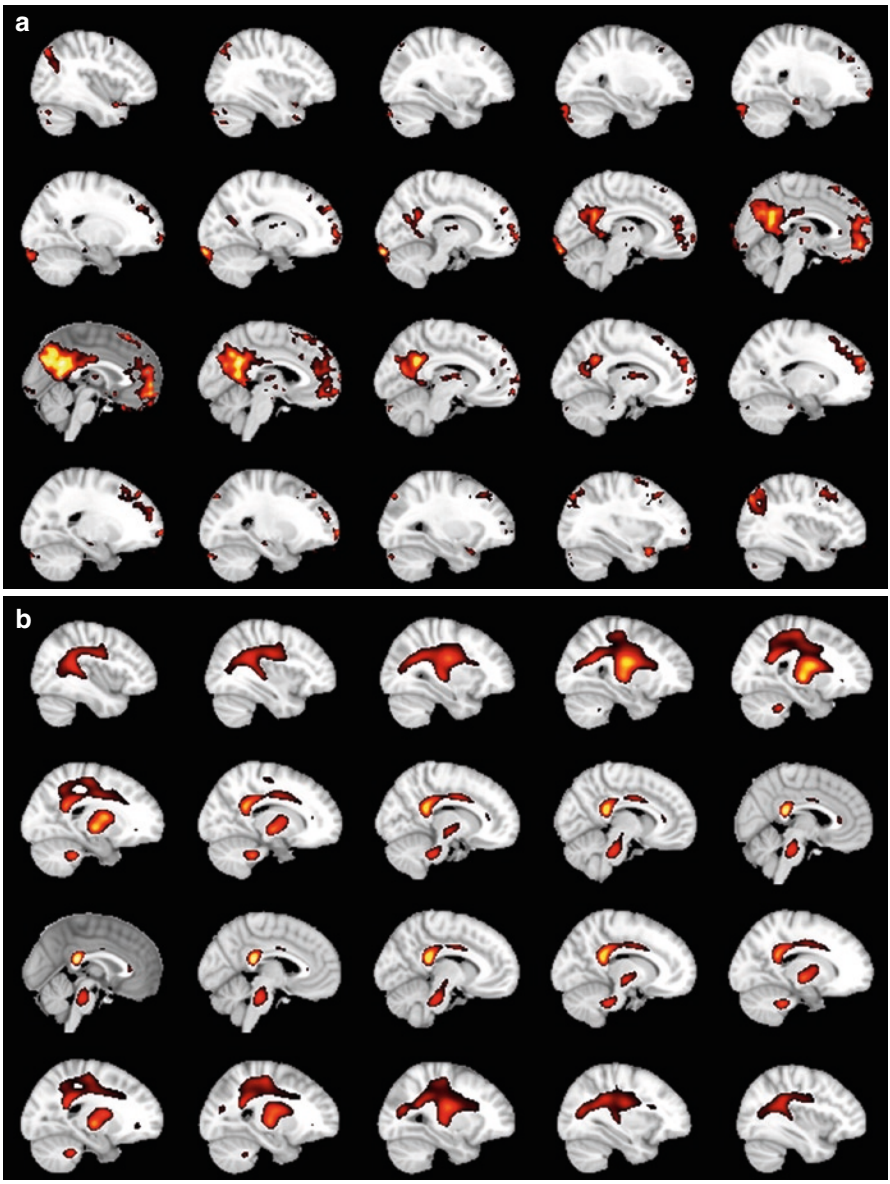

Fig. 2.9 The regions shown in color represent the brain areas where there is an association between DMN connectivity as measured with fMRI and white matter microstructure as measured with DTI without a priori selection of regions. One sees that the DMN as measured in the functional domain (**a**) is correlated to the FA values in regions that overlap the white matter tracts connecting the DMN regions (**b**) (Reprinted from Neuroimage: Teipel SJ, Bokde ALW, Meindl T, et al. White matter microstructure underlying default mode network connectivity in the human brain. Neuroimage 2010; 49(3): 2021–32. Copyright 2010, with permission from Elsevier)

between groups of subjects, classification at the individual level remains difficult as there is overlap between the groups and the overlap leads to decreased sensitivity and specificity in the prediction model. There have been various models developed for prediction of AD in MCI subjects, with most models reaching a range of 70–90% sensitivity and specificity – a range that is meaningful for a biomarker. Given the success on these methods in MCI subjects, it would be valuable to be able to apply these methods to cognitively healthy individuals that may be at risk for AD such as those with proven genetic risk factors or a strong family history.

Of interest in the development of these prediction and diagnosis models is that the measurement of longitudinal rate of change would provide a more sensitive and specific measure than a single cross-sectional measurement. The robustness of the measurement of longitudinal MRI measures is problematic as changes in the physical properties of the scanner with time, variations in the tissue contrast, noise from the scanner, and noise sources from analysis tools may limit the power of the longitudinal approach. However, the baseline measurements are in effect a measure of years of brain atrophy while the longitudinal measures are typically only a measure of the rate of change over a 12–18 month period. In the future, improvement in tools and methods may lead to an increase in the sensitivity and specificity when using longitudinal MRI data, but nonetheless, the longitudinal rate of change measure will likely prove an important biomarker for clinical studies of treatment effects.

In summary, the application of neuroimaging techniques to neurodegenerative disorders for the development of biomarkers is very promising. Alzheimer's disease and multiple sclerosis are probably two of the areas most advanced in the development of neuroimaging-based biomarkers with structural MRI generating the most mature methodology. The discovery of low-frequency fluctuations in the resting brain is probably one of the most promising and unexpected developments in neuroscience that may lead to developments of biomarkers for the diagnosis of neurodegenerative disorders. In parallel, there have been further methodological developments for measurement of the white matter tracts that underpin the network architecture of the brain and the development of mathematical techniques to quantify the risk level at the individual subject level.

Nuclear Brain Imaging in Neurodegeneration

Molecular imaging enables the visualization of cellular functions and molecular process in living organisms without perturbing them and thus is of key importance in the diagnosis and study of neurodegenerative conditions. The nuclear imaging techniques, positron emission tomography (PET) and single photon emission tomography (SPECT) form the backbone of current techniques. Computed tomography (CT) and MRI are currently limited to detecting tracers in 10^{-3}–10^{-5} mol/L concentrations, at which level they are frequently toxic to cells. But SPECT and PET imaging are far more sensitive with the latter able to detect tracers at 10^{-9}–10^{-11} mol/L, at concentrations of tracers that will not disturb normal function.

Radiopharmaceuticals

A radiopharmaceutical is the combination of a ligand and a radioisotope. The ligand will bind to the target molecule in vivo and the radioisotope will release a radioactive particle that will permit detection, quantification, and localization of the target. For example, in the common PET tracer 18-Flurodeoxyglucose, 18F-FDG, a positron-emitting tracer, F18 is linked to a glucose analogue, and the uptake of the tracer in various tissues reflects the rate of glycolysis. The positron emitted during the decay of F18 will interact with an electron and their mutual annihilation will result in the production of two 511 keV photons that can be detected.

SPECT, PET, and Combined Imaging

The choice of radioisotope will determine the imaging method. PET and SPECT will detect radioisotopes that release positrons and gamma rays, respectively. SPECT is in many ways an inferior method, as it requires placement of a lead collimator in front of the detector to aid spatial localization. This markedly reduces the sensitivity of the technique and makes quantification difficult. In addition, gamma-ray emitters tend to be large heavy metals that can be difficult to bind to small molecules without affecting their pharmaceutical properties. However, SPECT is more economical than PET; gamma-emitting pharmaceuticals tend to have long half-lives, so they can be produced off-site and the equipment is cheaper and more widely available as it can also be used for standard planar nuclear medicine studies. SPECT tracers using technetium 99m (^{99m}Tc) as the radioisotope are favored as most hospitals will have a ^{99m}Tc generator on-site and the photons produced are easy to image. PET is more sensitive and facilitates quantification, as it does not require a lead collimator – the two high-energy annihilation photons are produced at 180°, which allows reconstruction of the image along a line of response obviating the need for collimation.

Positron emitters tend to be small atoms like Carbon-11 or Flourine-18 that can be easily introduced into small molecules without distorting them. However, positron emitters are expensive to produce and have very short half-lives. Many PET radiopharmaceuticals require production of the radioisotope and radiopharmaceutical on-site, which is expensive and can require considerable local expertise.

Modern PET and SPECT cameras are combined with CT scanners. The CT images are produced to allow the cameras to compensate for attenuation, which makes tracers deep in the body seem to have a lower concentration than more superficial tracers as their activity is attenuated by the body before it can be quantified. Co-registered CT images allow accurate anatomic localization of the distribution of the radiopharmaceutical. The CT examination will result in an added radiation burden to the patient. Many PET/CT or SPECT/CT scanners will use a low-dose CT technique to minimize this. PET and SPECT images may also be fused with MRI. Dedicated PET/MRI scanners are being produced but are currently limited in distribution.

In most countries, the production of PET and SPECT radiopharmaceuticals is strictly regulated by both radiation protection and pharmaceutical legislation. Although a myriad

of different SPECT and PET tracers have been used in neurodegenerative conditions, only a few are licensed for use in the general population outside of clinical trials.

PET and SPECT in Alzheimer's and Other Dementias

There is extensive experience in using SPECT and PET tracers in the diagnosis and investigation of Alzheimer's disease. Most tracers demonstrate the neuronal loss associated with the condition. This will result in regional decreases in glucose utilization, which can be studied with 18F-FDG PET imaging (Fig. 2.10). Alternatively, the decreased regional perfusion associated with neuronal loss can be demonstrated by agents such as ^{99m}Tc-ECD or ^{99m}Tc-HMPAO SPECT imaging. Both these investigations have similar findings as outlined in Table 2.2.

It should be noted that these findings are most useful for discrimination in the early stages of the dementias. In advanced dementias, the changes become confluent and difficult to discriminate. Studies show that PET tracers typically have increased accuracy of 15–20% relative to SPECT. Analysis of the data may be done by direct visualization but many centers use a technique known as statistical parametric mapping, which will analyze the results of a given patient against a given number of age-matched controls. There are normal declines in metabolism and perfusion that occur differently in different populations and it is important to ensure that the correct database is used for analysis of a given patient's data.

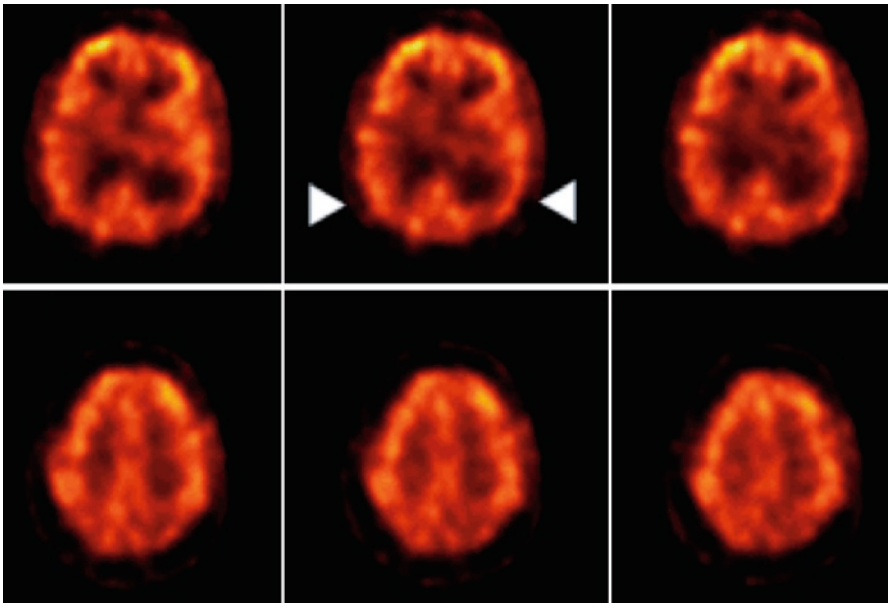

Fig. 2.10 Axial FDG-PET images demonstrate marked hypometabolism of both parietal lobes (*arrowheads*). This is a little more pronounced on the left. Findings are typical of Alzheimer's disease

Table 2.2 Regional deficits in metabolism and perfusion in neurodegenerative diseases

Etiology of dementia	Regional deficits (hypoperfusion or hypometabolism)
Alzheimer's disease	• Parietal, temporal, and posterior cingulated cortices are affected early • Sparing of primary sensorimotor and visual cortex subcortical nuclei and cerebellum • Changes start out asymmetric but become bilateral and confluent
Vascular dementia	• Changes affect cortical, subcortical areas, and cerebellum
Frontotemporal dementia	• Frontal and anterior and meso-temporal areas affected earlier and with greater severity than parietal lateral temporal cortex • Sparing of sensorimotor and visual cortex
Huntington's disease	• Caudate and lentiform nucleus affected early
Lewy body dementia	• Similar to AD but less sparing of occipital cortex

These tracers are probably best applied in the early stages of clinical disease, in patients with mild cognitive impairment. At this stage, the clinical sensitivity for AD using the "probable AD" category is 66 ± 17% relative to neuropathologically conformed diagnoses. By including "possible AD" patients, the clinical sensitivity can be increased to 90.5 ± 5.5%, but this is at the expense of specificity. The sensitivity of 18F-FDG PET is 91 ± 3%. Thus, 18F-FDG PET can lead to a substantial decrease in both false positives and negatives. An early definite diagnosis allows introduction of appropriate therapy and allows patients and families to plan future care. In the later stages of disease, where dementia is clinically apparent, the cost-benefit for using these tracers is diminished.

There are several more specific tracers under investigation for Alzheimer's disease. One, developed in the University of Pittsburgh, Pittsburgh compound B (PiB), which uses the positron emitter Carbon-11 as its radioisotope, binds specifically to amyloid plaques. These approaches will ultimately lead to greater diagnostic accuracy and may be of benefit in therapy research. Similar compounds using F-18 as the radioisotope are undergoing phase III trials and may be available for clinical use in the near future.

PET and SPECT in Parkinson's Disease and Movement Disorders

The principle pathological finding in Parkinson's disease (PD) is the degeneration of the pigmented nigral neurons, which project to the caudate nucleus and putamen; the principle neurotransmitter in this pathway is dopamine and this can be studied with the PET tracer 18F-Dopa. A number of studies have shown a mean reduction in 40% in striatal 18F-Dopa uptake between controls and patients with PD. In most of these cases, the loss is asymmetric and greater on the side contralateral to the side most clinically affected. Typically, the posterior putamen is most affected with sparing of the head of the caudate in early disease. There is also striatal 18F-Dopa reduction in other diseases with parkinsonism as a

clinical feature. In progressive supranuclear palsy, there is quite different 18F-Dopa loss with early involvement of the caudate nuclei and symmetric findings. In corticobasal degeneration, there is again symmetric loss of the uptake in the caudate and putamen. But, in this case, the findings are highly lateralized to the side of the disease. Lastly, in multiple system atrophy, the findings are intermediate between these conditions with more involvement of the caudate than is typical for PD. Patients with parkinsonism related to medication typically have normal 18F-Dopa distribution. Patients with more generalized neurodegenerative conditions such as Alzheimer's disease with parkinsonian features also typically have normal 18F-Dopa distribution.

18F-Dopa has very limited clinical availability but there is a widely available SPECT tracer Ioflupane Iodine-123 (commercially available under the name of DatSCAN), which models the presynaptic dopamine receptor (DaT) system. Other tracers, which can bind to ^{99m}Tc, may also become available. These tracers show excellent discrimination between patients with Parkinson's disease and normal controls or patients with benign essential tremor. In addition, Ioflupane is also able to discriminate between diffuse Lewy-body dementia and Alzheimer's disease. A recent AUDIT study demonstrated that SPECT with Ioflupane was an important tool in the management of movement disorders; the study described an improvement in clinical management of over one third of patients.

New Neurophysiological Techniques

Introduction

When we consider neurophysiology and neurodegenerative disease, we are generally referring to electroencephalography, which is the recording of the brain's electrical activity. There is a role for other neurophysiological techniques such as electromyography, nerve conduction studies, and evoked potentials in degenerative diseases such as ALS/MND, but the major contribution to development in neurophysiological diagnostics for neurodegenerative disease has been in increasing the yield from the electroencephalogram (EEG).

Electroencephalogram

Quantitative analysis of the EEG can play a significant role by providing valuable information in understanding the pathophysiology and in assisting the diagnosis of neurodegenerative diseases.

The ease of EEG recording of the electrical activity of the brain using an array of scalp electrodes provides researchers and clinicians with objective data for quantification and analysis. Analysis of EEG has been employed in a number of clinical neurodegenerative studies to understand the electrophysiological and functional changes associated with Parkinson's disease, Alzheimer's disease, ALS, Huntington's disease, and normal aging.

EEG is recorded using a dense grid of electrodes positioned at standardized locations on the scalp. Data from up to 250 electrodes may be recorded, along with a series of references electrodes. Reference points on the head include the tip of the nose, nasion, and inion. With this standard system of electrode placement, activity at specific brain locations can be recorded with specific electrodes and thus can easily be compared across individuals and neurodegenerative diseases.

Recording of EEG data generates a multi-channel time series; a sequence of data points for each electrode, measured at successive times, spaced at uniform time intervals. Time series analysis can be subsequently applied to extract meaningful statistics and other characteristics from the recorded EEG data.

While the generation of EEG is not fully understood, the electrical activity recorded by scalp electrodes is considered to be generated by the action potentials of cortical neurons, mostly typically by excitatory postsynaptic potentials. Therefore, analysis of EEG may offer insight into cortical processing of information.

The recorded neural activity is of the order of a few microvolts in amplitude and can easily be contaminated by noise and artefacts. Artefacts include interference from power lines (50 Hz) and other external electrical sources but also as a result of the patient's own physical activity; blinking generating electrooculogram (EOG), yawning, or moving their head during recording producing electromyogram (EMG) artefact. These artefacts can be recognized by a trained expert through visual inspection of the EEG waveforms and may be partially removed by specifically designed mathematical filters. This artefact removal step is necessary prior to clinical time series analysis of EEG.

Recent years have seen increased interest in developing reliable markers of age-related and disease-induced memory impairment. The National Institute on Aging has encouraged biomarker development, specifically where biomarkers are inexpensive to acquire, simple to use, and easy to implement. Recent improvements in acquisition technology and signal processing mean that EEG now satisfies these criteria. Age-related memory decline is not often necessarily associated with clear structural lesions and the observation that many age-related processes result in physiological dysfunction rather than neuronal loss suggests that techniques that can assess neuronal physiological dysfunction independent of structure, such as EEG, may be best suited to detecting changes or dysfunction associated with age-related memory decline. Given the observed overlap at the boundaries of normal aging and MCI, EEG may represent a non-invasive tool that could yield low-cost biomarkers for age-related and disease-induced neurodegeneration that may be capable of identifying subtle functional changes associated with normal aging or those that precede the structural or metabolic deficits.

Analysis Methods

Methods for time series analysis of EEG may be divided into two classes: time domain (amplitude variation with time) methods and frequency domain (power variation with frequency) methods.

The most fundamental clinical time domain analysis method of EEG is by visual inspection of the variation of EEG amplitude with time. Analysis through visual inspection is considered to be highly subjective and often of limited clinical value. Of greater clinical

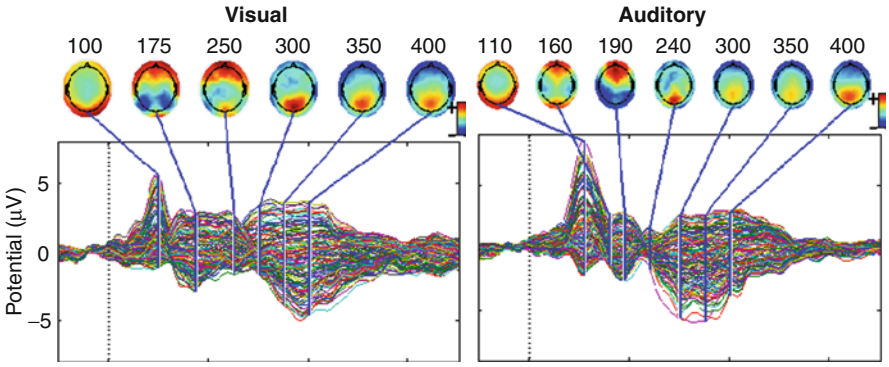

Fig. 2.11 EEG time domain responses to visual and auditory stimulation. Data from each 128 EEG electrodes is displayed superimposed. Above each time domain response are maps of the associated activity in specific locations in the brain at different times (milliseconds) "post-stimuli"

benefit is the quantifiable comparison of EEG activity at specific electrode locations with other locations or between patients and controls. Mathematical methods such as autocorrelation and cross-correlation may be applied to time series data from different electrodes to quantify the similarity of waveforms at different scalp locations.

Inspection of the time domain may obscure information possibly present in the frequency domain. EEG can easily be mathematically transformed from the time domain to the frequency domain (Fig. 2.11). The resulting power spectrum allows spectral analysis methods to be applied to EEG, describing it in terms of patterns of rhythmic activity and transients. The rhythmic activity is divided into nonoverlapping bands by frequency: Delta band (0.5–4 Hz), Theta band (4–8 Hz), Alpha band (8–12 Hz), Beta band (14–20 Hz), and Gamma bands (>30 Hz). Frequency analysis allows comparison of the power of EEG in each frequency band, between electrode sites, and between patient groups using methods such as coherence and cross-coherence.

It has been shown that modifications occur in the characteristics of resting EEG-associated normal physiological aging. These are observed as gradual changes in EEG spectral power, mainly represented by a pronounced amplitude decrease of dominant EEG oscillations, namely, in the alpha band. Studies based on large populations of healthy subjects has also confirmed an age-dependent power decrement of EEG frequency bands, specifically low-frequency alpha rhythms (8–10.5 Hz) in parietal, occipital, and temporal regions.

Mathematically, EEG is typically considered a linear stationary time series, where parameters such as the mean and variance also do not change over time. In practice, EEG is regarded as a stationary process only over a relatively short timescale of 3–4 s. This permits traditional linear time series analysis methods to be applied to EEG for clinical diagnosis. While these are often not computationally difficult to implement, they only give an estimate of the neuronal activity. This is because EEG signals are actually nonlinear and also non-stationary, often appearing to be random or aperiodic. This is especially the case in some pathological conditions, where spikes and bursts are often observed in EEG data. Methods based on nonlinear time series analysis and mutual information may be employed for more detailed quantitative investigation in such conditions.

Developments in signal processing mathematics to analyze nonlinear, nonstationary systems are set to make an impact in our understanding of neurodegeneration. Such analysis will allow pathological conditions, which include the transient irregular events, to be quantified with high resolution. Current linear time series analysis methods of correlation and coherence, together with nonlinear methods of mutual information allow quantification of the degree of interactions between different regions of the brain. However, they fail to provide information on the causality of such interactions or the direction of the information transferred. Therefore, new mathematical analysis methods will be important to probe further into the causes and progression of neurodegenerative diseases.

EEG has high temporal resolution, however low spatial resolution. As discussed earlier, other neuroimaging methods such as functional MRI provide higher spatial resolution. The combination of EEG simultaneously acquired with functional MRI offers both high temporal and spatial resolution. Multimodal neuroimaging (EEG, fMRI, PET) is set to further advance basic research and clinical studies in the understanding of neurodegenerative conditions.

Conclusion

Neuropsychological, radiological, and neurophysiological techniques have been applied successfully to aid in the clinical diagnosis of neurodegenerative disorders for the past two decades. In reviewing the rapid and almost exponential development of what were essentially one-dimensional and mostly static tools in the early 1980s, to what have become a rich, multidimensional, mixture of anatomic, dynamic, and functional techniques today, one is struck not by the level that has been attained but by the potential for true biomarker realization. Biomarkers have been traditionally considered characteristic biological properties that can be detected and measured in parts of the body like the blood or tissue but the techniques reviewed in this chapter can claim to have many of the characteristics necessary for the diagnostic and prognostic accuracy that we require of a biomarker. What this review also clearly shows is that rather than emphasizing what separates neurodegeneration, the new techniques are tending to reflect the new cohesion that underpins the characteristic properties of the degenerative process albeit caused by separable pathologies.

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Alzheimer's Disease

3

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Abstract Alzheimer's disease (AD) is the most common form of acquired dementia. The biggest risk factor for the development of AD is age, and with increasing longevity a feature of modern healthcare, the prevalence of dementia and most particularly AD is set to double over the next 20 years. The disease is characterized most commonly by memory, language, and executive dysfunction although other presentations such as visuospatial dysfunction, agnosia, and behavioral disturbance are common in younger onset and familial forms. The pathology is a unifying feature and much progress has been made in understanding the pathogenesis such that therapeutic intervention to truly modify the disease is only a matter of time.

Keywords Alzheimer's disease • Mild cognitive impairment • Amyloid plaques • Neurofibrillary tangles • Acetylcholinesterase inhibitors • NMDA receptor antagonists

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the brain characterized by an insidious onset of memory impairment, progressive cognitive deterioration, emergence of neuropsychiatric symptoms, and functional decline. Pathologically, it is characterized by the accumulation of amyloid plaques and intraneuronal neurofibrillary tangles, which are associated with neuronal dysfunction and eventual cell death. It is the most common form of dementia accounting for between 50% and 60% of all cases. The global prevalence of dementia is increasing and it has been projected that the number of people affected will double every 20 years to an estimated 81.1 million by 2040. AD is therefore the most common neurodegenerative disorder affecting between 20 and 30 million individuals worldwide. It is primarily an age-related disorder. The prevalence of dementia is low (approximately 1%) in individuals aged 60–64 but increases exponentially with age so that in individuals aged 85 years or over, the prevalence in the Western world is between 24%

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and 33%. AD has a complex multifactorial etiology and apart from age, genetic and environmental factors play important roles in the onset and progression of disease.

Risk Factors

Genetic Factors

From a genetic point of view, Alzheimer's disease is a heterogeneous disorder with both familial and sporadic forms. The vast majority of Alzheimer's disease is sporadic and of late onset (≥65 years), while a small proportion of all cases (<2%) may inherit the disease in autosomal dominant fashion. These variants are generally of early onset (<65 years). Autosomal dominant forms are mostly related to mutations in one of three genes: amyloid precursor protein gene (APP) on chromosome 21, presenilin 1 gene (PS1) on chromosome 14, and presenilin 2 gene (PS2) on chromosome 1 (Table 3.1). PS1 accounts for the majority of mutations while APP and PS2 mutations occur less frequently. All of these genes impact upon the production of the beta amyloid protein (Aß), which is the principal component of senile plaques hypothesized to be central to the evolution of Alzheimer's pathology. The vast majority of AD patients, however, have sporadic late-onset disease, which has a complex etiology attributed to interactions between environmental risk factors and individual genetic susceptibilities. Twin studies have estimated the heritability of late-onset sporadic AD to be approximately 76%.

The most well-established genetic risk factor for late-onset AD is the apolipoprotein E gene (APOE). Three APOE alleles have been identified: ε2, ε3, and ε4. The APOE ε4 allele has been linked to the development of AD, whilst epidemiologic as well as pathologic studies have suggested a possible protective effect for the ε2 allele. There is an apparent gene-dosing effect according to the actual genotype. One meta-analysis reported the odds of developing AD in heterozygous carriers of the APOE ε4 allele as threefold, while the odds for homozygous carriers compared to ε3/ε3 was over 11-fold.

Table 3.1 Established Alzheimer's genes and their functional relevance

Gene (protein)	Chromosome	Inheritance	Role in AD pathogenesis
APP (amyloid precursor protein)	21	Autosomal dominant	Mutations in the APP gene promote cleavage at β or γ sites leading to overproduction of Aβ
PSEN1 (presenilin 1)	14	Autosomal dominant	Mutations in the PS1 gene promote cleavage at the γ site leading to overproduction of Aβ
PSEN2 (presenilin 2)	1	Autosomal dominant	Mutations in the PS2 gene promote cleavage at the γ site leading to overproduction of Aβ
APOE (apolipoprotein E)	19	Modifies age of onset	Promotes the deposition of Aβ?

The APOE e4 allele operates mainly by decreasing the age of onset and is therefore a marker of susceptibility rather than a determinative gene. The mechanism whereby APOE ε4 influences the development of AD is complex and may be modified by other genes and environmental factors. APOE acts as a cholesterol transporter in the brain, which mediates neuronal protection and repair and is believed to participate in early Aß deposition. The APOE ε4 allele has been associated with increased severity of illness including faster cognitive decline, increased risk of conversion from mild cognitive impairment to AD, more neuropsychiatric symptoms, decreased survival time, and increased amyloid load at autopsy. The use of APOE genotype as a diagnostic tool has been examined in several studies but low sensitivity and specificity limit its usefulness and it is not currently recommended for diagnostic use. Table 3.1 summarizes established Alzheimer's genes and their functional relevance.

Although the APOE ε4 allele has been calculated to account for most of the genetic risk in late-onset Alzheimer's disease, a number of other candidate genes have been identified, which may also confer increased risk. A large meta-analysis from the AlzGene database identified an additional 13 potential susceptibility genes that are associated with relevant biological pathways in AD. More recently, genome-wide association studies have identified single nucleotide polymorphisms at loci (CLU, PICALM, and CR1) not previously associated with Alzheimer's disease. These genetic variants may be involved in reduced clearance of Aß. It is anticipated that studies using larger sample sizes will facilitate increased detection of additional genetic mutations of modest effect but which, in concert with other genetic and environmental factors, may precipitate clinical disease in vulnerable individuals.

Lifestyle and Vascular Risk Factors

Although several AD risk factors are genetic in nature and largely beyond our control, others are determined by environmental or lifestyle influences and may be amenable to modification. Recent years have seen an expansion in the number of epidemiological studies in AD and several risk factors that were traditionally considered as "vascular" have been associated with increased risk of AD (Table 3.2). Longitudinal studies such as the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study have found midlife hypertension, hypercholesterolemia, and obesity to be associated with increased risk of

Table 3.2 Potentially modifiable risk factors found to be associated with Alzheimer's disease in population studies

Risk factors for Alzheimer's disease	Protective factors for Alzheimer's disease
Hypertension/hypotension	Physical activity
Obesity	Cognitive and social stimulation
Diabetes mellitus	Diet (fish consumption > once/week)
Hypercholesterolemia	Alcohol (moderate wine consumption)
Hyperhomocysteinemia	Higher educational status (>15 year vs. <12 year)
Stroke	Purpose in life and conscientiousness
Smoking	
Depression, distress, and loneliness	

dementia and AD in later life. Clustering of risk factors was observed to increase the risk in an additive fashion. A dementia risk score using data gathered during the CAIDE study predicted dementia with a sensitivity of 0·77, specificity of 0·63, and negative predictive value of 0.98 over 20 years of follow up. This score included variables such as age (≥47 years), low education (<10 years), hypertension, hypercholesterolemia, and obesity. There is now a great deal of interest in developing approaches to help reduce the risk of AD in later life through identifying individuals who might benefit from intensive lifestyle consultations and pharmacological interventions in earlier life. It is also noteworthy that not all studies have replicated these findings and a recent systematic review concluded that the evidence for single clinically defined vascular risk factors was inconsistent at best while the strength of the association was increased by identifying interactions between risk factors such as hypertension *and* diabetes. In addition, the relationship between cognition and blood pressure is complex and diastolic hypotension has also been reported to increase risk. Although initial case control studies reported a protective effect for smoking, longitudinal studies have now established that smoking is associated with increased risk of AD. Longitudinal studies also show that stroke increases the subsequent risk of AD and hyperhomocysteinemia has similarly been reported to increase risk.

Factors that have been reported to be protective from population studies include regular fish consumption, moderate wine intake, and higher educational status. There is also now a significant amount of epidemiological data, which suggests that individuals who are more socially and physically active and engage in more cognitively stimulating activities are at decreased risk of developing dementia and AD. A number of psychological factors have also been found to be important. Depressive symptoms frequently precede the onset of cognitive decline by a short interval but depression occurring many years (>25 years) in advance of AD has been reported to be a risk factor. Psychological distress and loneliness have been reported to increase risk and investigators have postulated that stress effects may be mediated by the toxic impact of glucocorticoids and neuroendocrine dysregulation upon the hippocampus and limbic structures. Having a greater sense of purpose in life and conscientiousness appear to be protective and have both been independently associated with reduced risk of AD. Further research is needed to better define the nature of these associations and explore possible mechanisms through which preventive or therapeutic strategies might be explored. There are already many good reasons why maintaining good psychological health and promoting a physically, cognitively, and socially active lifestyle may be advisable and beneficial for patients.

Other Risk Factors

Data from epidemiological studies reported an association between nonsteroidal anti-inflammatory (NSAID) use and decreased risk of AD while interventional studies in this area have been negative to date. Lipid-lowering medications have similarly been reported to be associated with decreased risk while interventional studies of statins have been largely negative to date. Hormone replacement therapy (HRT) was associated with decreased risk of AD while an interventional study reported an increased risk of dementia, again highlighting the caution with which observational findings must be interpreted. Severe head injury

and exposure to toxins such as defoliants and fumigants have been associated with increased risk. Static risk factors include a family history of trisomy 21. Female gender has also been associated with increased prevalence AD. There are many possible reasons for this variable observation although a number of investigators have concluded that it is due to the longer life expectancy in females rather than gender-specific risk factors for the disease.

Pathogenesis

The exact cellular mechanisms leading to neuronal cell death in AD remain uncertain but multiple etiological and pathogenetic hypotheses have been put forward. Macroscopically, the brain in established AD shows a variable degree of cortical atrophy with widening of cerebral sulci and compensatory ventricular enlargement. Microscopically, the disease is characterized by amyloid plaques and neurofibrillary tangles (Fig. 3.1). The current criteria for a pathologic diagnosis of AD require the presence of both amyloid plaques and neurofibrillary tangles in excess of that anticipated for age-matched healthy controls. Amyloid plaques consist of a central core of amyloid protein surrounded by astrocytes, microglia, and dystrophic neurites. Neurofibrillary tangles contain paired helical filaments of abnormally

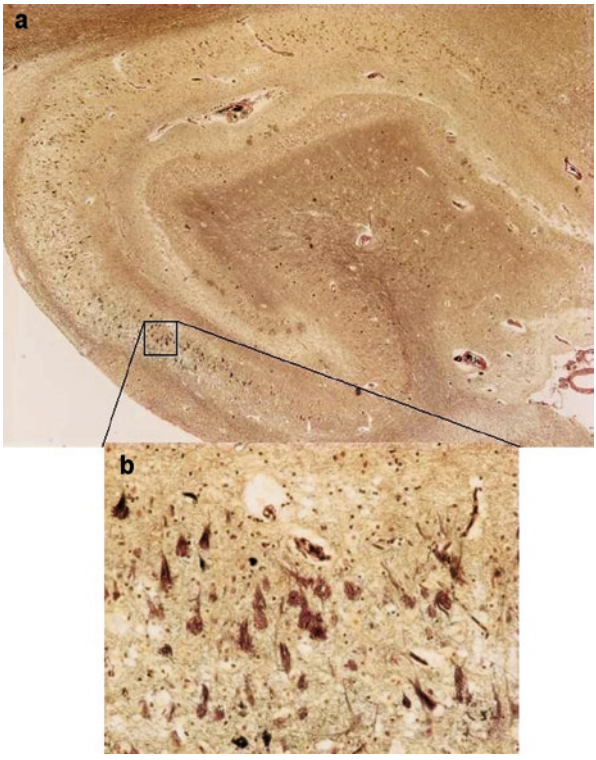

Fig. 3.1 Low power (**a**) and high power (**b**) views of hippocampus with neuritic amyloid plaques (*P*), which consist of a central core of amyloid protein surrounded by astrocytes, microglia, and dystrophic neurites and neurofibrillary tangles (*T*), which contain paired helical filaments of abnormally phosphorylated tau protein. The current criteria for the histopathological diagnosis of Alzheimer's disease require the presence of both entities

phosphorylated tau protein that occupy the cell body and extend into the dendrites. Neuronal loss or atrophy in the nucleus basalis, locus ceruleus, and raphe nuclei of the brainstem leads to deficits in cholinergic, noradrenergic, and serotonergic transmitters, respectively. The deficit in cholinergic neurotransmission and the observation that this correlated strongly with the degree of cognitive impairment led to the "cholinergic hypothesis" of AD and the subsequent development of cholinesterase inhibitors to redress this deficit.

Amyloid Hypothesis

The amyloid hypothesis remains the best defined and most studied conceptual framework for AD (Fig. 3.2). Over time, this hypothesis has undergone alterations primarily due to the fact that increased beta amyloid protein (Aβ) and plaque formation are no longer considered to be sole triggering factors for deleterious events leading to AD. The exact cellular mechanisms leading to neuronal cell death in AD remain uncertain. The amyloid cascade hypothesis holds that an imbalance between Aβ production and clearance plays a critical role in progression of AD. Aβ is derived from the much larger transmembrane protein, amyloid precursor protein (APP), by the action of two proteases referred to as beta (β) and gamma (γ) secretase. The initial cleavage of APP is mediated by β secretase and then, depending on the exact point of cleavage by γ secretase, three principle forms of Aβ com-

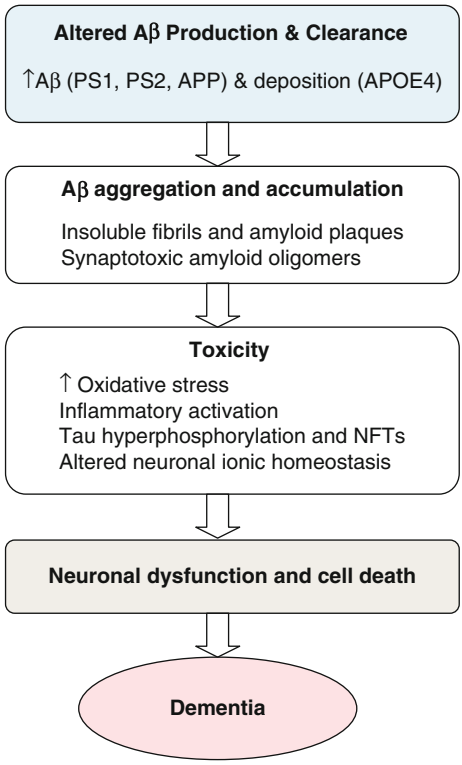

Fig. 3.2 Amyloid cascade hypothesis

prising 38, 40, or 42 amino acid residues, respectively are produced. Most mutations in the APP or presenilin genes alter APP processing resulting in increased levels of Aβ. At a certain critical concentration, Aβ monomers associate to form neurotoxic oligomers, which then further associate into insoluble fibrils and are deposited as amyloid plaques. The relative amount of Aβ 42 formed is important as this longer form of Aβis more prone to aggregate and form oligomers. Aβ oligomers could directly inhibit hippocampal long-term potentiation and impair synaptic function in addition to the inflammatory and oxidative stress caused by aggregated and deposited Aβ. Much is yet to be learned about the formation and toxicity of these soluble forms of Aβ and how they may trigger deleterious changes. The central significance of Aβ in the pathogenesis of AD has recently been called into question given negative outcomes from trials of therapeutic agents targeting this pathway. A more current view of the amyloid cascade hypothesis is that other events as well as Aβ are important in triggering degenerative processes. The concept of Aβ as only one of the factors that causes AD, explains it's less than perfect correlation with disease severity and it seems increasingly likely that Aβ, although necessary, is not by itself, sufficient for AD to occur.

Other Proposed Mechanisms

Although amyloid has received much attention with regard to halting the progression of AD, it is not the only target for disease-modifying therapies. Neurofibrillary tangles, which consist of aggregations of hyperphosphorylated tau protein, are another pathologic hallmark of AD. Tau binds to and stabilizes microtubules that are elongated polymers intrinsic to axonal structure and function. When tau is hyperphosphorylated, it aggregates into tangles with resulting destabilization of microtubules and compromised neuronal function. It is unclear whether neurofibrillary tangles are a cause or consequence of AD but their formation may be critical to AD-related cell death. Inflammatory mechanisms have long been known to play an important role in the evolution of AD pathology and many studies have shown a broad variety of inflammatory mediators, including acute phase proteins, cytokines, and chemokines within the vicinity of AD plaques. Neuroinflammation is still considered to be a downstream consequence in the amyloid hypothesis whereby Aβ within the CNS brings about activation of microglia, initiating a proinflammatory cascade that results in the release of potentially neurotoxic substances, including cytokines, chemokines, reactive oxygen and nitrogen species, and various proteolytic enzymes, leading to neurodegeneration. It has also been suggested that activation of microglia may lead to phosphorylation of tau and formation of neurofibrillary tangles. However, the exact role of inflammation in the pathology of AD and its mechanisms in terms of the cells involved, which include microglia, astrocytes, and T lymphocytes are still debated.

The frequent co-occurrence of cerebrovascular disease with AD and the fact that fewer neuropathologic lesions of AD appear to result in dementia in the presence of comorbid cerebrovascular disease has been well documented (as per the famous Nun study by Snowden et al. 2002). In fact, it is now recognized that mixed pathology is the rule rather than the exception and that cerebrovascular disease is clinically under-recognized and under-reported. The vascular hypothesis of AD goes further and proposes that cerebral

hypoperfusion and microvascular pathology may be the primary etiological factor in AD. It proposes that AD develops when two biological events converge; advancing age and the presence of vascular risk factors to create a critically attained threshold of cerebral hypoperfusion (CATCH). This leads to dysregulation of endothelial nitric oxide (NO) production, capillary degeneration, and mitochondrial oxidative stress. The resulting crisis leads to cellular and subcellular pathology involving protein synthesis, development of plaques, inflammatory response, and synaptic damage leading to the manifestations of AD.

Clinical Features

The typical clinical presentation of Alzheimer's disease is that of insidious progressive impairment of episodic memory representing early involvement of medial temporal lobe structures with the emergence of additional deficits such as aphasia, apraxia, agnosia, and executive deficits as the disease progresses. Findings from longitudinal studies indicate that neuropsychological deficits in multiple cognitive domains are evident several years in advance of a diagnosis of Alzheimer's disease. A recent meta-analysis reported that the largest deficits in preclinical Alzheimer's disease exist in the domains of perceptual speed, executive functioning, and episodic memory with smaller deficits in the domains of verbal ability, visuospatial skills, and attention. This is characterized clinically by initial forgetfulness for daily events with progressive involvement of language skills, decision making, judgment, orientation, recognition, and motor skills. Neuropsychiatric symptoms are frequently observed and occur in 60–98% of patients with dementia. They are a significant source of distress for patients and families and a major determinant of outcomes such as length of hospital stay and nursing home placement. They ordinarily increase with increasing disease severity but are observed early in the disease process and have been documented in 30–75% of patients with mild cognitive impairment. Apathy, anxiety, depression, and agitation occur most frequently. Delusions are also common and include themes of theft, intruders, imposters, or other ideas of persecution, reference, or infidelity. Visual and auditory hallucinations are the most common perceptual abnormalities although somatic, olfactory, and tactile hallucinations have also been reported. Functional decline starts with the impairment of higher order (instrumental) functions, such as the management of the household affairs or finances before more gross functions relating to basic self-care are affected. Atypical presentations of Alzheimer's disease do exist whereby visuospatial or language skills are more prominently impaired early in the course of the disease. These presentations are, however, relatively rare and the typical clinical course is one of insidious episodic memory decline with progressive involvement of other cognitive skills as outlined above.

Mild Cognitive Impairment

Neurodegeneration is estimated to start 20–30 years before clinical onset. During this preclinical phase, the burden of plaque and tangle pathology gradually increases until the threshold for clinical expression is reached. Mild cognitive impairment is a clinical

classification of patients who manifest cognitive deficits in excess of that expected for normal aging but who do not have significant functional impairment.

The initial diagnostic criteria specified the presence of subjective and objective deficits in memory, with the purpose of detecting patients with the earliest clinical signs of Alzheimer's pathology for recruitment to clinical trials. Patients in these studies were observed to convert to Alzheimer's disease at a rate of approximately 10–15% annually. The diagnostic criteria have since been broadened to include patients with deficits in domains other than memory, to reflect the heterogeneity of both progressive and nonprogressive pathologies represented within this classification. Patients with amnestic deficits in addition to deficits in other domains have the greatest risk of progression to Alzheimer's disease. Significant variation in rates of conversion to Alzheimer's disease has been observed depending on the diagnostic criteria used and populations investigated. A recent review of longer-term follow-up studies (5 years or more) indicated that the annual conversion rate of 10–15% only held true in samples monitored over a short observation period and that the conversion rate was highest shortly after presentation with a marked decline in subsequent years. The authors reported an average cumulative conversion rate of 31.4% over a mean observation period of 6 years in a sample, which included patients derived from both clinic and community populations.

Diagnosis

The diagnosis of Alzheimer's disease is based on a two-step process in which there is initial identification of a dementia syndrome and then the application of criteria based on the clinical features of the AD phenotype. It is important that disorders, which may mimic a dementia syndrome such as delirium or depression, are first excluded. A detailed history of the clinical features and longitudinal course as outlined above should be elicited. This is best obtained from a reliable informant, given the patient's judgment and insight is frequently impaired. The symptom profile will help distinguish Alzheimer's disease from other dementia syndromes such as vascular, Lewy body, or frontotemporal dementia. A general neurological and physical examination should be performed to both exclude comorbid medical conditions, which may have an adverse effect on cognitive function and detect other neurological disorders. The neurological examination is ordinarily unremarkable in early Alzheimer's disease but focal neurological or atypical features may be an indicator of pathologies such as normal pressure hydrocephalus, neoplasm, Parkinson's plus syndromes, or motor neuron disease, and should prompt appropriate referral. Motor or sensory abnormalities or disturbance of gait and seizures are uncommon until the later stages of the disease.

A mental state examination should detect the presence of mood or anxiety symptoms, which can mimic or complicate cognitive decline. This also provides an opportunity to exclude psychotic symptoms such as delusions or perceptual abnormalities. Neuropsychiatric symptoms must be enquired for as they may not be disclosed by patients or caregivers until they become intolerable or precipitate a crisis.

A number of instruments have been designed to quantify the frequency and severity of neuropsychiatric symptoms in patients with Alzheimer's disease such as the Neuropsychiatric Inventory (NPI) and Behavioral pathology in Alzheimer's disease

(BEHAVE-AD) rating scale. Function should equally be assessed through the use of structured questionnaires of basic activities of daily living (ADL) such as feeding and toileting and instrumental activities of daily living (IADL) such as shopping, cooking, managing finances, and medication. More complex instrumental functions are typically impaired in the earlier stages. The extent of cognitive testing will be determined by the clinical context and presentation as outlined below.

Diagnostic Criteria

The clinical criteria, which have been most often used to diagnose Alzheimer's disease, are those developed by the National Institute of Neurologic and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), which describe criteria for definite (clinical diagnosis with histologic confirmation), probable (typical clinical syndrome without histologic confirmation), and possible (atypical clinical features or comorbid pathology but no other identifiable cause of dementia, no histologic confirmation) Alzheimer's disease (Table 3.3).

Table 3.3 Summary of NINCDS-ADRDA criteria and proposed revised research criteria for the diagnosis of Alzheimer's disease

NINCDS-ADRDA diagnostic criteria	Revised research criteria
Probable Alzheimer's disease • The presence of a dementia syndrome established by clinical and neuropsychological examination • Deficits in two or more areas of cognition • Progressive worsening of memory and other cognitive functions • No disturbance of consciousness • Onset between the ages of 40 and 90 years • Absence of other disorders that could account for the progressive deficits in memory and cognition Possible Alzheimer's disease • This diagnosis may be made when there are variations in the presentation or clinical course of the dementia or when there is a second disorder sufficient to produce dementia which is not considered to be *the* cause of the dementia.	Probable Alzheimer's disease • The presence of core diagnostic criteria plus one or more supportive features B, C, D, or E *A. Core diagnostic criteria*: – Gradual, progressive change in memory reported by the patient or informant over >6 months – Objective evidence of impaired episodic memory on testing – The episodic memory impairment can be isolated or associated with other cognitive changes as the disease advances. *Supportive features*: B. Presence of medial temporal lobe atrophy C. Abnormal CSF biomarker D. Specific pattern on functional neuroimaging (PET) E. Proven autosomal dominant AD mutation within the immediate family
Definite Alzheimer's disease • Meets criteria for probable Alzheimer's disease and histopathological evidence has been obtained	Definite Alzheimer's disease • Both clinical and histopathological evidence or clinical and genetic evidence have been obtained

A dementia syndrome is ordinarily diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV), which specifies the presence of significant impairment in social or occupational functioning, which represents a decline from previous functioning. The DSM-IV and NINCDS-ADRDA criteria have been reported to have diagnostic accuracy between 65% and 96% when validated against neuropathological findings. However, specificity against other dementias has been reported to range from 23% to 88%. Recent advances in the diagnosis of Alzheimer's disease with the evolution of novel neuroimaging and neurochemical biomarkers has led to a proposal for revised research criteria incorporating novel biomarkers to improve diagnostic specificity (Table 3.3). These biomarkers include atrophy of medial temporal lobe structures determined through qualitative or quantitative MRI ratings, abnormal concentrations of amyloid beta 42 and total/phospho-tau in cerebrospinal fluid, hypometabolism (typically temporoparietal in AD) on positron emission tomography (PET) and determination of amyloid load using amyloid binding PET ligands such as Pittsburgh compound B (PIB).

Amyloid beta 42 is reduced in the CSF of AD patients (possibly as a result of deposition of the protein in senile plaques) and tau is increased (possibly a reflection of the release of tau in CSF with neuronal loss). The determination of optimal thresholds for detecting incipient AD according to CSF concentrations of amyloid beta 42 and total tau/phospho-tau continues to be refined with some variability between research centers; however, recent data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), suggests that specific cut-offs can be used to reliably predict which MCI individuals are most likely to progress to Alzheimer's disease dementia. The revised research criteria also differ from preexisting clinical criteria in that they no longer require the presence of significant functional decline to diagnose Alzheimer's disease given the increasing emphasis on identifying patients in the early clinical or preclinical stages of the disease for recruitment to clinical trials.

Investigations

Cognitive Testing

The extent and the type of cognitive testing to be undertaken will be determined by the clinical context and presentation. The Mini Mental State Examination (MMSE) is one of the best known and simplest bedside cognitive tests to administer. It takes 5–10 minutes to complete and is a useful measure of global cognitive function. A total score of 23 or less out of a possible perfect score of 30 is considered dementia, but it is important to note that thresholds vary according to age and education. In an educated population, an MMSE cut-off of 26 or below should raise suspicion of dementia, as this is the cut-off utilized in more recent research studies. The MMSE may not be sensitive to very subtle cognitive impairment, but can be useful as a general screening tool or to monitor performance over time. The MMSE declines by approximately 2.8 points per year in patients with Alzheimer's disease, with a slower decline in the milder stages and faster decline in the moderate to severe stages of the disease. The Montreal Cognitive Assessment (MOCA) is a new screening test with a similar 30-point format to the MMSE. It includes additional tests of

visuospatial and executive function, which make it more sensitive in patients with mild cognitive impairment. Other lengthier tests of global cognitive function include the Addenbrookes Cognitive Examination (ACE-R) and Cambridge Cognitive examination (CAMCOG). Patients with minor impairments, high levels of educational attainment, or atypical clinical features can perform deceptively well on bedside tests and may require more comprehensive assessment in specialist centers. Measures of free recall, particularly verbal recall, have consistently been shown to be impaired in the earliest clinical stages of Alzheimer's disease and predict early conversion from mild cognitive impairment. Predictive accuracy may be increased by combining tests of free recall with tests of executive function, processing speed, and semantic fluency.

Blood Tests

The bloods tests, which are routinely ordered as part of a cognitive screen include full blood count, B12/folate, renal/liver/bone profile, and thyroid function tests. This may be supplemented by screening for vascular risk factors with a fasting lipid profile and fasting glucose. Syphilis serology may be requested but is not routinely screened in many centers depending on the risk profile of the patient. Nonspecific markers of inflammation, such as ESR or CRP may be helpful where infective or inflammatory diseases are suspected.

Neuroimaging

Structural neuroimaging should be used in the evaluation of every patient suspected of dementia. Non-contrast CT can be used to identify surgically treatable lesions and vascular disease. MRI (with a protocol, including T1, T2, or FLAIR sequences, and susceptibility weighted sequences) can increase sensitivity for subcortical vascular contributions to cognitive decline and exclude other intracranial pathology or identify regional atrophy. Atrophic changes in medial temporal lobe structures such as the entorhinal cortex and hippocampus, as well as in parietal cortices may be seen on neuroimaging, which may become more marked and generalized as the disease advances (Fig. 3.2). However, volumetric changes may be minimal or absent in the very early stages of Alzheimer's disease. Functional neuroimaging with positron emission tomography (PET) or single photon emission computed tomography (SPECT) may usefully augment structural imaging where uncertainty exists regarding the clinical features and presentation. A reduction in blood flow or glucose hypometabolism in temporoparietal areas is most commonly described in AD.

Other Investigations

Electroencephalography (EEG) may be a useful adjunct and should be included in the diagnostic workup of patients suspected of having Creutzfeldt–Jakob disease or transient

epileptic amnesia. CSF analysis is mandatory when inflammatory disease, vasculitis, or demyelination is suspected. CSF concentrations of amyloid beta 42 and total tau/phospho-tau are not routinely requested and their use is largely confined to clinical research settings at present.

Management

Cognitive Symptoms

Acetylcholinesterase inhibitors are currently the mainstay of pharmacological therapy for Alzheimer's disease. The acetylcholinesterase inhibitors in use are donepezil, galantamine, and rivastigmine, which act to increase cholinergic neurotransmission through inhibition of the enzyme, acetylcholinesterase. The three compounds have certain unique pharmacological properties although no difference in efficacy between the three medications has been consistently demonstrated. Prescriber choice is ordinarily determined by side effect profile and individual familiarity (Table 3.4). Donepezil and galantamine are selective acetylcholinesterase inhibitors while rivastigmine inhibits acetylcholinesterase and butyrylcholinesterase with similar affinity. Galantamine also allosterically modulates presynaptic nicotinic receptors. The efficacy of these medications has been studied in over 30 randomized double-blind clinical trials and they have been shown to have a treatment effect on average of 2.5–3.5 points on the Alzheimer's disease assessment scale, cognitive subscale (ADAS-Cog, range 0–70) over 6 months compared with patients receiving placebo. There is some variability between studies but approximately twice as many patients who receive a cholinesterase inhibitor have a four-point difference on the ADAS-Cog (25–50% vs. 15–25%) and approximately three times as many patients who receive a cholinesterase inhibitor have a seven-point difference (12–20% vs. 2–6%) on the ADAS-Cog compared to those taking placebo. A seven-point difference is equivalent to slowing the symptoms by approximately 1 year and more patients have less decline rather than a measurable improvement in symptoms. It is important to discuss this point with patients and their families who may anticipate improvement rather than relative stability.

Table 3.4 Summary characteristics of the cholinesterase inhibitors

	Mechanism of action	Common adverse effects	Starting dose	Usual treatment dose
Donepezil	Acetylcholinesterase inhibitor	Nausea/vomiting/ insomnia/diarrhea	5 mg od. (p.o.)	10 mg od. (p.o.)
Galantamine	Acetylcholinesterase inhibitor and modulates presynaptic nicotinic receptors	Nausea/vomiting/ insomnia/diarrhea	4 mg bd or 8 mg XL od. (p.o.)	12 mg bd or 24 mg XL od. (p.o.)
Rivastigmine	Acetylcholinesterase and butyrylcholinesterase inhibitor	Nausea/vomiting/ insomnia/diarrhea	1.5 mg bd (p.o.) or 4.6 mg od (top)	6 mg bd (p.o.) or 9.5 mg od (top)

A Cochrane review concluded that donepezil, rivastigmine, and galantamine are efficacious in mild-to-moderate Alzheimer's disease and that treatment benefits included small improvements on measures of activities of daily living and behavior in addition to cognitive measures. There is nothing to suggest that the effects are less for patients with severe dementia although there is less evidence in this regard.

Overall, these medications are well tolerated and adverse effects such as nausea, vomiting, or diarrhea are most frequently reported. This can ordinarily be avoided by starting at a low dose, which is then titrated upward. Coadministration with food also delays absorption and can reduce gastrointestinal side effects. Rivastigmine is now available as a daily patch, which has a more favorable gastrointestinal side effect profile than oral rivastigmine. Other important possible adverse effects to consider include cholinergically mediated exacerbation of chronic obstructive pulmonary disease, peptic ulcers, or atrioventricular conduction abnormalities. Both donepezil and galantamine are metabolized by the cytochrome P450 enzymes, CYP2D6 and CYP3A4, and can thus interact with drugs that inhibit these enzymes. Rivastigmine has less potential for interaction given that it is metabolized at the site of action and does not have a hepatic metabolism.

The National Institute for Clinical Excellence in the UK (NICE) has questioned the cost-effectiveness of cholinesterase inhibitors and has controversially restricted their use to Alzheimer's patients with a MMSE score between 10 and 20 only. This decision has been criticized given that prescription on the basis of MMSE score alone is likely to exclude patients who might otherwise benefit. A beneficial response to a cholinesterase inhibitor may be determined by the clinician's global assessment of cognitive, functional, and behavioral symptoms taking into account the report of the primary caregiver. Observation for up to 6 months may be necessary to assess for potential benefit. Brief tests of cognitive function may be relatively insensitive to the cognitive effects of acetylcholinesterase inhibitors. Medication should be discontinued if it is poorly tolerated or if deterioration continues at the pretreatment rate. There is some evidence that patients who either do not tolerate or respond to one cholinesterase inhibitor may benefit from another. It is important to note that acetylcholinesterase inhibitors are a symptomatic treatment and do not alter the underlying neurodegenerative process which is progressive.

Acetylcholinesterase inhibitors have been used in a small number of interventional studies to see if they can delay transition to Alzheimer's dementia in patients with mild cognitive impairment. There is currently little compelling evidence to recommend their use in such patients given that the majority of studies to date have failed to meet their primary efficacy objectives. One group reported delayed progression to Alzheimer's disease over 12 months but not over 3 years, while another noted a small beneficial effect on cognition, which did not translate into improved function. Various explanations for these largely negative findings have been proposed, including the heterogeneity of patients under study, the possibility that there is simply less cholinergic dysfunction in patients with mild cognitive impairment, or that current outcome measures are insufficiently sensitive to changes in patients with mild disease.

Memantine is a noncompetitive NMDA receptor antagonist, which is believed to protect neurons from glutamate-mediated excitotoxicity, which may occur in Alzheimer's disease. Memantine has been shown to have a small beneficial effect on measures of cognition, function, and behavior in moderate-to-severe Alzheimer's disease with a barely

detectable clinical effect in patients with milder disease. Memantine is generally well tolerated with few adverse events. There is also evidence to suggest that the addition of memantine to donepezil in patients with moderate-to-severe disease may yield some symptomatic benefit. In clinical practice, it may be added to standard therapy once patients decline to a moderate stage of disease and titrated upward to 10 mg twice daily. In the UK, NICE has restricted the use of memantine to clinical research only given concerns regarding cost-effectiveness. Despite the theoretically neuroprotective properties of memantine, it is felt that current drug trials are too short to assess if the drug has any disease-modifying effects.

Neuropsychiatric Symptoms (See Also Chap. 12**)**

A number of instruments have been designed to quantify the frequency and severity of neuropsychiatric symptoms in patients with Alzheimer's disease as outlined above. Non-pharmacological interventions are ordinarily first line and should be exhausted before pharmacological approaches are considered. The type of neuropsychiatric symptoms together with their frequency, diurnal pattern, and identifiable triggers or reinforcers should be documented. This will help in the formulation of a tailored and targeted treatment approach. Understanding the reasons for the behavior from the patient's perspective are central to any intervention. First, consider unmet medical needs, such as pain, delirium, or a recent change in medication. Environmental and psychosocial factors, which increase the likelihood of behavioral disturbance, include overcrowding, lack of privacy, noise, or poor communication between carers and patients. Orientation through the use of a memory book, family photographs, and a calendar around the patient's bed can help decrease agitation. Motor disturbances may alternately be an expression of discomfort, fear, paranoia, or simply boredom. Education for carers regarding the behavioral management of such symptoms is helpful and should be considered as part of an initial treatment approach.

Pharmacological treatments are only helpful for specific symptoms and their use should be targeted. This is discussed in Chap. 12. There is evidence to support the use of antidepressant medication for the treatment of depression in Alzheimer's disease although findings have been inconsistent. SSRIs are generally favored as first-line agents given the possible adverse effects associated with tricyclic agents in older adults. Benzodiazepines should generally be avoided except for short term or occasional use for anxiety symptoms and should be limited to shorter acting agents. The beneficial effects of cholinesterase inhibitors and memantine in treating neuropsychiatric symptoms are not well established with some meta-analytic data to suggest small benefits of questionable clinical significance.

The best-studied pharmacologic agents for neuropsychiatric symptoms are antipsychotic medications. Not all studies, however, have demonstrated a beneficial effect for antipsychotic medication and there are significant concerns regarding tolerability and safety. This is further discussed in Chap. 12.

Current guidelines recommend that the use of antipsychotic medication be reserved for patients with severe symptoms only (i.e., dangerous or distressing) where alternate treatment approaches are not practicable. Medication should be titrated from a low dose, have a specific target symptom, and be time limited (3ts approach).

It is good practice to document clearly the relevant considerations before starting an antipsychotic and a date to review the need for its continued use. There is evidence that patients established on antipsychotic medication for 3 months or more may have this safely discontinued in all but patients with more severe neuropsychiatric symptoms at baseline.

Supporting Caregivers and Legal Considerations

The physical and emotional health of the primary caregiver is critical to optimal care of the patient with Alzheimer's disease. Caregivers have increased rates of psychological and physical morbidity, which in turn predict early transfer to long-term care and escalation of costs. One of the most widely used tools to assess the demands of caregiving on the caregiver is the Zarit burden inventory, which is a 22-item, self-administered questionnaire. Multimodal and multidisciplinary interventions tailored to the needs of individual caregivers have been shown to achieve improved outcomes for patients and carers and can delay time to institutional care. Legal issues should also be addressed with patients and carers such as advance directives and power of attorney as appropriate. Voluntary organizations such as the Alzheimer's association (www.Alz.org) and the Alzheimer's society (www.alzheimer.org.uk) have an important role to play and can provide patients and their families with useful information regarding Alzheimer's disease and the availability of daycare and respite services locally.

Lifestyle Issues, Cognitive Stimulation, and Alternate Therapies

In recent years, there has been an increasing amount of epidemiological evidence, which links low educational level, vascular risk factors, and decreased social activation with increased risk of Alzheimer's disease. These findings, coupled with an increased understanding of neural plasticity, have stimulated interest in the area of lifestyle interventions to improve cognitive function. Physical activity has previously been reported to have beneficial effects on certain cognitive domains and a more recent interventional study, which randomized 170 participants with memory complaints (60% of whom had mild cognitive impairment) to either a 24 week home-based program of physical activity or to education and usual care reported a 1.3 point difference on the ADAS-Cog in favor of the intervention. The utility of cognitive training techniques and whether gains on neuropsychological test scores translate into everyday functional improvement continues to be explored.

One systematic review of studies, which included only patients with early Alzheimer's disease or vascular dementia, concluded that there was no evidence for the efficacy of cognitive training while another review that examined the benefits of cognitive exercise on longitudinal neuropsychological performance in healthy older adults reported strong effect sizes. A recent 5 year follow up of community-dwelling older adults (MMSE > 22 at baseline), who had received cognitive training in reasoning, reported less decline in self-reported instrumental activities of daily living.

Further research is warranted in clearly defined at-risk populations to determine whether cognitive training may prevent or delay incident dementia.

Vascular risk factors such as hypertension, hypercholesterolemia, obesity, diabetes, and smoking in midlife and later years have been associated with increased risk of Alzheimer's disease. It is already known that comorbid cerebrovascular disease facilitates the clinical expression of Alzheimer's pathology, but there is now increasing knowledge regarding converging and shared pathogenic mechanisms.

There is mixed evidence regarding the treatment of hypertension for prevention of dementia, and interventional studies of statins have had negative results on cognitive outcomes to date. There remain compelling cardiovascular and cerebrovascular indications for the detection and treatment of vascular risk factors, which should ordinarily be addressed in the course of cognitive screening. Patients sometimes enquire about the benefit of alternative therapies such as Gingko biloba or vitamin E. Recent Cochrane reviews have concluded that there is no consistent evidence to recommend their use in patients for Alzheimer's disease.

Recent Advances

Disease-Modifying Therapies

In addition to ongoing research in cognitive and lifestyle interventions to delay or prevent the onset of Alzheimer's dementia (as outlined above), there are currently a large number of clinical trials underway in the area of potentially disease-modifying pharmacological therapies. Given the projected expansion in Alzheimer's disease worldwide, the public health implications of an intervention, which would delay disease onset by even a modest interval, would be highly significant. Disease-modifying therapies would differ from existing symptomatic therapies in that they should delay disease progression through impacting upon underlying pathophysiological processes with resultant long-lasting changes in disability. Accurate characterization of the underlying pathophysiology of Alzheimer's disease, as outlined above, has suggested a number of targets for potential disease-modifying treatments. Therapeutic agents under investigation may be broadly considered under the headings of anti-amyloid, tau related, neuroprotective, and neurorestorative therapies (Table 3.5).

Anti-amyloid Therapies

Anti-amyloid agents generally act upon the production, aggregation, or clearance of the Aβ peptide. These therapies target different parts of the amyloid cascade and include agents that reduce amyloid production through inhibition or modulation of γ and β secretases, agents, which prevent the oligomerization and fibrillization of Aβ and immunotherapeutic agents, which facilitate clearance of Aβ. The central significance of amyloid in the pathogenesis of AD has recently been called into question given negative outcomes from trials of certain agents targeting this pathway. Tarenflurbil, an agent that modulates γ secretase activity, failed to achieve significance on its primary endpoints in a phase III trial and another agent,

Table 3.5 Summary of disease-modifying agents and approaches to Alzheimer's disease

Therapy	Mechanism
Amyloid-based therapies	Reduce production of Aβ(beta)-42
Secretase inhibitors and modulators	Prevent the oligomerization and fibrillization of Aβ(beta)
Anti-aggregation agents	Decrease Aβ(beta) production
Statins	Promote clearance of amyloid plaques and oligomeric forms of amyloid
Active and passive amyloid vaccines	
Tau-related therapies	Decrease hyperphosphorylation of tau
Kinase inhibitors	
Neuroprotective therapies	Reduce oxidative injury
Antioxidants	Reduce inflammation-mediated injury
Anti-inflammatory agents	
Neurorestorative therapies	Promote neuronal survival and repair
Nerve growth factor (NGF) and neurotrophins	Neuronal regeneration
Stem cell therapy	Replacement of cells
Cell transplantation	

Tramiprosate, which binds soluble Aβ(beta), thus preventing amyloid deposition, was equally disappointing. Immunotherapy forms another potential strategy in anti-amyloid therapy, which endeavors to remove toxic Aβ from the brain. Research into this area began in earnest when it was found that it was possible to prevent or reverse Aβ(beta) accumulation in the brain of an animal model by active immunization with Aβ(beta)42. A phase II trial utilizing this method demonstrated effective removal of Aβ(beta) plaques but was stopped prematurely because 6% of patients developed meningoencephalitis. The specificity of Aβ(beta) antibodies has since been investigated and active immunization therapies targeting different regions of Aβ(beta)42 are currently under investigation. It was similarly found that passive immunization by peripheral infusion of Aβ(beta) antibodies facilitated Aβ(beta) clearance in animal models and subsequent clinical trials have yielded variable results. One phase II trial utilizing a humanized monoclonal antibody demonstrated clinical efficacy in a subgroup of patients who were non-APOE ε4 carriers but failed to achieve statistical significance in the overall study population. A second smaller Phase II trial with this antibody demonstrated evidence of decreased amyloid burden on PiB–PET amyloid imaging, but no clinical benefit was observed.

Other investigators have utilized intravenous immunoglobulin, which contains naturally derived human antibodies against Aβ(beta), and have presented promising results. Phase III trials of passive immunization techniques are currently underway.

A number of differing hypotheses have been proposed to explain how immunotherapy may result in Aβ(beta) clearance. It has been proposed that microglial activation with resulting endocytosis and phagocytosis of Aβ(beta) neuritic plaques facilitates clearance while alternately, it has been suggested that circulating antibodies may draw soluble Aβ(beta) across the blood−brain barrier, thus preventing detrimental binding within the CNS. Epidemiological studies have linked cholesterol-lowering statin medication with reduced risk of AD. This finding together with laboratory data indicating a possible

mechanism through reduced Aβ(beta) production has triggered enquiry into the possible usefulness of statins for AD. However, there is no evidence from randomized controlled trials conducted to date that statins are effective in this regard.

Tau-Related Therapies

The formation of neurofibrillary tangles is dependent upon hyperphosphorylation of tau and tau phosphorylation is regulated by a balance between multiple kinases and phosphatases. Glycogen synthase kinase 3 (GSK-3β(beta)) is a key tau kinase, and medications, which are known to inhibit GSK 3β(beta), such as lithium, have shown positive effects in animal studies. Valproic acid has similarly been reported to inhibit GSK 3β(beta). The need to expand therapies for AD beyond amyloid-based approaches means that kinase inhibitor therapeutics now forms an expanding area of research with ongoing exploration of new and existing compounds, which target GSK 3β(beta) and other kinases implicated in the hyperphosphorylation of tau.

Neuroprotective Therapies

These therapies target the neurotoxic effects of Aβ through numerous secondary pathways. These include oxidation, inflammation, and demyelination. Astrocyte activation has been hypothesized to play a role in AD pathogenesis. The astrocyte-modulating compound ONO-2506 is undergoing assessment in AD patients. The receptor for advanced glycation end-products (RAGE) is a ubiquitous cell surface receptor, which has been postulated to mediate many of the toxic and neuroinflammatory effects of Aβ(beta). A RAGE inhibitor study is currently underway. AMPA type glutamate receptors are believed to mediate most fast synaptic neurotransmission in the brain and positive modulation of these receptors may potentially enhance cognition. Phase II trials of the AMPA receptor modulator CX516 have shown minimal but promising efficacy. More recently, an antihistamine (dimebon) with postulated mitochondrial stabilizing properties was tested in a trial in patients with mild-to-moderate Alzheimer's disease and demonstrated significant efficacy on cognitive, functional, and neuropsychiatric outcome measures, although these findings were not replicated in phase III studies which were subsequently discontinued.

Neurorestorative Therapies

These approaches consist of nerve growth factor (NGF) and neurotrophin therapies, stem cell approaches, and transplantation that may assist in cell survival or replacement and regeneration.

NGF, like other neurotrophins, promotes cell survival by signaling through specific tyrosine kinase receptors to effectively block apoptosis from occurring in either a developing or damaged neuron. The impermeability of the blood–brain barrier to exogenous NGF and other neurotrophins is a significant challenge for the development of potential therapeutic agents in AD and strategies to circumvent this difficulty are being researched.

Novel Biomarkers

Diagnosis of Alzheimer's disease in its earliest clinical stages can be difficult and biological markers of underlying Alzheimer's pathology have become an increasingly important component of early diagnostic evaluation. This not only improves diagnostic accuracy but assists with prognosis and evaluation of response to potential disease-modifying therapies, which are likely to be of greatest benefit if used before the onset of significant functional impairment. Novel neurochemical, structural, and functional neuroimaging methodologies increasingly augment standard neuropsychological investigations and clinical evaluations as outlined above. These include cerebrospinal fluid levels (CSF) of amyloid beta 42, tau, and hyperphosphorylated tau, which have displayed good accuracy in identifying incipient AD among subjects with MCI. Methods of CSF analyses continue to be refined and a recent meta-analysis reported significant variability in absolute concentrations between centers. A variety of potential plasma biomarkers for incipient AD have been identified including plasma amyloid beta 42 or plasma amyloid beta 42/40 ratio and additional proteins identified through the use of proteomic methodologies. To date, no single plasma biomarker of Alzheimer's pathology has displayed sufficient sensitivity or specificity although combining biomarkers from different metabolic pathways may increase diagnostic accuracy.

Neuroimaging Biomarkers

Recent advances in neuroimaging techniques have greatly enhanced clinical research in early Alzheimer's disease. In particular, PET tracers, which are derivatives of thioflavin and bind to fibrillar forms of amyloid-beta, now allow the detection of amyloid pathology in vivo. The majority of studies published to date have utilized 11C-Pittsburgh Compound B (PiB), but a number of 11-F tracers, which have a much longer half-life, are under active development. The PET amyloid imaging studies to date have consistently reported a high percentage (85–90%) of clinically diagnosed AD patients and approximately 50–65% of MCI subjects demonstrating evidence of amyloid pathology, consistent with autopsy series. Of particular interest are the reports of approximately 20–40% of cognitively normal older individuals with evidence of amyloid pathology, consistent with the hypothesis that the pathophysiological process of AD may begin years, if not decades prior to the diagnosis of clinical dementia.

Novel methods for structural MRI continue to evolve, including cortical thickness measures and tensor morphometry. These techniques have demonstrated evidence of subtle atrophy in MCI and very mild AD. Other novel neuroimaging techniques are also under active investigation, including functional magnetic resonance imaging (fMRI). fMRI can be performed during cognitive tasks, such as episodic memory, and has consistently shown abnormal hippocampal function during memory encoding in mild AD patients. Recent fMRI studies have focused on functional connectivity, that is, the correlation in neural activity between brain regions during the resting state (Chap. 2). These studies suggest that a specific network of brain regions, including the posterior cingulate, precuneus, lateral parietal, medial frontal regions, and the hippocampus, collectively known as the "default

network" is disrupted in AD. Similar disruptions in functional connectivity have been reported in MCI and even in amyloid-positive normal older individuals, suggesting that alterations in this network may be an early sensitive marker of brain dysfunction.

Future Directions

The AD field continues to evolve toward earlier diagnosis, in the hope that earlier intervention with potential disease-modifying therapies will be more efficacious. Several efforts to further "re-define" the diagnostic criteria across the continuum from normal aging through MCI and very mild AD are ongoing. As mentioned above, recently revised criteria suggest that older individuals with memory impairment and evidence of amyloid pathology and/or atrophy should already be considered very mild AD. Clinical trials of potential amyloid-lowering agents in these individuals at the border zone between MCI and early dementia are already ongoing.

There is now a movement to define an even earlier stage of "preclinical" AD, which encompasses individuals with evidence of amyloid pathology on PET imaging or CSF markers, but who have no clinical symptoms or only very subtle cognitive decline. Several recent studies have demonstrated that clinically normal older individuals with high amyloid burden demonstrate functional and structural brain alterations similar to those observed in MCI and AD. Furthermore, these studies suggest that amyloid-positive older individuals may already have subtle memory impairment, particularly evident when level of cognitive reserve or baseline intellectual capacity is taken into account. Although one study has reported that amyloid positivity in normal older individuals is predictive of subsequent clinical decline, further longitudinal study is required to determine if the presence of amyloid in cognitively normal individuals is both necessary and sufficient to reliably predict progression to the clinical dementia of AD. A large international effort to acquire longitudinal biomarkers in presymptomatic carriers of autosomal dominant mutations (the Dominantly Inherited Alzheimer Network—DIAN study) is also beginning to develop methods to track disease progression in the preclinical stages of AD. These studies are critical to moving the field toward a different treatment paradigm. Similar to cardiovascular disease and cancer, the optimal treatment for AD may be at these very early stages, perhaps prior to the emergence of any clinical impairment.

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Dementia and Cerebrovascular Disease

4

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Abstract Vascular dementia (VaD) is a term that implies acquired cognitive impairment as a result of a variety of often distinct forms of cerebrovascular disease. This is one of the most common forms of dementia and is often seen in association with Alzheimer's disease in older age. VaD arises as a consequence of ischemic insults such as hemorrhage and hypoperfusion that trigger neurodegeneration by depriving nerve cells of oxygen and glucose. It is unique amongst the neurodegenerative diseases in being dependent on a pathological process that largely originates outside the brain and whose course may be significantly altered by risk factor modification. Despite its ubiquity, diagnostic accuracy is poor and requires high-quality neuroimaging and the coexistence of vascular pathology. The mainstay of treatment is primary and secondary prevention of strokes. There are currently no pharmacological agents licensed for the treatment of VaD but a number of investigational agents are showing promise.

Keywords Vascular dementia • Subcortical dementia • Cerebrovascular disease • Hypoxia • Hypoperfusion • Hemorrhage

Introduction

Dementia is a syndrome of acquired intellectual deficit resulting in significant impairment of social or occupational functions. The association between cerebrovascular disease (CVD) and dementia has been a controversial topic for decades. At one point, CVD was considered the dominant cause of dementia; then, it was thought an exceedingly rare cause. More recently, the pendulum has swung back to a larger role for CVD in cognitive disorders, although challenges to the concept remain. Vascular dementia (VaD) comprises dementias resulting from all types of vascular pathologies: cortical vascular dementia, subcortical ischemic dementia, strategic-infarct dementia, hypoperfusion dementia, hemorrhagic dementia, and dementias resulting from specific arteriopathies.

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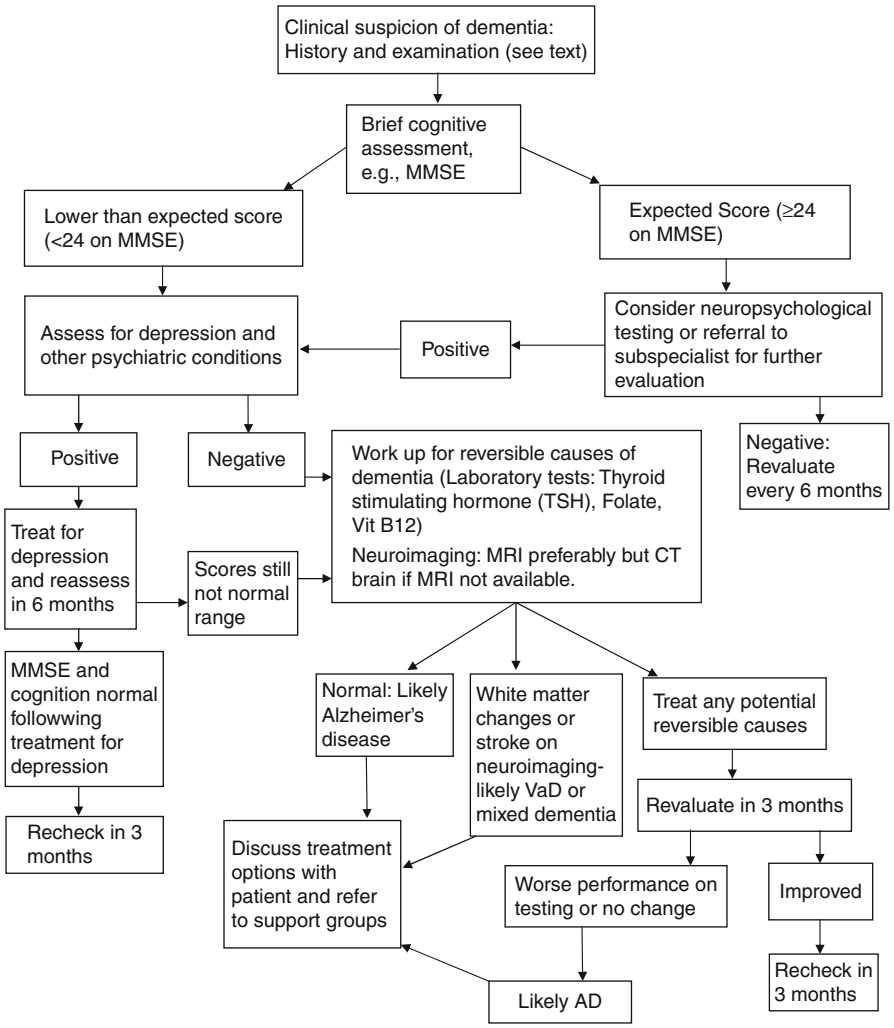

Fig. 4.1 Algorithm for initial evaluation of a patient with dementia

The diagnosis of VaD requires the presence of cognitive decline (loss of memory and deficits in at least two other domains) resulting in impaired functional abilities (Fig. 4.1). Evidence of CVD must be confirmed by neuroimaging for a diagnosis of probable VaD, and the onset of dementia and CVD must be reasonably related temporally. Several specific diagnostic criteria are used to assist the diagnosis of VaD including the *Diagnostic Manual on Mental Disorders*, 4th edition (DSM-IV) criteria, the *International Classification of Diseases*, 10th edition (ICD-10), the National Institute of Neurological Disorders and Stroke, Association International pour le Recherché at L'Enseignement en Neurosciences (NINCDS-ARIEN) criteria, and the Hachinski Ischemic score. Unfortunately, however, diagnostic accuracy for VaD is low. For example, a population-based clinic-pathologic

Table 4.1 NINDS-ARIEN criteria for diagnosing vascular dementia

Cerebrovascular disease • Focal central nervous system signs • Evidence of cerebrovascular disease by neuroimaging
A relationship between the two manifest by one or more of the following • Dementia onset within 3 months after having a stroke • Abrupt deterioration in cognition or fluctuating stepwise course

study in the United Kingdom found that the NINCDS-ARIEN diagnostic criteria had a sensitivity of 43% and a specificity of 95%. Similarly, in a US-based cohort study of patients diagnosed with dementia, application of the NINCDS-ARIEN criteria gave a proportionate risk for VaD of 4%, whereas application of the DSM-IV criteria in the same patient population gave a rate of VaD of 29%. Neither estimate correlated closely with the ultimate neuropathologic diagnosis. Overall, the NINCDS-ARIEN criteria (Table 4.1) appear to be the most specific and are used most commonly in research.

As not all patients fulfill the strict criteria for dementia, and many may be significantly cognitively impaired without memory loss, the term vascular cognitive impairment (VCI) has been suggested. VCI includes VaD, but also encompasses mixed Alzheimer disease (AD) and VaD, as well as VCI without dementia and hereditary disorders.

Prevalence

VaD is historically considered the second most common cause of dementia in the elderly after AD. Between 1% and 4% of people over 65 years suffer from VaD and the prevalence appears to double every 5–10 years after the age of 65 years. Post-stroke dementia is extremely common and occurs in up to one third of patients with a clinically evident ischemic stroke after the age of 65. Cognitive decline of any severity may be present in over 60% of stroke patients ranging in age from 55 to 85 years. While it is clear that AD and VaD often coexist in the elderly population, it has been much harder to estimate the prevalence of this "mixed dementia." Autopsy series report the coexisting vascular pathology occurs in 24–28% of AD cases and, conversely, half of patients with vascular disease, who become demented, also have AD pathology. Patients often have clinical features of both AD and VaD, and both conditions share similar risk factors and pathogenic mechanisms.

Clinical Features

Due to the variety of pathogenic mechanisms, the clinical manifestations of VaD can be varied and are determined by the size, location, and type of cerebral damage. There are several conditions that can mimic the appearance of dementia, which should always be excluded at the outset of investigation (Table 4.2). Classically, the clinical features include an abrupt onset, stepwise deterioration, fluctuating course, and are often accompanied by

Table 4.2 Conditions which can mimic dementia

Worried well – not demented
Mild cognitive impairment – reduction from baseline in one or several cognitive domains but no functional impairment
Affective disorders: Depression, manic-depressive disease
Other psychiatric conditions: obsessive compulsive disorders, old age psychosis, and paranoid (delusional) disorder
Acute or prolonged confusion (Up to 6 months) − delirium
Adverse effects of medications
Unrecognized complex partial seizures
Unrecognized drug or alcohol abuse
Single-domain cognitive deficits such as Korsakoff's disease

Table 4.3 Key differential diagnostic features of vascular dementia (VaD)

Features typical of a classic presentation of VaD
• Focal neurological symptoms and signs (e.g., visual disturbances, sensory or motor symptoms, hemiparesis, visual field defects, extrapyramidal signs, etc.)
• Presence of cerebrovascular lesions on brain imaging
• Preservation of emotional responsiveness and personality
• Depression
• Impairment of executive function (ability to plan, strategize, and execute commands)
• Stepwise deterioration in cognition
• Incontinence
• Somatic symptoms
• Visuospatial dysfunction
• Dysphasia
• Emotional lability
• Nocturnal confusion and wandering
Features that make a diagnosis of pure VaD unlikely
• Early onset of memory deficit
• Progressive decline of memory deficit and other cognitive functions (e.g., Language, perception, and motor skills)
• Absence of cerebrovascular lesions on brain imaging

focal motor and sensory abnormalities, including early onset of urinary incontinence and gait disorders (Table 4.3). However, subcortical VaD can present with a gradual onset and deterioration similar to the pattern seen in AD. Even within VaD, the clinical features can be further subdivided.

Cortical VaD

This is predominantly characterized by the abrupt onset of unilateral sensorimotor changes along with aphasia, apraxia, or agnosia (cortical cognitive impairments). Most patients have an element of executive dysfunction, as expressed by difficulties in areas such as initiation, planning, and organization of activities. There may be day-to-day fluctuations in severity with long plateaus between events.

Strategic Infarct

Single strategic infarcts have the potential to cause cognitive and other deficits that are dependant on the area of the brain affected. Particular cerebral regions, known to produce symptoms of acute onset VaD when affected include the thalamus, basal forebrain, and caudate. From a cognitive perspective, memory impairment, dysexecutive syndrome, confusion, and fluctuating levels of consciousness can occur. Behavioral changes include apathy, lack of spontaneity, and perseveration.

Subcortical VaD

Cerebrovascular lesions in the subcortical area tend to cause slow but episodic deterioration in executive functioning and abstract thought, as well as mood changes including depression, personality changes, and emotional lability. Although, in many instances, memory deficits are less severe, the difficulties with complex tasks lead to decreased performance in activities of daily living. Binswanger's disease (also known as subcortical leucoencephalopathy) is due to diffuse white matter disease. In Binswanger's disease, vascular changes observed are fibrohyalinosis of the small arteries and fibrinoid necrosis of the larger vessels within the brain.

With regard to the clinical course of the disease as a whole, the median survival from dementia onset to death is 3.9 years for patients with VaD, as compared with 7.1 years for patients with AD, and 5.4 years for patients with mixed dementia.

Neurodegeneration and VaD

VaD arises as a consequence of hypoxia and ischemic insults, including hemorrhage and hypoperfusion, that trigger neurodegeneration by depriving neurons of oxygen and glucose. Hypoxia and ischemia initiate a neurodegenerative signaling cascade, involving the release of glutamate, activation of the *N*-methyl *D*-aspartate (NMDA) receptor, accumulation of free calcium Ca2+ intracellularly, free radical formation, and subsequent necrosis and apoptosis. Acute hypoxia also leads to microglial activation and the synthesis of inflammatory mediators, which are also injurious to neurons in the ischemic penumbra.

Biomarkers and VaD

Unlike AD, there are currently no established biochemical markers for VaD. Commonly, AD and VaD pathology coexist in what is termed "mixed" dementia (MD). As a result of this coexistence, in many cases, an exact diagnosis of either AD or VaD can be difficult on clinical grounds alone, and therefore biological markers may be of use in assisting this distinction. Recent studies have suggested that levels of neurofilament light protein (NFL)

in the cerebrospinal fluid (CSF) may correlate with the degree of white matter lesions on magnetic resonance imaging. Studies investigating CSF levels of amyloid-β(beta)40 (Aβ(beta)-40), amyloid-β(beta)42 (Aβ(beta)-42), total tau (Tt), and phosphorylated tau (Tp), have shown inconsistent results, but overall patients with VaD have lower CSF levels of Tt and Tp, and higher levels of Aβ(beta)-40 and Aβ(beta)-42, than either MD or AD. Many studies have failed to find a difference in the levels of these biomarkers in patients with VaD, when compared to non-demented populations. No serum or plasma biomarkers have shown consistent results to date.

Cardiovascular Risk Factors and Dementia

Many links exist between vascular disease and AD. Cerebral atherosclerosis is associated with a higher risk of AD. Cardiovascular risk factors are associated with clinically diagnosed AD and VaD. The commonalities in association between cardiovascular risk factors and dementia labelled as AD or VaD underline the relevance of vascular disease to dementia in general, and the flaws in simplistic diagnostic categories.

When discussing the cardiovascular risk factors for VaD, it is best to categorize them into modifiable and non-modifiable risk factors.

The most important non-modifiable risk factors are gender and age, followed by genetic predisposition, ethnicity, and a previous history of stroke. Both incidence and prevalence of VaD increase with age and tend to be higher in men. Dementia affects about 7% of the general population older than 65 years and 30% older than 80. Genetic defects for several monogenic disorders have been identified. These include cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), which is a cause of small vessel disease, migraine, and stroke leading to cognitive impairment within 20 years of the onset of symptoms. Other genetic disorders include hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D), a syndrome of primarily hemorrhagic strokes resulting in cognitive impairment and dementia in the majority of cases. Ethnicity appears to be of importance given that previous studies suggest that VaD represents over 50% of all dementias in Japan; however, there may have been an over-diagnosis of VaD in some of these studies. Recent regional Chinese studies have demonstrated comparable prevalence rates for all dementia subtypes in China and Western countries. There is a history of prior stroke in 76% of patients with VaD and in 57% of those with VCI, as compared with only 5–7% of people with AD.

Modifiable risk factors for VaD are those that reduce one's risk for cardiovascular disease, i.e., hypertension, diabetes mellitus (DM), hyperlipidemia, and smoking. Epidemiological data shows that hypertension (especially in midlife) is one of the most potent risk factors for VaD, and it has been shown that control of hypertension can reduce one's risk of VaD. Patients with diabetes are more than three times more likely to develop stroke-related dementia than the general population. Dyslipidemia, although a well-established risk factor for ischemic heart disease, has been convincingly demonstrated as a risk factor for AD or VaD. Elevated levels of non-high-density lipoprotein cholesterol (non-HDL-C), and low-density lipoprotein cholesterol (LDL-C), and

decreased levels of high-density lipoprotein cholesterols (HDL-Cs), have been shown to be weak risk factors for the development of VaD. The evidence for smoking and dementia is also somewhat ambivalent, although recent studies have suggested that smokers have twice the risk of developing VaD, compared to ex-smokers and nonsmokers.

There is also an overlap between cardiac disease and the development of dementia. Cognitive impairment is seen in 26% of patients discharged from hospital following treatment for heart failure. The degree of cognitive impairment correlates with the degree of left ventricular impairment and systolic blood pressure levels less than 130 mmHg. This highlights the potential for hypotension and diminished cardiac reserve to exacerbate cerebral hypoperfusion, contributing to subsequent dementia. Similarly, following coronary artery bypass graft (CABG) surgery, the reported incidence of "early" cognitive impairment ranges from 33% to 83%. In this group of patients, widespread atherosclerotic disease can predispose to vascular sequelae leading to neurologic dysfunction. Long-term cognitive outcomes are more favorable for off-pump CABG, but late postoperative dementia is predicted by early cognitive deterioration. Aggressive postoperative risk factor control appears to impact favorably on cognitive outcomes.

Primary Prevention of VaD

Primary prevention aims to reduce the incidence of VaD by early detection and optimum treatment of known vascular risk factors for cardiovascular disease and stroke, prior to the onset of such diseases. Targeting high-risk groups, such as patients with hypertension, affords the best opportunity for reducing the incidence of dementia in the general population. Initial results from trials examining the effects of antihypertensive therapy on dementia were conflicting. Longitudinal data from the Rotterdam study of 7,046 elderly participants showed that the relative risk of VaD was reduced by over a third, over a mean 2.2 years follow up in those who were receiving antihypertensives at baseline. Two subsequent prospective randomized studies, the Medical Research Council (MRC) (diuretic/β(beta) blocker-based therapy) and the Systolic Hypertension in the Elderly Programme (SHEP) (Diuretics ± β(beta) blocker therapy) studies, showed no benefit in preventing dementia. However, further evaluation of the latter trial revealed that cognitive and functional evaluations may have been biased toward the null effect by differential dropout. Another randomized trial, the Systolic Hypertension in Europe [Syst-Eur] trial, demonstrated that treatment with the dihydropyridine calcium channel blocker nitrendipine reduced the incidence of dementia (both AD and VaD) by 55% over 2 years, although only small numbers of new cases were identified in either group. Further studies are underway examining the possible neuroprotective properties of certain antihypertensive agents, and how these may be responsible for the reduced incidence of dementia following treatment. Given the strength of midlife hypertension as a risk factor for the development of dementia, perhaps one of the strongest indications for aggressive management of high blood pressure at this stage of life is the reduction in the incidence of dementia seen in later life.

Secondary Prevention of VaD

Secondary prevention of VaD mainly focuses on stroke management and the prevention of recurrent stroke. Treatment with antiplatelet agents should be initiated as indicated by the nature of the patient's underlying vascular pathology. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial confirmed the benefits of blood pressure lowering in secondary prevention. Although the primary outcome of PROGRESS was stroke incidence, dementia and cognitive function were secondary outcomes. Treatment with the long-acting angiotensin-converting enzyme (ACE) inhibitor perindopril, combined with the diuretic indapamide significantly reduced the incidence of dementia by 34% in patients with recurrent stokes. Similarly, less cognitive decline was noted in patients who received active treatment. It was also observed in this study that treatment with combination therapy led to greater reductions in blood pressure and was more effective at reducing the risk of dementia than monotherapy. A PROGRESS magnetic resonance imaging (MRI) sub-study investigated the effect of antihypertensive therapy on the progression of white matter intensities (WMH). We know that WMH are associated with VCI and VaD and are often observed on brain MRI in elderly patients. There was a significant reduction in the total volume of new WMH in patients who received perindopril ± indapamide. Therefore, active management of high blood pressure stopped or delayed the progression of WMH in patients with known cardiovascular disease.

Treatment of hypercholesterolemia also affords us a possible opportunity to reduce the incidence of VaD. It is clear that the use of 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins) have a well-defined role in the secondary prevention of stroke. What is less clear is their role in preventing cognitive decline. Several observational studies have suggested that treatment with statins lowers one's risk for developing dementia; however, most of the available data fails to distinguish between AD, VaD, and other causes of dementia. Two randomized studies the Heart protection Study (Simvastatin) and the Prospective Study of Pravastatin in the Elderly at Risk study (PROSPER), failed to identify a treatment benefit of statin therapy on cognition or dementia. It has been suggested that the follow-up period in these studies may have been too short to clearly demonstrate a treatment benefit, if one was present.

Treatment of VaD

The mainstay of management of VaD is the prevention of new stokes, as discussed above. There are currently no pharmacological agents licensed for the treatment of VaD. Studies of vasodilators, nootropics, ergot alkaloids, antioxidants, and hyperbaric oxygen have largely failed to demonstrate any symptomatic benefit to treatment. However, low numbers of participants, short follow-up periods, and the absence of clear endpoints has limited the power of several of these trials. Therefore, further studies are necessary to investigate the role these agents may play in the treatment of VaD.

Propentofylline is a xanthine derivative with purported neuroprotective effects, by acting as a glial cell modulator. Several double-blinded randomized placebo-controlled trials have demonstrated significant symptom improvement and long-term efficacy, when used for the treatment of VaD. The use of certain dihydropyridine calcium channel blockers (DHP-CCB), such as nimodipine and nicardipine, have been associated with favorable outcomes in clinical trials; however, the beneficial effects were greater in subcortical dementia and were short lived. While the exact mechanism of action is unclear, certain DHP-CCB have been associated with increased cerebral perfusion and reduced cellular apoptosis, as well as generally lowering blood pressure.

Autopsy reports of patients with VaD have shown significantly reduced choline acetyltransferase activity in several brain regions including the caudate and putamen, hippocampus, and temporal cortex, supporting evidence for a role for cholinergic depletion in the pathogenesis of VaD. While the magnitude of the loss of cholinergic neurons is less in VaD compared to AD (40% versus 70%), it is reasonable to hypothesize that in a similar way to AD, enhancing cholinergic transmission may be a rational treatment approach for VaD. Several trials have examined the use of the three acetycholinesterase inhibitors (AChI) used for the treatment of AD (donepezil, rivastigmine, and galantamine) in patients with VaD. Rivastigmine is a second-generation AChI with the capacity to inhibit both acetylcholinesterase and butyrylcholinesterase. In a randomized open-label 1 year study, 208 patients with VaD were treated with rivastigmine. There was a slight improvement in executive function (clock drawing tests) and in behavior; however, the results of further blinded, placebo-controlled trials are awaited. Galantamine is an AChI that also modulates central nicotinic receptors. The analysis of two large studies involving VaD patients failed to demonstrate a significant improvement in overall cognition and memory scores with treatment; however, there did appear to be a slight improvement in executive function. The most positive results have been seen with donepezil. Donepezil is a piperidine-based agent, and is a noncompetitive, reversible antagonist of cholinesterase, and is highly selective for acetylcholinesterase. Efficacy and safety has been shown in two large randomized placebo-controlled trials, and confirmed in a Cochrane review. Altogether, 1,219 patients with VaD, according to NINDS-ARIEN criteria, were recruited for 24-week trials. The patients were randomized to placebo, donepezil 5 mg, or donepezil 10 mg per day. There was a statistically significant improvement in cognition, global functioning, and activities of daily living in both treatment groups compared to placebo. Overall, there is evidence to suggest that the use of certain AChIs in VaD may offer some symptomatic relief. The degree of improvement on cognitive measures although statistically significant, does appear to be small and may be short lived. The presence of side effects associated with these medications may limit their use in patients with pure VaD.

Memantine is a noncompetitive NMDA receptor antagonist that has been tested in two trials of patients with mild/moderate VaD. Memantine is licensed for the treatment of severe AD. A total of 815 patients were randomized to treatment with 20 mg daily or placebo over 28 weeks. There was significant improvement in cognitive function and a slight improvement in behavior from baseline, over placebo. It appeared to be well tolerated. The mechanism of action of memantine in improving cognition is not clearly understood.

Future Directions in VaD

Given that AD, VaD, and a mixture of both account for the vast majority of cases of dementia, a discussion on future directions for VaD must also look at the future directions for all dementias. There are several aspects of neuroimaging that are likely to make a significant contribution to our diagnostic capabilities over the coming years. Structural imaging with newer-generation MRI scanners have facilitated exact measurement of regions of white matter disease, and hippocampal volume, which enables clearer diagnosis of dementia. Functional imaging techniques such as magnetic resonance spectroscopy, or functional MRI (fMRI) highlight levels of impaired cerebral perfusion and neuronal dysfunction, even in the absence of any structural abnormalities. New positron emission tomography (PET) techniques using ligands such as Pittsburgh Compound-B have enabled visualization and quantification of amyloid within the brain. These techniques will assist with an earlier diagnosis of dementia, perhaps before the clinical onset of symptoms enabling earlier treatment; however, further research is required to establish appropriate cut-off values that are specific and sensitive enough to differentiate patient from normals.

As discussed earlier, there are currently no established biomarkers to assist the diagnosis of VaD. The identification and understanding of biomarkers for AD has led to their introduction in many of the new criteria for diagnosis of AD. In the future, one would hope that our understanding of these biomarkers and their correlation with neuropathology, as well as the identification of new biomarkers, would lead to a greater understanding in the crossover between vascular disease and VaD, and an ability to distinguish between the two.

Despite these predicted advances in biotechnology, it is likely that the mainstay of treatment for VaD will depend on aggressive management of vascular risk factors prior to stroke, and careful monitoring and follow-up post stroke. Future studies are required to develop a predictive risk score for post-stroke dementia, and to evaluate sort cognitive screening instruments identifying high-risk patients with VCI.

It will become increasingly important as newer treatments for AD and VaD become available, that we have an understanding of the interplay between the two pathological mechanisms for both conditions.

Conclusions

Despite being the second most common form of dementia after AD, with which it shares important pathologic features and symptoms, VaD frequently goes undiagnosed. There is likely to be an exponential increase in the incidence of VaD over the coming years, given the aging demographic profile of countries worldwide, especially in developing countries. Although no treatments are currently licensed for the symptomatic treatment of VaD, there does appear to be mild symptomatic benefit to treatment with certain cholinesterase inhibitors and memantine. Without doubt, the primary treatment goal currently is to reduce one's risk of suffering a primary cerebrovascular event, and where one has occurred, to limit the risk of recurrent events. This requires aggressive vascular risk factor management.

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Parkinson's Disease

5

Richard A. Walsh, Timothy Lynch, and Stanley Fahn

Abstract Parkinson's Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. The majority of cases are sporadic, commonly referred to as idiopathic Parkinson's disease (IPD). The cardinal clinical features are bradykinesia, rigidity, rest tremor, and postural instability. A flexed posture and the freezing phenomenon are also commonly seen.

Initial descriptions of Parkinson's disease (PD) and its management following the introduction of levodopa concentrated on the cardinal motor features. Long-term studies and clinicopathological correlation make it clear, however, that this is a disease with diverse effects, also affecting cognition, mood, autonomic function, and the sleep cycle. Patient care has accordingly become increasingly complex. With the exception of deep brain stimulation, diagnostic and therapeutic options have changed little in the past 20 years. Validated biomarkers and disease-modifying therapies are still required. This chapter aims to practically address common clinical issues and update the practitioner on advances in the field.

Keywords Parkinson's disease • Synucleinopathy • Lewy body • Neurodegeneration • Levodopa

Pathology

IPD arises as a result of degeneration of neurons in the substantia nigra pars compacta. The pathological hallmark is the α(alpha)-synuclein containing Lewy body, an eosinophilic, proteinaceous cytoplasmic inclusion seen in surviving neurons (Fig. 5.1).

Staining for Lewy pathology with antibodies to α(alpha)-synuclein indicates that the first location of pathologic change is in the olfactory apparatus and caudal brainstem, especially the dorsal motor nucleus of the vagus in the medulla. Neural involvement

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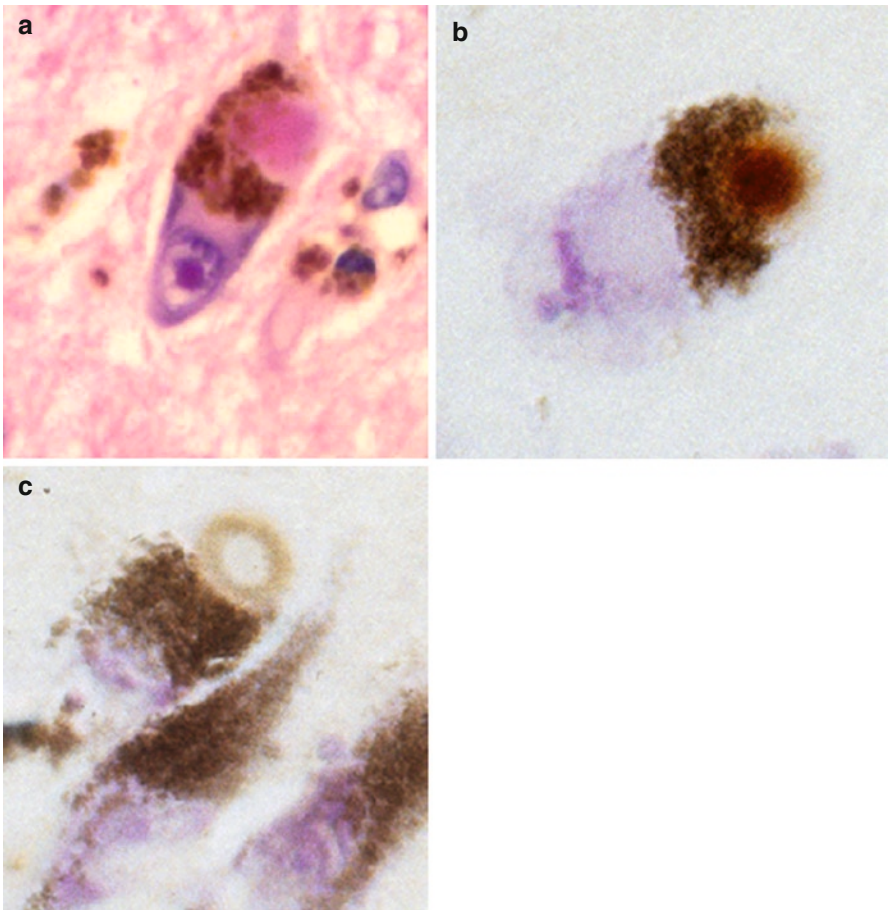


Fig. 5.1 (**a**) H and E staining of a substantia nigra neuron containing a Lewy body; (**b**) The core of each Lewy body stains more strongly for α(alpha)-synuclein than the characteristic halo (**c**), which is strongly immunoreactive for ubiquitin

progressively spreads rostrally up the brainstem in a fashion hypothesized by Braak and colleagues, who have studied the pattern of α(alpha)-synuclein involvement in autopsied brains. The cerebral cortex is involved late in this schema, in keeping with the evolution of cognitive impairment, (if not frank dementia) in patients with long-standing IPD. When the motor symptoms of IPD are evident, the substantia nigra already has lost about 60% of dopaminergic neurons, and the dopamine content in the striatum is about 80% less than normal. Involvement of non-dopaminergic neurons including cholinergic neurons in the nucleus basalis of Meynert, noradrenergic neurons in the locus coeruleus and serotonergic neurons in the midline raphe may be significant in the non-motor symptoms.

Diagnosis

The diagnosis of IPD remains essentially a clinical one. If made by a neurologist, the diagnosis based on clinical impression has been shown to have a positive predictive value of 76–98.6% for those working in a specialist movement disorders service. The United Kingdom Parkinson's Disease Society Brain Bank criteria are typically used in studies of IPD; bradykinesia with one of tremor, rigidity, and postural instability are required in the absence of exclusion criteria (Table 5.1). Retrospective application of these criteria to patients diagnosed with IPD in life demonstrates positive predictive values of between 82% and 92%. This diagnostic accuracy may be improved if a levodopa response and asymmetry are also sought but sensitivity may be lost.

Some physicians will use the "levodopa challenge" where a response to a single dose of up to 300 mg of levodopa is reassuring. Tremor-predominant forms of IPD may not, however, demonstrate any response to levodopa and some atypical forms of parkinsonism will, thus causing diagnostic confusion. Others avoid this challenge, particularly in younger patients, given concerns that even a single dose of levodopa may "prime" the basal ganglia for dyskinesia.

An important aspect of the initial and subsequent clinical assessments is to look for atypical features suggesting an alternative diagnosis, having important implications for predicting survival and treatment response. Some conditions mimicking IPD will require alternative treatment strategies (Table 5.2). Also, it is not uncommon for IPD to present with symptoms not readily attributed to the disease. Some of these patients will carry alternative diagnoses before the more obvious parkinsonian features appear (Table 5.3).

Table 5.1 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crisis (unless drug induced)
- Neuroleptic exposure at time of diagnosis
- Sustained remission
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia
- Babinski sign
- Presence of cerebral tumor or communicating hydrocephalus on imaging
- Failure to respond to an adequate dose of levodopa (up to 2,000 mg)
- Scans without evidence of dopaminergic deficit (SWEDDs)

Table 5.2 Clinical features of the Parkinson-plus (Atypical) disorders

Progressive supranuclear palsy • Early falls • Prominent axial rigidity • Pure freezing of gait and early freezing • Arm abduction when walking • Frontalis overactivity • Vertical gaze palsy or "round the houses" vertical saccades • Deep naso-labial folds • Blepharospasm • Square-wave jerks • Slowing of horizontal saccades • Apraxia of eye opening • Characteristic voice is a hoarse, throaty growl, with some hesitation between words
Multiple systems atrophy • Prominent cerebellar or autonomic features • Flexed posture • Anterocollis • Myoclonus or polyminimyoclonus • Laryngeal stridor (may only be nocturnal) • Early orofacial dyskinesia with levodopa • Pyramidal tract signs (e.g., extensor plantar responses, spastic "catch" at wrist) • Purple discoloration of the feet due to abnormal vascular autonomics
Corticobasal degeneration • Unilateral dystonia • Alien-limb phenomenon • Unilateral stimulus sensitive myoclonus • Cortical sensory loss • Dyspraxia

Table 5.3 Parkinsonian symptoms and signs commonly attributed to other disorders

• Fatigue • Dyspnea • Bradyphrenia • Depression • Joint pain (particularly shoulder pain) • "Radicular" pain (true radicular pain may worsen in "off" states) • Foot cramps/dystonia • Dysphonia • Anxiety/panic attacks • "Weakness," affecting ability to rise from chairs or apparently unilateral weakness

Differential Diagnosis of Parkinsonism

Atypical Parkinsonism

Approximately three quarters of patients presenting with parkinsonism have typical motor features, and are most likely to have pathologically confirmed IPD. The remaining 25% of patients will have so-called atypical parkinsonism, also called Parkinson-plus syndromes. This group of primary degenerative parkinsonian disorders includes progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD) and are covered in Chap. 9. All may start with an asymmetrical clinical syndrome indistinguishable from IPD. These forms of parkinsonism all share a tendency to be poorly responsive to levodopa, be largely symmetrical (with the exception of corticobasal degeneration), and have little or no rest tremor (although myoclonus mimicking tremor may be evident). Table 5.2 highlights clinical features that should raise suspicion of an atypical parkinsonism.

Dementia with Lewy Bodies

Patients presenting with dementia before, or within 1 year of manifesting parkinsonism, are by convention given a diagnosis of dementia with Lewy bodies (DLB). Visual hallucinations are common and the course of cognitive impairment is typically fluctuating. Some patients will have prominent autonomic dysfunction. Patients with dementia beginning after 1 year are diagnosed with PD with dementia (PDD). Both these conditions may represent different points on the spectrum of "Lewy body disease" with a larger cortical burden of Lewy bodies than in patients with IPD.

Secondary Parkinsonism

Drug-Induced Parkinsonism

Parkinsonism can follow exposure to drugs with an antagonistic effect at D_2 receptors. This is the most common cause of secondary parkinsonism and is typically seen in patients requiring antipsychotic treatment. Newer, "atypical" neuroleptics with less affinity to the D_2 receptor are less likely to result in extrapyramidal side effects and are preferred when treating psychosis in IPD. The commonly used antiemetic drugs metoclopramide and prochlorperazine also have a D_2 antagonist effect. Other drugs known to induce parkinsonism include lithium, tetrabenazine, reserpine, valproate, and the calcium channel blockers, cinnarizine and flunarizine.

Drug withdrawal typically results in a slow improvement although latent parkinsonism may have been unmasked and full recovery may not occur.

Vascular Parkinsonism

This is also known as "lower body parkinsonism" due to prominent gait disturbance and relatively less arm involvement. Often, these patients will have early freezing, which is not typically seen in IPD. This is an important cause of parkinsonism in older patients and those with a history of vascular risk factors (particularly hypertension). The pathophysiology is related to small vessel disease with prominent periventricular ischemia. Patients with basal ganglia infarcts are more likely to respond to levodopa. Magnetic resonance imaging (MRI) of brain is useful to identify those patients who may have a vascular cause of parkinsonism. Other clinical features that can help differentiate vascular from idiopathic parkinsonism are a postural, more than, resting tremor and preserved olfaction.

Fragile X Pre-mutation

The pre-mutation state of Fragile X can present with tremor, parkinsonism, and autonomic features, and may therefore be misdiagnosed as either IPD or MSA. An accurate family history is vital, looking for evidence of a related child with learning disability or autism. The presence of ataxia is another important clue. In one series of 26 patients with pre-mutations of the FMR1 gene, 57% of cases had mild bradykinesia, resting tremor was present in 40%, and 71% had upper limb rigidity.

Others

Secondary parkinsonism can also occur following toxin exposure, including manganese, carbon disulphide, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

Rarely parkinsonism can arise as a consequence of central nervous system (CNS) tumors, more commonly supratentorial meningiomas causing basal ganglia compression than by direct tumor infiltration.

Functional parkinsonism is well recognized but rare. Clues to the diagnosis are a history of previous psychogenic illness, an abrupt onset, entrainment of tremor, selective disability, and distractibility.

Disorders That Can Mimic Parkinsonism

Essential Tremor

Essential tremor (ET) is one of the most common disorders mistaken for IPD, characterized by a postural and kinetic tremor without rest tremor. Patients with ET can have cogwheeling but without rigidity. Where there is a combination of a resting hand tremor with essential tremor, the physician should consider rest tremor appearing late in ET, or the combined resting-postural tremor syndrome.

Parkinsonism and essential tremor could also represent the co-occurrence of two common movement disorders.

Dystonic Tremor

Dystonic tremor usually occurs in a dystonic body part. Some distinguish this from "dystonia with tremor," tremor observed in an unaffected body part with dystonia elsewhere. Dystonic upper limb tremor will sometimes have a "null-point" where rotation of the affected limb will reach a point where the tremor is abolished. Like ET, dystonic tremor of the upper limbs will not have the latent period before reemerging on changing position as seen in IPD. Dystonic tremor tends to be more irregular and jerky in character and may have a torsional component.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) presents with one or all features of a triad of gait apraxia, urinary incontinence, and cognitive impairment. Gait can be similar to that of vascular parkinsonism because of involvement of periventricular descending corticospinal tracts. Imaging is essential in demonstrating dilatation of all ventricles out of proportion to the degree of cortical atrophy. Diagnosis is made most reliably by removal of a large volume (at least 40 mL) of cerebral spinal fluid (CSF) via lumbar puncture, which can also predict the potential for improvement with shunt placement although this remains controversial. Video of gait and cognitive assessment performed pre- and post-lumbar puncture is useful for later assessment.

The Role of Imaging in Diagnosing Parkinson's Disease

With a classical clinical picture, there is little or no role for neuroimaging in making a diagnosis of PD. Positron emission tomography (PET) with the fluorodopa ligand and single photon emission computed tomography (SPECT) are the principal options.

In SPECT studies, radioligands of the dopamine transporter (DAT) are used to determine the presynaptic integrity of nigrostriatal neurons. The DAT is exclusively localized to dopamine producing neurons. Advantages of the technique are the wide availability of SPECT scanners and the ability to continue dopaminergic medication at the time of imaging. Patients with IPD will demonstrate reduced radiotracer uptake in the striatum bilaterally, which tends to be asymmetrical, particularly affecting the posterior putamen (Fig. 5.2). Scans without evidence of dopaminergic dysfunction (SWEDDs) is the term applied to normal scans of patients with a clinical diagnosis of IPD. The diagnosis in these patients likely represents a false positive as no long-term data or postmortem studies have subsequently proven a diagnosis of IPD. Many of these patients will have a true diagnosis of essential or dystonic tremor, and some may have dopa-responsive dystonia, in which parkinsonism can be a feature.

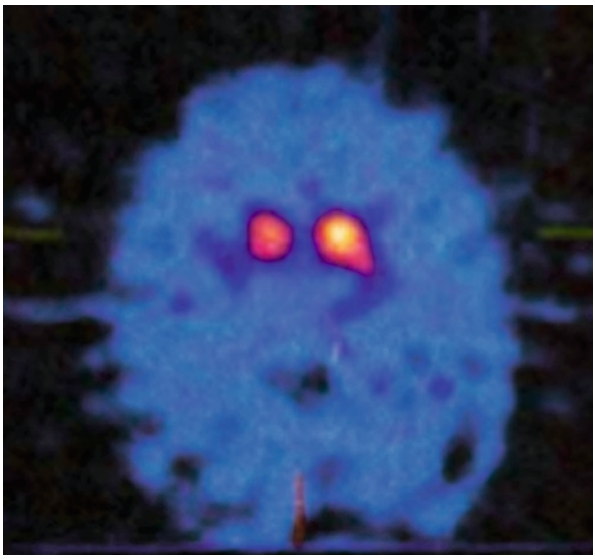


Fig. 5.2 Transaxial sections of an I-123 Ioflupane SPECT (DaTSCAN) from a patient with idiopathic Parkinson's disease demonstrating bilateral loss of uptake in the posterolateral aspect of the putamen bilaterally, more prominent on the rightside

SPECT imaging has no role in differentiating atypical parkinsonism from IPD, because both have reduced DAT imaging. Its main use is in differentiating IPD from ET, drug-induced tremor, or psychogenic tremor, all of which should have normal imaging. Transcranial sonography has emerged as an alternative imaging modality, with nigral hyperechogenicity having a sensitivity of up to 90% for IPD. Correlation with disease stage or severity has not been proven, and the significance of abnormalities in approximately 10% of clinically unaffected individuals has yet to be established.

Genetics

Case-control studies have confirmed a higher prevalence of IPD amongst first-degree relatives of affected patients supporting a genetic component to the disease. The relative contribution of environmental and genetic factors to the pathophysiology of idiopathic PD is unclear. A number of Mendelian single gene defects are associated with familial clustering of Parkinson's disease, although this accounts for less than 10% of all PD.

Familial PD has both clinical and pathological overlap with IPD but commonly has a younger age of onset. The first single gene mutation identified as a cause of familial PD was in the gene coding for α(alpha)-synuclein 14 years ago. There has been more recent interest in the study of common variants or single nucleotide polymorphisms (SNPs) in the genes associated with familial PD. Common variants may be associated with an increased

risk of sporadic PD although effect sizes are small and larger study populations are required to adequately power case-control studies. Some of the genes and their products associated with familial PD are discussed below.

α(Alpha)-Synuclein (Park 1)

The *SNCA* gene encoding the α(*alpha*)-synuclein protein is located on chromosome 4q21.3. α(*alpha*)-synuclein is an abundant presynaptic protein of unclear function. The resulting parkinsonism transmits in an autosomal dominant pattern. It is rare, being reported only in a few families in Greece, Italy, Germany, and Spain. The protein, α(*alpha*)-synuclein, is present in Lewy bodies. Duplication and triplication of the α(*alpha*)-synuclein gene also causes familial parkinsonism (PARK4), revealing that over-expression of the normal (wild-type) synuclein protein is sufficient to provoke dopaminergic neurodegeneration. This supports a pathogenic role for α(*alpha*)-synuclein in IPD. There is debate as to whether Lewy bodies are contributing to the pathogenesis of PD or if the aggregation of α(*alpha*)-synuclein fibrils to form Lewy bodies is an effort of the cell trying to protect itself from toxic α(*alpha*)-synuclein oligomers.

Parkin (Park 2)

The Parkin gene is found on chromosome 6q25.2–27 and is the most common genetic cause for early onset PD (before age 50), accounting for 50% of familial and 20% of sporadic early onset disease. *Parkin* mutations give rise to autosomal recessive PD that can have typical features of IPD, but may also demonstrate hyperreflexia, dystonia at presentation, and sleep benefit. Rest tremor is not prominent. Postmortem studies have shown nigral degeneration in patients with *Parkin* mutations but without Lewy bodies in most reported cases.

Pink1 (Park 6)

After *parkin* mutations, *PINK1* mutations are the second most common cause of early onset PD, sharing autosomal recessive inheritance. Disease progression is usually slow with early levodopa-induced dyskinesias. The *PINK1* gene codes for a mitochondrial protein that is a recognized component of Lewy bodies seen in late-onset IPD, and the few available autopsy studies have identified typical neuropathological findings.

DJ-1 (Park 7)

Mutations in the *DJ-1* account for 1–2% cases of early onset familial PD. The presentation is with a typical early onset parkinsonism, often with dystonic and neuropsychiatric features. Unlike the unaffected heterozygous state with Parkin and PINK1 mutations, carriers do not demonstrate functional neuroimaging evidence of nigrostriatal dysfunction.

LRRK2 (Park 8)

PARK8 is mapped to chromosome 12q12 and encodes for a previously unknown protein named leucine-rich repeat kinase-2 (*LRRK2*), ubiquitously expressed in the CNS. Seven pathogenic *LRRK2* mutations have been found, and are the most frequent genetic cause of familial PD. They account for up to 5% of sporadic PD in the Caucasian population. In Ashkenazi Jews and North African Berber Arabs, *LRRK2* mutations have been found in up to 20–40% of both familial and sporadic cases of PD. The most prominent mutation in the Caucasian population is the G2019S substitution. *LRRK2* mutations result in an autosomal-dominant parkinsonism that resembles typical late-onset IPD. Cognitive impairment is usually not a feature. Although the neuropathology associated to *LRRK2* mutations is highly variable, degeneration of substantia nigra neurons has been consistently observed.

Others

Glucocerebrosidase (GBA) gene mutations, when homozygous, cause autosomal recessive Gaucher's disease. Heterozygous carriers are at increased risk of developing parkinsonism that is indistinguishable from IPD. Up to 30% of Ashkenazi Jews with PD have been found to have this mutation; the mutation causes PD in other ethnic groups as well. Dopa-responsive dystonia may present during adulthood as slowly progressive parkinsonism and tends to respond to low doses of levodopa. Parkinsonism can also be a predominant feature of the Westphal variant of Huntington's disease, although this is usually in juvenile patients and family history should be informative. Some forms of spinocerebellar ataxia (SCA2 and SCA3) can present with a levodopa-responsive parkinsonism with minimal cerebellar features.

Clinical Features

Motor

Rest Tremor

Rest tremor, typically of 4–5 Hz, is the first symptom recognized in 70% of patients, but may be absent in 20%. The classic "pill-rolling" tremor involves the thumb and forefinger. Rest tremor disappears with action but reemerges after a latent period of seconds as the limbs maintain a posture (*reemergent tremor*). Tremor increases with walking (a possible early sign), stress, or excitement. Tremor is also common in the lips, chin, and tongue but not the head.

Bradykinesia with Decrement

Bradykinesia encompasses slowness of movement, difficulty initiating movement, and loss of automatic movement. Decrement refers to a reduction in amplitude of movement, particularly with repetitive movements. Often, different tactics need to be used by the examiner

to bring out bradykinesia that might only be seen during certain actions, such as finger tapping, pronation–suppination movements, or opening and closing the fists. The face loses spontaneous expression (*hypomimia*) with decreased frequency of blinking. Speech becomes soft (*hypophonia*), and the voice has a monotonous tone with a lack of inflection (*aprosody*). Some patients do not enunciate clearly (*dysarthria*) and do not separate syllables clearly, thus running the words together (*tachyphemia*) and others stutter (*palilalia*). Bradykinesia of the dominant hand results in small and slow handwriting (*micrographia*). Difficulty rising from a deep chair, getting out of cars, and turning in bed are symptoms of truncal bradykinesia. Subtle signs of bradykinesia can be detected if one examines for slowness in shrugging the shoulders, smiling, lack of gesturing in conversation, and decreased blink frequency. Walking is slow, with a shortened stride length and a tendency to shuffle with decreased heel strike; arm swing decreases and eventually is lost.

Rigidity

Rigidity is an increase of muscle tone on passive movement and is not velocity dependent as seen with spasticity. Resistance is equal in all directions and usually has a "cogwheeling" character caused by the underlying tremor even if not visible. Rigidity of the passive limb increases while another limb is engaged in voluntary active movement, also known as the co-activation or facilitation test. Axial rigidity at the neck can similarly be accentuated by asking the patient to open and close both hands. Mild upper limb rigidity can be elicited by standing behind the patient and rocking their shoulders back and forward to produce passive arm swing that will be reduced on the more affected side.

Loss of Postural Reflexes

Loss of postural reflexes leads to falling and eventually to an inability to stand unassisted. These reflexes are tested by the pull-test during which the examiner, who stands behind the patient, gives a sudden firm pull on the shoulders after explanation of the procedure, and checks for *retropulsion*. With advance warning, an unaffected person can recover within two steps.

Flexed Posture

This commonly begins in the elbows and spreads to involve the entire body. The head is bowed, the trunk is bent forward, the back is kyphotic, and the arms are held in front of the body with the elbows, hips, and knees flexed. Walking is marked by *festination*, whereby the patient walks faster and faster with short steps, trying to move the feet forward to be under the flexed body's center of gravity to prevent falling. Deformities of the hands include ulnar deviation, flexion of the metacarpophalangeal joints, and extension of the interphalangeal joints (*striatal hand*). The hallux may be dorsiflexed (*striatal toe*). Lateral tilting of the trunk can develop, and extreme flexion of the trunk (*camptocormia*) is sometimes seen, which should be abolished when lying flat.

Freezing

This manifests as the transient inability to perform active movements. Freezing occurs suddenly and is transient, usually lasting seconds. It will typically occur when the patient begins to walk (*start hesitation*), attempts to turn while walking, or (approaches) a destination, such as a chair in which to sit (*destination hesitation*). Tight spaces can also provoke freezing, such as doorways, as can time-restricted activities such as crossing heavily trafficked streets or answering the phone. The combination of freezing and loss of postural reflexes is particularly devastating, and a common cause of falls.

Non-motor Symptoms

Later in the clinical course, non-motor and axial motor symptoms become prominent and account for greater disability, being poorly responsive to dopaminergic treatment (Table 5.4). After 20 years of disease in the Sydney Multicentre Study, falls were experienced by 87%, moderate dysarthria in 81%, dementia in 84%, visual hallucinations in 74%, postural hypotension in 48%, and urinary incontinence in 71%. Some non-motor symptoms can be observed as "pre-motor" phenomena, appearing before typical motor features. These include constipation, rapid-eye-movement (REM) sleep behavior disorder, olfactory impairment, and mood disorders. Some of the more troublesome problems and their management are discussed below.

Autonomic Involvement

Constipation

Constipation is almost universal in PD and can influence the efficacy of oral therapies by causing erratic absorption. Treatment with a regular stool softener, sometimes combined with a stimulant laxative is usually effective and most patients will require a regular laxative. The use of abdominal plain films can guide the use of laxatives and should be considered in patients whose motor control has deteriorated or where response to levodopa is variable.

Dysphagia

Dysphagia is not uncommon. Rarely recurrent aspiration pneumonia can complicate late stages of the disease. Patients benefit from access to a speech and language therapist to teach strategies to improve swallowing. Dysphagia is not typically levodopa responsive and can deteriorate after deep brain stimulation. A dry oropharyngeal mucous membrane due to anticholinergic agents is one readily treatable cause of swallowing impairment.

Table 5.4 Non-motor symptoms in Parkinson's disease

Neuropsychiatric • Depression • Anxiety, panic attacks • Hallucinations, illusions, delusions • Dementia, mild cognitive impairment • Obsessional, repetitive behaviors[a] • Delirium[a] • Anhedonia
Autonomic symptoms • Orthostatic hypotension • Nocturia, urgency, frequency • Paroxysmal sweating • Seborrhea • Erectile impotence • Xerostomia
Gastrointestinal • Ageusia • Sialorrhea • Nausea and vomiting • Dysphagia • Constipation • Incontinence
Sensory symptoms • Pain (can be pseudoradicular) • Paresthesia • Olfactory disturbance • Visual blurring
Sleep disorders • REM sleep behavior disorder • Difficulty initiating or returning to sleep, insomnia • Restless legs syndrome • Periodic limb movements in sleep • Vivid dreaming • Nocturnal hallucinations • Excessive daytime somnolence
Others • Fatigue • Seborrhea • Weight loss or gain[a]

[a]May be drug related

Sialorrhea

This is a manifestation of reduced swallow frequency in IPD as opposed to excessive saliva production. Anticholinergics are effective, but most available agents are tertiary amines that enter the CNS and can impair memory or cause hallucinations in older patients. Quaternary amines do not penetrate the CNS and are preferable. Sublingual 1% atropine can be used with some success. Injections of botulinum toxin into the salivary glands can be attempted. Pharyngeal weakness due to local toxin diffusion is a potential complication but is rarely encountered with dry mouth being a more common side effect.

Orthostatic Hypotension

Orthostatic hypotension (OH) can cause significant morbidity and contributes to the risk of falling. Conservative measures such as increased fluid intake, additional dietary salt, avoidance of hot baths and large meals, and the use of compression stockings can help. More resistant symptoms can respond to the sympathomimetic midodrine, starting with 5 mg and titrating up to three doses of 10 mg a day if necessary. Fludrocortisone can be used, typically starting at 0.1 mg/day. Supine hypertension can result from increased salt and mineralocorticoid ingestion. Elevation of the top of the bed to 30° at night can help this by reducing renal mineralcorticoid production. OH can be aggravated by dopaminergic therapy (dopamine agonists in particular), dehydration, and constipation.

Urinary Symptoms

Detrusor hyperreflexia predominates in IPD, causing frequency, urge, nocturia, and sometimes incontinence. In older male patients, the picture may be mixed with prostatism and anticholinergics are ideally prescribed after bladder ultrasound to determine residual volume, avoiding exacerbation of preexisting outflow obstruction. Equally important is the propensity of these agents to cause cognitive impairment in older patients with IPD, in particular the tertiary amines that cross the blood-brain barrier.

Trospium chloride is a quaternary amine that may have a better side effect profile although there is little trial data available addressing this issue. Reduction in late-night fluid intake can help nocturia. In patients treated for OH, nocturia can occur as a result of nocturnal pressure natriuresis secondary to supine hypertension.

Sexual Dysfunction

Sexual dysfunction is more commonly encountered in IPD than in the general population. Men with erectile dysfunction can be treated with agents such as sildenafil (this can exacerbate OH). Female patients may report reduced libido and conversely hypersexuality can

occur with dopamine agonist treatment as a manifestation of an impulse control disorder (discussed later).

Pain

Pain is not uncommon and can vary from uncomfortable paraesthesias to nociceptive or neuropathic sounding pain. Patients can initially present with pain in a joint on the symptomatic side, typically a shoulder, probably due to hypokinesis and immobility. Adequate treatment and physiotherapy can improve this considerably. Some patients complain of pain down one side of their body or in an apparently radicular distribution, both of which will respond to levodopa suggesting a central dopamine deficit as the underlying cause. True radiculopathies from nerve root compression can also worsen in the "off" state. Restless legs syndrome can be seen in association with IPD and can give rise to an aching discomfort in the legs at night, which can improve with a low dose of a dopamine agonist taken at night.

Abnormal Sweating

The pathophysiology of abnormal sweating in IPD is unclear but Lewy body pathology involving the hypothalamus may be contributory. Sympathetic cholinergic fibers are the final common pathway, which mediate the sweating response although dopamine would appear to play a role, as excessive sweating of the head and upper body can occur as an "off" phenomenon, often in bed at night. Sweating can also occur in the context of dyskinesias, but is usually less prominent than the paroxysmal attacks of drenching sweats reported in "off" periods. Other causes of excessive nocturnal sweating should be considered including thyrotoxicosis and latent tuberculosis infection.

Sleep Disturbance and Daytime Somnolence

Sleep disruption is common and multifactorial in IPD. Patients experience difficulty initiating sleep, fragmented sleep, REM sleep behavior disorder (RBD) and inversion of the sleep–wake cycle. RBD can predate the clinical onset of IPD. Sleep disruption can exacerbate the *e*xcessive daytime somnolence that is both associated with the disease itself and dopaminergics.

Sleep disruption in IPD probably relates to degeneration of brainstem nuclei that regulate the balance between sleeping and waking states. The pedunculopontine and subcoeruleal nuclei are thought to play a role in maintaining the normal muscle atonia of REM that is lost in RBD. Involvement of nondopaminergic nuclei important in maintaining arousal including the raphe nuclei (serotonin), locus coeruleus (noradrenaline), the tuberomamillary nucleus (histamine) may account for daytime somnolence. The burden on bed partners can be significant. Factors contributing to sleep disruption and therapies are given in (Table 5.5).

Table 5.5 Causes and treatment of sleep disturbance in Parkinson's disease

Bradykinesia and rigidity	Can make it difficult to turn in bed to find a comfortable position. Contribute to difficulty initiating sleep or returning to sleep after an arousal. Some patients overcome this by using satin sheets and night-clothes to facilitate movement.
Restless legs syndrome (RLS)	Will respond to dopamine agonists and levodopa preparations given late at night. Treatment can be complicated by augmentation whereby symptoms become longer lasting, more severe, and more extensive. It is important to ensure dyskinesias are not the cause of disturbed sleep as increased dopaminergic treatment will exacerbate this. Opioids, such as propoxyphene, can often suppress RLS and not cause augmentation.
Periodic limb movements in sleep	Periodic episodes of rhythmic extension of the hallux with dorsiflexion of the ankle, sometimes extending proximally to involve knee and hip flexors. Commonly associated with RLS and can also respond to dopaminergic drugs. Opioids can also be of benefit in resistant cases. Propoxyphene 65 mg late in the day before the onset of symptoms is usually effective. Start with a half-tablet, and titrate up to two tablets if necessary.
Nocturia	Common in this age group. Anticholinergics can help but may exacerbate vivid dreams or hallucinations. Sometimes responds to dopaminergic treatment. Rule out coexisting pathology with referral to urology for assessment where appropriate.
Vivid dreams	Are usually not disruptive to sleep but can be upsetting. Can resolve with a reduction in dopaminergic or anticholinergic drugs taken at night. Can be exacerbated by amphetamine metabolites of selegiline, which should be taken early in the day. Low-dose quetiapine, starting at 12.5–25 mg at night, can help if required.
Nocturnal hallucinations	Are associated with cognitive impairment in IPD and along with vivid dreams can respond to a low dose of quetiapine that can also improve insomnia due to its soporific effects. Donepezil 5–10 mg nocte can also be helpful.
REM sleep behavior disorder (RBD)	Semi-purposeful movements in sleep, typically as if kicking or fighting off an attacker. Occurs as a consequence of losing normal physiological paralysis during REM sleep. RBD is typically reported by bed partners who should be questioned. A small dose of clonazepam, 0.25–1 mg at night, can be very effective. Melatonin, 3–12 mg at night, is an alternative when clonazepam exacerbates daytime somnolence and is generally well tolerated.
Insomnia or early morning wakening	Can be markers for underlying depression. Tricyclic antidepressants such as amitriptyline may have a role in this setting to improve mood and produce a hypnotic effect (use with caution in patients taking an MAO-B inhibitor). Drugs that may be interfering with sleep such as selegiline or modafinil should be withdrawn or taken early in the day to minimize their stimulant effect. There is no specific contraindication to the use of benzodiazepines as night sedation although any "carry-over" into the next day can affect cognition and increase risk of falling.
Sleep disordered breathing	May be (due to sleep apnoea) and important to consider as treatment with noninvasive ventilatory support at night can be very effective. May not always have the typical body habitus seen in obstructive sleep apnea.

Neuropsychiatric

Parkinson's Disease and Dementia

Dementia is not typically an early feature of PD and if evident within 1 year of presentation, a diagnosis of dementia with Lewy bodies (DLB) is made, otherwise the term Parkinson's disease and dementia (PD–D) is used. The overall prevalence of dementia in PD is high at approximately 40%, increasing in frequency with advancing years. The risk of developing dementia is 2.8-fold greater than controls.

The pathological substrate of dementia in PD remains uncertain. The involvement of subcortical structures, in particular the medial nigra and thalamus, may be important but cortical Lewy body burden and co-existent Alzheimer's disease pathology have also been shown to correlate with cognitive impairment. Cholinergic cell loss is more severe than that seen in Alzheimer's disease with severe neuronal loss in the basal nucleus of Meynert. The relative contribution of noradrenergic, dopaminergic, and serotonergic neurons to PD–D is unknown.

The hallmark of cognitive impairment in IPD is executive dysfunction with impaired inability to plan, organize, or regulate internally generated goal-directed behavior. Memory impairment is not as prominent as in Alzheimer's disease (AD) although responses can be slow (*bradyphrenia)*. Memory deficits usually improve with prompting, suggesting a problem with memory retrieval rather than encoding. Verbal fluency and visuospatial function may also be affected. Hallucinations are more common than in AD, present in up to 70% of patients.

Once infectious and drug-related confusional states have been out-ruled, treatment with a cholinesterase inhibitor should be considered. Both rivastigmine and donepezil are effective for cognitive and behavioral symptoms without worsening parkinsonism, although tremor can worsen. Hallucinations can respond to cholinesterase inhibitors, but if antipsychotics are sometimes required, clozapine or quetiapine can be used although controlled trials are lacking. Clozapine is associated with a low risk of agranulocytosis (1–2%), so baseline full blood count with subsequent monitoring is required; weekly initially for at least 18 weeks with local guidelines being followed thereafter. Treatment is started at 6.25 mg at bedtime and gradually titrated to response to 25–75 mg per day. Quetiapine may be less effective than clozapine although it is generally used first as it is not associated with hematological adverse effects. It is usually started at 12.5–25 mg at bedtime. Other atypical neuroleptics, risperidone, olanzapine, and aripiprazole have all been associated with worsening of parkinsonism. There is insufficient evidence to recommend use of the glutamate antagonist memantine in PD–D.

Depression

Prevalence data for depression in IPD varies and is dependent on diagnostic criteria. Depressive symptoms often go undiagnosed, with hypophonia, poor sleep pattern, and flattened affect being more commonly attributed to parkinsonism. Depression in IPD has a higher prevalence than in other chronic, incapacitating illnesses suggesting an endogenous

component. This has been attributed to global monoamine depletion in IPD, in particular that involving noradrenergic neurons. Dopamine receptors are likely to play a role in regulation of mood. SSRI agents reduce dopamine uptake in the prefrontal cortex and chronic treatment leads to changes in D2/D3 receptor sensitivity in the nucleus accumbens.

SSRIs are commonly prescribed for depression in IPD. They are well tolerated but have a theoretical risk of inducing a serotonin syndrome when administered with an MAO-B inhibitor. This does not seem to be relevant with the doses used in clinical practice. Agents targeting dopaminergic and noradrenergic systems may be superior.

The tricyclic antidepressants desipramine (25–50 mg nocte) and nortriptyline (20–40 mg nocte) inhibit noradrenaline uptake and have a better side effect profile than amitriptyline due to less anticholinergic activity. Nortriptyline was found to be more effective than slow release paroxetine in one randomized double-blinded trial. The dopamine agonists, pramipexole and ropinirole, have been also shown to be effective. The effect appears to be independent of any effect on motor function and may relate to an effect on limbic D2/D3 receptors.

Anxiety

Anxiety is a known preclinical risk factor for IPD, suggesting that, in at least some patients, it is a disease phenomenon and not a reaction to it. Panic attacks can occur in "off" states and can be managed by minimizing motor fluctuations and "off" time. It is important to be aware that manic and anxiety states have been reported following dopamine agonist treatment. Some patients benefit from the short-acting benzodiazepines alprazolam (0.25–1 mg TID) and lorazepam (0.5–1.0 mg TID). Tricyclic antidepressants or SSRIs are sometimes required where there is additional depression (see section above).

Apathy

Apathy is characterized by a reduction in goal-directed behavior and is thought to be related to executive dysfunction in IPD. Disturbance of striato-frontal circuitry may be important. Dopaminergic reward pathways between the midbrain and limbic cortex are affected in IPD. Patients may not report depressive symptoms and typically will not share the frustration of caregivers with respect to their lack of motivation and drive. Stimulants such as modafinil are sometimes effective and empirical use of dopaminergics may help. A broader approach increasing monoamine transmission with SSRIs, SNRIs, and TCAs can also be used.

Treatment of Motor Symptoms: Overview

Treatment must be tailored to the individual patient; each with a unique set of symptoms, different functional requirements, and responding differently to various treatments. The goal is to maintain independence for as long as possible while attempting to address motor

and non-motor symptoms of the disease. Because no treatment has been shown unequivocally to have a neuroprotective effect (discussed later), pharmacological treatment in the early stages is focused on symptomatic management. Levodopa is the most effective oral treatment for bradykinesia and rigidity. Much of the therapeutic effort in advanced disease involves control of the complications associated with chronic levodopa use, namely, fluctuations, dyskinesias, and increasingly recognized neuropsychiatric aspects. Importance has therefore been placed on the timing of levodopa introduction, particularly in younger patients who have longer to live with dyskinesias, should they develop. Advanced IPD is characterized by these treatment complications, non-motor symptoms, and motor symptoms that are not levodopa responsive. Non-pharmacological treatments, in particular physiotherapy, have a significant role. Physiotherapy involves patients in their own care, promotes exercise, keeps muscles active, and preserves mobility. This approach is particularly important as IPD advances because many patients will tend to remain sitting and inactive, exacerbating their immobility.

Symptomatic Treatment of Motor Symptoms

Levodopa

Dopamine is unable to cross the blood-brain barrier, but its precursor levodopa is and remains the most effective oral therapy. Early concerns that levodopa might be toxic to dopaminergic neurons proved to be unfounded and with respect to the pre-levodopa era, mortality and morbidity rates in PD have fallen. Dopamine has a strong effect on the area postrema, a fourth ventricular structure with high density of dopamine receptors and without protection from the blood-brain barrier. Nausea and vomiting are therefore common side effects.

Levodopa is routinely administered with a dopadecarboxylase inhibitor (carbidopa or benserazide) to prevent its peripheral breakdown to dopamine; these agents do not penetrate the blood-brain barrier. They potentiate the effects of levodopa, allowing about a fourfold reduction in dose to obtain the same benefit. Approximately 75 mg to 100 mg of carbidopa is required to completely suppress peripheral dopadecarboxylase. Some formulations contain additional carbidopa if this is an issue; Sinemet Plus combines 25 mg of carbidopa with 100 mg of levodopa instead of the 10 mg in Sinemet 110. Additional carbidopa can also be prescribed in 25 mg tablets. Domperidone is preferred if an antiemetic is required. Unlike prochlorperazine and metoclopramide, it does not cross the blood-brain barrier and will not therefore exacerbate parkinsonism. Domperidone is not available in the United States where trimethobenzamide hydrochloride (Tigan) can be used instead. Domperidone (Motilium) should be taken 30 min before each dose and can usually be discontinued gradually within weeks. Other common side effects reported when initiating levodopa treatment include orthostatic hypotension, confusion, hallucinations, and sedation.

Levodopa is available in a number of forms and doses that allow treatment to be tailored to the individual needs of each patient. Sinemet (levodopa/carbidopa) is available in strengths of 50/12.5 mg, 100/10 mg, 100/25 mg and 225/50 mg. Madopar (levodopa/benserazide) is only available in Europe and in strengths of 100/25 mg and 50/200 mg.

There is also a water-dispersible formulation of Madopar (50/12.5 mg and 100/25 mg) with a more rapid onset and shorter duration of action. In practice, doses over 1,200 mg daily are not often used.

Levodopa, carbidopa, and the COMT inhibitor entacapone are available in a single tablet (Stalevo). This comes in a number of strengths of levodopa (50, 75, 100, 125, 150, and 200 mg), each combined with 200 mg of entacapone. This reduces the total number of tablets taken daily and reduces "off" time in patients experiencing the wearing-off phenomenon. Entacapone prolongs the half-life of levodopa from 90 min to approximately 180 min. It was thought that concurrent entacapone may reduce the pulsatile stimulation of dopamine receptors and avoid levodopa-induced dyskinesias, but a clinical trial showed the opposite effect; there were earlier and more severe dyskinesias when concurrent entacapone was utilized when levodopa therapy was started.

Both Sinemet and Madopar are available in modified release formulations that are sometimes used to smooth-out motor fluctuations or for nighttime symptoms. Onset of action can be delayed and bioavailability is approximately 75% of standard release formulations because the entire content of the extended-release formulation is not absorbed before the tablet passes the duodenum and jejunum (the sites where levodopa is absorbed).

Dopamine Agonists

Dopamine agonists (DA) directly stimulate dopamine receptors and are not reliant on degenerating striatal nerve terminals for uptake and conversion into an active product. For most patients, DA are effective as a monotherapy in the early stage of the disease, allowing later introduction of levodopa and thus delaying motor complications. Dopamine agonists will rarely induce dyskinesia but are less effective for the symptomatic management of IPD; most patients require the addition of levodopa within a few years. Dopamine agonists do not delay the time to onset of dyskinesias once levodopa is added when compared with patients starting on levodopa from the outset.

The earliest DA in use were the ergot derivatives bromocriptine, pergolide, lisuride, and cabergoline. Retroperitoneal, pleural, and pericardial fibrosis, and restrictive fibrotic valvulopathy were reported with pergolide and cabergoline, attributed to the activation of the $5HT_{2B}$ receptor. Pergolide is no longer available in the U.S. Lisuride, a short-acting ergoline agonist given subcutaneously is not associated with fibrotic complications ($5HT_{2B}$ antagonist), but has never been in common usage due to the emergence of apomorphine.

The non-ergoline agonists, pramipexole, ropinirole, and rotigotine are currently the most frequently prescribed oral DA. Pramipexole and ropinirole are available in multiple daily dosing formulations and more recently in modified release formulations taken once daily. These formulations may have benefits in improving compliance and nocturnal or early morning symptoms. Rotigotine is administered transdermally, avoiding delays of gastric motility, first-pass metabolism, and competition with dietary protein. Skin site reactions are relatively common but mild, occurring in up to 40% of patients. Typical initiation, maintenance, and maximum doses for the non-ergoline DA are given in Table 5.6. The clinical response to pramipexole at doses greater than 0.7 mg TID may not be greater

Table 5.6 Commonly used nonergot dopamine agonists and typical dose schedules

Dopamine agonist	Start dose (mg)	Week 2 (mg)	Week 3 (mg)	Week 4 (mg)	Therapeutic range mg/24 h	Max dose
Ropinirole	0.25 TID	0.5 TID	0.75 TID	1.0 TID	9.0–12.0	8 mg TID
Pramipexole (salt)	0.88 TID	0.18 TID	0.36 TID	0.7 TID	0.36–0.7	1.08 mg TID
Rotigotine	2	4	6	8	4.0–8.0	16 mg/24 h

than that at lower doses although side effects will be more frequent. Conversely, ropinirole is often not titrated quickly enough to an effective treatment dose (minimum of 3 mg TID) due to its low initiation dose. Rotigotine should be titrated straight up to 8 mg/24 h if tolerated whether as a monotherapy or in combination with levodopa. Dose increases are then in 2 mg increments at weekly intervals until a satisfactory response is obtained.

Dopamine agonists have a less favorable side effect profile than levodopa and are more likely to cause confusion, hallucinations, nausea, postural hypotension, and ankle edema. Some patients may idiosyncratically have a better tolerance for one agonist over another. Much attention has been paid to reports of sudden unheralded episodes of sleep or "sleep attacks" with DA. Daytime somnolence is a common problem in IPD. Further study of this phenomenon suggests that these "sleep attacks" may represent unintended sleep episodes in individuals with excessive daytime somnolence from disturbed sleep and dopaminergic treatment. Tolerance to the feeling of chronic sleepiness and memory impairment may give the impression of sudden "attacks" of sleep. The soporific effect of dopaminergic therapy would appear to be the same whether dopamine agonist or levodopa is prescribed. Nonetheless, patients on DA, who are driving and reporting frequent unintended and reportedly unpredictable episodes of sleep, should have their dose reduced and be advised not to drive until there is improvement.

Monoamine Oxidase Type B (MAO-B) Inhibitors

Selegiline and rasagiline are irreversible MAO-B inhibitors that have a mild symptomatic effect. MAO-B is an enzyme responsible for the central clearance of dopamine, and its inhibition augments the effect of levodopa. Both drugs can be used for the management of symptoms in early IPD or as an adjunct to levodopa to reduce "off" time during motor fluctuations. As a monotherapy, selegiline can delay the need for levodopa by an average of 9 months. Selegiline has few adverse effects when given alone. When given concurrently with levodopa, it can increase the dopaminergic effect causing dyskinesias and hallucinations. Selegiline has amphetamine metabolites that can disturb sleep if given late at night. A dose of 5 mg once or twice daily, ideally before midday, is typically used. Above 10 mg, selectivity for MAO-B is lost, risking a sympathetic crisis. Rasagiline, 1 mg once daily, is a second-generation irreversible MAO-B inhibitor providing a stronger symptomatic effect. It has no amphetamine-like breakdown products and may be associated with less sleep disturbance.

Amantadine

Amantadine is a mild indirect dopaminergic agent that augments dopamine release. It also has some anticholinergic and antiglutamatergic properties. Amantadine is now uncommonly used in the treatment of early IPD due to the availability of other symptomatic treatments with better side effect profiles. In advanced IPD, amantadine is used for its antidyskinetic effect, possibly as a result of its glutamate antagonism. Unfortunately, patients will often report a falloff of benefit after several months. Adverse effects include livedo reticularis (a reddish mottling of skin) on the legs, dry mouth, ankle and leg edema, postural hypotension, visual hallucinosis, and nightmares. Amantadine has a long half-life of about 12 h, and if side effects occur, it can be stopped abruptly. The usual dose is 100 mg two times per day, but sometimes a higher dose (up to 200 mg twice daily) may be required for dyskinesias.

Anticholinergic (Antimuscarinic) Drugs

Anticholinergic agents are less effective antiparkinsonian agents than are dopaminergic drugs (estimated to improve parkinsonism by about 20%), but can be a more effective treatment for tremor. Their exact mechanism of action is unknown; they may redress an imbalance between cholinergic and dopaminergic transmission in IPD. Trihexyphenidyl is a widely used anticholinergic agent. A common starting dose is 2 mg TID. It can be gradually increased to 15 mg or more per day although doses as high as this are rarely tolerated. Biperedin and procyclidine are alternatives.

Adverse effects are common with many patients reporting poor short-term memory. All patients should have a baseline cognitive assessment performed before starting treatment. These agents are preferably avoided if a patient or relative report prior memory impairment. Occasionally, hallucinations and psychosis occur, particularly in the elderly; these drugs should therefore, as a rule, be avoided in patients older than 65 years of age, although this is best judged on "biological age." In older patients, amitriptyline or diphenhydramine are sometimes beneficial, without the central side effects of more potent anticholinergic agents and can also be used as a hypnotic. Anticholinergics can reduce sialorrhea when tolerated. Peripheral side effects are common, including dry mouth, blurred vision, constipation, and urinary retention. One approach is to treat these adverse effects by appropriate antidotes instead of discontinuation. Pilocarpine eye drops can overcome dilated pupils that can cause blurred vision, and can be useful if glaucoma is present. Pyridostigmine, up to 60 mg TID, can help to overcome dry mouth, urinary difficulties, and constipation.

COMT Inhibitors

When levodopa is administered with a dopa decarboxylase inhibitor, cathchol-O-methyltransferase (COMT) then becomes the main enzyme responsible for its breakdown in the periphery. COMT inhibitors prolong the pharmacological effect of levodopa, doubling its elimination half-life and augmenting its peak dose effect. They are useful in

managing end of dose deterioration and reducing "off" time but may exacerbate peak-dose dyskinesias resulting in a need to reduce individual levodopa doses by 15–30%. Entacapone and tolcapone are approved for use in IPD. Entacapone acts peripherally only and because it has a very short half-life, 200 mg is given with each dose of levodopa. A combined formulation with levodopa and carbidopa (Stalevo) has similar efficacy to these compounds administered separately. Tolcapone acts both centrally and peripherally. It is initially prescribed at 100 mg TID and is more potent than entacapone. It has been associated with liver enzyme elevations, and three deaths from hepatic failure occurred in patients not having regular monitoring. It is therefore regarded as a second-line agent. Regular monitoring of liver parameters should allow the drug to be used safely with immediate discontinuation if ALT or AST exceed the upper limit of normal.

Neuroprotection

No definitive evidence has been found of neuroprotection using any agent in IPD. There are a number of issues that need to be addressed before neuroprotective strategies in PD can be properly investigated:

1. Timing of neuroprotection: At presentation, the majority of nigrostriatal neurons have already been lost; therefore any neuroprotective agent may be too late to be effective. Studies of at-risk asymptomatic carriers of disease-causing genes (e.g., LRRK2) may prove useful in teasing out this issue. However, in some cases at least, familial PD may have a different disease mechanism to sporadic disease. Familial cases are also uncommon and age of onset and penetrance are variable, making interpretation difficult. The identification of preclinical markers in sporadic IPD is therefore of great interest.
2. It is quite possible that IPD represents a heterogeneous group of mechanisms giving rise to a final common phenotype. If this is so, the identification of a single effective neuroprotective agent will be difficult. Clarification of the pathophysiology of IPD will help target specific neuroprotective therapies tailored to one or more responsible mechanisms.
3. Outcome measures that satisfactorily measure neuroprotection are needed. Clinical markers do not necessarily correlate with disease modification, particularly when the agent being studied has symptomatic effects. In IPD, the Unified Parkinson's Disease Rating Scale (UPDRS) is commonly used. The patient scores non-motor domains but many are not included. These symptoms may be more important in assessing disease modification as they generally are not levodopa responsive and thus are unmodified by any symptomatic drug effect. The addition of imaging studies to assess striatal dopamine receptor density may be of value as a surrogate of neuronal loss.
4. Trial design is vital to allow interpretation of any findings. A "wash-out" design allows, in theory, the symptomatic effect of a drug to wear off and thus leaving only a putative neuroprotective effect to account for a group difference. The biological effect of

dopaminergic drugs may however last long beyond their pharmacological effect making interpretation difficult. "Delayed-start" trials have attempted to address this issue by starting one group of patients on a study drug before the other. Failure of the delayed-start group to "catch up" with the early start group supports a possible neuroprotective effect of early treatment. This approach also has potential flaws. If a beneficial effect takes a long time to become established, the delayed-start group may not have had sufficient exposure to the study drug, Also, a strong symptomatic effect can be sufficient to mask any disease-modifying effect.

Selected Trials of Interest

- Antioxidants have been investigated because the metabolism of dopamine by MAO-B produces free radicals. The DATATOP trial compared the effects of the MAO-B inhibitor selegiline (10 mg/day) and the antioxidant tocopherol or vitamin E (2,000 U/day). Selegiline delayed the requirement of levodopa by a mean of 9 months. Because of an unexpected symptomatic effect of selegiline, disease modification could not be proven. The subsequent trial with selegiline, the BLIND-DATE trial, added selegiline or placebo to patients already taking levodopa. The results showed less clinical worsening of UPDRS scores, less freezing of gait, and a lesser increase of additional levodopa in the group taking selegiline compared to the placebo group despite the liberty to take as much levodopa as needed. This supports the possibility of disease modification but doesn't prove it.
- The recent ADAGIO trial attempted to readdress the question by studying a different MAO-B inhibitor, rasagiline (1 mg or 2 mg), versus placebo using a delayed start protocol. The delayed start group demonstrated significant differences in UPDRS (1.7 points) with respect to the 1 mg dose of rasagiline at the end of 52 weeks. Questions remain, however, as strangely, the findings using a 1 mg dose were not replicated in the group receiving 2 mg.
- Coenzyme Q10, an antioxidant and mitochondrial-active agent, at 1,200 mg/day showed some reduction of parkinsonism in a randomized, placebo-controlled, double-blind pilot study of 80 patients not requiring treatment for their disability. The trial met prespecified criteria looking for a linear response between dose and change in UPDRS ($p = 0.09$). The placebo group and patient group receiving 1,200 mg differed significantly with respect to this change (+11.99 vs. +6.69, respectively). A larger Phase III trial of coenzyme Q10 is in progress.
- The ELLDOPA study was designed to determine if levodopa has a toxic effect on dopaminergic neurons. A placebo group was compared with three groups receiving levodopa at varying doses, 150 mg, 300 mg, and 600 mg per day. All subjects had early PD (less than 3 years). Treatment was for 40 weeks with a 2 week washout period before final assessment. The placebo group UPDRS worsened after 42 weeks while the high-dose levodopa group maintained their improvement of −1.4 points with respect to baseline. This result raised the question of a neuroprotective effect of levodopa; however, the improvement could be due to a prolonged symptomatic effect insufficiently washed out over 2 weeks.

Treatment According to the Stage of Parkinson's Disease

When and How Should Treatment Be Started in Early Stage Disease?

In the absence of definitive evidence favoring a disease-modifying drug, authorities in the past have generally agreed that treatment is not necessary when symptoms are not causing disability. This practice was motivated by a desire to avoid unnecessary side effects that might outweigh a small benefit.

With the advent of newer agents that may have a disease-modifying role, some consider that initiation of treatment at the time of diagnosis is warranted to slow degeneration in an already considerably depleted substantia nigra. It is proposed that dopamine depletion in the basal ganglia leads to maladaptive, compensatory changes within basal ganglia circuits, which may also put additional metabolic stress on a failing system. Early symptomatic treatment might prevent or delay decomposition by normalizing basal ganglia function. This hypothesis is based on the apparent benefit of early treatment demonstrated in trials of drugs that all have some symptomatic benefit, including levodopa, selegiline, and rasagiline. This was examined in the recent PROUD study, which assessed early versus delayed start pramipexole. No difference was found between early and delayed treatment groups.

Many neurologists will now empirically start with either selegiline or rasagiline monotherapy, providing well-tolerated, once daily dosing with mild symptomatic benefit before starting more potent dopaminergic drugs or an anticholinergic for tremor predominant disease. The next step is typically the addition of a dopamine agonist (especially in young patients more prone to develop dyskinesias) due to their low propensity to induce dyskinesias and their ability to provide early symptom control in most patients.

Stage When Symptoms and Signs Require Treatment with Levodopa

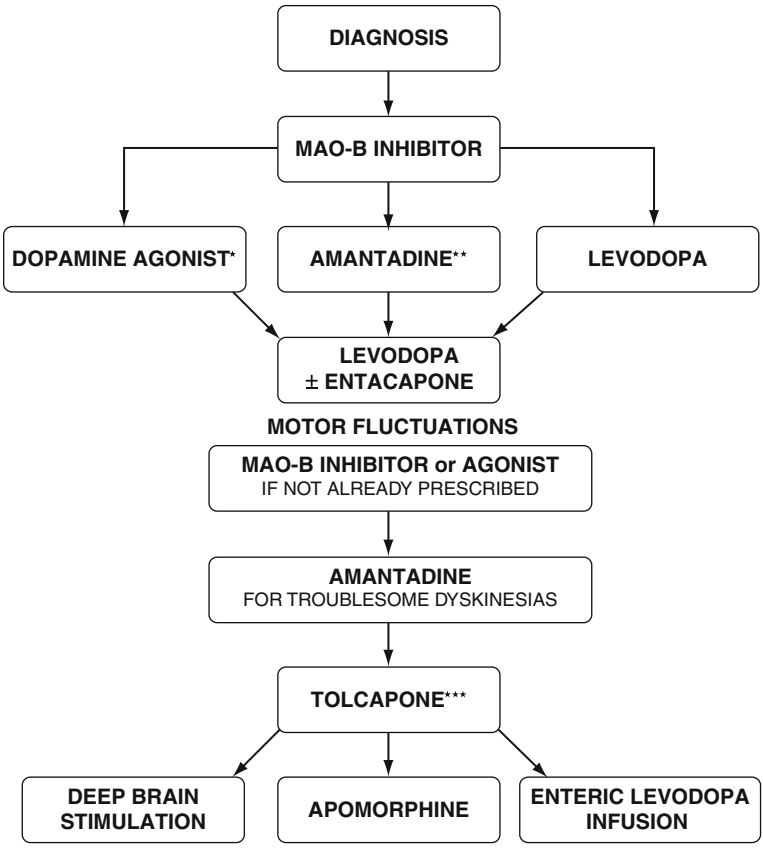
Incremental addition of dopamine follows when symptom control is no longer adequate. Levodopa can be introduced as a first-line agent in treatment-naïve patients, but this approach is usually reserved for older patients (>70 years of age, e.g.), patients with cognitive impairment in whom a greater risk of neuropsychiatric complications with DA could be expected, or when a patient is at a high risk of injury due to falls.

The conflict exists between the development of dyskinesias after chronic levodopa treatment and its superior efficacy and tolerability when compared to dopamine agonists. After 5 years of levodopa therapy, about 75% of patients will have some form of motor complication. Those in favor of early levodopa point out the relatively poor tolerability of DA and better quality of life scores with early levodopa compared to those started on an agonist. They also highlight follow-up of these two groups showing that only mild dyskinesias are significantly more frequent in those receiving levodopa ab initio. Furthermore, it is sometimes suggested that earlier levodopa is reasonable with infusional and surgical options now available if dyskinesias become an issue.

Those favoring initial dopamine agonist treatment point out that in young patients having many years of treatment ahead of them, disabling dyskinesias should be avoided for as

long as possible if an effective alternative is available. Infusional and surgical options for the management of motor complications are only suitable for some patients and carry their own risks and side effects. It is usually possible to tailor treatment for patients based on individual social and occupational requirements.

The pragmatic approach is to introduce levodopa without undue delay when other anti-parkinsonian medications, typically dopamine agonists, at maximum tolerated doses are no longer bringing about satisfactory symptom control. An algorithm giving an overview of treatment options over the natural history of IPD is given in Fig. 5.3.



*Dopamine agonists are more likely to cause cognitive impairment and hallucinations than levodopa. Ergot derived agonists are associated with a fibrotic cardiac valvulopathy.

**Amantadine should be avoided where there is pre-existing cognitive impairment or hallucinations.

***Tolcapone is a second line COMT inhibitor after entacapone due to a rare association with hepatic failure. Liver function needs to be regularly followed while on treatment.

Fig. 5.3 Suggested treatment algorithm in idiopathic Parkinson's disease. Treatment needs to be individually tailored to each patient's age, requirement, and drug side effect profiles

Initiating Levodopa

Most treatment-naïve patients will tolerate initiation of levodopa/carbidopa at 50/12.5 mg TID. Each dose of 50/12.5 mg can then be gradually replaced by levodopa/carbidopa tablets of 100/10 mg or 100/25 mg until 100 mg of levodopa TID is reached. Many neurologists will initiate treatment using 100 mg doses of levodopa but a more cautious titration can be used in elderly patients. Nausea is the main side effect in treatment-naïve patients and can be treated with domperidone, 10 mg 30 min before or with each dose. Nausea and vomiting will usually settle within 2 weeks. For patients with persistent symptoms, the formulation with a higher dose of carbidopa should be used (Sinemet Plus, carbidopa/levodopa 100 mg/25 mg) to maximize peripheral dopa decarboxylase inhibition or this formulation can be used from the start.

There is no evidence that initiation of levodopa combined with a COMT inhibitor is of any benefit in delaying motor complications. In the early stage of levodopa therapy, before complications have developed, use of extended-release carbidopa/levodopa has no advantage over use of the standard preparation in delaying motor fluctuations. Some patients benefit from the use of dispersible levodopa in the morning to achieve faster onset of action allowing them enough freedom of movement to get dressed and washed. This approach can be useful for early morning dystonia. Dispersible levodopa can also be used on an "as required" basis for sudden "off" periods although subcutaneous apomorphine boluses can prove more practical in this situation.

Management of Advanced Parkinson's Disease

Some patients with longstanding IPD can be effectively managed on oral dopaminergics with occasional adjustments to manage the complications of chronic treatment. Others cannot achieve adequate control despite optimum oral treatment. This group experiences dyskinesias, constant swinging between "off" and "on" states, and unpredictable "offs." Options at this stage include subcutaneous apomorphine, jejunal levodopa via gastrojejunostomy (Duodopa), or stereotactic deep brain surgery (DBS). Most patients at this stage have developed additional non-motor features of IPD including cognitive impairment and mood disorders that need to be considered when choosing further strategies. Treatment with these advanced therapies usually allows reduction of total dopaminergic drug dose but almost all patients continue to require some oral medication.

Infusional Apomorphine

Continuous subcutaneous apomorphine infusion was introduced in the 1980s and is useful in advanced IPD with motor fluctuations refractory to the usual strategies. Symptoms that are not levodopa responsive will not improve. The drug is delivered via a pump connected to an infusion catheter. The needle sits subcutaneously in the abdominal wall or thigh. The rate of infusion can be adjusted with the ability to deliver bolus doses when required. Most patients require between 50 and 200 mg apomorphine per day. Some patients will take the

pump off at night but continuous infusion is possible if nocturnal symptoms are a problem. Total daily dose of levodopa can typically be halved.

The most common side effects with apomorphine are nausea, postural hypotension, daytime somnolence, and psychotoxicity. Patients need to be pretreated with domperidone for 48 h and this is continued for as long as needed afterward, usually less than 3 months. Abdominal wall nodules can form at infusion sites. Strict adherence to an aseptic technique during needle placement and regular rotation of sites can limit this problem. Ultrasound therapy and silicone gel patches can reduce the size of nodules once formed. Coombs-positive autoimmune hemolytic anemia is a rare and reversible side effect so a full blood count, reticulocyte count, and Coombs's test should be performed intermittently. Patients should be warned that apomorphine can indelibly stain clothing an olive green color.

Patients being considered for an apomorphine infusion first need to be shown to be responsive to and tolerant of an apomorphine challenge as described below. For patients already using intermittent boluses with an apomorphine pen, this is not necessary:

1. The patient is pretreated with domperidone, 20–30 mg TDS for 48 h.
2. Anti-Parkinson medications should not be taken for 4–6 h prior to the challenge. Prolonged release dopaminergics should be omitted the day before.
3. A pretreatment assessment is performed, typically including the motor subscale of the UPDRS or some other objective test of motor function (e.g., a timed walk).
4. An initial dose of 2 mg is administered. The clinical examination is repeated and the patient is observed for up to 30 min.
5. Increasing doses (in 1–2 mg increments) are given every 45 min until a 20% improvement is documented or a maximum dose of 10 mg is reached. No response at 7 mg should be considered a negative challenge.
6. The challenge is positive if a 20% improvement in pretreatment motor function is observed.

Infusional Levodopa via Jejunostomy

Delayed gastric emptying in IPD can lead to erratic and unpredictable delivery of levodopa to the small intestine. Levodopa can be administered in a gel formulation (Duodopa) by infusion through an endoscopically placed gastrostomy with a jejunostomy tube to ensure a more constant and reliable rate of delivery. This method of levodopa administration appears to have similar efficacy to subcutaneous apomorphine, reducing daily "off" time by up to 80%. The total daily dose of Duodopa required can be reduced by 20–30% with addition of a COMT inhibitor if not already being used. Patients can be treated over 16 h with a break at night or continuously over 24 h for nocturnal symptoms. This form of infusion may be useful for patients intolerant of apomorphine or those with intolerable infusion site complications. Important considerations are the need for the patient or carer to understand how to manage the pump and the relatively high frequency of complications relating to tube placement including hemorrhage, peritonitis and the possibility that tubes can kink, become displaced, and require replacement.

Surgical Procedures

Prior to the development of levodopa, a number of surgical techniques were attempted to treat the motor symptoms of IPD. Thalamotomy emerged as the most effective, particularly for tremor. Surgical options faded from prominence with the miracle of levodopa; however, the prevalence of motor complications after long-term levodopa exposure has renewed interest. DBS has replaced ablative procedures as the technique of choice, as it does not destroy brain tissue, it is potentially reversible, and adjustments can be made postoperatively. The gait, speech, swallow, and cognitive disturbances that are associated with bilateral ablative procedures are also less of a concern as stimulation can be reduced or aborted if required.

DBS does not offer superior control of the cardinal symptoms of IPD compared to levodopa. Its role is in the management of motor complications and the management of treatment-refractory tremor. Levodopa-responsive patients with dyskinesias or motor fluctuations affecting their quality of life are the best candidates.

The best results from DBS are seen with younger patients. The presence of cognitive impairment is a relative contraindication as cognition can worsen with any surgical penetration of the brain. However, recent prospectively gathered data from patients undergoing stimulation of the subthalamic nucleus is reassuring. Other adverse effects from DBS include hemorrhage, infection, speech impairment, dystonia, and wire breakage. Even in young patients, there can be impaired cognition, depression with suicide attempts, and an incomplete response. Postoperative follow-up programming of the stimulators is an ongoing process.

Targets for ablative and DBS procedures are discussed below:

- *Thalamotomy and thalamic stimulation*: The target is the ventral intermediate nucleus and best effects are seen for contralateral intractable tremor that can be relieved in at least 70% of cases. The effect on other parkinsonian features is less impressive. Although a unilateral lesion carries a small risk, bilateral operations result in dysarthria in 15–20% of patients. Thalamic stimulation seems to be safer than ablation and can be equally effective against tremor.
- *Pallidotomy* and *pallidal stimulation*: The effects of globus pallidus stimulation are broadly similar to pallidotomy. The target is the posterolateral part of the globus pallidus interna (GPi) and outcomes are best treating contralateral dyskinesia with less benefit for bradykinesia and tremor. The target in the GPi is believed to be the site of afferent excitatory glutamatergic fibers coming from the subthalamic nucleus, which is overactive in IPD.
- *Subthalamotomy and subthalamic nucleus* (*STN*) *stimulation*: The beneficial effect of targeting this nucleus fits well with observed STN overactivity in IPD. The STN has a central role in the classic model of basal ganglia function, providing excitatory input to the GPi. Subthalamotomy has been infrequently performed in IPD because of the potentially serious side effect of producing contralateral hemiballism. This risk is not present with DBS, which is now the most commonly performed procedure in the treatment of bradykinesia, rigidity, and tremor. The antiparkinsonian effect is no better than the best levodopa effect (except for tremor where surgery seems to be superior).

Management of Acute Deterioration in Parkinson's Disease

Sustained functional deterioration in IPD should be investigated thoroughly for a reversible cause. Like many chronic neurological conditions, any systemic illness can cause an acute deterioration from baseline. If treatable, a return to baseline should be expected but this can take weeks after the original insult has resolved. Two causes of acute deterioration worth highlighting are missed medications and inappropriate exposure to dopamine antagonists. Both problems can occur when patients are admitted for surgery, either as an emergency or electively. Involvement of a neurology team in these cases is useful, particularly for patients who are fasting or with advanced disease. Causes of acute deterioration to consider in IPD and their management are given below. In general, an increase in levodopa dose in the setting of one of these precipitants is preferably avoided.

- *Sepsis*: Perform a full septic screen and treat appropriately with advice from microbiology if required.
- *Dehydration*: Rehydrate and correct any electrolyte disturbances.
- *Constipation*: Treat with laxatives and confirm resolution on plain film of abdomen. The aim should be to have at least one normal or soft bowel motion daily.
- *Stress or anxiety*: Treat appropriately with psychiatry advice if required.
- *Missed medication or inappropriate sudden withdrawal of medication*: Reinstate at previous effective dose.
- *Exposure to dopamine antagonists* (*e.g., prochlorperazine*): Discontinue drug, use an acceptable alternative.
- *Concurrent, medical, or surgical illness*: Supportive care, physiotherapy to maintain mobility and expect slow return to baseline level.
- *Hardware or battery failure if deep brain stimulator in situ*: Immediate neurosurgical referral.
- *Cervical spine injury*: Consider if after a fall there is a deterioration in gait with pyramidal signs in the lower limbs or a history of cervical spondylosis. Compromise of the cervical spine should also be considered in patients with deteriorating mobility despite increasing amounts of levodopa, particularly when resulting dyskinesias are limited to the head and neck region.
- *Serotonin syndrome*: Consider if there has been a recent introduction of an SSRI or TCA; stop any potential causative agent and support acutely.
- *Depression*: Common in PD and may present with somatic symptoms resembling hypophonia and bradyphrenia. Consider an SSRI or tricyclic antidepressant.

Long-Term Complications of Treatment

Motor Fluctuations

The pharmacokinetics of levodopa show a peak plasma concentration in about 30 min, and an elimination phase of about 90 min. Despite this, patients typically report no variability in their symptoms initially despite a TID dosing regime. This long-duration benefit may be

due to the buffering effect of dopamine storage in surviving nigral nerve terminals and to a long-lasting postsynaptic effect, facilitating this early "honeymoon period." Ongoing neuronal loss accompanied by functional receptor changes in the striatum may be important in the genesis of motor complications. Over time, the clinical response becomes shorter, unpredictable, and often inadequate. The long-duration benefit is lost and only the short-duration benefit is seen.

Motor fluctuations typically begin with an end-of-dose deterioration or *wearing off*, defined as a return of parkinsonian symptoms less than 4 h after the last dose. Patients gradually become aware of increasing contrast between "on" and "off" time. Initially, "off" time will be prior to a scheduled levodopa dose, but unpredictable "offs" unrelated to the timing of medications may evolve. Patients sometimes report a "not on" (dose failures) or "delayed on" phenomenon where they get no response or a delayed response to a particular dose. Most dose failures are due to delay in levodopa entering the duodenum where it can be absorbed. Having the patient crush the tablet between his teeth and swallowing with ample amount of water could dissolve levodopa faster and facilitate its entry into the small intestine. Motor "offs" can be accompanied by non-motor "offs" with patients reporting anxiety, autonomic symptoms, dysphoria, and pain during these periods. Non-motor "off's" do not always coincide with motor fluctuations and may be difficult to recognize. Patients with non-motor "offs" tend to take more frequent dosings of levodopa in an effort to avoid these intolerable "offs."

Treatment adjustment aiming for continuous dopaminergic stimulation remains a mainstay of treating motor fluctuations. Changes in dosing schedules and the addition of drugs that prolong the life of dopamine at the dopamine receptor can assist in "smoothing out" the levodopa response. Strategies that are commonly used are given in Table 5.7.

Dyskinesias

These are frequently mild choreic movements that are often unnoticed by the patient and managed with small reductions in levodopa if bothersome. In some cases, dyskinesias are disabling and severe, consisting of chorea, ballism, dystonia, or a combination of these. Dyskinesias are more common in young-onset patients, of whom 70% are affected after 3 years of treatment. Initially, patients will spend only a small part of the day in either the "off" or dyskinetic state with the "on" period in between representing the target "therapeutic window" where function is adequate. Over time, this window shrinks in duration with patients flipping from the "off" state to being dyskinetic. Patients at this stage will often prefer to be dyskinetic as it is only when dyskinetic that they can have some freedom of movement. Distressed relatives may not appreciate this functional significance of dyskinesias. Dyskinesias can be subdivided into: 1) peak-dose dyskinesias, appearing at the height of antiparkinsonian benefit, 20 min to 2 h after a dose, 2) diphasic dyskinesias, usually affecting the legs, appearing at the beginning and end of the dosing cycle, and 3) "off" dystonia, which can be painful, sustained cramping, appear during "off" states and may be seen as early morning dystonia presenting as foot cramps. Judicious introduction of levodopa with or without dopamine agonists can delay the onset and reduce the severity of dyskinesias, although over time they are inevitable, particularly in younger patients. Treatment strategies are outlined in Table 5.8.

Table 5.7 Management of motor fluctuations in Parkinson's disease

- Levodopa should be taken 1 h before or an hour after eating to enhance passage from stomach to small intestine and to reduce competition against amino acids for large neutral amino acid transporters in the small intestine. This can improve the "delayed on" or "no-on" phenomena.
- Constipation is almost universal in PD. Regular bowel habit can contribute to an overall strategy to make levodopa absorption and motor response more predictable.
- Additional doses reduce the inter-dose interval and can resolve wearing off. Patients with advanced IPD will commonly require levodopa every 3 hours throughout the day.
- Addition of dopamine agonists, which have longer half-lives, particularly modified release formulations of ropinirole, pramipexole, or the rotigotine patch, reduce both the frequency and the depth of the "off" states.
- Addition of selegiline, rasagiline, or COMT inhibitors (entacapone or tolcapone) can improve mild wearing-off. The addition of COMT inhibitors may require a reduction in levodopa dose of 15–30% as peak-dose dyskinesias can be precipitated, or worsen.
- Slow-release forms of carbidopa/levodopa (Sinemet CR) have been used to improve wearing off, although plasma levodopa levels can be erratic and response unpredictable
- Patients who have rapid transitions between "on" and "off" can benefit from dispersible forms of levodopa (Madopar Dispersible). This speeds up the transit of levodopa to the small intestine giving them a "kick-start." Prefilled apomorphine pen devices delivering bolus doses subcutaneously can also be used for a similar effect.
- Infusional therapies aim to achieve continuous dopaminergic stimulation to smooth out motor fluctuations. Levodopa in a gel is infused directly into the small intestine (Duodopa), avoiding erratic passage through the stomach. Subcutaneous apomorphine bypasses the gut to provide continuous symptomatic relief although patient selection is important.

Table 5.8 Strategies for the management of dyskinesias in Parkinson's disease

1. Peak-dose dyskinesias can be improved by small reductions in each levodopa dose, facilitated by the addition of a dopamine agonist. COMT and MAO-B inhibitors can be added to facilitate weaning of levodopa that might lead to wearing off; alternatively, the inter-dose interval can be reduced.
2. Avoid long-acting formulations of levodopa that can accumulate over the course of the day, leading to dyskinesias that can be prolonged.
3. Amantadine can reduce the severity of dyskinesias, but a dose of at least 400 mg/day is usually required and any benefit may not persist. Cognitive impairment, nightmares, hallucinations, and myoclonus are not uncommon side effects and limit its use in older patients.
4. Diphasic dyskinesias are more difficult to treat. Increasing the dosage of levodopa can be effective but peak-dose dyskinesia usually ensues. A switch to a dopamine agonist is more effective; low doses of levodopa are used as an adjunctive agent.
5. The principle of treating "off dystonia" is to try to keep the patient "on" most of the time. Here again, using a dopamine agonist as the major antiparkinsonian drug, with low doses of levodopa as an adjunct, can often be effective.
6. If adjustment of oral medications is ineffective, infusional (subcutaneous or jejunal) or surgical options should be explored with good results in appropriately selected patients.

Freezing

Freezing, a sudden inability to move lasting seconds to minutes, can be seen at any stage of PD but typically is seen with motor fluctuations in advanced disease. If early in the illness, think of atypical parkinsonism such as PSP or vascular parkinsonism. Any movement can be involved, but freezing of gait is the most disabling form and can be an important cause of falls where upper body momentum causes loss of balance on freezing when walking or turning. "Off-freezing" must be distinguished from "on-freezing." Off-freezing was described before the advent of levodopa therapy and therefore is a disease phenomenon and not a complication of treatment; it responds to levodopa. On-freezing remains an enigma; patients can be seen to freeze despite good control of all other symptoms. The etiology is unknown but non-dopaminergic systems are probably involved.

Although rarely successful, reduction of the total amount of "off" time by increasing dopaminergic medications is the best approach to treating "off-freezing." There is no proven treatment for "on-freezing" but reduction of total levodopa dose can sometimes help, but this can worsen all other levodopa-responsive symptoms. Both on- and off-freezing seem to correlate with both the duration of illness and the duration of levodopa therapy. Early use of the MAO-B inhibitors rasagiline and selegiline may reduce the risk of developing the freezing phenomenon. Non-pharmacological approaches include walking aids to reduce the risk of falling. The use of sensory cues takes advantage of *kinesie paradoxale* whereby the inclusion of a sensory stimulus into the motor routine appears to activate a more effective motor program. Examples include the use of a metronome, a bar on a walking cane to step over, or internally generated cues such as counting or attempting to walk like a soldier.

New targets for DBS aim to target those motor symptoms not responsive to levodopa, in particular freezing and postural instability. Initial unblinded studies of surgery targeting the pedunculopontine nucleus suggested that stimulation of this mainly cholinergic nucleus might be of benefit in freezing of gait, but this has not been borne out in blinded studies.

Neuropsychiatric

Confusion, agitation, hallucinations, delusions, paranoia, and mania are probably related to activation of dopamine receptors in non-striatal regions although psychosis can be a primary disease phenomenon, especially if the patient has developed dementia. Dopamine agonists more often bring out these complications, particularly at high doses. Early hallucinations or psychosis should prompt the question of underlying Lewy body dementia or concomitant Alzheimer disease. Where possible, reversible causes of any deterioration should be sought before this assumption is made:

1. Eliminate sepsis, dehydration, and electrolyte imbalances as a cause of a delirium.
2. Addition of an atypical neuroleptic, preferred for their affinity for D4 more than D2 receptors, such as quetiapine and clozapine.
3. Discontinue any drugs that may be responsible, typically in the following order based on propensity to cause neuropsychiatric side effects – anticholinergics, amantadine, MAO-B inhibitors, and dopamine agonists.
4. If discontinuation of the above is ineffective, patients on a high dose of levodopa should have their dose reduced down to the minimal effective dose.

Neuroleptic drugs can induce drowsiness and should therefore be given at bedtime. Start with a dose of 12.5 mg of quetiapine to avoid the biweekly blood counts required with clozapine although it is less effective (see above). If clozapine is not tolerated, other drugs, including small doses of olanzapine, molindone, aripiprazole, or pimozide can be used. If the parkinsonism deteriorates, lowering the dosage of levodopa to avoid the psychosis is preferable to maintaining a high dose of the antipsychotic. Levodopa should not be discontinued suddenly; abrupt cessation may induce a neuroleptic malignant-like syndrome, sometimes referred to as parkinsonism–hyperpyrexia syndrome.

Impulse Control Disorders

Impulse control disorders (ICDs) are seen in the general population, but are more common in IPD. ICDs represent an inability to resist a drive or temptation to perform an act harmful to others or oneself. Pathological gambling is most often encountered, but hypersexuality, excessive shopping, reckless generosity, and hyperphagia are also described. Significant financial, personal, and social harm can be done. Young male patients with early onset disease are at particular risk.

ICDs appear to be specific to treatment with dopamine agonists with a dose-response effect. This may be due to their affinity for D3 receptors of the mesocorticolimbic pathways, stimulation of which is integral to reward and reinforcement behavior. *Dopa dysregulation syndrome* (DDS) is a related phenomenon whereby a patient will take excessive and repeated doses of levodopa or a fast-acting agonist such as apomorphine, often despite disabling dyskinesias. Soluble forms of dopamine are often preferred due to their rapid onset of action. *Punding* is repetitive behavior involving purposeless motor tasks such as picking at oneself, taking apart watches and radios, or sorting and rearranging of common objects, such as lining up pebbles, rocks, or other small objects.

The management of ICDs involves early recognition and reduction of dopamine agonist doses to a minimum or stopping completely. This approach is effective in the majority of cases. Change to an alternative agonist is of little value, and in some cases, levodopa will have to be increased to compensate for loss of the agonist. Patients with dopa dysregulation syndrome need to have their levodopa dose reduced to see an improvement. Fast-acting, water-soluble forms should be avoided completely. A difficult aspect of managing ICD and DDS is obtaining the history from the patient or family due to embarrassment. Specifically asking for behavioral changes in the spectrum of ICD is therefore vital.

Recent and Future Developments

New Agonists, Continuous Dopaminergic Stimulation

Continuous dopaminergic stimulation remains a target to achieve sustained control over symptoms without the complications associated with prolonged treatment. A number of treatment options are now available, which blunt the peaks and troughs of pulsatile stimulation, including direct infusion of levodopa into the small intestine (Duodopa) and

transdermal delivery of rotigotine. Some dopamine agonists are now available in a once-daily formulation that may further smooth the response to treatment. New dopamine agonists and delivery methods in the future will need to be potent enough to remain effective without the addition of levodopa since it appears that initial agonist treatment does not prolong the latent period before the onset of levodopa-induced dyskinesias.

Dopaminergic Cell Transplantation

To date, no double-blind controlled trial has shown a benefit of dopaminergic cell transplantation in IPD. Individual case series have been promising with postmortem and radiological (^{18}flourodopa PET) evidence of functioning graft tissue with some patients enjoying significant and even complete withdrawal of oral therapies. An important adverse effect noted in over 50% of transplanted patients in one study is so-called "off medication dyskinesias." This form of dyskinesia can be persistent, lasting for days or weeks. It is also possible that in time transplanted neurons will be susceptible to the same degenerative process that affected native neurons in the first place. More research is required to determine what immunosuppressive regime, quantity of transplanted cells, and target patient group are required to improve outcomes. Importantly, even if eventually successful, dopaminergic cell transplantation may not benefit the disabling non-dopaminergic symptoms of IPD.

Stem Cell Implantation

Stem cell-based therapies are an attractive option given the potential of these cells to repair degenerating or injured neural circuits and the ability to generate cell lines in vitro. Stem cells can be derived from preimplantation human blastocysts. Neural progenitor cells are alternative sources of implantable cell lines, derived from embryonic tissue or postoperative adult specimens. Induced pluripotent stem cells are generated from skin fibroblasts through genetic manipulation and are an exciting proposition in that they avoid the ethical dilemma of using fetal tissue, they are in abundant supply, and do not necessitate immunosuppression.

No trials to date have evaluated the effect of stem cells in human patients, but animal studies are ongoing. Before a human trial can take place, the safety profile of implanting stem cells needs to be further evaluated. A major concern has been the development of malignant tumors following the implantation of undifferentiated stem cells in animal studies and in one reported human case involving a young boy with ataxia telangiectasia, who developed a multifocal glioma derived from transplanted stem cells. Furthermore, the ethical issues surrounding stem cell-based therapies need to be resolved individually in every jurisdiction. Like dopaminergic cell transplantation, even if successful, stem cell implantation is unlikely to address the many non-motor features of IPD.

Management of Non-dopaminergic Symptoms

Much of the Parkinson's disease research literature has been devoted to the management of the complications of long-term levodopa treatment. Infusional dopaminergic treatments and

functional neurosurgery have reached a point where motor fluctuations can be addressed to some satisfaction, although more options are needed for patients not suited to current treatment modalities. Attention will increasingly turn to the non-dopaminergic symptoms experienced in advanced PD, in particular dementia, freezing, and postural instability. Cholinesterase inhibitors offer limited benefit in the management of dementia in the context of PD. Their general role in mild cognitive impairment is uncertain and many patients with cognitive impairment in PD will only have subtle frontal–dysexecutive features. Safinamide targets dopaminergic and glutaminergic targets and may have neuroprotective properties and a role in cognitive impairment, although clinical trials are required.

Gene Therapy

Gene therapy has the potential to restore striatal dopaminergic function to a more physiological level by delivering proteins such as aromatic acid decarboxylase (AADC), 3,4-dihydroxyphenylalanine (DOPA), and glutamic acid decarboxylase (GAD) via an adeno-associated viral vector. Alternatively, genes coding for trophic factors delivered to the basal ganglia might preserve or prolong survival of remaining dopaminergic neurons.

Neuroprotection

Because the exact etiology of IPD is unknown, it remains difficult to know where the development of a neuroprotective agent should be targeted. A number of potential targets have emerged, most notably mitochondrial dysfunction from the study of inherited forms of the disease. Other possibilities include abnormalities in apoptotic pathways, excitotoxicity, and oxidative stress. A combination of factors may be at play with a cumulative effect to produce the parkinsonian "phenotype." Identification of genes, which are risk factors for the development of IPD from genome-wide association studies, may be informative in the design of neuroprotective regimes to target these potential risk factors individually. As stated previously, by the time patients present for treatment, the majority of nigrostriatal dopaminergic neurons have been lost. If a disease-modifying agent is found it will need to be introduced as early as possible. To enable this, a reliable biomarker of underlying susceptibility to PD in asymptomatic, at-risk individuals needs to be identified.

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Frontotemporal Dementia

6

Colin P. Doherty, Siobhan Hutchinson, Sharon Abrahams, and Robert F. Coen

Abstract Frontotemporal dementia (FTD) is a clinical term that encompasses a spectrum of disorders that affect predominantly language and behavior to varying degrees. Progressive nonfluent aphasia (PNFA) affects mainly language output, semantic dementia (SD) affects mainly language comprehension, and behavioral variant FTD (bv-FTD) affects mainly behavior. FTD is the most common form of young onset dementia. In this chapter, the main clinical, neuropsychological, radiological, and biomarker characteristics are described. Treatment is largely symptomatic but progress in the pathological, molecular, and genetic classification of FTD continues to burgeon, leading to exciting possibilities for disease modification.

Keywords FTD • Semantic dementia • Progressive nonfluent aphasia • Behavioral variant • Social cognition • Tau • TDP-43

Clinical Features of Frontotemporal Dementia

Introduction

In the past 20 years, clinical and basic research have expanded our knowledge of frontotemporal dementia so that it has evolved into a group of overlapping clinical syndromes associated with a range of neurodegenerative pathologies and genetic bases. Clinical–pathological correlation is difficult and by no means definitive. Two patients with a similar clinical syndrome may have different pathologies. Ongoing research into biomarkers will aid disease classification but currently terminology can be confusing as it will often depend upon whether there is a clinical, pathological, or genetic basis to the paper being read. The term frontotemporal dementia is used in two different ways throughout the literature, as is evident even on a cursory comparison of the two major sets of clinical

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diagnostic criteria. Both encompass three prototypic presentations including what has been termed a frontal or behavioral variant, a syndrome of progressive nonfluent aphasia, and a temporal variant characterized by a syndrome of fluent aphasia with associative agnosia referred to as semantic dementia. The site of atrophy is the main determinant of the presenting syndrome. Neary et al. use the umbrella term frontotemporal lobar degeneration (FTLD) for all of the above and reserve the term frontotemporal dementia to refer specifically to the frontal/behavioral variant. In contrast, McKhann et al. use the term frontotemporal dementia (FTD) to refer to all of the above presentations. For the purposes of this chapter, we use the term frontotemporal dementia (FTD) in the general sense of McKhann et al. and the three common subtypes we refer to as behavioral variant FTD (bv-FTD), progressive nonfluent aphasia (PNFA), and semantic dementia (SD). The syndromes that present with language difficulty, PNFA and SD, are often referred together in the literature as primary progressive aphasia but we will discuss them separately here.

History

Arnold Pick is credited with the first description of a progressive disorder of behavior and language associated with circumscribed atrophy of the frontal and temporal lobes. Later, Alois Alzheimer described the classical histological changes associated with "Pick's disease" of interneuronal inclusions and ballooned neurons. In the 1980s, two groups in Lund, Sweden, and Manchester, United Kingdom, published separately large series of patients with frontotemporal atrophy and dementia with prominent behavior and language difficulties. They noted that Pick-type histology was only one of three main histological changes seen and they came up with the first consensus criteria for FTD. At the same time, Mesulam described a series of patients with a progressive language disorder with sparing of other cognitive deficits and non-Alzheimer's pathology, which he termed primary progressive aphasia. Over the subsequent decade, further clinical, imaging, and pathological studies prompted the consensus group to refine the criteria in 1998. They separated the disorders of language, SD and PNFA, from the behavioral disorder (bv-FTD). The separation of the three syndromes has led to concentrated research in each. Genetic advances have been significant and molecules have been identified, which may play a role in pathogenesis (Fig. 6.1). However, significant overlap between the clinical syndromes is still apparent. Indeed, in familial FTD, each of the different clinical syndromes can be seen in the same kindred. Also, in the later stages of each syndrome, patients will often have a mixed clinical picture of behavior, language, and semantic difficulties.

Epidemiology and Demographics

FTD is the third most common form of cortical dementia after Alzheimer's disease (AD) and Lewy body disease. Prevalence studies of FTD have varied results with 15 per 100,000 reported in the UK in the 45–64 years of age group, making it equivalent to AD in this younger age group. However, in the Netherlands, the prevalence was lower at 4 per 10,000

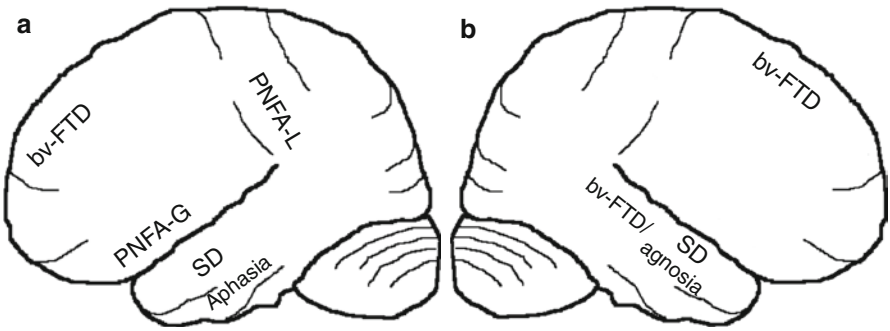

Fig. 6.1 (**a**) Left and (**b**) right view of FTD brain

in the 50–59 years age group. Age of onset is typically younger than other forms of dementia being between 45 and 65 years, though cases are reported outside this range. The incidence in men and women is equal. The duration of illness from onset to death has a range from 2 to 20 years but a mean of 6–8 years. The presence of motor involvement is associated with shortened survival. Familial history of early onset dementia in first-degree relatives is thought to be found in 5–10% of cases. In FTD, bv-FTD is the commonest syndrome affecting 55% of all cases, PNFA accounts for 25% and SD for 20%. Demography does differ between the syndromes: SD has a later age of onset, slower rate of progression, and less frequently reported family history, whereas bv-FTD has the earliest age of onset; most rapid progression and highest reported family history.

Clinical Features

As with other forms of cortical dementia, symptoms are gradual in onset and progressive over time. Patients often do not come to medical attention early on in the disease as frequently behavioral symptoms are excused as midlife change and language symptoms as normal aging (Fig. 6.2).

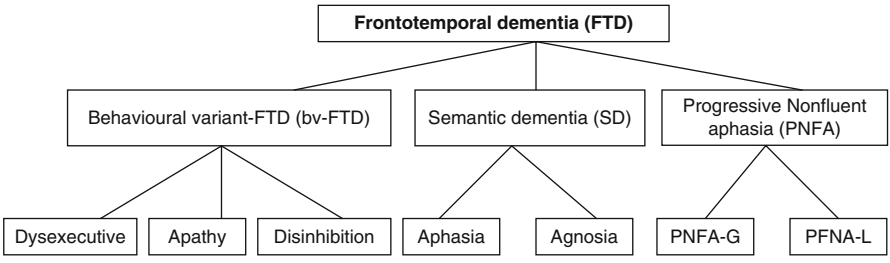

Fig. 6.2 Classification of subtypes of frontotemporal dementia (FTD): Progressive nonfluent aphasia – grammatical (PNFA-G), progressive nonfluent aphasia – logopenic (PNFA-L)

bv-FTD

The clinical features of bv-FTD involve both behavioral and cognitive symptoms. Heterogeneity arises from the fact that bv-FTD can present with at least three distinct syndromes (disinhibited, apathetic, dysexecutive) each linked to discrete frontal–subcortical circuits. Orbitofrontal atrophy is particularly associated with disorders of self-regulation and disinhibition. Dorsolateral prefrontal atrophy gives rise in particular to a dysexecutive syndrome. A more anterior cingulate locus results in pronounced apathy and frontal abulia. Behavioral disorders are common, particularly in frontal and right temporal cases. Both temporal and frontal variants are associated with a loss of empathy, and insight is typically lacking in frontal variant cases.

The presentation is usually due to a change in the patient's behavior noted by their family or friends as lack of insight, or more correctly, lack of concern for their condition. It is usually socially inappropriate interpersonal behavior that is noted initially due to disinhibition of verbal, physical, or sexual impulses and impulsivity. Difficulties with interpersonal conduct are not only due to disinhibition but also due to difficulties with emotional processing and social awareness or social cognition. Patients may lose the ability to express and recognize facial or vocal expressions of emotion, referred to as emotional blunting. In addition, they have difficulty determining what others would think in certain situations; this is referred to as loss of theory of mind. This results in problematic social interactions, an early loss of empathy, and a reduced concern for those around them. These behaviors are seen as out of character by the caregiver and as a significant personality change. It is important to note that for these reasons distress is more common in the caregivers of bv-FTD patients, compared with caregivers of those with other forms of cortical dementia.

In tandem with decline in interpersonal conduct, there is a change in personal conduct that is usually due to inertia or apathy but rarely there may be hyperactivity. Apathy or the loss of drive/initiation is often noted by caregivers and can be mistaken for depression. It is one of the factors that contribute to the decline in personal hygiene and grooming that is frequently reported.

The cognitive symptoms experienced are due to executive dysfunction; therefore, patients have difficulties in planning, problem solving, organization, attention, and mental flexibility. These are symptoms that are not easily identified either by the caregiver or history taker, but a decline in the ability to perform tasks at work and home (activities of daily living or ADL) due to these symptoms is frequently reported. Other symptoms that may be witnessed during the examination or acknowledged by the caregiver when directly questioned include perseverative and stereotyped (ritualistic/compulsive) behavior and speech, altered speech production (aspontaneity), hyperorality and bingeing or overconsumption, and incontinence.

Semantic Dementia

Patients who present with language difficulty will be more aware of this symptom than those with behavioral problems and will frequently complain that they have forgotten the word for things. Memory, however, is not impaired and patients will be oriented, able to keep appointments, learn and remember visuospatial information. The speech of a patient with SD remains fluent, with normal use of grammar; however, there will be hesitation in word finding, loss of vocabulary, and semantic paraphasias and words may be substituted for a vague, nonspecific

term. Speech, therefore, becomes empty with loss of content though not tangential as we see in AD. There is anomia, with loss of comprehension of that word and object, which is demonstrated by being unable to match the object with semantically similar objects or being able to pick an object from description of its use. Knowledge loss appears to affect exemplars first, so a patient may be initially unable to recognize a rabbit, but tell you that it is an animal. Knowledge of more personally relevant objects is more resistant. Repetition is not impaired and patients can repeat multi-syllable words without difficulty. Writing to dictation is unimpaired. Patients with SD develop surface dyslexia in reading where the word is read phonologically correctly but loss of knowledge of the word produces the error (e.g., choir is pronounced "cho–er"). A rarer nondominant form of SD with predominant agnosia (a failure to recognize objects or people) instead of aphasia is increasingly recognized. Patients with nondominant agnosia also appear to have a more behavioral presentation and are more likely to have difficulties with social cognition, becoming withdrawn and losing empathy rather than showing the impulsive disinhibition of bv-FTD (Fig. 6.1b).

Progressive Nonfluent Aphasia

In PNFA, there is a breakdown in spontaneous speech that is noted by the caregiver and examiner. The speech of a patient with PNFA is generally nonfluent with variable loss of grammar and phonemic paraphasias (word substitutions). There will be anomia on direct object naming but knowledge of the object will be intact, distinguishing it from SD. They may be able to pick the correct name from choice and will be able to match the object with others semantically linked to it. Recently, a panel of 20 experts has published consensus criteria for the Classification of Primary Progressive Aphasia and its Variants. In this classification Semantic Dementia remains intact but PNFA has been subdivided. PNFA-G is a predominantly agrammatic form with primary difficulties with grammar, syntax, oral praxis, and fluency. PNFA-L, logopenic progressive aphasia is characterized by fluctuating interruptions of fluency due to word finding difficulties, but with intact syntax and without agrammatism. PNFA-L is rarer than PNFA-G and is associated with episodic memory difficulties (Fig. 6.1a). Interestingly, many described patients have Alzheimer's disease pathology at postmortem. Classification of progressive aphasia can then be further specified as "imaging-supported" if the expected pattern of atrophy is found and "with definite pathology" if pathologic or genetic data are available.

Clinical Examination and Investigations

Clinical examination should focus on qualifying the cognitive deficits specific to each syndrome in addition to noting which cognitive functions are spared. Orientation, calculation, visuospatial skills, and memory should be relatively well preserved early in FTD. This profile of cognitive deficits and preserved function can be reliably demonstrated with clinic-based mental state testing. A variety of rapid clinic-based screening tests are used by clinicians such as:

- *The Montreal Cognitive Assessment* (MOCA) is sensitive to the presence of cognitive impairment and has the advantage of being rapid test that reliably distinguishes pseudodementia. Also, bv-FTD patients may not participate in lengthy testing because of features of their behavioral disorder: apathy, inattention, perseveration, and poor organization.

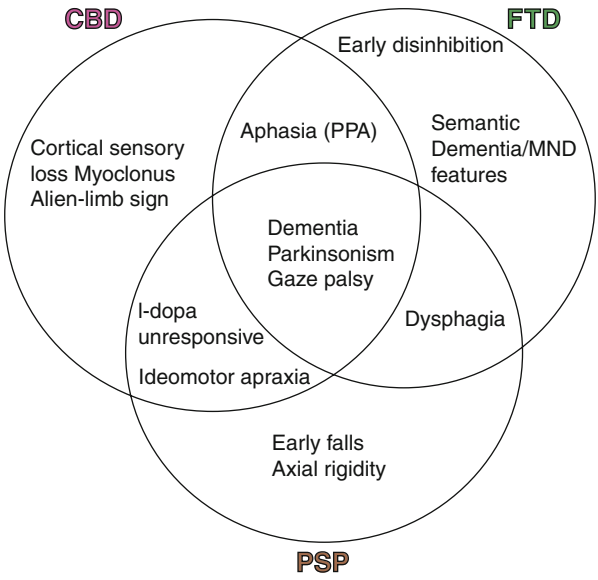

Fig. 6.3 Clinical crossover of frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy (Courtesy of Dr. B. Murray, Hermitage Hospital, Dublin)

- *The Addenbrooke Cognitive Examination–Revised (ACE-R)*. This Screening measure takes about 20 min and is sensitive to differences in early AD and FTD.
- *Rey Osterrieth Complex Figure.* Many language-based tests will be impossible in PPA patients and will need to be adapted, for example, memory testing using the Rey Osterrieth figure is more suitable than word list learning.
- *Frontal Assessment Battery (FAB).* May assist in differentiating FTD from non-FTD dementias.
- *Frontotemporal Behavioral Scale (Lebert et al. Based on caregiver interview).* It is useful in bv-FTD to quantify behavioral change by using a measure such as the Frontotemporal Behavioral Scale.

The rest of the clinical examination should focus on the presence of motor signs. FTD is known to overlap with corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) and with amyotrophic form of motor neuron disease (FTD-MND), and 10% of FTD cases may develop MND. The presence of extrapyramidal signs, muscle wasting, fasciculations, or unilateral apraxia adds to the behavioral and cognitive profile in characterizing the syndrome (Fig. 6.3).

Further Tests

- *Biochemical and metabolic laboratory tests.* Blood tests and serological markers that can point to potentially reversible syndromes that may mimic FTD are listed in Table 6.1.
- *Neuropsychological assessment* consisting of a more extensive investigation of the cognitive impairment is important to both qualify and quantify the cognitive profile to aid diagnosis.
- *Electroencephalography* was thought to be normal early in FTD and that this was useful to differentiate from AD, but this has not proved to be a reliable discriminator.

Table 6.1 Laboratory tests for differential diagnosis of FTD

Hematological malignancies with CNS involvement FBC and differential Serum protein electrophoresis Bone marrow aspiration
Biochemical disorders: Wilson's disease; porphyria Electrolytes Renal function tests Liver function tests Urinary and fecal porphyrins
Metabolic or endocrine: Hypothyroidism, adrenoleukodystrophy Thyroid function tests Very long chain fatty acids
Vascular: CADASIL, *MELAS*, *Multiple strokes* Notch 3 mutation MELAS mutation Thrombophilia screen
Infective: HIV dementia, *syphilis*, *PML* HIV testing VDRL/TPHA JC virus
Immunological: Multiple sclerosis, *CNS vasculitis*, *paraneoplastic* Oligoclonal bands Connective tissue work-up TPO antibodies Potassium channel Abs NMDA receptor Abs Anti-GAD Abs
Other degenerative disease: *Creutzfeldt-Jacob disease*, *atypical AD*, *ALS/FTD* EEG and 14–3–3 and s100 proteins in CSF MRI and PET/SPECT EMG

- *Brain imaging* is useful to examine for focal atrophy though requires high-resolution T1 images and even then atrophy may not be notable at presentation. Functional imaging (PET or SPECT) can be useful to distinguish more AD-like from more FTD-like patterns of hypometabolism or hypoperfusion.

Diagnostic Criteria

The diagnostic criteria in FTD have been subject to a number of changes over the years and new consensus criteria are set to emerge soon. The first set of criteria was devised at a consensus meeting in 1996 where it was decided to separate the three clinical syndromes in

Table 6.2 Clinical criteria for frontotemporal dementia

1. The development of behavioral or cognitive deficits manifested by either:
   a. Early progressive change in personality, characterized by difficulty in modulating behavior, often resulting in inappropriate responses or activities.
   b. Early and progressive change in language, characterized by problems with expression of language or severe naming difficulty and problems with word meaning.
2. The deficits outlined in 1a or 1b cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
3. The course is characterized by gradual onset and continuing decline in function.
4. The deficits outlined in 1a or 1b are not due to other nervous system conditions (e.g., cerebrovascular disease), systemic conditions (e.g., hypothyroidism), or substance-induced conditions.
5. The deficits do not occur exclusively during delirium.
6. The disturbance is not better accounted for by a psychiatric diagnosis (e.g., depression).

FTD, and criteria were devised for each. Core diagnostic features that were thought to be integral to each syndrome must be present to make the diagnosis. Supportive diagnostic features were not considered necessary for a diagnosis but were included as being characteristic of the syndrome and "adding more weight" to the diagnosis. Exclusion criteria were listed to prevent the inclusions of other forms of cortical dementia, specifically AD, acute neurological, and psychiatric disorders. All must be absent in order to make a diagnosis.

In the 12 years subsequent to the Neary et al. consensus meeting, clinical study of FTD has questioned the criteria and there are currently calls for revision. Some researchers (Table 6.2) have suggested simplifying the clinical criteria into either behavior or language presentation of FTD and then qualifying this classification further with a neuropathological diagnosis when and if a patient comes to autopsy. However, most researchers in the language presentation of FTD would view SD and PNFA as separate entities. The risk of combining these syndromes is that important clinical findings, including potential biomarkers, are missed because the population studied is heterogeneous. In the debate on "lumping or splitting" diagnoses, the current rationale is to clinically qualify each case as carefully as possible, while attempting to avoid a situation where clinical diagnosis becomes too complicated for clinical practice.

Syndromes That Overlap and Mimic FTD

The FTD syndromes, though defined on cognitive and behavioral criteria, will frequently include motor symptoms and signs. Research has shown the significant pathological and molecular overlap between FTD and other neurodegenerative disorders and hence the crossover in clinical features. Table 6.3 summarizes the syndromes that overlap.

On the other hand, there are a range of clinical disorders that have no pathological overlap but whose clinical phenotype can mimic those of FTD. Table 6.3 summarizes the syndrome that mimics FTD.

Table 6.3 Overlap and mimic syndromes

Overlap syndromes

Corticobasal degeneration (see Chap. 10): CBD is a progressive disorder characterized by asymmetrical motor and sensory cortical and extrapyramidal dysfunction. It is classically associated with tau pathology. Typically, the patient presents to a movement disorder clinic with a "useless arm" due to unilateral rigidity, bradykinesia, apraxia, tremor, and dystonia. Cognitive symptoms have been underreported in CBD but a nonfluent aphasia is now regarded as one of the core features.

Progressive supranuclear palsy (see Chap. 10): PSP or Richardson's syndrome is a quickly progressive disorder of bulbar palsy, supranuclear gaze palsy and axial rigidity, and postural instability causing unexplained falls. However, PSP pathology is associated with a range of clinical syndromes, including a parkinsonian syndrome, CBD, and PNFA. Patients with PNFA, who are found to have PSP pathology, are more likely to have a prominent early apraxia of speech, though notably do not develop other features of PSP. Again, PSP pathology is also seen in bv-FTD but less commonly in SD.

FTD-MND (see Chap. 7): The association between MND and dementia has been described for over a century. After investigation of a series of MND patients with dementia in 1980s, the dementia was characterized as a frontal atrophy with progressive behavioral and dysexecutive change and therefore, the term FTD with MND (FTD-MND) was adopted. Up to 50% of MND may have cognitive or behavioral abnormalities when tested.

Mimic syndromes

Psychiatric illness: Initial presentation with behavioral change is frequently interpreted by the family and medical professionals as a psychological reaction or psychiatric disorder. For example, apathy may be interpreted as depression and irritability or disinhibition as a midlife personality change or secondary to substance abuse. Association with other symptoms of FTD and the time course of "insidious onset and gradual progression" can help differentiate FTD from psychiatric disorders.

Alzheimer's disease (see Chap. 3): AD is also a dementia of insidious onset and gradual progression that has language and behavioral dysfunction. Although the presence of early amnesia should point to a diagnosis of AD and, conversely, early behavioral change is more typical of FTD, later dementia in FTD and AD can be very similar. Some FTD group studies have noted as high as 11% of patients have amnesia at presentation. Similarly, visuospatial skills tend to be preserved in early FTD and impaired in AD.

Vascular dementia (see Chap. 10): Apathy or abulia, frontal executive dysfunction, frontal release signs, and parkinsonian features are common in VD and FTD. Again, the association with other symptoms may help in differentiating the two disorders. However, the stepwise time course and presence of corticospinal tract signs would suggest VD over FTD. MRI may be helpful, indicating FTD if atrophy is focal, lobar atrophy and VD if periventricular ischemia is severe.

Other neurodegenerative disorders: Disorders with cognitive and motor involvement should have distinguishable features (in brackets); differing collections of symptoms and differing time course: Parkinson's disease (tremor); Multisystem atrophy (cerebellar ataxia); Huntington's disease (chorea).

Phenocopies: There are recent reports of patients who have a typical clinical presentation of bv-FTD but who have extremely slow progression. Such cases are described as "phenocopies" and as yet, there is no pathological correlation with such cases. It has been found that abnormal executive function, MRI atrophy, and impaired ADLs are the best discriminators of true bv-FTD from such phenocopies.

Neuropsychology

Given the wide variability of presentations in FTD and the fact that there are a number of other overlapping conditions, neuropsychological assessment can greatly contribute to differential diagnosis. Neary et al. include guidelines regarding the typical neuropsychological findings that characterize the prototypic presentations. Depending on the presenting signs and symptoms, different tailored batteries will be appropriate, but in all cases, there are several core aspects of the assessment that should be emphasized. Given that FTD can frequently present with alterations in behavior and personality, there should not be an over-reliance on cognitive testing per se. Depending on the locus of pathology, patients may do extremely poorly on conventional "frontal lobe" tests such as the Wisconsin Card Sorting Test, Trail Making, and verbal fluency, or they may, in fact, perform normally, yet still show major impairment in self- and social regulation. Therefore, it is essential to obtain good collateral information on everyday behavioral alterations using suitably designed instruments. One such is the Frontal Systems Behavior Scale (FrSBe), which built on Cummings' neuroanatomical model to provide self- and informant-based ratings of apathy, disinhibition, and executive dysfunction both premorbidly and currently. In addition to permitting age and gender graded interpretation of behavior change, the self- and informant-based ratings can be compared to evaluate the degree of insight or lack thereof.

Observation of the patient during interview and testing is also an essential aspect of the assessment. Qualitative analysis is as important as the patient's quantitative performance on neuropsychological tests. For example, patients with Alzheimer's disease (AD) or FTD may perform equally poorly on a visuoconstruction task such as copy of the Rey Osterreith Figure or Block Design, even though constructional praxis and visuospatial integration is typically well preserved in FTD. The quality of performance on task may be more telling, with AD patients typically aware of their difficulties, applying effort, and attempting to rectify errors. In contrast, FTD patients frequently lack awareness or concern regarding poor performance, with cursory effort and little attempt to rectify errors. Task failure in FTD may reflect poor planning and organization, regulation and monitoring of behavior, and attention to qualitative aspects of the patient's performance can aid differential diagnosis.

Some screening tests have been designed specifically for the purpose of discriminating FTD from non-FDT dementias such as the Addenbrooke's Cognitive Examination (ACE-R). It was designed to differentiate AD from FTD using a ratio based on the tendency for AD patients to be more impaired on tests of memory and orientation and less impaired on tests of language and verbal fluency, whereas FTD patients tend to exhibit the opposite pattern. Brief measures designed to assess frontal lobe/executive deficits include the Executive Interview (EXIT) and the Frontal Assessment Battery (FAB), which may assist in differentiating FTD from non-FTD dementias. In contrast, formal neuropsychological assessment entails a much more detailed evaluation of the specific profile of behavioral, cognitive, and emotional alteration, which can assist in identifying FTD variants, discriminating organic from nonorganic causes of behavior change, and in identifying FTD-like features that can be early manifestations of overlap conditions such as MND, CBD, or PSP. A typical selection of neuropsychological tests useful in evaluating FTD and its variants is

Table 6.4 Selected neuropsychological tests useful in assessment of FTD

Wechsler Adult Intelligence Scale (WAIS-IV)
Similarities (verbal abstract reasoning)
Vocabulary (word knowledge)
Matrix reasoning (nonverbal abstract reasoning)
Block Design (visuoconstructional problem solving)
Wechsler Memory Scale (WMS-IV)
Logical memory (story recall)
Visual Reproduction (visual recall)
Rey Osterrieth Complex Figure (copy, delayed recall)
Addenbrooke's Cognitive Examination (ACE-R)
Frontal Assessment Battery (FAB)
Modified Wisconsin Card Sorting Test
Trail Making Test (Part A and B)
Stroop Test
Test of Premorbid Functioning (premorbid intellect vs. surface dyslexia)
Verbal Fluency (semantic categories and FAS test)
Boston Naming Test
Word-picture matching (single-word comprehension)
Pyramids and Palm Trees Test (verbal/visual semantics)
Test for Reception of Grammar (TROG)
Token Test
Boston Diagnostic Aphasia Examination (expression/comprehension subtests)
Iowa Gambling Task
Faux Pas Test
Frontal Systems Behavior Scale (FrSBe)
Frontotemporal Behavioral Scale
Delis-Kaplan Executive Function System (D-KEFS)

provided in Table 6.4. Depending on the depth of detail required, there are also purpose-designed comprehensive batteries to evaluate a broad range of cognitive processes dependent on the integrity of the frontal lobes, most notably the Delis-Kaplan Executive Function System (D-KEFS). However, as is always the case in neuropsychological assessment, the nature and extent of the evaluation will be determined by the referral question and the characteristics of the client.

Patients with an orbitofrontal–ventromedial prefrontal locus of pathology, which may be focal at the onset of bv-FTD, may perform normally on a variety of the tests traditionally considered sensitive to frontal lobe/executive dysfunction but have a profound deficit in everyday decision making and social regulation and behavior change. A number of more experimental cognitive tests have been developed, which are more sensitive to such abnormality The Iowa Gambling Task assesses decision making and learning in high- and low-risk situations. During the task, healthy individuals learn to avoid the risky choices while those with FTD continue to make high-risk choices, which results in an overall net loss. Another recent test sensitive to orbitofrontal dysfunction is the Faux Pas test, based on "theory of mind" (or ability to infer another's thoughts and feelings). Changes in this ability may underlie some of the changes in personality and social functioning frequently

seen in FTD patients. The task entails hearing 20 short stories, 10 of which contain a social faux pas, and 10 of which are neutral. Following each, questions are asked to evaluate the patient's social awareness and social understanding. Patients with bv-FTD, but not patients with AD, do poorly on this test.

Biomarkers

Introduction

Biomarkers are characteristic biological properties that can be detected and measured in parts of the body like the blood or tissue and may extend to brain imaging or neurophysiological tests. They may indicate either normal or diseased processes in the body. Disease-related biomarkers give an indication of whether there is a threat of disease (risk indicator or predictive biomarkers), if a disease already exists (diagnostic biomarker), or how such a disease may develop in an individual case (prognostic biomarker). In FTD, a number of biomarkers are being used clinically and in a research capacity including MRI (both qualitative and quantitative), PET, SPECT, neurophysiology (EEG and ERP), biological markers from CSF, and finally genetic analysis.

Brain Imaging

Brain atrophy is one of the cardinal features of all neurodegenerative processes, even if it occurs at vastly different rates and by vastly different and sometimes convoluted processes. The most convincing hypothesis underlying the atrophic process is that we can no longer think of this as a generalized shrinkage but more along the lines of a Wallerian degeneration constrained by neuronal and functional networks. The process often starts focally and spreads along these networks whose predictability gives us the clinical phenotypes we know.

MRI

Brain imaging is an essential and routine examination in any dementia to exclude alternative pathology and aid in the diagnostic process. T1-weighted magnetic resonance imaging is the method of choice for evaluation of structural changes in the brain. In particular, the addition of coronal imaging to the standard axial slicing allows for the detection of visually obvious atrophy in frontal and temporal regions. T2-weighted imaging usually using fluid-attenuated sequences (FLAIR) allows for the evaluation pathology that might exclude FTD or point to a mimic syndrome such as vascular-related white matter pathology. Quantitative MRI is generally a research tool and embodies the three main techniques: volumetric analysis of specific brain regions, voxel-based morphometry (VBM), and serial co-registration.

Typical Brain Imaging Findings in FTD

Bv-FTD. Brain atrophy on static MRI is the most reproducible features of all FTD subtypes and the capacity to identify this reliably is limited in the clinic to the experience and expectations of the observers (Fig. 6.4a). In research work, serial co-registration, region of interest, volumetric analysis, and VBM have provided a key dimension to the analysis of the in vivo brain and it is an important challenge to improve these techniques to allow their routine use in clinical situations. The presence of true focal atrophy has a high positive predicative value for clinical dementia. On the other hand, the absence of atrophy has been noted increasingly in cases deemed to have all clinical, behavioral, and neuropsychological

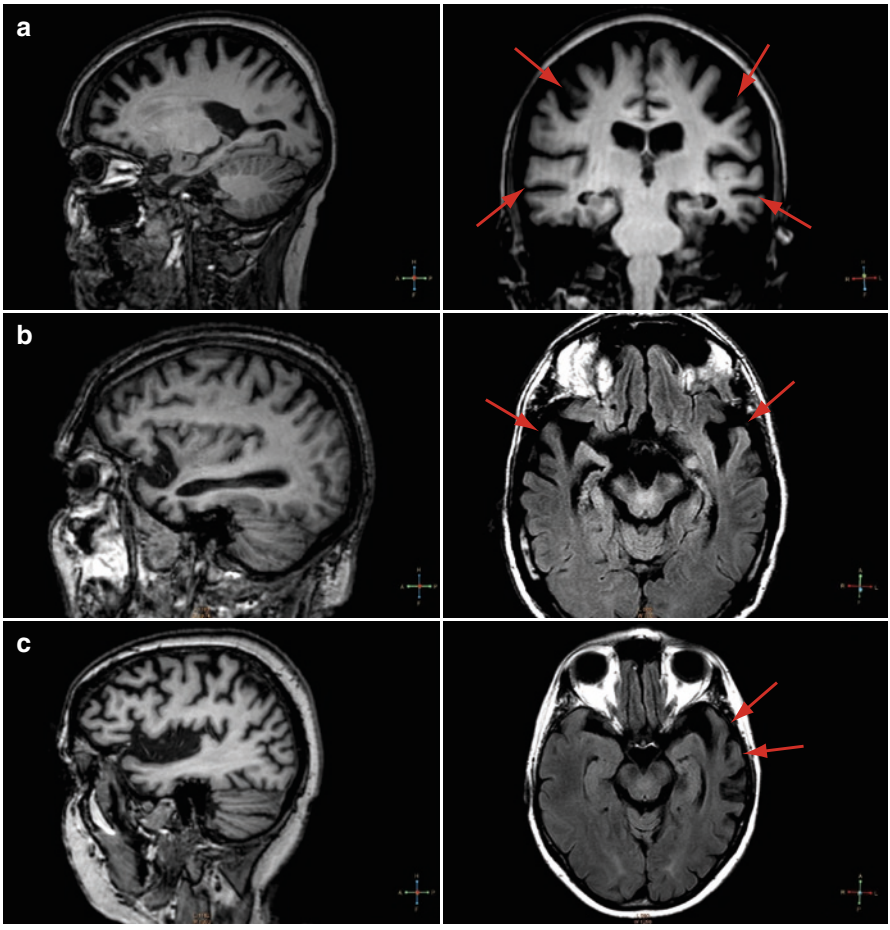

Fig. 6.4 (**a**) Behavioral variant FTD. Note generalized atrophy in frontal and temporal regions (*arrows*) with slight asymmetry favoring more atrophy on the left. (**b**) Semantic dementia. Note anterior temporal tip atrophy bilaterally (*arrows*). (**c**) Progressive nonfluent aphasia. Note asymmetric atrophy favoring the left temproal lobe (*arrows*)

features of bv-FTD. This raises the question of either a behavioral phenocopy of FTD or else cases where atrophy is either negligible or will occur later in the disorder.

On standard MRI, specific asymmetric lobar atrophy in the frontal regions with or without temporal atrophy is the best predictor of the bv-FTD subtype. Recent research has shown that the process starts in the orbitofrontal and cingulate regions and spreads to insular cortex and thence to the basal ganglia. Using functional techniques, hypoperfusion of frontal regions in SPECT has been shown to be sensitive but not specific for bv-FTD, although again asymmetry of perfusion of the frontal regions using either PET or SPECT in individual cases, especially where there does not appear to be much atrophy, improves the specificity. In research, PET studies have tended to show generalized hypometabolism but most significant in the mesial frontal regions consistent with the focal onset of many bv-FTD patients. This finding has been enhanced by a series of VBM-based studies that have pointed to regional sites within the mesial frontal zones that correlated with specific behavioral manifestations such as apathy (frontal pole), disinhibition (subcallosal region), and abnormal motor control (dorsal medial atrophy).

SD. MRI findings in SD tend to be more consistent (Fig. 6.4b). Cases typically have focal anterior temporal pole atrophy with involvement of the inferior surface (especially the fusiform gyrus) more than superior. The atrophy is typically bilateral but asymmetric cases of predominantly left-sided atrophy are more common than those with predominantly right-sided atrophy, for reasons that are unclear. In addition, a variable amount of frontal atrophy is almost always found in these cases. Functional imaging does not usually add anything in the clinical setting, with dramatic hypometabolism evident in the regions of the anterior temporal lobes that are almost universally affected by regional atrophy.

It is clear that while atrophy maybe widespread in both frontal and temporal lobes as in other cases of FTD, it is the predominance of the anterior and inferior temporal lobe atrophy findings that appear to correlate with the main clinical findings in SD. Loss of ability to form semantic word associations correlates most strongly with damage in the region of the left anterior fusiform gyrus.

PNFA. Imaging findings in PFNA are less reliable than in either bv-FTD or SD, but most MRI studies report predominant involvement of the left hemisphere, specifically atrophy of the perisylvian fissure, inferior frontal lobe, anterior insula, and basal ganglia (Fig. 6.4c). In studies of functional imaging such as PET, the abnormal findings are also widely distributed but tend to focus on the left frontal regions. In PNFA-G, imaging findings using VBM have found atrophy in the region of the first frontal convolution (Broca's area). In PNFA-L, VBM findings have shown abnormalities further back than in the agrammatic form with the angular and supramarginal gyrus and other posterior perisylvian regions involved.

Neurophysiology

Electroencephalography

The use of EEG in dementia was more widespread before the advent of brain imaging but even then its clinical and diagnostic use was limited. There is a tendency for the background

organization features of the EEG to be preserved in FTD whereas in AD, the emergence of background slowing is common as the disease progresses. The reasons for such preservation in FTD are unclear but the observation may reflect the relatively rare association between FTD and seizures compared to AD. In the research lab, quantitative EEG (qEEG), which is a digital algorithm of the different wave frequencies, has tended to confirm the preservation of resting alpha rhythm but the loss of some faster frequencies in the beta range. Further work in this area is required before EEG is to be considered a useful biomarker.

Electromyography

Because of the coexistence of ALS/MND and FTD, EMG has become an important diagnostic tool in young-onset dementia that have associated motor or swallowing difficulties (see Chap. 7). As yet, the status of EMG as a biomarker is unclear, as the use of EMG in unselected FTD cohort is not likely to be either cost-effective or clinically valuable.

CSF

Cerebrospinal biomarkers in FTD remain elusive but hope remains for a breakthrough in the next few years. Progress in CSF biomarkers in AD (total tau measurement, hyperphosphorylated tau and Aβ(beta) (1–42) has not been mirrored in FTD (see Chap. 3). The most obvious reason for this is the pathological heterogeneity of FTD compared to AD. For obvious reasons, measuring tau is unlikely to be of value in so-called tau negative ubiquitin-positive pathological subtypes. The situation is not helped by the overlap between clinical and pathological phenotypes such that any of the three major subdivisions of FTD – bv-FTD, SD, or PNFA – could eventually prove to have either tau-positive or ubiquitin-positive inclusions. The exceptions to this general rule are CBD, which is usually a tauopathy and FTD/ALS, which is generally positive for TDP-43. Finally, there is the problem FTD phenocopies, which may include normal brains and also AD, which may present as a PNFA, particularly of the logopenic variant (see Chap. 3). While it fails to clearly differentiate between AD and FTD, there is a confluence of research that shows a reduction in Aβ(beta) 1–42 as is seen in AD.

Neuropathology of FTD

The neuropathology associated with the clinical entities of FTD (bv-FTD, PNFA, SD) is heterogeneous with the common feature being a relatively selective degeneration of the frontal and temporal lobes. As in other neurodegenerative conditions, most pathological subtypes of FTD are characterized by specific kinds of intracellular protein inclusions. In the past few decades, the biochemical composition of many of these inclusion bodies has been determined. There is a growing trend to classify FTD based

on the presumed molecular defect. This is because it is thought that the molecular defect most closely reflects the underlying pathogenic process and because many of the eponymous and descriptively named syndromes of the past are now known to have imperfect clinicopathological correlation. Table 6.5 summarizes the timeline of FTD discovery over the last 100 years.

Table 6.5 Timeline of discoveries in the molecular pathology of FTD

Year	Event
1892	Arnold Pick describes patients with progressive impairment of behavior and language.
1911	Alois Alzheimer describes macroscopically, atrophy of frontal and anterior temporal lobes and microscopically; round silver impregnated inclusions and swollen neuronal perikarya (cell bodies) in the brains of these patients.
1927	Schneider calls these cells Pick bodies, the defining histopathological lesion of Pick's disease.
1939	Sander describes large pedigree (Dutch Family 2) of autosomal dominant dementing disorder characterized by behavioral disturbance, disinhibition, language disturbance, and hyperorality. Locus for this family found in 1997 (see below).
1987	Gustafson (Lund) describes frontal lobe degeneration of non-Alzheimer type.
1996	Snowden (Manchester) describes similar descriptions called frontotemporal lobar degeneration. Both groups collaborated on the first consensus criteria the so-called Lund-Manchester Criteria for frontotemporal dementia (FTD).
1994–1996	Two separate kindreds of dementia with parkinsonian features are linked to locus *Chr 17q21–22.* Dutch family 2 linked here in 1997 and at least 13 other families linked soon thereafter. Neurons with tau inclusions (see Fig. 6.5a) linked the neuropathology of the Chr 17q families with FTD with or without parkinsonism (FTD17-T or FDTP17-T), which is the region that includes the gene for tau (MAPT). Since then, 44 mutations in MAPT have been described in families with FTD17-T.
2000	Several reports of families with non-Alzheimer dementia with ubiquitin-positive but tau-negative pathology mapped to the same region of Chr 17 (see Fig. 6.5b).
2006	A number of research groups show mutations in the *progranulin gene* (*GRN*), a gene located on Chr 17 very close to MAPT (FTD17-U). To date, 68 mutations in PGRN have been found in FTD17-U families. TAR DNA binding protein (TDP-43) identified as the major component of ubiquitinated inclusions in FTD17-U. FTD17-U with TDP-43 is the major pathology in FTD/ALS.
2004–2006	In 2004, a series of mutations in the gene encoding *valosin-containing protein* (*VCP*) are found to cause a rare condition of FTD, inclusion body myocytis and Paget's disease of bone. Mutations in the gene (TARDBP) encoding TDP-43 have been found in ALS, ALS/FTD and, rarely, in FTD alone. Also, in 2005, mutations in *charged multivesicular body protein 2b CHMP2B* gene on Chromosome 3 were found to cause a familial FTD first identified in Jutland in 1980s.
2009	*FUS* (*fused in sarcoma*) protein identified as protein in some FTD17-U, TDP-43 negative inclusions. Mutations in FUS gene have been found in familial ALS and, more recently, in FTD without ALS.

Common Features

The most common gross neuropathological finding is focal, often asymmetric, lobar atrophy of the frontal lobe, and/or temporal lobes with microscopic neuronal loss in the superficial laminae of the cortex. Importantly, normal brain imaging studies do not exclude microscopic FTD pathology. Crucially also is the observation that pathological subtypes of FTD do not map onto clinical features in a one-to-one manner. The association of a highly specific constellation of symptoms and signs with a variety of neuropathological findings may seem paradoxical but may be understood in terms of systems neurodegeneration, .i.e., degeneration of neuronal populations that are connected structurally and functionally.

In 1911, Alois Alzheimer described round silver-impregnated inclusions and swollen neuronal perikarya (cell bodies) in cases of dementia with prominent language and behavioral symptoms, first described clinically by Arnold Pick in 1892. The inclusions would become known as Pick bodies, the defining histopathological lesion of Pick's disease. After a period where little progress was made beyond those original descriptions, renewed interest in the family of non-Alzheimer dementias with prominent frontal and temporal atrophy showed that only minority had classic Pick-type pathology. In the last 30 years, significant progress in descriptions of the pathological subtypes has been made.

Pathological Subtypes

Recent advances in molecular genetics, biochemistry, and neuropathology of FTD prompted the Midwest Consortium for Frontotemporal (Lobar) Degeneration and other groups to review and revise the existing neuropathological diagnostic criteria for FTD. The proposed criteria for FTD are based on existing criteria, which include:

The Tauopathies

Tau is a microtubule-associated phosphoprotein that binds to tubulin and stabilizes the cytoskeletal structures of axonal transport. Tau staining can be demonstrated in the following; FTD with pick bodies, CBD, PSP, sporadic multiple system tauopathy with dementia, argyrophilic grain disease, neurofibrillary tangle dementia, and FTD with microtubule-associated tau (MAPT) gene mutation, also called FTD with parkinsonism linked to chromosome 17 (FTDP-17) (see below). Abnormal tau aggregates that are seen not only in FTD, CBD, and PSP but also in AD provide a toxic gain of function mechanism for neurodegeneration. The microscopic appearance of the cortex shows loss of neurons, widespread spongiosis, and astrocytosis obscuring normal pathology. Pick bodies as originally described by Alzheimer are now known to be spherical cytoplasmic inclusions that are tau positive. Pick bodies are typically found in the cingulated gyrus, insula, inferior parietal lobule, and inferior temporal gyri. They are also found in the mesial structures, particularly the granule cells of the dentate fascia (Fig. 6.5a). White matter pick bodies are more common in CBD and PSP but can be found in FTD. Pick bodies may also be found in the basal ganglia and substantia nigra.

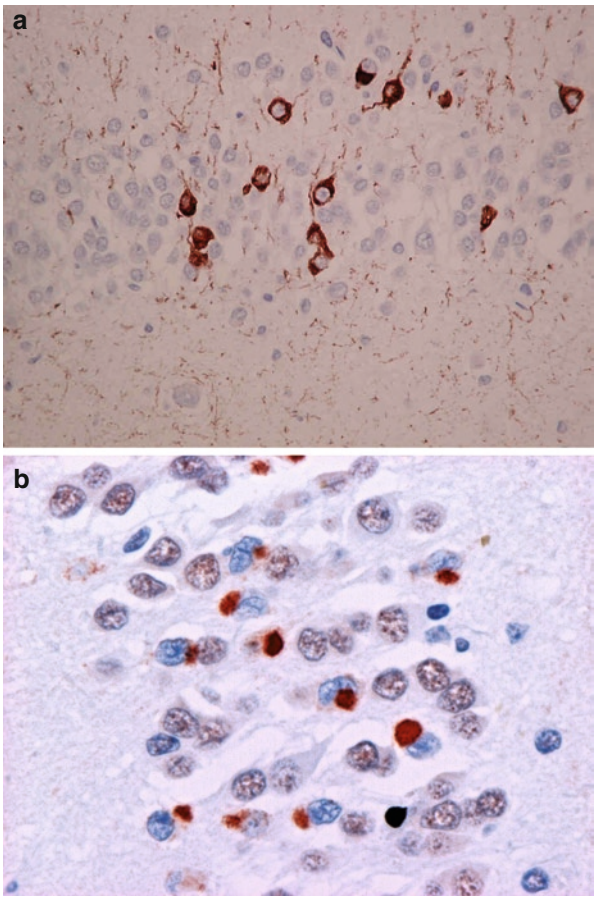

Fig. 6.5 Microscopic staining in FTD. (**a**) Tau-positive staining in FTD17-T (*arrow*) (Courtesy Prof. Michael Farrell); (**b**) TDP-43 staining in FTD-U/ALS (*arrow*) (Courtesy Prof. Ian R. A. Mackenzie)

Ubiquitin Positive (Tau-Negative) Pathology

This is now understood to be the most commonly found pathology in FTD. In 2004, the first ubiquitin protein was identified in an FTD phenotype as intermediate filament in a disorder known as neuronal intermediate filament inclusion disease (NIFID). In the majority of cases, however, the ubiquitinated inclusions contain a protein called TDP-43 (FTD-TDP).There are four subtypes of this type of pathology described in the recent consensus criteria by Cairns et al:

- Type 1 with neurites predominantly.
- Type 2 with cytoplasmic inclusions predominantly.
- Type 3 with intranuclear inclusions.
- Type 4 associated with VCP mutations (see below).

Recently, other non-TDP-43 proteins have been identified as in ubiquitin-positive, tau-negative cases. About 10% of cases have been shown to stain positively for the FUS (fused

in sarcoma) protein, although these are not due to FUS gene mutations. A smaller number that are IF-, FUS-, and TDP-43 negative have mutations in the CHMP2B gene (see below).

Microscopically, brains with TDP-43 inclusions show neuronal loss, microvacuolation, and gliosis of superficial cortical laminae. There may be loss of brainstem and spinal motor neurons with astrocytosis as can be seen in classical ALS. The defining lesion is the ubiquitin-positive cytoplasmic inclusion found in neurons in the granule cell of the hippocampal dentate fascia and in the superficial cortical layers (Fig. 6.5b).

Dementia Lacking Distinctive Histology

This is a rare and controversial entity – new analyses have allowed many cases to be reclassified into one of the positively defined subgroups above.

Genetics

Introduction

The progress in this area, moribund for decades despite the recognition of the importance of heritability since the 1920s, has been rapid and ever-expanding.

Distinguishing Sporadic and Genetic Forms of FTD

The traditional disease dichotomy of "sporadic" versus "genetic" is still used but is increasingly difficult to support, due to the likely polygenic factors influencing sporadic FTD. Nevertheless, the first step in determining whether there is a genetic influence in a disorder is to establish the frequency of a family history of the disorder.

At the clinical epidemiology level, the accuracy of ascertainment of familial disease is confounded by informant reliability, the late onset of the disease, and the possibility of death before disease expression, and the variable phenotype of FTD-related diseases. The earliest well-documented large pedigree was first reported in 1939 by Sanders and colleagues, who described an autosomal dominant dementing disorder with behavioral and cognitive disturbances with relative preserved memory, affecting a Dutch kindred known as Dutch family 2. However, the earliest estimates of the frequency of family history came from the Lund and Manchester clinicopathological series, which estimated that up to 50% of patients with FTD had a first-degree relative with dementia. More recent studies have tended to corroborate this figure.

Pathological features can help discriminate familial and nonfamilial forms. Numerous mutations in the tau gene on chromosome 17 account for between 10% and 40% of familial forms. Tau positivity is therefore a strong indicator of possible genetic origin.

Conversely, tau-negative, ubiquitin-positive pathology may be the result of a progranulin mutation, which may account for up to 25% of familial forms of FTD in some populations.

Mutations in Genes Causing FTD

In chromosome-17-linked FTD families, mutations in the gene encoding the microtubule-associated protein tau (*MAPT*) and the progranulin gene (GRN) are identified. In FTD populations, the *MAPT* mutation frequency ranges from 8% to 50%, that of *GRN* from 5% to 26%. Also, mutations in the gene encoding the chromatin-modifying protein 2B (*CHMP2B*) at chromosome 3p11.2 have been identified in autosomal dominant FTD. Inclusion body myopathy with early onset Paget's disease and frontotemporal dementia (IBMPFD) was associated with mutation in the valosin-containing protein gene (*VCP*) at chromosome 9p13-p12, and amyotrophic lateral sclerosis (ALS) with FTD was linked to a locus at chromosome 9q21-q22.

Below is a description of the currently well-characterized genetic forms of FTD. A standardized way of abbreviating familial FTD has been agreed but is constantly being updated. Following FTD (also known as FTLD), a P is added if extrapyramidal parkinsonian features are present. The chromosomal linkage is hyphenated and the T is placed to indicate whether tau inclusions are seen. In tau-negative disease, U (ubiquitin proteasome system) is added after the hyphen to indicate ubiquitin staining but recently with the identification of many of the ubiquitinated proteins, the term FTD-U is now reserved for only a minority of cases.

FTD with Parkinsonism Linked to Chromosome 17: FTDP-17 T and the MTAP Gene

In adult human brain, six tau isoforms are produced from a single gene on chromosome 17 by alternative mRNA splicing. In 1994, a large Irish and American kindred was described whose genetic locus was linked to 17q21–22 where the tau gene is located. Originally known as disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC), an important clue to future dilemmas was in the clinical description: the phenotype was hugely variable. A number of other research groups linked equally diverse clinical kindreds and names such as hereditary frontotemporal dementia (HFTD), multiple system tauopathy dementia (MSTD), and pallidopontonigral dementia (PPND) emerged. Pathological features were more uniform with all studied members showing frontotemporal atrophy and tau deposition. In 1997, a consensus conference allowed for the categorization of most descriptions as "FTD with Parkinsonism linked to chromosome 17." Most recently, it has become clear that such widely varying clinical syndromes such as PSP, CBD, and FTD can coexist within families with MAPT mutations.

The age of onset of FTDP-17 is between 30 and 65 years. Behavioral and cognitive problems predominate and memory and praxis are relatively preserved. By definition, most have prominent parkinsonian features and amyotrophy is rare.

To date, 44 mutations in MAPT in 132 kindreds have been described. Most coding mutations occur in the microtubule binding repeat region or very close to it. These potentially lead to a partial loss of function of tau with reduced tau binding to microtubules.

FTD Linked to Chromosome 17: FTD-17TDP the Progranulin Gene and the Valocin-Containing Protein Gene

In 2000, several pedigrees linked to chromosome 17 were identified without MAPT mutations but with typical ubiquitin-positive, tau-negative inclusions. In 2006, several research groups described a serious of mutations in the GRN gene. To date, 68 mutations in 210 families have been found. The average age of onset of dementia in progranulin families is the sixties with the clinical spectrum encompassing apathy, typical cognitive features of FTD, and some with FTD/MND (see below). Progranulin is associated with tumorigenesis when overproduced; however, the mutations seen in GRN associated with FTD are associated with reduced circulating levels of progranulin.

Because progranulin is not incorporated into ubiquitinated inclusions, a search for the FTD-U disease protein was undertaken and in 2006 an international research team identified the protein as TAR DNA binding protein, also known as TARDBP or as TDP-43. This cellular protein is encoded by the TARDBP on chromosome 1. This protein was originally identified in the brains of patients with FTD/ALS but it is now known to be the major protein in FTD-17U and has been termed FTD-TDP; four subtypes have recently been identified. Type four has been associated with brain pathology seen in a small number of cases of FTD combined with inclusion body myositis and Paget's disease of bone. Four families with this condition linked to the short arm of chromosome 9, and in 2004 a series of mutations in a valosin-containing protein (VCP) were found. To date, 13 mutations have been found in 30 families.

FTD with Motor Neuron Disease

It has long been recognized that cognitive and behavioral impairment is a feature of a substantial minority of cases of ALS/MND and that some 15% reach agreed clinical criteria for FTD (see Chap. 9 for discussion). However, genes that have been described in superoxide-dismutase-related familial ALS rarely cause FTD. The pathological findings in ALS/FTD are typical of FTD-17TDP (see above), which, in non-ALS cases, have been linked to progranulin mutations with TDP-43 immunostaining. While GRN mutations have yet to be convincingly confirmed in ALS or ALS/FTD, over 31 TDP-43 gene mutations have been found in patients with both sporadic and familial ALS, and dementia has been noted in some affected kindreds.

FTD-FUS, Tau Negative and TDP-43 Negative: The FUS Protein

In 2009, international collaborators identified a subgroup of FTD patients representing about 10% of cases, with an unusual clinical phenotype and pathology characterized by

frontotemporal degeneration with neuronal inclusions composed of a ubiquitinated protein, which is TDP-43 and tau negative. All cases were of a bv-FTD phenotype with early onset (mean age of onset of 41 years), with a high prevalence of psychotic symptoms without aphasia or significant motor features. Pathology in all of these cases was characterized by positive FUS (Fused in Sarcoma) immunohistochemistry labeling of the neuronal inclusions. No actual mutations in the FUS gene were found in any of these cases.

FTD-UPS, Tau Negative, TDP-43 Negative, FUS Negative: The CHMP2B Gene

In 1984, a researcher came across a very large family in Jutland in Denmark with an unusual dementia. There were over 27 affected individuals with a very wide clinical variability. In 1995, genetic linkage to chromosome 3 was established. Since then, three kindreds have been described with mutations in a gene coding for the charged multivesicular body protein 2B (CHMP2B). The pathology is a ubiquitinated protein that is tau, TDP-43 negative, and FUS negative. More recently, a number of apparently sporadic cases with the young-onset atypical phenotype described above have been shown to have CHMP2B mutations.

There remain a small number of cases that are negative for tau, TDP-43, and FUS staining but that do not have associated CHMP2B mutations, Some of these stain for intermediate filament as in neuronal intermediate filament inclusion disease. Finally, a number of FTD-U proteins remain unidentified, suggesting that the full compliment of FTD pathologies is yet to be elucidated.

Presenilin Mutations and FTD

Recently, several families with FTD have been shown to have mutations in Presenilin1, a gene usually associated with familial Alzheimer's disease. This finding confirms the notion of convergence amongst mechanisms of neurodegeneration and is reciprocal to recent finding of MAPT polymorphisms in large AD cohorts. The exact role of presenilin in FTD is unclear

Genetics of Sporadic FTD

Despite the rapid growth in understanding of familial forms of FTD, the majority of FTD cases are sporadic, with only about 40% having a family history of dementia. However, in sporadic cases, abnormal aggregations of tau are often found, similar to that in the familial form. In the late 1990s, a series of single nucleotide polymorphisms (SNPs) in exons and flanking introns in the tau gene region, were found to be in linkage disequilibrium constituting two distinct haplotypes H1 and H2. The H1 haplotype is the most frequent seen in Caucasian populations. An association of the extended tau H1 haplotype and a number of tau-based dementias has been reported, including FTD. Furthermore, the tau H1 haplotype

increases the risk for FTD through a combined effect with Apo-E-4 and Apo-E-2 alleles. The mechanism of risk increase is unknown.

Therapy for FTD

Introduction

Currently, there are no approved disease-modifying therapies for FTD. However, the explosion in the understanding of the molecular pathology of FTD over the last decade has led to a plethora of potential targets for therapy, which have been the subject of numerous ongoing trials, some of which have competed phase III studies.

Current therapeutic management involves many approaches to symptom control and support of patient and carers.

Therapy should be based on a palliative, multidisciplinary approach to care, which should be employed from communicating the diagnosis, through managing difficult behaviors and troubling physical symptoms to the agonal stages (see also Chap. 13).

The Potential for Disease-Modifying Therapy

Therapeutic compounds for FTD have largely been drugs approved for use in other neuropsychiatric disorders including dementias such as AD. A study of memantine, an NMDA receptor antagonist approved for moderate-to-severe AD, has been shown to transiently improve the total NPI (neuropsychiatric inventory) score primarily in the bv-FTD group.

Preclinical and early clinical phase trials of true disease-modifying therapies are underway. The main targets are:

MATP in FTD with Tau Pathology

Tau is expressed in the axon of the neuron where it promotes microtubule stability. Mutations result in errors of tau splicing, cleavage, and phosphorylation. A combination of toxic gain-of-function and loss-of-function is the likely pathogenic mechanism of degeneration. Biochemical strategies for interrupting abnormal tau accumulation such as inhibiting aggregation, cleavage and expression, and interfering with splicing and stabilizing microtubules are all being explored. Immune suppression to alter abnormal tau accumulation is also under consideration.

TDP-43 in FTD-U

TDP-43 is a nuclear protein that can bind to DNA and RNA. The pathology of the inclusions seen in FTD-U is characterized by hyperphosphorylation and ubiquitination on

TDP-43, and the pathogenesis may be a mixture of gain and loss of function. Immune therapy or efforts to block cleavage may have therapeutic value in removing abnormal TDP-43.

Mutations in Progranulin Lead to Reductions in mRNA

PTC124, a new chemical entity that selectively induces ribosomal read through premature but not normal termination codons, is in preclinical trials for FTD-associated progranulin mutations.

Symptom Control and Support

Behavioral and Psychiatric Problems

A multidisciplinary approach to the range of behavior and neuropsychiatric manifestations in bv-FTD is essential. Sensitive communication of the diagnosis to patients, families, and caregivers is required. This should be done in a specialist environment with an understanding of the unique features of FTD such as the personality changes, loss of empathy, and socially embarrassing behaviors. A range of therapies have been used in the last number of years to treat the behavioral manifestations of FTD. Selective serotonin reuptake inhibitors have been amongst the most widely studied drugs and now considered first-line treatments. Memantine has shown promise (see above) but placebo-controlled trails are awaited. Finally, atypical antipsychotic agents such as quetiapine may be considered for treatment of agitation, delusions, and aggression.

Cognitive Impairment

There are no approved therapies for cognitive impairment. Acetylcholinesterase inhibitors, widely used in mild-to-moderate AD, may worsen behavioral symptoms in FTD. Neuropsychological strategies can help patients and caregivers cope with the worst effect of cognitive impairment.

Speech and Language Therapy

Speech and language therapy in PNFA may offer some benefit to patients early in the course of the illness, as does utilization of communication aids by caregivers.

Sleep

Sleep disturbances should be managed by maintaining a regular sleep regime and may be aided by the use of the sedating antidepressant Trazodone. With altered dietary behaviors and weight gain, obstructive sleep apnea may become a problem and can be responsible for sudden worsening of cognitive function.

Motor Impairment

Parkinsonism and amyotrophy are the most common motor manifestations of advanced FTD and approaches to managing these aspects of the disorder are dealt with in Chaps. 5 and 7.

Incontinence

Prominence of early bladder difficulty should give rise to suspicion of disorders of autonomic control such as PSP rather than FTD. However, early involvement of the medial frontal lobe in both bv-FTD and CBD can lead to incontinence, which should be managed with intermittent catheterization, indwelling catheters, and the use of a leg bag or in some cased urinary diversion. The use of anticholinergics must be tempered by the possibility of increasing confusion.

Palliative Care

The inexorable decline in function and quality of life that currently follows a diagnosis of FTD should always be met with a plan for palliation and appropriate end of life care. There has been significant improvement in the knowledge and understanding of this process amongst palliative care specialists. For further discussion, see Chap. 13.

Support of Carer

It has been recognized that carers of patients with FTD report significant distress and depression even when compared to carers of patients with other forms of dementia. This is most likely due to the FTD patient's behavioral dysfunction and poor social cognition. The multidisciplinary team should be aware of these stressors on the carer. Support to the carer can be provided through advice and instruction on how to manage disruptive behavior, and the availability of respite care.

Significant Advances in the Past 5 Years and a Look to the Future

Phenotypic Variability and Clinical Presentation

Frontotemporal dementia is remarkable for the striking variability in clinical presentation and, as has become more evident in recent years, heterogeneity in the underlying patterns of brain atrophy, the latter, to a large extent, accounting for the former. Apart from the original prototypic behavioral and aphasic (fluent and nonfluent) forms pronounced apathy has been associated with dorsolateral and medial frontal lobe atrophy, disinhibition with orbitofrontal and temporal lobe changes, and a variety of behavioral features specifically with the right temporal lobe. Distinct anatomical subtypes of

behavioral variant FTD have been identified, including frontal-dominant subtype, temporal-dominant subtype, and frontotemporal and temporofrontoparietal subtypes.

Furthermore, it has been an assumption that FTD is not a dementia of old age, yet a prevalence rate of 3% has been reported for bv-FTD in 85 year olds. There has also been a growing literature in relation to distinguishing between true FTD and behavioral phenocopies, with implications for differential diagnosis, prognosis, and possible intervention. There have also been huge strides in elucidating the major overlap that exists between FTD and conditions with which it was not initially associated, including ALS, CBD, and PSP.

Neuropsychology

It has become evident that some of the features that were originally believed to be defining characteristics of FTD require clarification. For example, early severe memory impairment has generally been considered to contraindicate FTD, but in fact, severe amnesia can be a presenting feature in a few cases. In a similar vein, prominent psychotic features are not anticipated in FTD, but recent studies show that in some cases a schizophrenia-like psychosis can present several years before the emergence of more obvious FTD. Progress has also been made in developing novel tools to investigate distinctive features of FTD such as breakdown in social judgement, decision making, empathy, and emotion processing, with implications both for differential diagnosis and for understanding the anatomical substrates of higher order cognition, emotion, and social behavior. New diagnostic criteria will emerge soon, which are based on a greater understanding of the types of behavior change manifest and interaction with dysfunction in social cognition. Moreover, the relationship of FTD and MND has evolved with the demonstration of a spectrum of cognitive impairment in these disorders and with a possible subclinical FTD syndrome in a large number of MND cases.

Biomarkers

Brain Imaging

Advances in brain imaging have grown at a remarkable pace in the last 5 years. Specific pattern of lobar atrophy can now be reliably mapped to clinical phenotypes. Indeed, some have argued that the presence of atrophy of the polar regions of the temporal lobe along with the fusiform gyrus are so reliable that they should form part of the diagnostic criteria at least for SD, with patterns in other subtypes not far behind in terms of reliability. A key challenge for the future is to try and improve the automation of computer-aided quantitation of MRI such that techniques such as VBM and DTI can be of use diagnostically at the individual patient level. The advent of 3 T MR imaging with double the field strength and four times the resolution as a standard clinical imaging modality will go hand in hand with the addition of the automated techniques to improve diagnostic accuracy. Finally, the role of functional imaging has yet to be fully elucidated and there is an urgent requirement for

a protein ligand that can reliably detect abnormal pathology in FTD similar to the discovery of Pittsburgh Compound B (PIB), which detects the presence of amyloid in the brain (see Chap. 3).

Blood and CSF Biomarkers

Detection of low or high levels of tau, progranulin, or TDP-43 are the holy grail of biomarker research in FTD since they would be conforming with key elements of what is already known about the molecular pathogenesis. To date, such biomarkers remain elusive. For the moment, the consistent finding of lower levels of Aβ(beta) 1–42 similar to that in AD has yet to be explained. Recently, a subgroup of FTD patients has been shown to have remarkably high CSF levels of both light chain and hyperphosphorylated heavy chain neurofilaments (NfL and NfH). The degree of NfH phosphorylation is increased in FTD compared to both AD and controls. The pathological significance of these neurofilaments remains to be determined. Finally, the search for novel biomarkers has involved the use sophisticated mass spectroscopy. Among candidates that have been found are the neurosecretory protein VGF, transthyretin, S-cysteinylated transthyretin, truncated cystatin C, and a fragment of chromogranin B.

Molecular Pathology

Improvements in assays of the functional effects of the tau mutations may enable us to link the size of molecular effects to the severity of the clinical phenotype. It already seems likely that a large effect on microtubule-binding and tau aggregation equates to a more severe phenotype. In addition, the exon-10 splice site mutations appear to correlate with clinical phenotype based on the degree to which they disrupt splicing.

Future Advances in Treatment

Treatment for FTD, a condition for which there was at best a small range of drugs for symptom control available until recently, has advanced hugely. The development of multidisciplinary clinical teams for diagnosis and follow-up has brought a range of expertise to bear on the difficult problems that this dementia of predominantly young people with families brings. Clinical nurse specialists, clinical psychologists, speech therapist, social workers, physiotherapists, and palliative care specialists along with neurologists with a special interest in cognitive neurology all have a role to play in both patient and caregiver support. The enhancements provided by teams of this type are aided by the use of a range of pharmacological therapies for symptom control.

The goal for the next 5 years, however, is to find the elusive disease-modifying therapy that can give hope to the afflicted and to the many families concerned for the future of children and relatives of those with a disease with a highly likelihood of familial disposition. The advances in the understanding of the neuropathology and molecular pathology of

FTD have thrown up tantalizing targets for therapy. Studies on the interruption of the deposition of abnormal tau are ongoing and will undoubtedly lead to approved treatments for both AD and FTD. Treatments directed against other targets such as progranulin and TDP-43 will not be far behind.

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Amyotrophic Lateral Sclerosis

7

Orla Hardiman

Abstract Amyotrophic lateral sclerosis or motor neuron disease is a progressive motor system degeneration. Extra motor involvement also occurs, primarily in the form of executive dysfunction. Up to 15% of those with ALS also develop frontotemporal dementia. The pathophysiology of ALS is not well understood. Five percent of cases have a positive family history, and a number of causative and "at risk" genes have been identified. Diagnosis is clinical, and investigations are aimed at excluding other treatable conditions. Optimal management of ALS requires a multidisciplinary team. Most ALS patients develop respiratory failure, and early intervention with noninvasive ventilation can improve survival and enhance quality of life. Patients with ALS should be encouraged to consider an advance directive regarding their end of life.

Keywords ALS • MND • Pathogenesis • Diagnosis • Multidisciplinary management • End of life

Introduction

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is the commonest neurodegenerative condition of the young and middle aged. The disease is characterized by progressive upper and lower motor neuron degeneration. Mean life expectancy is 3–5 years from first symptom. Although primarily a disorder of the motor system, ALS also has nonmotor features and can overlap clinically and pathologically with other neurodegenerative conditions including frontotemporal dementia (FTD). Once symptoms develop, the course of ALS is progressive, and death is usually from respiratory failure. Although treatment options are limited, multidisciplinary management can preserve quality of life and interventions such as noninvasive ventilation can improve survival.

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Clinical Features

The clinical onset of ALS is usually asymmetric. The first symptom may be a gait disturbance (e.g., tripping, dragging one leg) or difficulty with fine movements in the upper extremities, e.g., fastening buttons. As motor neurons are affected segmentally, clinical presentation depends on where in the neuroaxis the disease is first manifest. Up to 25% of patients present with bulbar symptoms such as dysarthria and dysphagia and 1–5% present with respiratory failure. The site of disease onset is of prognostic significance, as limb onset carries a better prognosis than bulbar onset, and lower limb onset carries a better prognosis than upper limb onset. Respiratory onset disease carries the worst prognosis.

People with ALS almost never describe fasciculations as a key part of their presenting symptomatology, and people presenting with fasciculations in the absence of muscle weakness or other neurologic signs rarely have ALS.

The clinical hallmark on neurological examination is the presence of both upper and lower motor neuron signs that are not attributable to other causes. A combination of upper and lower motor signs occurring concomitantly at the same spinal level s (e.g., brisk reflexes in a weak, fasciculating limb) should raise a differential diagnosis of ALS, although cervical spondylotic myelopathy could also produce this clinical picture. Bladder function is not usually impaired in the early stages of the disease. Up to one quarter of patients complain of minor sensory symptoms, however formal sensory examination is generally normal.

The time from symptom onset to diagnosis is usually in the order of 9–15 months. Many people will have seen two or three other specialists before they are correctly diagnosed.

A recognizable phenotype of frontotemporal dementia (FTD) occurs in up to 15% of patients with ALS. This is characterized by personality change, irritability, obsessions, poor insight, and pervasive deficits on frontal executive tests. A milder form of cognitive impairment occurs in up to 50% of patients with ALS, and can include subtle executive deficits, apathy, verbal fluency deficits, and changes in memory. Behavioral change may also be reported by a spouse or relative and may not be apparent during formal clinical interview. Cognitive dysfunction can precede or follow the onset of motor symptoms.

There is currently no definitive screening test for cognitive impairment in ALS. Verbal fluency is a sensitive marker of cognitive impairment in ALS, and a simple 2 min word-generation test can help to identify patients in whom a more detailed neuropsychological evaluation may be required. Patients with severe deficits in verbal fluency are more likely to exhibit frontal and executive deficits on more formal testing although these tests are also predicated on premorbid intellectual ability. Short batteries of tests, such as the MMSE, are not sensitive to frontotemporal syndromes and should not be used for diagnostic purposes.

In patients with features of frontotemporal dementia, behavioral change can be assessed using carer-based instruments such as The Neuropsychiatric Inventory or Frontal Systems Behavioral Scale. These questionnaires are completed by caregivers and can convey how the patient functions on a day-to-day basis compared with his or her premorbid status. However, cognitive impairment may be underestimated in the absence of a complete neuropsychological battery.

Once symptoms and signs of ALS develop, the condition progresses. Functional decline can be measured using the revised ALS Functional Rating Scale (ALSFRS-R) (Table 7.1).

Table 7.1 ALSFRS-revised

1. Speech	
4	Normal speech
3	Detectable disturbance
2	Intelligible without repeating
1	Speech with nonverbal communication
0	Loss of useful speech
2. Salivation	
4	Normal
3	Slight but definite excess of saliva
2	Moderate excessive saliva, minimal drooling
1	Marked excessive of saliva, some drooling
0	Marked drooling, requires constant tissue
3. Swallowing	
4	Normal eating habits
3	Early eating problems, occasional choking
2	Dietary consistency changes
1	Needs supplemental tube feeding
0	Nil orally
4. Handwriting	
4	Normal
3	Slow or sloppy, all words legible
2	Not all words legible
1	Able to grip pen but cannot write
0	Unable to grip pen
5. Cutting food and handling utensils	
4	Normal
3	Slow and clumsy but no help needed
2	Can cut most foods, although clumsy and needs some help
1	Food must be cut by someone else
0	Needs to be fed
6. Dressing and hygiene	
4	Normal
3	Independent but decreased efficiency
2	Some help with closures and fasteners
1	Provides minimal assistance to caregiver
0	Unable to perform any task
7. Turning in bed	
4	Normal
3	Slow and clumsy
2	Can turn alone with difficulty
1	Can initiate but cannot turn or adjust sheets
0	Total dependence

(continued)

Table 7.1 (continued)

8. Walking	
4	Normal
3	Early ambulation difficulties
2	Walks with assistance
1	Non ambulatory, functional movement
0	No purposeful leg movement
9. Climbing Stairs	
4	Normal
3	Slow
2	Mild unsteadiness / fatigue
1	Needs assistance
0	Cannot do
10. Dyspnea	
4	None
3	Occurs when walking
2	Occurs when eating, bathing or dressing
1	Occurs at rest
0	Considerable difficulty
11. Orthopnea	
4	None
3	Some difficulty, does not routinely use more than two pillows
2	Needs extra pillows to sleep
1	Only sleeps sitting up
0	Unable to sleep
12. Respiratory insufficiency	
4	None
3	Intermittent use of noninvasive ventilation
2	Continuous use of noninvasive ventilation at night
1	Continuous use of noninvasive ventilation day and night
0	Mechanical ventilation via tracheostomy

Most patients die within 3–5 years of diagnosis. Up to 10% of patients experience a more protracted disease course, and may live for up to 10 years from the time of first symptom.

Variants of ALS include primary lateral sclerosis (PLS), in which clinical signs are confined to upper motor neurons, and progressive muscle atrophy, in which signs are confined to the lower motor neuron. Diagnostic criteria for PLS require the presence of signs for a minimum of 3 years. These ALS variants can be difficult to diagnose in the early stages, and prognosis is generally better than in typical ALS.

Restricted forms of ALS have also been described, including flail arm and flail leg syndromes, and monomelic disease. The former two are more common in men, and carry a better prognosis than typical ALS.

Table 7.2 Variants of ALS/MND

Disease	Clinical features	Other comments	Median survival
ALS	Both upper and motor neuron signs in multiple spinal segments	Most common adult-onset form of motor neuron disease	3–5 years
Primary lateral sclerosis	Upper motor neuron signs only	Many patients eventually develop clinical or electrophysiological signs of LMN involvement. ALS develops in up to 77% within 3–4 years	For those who remain with a diagnosis of PLS, median survival =20 years or more
Progressive muscular atrophy	Lower motor neuron signs only	Variable evolution to ALS	5 years, a subset survive 20 years or more
Progressive bulbar palsy	Speech and swallowing affected initially due to LMN involvement of CN IX, X, XII.	Symptoms include dysarthria, dysphagia, and dysphonia. Aspiration pneumonia is usually the terminal event	2–3 years
Bulbospinal muscle atrophy (Kennedy's disease)	Speech and swallowing affected, proximal limbs	X-linked recessive inheritance pattern. Pure lower motor neuron condition due to trinucleotide repeat in androgen receptor	10 years or more

CN cranial nerves, *UPM* upper motor neuron, *LMN* lower motor neuron

Other variants include bulbospinal muscular atrophy (Kennedy's disease). This X-linked disorder is due to an expansion of trinucleotide repeats in the androgen receptor. The clinical features include slowly progressive lower motor neuron signs in bulbar and proximal limbs. Fifty percent of cases have gynecomastia. Progression is usually slower than in typical ALS. Nerve conduction studies can be helpful as, in contrast to ALS, the sensory nerve action potentials may be absent in Kennedy's disease. (Table 7.2)

The majority of ALS patients die from respiratory failure. Prognostic indicators include time from first symptom to diagnosis (longer duration carries a better prognosis), presence of dementia (poorer prognosis), bulbar or respiratory onset disease (poorer prognosis), older age of onset (poorer prognosis), marked weight loss (poorer prognosis), and presence of pure upper or pure lower motor syndromes (better prognosis) (Table 7.3).

Discussing the Diagnosis

Once the diagnosis has been established, the patient should formally meet with an experienced doctor who has been involved in the care, to discuss the outcome of the investigations. Specific techniques should be used as outlined in Table 7.4, including the provision of a quiet space and adequate time to discuss the diagnosis. The patient should be accompanied by a

Table 7.3 Prognostic indicators

Poor prognostic indicators
Short interval between first symptom and diagnosis
Bulbar onset disease
Respiratory onset disease
Malnutrition/hypermetabolism
Rapidly progressive decline in ALSFRS
Presence of dementia
Familial disease (some SOD1 mutations)
Beneficial vascular risk profile
Increased homocysteine
Vital capacity <50% of normal
Sniff nasal inspiratory pressure <40 cmH_2O
Good prognostic indicators
Long interval between first symptom and diagnosis
Lower limb onset
Flail arm/flail leg syndrome
Upper motor neuron predominant disease
Lower motor predominant disease
Familial disease (some SOD1 mutations)
Age of onset <50 years

Table 7.4 How should a physician tell the patient that they have ALS

Task	Recommendations
Location	Off the ward, in a quiet room Not in an out-patient clinic
Participants	Senior clinician Patient Family member Nursing staff
Breaking the news	Ask what the patient/family knows about their condition Approach the diagnosis with sensitivity Use diagrams to help explain the concept of upper and lower motor neurons Be honest about prognosis Acknowledge the distress that the diagnosis causes Allow plenty of time for questions Allow time for reflection
Hope and reassurance	Provide hope: up to 10% of patients survive for > 10 years Identify positive prognostic indicators Explain that support is available, and that the patient and family are not alone Reassure that as the condition progresses, interventions can help to maintain independence, quality of life, and dignity Reassure that decline occurs gradually Provide information about voluntary organizations Discuss likely opportunities to participate in research and clinical trials
Honesty	Be honest but empathic
Communication	Simple language, no jargon

close friend or family member. The level of information the patient has about the disease should be explored. Some patients have specific concerns including a fear of choking to death; reassurance can be provided about these and other anxieties relating to the progress of the disease. Patients should be provided with a follow up appointment within 2–4 weeks of diagnosis. Some patients seek a second opinion. This should be facilitated.

Epidemiology

The incidence of ALS/MND in Europe is approximately 2 per 100,000 and the overall lifetime risk is approximately 1:400. In populations of non-European or mixed ethnicity, the frequency of ALS is lower. While the reasons for this difference remain unclear, preliminary evidence suggests that genetic admixture may be protective. Careful evaluation of populations over a long period of time has indicated that the adjusted age-specific incidence of the disease is not increasing.

ALS is more common in males than females by a ratio of approximately 1.5:1. This disparity is mostly due to the increased frequency of spinal-onset ALS in men. In contrast to Parkinson's disease and Alzheimer's disease, the risk of developing ALS peaks between the ages of 50–75, and declines thereafter. This suggests that ALS is not a disease of aging, but a disease for which age is one of a number of risk factors.

As ALS is a rare disease, environmental factors that confer increased risk have been difficult to identify. Case-controlled studies seeking to establish exposure risks are often inadequately powered and confounded by methodological errors. High incidences of ALS in Guam and the Kii Peninsula in Japan have been associated with cyanobacterial neurotoxins including BMAA, although definitive evidence in this regard is lacking. Clustering of ALS has been identified in certain occupations including Italian soccer players. The factors that lead to this apparent increased risk remain to be determined. Other environmental factors that have been associated with ALS have included smoking, exposure to pesticides and organic toxins, and electromagnetic radiation. With the exception of smoking, definitive evidence of risk remains to be established and will require large unbiased population-based case-controlled studies for confirmation.

Genetics

Approximately 5% of ALS is familial with a Mendelian pattern of inheritance. A total of 12 genes and loci of major effect have been identified. (Table 7.5) The majority are autosomal dominant in inheritance pattern.

Mutations in superoxide dismutase (SOD1) account for up to 20% of all familial ALS, and up to 5% of apparently sporadic disease. Mutations in two different DNA/RNA binding proteins, TDP-43 and FUS/TLS, account for a further 15% of familial ALS. Both TDP-43 and FUS code for proteins involved in gene regulation including transcription, RNA splicing, RNA transport, and translation, and in the regulation and processing of small regulatory RNAS (microRNAs). Mutations in another RNA regulatory protein ANG accounts for up to 1% of sporadic cases. OPTN, coding for optineurin, is a causative gene

Table 7.5 Known causative genes/loci in ALS

Name	Gene	Locus	Protein
ALS1	SOD1	21q22.1	Cu/Zn Superoxide dismutase
ALS2	ALS2	2q33–35	Alsin
ALS3		18q21	
ALS4	SETX	9q34	Senataxin
ALS5		15q15-q22	
ALS6	FUS	16q15-q22	FUS
ALS7		20ptel	
ALS8	VAPB	20q13.33	VAMP-associated protein
ALS9	ANG	14q11	Angiogenin
ALS10	TARDBP	1q36	Tar DNA-binding-protein 43
	OPTN	10p14	Optineurin
ALS-FTD		9q21–22	
ALS-FTD		9p13.2–1,3	

of primary open-angle glaucoma. ALS-causing mutations of OPTN abolish the inhibition of activation of nuclear factor kappa B, and alter the cytoplasmic distribution of optineurin. The frequency of OPTN mutations in familial and sporadic ALS remains to be determined. Of the known genes, only SOD1, TDP-43, OPTN, ANG, and FUS mutations have been associated with typical ALS; the remainder are associated with unusual phenotypes or have been described in small numbers of kindred.

Ninety five percent of people diagnosed with ALS have no family history and are classified as having sporadic disease. Family aggregation studies have identified an overlap between ALS and some more common neurodegenerations, suggesting the existence of susceptibility genes that may increase the overall risk of neurodegeneration within kindreds.

Candidate gene studies have identified a number of "at risk" genes that increase disease susceptibility, although the relative contribution of each identified gene rarely exceeds an odds ratio of 2.0, and in most cases, the mechanism by which the risk is conferred remains to be elucidated (Table 7.6).

Genome-wide association (GWA) studies in ALS have been disappointing, as no single gene of major effect has been identified. Studies have lacked power related to sample size, and "hits" have been accordingly difficult to replicate in a second population. However, increased international collaboration coupled with the combination of detailed clinical phenotyping with next-generation bioinformatic technology is likely to provide a wealth of new information about ALS pathophysiology. This, in turn, will provide exciting new avenues for developments in disease therapeutics.

Genetic Testing

Because most ALS is nonfamilial, there is currently little advantage in testing sporadic individual patients for known gene mutations. Genetic testing should only be undertaken in known familial disease, where the presence of mutations in known genes might accelerate the diagnostic process. Genetic counseling is recommended prior to testing.

Table 7.6 Known susceptibility genes for ALS

Gene	Functional significance
Oxidative stress	
SOD1	Cytoplasmic antioxidant soluble form may become neurotoxic
HFE	Regulator of iron metabolism
Cytoskeleton, *microtubule*, *axonal transport*	
MAPT	Microtubule protein disruption, involved in other neurodegenerative diseases
NEFH	Neurofilament protein, mutations alter axonal transport
PRPH	Intermediate filament, transgenic mice develop motor neuron degeneration
DCT1	Disruption in dynein/dynactin complex alters axonal transport, produces phenotype in mice
KIFAP3	Kinesin-associated protein, modulates survival
Metabolism	
PON 1–3	Paraoxonases are important detoxifying enzymes. Association in five different populations, but different haplotypes implicated in different ancestral populations
Progranulin	Gene of major effect in FTD. Coding variations associated with ALS in some populations, similar in function to angiogenin
DNA/RNA repair	
ANG	RNA ribonuclease and hypoxia responsive agent; overlap in function with VEGF and progranulin
APEX	DNA repair enzyme
SMN1, SMN2	Affects RNA splicing, gene of major effect in spinal muscular atrophy
TDP-43	RNA regulator
ELP 3	RNA polymerase
Excitotoxicity	
UNC13A	Also links to familial ALS FTD
Unknown	
9p13.2–21,3	

Presymptomatic genetic testing should only be performed in first-degree adult blood-relatives of patients with a known gene mutation. As many mutations in ALS are incompletely penetrant, the identification of a mutation in an asymptomatic relative cannot accurately predict development of the disease. Testing should be performed on a strictly volunteer basis and should follow extensive genetic counseling.

Overlap Syndromes

Up to 15% of patients with ALS have frontotemporal dementia (FTD), and up to 30% of those with FTD have neurophysiologic evidence of anterior horn cell degeneration (see Chap. 6). A smaller percentage (2–5%) of patients with ALS has evidence of

other forms of dementia, including features of Alzheimer's disease. Patients with ALS are more likely to have a family history of neurodegenerative disease, suggesting common genetic susceptibilities. Parkinsons and dementia have been described in Guam, and the Kii peninsula in Japan. Outside of these areas, occasional patients with extrapyramidal syndromes and anterior horn cell degeneration have been reported and a small minority of ALS patients are ataxic. Rarely, Huntington's disease can present with amyotrophy (see Chap. 8).

Diagnostic Criteria

Formal diagnosis of ALS is based upon clinical criteria that include the presence of upper motor neuron (UMN) and lower motor neuron (LMN) signs, progression of disease, and the absence of an alternative explanation. There is no single diagnostic test that can confirm or entirely exclude the diagnosis of motor neuron disease.

The *El Escorial* criteria were developed in 1990 by the World Federation of Neurology (WFN) for research and clinical trial purposes. These guidelines were subsequently revised in Airlie House in April 1998 (Table 7.7).

Both sets of criteria are based on the degree of certainty of diagnosis, which in turn is based on clinical assessment and the presence of upper and lower motor neuron signs together in the same topographical anatomic region in the brainstem, cervical, thoracic, or lumbosacral spinal cord. Although not validated at the time of inception, a number of inter-rater reliability studies have shown that among experts, the criteria are in general uniformly applied and reproducible. Notwithstanding, the criteria have been criticized as being too restrictive, as up to 10% of patients with ALS remain within the "possible" category at the time of death and are thus excluded from most clinical trials, which require a diagnosis of "probable" " or "definite" ALS. The *El Escorial* and Airlie House criteria are not helpful in day-to-day management of ALS and should be reserved for classification of patients for research purposes.

Differential Diagnosis of ALS

Some conditions can closely resemble ALS and should be actively considered in the differential diagnosis. Consideration of the "mimic syndromes" is important, as the diagnosis of ALS is based primarily on clinical examination, supported by a series of laboratory investigations to exclude other conditions.

The majority of likely mimic syndromes are listed in Table 7.8. In practice, the most frequent conditions mistaken for ALS are multifocal motor neuropathy with conduction block and cervical spondylotic myelopathy.

Based on these studies, factors that should lead to revision of the diagnosis of ALS can be divided into two broad categories:

Table 7.7 El Escorial and Airlie House criteria for diagnosis of ALS

1. The presence of:
   (a) Evidence of LMND degeneration by clinical, electrophysiological, or neuropathological examination
   (b) Evidence of UMN degeneration by clinical examination; and
   (c) Progression of the motor syndrome within a region or to other regions, as determined by history or examination;

and:

2. The absence of:
   (a) electrophysiological and pathological evidence of other disease processes that might explain the signs of LMN or UMN degeneration; and
   (b) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

El Escorial Criteria

Definite ALS: UMN and LMN signs in three regions.

Probable ALS: UMN and LMN signs in at least two regions with UMN signs rostral to (above) LMN signs.

Possible ALS: UMN and LMN signs in one region, UMN signs alone in two or more regions, or LMN signs above UMN signs.

Suspected ALS: LMN signs only in two or more regions.

Airlie House (*modified*) *criteria*

Clinically definite ALS: clinical evidence alone of UMN and LMN signs in three regions.

Clinically probable ALS: clinical evidence alone of UMN and LMN signs in at least two regions with some UMN signs rostral to (above) the LMN signs.

Clinically probable—laboratory-supported ALS: clinical signs of UMN and LMN dysfunction are in only one region, or UMN signs alone in one region with LMN signs defined by EMG criteria in at least two limbs, together with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

Possible ALS: clinical signs of UMN and LMN dysfunction in only one region, or UMN signs alone in two or more regions; or LMN signs rostral to UMN signs and the diagnosis of clinically probable—laboratory-supported ALS cannot be proven.

Suspected ALS: this category is deleted from the revised El Escorial Criteria.

Failure of symptom progression – In general, patients with common mimic syndromes do not progress as rapidly as those with ALS, and tend to survive for longer periods.

Atypical history or symptoms – Common clinical features that lead to a reconsideration of the diagnosis of ALS include the presence of isolated upper or isolated lower motor neuron signs (leading to possible diagnoses of hereditary spastic paraparesis, multiple sclerosis, and motor neuropathy, respectively); the development of sensory complaints or bladder involvement (leading to diagnoses of myelopathy or demyelinating disease); the absence of upper motor neuron signs rostral to lower motor neuron signs; or the absence of bulbar signs in patients with prominent spinal signs (leading to a diagnosis of cervical myelopathy); and a family history of males only affected, and no male-to-male transmission (suggesting X-linked bulbospinal muscle atrophy (Kennedy's disease). The presence of asymmetric weakness and wasting in a C8 T1 distribution in a young man should raise the possibility of Hirayama disease (Table 7.9).

Table 7.8 Differential diagnosis of MND

Hereditary	• Kennedy's disease • Hereditary spastic paraparesis • Acid maltase deficiency • Facioscapulohumeral muscular dystrophy • Adrenomyeloneuropathy • Huntington's disease • Hexosaminidase deficiency
Metabolic/toxic	• Hyperthyroidism • Hyperparathyroidism • Heavy metal intoxication • Lathyrism • Organophosphate toxicity
Immune/inflammatory	• Multifocal motor neuropathy with conduction block • Chronic inflammatory demyelinating polyneuropathy • Myasthenia gravis • Inclusion body myositis • Polymyositis • Multiple sclerosis • Paraneoplastic disorders
Structural	• Cervical spondylotic myelopathy • Syringomyelia/bulbia • Post-irradiation myelopathy/plexopathy • Tumor • Cerebrovascular disease
Other neurodegenerative diseases	• Corticobasal degeneration • Multiple system atrophy • Progressive supranuclear palsy • Parkinson's disease • Huntington's disease
Other motor neuron diseases	• Primary lateral sclerosis • Progressive muscular atrophy • Spinal muscular atrophy • Post-polio spinal muscle atrophy • Benign fasciculation syndrome • Hirayama disease

Table 7.9 Clinical features that should prompt a search for mimic syndromes

• History of poliomyelitis
• Family history with no affected females and no male-to-male transmission
• Symmetrical signs
• Pure upper or pure lower motor neuron syndrome
• Upper motor signs caudal to lower motor neuron signs, with no bulbar involvement
• Development of sensory signs
• Development of sphincter disturbances

Diagnostic Tests

There is no definitive diagnostic test for ALS. The combination of suggestive clinical signs with negative laboratory and imaging studies supports the diagnosis. Progression of the condition is a prerequisite for diagnosis (Fig. 7.1).

Essential Investigations

Routine laboratory investigation of a patient with apparently "typical" ALS should include ESR, serum and urine protein electrophoresis, thyroid function tests, and serum calcium and phosphate (Table 7.10).

CSF analysis should be performed. CSF protein levels above 80 mg% are unusual and should prompt a search for other pathology, particularly for the presence of an associated lymphoproliferative disease. Heavy metal screen should be performed in those with a potential history of exposure. Hexosaminidase A and B activity should be tested in patients of Ashkenazi Jewish extraction.

Neurophysiologic studies can assist in the diagnosis by demonstrating ongoing denervation (fibrillation potentials and positive sharp waves) and reinnervation (large polyphasic units) in affected and clinically unaffected limbs, with normal sensation, and normal or near-normal motor nerve conduction velocities. For corroboration of diagnosis, the distribution of denervation-associated changes on EMG should be outside the anatomic territories of peripheral nerves and roots. At least two proximal and two distal muscles in each of the four limbs should be sampled by EMG.

Prolonged F response and the presence of conduction block should suggest an alternative diagnosis, such as multifocal motor neuropathy. Sensory nerve action potentials (SNAPs) are preserved in ALS. Abnormalities in SNAPs should prompt a search for an alternate diagnosis. In males, the possibility of Kennedy's disease should be considered.

Electrophysiological results should be evaluated in conjunction with the clinical and other ancillary findings. A recent algorithm to enhance the electrophysiologic criteria for ALS diagnosis (The Awaji Algorithm) has been published by de Carvehlo et al. (see Further Reading at the end of this chapter).

At present, there are no validated, reliable, and accessible neurophysiologic investigations to establish the presence of upper motor neuron dysfunction, although a number of recent studies using transcortical magnetic stimulation have suggested increased cortical excitability in ALS. At present, none of the measures of central motor function in ALS is likely to be useful for monitoring patients in a clinical trial setting.

Neuroimaging studies should be used to exclude other conditions that may cause UMN and/or LMN signs. Advanced neuroimaging in ALS is unlikely to be useful in primary diagnosis of ALS, or as an easily available biomarker of progression. However, detailed neuroimaging using modern scanners has potential as a research tool to further characterize anatomic pathways involved in ALS.

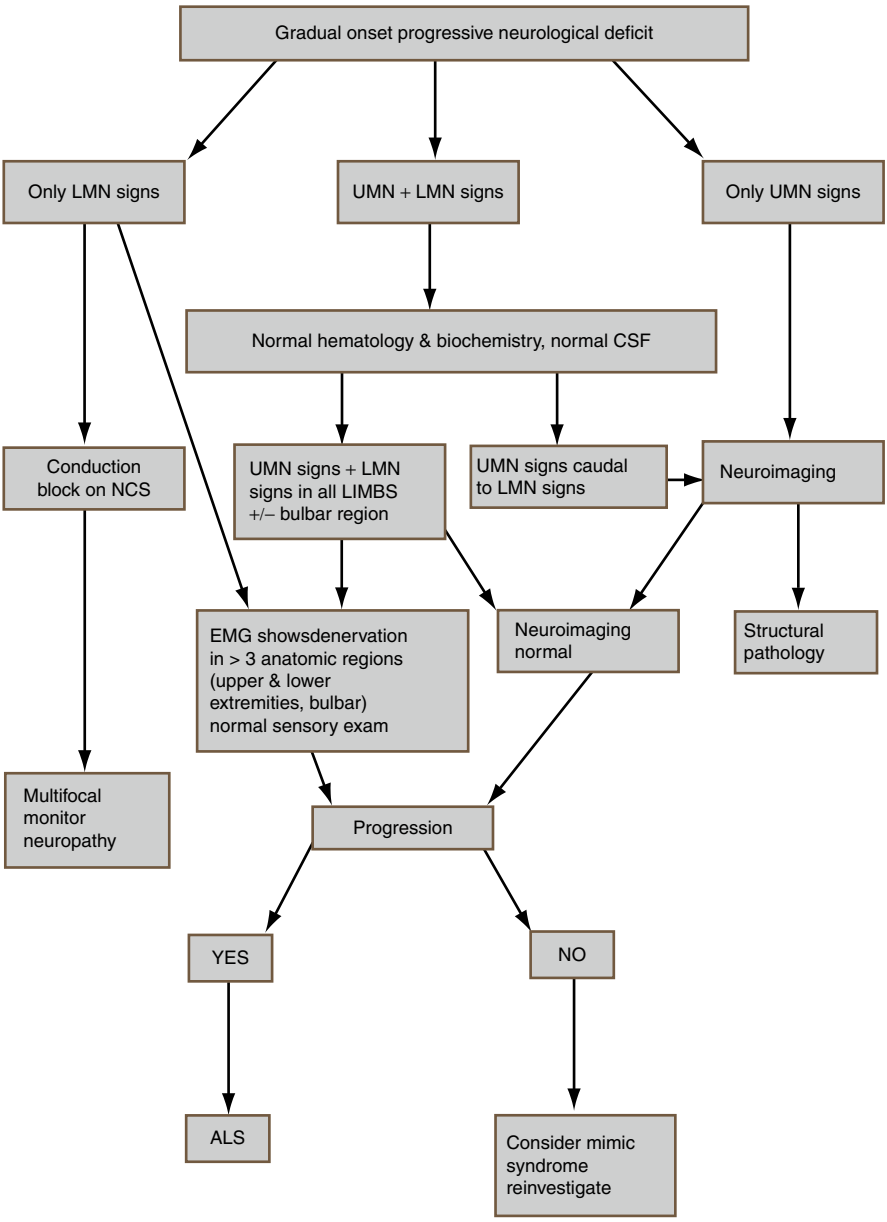

Fig. 7.1 Diagnostic algorithm for ALS (*UMN* upper motor neuron, *LMN* lower motor neuron, *NCS* nerve conduction studies)

Table 7.10 Essential investigations

Blood erythrocyte sedimentation rate (ESR)
C-reactive protein (CRP)
Hematological screen
ASAT, ALAT, LDH
TSH, FT4, FT3 hormone assays
Vitamins B12 and folate
Serum protein electrophoresis
Serum immunoelectrophoresis
Creatine kinase (CK)
Creatinine
Electrolytes (Na^+, K^+, Cl, Ca^{2+}, PO_4^{3})
Glucose
Hexoaminidase A and B assay (where clinically indicated)
Ganglioside GM-1 antibodies (where clinically indicated)
Serology (*Borrelia*, virus including HIV) (where clinically indicated)
CSF Cell count, protein, glucose
Neurophysiology: EMG, nerve conduction velocity
Radiology MRI/CAT (head/cervical, thoracic, lumbar)
Chest x-ray

Biomarkers in ALS

There is a growing interest in identifying biomarkers for diagnosis, progression, and prognosis in ALS. To date, no biomarker has been of sufficient sensitivity and specificity to incorporate into clinical practice. Although protein profiling in CSF has yielded findings that are of interest, standardized handling of spinal fluid will be required to ensure reproducibility of results. Neuroimaging and quantitative neurophysiological techniques such as motor unit number estimation (MUNE) are considered to have potential but are both cost- and labor intensive. Disease signatures may also be possible using transcriptomics and metabolomics. However, it is likely that further subcategorization based on clinical phenotype will be necessary to generate reproducible biomarkers.

Management of Progression of ALS

Evidence-based guidelines for clinical management have been published by the European Federation of Neurological Sciences and by the American Academy of Neurology. (See Further Reading at the end of this chapter.) Both sets of guidelines emphasize the importance of multidisciplinary care, which provides the cornerstone of ALS management. The multidisciplinary team should include a neurologist, a respiratory physician, a palliative care physician, and allied professions including physiotherapy, occupational therapy, speech and language therapy, nutrition, and medical social services (Table 7.11 see also Chap. 13). Those who received care at a multidisciplinary clinic have a better prognosis

Table 7.11 Multidisciplinary team for ALS management

Neurologist	Diagnosis, disclosure of diagnosis,treatment and symptom management, initiation of respiratory and nutritional interventions, and unbiased information regarding research developments
Family doctor	Symptom control, drug monitoring, liaison with other teams
MND specialist nurse	Point of contact for patients and families, coordination of care, home visits, practical advice regarding accessing support services, patient advocacy
Speech and language therapist	Evaluation and monitoring of dysphagia and aspiration, speech therapy, and advice regarding communication devices
Occupational therapist	Optimization of the patient's environment. Advice re safety awareness, adaptive and splinting devices, activity modification, driving, energy conservation, home modification
Dietitian/nutritionist	Evaluation of nutritional status and the need for tube feeding, management of dysphagia, management of enteral feeding
Physiotherapist	Evaluation of muscle strength and function, advice re walking aids and orthoses, management of spasticity, safety awareness
Social worker	Advice and counseling re employment, change in lifestyle and financial issues, support for carers
Palliative care	Symptom control, pain management, maintenance of quality of life, preservation of dignity
Psychiatry and neuropsychology	Evaluation and management of cognitive impairment/dementia, adjustment disorders, anxiety and depression
Respiratory physician	Assessment of respiratory dysfunction, initiation of noninvasive ventilation, monitoring of noninvasive ventilation

than those attending a general neurology clinic, and because symptoms are addressed and treated early, management in a specialized setting is also more cost effective.

Despite a large number of clinical trials of various agents, the anti-glutamate agent Riluzole remains the one evidence-based disease-modifying drug for ALS. Patients with ALS should be offered Riluzole at the time of diagnosis, as clinical trials have repeatedly demonstrated that early treatment with Riluzole can increase survival by a mean of approximately 3 months.

Symptomatic Therapies

The aim of symptomatic therapy is to improve the quality of life of the patient and carer. The commonest symptoms and their management are outlined below.

Cramping and Spasticity

Cramping can be treated with massage and physiotherapy. Quinine sulfate (200 mg) is also effective, as are phenytoin, carbamazepine, and benzodiazepines.

Spasticity can be treated with physiotherapy and hydrotherapy. Baclofen and tizanidine are effective pharmacologic agents.

Sialorrhoea and Bronchial Secretions

Sialorrhoea (drooling or excessive salivation) is distressing to patients, and increases the risk of oral infections. It is associated with dysphagia, and a failure to effectively handle salivary secretions.

Sialorrhoea can be difficult to manage, although patients and carers can be trained to use a portable suction machine. Treatments include amitriptyline (25–50 mg), oral or transdermal hyoscine, atropine drops, or glycopyrrolate. For more severe sialorrhoea, botulinum toxin can be effective, as can salivary gland irradiation.

Bronchial secretions can be treated with mucolytics and nebulized beta adrenergic antagonists and/or anticholinergics. In some instances, use of mechanical cough-assisting devices (insufflator-exsufflator) can be beneficial.

Pseudobulbar Affect

Pathological weeping or laughing occurs in up to 50% of patients. A combination of dextromethorphan and quinidine may be beneficial, although treatment may be limited by side effects. Fluvoxamine, amitriptyline, and citalopram can also be of benefit.

Anxiety and Depression

Counseling for patients and carers is useful in managing the reactive depression associated with recent diagnosis. For more protracted depression, SSRIs can be helpful. Anxiety can be treated with benzodiazepines or buproprion.

Pain

Pain is not uncommon in ALS. Treatment should begin with simple analgesics such as paracetamol, followed by weak opioids such as tramadol, followed by strong opioids such as morphine or ketobemidone.

Communication

Dysarthria progressing to mutism occurs in bulbar ALS. As dysarthria develops, patients should be reviewed by an experienced speech and language therapist. The goal should be to optimize the communication both for the patient and the carer. Prosthetic treatments (palatal lift and/or palatal augmentation prosthesis) can be helpful to improve articulation. Augmentative and alternative communication (AAC) devices can be used in those with

intact cognition. Useful technological advances include brain–computer interfaces and thought translation devices, though these are not yet widely available.

Respiratory Insufficiency

The majority of ALS patients die of respiratory failure, and the presence of respiratory muscle weakness is an independent predictor of quality of life. Symptoms of respiratory insufficiency may be subtle. Patients should be asked directly about dyspnea, orthopnea, disturbed sleep (sleep fragmentation due to hypoventilation), nightmares, morning headaches, daytime somnolence and fatigue, poor concentration/memory, and nocturia. Assessment of respiratory insufficiency includes history and examination, pulmonary function tests, and overnight pulse oximetry and early morning arterial blood gases.

Forced vital capacity is most widely used in the assessment to respiratory insufficiency in ALS but limitations include insensitivity to significant changes in respiratory function partly because the shape of the lung pressure–volume curve, and difficulties in performing the test due to muscle weakness or apraxia. Sniff nasal inspiratory nasal pressure (SNIP) is a more accurate measure of declining respiratory function, although its use is also limited by apraxia. SNIP is particularly useful in patients with bulbar involvement since a face mask is not required. The SNIP correlates well with diaphragm strength and nocturnal hypoxemia and is sensitive to changes in respiratory muscle strength. A SNIP of <40 cm H2O had a higher sensitivity for predicting 6 month mortality compared with a FVC of <50%.

Transcutaneous carbon dioxide/oxygen sensor can be useful during home visits as it avoids the need for regular arterial blood gases. While not used as a primary tool in the assessment of the need for noninvasive ventilation, it can be a useful adjunct (Table 7.12).

Noninvasive positive pressure ventilation (NIPPV) should be introduced early. Current recommendations are that NIPPV should be offered to any patient with respiratory symptoms and vital capacity less than 50% of predicted, a SNIP of less than 40 cm H_2O, or where symptoms of respiratory insufficiency are associated with nocturnal hypoxemia. An elevated early morning blood CO_2 level is an absolute indication.

Table 7.12 Indications for initiation of noninvasive ventilation

European consensus criteria for NIV (European ALS/MND Consortium and European Neuromuscular Centre workshop on noninvasive ventilation in MND, May 2002)	
Suggested criteria for noninvasive ventilation	
Symptoms related to respiratory muscle weakness. At least one of	Dyspnea, orthopnea, disturbed sleep (not caused by pain), morning headache, poor concentration, anorexia, excessive daytime sleepiness (ESS > 9)
and	
Evidence of muscle weakness	FVC ≤ 80% or SNIP ≤ 40 cm H20
and	
Evidence of either	Significant nocturnal desaturation on overnight oximetry or Morning ear lobe gas pC02 ≥ 6.5kPa

NIPPV extends survival, particularly in those who are compliant with ≥ 5 h of NIPPV each day and those without severe bulbar dysfunction. Treatment with NIPPV also improves quality of life (QOL) in patients without increasing caregiver burden or stress. Some patients have difficulty tolerating NIPPV. Factors that adversely affect the ability of patients to tolerate NIPPV include the presence of bulbar symptoms, the ability to manually adjust the mask, and the presence of cognitive impairment. Pulse oximetry should be performed following commencement on NIPPV, and patients should be reviewed at regular intervals by a respiratory physician to ensure that the pressure settings are optimized.

Weight Loss and Nutritional Support

Weight loss and malnutrition are common features of ALS. Nutritional decline can occur in the context of evolving dysphagia. In those without significant bulbar features, weight loss can result from difficulties in finishing meals because of upper extremity weakness. Weight loss may also be due to hypermetabolism, particularly in those with respiratory compromise. Dysphagia increases the risk for insufficient calorie intake, aspiration, and choking. Dysphagia can be evaluated using bedside clinical scales and with videofluoroscopy and fiber-optic examination. Management includes modification of food and fluid consistency, postural advice (e.g., chin tuck: flexing the neck forward on swallowing to protect the airway), and parenteral feeding by gastrostomy.

Gastrostomy placement is indicated for those who have symptomatic dysphagia or significant weight loss. Advantages include improved nutrition, although the survival effect is likely to be marginal. Radiologically inserted gastrostomy (RIG) is preferred over endoscopic gastrostomy in patients with pronounced bulbar symptoms and/or respiratory compromise. If there is evidence of respiratory insufficiency, noninvasive ventilation should be introduced before gastrostomy (Fig. 7.2).

Management of Cognitive Impairment in ALS

Most studies of treatment of FTD are relatively small and uncontrolled. The management of cognitive decline in ALS is accordingly difficult. Off-label use of medications more commonly includes donepezil, rivastigmine, galantamine, and memantine.

SSRIs are commonly used for aggression, agitation, disinhibition, and depression in FTD. Treatment with SSRI is well tolerated, and they are currently the drugs of choice for behavioral control in FTD. Nocturnal agitation can be treated with low-dose olanzapine, rispiridone, or quetiapine. Comanagement with neuropsychiatry is recommended.

Quality of Life

Quality of life (QOL) is determined by the pleasure and satisfaction an individual draws from living. Health-related QOL is determined by the impact of an individual's health on their experience of living. In ALS, health-related QOL declines commensurately with

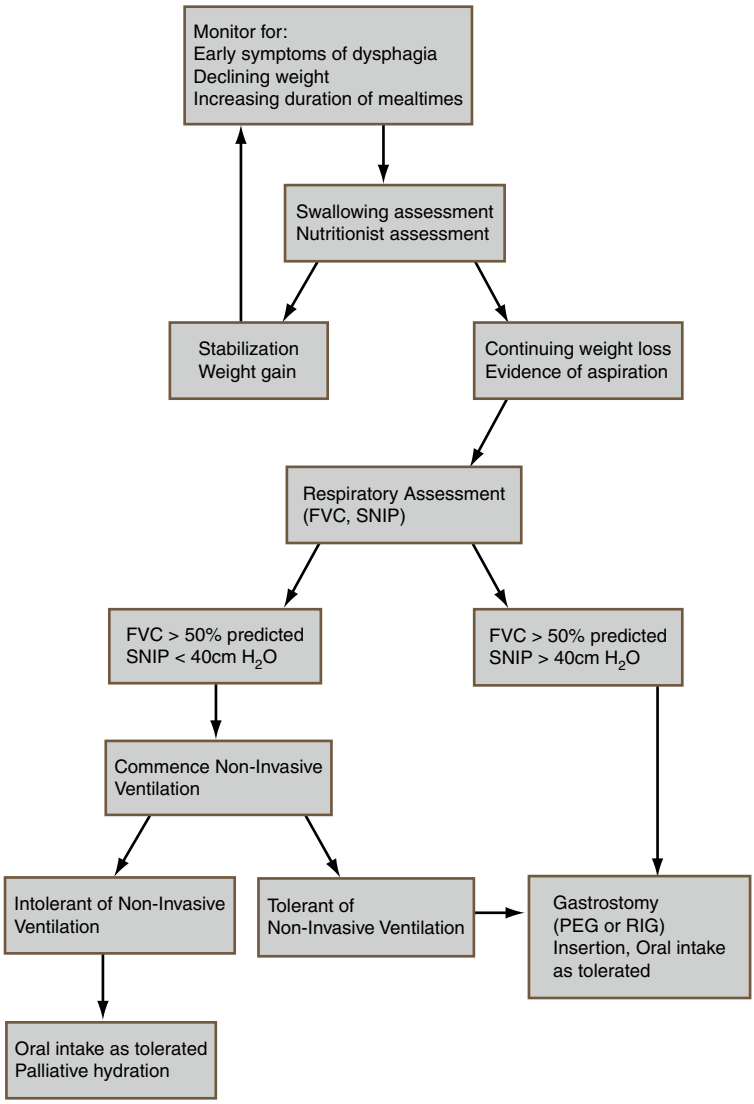

Fig. 7.2 Algorithm for management of nutritional decline in ALS (*FVC* forced vital capacity, *SNIP* sniff nasal inspiratory pressure, *PEG* percutaneous endoscopic gastrostomy, *RIG* radiologically inserted gastrostomy)

physical decline, and high levels of psychological distress can occur. However, self-assessed QOL, as measured by scales in which the individual selects what is most important to them (e.g., the Schedule for Evaluation of Individual Quality of Life (SEIQoL)), does not generally decline in ALS. Moreover, the majority of patients with ALS do not exhibit high scores on depression and anxiety scales. This is because most individuals perform a psychological shift toward domains that can continue to be enjoyed despite the

evolution of neurological deficits. Recognition of the ability of patients to undertake this psychological shift is an important aspect of caring for those with ALS and should be recognized by health professionals, as perceived QOL may impact on decision-making, both by the patient and the health care professional.

Carer Burden

A diagnosis of ALS impacts the entire family. The role of the patient within the family may change – the breadwinner may become a dependent and the primary carer within the family may become the person requiring most care. These changes can have a major destabilizing effect on intimate relationships.

As the condition progresses, there is an increasing and often unacknowledged burden on the primary carer, both from a physical and emotional perspective. Many studies have shown that the self-reported QOL of carers may be lower than that of patients. The burden of care may be increased considerably when the patient is cognitively impaired. Supportive strategies including counseling for family members should be available. In the later stages of illness, regular respite and psychological support should be available for the primary carer.

Palliative Care and End-of-Life Decisions (See also Chap. 13)

ALS is an inexorably progressive condition that significantly reduces life expectancy. A palliative care approach should be taken from the time of diagnosis. The aim of palliative care is to maximize QOL of patients and families by relieving symptoms, providing emotional, psychological, and spiritual support as needed, removing obstacles to a peaceful death, and supporting the family in bereavement. From the time of diagnosis, patients should be provided with a realistic projection of the trajectory of their disease. As the condition progresses, they should be encouraged to consider an advance directive regarding their end of life. Candid discussions about the relative merits and demerits of full mechanical ventilation should take place in a planned manner, and in a comfortable and quiet setting. Assurances should be provided that palliative care strategies can control symptoms in the terminal phase of the illness. Opioids and benzodiazepines (where necessary for anxiety) can be used for symptomatic treatment of dyspnea. Pain should be managed with opioids. Neuroleptics can be used for treating terminal restlessness and confusion due to hypercapnia.

Most Important Recent Advances

While ALS was originally considered to a pure motor system degeneration, ongoing research in cell and molecular biology suggests that the pathophysiology of ALS and FTD are closely intertwined. A number of genes are known to cause both ALS and FTD (Table 7.13). Advances in neuroimaging and neuropathology have demonstrated

Table 7.13 Genes causing ALS and FTD

Chromosome 17q 21–22; MAPT gene	Disinhibiton-dementia-Parkinson-amyotrophy complex (DDPAC): semantic language abnormalities
Chromosome 9p 13.2–21.3	Motor symptoms followed by personality and behavioral abnormalities between 4th and 7th decades
Chromosome 9q21-q22	Five with ALS and mild cognitive impairment, 9 pure FTD, ALS and/or ALS/FT
9p13.3–12, valosin-containing protein	Autosomal dominant inclusion body myopathy, Paget's disease of bone, FTD
3p12, CHMP2B	FTD and later motor syndrome (not typical ALS)
Point mutation (R1101K) in the DCTN1 gene	FTD and ALS segregate as separate traits
TDP-43	ALS-FTD
FUS	ALS-FTD
SOD1	ALS-FTD (rarely)
ANG	ALS-FTD (rarely)
Progranulin	Mostly FTD, polymorphisms associated with phenotype in ALS

involvement of regions of the brain outside the motor system in ALS. Detailed neuropsychological assessment of ALS patients has also identified corresponding changes in up to 50% of patients, with evidence of frontotemporal dementia in up to 15%. These advances have radically changed the perspective of clinicians and researchers, and have opened new and exciting frontiers in research.

Although effective disease-modifying drugs for ALS remain elusive, much progress has been made in understanding and managing the disease. From a laboratory perspective, there has been a veritable explosion of new genes that are implicated in ALS and ALS/FTD. This has led to the important observation that disruptions in RNA processing may contribute to disease pathogenesis. SOD1 mouse models have identified the pivotal importance of glial tissue in the pathogenesis and progression of the disease. However, the limitations of the murine SOD1 model of ALS have also become apparent, and new guidelines are under consideration to harmonize mouse studies. Moreover, the identification of new genes has provided a timely opportunity to generate new animal models, including a mutant TDP-43 transgenic mouse.

From a clinical perspective, it is now increasingly recognized that the incidence and, possibly, the phenotype of ALS is likely to differ across populations – this important observation opens new avenues of comparative epidemiologic and population genetics research.

Although clinical trials have been disappointing, there have significant developments in clinical trial design and an improved recognition of the pitfalls in attempting to translate positive findings from laboratory animals into humans. It is now acknowledged that the failure of some of the more promising compounds in Phase II and III trials may have

reflected a relative paucity of preclinical data regarding the biological activity of the therapy. This has been coupled, in some instances, with a failure to identify the appropriate dose range for testing.

Notwithstanding the disappointing outcome of recent trials, clinical management has significantly improved in the recent past. There is now robust evidence to indicate that survival is enhanced by attendance at a multidisciplinary clinic. Close attention to respiratory status has led to increasing use of noninvasive ventilation, with attending survival benefits of up to 9 months.

The pace of research in ALS has increased considerably in the past decade; the coming decade is likely to yield exciting results both in clinical management and in helping to understand underlying disease pathophysiology.

Most Important Developments in the Coming Years

ALS research is poised on the brink of some major and exciting advances both in clinical and basic science research. ALS researchers throughout the world are coalescing to form a variety of consortia that will pool and maximize both resources and expertise. The close biological relationship between ALS and FTD will continue to provide insights into disease pathogenesis. The recent recognition of the likely importance of RNA regulation in both diseases will have wide-ranging implications in research in molecular and cell biology.

Translation of potential therapeutic agents from animal to human models of disease will benefit from the lessons learned over the past decade. New clinical trials in ALS will be underpinned by a detailed knowledge of drug activity, bioavailability, and efficacy in both the preclinical and clinical setting, coupled with robust proof of biological activity in the target tissue.

The new fields of transcriptomics and metabolomics are likely to be harnessed in the quest for biomarkers. Advances in high-resolution neuroimaging is also likely to be helpful in tracking disease progression, as will advances in neurophysiology and neurophysics. And finally, brain–computer interfaces will help to provide improved aids by using EEG signals recorded from the scalp to enable patients to both communicate, and to interact with their environment using modern robotics.

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Huntington's Disease

8

Niall P. Pender and Walter J. Koroshetz

Abstract Huntington's disease (HD) is an autosomal dominant neurodegenerative brain disorder. The mutation was identified in 1993 as an expanded CAG repeat that codes for an abnormally high number of glutamines in the huntingtin protein. At present, there is no known treatment to slow the pace of neurodegeneration, which generally leads to death over a 20-year period after clinical diagnosis. The clinical manifestations of the disease vary widely but they generally include dysfunction in cognition, mood, voluntary motor control, and most patients have the signature finding of chorea.

Keywords Huntington's disease • Chorea • Huntingtin (protein) • CAG repeat • Neurodegeneration • Neurogenetic (disorder) • Presymptomatic genetic testing • Motor control • Neuropsychiatric • Cognitive disorder • Behavioral difficulties

Introduction

Huntington's disease (HD) results from an expansion of the trinucleotide repeat (cytosine adenine guanine; CAG) at a gene on chromosome 4. While there is no unique set of symptoms, which indicate the onset in HD, many patients present initially with symptoms that reflect early neurological impairment, such as brief random irregular muscle jerks (chorea), writhing movements (athetosis), difficulty walking, and a tendency to fall or clumsiness. Many also present with a range of psychiatric problems including depression and anxiety. The rate of suicide in patients with HD is higher than normal base rates and accounts for 7% of deaths in nonhospitalized HD patients and 1.8–5.3% among individuals at 50% risk. There are also reports of self-injury, alcohol abuse, criminal offences, and marital difficulties. Cognitive impairments such as poor short-term memory, poor concentration, deterioration in work performance, and poor judgement have been noted in the early stages. As a result of degeneration in the fronto-striatal regions leading to behavioral disinhibition,

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patients can become aggressive or violent as the disease progresses. It has been recognized that the initial site of deterioration in HD lies within the basal ganglia and that as the disease progresses, the damage extends to encompass the cortical structures.

Clinical Course

HD is rare but usually develops in patients between ages 30 and 50. The age of onset does, however, vary from 2 years to mid 80s. It has been estimated that over 25% of cases begin after the age of 50 years, whereas 7% begin before 20 years of age.

As an autosomal dominant condition, the disease has almost equal prevalence in males and females but a marked variability in the age of onset both within and between families has been noted. As the CAG repeat is unstable in spermatogenesis, inheritence of a longer repeat expansion leading to apparent sporadic cases and earlier age of onset is associated with transmission of the HD gene throughthe male line of a family.

Since the genetic test became available, it has been observed that only between 40% and 79% of individuals at risk for the condition reported an intention to take the test. However, careful genetic counselling and pretest screening is essential to manage the numerous ethical and psychological consequences of preparing to take such a test.

As the mutation is present from birth and the condition is slowly progressive, the precise onset of disease may be difficult to identify. By convention, the disorder is usually diagnosed when chorea manifests. However, most patients have changes that predate chorea, which are frequently detected by close family members, some of whom have witnessed similar changes in the parent or siblings. The early changes may be in behavior, memory, mood, speech pattern, facial expression, or gait and posture. Drop in job performance and marital discord can lead to major upheaval in those who have inherited the mutation but do not yet have chorea.

Table 8.1 lists the most common measures of disease progression and functional capacity for the clinic.

Table 8.1 Common measures of functional disability and disease progression

Title	Authors	Scale description
Functional Capacity Rating Scale	Shoulsan and Fahn (1979)	Measures functional capacity across five domains on a scale of 1–5
Unified Huntington's Disease Rating Scale (UHDRS)	Kieburtz and Huntington's disease study group (1996)	A multi-domain measure of disease progression across six domains of function. Includes a Functional Assessment and Total Functional Capacity Scale
Core Assessment Program for Intracerebral Transplantation in Huntington's disease (CAPIT-HD)	Quinn et al. (1996)	A multi-domain assessment protocol originally developed for the transplantation program

The course of Huntington's disease can nevertheless be variable. The average age of motor onset is around 42 years but HD can begin in childhood or even in the elderly. The extremes of onset age are determined in large part by the inherited CAG repeat length. Normal individuals have repeat lengths less than 32 in the huntingtin gene; persons with Huntington's disease generally have repeat lengths greater than 36, but frequently of 40–50. Childhood onset of disease is usually caused by an especially large CAG repeat (i.e., >50).

Children affected by HD generally present with a bradykinetic form of the disease and appear parkinsonian. They may have seizures. Generally, the first signs are related to drop in school performance. In rare families, parents of affected individuals do not have clinical evidence of disease despite living to an advanced age. The parents in these families have repeat lengths in the intermediate range, between 32 and 36. Their symptomatic offspring, however, have mutations with longer repeat lengths. When this occurs, the disease gene is generally inherited from the father. This "anticipation" occurs due to an expansion of the unstable CAG repeat in the development of the sperm.

More commonly, disease onset is in midlife. The individual with early signs of HD has grown up in a family in which one of the parents became affected and the parent may have passed through the course of the disease and died. The newly affected individual's family life may have been severely disrupted during their childhood by the parent's change in behavior. The psychological stress in such persons is difficult to underestimate. They, and their siblings, have been dreading the 50/50 chance that they will become affected. For example, benign myokymia is often misinterpreted as chorea. A fall or stumble can precipitate a fear that the disease has come. Depression and suicide rates are increased in persons at risk for HD even in the years before the diagnosis. Therefore, the physician treating a patient with Huntington's should be sensitive to the fears and complaints of the family, including at-risk siblings and offspring.

Prevalence

Prevalence rates have varied within and between countries, but the prevalence has been thought to range between 5 and 10/100, 000. A higher prevalence has been reported in South Wales and Venezuela as compared to a lower rate found in Finland, Japan, and African-American populations. This variability is due, predominantly, to the relative mobility of carriers of the gene and the existence of isolated "pockets" of families living in close proximity.

Pathology

Huntington's disease causes progressive brain atrophy. There is a particularly severe degeneration of the caudate nucleus that begins in the tail of the caudate and then affects the most dorsal medial aspect. Eventually, the caudate atrophies to a thin tissue paper-like

gliotic structure that is devoid of usually predominating medium spiny neurons. This gives a box car appearance of enlarged lateral ventricles on computed tomography (CT) scan. There is also much more widespread brain degeneration with cortical loss, white matter loss, and extensive gliosis (Fig. 8.1). Remaining neurons in multiple brain regions show intranuclear inclusions of the huntingtin protein. Like many neurodegenerative disorders, Huntington's disease is associated with abnormal protein accumulation and misfolding of the accumulated proteins. The role of non neuronal cells is gaining support in both HD and ALS. In both cases genetic animal models with the mutation in microglia or glial cells but not neurons is associated with pathologic changes.

Symptomatology

Huntington's disease is associated with a triad of difficulties including the movement disorder as well as cognitive and neuropsychiatric conditions. Each of these is associated with a complex set of psychosocial problems. Patients with Huntington's disease face a range of difficulties from diagnosis to death and these difficulties are not confined to the patient themselves but also to the family. As an autosomal dominant disorder, the disease has a particular resonance with families of sufferers.

Movement Disorder

By the time that chorea manifests, Huntington's disease generally includes some alteration in voluntary motor control. The ability to make rapid, repetitive, sequential movements is often abnormal.

Tests such as alternately tapping the thumb against the tips of the fingers, repetitively tapping the tip of the tongue against the top lip, alternately tapping the top, then the palm of one hand against the palm of the other hand all show slowing and irregularities in timing. There is generally great difficulty keeping the tongue protruded over a short, i.e., 10 s period.

Eye movement abnormalities are common. These include inability to make smooth pursuits due to intrusive saccades and delays in initiation of saccades. There is also dramatic slowing of saccadic velocity in some patients.

The gait of the person with early Huntington's disease demonstrates increased variability in step length and distance from the intended path. Inability to maintain position after gently pulling the patient backward, and trouble performing tandem walking is common. Though the cerebellum is generally spared, the finger to nose test and heel to shin test generally shows dysmetria.

Chorea, from the Greek for dance, often starts as a quick flick at multiple joints in the fingers or fingers and wrist while walking. It commonly worsens to twisting turns of the limbs, involuntary neck and facial movements, with blinks, and writhing tongue movements. The progressive involvement of lingual and bulbar control leads to dysarthria and dysphagia. Food with a soft, moist consistency such as pudding is easiest to swallow. Maintaining adequate nutrition can be challenging and motor symptoms tend to worsen

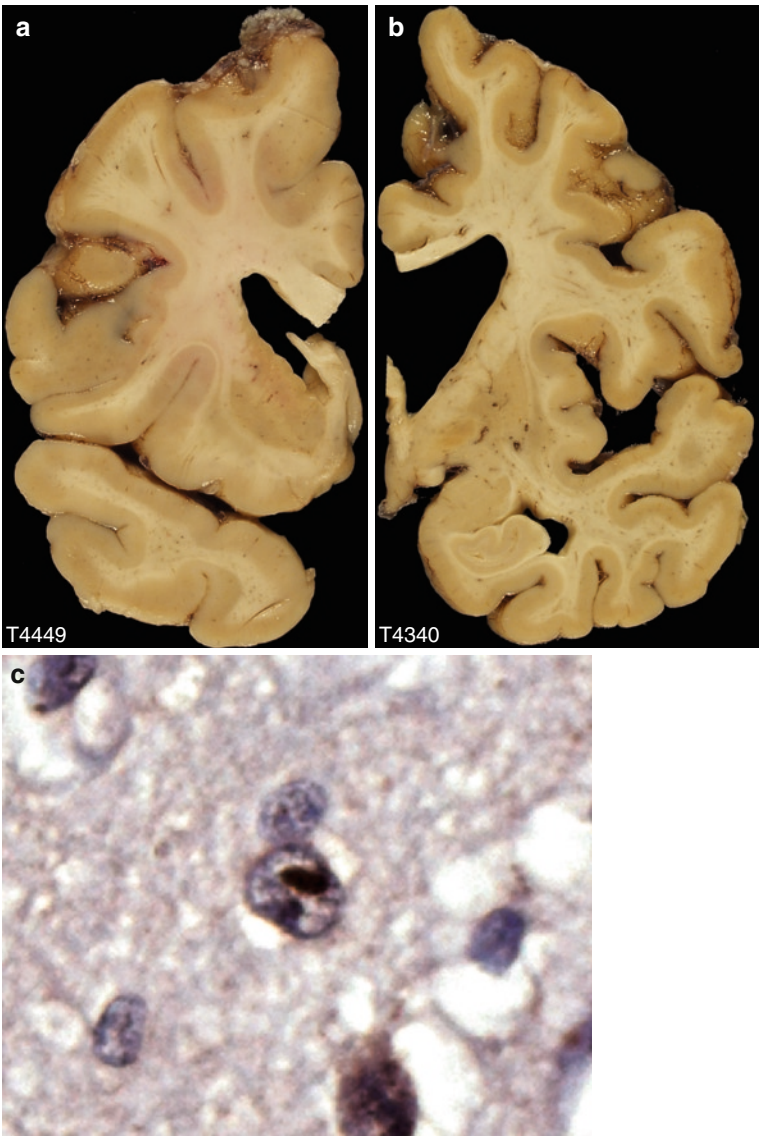

Fig. 8.1 Neuropathology of Huntington's disease. (**a**) The caudate nucleus bulges into the ventricle in normal individuals but is flattened in this 55-year-old person dying with Huntington's disease as seen in this coronal section through one brain hemisphere. Characteristically, the atrophy is more severe in the dorsal aspects of the caudate. (**b**) The caudate is barely visible in this 75 year old with severe degeneration of the caudate and globus pallidus. (**c**) The center neuron contains a classic intranuclear inclusion composed of aggregates of the mutant huntingtin protein (Courtesy of Dr. Jean Paul Vonsattel of Columbia University)

as patients lose weight. Most become almost mute in the later stages of the illness and are completely unable to swallow without aspirating. Chorea, which can be of large amplitude and forceful enough to cause self-injury, tends to slow over years and the involuntary movements evolve to dystonia in the later stages of the illness. Walking becomes more and more associated with falls and eventually, the person is wheelchair or bed bound. Tone increases with disease progression. There is commonly a dramatic, reflexive increase in tone when the limb is activated. Reflexes are hyperactive. The Babinski often becomes positive.

In contrast to the major motor findings, sensory abnormalities are minimal or absent. Some believe that patients with advanced HD have decreased pain sensation.

Cognition

Many of the early studies reported general intellectual and cognitive decline in HD, which is worse than other neurodegenerative conditions. However, intellectual ability generally remains stable over time, with the most pronounced deficits seen in executive domains in parallel with pathological changes. Zakzanis, in a meta-analysis of the literature, which incorporated the results from 760 patients, noted that maximum differences between controls and HD patients, using the effect size statistic, were found on tests of construction, and memory.

Snowden et al. reported the results of a longitudinal follow-up of 87 HD patients recorded over 3 years. Their sample ranged in disease severity from severe to mild on the Shoulsan and Fahn Scale. At 1 year follow-up, large effects were noted for executive and memory tasks; particularly, verbal fluency, the Stroop test, and object recall. The Motor Impairment Scale of the UHDRS contributed to change on the Stroop and object recall. Illness duration made only a minor contribution to change on object recall. CAG repeat, age, and sex did not contribute to change. At 3 year follow-up, a similar pattern of scores was obtained. Speed-based tasks and memory changed significantly over time. The observed impairment was thought to relate to a primary impairment in executive functioning, which impacted on encoding and retrieval.

Thus, many studies of cognitive functioning in HD report generalized decline in cognitive functioning over the course of the condition. However, the specific nature of this decline varies between studies. It is likely that this reflects an inherent variation in the presentation of the disease within and between families, as well as poor study design and differing measures. In particular, because of the relative rarity of the disease, many studies are insufficiently powered with respect to patient numbers.

Language Ability

Traditionally, HD patients do not present with clear cortical aphasia. However, as more sophisticated testing has emerged, it has become clear that many patients presented with a range of language-based functions, some of which are masked by the severity of dysarthria. Comprehension is generally thought to be intact. However, HD patients have been shown to be impaired in the comprehension of affective and propositional (command or question) prosody.

Executive Functions

Recently, there has been increased interest in the executive deficits experienced by patients with HD. This not only results from the earlier application of more sophisticated diagnostic testing that enables patients to complete tests sooner in the course of the disease, but also reflects the improved resolution of current neuroimaging techniques. Such techniques have facilitated a greater description of the nature of the lesions in HD and identified degeneration in the frontal lobes via fronto-striatal connections. That is, the nature of the reciprocal connections between the basal ganglia and the oculomotor region, dorsolateral prefrontal cortex and lateral orbitofrontal area result in significant degeneration in fronto-striatal mediated cognitive and behavioral functions.

HD patients have been shown to be impaired on tests of planning, self-order working memory, and tests of response set, all indicators of executive dysfunction. Rosser and Hodges reported that patients with HD and Alzheimer's disease were impaired on letter and category fluency tasks. However, HD patients appeared to find letter (phonological) fluency harder than category (semantic) fluency. This was the opposite pattern to patients with Alzheimer's disease.

In summary, patients with HD show deficits on a range of tests of executive function. These take the form of planning, executing, and inhibiting behavior. In the context of the neuropathological data, it is not surprising that HD patients should present with such difficulties. Loss of frontal white matter and neuronal cell loss have been reported in many studies and metabolic deficits in the frontal lobes have been associated with the degree of cell loss in the basal ganglia.

Attentional and Perceptual Functions in HD

In many studies, HD patients were found to be impaired on tests of alertness, divided attention, and response flexibility. While clear disorders of perception are rare, there has been increasing interest and controversy surrounding the issue of patient's ability to perceive emotional cues. HD patients were impaired at interpreting facial and vocal expressions of emotion, and similarly, those relating to fear and disgust were disproportionately impaired. HD patients have also been shown to be impaired at comprehending emotional prosody in speech, matching facial affect, facial recognition, and discriminating faces.

These deficits suggest that patients have difficulty perceiving their environment, interpreting and identifying the expressions of others, and perceiving their own physical symptoms.

Memory

There has been a great deal of debate concerning the nature of the memory impairment in HD and the pattern of impaired and preserved skills in this patient group. It has been clear for many years that patients present with a form of memory impairment that, while severe, is distinct from other dementias such as Alzheimer's disease.

Global memory deficits are common in HD and this is unsurprising given the links between the striatum and limbic system, the reported deficits in temporal lobe function, and

the deficits in frontal function in this population. Unlike Alzheimer's patients where episodic memory is better for older memories, HD patients show no advantage for older memories over more recent ones. This is known as a flat temporal gradient. Procedural learning is also impaired. In particular, procedural motor tasks are more impaired than lexical tasks. It has been suggested that recognition memory is disproportionately preserved until later stages and therefore, retrieval or encoding deficit are favored by many authors. That is, the memory impairment in HD, which begins early in the course of the disease, is related to the more extensive and global deterioration in fronto-striatal functions.

Neuropsychiatric and Behavioral Features

Depression is very common in HD. Emotional dyscontrol with outbursts of anger with a physical component can be a major source of upset in the family or in the long-term care facility. Obsessive compulsive behaviors are also common. Some have paranoid delusions but hallucinations are rare. These behaviors can lead to antisocial acts that run afoul of the law. Over time, persons with HD become more and more restricted mentally. In early stages of illness, they perform cognitive tests more slowly. By history, they are less active mentally and can display prominent apathy. In general, patients with Huntington's disease don't completely lose one specific cognitive domain but rather lose the ability to engage these domains for goal-directed behavior. Communication can be especially difficult in the later stages. This can also be a source of tremendous frustration when the patient's primal needs are not met and communication is not possible to resolve these needs. As an example, it is not unusual for patients in the later stages to become anxious and upset when hungry but not able to transmit the fact that they are hungry to their caretakers.

Behavioral Difficulties

The behavioral features of HD can be conceptualized as frontal disconnection syndromes. The earliest changes can be seen as irritability with a low tolerance of frustration. These features gradually deteriorate and the episodes can become increasingly explosive and disproportionate. These features resemble the personality conditions often associated with frontal lobe impairment such as the pseudopsychopathic and the pseudodepressive states of apathy and self-neglect. Agitation and aggression can often occur in the latter stages of the disease and are often difficult to ameliorate. Up to 40% of patients suffer from affective disorders with hypomania and mania seen in 5–10%. These may occur before any signs of the disease are apparent. These underlying organic symptoms do also coexist with the psychological reaction to living with such a devastating condition. The risk of suicide is increased in HD as a result, and up to 6% of patients will die by suicide.

Managing psychiatric symptoms is difficult and is exacerbated by the cognitive and physical disabilities. A marked loss of insight early in the disease might appear protective at times but can also hamper attempts to manage symptomatology. Pharmacological treatment has been widely discussed and is usually symptomatic management.

Family and Psychosocial Issues

There are, understandably, significant family stressors and there are marked difficulties for both affected and unaffected siblings. The suicidal rates are higher in unaffected siblings, so-called survivor guilt than the general population. Similarly, unaffected parents suffer the difficulties of caring for spouses and affected children with economic and psychological difficulties. Significant support is needed for HD families from the multidisciplinary team.

Care and Disability Management of the Person with the Huntington's Mutation

The offspring of persons with Huntington's disease have a 50% chance of inheriting the disease. The penetrance is high. Though there can be variability, most develop signs at about the same age as their parents did. The genetic test for the huntingtin mutation is clinically available from analysis of blood DNA. The decision to be tested is a very personal one and needs to be supported with appropriate genetic counselling. The first reaction of many at-risk persons is to jump at the chance of being tested to "get rid" of the fear of whether they have inherited the "bad gene." However, those that do not have the mutation do not face the tragedy of the illness, and those that have inherited it can have their fears substantially enhanced by a "positive" test. Key to the counselling process is to ensure that the at-risk individual has a sense of how it will be helpful for them to know that they will get the disease in the future. Decisions surrounding whether to have children generally predominate in presymptomatic testing but, as might be expected, many choose not to be tested. Most agree that children should not be tested.

As symptoms of HD develop in a person at risk, the diagnosis is made when the physician is convinced by the chorea or some other neurological sign. Gene testing may be helpful if there is a need for the diagnosis and the signs are equivocal. It may be helpful in cases in which there is no family history, though the implications of genetic testing need to be planned for including the discovery of nonpaternity, or the establishment of risk within a larger family. Other diagnostic tests are not necessary in the clear-cut case of HD though the MRI shows progressive atrophy of the caudate throughout the course of the disease.

In the early stage of Huntington's disease, as well as in the later stages, the psychiatric manifestations require management. Depression in HD can respond to antidepressant medication but the response is often partial. Obsessive compulsive behaviors can be very difficult to control but may respond to serotonin-uptake inhibitors that are effective in the treatment of OCD. Sleep disorders are common and sleep studies show that awakenings from sleep are often associated with an involuntary movement. Some develop completely reversed sleep–wake cycles, remaining awake at night and sleeping much of the day. Longer acting benzodiazepines such as clonazepam at bedtime can improve sleep.

Mood disorders with frequent episodes of emotional upset can respond to mood stabilizers such as valproic acid, carbamazepine, and serotonin-uptake inhibitors. Antipsychotics are sometimes necessary in persons with delusions and are often tried in persons with disruptive, self-injurious, or violent behaviors. Atypical antipsychotics such as quetiapine

may be more effective than standard neuroleptics and they also do not contribute to dystonia and motor dyscontrol to the same extent. Some seem to respond to high doses of beta blockers. Because these medications are generally not as beneficial as one might hope and they are fraught with side effects, it is important to attempt to determine if there are environmental contributors to the disruptive behaviors.

Changes in mealtimes, discomfort in the wheel chair, misinterpretation of the caregiver, nicotine withdrawal, interruption when drowsy, etc. can be the source of behavioral disturbance.

There is no treatment for the motor dyscontrol though a novel "dopamine stabilizer," ACR16, has shown promise in an initial clinical trial. Replication studies are underway by the company, NeuroSearch. Speech and swallowing therapy may help teach safe swallowing. Physical activity to maintain muscle tone may be helpful. Chorea will respond to low doses of neuroleptics or to tetrabenazine, though it is important to check whether the drugs are associated with better overall motor function due to the bradykinesia and dystonic side effects. Often, the environment needs to be modified. Padding wheel chairs and bed rails, to avoid trauma from the chorea, may be critically important. Abnormal movements may be so severe that the patient is not safe in a bed and better cared for on a large mattress that rests on the floor. Use of restraints is especially problematic as, combined with the choric movements, the restraint ties can lead to significant harm, even strangulation.

Feeding the person with advanced HD is also challenging. Oral feedings need to be changed over time to a softer but thick consistency. Early on, thin liquids like water and dry crumbly foods cause cough and aspiration. Then, solid foods are too difficult to chew and swallow. One characteristic of persons with HD is that they tend to overstuff the mouth as their swallowing efficiency decreases and swallowing takes more and more time. Caregivers may continue oral feeding into the late stages with pureed foods but feeding is done very slowly over long time periods. Weight management is important as patients with HD tend to deteriorate with weight loss and, in some cases, have improved with weight gain. The decision to insert a feeding tube is especially difficult and needs to be discussed with the patient or family years before the decision is anticipated. Otherwise, the patient may be unable to communicate when the feeding crisis occurs. In general, patients with HD die of aspiration pneumonia, so a feeding tube can prolong life for those who are very severely disabled.

Pathogenesis of HD

The discovery of the Huntington's disease mutation raised the expectations that a treatment to slow progression of disease might come from research. At phenotypic level, research continues to investigate the manifestation of cognitive and behavioral impairments in HD. In particular, it is important to examine variations in the phenotype with age and CAG repeat length as well as investigations of the influence of fronto-striatal executive dysfunction on other cognitive domains.

Genetic animal models of the disease in flies, rodents, sheep, and nonhuman primates are now available or are soon to be available for therapeutic research. The normal huntingtin

protein is found throughout the cytoplasm of all cells in the body. The mutated huntingtin protein forms abnormal aggregates in neurons. A number of other CAG repeat neurodegenerative disorders have been discovered in which the abnormally long glutamine repeat is found in different proteins. All are characterized by aggregation of the abnormal protein in neurons. In patients with Huntington's disease (except the very rare person who is homozygous for the mutation), there is one normal copy of the gene and one mutated copy. It is now known that one normal copy is sufficient for normal brain function, so the disease is caused by some abnormal toxic effect(s) of the protein due to the elongated glutamine repeat. A variety of theories of pathogenesis are supported by variable levels of evidence and some therapeutic agents are now being tested in patients. The huntingtin protein has been implicated in a host of important cellular functions and the exact mechanism by which the mutation causes cell death is not clear. Mutant huntingtin affects the transcription of different classes of other genes. It interacts with proteins important in vesicular trafficking, intracellular transport, mitochondrial and synaptic function. Experiments have also shown that expression of the mutant protein, even if confined to glia, is still toxic to neurons.

Development of Neuroprotective Therapies

At present, there is no medical treatment that is known to affect the rate of progression of HD. The one possible exception is the maintenance of caloric requirements, as weight loss has been associated with more rapid deterioration. The goal of scientists is to develop a neuroprotective therapy that can be used safely in persons who are gene positive to prevent the onset of disability. The National Institute of Neurological Disorders and Stroke is currently funding a large trial of coenzyme Q10 to slow progression of HD in symptomatic patients. A prior trial of Coenzyme Q10 failed to demonstrate a large effect but there was a trend toward benefit that warranted a second study of higher dose. Among its putative actions, Coenzyme Q10 is important in mitochondrial function and there is some evidence of mitochondrial dysfunction in HD. In another attempt to improve energy metabolism, creatine supplementation is also being studied in an NIH-funded trial. Phosphocreatine is a major source of stored energy in the brain.

A major focus of research is on how best to "turn off" the mutant huntingtin gene. Recent research has shown that complete loss of the huntingtin protein is embryonically lethal suggesting that complete "turn off" of both alleles would be dangerous. The discovery that short strands of RNA can attach to messenger RNA and prevent transcription of protein raises the possibility that such interference RNA (iRNA) can be engineered to stop the production of the mutant protein. Whether iRNA treatment would be beneficial if it "turns down" expression of both the mutant and the normal allele is not clear. If not, then an allele-specific iRNA may be custom engineered for individual families so that it interacts with only the mutant gene. Antisense RNA therapy is also being pursued with similar aims. The challenge facing human use of these exciting therapies is how to deliver to the brain without adverse effects.

A variety of efforts are now ongoing to understand how to clear the protein aggregates from neurons, which seem to be the signature feature of most neurodegenerative diseases.

To that end, techniques are being developed to introduce key components of antibodies into cells, called intrabodies. These are designed to attach to and promote clearance of abnormally deposited proteins like mutant huntingtin. Drugs, which promote the metabolism of protein deposits, may also prove beneficial. There are now attempts to use high-throughput screening techniques to find drugs that prevent the aggregation or decrease production of the huntingtin protein. The mutant huntingtin protein also has been shown to alter the transcription of a variety of other genes. The downregulation of brain-derived neurotrophic factor (BDNF) is one example of an important consequence of the effect of huntingtin on gene transcription. Drugs, which modify gene transcription, particularly histone deacetylase (HDAC) inhibitors are under study as potential therapeutic agents.

Conclusions

Huntington's disease is a progressive neurodegenerative disease for which there is currently no cure. However, despite this, there is a wealth of information available to provide evidence-based efficacious treatments for the management of the patient's condition. Patients present with a triad of cognitive, movement, and psychiatric difficulties, which progress slowly over a 15–20 year period. Each of these domains requires careful assessment and management in order to maintain the person's quality of life and functional ability. Extensive advances have been made in the understanding of the pathophysiology of the condition but further care is required if services are to avoid a nihilistic approach to HD.

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Parkinsonism Plus Syndromes

9

Fiona M. Molloy and Daniel G. Healy

Abstract Parkinson's plus syndrome is a term that refers to disorders of movement and cognition that are often confused with Parkinson's disease. The three main disorders are progressive supranuclear palsy (PSP), multisystem atrophy (MSA), and corticobasal degeneration (CBD). These syndromes are pathologically diverse encompassing a number of distinct proteinopathies but have in common clinical features of movement abnormality, cognitive decline, a more rapid clinical course than Parkinson's disease, and a generally poor therapeutic response to levodopa. The diagnosis is largely clinical with some reliable radiological features. Therapy is largely in the realm of multidisciplinary symptomatic support but advances in molecular and biological understanding is leading to exciting therapeutic avenues.

Keywords Corticobasal degeneration • Mid brain atrophy • Mulitsystem atropy • Parkinson's plus • Pontocerebellar atrophy • Shy-Drager syndrome • Supranuclear palsy

Introduction

The three main parkinsonism plus disorders are progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD). These are neurodegenerative disorders that are frequently confused with idiopathic Parkinson's disease (PD). In fact, about 30% of pathologically proven parkinsonism plus syndromes are initially misdiagnosed as PD. Other causes of parkinsonism, other than PD and the parkinsonism plus disorders, include secondary parkinsonism and hereditary neurodegenerative disorders, but these are outside the scope of this chapter (Table 9.1).

Accurate differentiation between parkinsonism plus syndromes and PD is important for several reasons, the two most significant being:

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Table 9.1 Classification of parkinsonism: a subdivision of parkinsonism according to known etiology

Idiopathic Parkinson's disease	• Parkinson's disease • Genetic forms of Parkinson's Disease
Parkinsonism plus syndromes	• Progressive supranuclear palsy • Multiple system atrophy • Cortico-basal ganglionic degeneration • Parkinsonism-dementia complex
Hereditory neurodegenerative parkinsonism	• Huntington's disease • Wilson' disease • Autosomal dominant spinocerebellar ataxias • Lubag (X-linked dystonia-parkinsonism) • Neuroacanthocytosis • Familial basal ganglia calcification • Frontotemporal dementia with parkinsonism • Brain iron accumulation disorders • Pallidopyramidal syndromes (usually genetic)
Secondary (acquired, symptomatic) parkinsonism	• Infectious: postencephalitic, AIDS, SSPE, Creuzfeldt−Jakob disease • Drugs: dopamine receptor blocking drugs; reserpine, lithium, flunarizine, valproate • Toxins: MPTP, CO, Mn, Hg, cyanide, methanol, ethanol • Vascular: multi-infarct • Trauma: pugilistic encephalopathy • Other: parathyroid abnormalities hypothyroidism, hepatocerebral degeneration, brain tumor, paraneoplastic, normal pressure hydrocephalus

- Life expectancy is much lower in parkinsonism plus.
- Treatments such as levodopa and deep brain stimulation are generally ineffective in parkinsonism plus.

A complete history and neurological examination is critical in establishing a correct diagnosis. Atypical features such as eye movement disorders, early falls, and early cognitive impairment should raise suspicion of a parkinsonism plus syndrome, and all patients with suspected PD should have regular reviews and examinations. Table 9.2 provides a guide to some clinical red flags that should make the examiner consider an alternative diagnosis to PD.

Multiple System Atrophy

Clinical Features

Like PSP and CBD, MSA is a progressive, sporadic, adult-onset neurodegenerative disorder. The first cases were described over a 100 years ago by Dejerine and Thomas who referred to olivopontocerebellar atrophy. The term MSA was introduced in 1969 by

Table 9.2 Red flag features in parkinsonism. A list of red flag clinical markers, which may help the clinician differentiate parkinsonism plus disorders at the bedside

Clinical feature	Likely cause of parkinsonism
Young onset	Juvenile PD, MSA
Axial rigidity	PSP
Pill rolling rest tremor	PD
Myoclonus	MSA, CBD
Vertical gaze palsy	PSP
Early falls backward (1st year)	*PSP*
Asymmetric onset	*PD, CBD*
Alien limb/apraxia	*CBD*
Poor response to levodopa	*PSP, CBD, MSA*
Dysautonomia	*MSA*
Early cognitive impairment	*PSP, CBD*
Laryngeal stridor	*MSA*
Palilalia	PD, PSP
Cerebellar signs	*MSA*
Pyramidal signs	*MSA*

Graham and Oppenheimer indicating that multiple brain systems are involved (extrapyramidal, pyramidal, cerebellar, and autonomic [in any combination]). Patients are clinically classified according to the predominant motor presentation, for example, cerebellar (MSA-C) and parkinsonian (MSA-P) subtype. When autonomic failure predominates or there is primary autonomic failure, MSA is sometimes termed Shy-Drager syndrome, although this term is rarely used nowadays.

Table 9.3 shows an international bedside classification system for MSA according to differing levels of diagnostic certainty: possible, probable, or definite. Autonomic dysfunction is usually the earliest feature in both MSA-P and MSA-C, with 97% ultimately developing symptoms. Genitourinary dysfunction is the most frequent initial complaint in women, and early erectile dysfunction is invariable in men. Orthostatic hypotension is common and is present in at least 68% of patients. Symptoms associated with orthostatic hypotension include light headedness, dizziness, blurred vision, fatigue, yawning, and syncope. Akinesia and rigidity are prominent in MSA-P but are usually also evident in the later stages of MSA-C. Cerebellar dysfunction is predominant in MSA-C with gait and limb ataxia the prominent features. Notable features supporting a diagnosis of MSA include rapid progression (wheelchair bound <10 years from onset), orofacial dystonia, camptocormia (forward trunk flexion), Pisa syndrome (lateral trunk flexion), disproportionate antecollis (severe neck flexion), dysphonia (hoarse/harsh/high pitched), dysarthria, dysphagia, inspiratory stridor (involuntary deep sighs), cold hands and feet, emotional incontinence, pyramidal signs (Babinski and hyperreflexia), and a jerky myoclonic postural/action tremor. A pill-rolling or rest tremor should suggest PD. Only one-third of patients with MSA-P respond to levodopa and about 90% are unresponsive to long-term therapy.

MSA progresses rapidly and most patients develop motor impairment within 1 year of onset. Motor impairment can be caused by cerebellar dysfunction, and corticospinal tract

Table 9.3 Criteria for diagnosis of MSA

Definite MSA Neuropathological findings of widespread and abundant CNS alpha-synuclein-positive glial cytoplasmic inclusions with neurodengenerative changes in striatonigral or olivopontocerebellar structures
Probable MSA A sporadic progressive, adult (>30 y)-onset disease characterized by • Autonomic failure involving urinary incontinence or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mmHg diastolic and • Poor levodopa-responsive parkinsonism or • A cerebellar syndrome/dysfunction
Possible MSA • Parkinsonism or • A cerebellar syndrome/dysfunction and • At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency, or incomplete bladder emptying, erectile dysfunction or significant orthostatic blood pressure that does not meet the level required in probable MSA) • At least one of the additional features shown in Table 9.4

Modified from the second consensus statement on the diagnosis of multiple system atrophy – Gilman et al. 2008

Table 9.4 Additional features of possible MSA

Possible MSA-P or MSA-C • Pyramidal signs – Babinski sign with increased tendon reflexes • Stridor
Possible MSA-P • Rapidly progressive parkinsonism • Poor response to levodopa • Postural instability within 3 years of motor onset • Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction • Dysphagia within 5 years of motor onset • Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum • Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
Possible MSA-C • Parkinsonism • Atrophy on MRI of putamen, middle cerebellar peduncle, or pons • Hypometabolism on FDG-PET in putamen • Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

MSA multiple system atrophy, *MSP-P* MSA with predominant parkinsonism, *MSA-C* MSA with predominant cerebellar ataxia, *FDG* (18) fluorodeoxyglucose

dysfunction can also occur but is not a major symptomatic feature of the condition. At least 50% of all patients with probable MSA are disabled or wheelchair-bound within 5 years after onset and the median survival is 9.5 years.

Epidemiology

There is an estimated incidence of 1.2–4.1 cases/100,000 population/year, with an estimated prevalence of 0.9–8.4 cases/100,000. However, like PSP and CBD, this is probably underestimated, as misdiagnosis is not uncommon. About 30% of patients with late-onset sporadic cerebellar ataxia have MSA. MSA has been reported in Caucasian, African, and Asian populations. MSA-P predominates in western countries (68–82%), and in eastern countries, MSA-C is common with 67% of patients. There is a male predominance (2:1), and the mean patient age at onset is 54.3 years with a range of 33–78 years.

Neuropathology and Molecular Pathology

The neuropathology of MSA-C is olivopontocerebellar degeneration (inferior olivary nucleus, pons, and cerebellum) and MSA-P is striatonigral degeneration (substantia nigra, putamen, caudate nucleus, and globus pallidus). Even though they can be clinically very different, MSA-C and MSA-P share oligodendroglial cytoplasmic inclusions (GCIs) as a unifying pathological feature (Fig. 9.1). Both subtypes display neural loss and gliosis in their respective regional brain distribution and both are frequently accompanied by neurodegeneration of the autonomic nervous system; the severe clinical correlate of this is Shy-Drager syndrome.

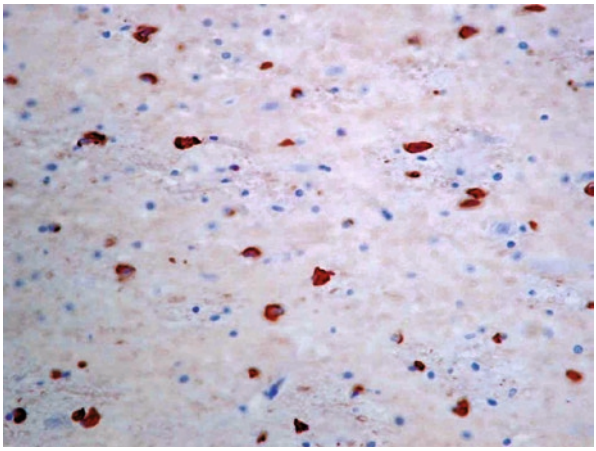

Fig. 9.1 Alpha-synuclein immunostaining to show cytoplasmic immunopositivity in glial cells (glial cytoplasmic inclusions [*GCI*]) within subcortical white matter (magnified ×40 before photo enlargement) (Photo courtesy Professor Michael Farrell)

Table 9.5 Neurodegenerative disorders classified on whether microtubule-associated tau or alpha-synuclein is the primary protein aggregate

Synucleinopathies	Tauopathies
Progressive supranuclear palsy	Parkinson's disease
Frontotemporal dementia	Multiple system atrophy
Corticobasal disease	Lewy body dementia
Pick's disease	
Argyrophilic brain disease	
PD—dementia complex—Guam	
Post-encephalitic PD	

Approximately 30% of Caucasian patients have principally striatonigral pathology, 20% olivopontocerebellar pathology, and the remaining 50% have equal amounts of both. Pathological degeneration of the putamen appears to correlate with the poor levodopa response in MSA.

Oligodendroglial cytoplasmic inclusions, which define MSA neuropathology, are formed by fibrillized alpha-synuclein protein. Genome studies have found genetic association between common single nucleotide polymorphisms (SNPs) in the alpha-synuclein gene and MSA risk and transgenic mice over-expressing alpha-synuclein develop oligodendroglial cytoplasmic inclusions. This makes MSA a "synucleinopathy" similar to PD and dementia with Lewy Bodies (see Table 9.5).

Aberrant myelin basic protein may also be pathogenic in MSA, raising the possibility that this is a primary disorder of myelin-producing oligodendroglial cells. However, no studies to date have linked these two plausible hypotheses.

Laboratory Tests

Investigations of autonomic function include the table-tilt test to measure orthostatic blood pressure and sphincter electromyography. The latter detects denervation in the external urethral sphincter secondary to degeneration of Onuf's nucleus in the spinal cord. Cardiac scintigraphy demonstrates reduced sympathetic MIBG uptake in the heart in PD but not MSA. Clinically, this test is more commonly used in Eastern countries than in the West.

Radiological Findings

Magnetic resonance image (MRI) findings in MSA-P often show decreased signal bilaterally in the posterolateral putamen on T2-weighted images. In addition, to putaminal hypointensity on T2, a characteristic finding in MSA is the slit-hyperintensity in the lateral margin of the putamen. The MRI abnormalities of MSA-C consist of atrophy of the pons, middle cerebellar peduncles, and cerebellum. A characteristic "hot cross bun sign" is produced by selective loss of myelinated transverse pontocerebellar fibers and neurons in the pontine raphe with relative preservation of the pontine tegmentum and corticospinal tracts.

Management

There is no effective drug therapy and a multidisciplinary approach is recommended. Orthostatic hypotension is often the earliest and most debilitating symptom. The addition of liberal salt, increasing fluid intake, head elevation when sleeping, and elastic stockings may improve standing blood pressures. It is worth considering levodopa replacement but the results are usually poor. Several drugs are used for the management of orthostatic hypotension, including fludrocortisone (mineralocorticoid), midodrine (alpha1-adrenoreceptor agonist), droxidopa (synthetic precursor of norepinephrine), and nonsteroidal anti-inflammatory drugs (NSAIDs) (possible inhibition of vasodilator prostaglandins). Therapy can be limited by supine hypertension, which affects up to 60% of patients. Bladder symptoms including urinary retention and incontinence are relatively common and troublesome problems. Formal urodynamics with measurement of post-micturition volumes are important. Overactive bladder symptoms may improve with anti-muscarinics such as oxybutynin or tolterodine while some patients require intermittent self-catheterization. Medication may also be considered for constipation and erectile dysfunction.

Progressive Supranuclear Palsy

Clinical Features

Steele, Richardson, and Olszewski presented the first clinicopathological descriptions of PSP in 1963 and 1965. Unsteadiness of gait and falls within the first year, frequently backward, is the presenting feature in more than 60% of cases. Bradykinesia and rigidity may be associated, often resulting in a misdiagnosis of PD. In a minority of cases, gaze palsy, dysarthria, or dysphagia may be the prominent early symptoms. The illness progresses to an immobile state over less than 10 years in the majority of cases.

In contrast to the short and shuffling gait, stooped posture, narrow base, and flexed knees typically seen in PD, the PSP patients tend to be erect with a stiff and broad-based gait with a frontal recklessness. They tend to pivot when turning, which further compromises balance. The speech is dysarthric rather than hypophonic and there is no rest tremor. Some PSP patients may present with a syndrome of pure akinesia manifest by freezing and gait initiation failure, marked impairment of speech (stuttering, stammering, hypophonia) and micrographia, eyelid motor disturbance (blepharospasm, eyelid apraxia) without significant rigidity or tremor or dementia, and without response to levodopa. Although the PSP gait can appear ataxic, cerebellar signs are not a feature.

Oculomotor abnormalities are common in PSP. Symptomatic eye movement difficulty is typically present within 4 years after the onset. Prior to this, most patients have slowing of vertical saccades, saccadic pursuit, break down of opticokinetic nystagmus in the vertical plane, poor convergence, and square-wave jerks (SWJs). The latter occurs in nearly all patients with PSP and rarely in PD. Vertical supranuclear ophthalmoparesis is a prominent feature of PSP. The patient loses range of vertical gaze, with downgaze usually worse than upgaze. This gaze restriction can be overcome by using the vestibulo-ocular reflex (Dolls

eye manoeuver) achieved by passive flexion/extension of the neck. Involuntary orbicularis oculi contractions producing blepharospasm and "apraxia" of eyelid opening and eyelid closure affect up to one-third of PSP patients.

Pseudobulbar symptoms in PSP patients are characterized by dysarthria, dysphagia, and emotional lability. The classic speech is a low-pitched dysarthria. Some patients have severe stuttering and palilalia.

Cognitive impairment is a prominent feature of PSP, often presenting as cognitive slowing, impairment of executive functions, and with a subcortical dementia picture. Apathy and hypoactive behaviors have been attributed to a dysfunction in the frontal cortex and associated circuitry. Sleep problems are common and often correlate with worsening dementia.

In addition to the classical presentation of PSP, there is a more benign form known as PSP-P, with clinical similarity to PD, good response to levodopa, and delayed onset or absence of supranuclear palsy. Pathologically, these phenotypes are characterized by differences in the isoform composition of insoluble tangle-tau isolated from the brainstem.

Relative sparing of olfaction helps to differentiate PSP from PD and MSA.

Death, often by aspiration, usually occurs within 10 years of onset with a mean survival of about 6 years.

Epidemiology

There is an estimated incidence of 0.3–1.1 cases/100,000 population/year, with an estimated prevalence of 6.2–7.4 cases/100,000. No racial predilection is known. Men are more commonly affected and the mean age of onset is 63 years.

Neuropathology and Molecular Pathology

PSP shares histological and molecular similarities with other "tauopathies" such as Alzheimer's disease, frontotemporal dementia, and argyrophilic grains disease (Table 9.5). Tau is a microtubule-associated protein, meaning that it regulates the structure and stability of a major axon protein trafficking system. When tau protein is hyperphosphorylated, it tends to form aggregates/inclusions. These are termed neurofibrillary tangles when occurring in glial cells, coiled bodies in oligodendrocytes, and "tufted" inclusions in astrocytes (Fig. 9.2). The neurofibrillary tangles in PSP are single straight filaments and are common in subcortical regions whereas in Alzheimer's disease, they are paired helical filaments and cortical.

Alternative exon splicing of the tau gene produces six isoforms in human brain. Isoforms containing exon 10 have four microtubule-binding domains (4R tau) and those that splice out exon 10 have three (3R tau). In the normal brain, 3R and 4R tau isoforms have similar ratios; in PSP and CBD there is a 4R preponderance, and in Pick's disease a 3R preponderance. Certain tau gene mutations, including some that disrupt the stem loop structure that splices exon 10, cause an autosomal dominant frontotemporal dementia with parkinsonism (FTDP-17) supporting the key role of the tau gene in tauopathy-associated neurodegeneration (see Chap. 6).

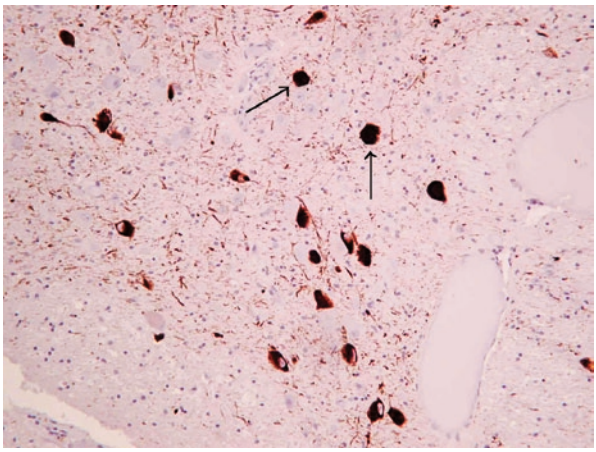

Fig. 9.2 Tau immunostaining to show neuronal cytoplasmic tau-positive neurofibrillary tangles (*arrows*). (Photo courtesy Professor Ian R.A. Mackenzie)

Certain tau mutation carriers with FTDP-17 have a phenotype similar to PSP but tau mutations do not cause PSP and in clinical practice familial clustering of PSP is very rare. However, one of the most compelling and robust associations between gene and phenotype across all known human disorders is the association between sporadic PSP and a specific H1 haplotype formed by a balanced inversion of the region surrounding the tau gene about three million years ago. A number of polymorphisms on the H1 haplotype that influence gene expression have been implicated. Genetic testing of the tau gene is unnecessary in PSP unless one is considering an alternative differential diagnosis such as autosomal dominant FTDP-17.

Radiological Findings

Generalized brain atrophy is common in PSP, especially in the frontal lobes, but the characteristic finding of dorsal midbrain atrophy is best seen on a dedicated axial MRI where it produces a picture reminicent of "Mickey Mouse" (Fig. 9.3), and on sagittal views where it produces a picture similar to a hummingbird (Fig. 9.4).

Laboratory Tests

There are no diagnostic tests currently available for PSP; the diagnosis remains a clinical one (Table 9.6).

Management

There is no effective treatment for PSP and therapy is generally supportive in nature. A multidisciplinary team approach is recommended; physiotherapists may improve mobility, prevent contractures, and provide hip protectors and walking aids; occupational therapists

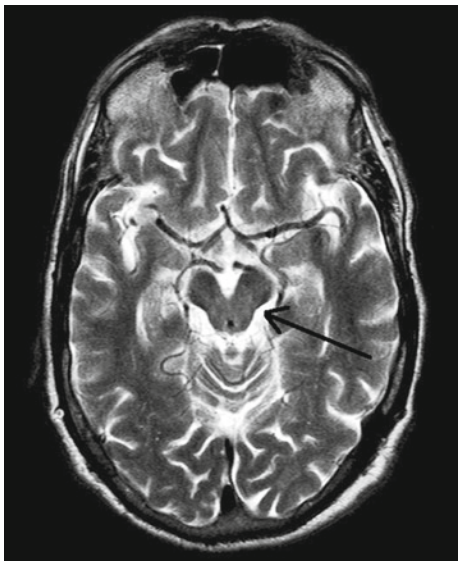

Fig. 9.3 Axial T2-MRI showing voulme loss in midbrain giving "Mickey Mouse" appearance (*arrow*) in PSP

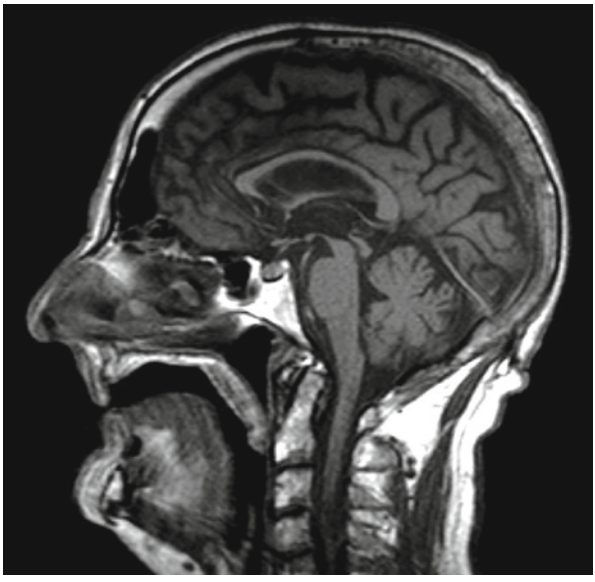

Fig. 9.4 Sagittal T1-MRI through the brainstem showing volume loss in the midbrain with relative preservation of the pons in PSP. The upper convexity of the midbrain is lost giving a "hummingbird" appearance

and social workers can assist with adapting patients' homes. Speech and language therapists may provide communication devices if required.

If parkinsonism is a prominent feature, a trial of levodopa is recommended, increasing the dose to at least 1 g/day before deciding it is of no benefit. Forty to fifty percent show some improvement although this is often short lived. Adverse effects include visual hallucinations and rarely dystonia, dyskinesias, and apraxia of eyelid opening. Amantidine may benefit 15% of patients but the response is usually modest. Dopamine agonists,

Table 9.6 Clinical research criteria for the diagnosis of PSP.

Possible PSP • Gradually progressive disorder • Onset age ≥ 40 or later • Vertical (upward or downward gaze) supranuclear palsy[a] *or* slowing of vertical saccades[a] and prominent postural instability with falls in the first year of disease onset[a] • No evidence of other disease that could explain the foregoing features, as indicated by mandatory exclusion criteria
Probable PSP • Gradually progressive disorder • Onset age ≥ 40 or later • Vertical (upward or downward gaze) supranuclear palsy[a] and prominent postural instability with falls in the first year of disease onset • No evidence of other disease that could explain the foregoing features, as indicated by mandatory exclusion criteria
Definite PSP • Clinically probable or possible PSP and histopathologic evidence of typical PSP[b]
Mandatory exclusion criteria • Recent history of encephalitis • Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy • Hallucinations or delusions unrelated to dopaminergic therapy • Cortical dementia of Alzheimer's type • Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia (marked hypotension and urinary disturbances) [a] • Severe, asymmetric parkinsonian signs • Neuroradiologic evidence of a relevant structural abnormality (i.e., basal ganglia or brainstem infarct, lobar atrophy) • Whipple's disease, confirmed by polymerase chain reaction, if clinically indicated
Supportive criteria • Symmetric akinesia or rigidity, proximal more than distal • Abnormal, neck posture, especially retrocollis • Poor or absent response of parkinsonism to levodopa therapy • Early dysphagia and dysarthia • Early onset of cognitive impairment including at least two of the following: apathy, impairment in abstract thought, decreased verbal fluency, imitation behavior, and frontal release signs

Based on the report of the NINDS-SPSP international workshop. Litvan et al., Neurology. 1996;47:1–9

This provides a useful clinical and research guide to the diagnosis of definite (pathology), probable, and possible PSP

[a]Upward gaze is considered abnormal when pursuit or voluntary gaze, or both, have a restriction of at least 50% of the normal range

[b]Definite PSP is a clinicopathologic diagnosis

monoamine oxidase inhibitors, and catechol-O-methyl transferase inhibitors are of no proven benefit. Anticholinergics should be avoided as there is an unusual sensitivity to cholinergic blockade in these patients. Lorazepam and low-dose quetiapine could be considered for management of psychiatric and behavioral symptoms.

Blepharospasm, with or without eyelid freezing, can be effectively treated with botulinum toxin. Dysphagia is progressive and some patients choose percutaneous endoscopic gastrostomy (PEG) insertion.

Corticobasal Degeneration

Clinical Features

CBD was first described by Rebeiz et al. in 1968 in three patients of Irish descent with parkinsonism, myoclonus, supranuclear palsy, and apraxia who were found at autopsy to have "corticodentatonigral degeneration with neuronal achromasia." This disorder has an insidious onset with progressive asymmetric rigidity and apraxia. Severe disability and death typically occurs within 10 years. Definite diagnosis requires histological examination.

Cortical dysfunction may manifest as asymmetric ideomotor apraxia (disorder of skilled, learned, purposeful movement) and/or an alien limb ("My hand has a mind of its own"). Eye movement abnormalities with slow initiation of horizontal movements as well as upgaze are common. However, restricted downgaze is suggestive of PSP. In a series of 147 cases collected from eight centers, the following features were most common: parkinsonism, (100%), higher cortical dysfunction (93%), dyspraxia (82%), gait disorder (80%), dystonia (71%), tremor (55%), myoclonus (55%), alien limb (42%), cortical sensory loss (33%), dementia (22%). Asymmetrical limb contractures are more prevalent in this condition than in the other parkinsonism plus syndromes. The motor alien hand must be differentiated from sensory or posterior syndrome associated with a lesion in the thalamus and temporal-occipital lobe. In autopsy-proven cases of CBD, the following were found to be the best predictors of the diagnosis of CBD: limb dystonia, ideomotor apraxia, myoclonus, and asymmetric akinetic-rigid syndrome with late onset of gait or balance disturbance.

Epidemiology

There is an estimated incidence of 0.02–0.92 cases/100,000 population/year, with an estimated prevalence of 4.9–7.3/100,000. No racial predilection is known. The condition tends to occur in older age groups (60–80 years), with a mean age of onset of 63 years. CBD may be more common in women.

Radiological Findings

MRI brain findings are nonspecific but often show asymmetric posterior parietal and frontal cortical atrophy. Atrophy of the corpus callosum has also been described.

Neuropathology and Molecular Pathology

CBD is another tauopathy with similar molecular characteristics to PSP, differing mainly in regional brain pathology. Rebeiz described CBG in 1968 as "corticodentatonigral degeneration with neuronal achromasia"; patients with prominent frontoparietal degeneration get limb apraxia and dementia and those with prominent frontotemporal atrophy get progressive primary aphasia. Severe substantia nigra depigmentation is invariable and most patients have some extrapyramidal features/parkinsonism.

CBD and PSP are both 4R tauopathies and the tau H1 haplotype is a shared risk factor. Almost half of all CBD patients are misdiagnosed PSP in life and 30% of CBD turns out to be PSP at postmortem. However, CBD and PSP are not different spectrums of the same disorder since their classical clinical presentations can be strikingly different and the neuropathological diagnostic criteria of CBD and PSP are validated with high sensitivity and specificity. Both share neuronal tau accumulation but astrocytic plaques are the hallmark of CBD and tufted astrocytes the hallmark PSP. Prominent cortical and subcortical neuronal loss, often highly asymmetric, also separates CBD from PSP. Ballooned swollen neurons with loss of cytoplasmic staining (achromasia), is supportive when present in the cortex and basal ganglia.

Management

To date, no effective treatment has been found. Initially, the extrapyramidal symptoms including rigidity, bradykinesia, and tremor may respond to levadopa. Clonazepam and levetiracetam can be tried for myoclonus. Painful rigidity and dystonia may improve with botulinum toxin injections. Physical and occupational therapy can be helpful in patients with impaired gait secondary to visual agnosia.

Other Environmental Tauopathies

Clusters of PSP-like disorders exist in a number of remote parts of the world. In Guadeloupe, a PSP-like presentation of parkinsonism is as common as idiopathic PD. The consumption of soursop, which contains high concentrations of annonacin, has been suggested as annonacin can cause direct inhibition of Complex 1. Interestingly, association between Guadeloupian parkinsonian and the H1 tau haplotype has been reported, as has 4R tau pathology at postmortem.

A parkinsonism–dementia complex sometimes with features of motor neuron disease is another tauopathy described amongst the Chamorro population of Guam and isolated villages on the Kii peninsula of Japan. The incidence of this disorder has declined since the original 1945 description by Zimmerman. Flour made from the false sago palm (*Cycas micronesica*) has been implicated as it contains high levels of an excitatory amino acid BMAA, but this theory remains completely unproven. Familial clustering is described as is weak genetic association with the tau gene.

Encephalitis lethargica (EL) is characterized by somnolence, sleep inversion, oculogyric crises, and behavioral disorders. Most cases of EL occurred during the 1918/19 influenza pandemic and an etiological association has been suggested but not proven. Many patients who recovered from the somnolent phase developed partial dopa responsive parkinsonism sometimes years after the acute disease. Sporadic cases still occur rarely. Pathologically, EL shows subcortical and brainstem neurofibrillary pathology comprised of both 3R and 4R tau.

Hereditary Mimics

A number of single gene disorders can occasionally mimic the atypical parkinsonisms. Progranulin mutation carriers, who lack tau neuropathology, typically present with a frontal lobe behavior and language disturbance but can resemble PSP and CBD. LRRK2 mutation carriers typically display PD and Lewy body neuropathology, but in some kindreds, primary tau pathology resembling PSP occurs for unknown reasons. The fragile X tremor-ataxia syndrome (FXTAS) and a number of the autosomal dominant spinocerebellar ataxias (SCA) clinically mimic MSA-C.

Biomarkers in PSP, MSA, and CBD

Presently, there are no fully reliable markers for PSP, MSA, or CBD although, as discussed, standard MRI often shows characteristic features in PSP (mid brain atrophy [humming bird sign]), MSA (pontocerebellar atrophy [hot cross bun and lateral putaminal sclerosis]), and CBD (frequent asymmetrical parietal lobe atrophy).

Phosphorylated tau protein has been examined in the CSF as a potential biomarker for PSP but results are inconsistent and confounded by elevated tau protein in overlapping neurodegenerative disorders like Alzheimer's disease.

Functional evaluation of the presynaptic dopaminergic system using dopamine transporter single photon emission computed tomography (SPECT) scanning is widely available in clinical practice does not reliably differentiate PD, PSP or MSA and, therefore, is of little value. Studies of dopamine D2 receptors SPECT have shown normal or upregulation in PD whereas, typically, this is reduced in MSA and PSP.

A better modality is fluorodeooxyglucose positron emission tomography (FDG-PET) although this is not widely available. Recent computer programs for FDG-PET that recognize disease-specific patterns show remarkable accuracy in differentiating parkinsonisms even before examined by a clinician. In PD, the pattern is increased pallidothalamic and pontocerebellar metabolic activity and reduced activity in premotor cortex, supplementary motor area, and parietal association regions. MSA is characterized by bilateral metabolic reductions in putamen and cerebellar activity, and PSP by reductions in the upper brainstem, medial frontal cortex, and medial thalamus.

FDG-PET is most specific in the early phase of disease when the clinical diagnosis is hardest and accords with the time window where disease-modifying treatments might be most effective. Functional imaging of the cholinergic system and of activated microglia hold promises for the future. Imaging technologies that directly indentify intraneuronal inclusions such as NFTs and Lewy bodies are likely in the future.

Rapid eye movement (REM) sleep behavior disturbance (RBD) is common to synucleinopathies (PD, MSA) and rare in tauopathies (PSP, CBD) and invariably precedes the movement disorder. The vast majority of patients diagnosed with RBD go on to develop PD or MSA, marking RBD a clinically useful biomarker and identifying a target patient group for future disease-modifying therapies. Neuropsychological tests (e.g., Frontal Assessment Battery) may show disproportionately early frontal pathology, apathy, and/or executive dysfunction and differentiate PSP from PD and other atypical parkinsonisms. The simple 3-clap applause test is a very sensitive bedside test with perseveration, pointing to PSP.

Future Advances

Drugs that inhibit alpha-synuclein aggregation have been an area of active investigation in MSA and PD. The antibiotic rifampicin inhibits alpha-synuclein aggregation in transgenic mouse models of MSA. An important rodent study showed that embryonic striatal graft transplantation restored L-dopa responsiveness, which if applied to humans might be analogous to turning the parkinsonism of MSA into that of PD.

The NNIPPS study is the only large placebo-controlled double-blind trial in PSP (362 patients) or MSA (398 patients), and this failed to show any benefit from the anti-excitotoxin drug riluzole.

In PSP and CBD, one of the most tractable treatment strategies is to block the hyperphosphorylation of tau since this is the step that blocks tau from binding to microtubules and thus prevents the resultant microtubule instability and transport impairment. Therefore, one therapeutic approach is protein kinase inhibitors that inhibit tau phosphorylation. Like other neurodegenerative conditions, strategies that promote tau clearance through proteolytic and/or autophagosomal degradation pathways are also under consideration. Anti-tau immunization has been attempted in transgenic mice with encouraging early data. Interfering with splicing machinery to decrease the 4R:3R ratio might be another approach.

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Prion Diseases

10

Simon Mead and Peter Rudge

Abstract Prion diseases are a diverse group of neurodegenerative disorders of humans and animals. Generally these are recognized as rapidly progressive cognitive disorders with additional neurological signs such as myoclonus, ataxia, and pyramidal and extrapyramidal dysfunction. Inherited forms of prion disease may be highly atypical with clinical durations up to 20 years and can mimic any other neurodegenerative disease in the earlier stages. MRI, CSF, and genetic analyses are particularly helpful investigations, although tissue biopsy may be needed in some patients. Symptom management strategies, experimental therapeutics, and public health measures are discussed.

Keywords Prion • Creutzfeldt–Jakob disease (CJD) • Transmissible spongiform encephalopathy • Dementia • *PRNP*

Introduction

Prion diseases are a diverse group of human and animal neurodegenerative disorders; examples include sheep scrapie, bovine spongiform encephalopathy (BSE), and human Creutzfeldt–Jakob disease (CJD). The most notable feature of these diseases is the potential for transmission between humans and animals. The pathogenesis of these conditions involves a cell surface glycoprotein termed the "prion protein" (or PrP^{C}, "C" for cellular or normal isoform). Human prion diseases are most usefully classified by etiology as inherited, acquired, or unknown (sporadic). In general, physicians should consider these diseases in patients presenting with rapidly progressive dementias and in those with dementia and additional neurological signs or psychiatric symptoms. As will be described below however, the group is remarkable for its heterogeneity and has mimicked virtually all other neurodegenerative syndromes in the early phases.

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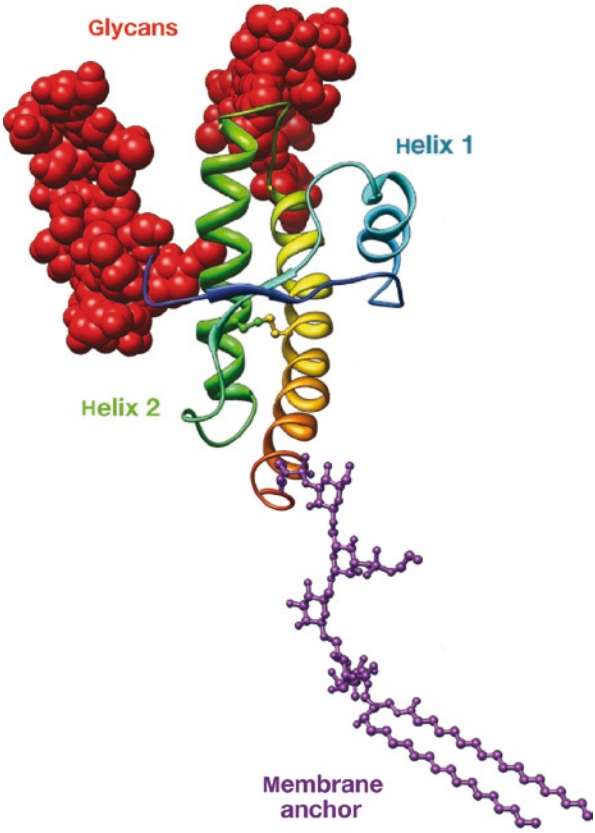


Fig. 10.1 Image of the structure of PrP^{C} showing three alpha helices, a single disulphide bond, up to two carbohydrate moieties, and attachment to the cell surface via a glycosylinositolphosphate anchor. An N-terminal region containing octapeptide repeats appears to be unstructured and is not shown

The infectious agent of prion disease comprises an abnormal isoform of the prion protein (termed PrP^{Sc}, "Sc" for scrapie isoform). PrP^{C} is found on cell surfaces throughout the body, but with enhanced expression in the nervous and immune systems. It predominantly has an alpha-helix structure and its function is unknown (Fig. 10.1). The disease-associated form of the protein is largely of beta-sheet structure although the precise structure of the infectious form remains uncertain. Many prion diseases are transmissible; it is hypothesized that transmission occurs because the misfolded protein acts as a template that encourages conversion of normal host prion protein into the form detected in disease.

Clinical Features of Prion Diseases

General Overview

Although there is considerable heterogeneity in the clinical picture of the prion diseases, there are a number of core features. All are associated with *cognitive* decline at some stage of the illness, which characteristically is rapid. This decline may remain focal for some

time but ultimately becomes global. Memory, speech, and executive functions are often involved early. Many patients are profoundly apraxic and some have complex articulation and language disturbances. The latter preferentially involves expression rather than comprehension in most cases and can be extremely prominent in some genetic types. Other features dependent on parietal function, such as getting lost in familiar surroundings and dressing apraxia, are frequent. High-order visual dysfunction is uncommon except in the Heidenhain variant of sporadic CJD. Executive dysfunction is common and often associated with behavioral change. The latter may require careful management and comprise irritability, aggression, or withdrawal from normal social interchange.

Neurological symptoms and signs indicate involvement of multiple components in the nervous system, which is often the first clue to a prion disease vs. more common dementias. In the motor systems, ataxia, especially of gait, and dysarthria are early features in many types of CJD, including variant CJD (vCJD), kuru, iatrogenic CJD (iCJD), and some types of sporadic CJD. Abnormal movements, especially myoclonus of cortical or subcortical type, are characteristic of most types of prion disease, especially sporadic CJD. Chorea is found in a proportion of sporadic and variant CJD, and exceptionally alien limb phenomena and epilepsia partialis continua have been reported. Stiffness with increased tone in the limbs and neck occurs in many types of CJD. This tone increase commonly has extrapyramidal features, especially in the upper limbs, in addition to spasticity. Fasciculation rarely occurs. Power, in general, is relatively preserved but hemiparesis or a stroke-like onset has been described.

Sensory loss is not often detected because the patients are frequently not capable of cooperating with the examination. Hyperesthesia is typical of vCJD and loss of thermal sensation occurs in some inherited prion disease. Late in the course of all these diseases, incontinence develops. Ultimately, most patients enter a state of akinetic mutism. Death generally follows decreasing conscious level, pneumonia, and respiratory failure or sepsis.

Sporadic CJD

Sporadic CJD (sCJD) is the most frequent type of spongiform encephalopathy in man. Although a rare disease with an incidence of 1–2 per million throughout the world, ascertainment in old age, when dementia is highly prevalent, remains an important unknown. The most frequent phenotype is of a rapidly progressive disease characterized by cognitive decline, visual disturbance, apraxia, ataxia, and myoclonus. Typically, the age of onset is between 55 and 70 years but many cases occur outside this range; cases in the 70–85 years range have probably been overlooked in the past but cases under the age of less than 45 years are rare. Only three cases of sporadic CJD younger than 30 years old have been identified in the United Kingdom since 1970. The disease affects males slightly less frequently than females. Death typically occurs in 5 months from onset in the majority, with only an atypical 10% surviving over 2 years from onset.

Clinicians have long recognized different phenotypes of sCJD, that described by Jones and Nevin being the most frequent. Myoclonus is characteristic at some stage of the disease in virtually all cases but can be subtle. The Heidenhain variant is not infrequent and is characterized by visual disturbance culminating in cortical-type blindness.

Other phenotypes include an ataxic variant, a thalamic variant, and a panencephalitic type with extensive white matter change, these latter being mainly in the Japanese literature but may merely reflect long duration of disease where more gray matter is destroyed. It is unclear if the demyelination is primary or secondary. It is uncertain if an amyotrophic type occurs and these cases, if they exist, have not been transmitted. Some case series describe groups with long, pure cognitive and/or psychiatric phases early in the clinical course. Whether or not these different phenotypes represent distinct disease entities or extremes of a range of involvement of different neurological systems is not clear.

Diagnostic Criteria

The World Health Organization has drawn up criteria for diagnosing various types of CJD and recently magnetic resonance imaging (MRI) criteria have been recommended to be added (Table 10.1). While these criteria are useful in epidemiological surveys ensuring uniformity of data, they may be restrictive in clinical trials where early diagnosis is essential.

Inherited Prion Disease

There are at least 30 different pathological mutations causing inherited prion disease (IPD) (Fig. 10.2). There are broadly two types of mutation viz alteration of the normal number of a nonapeptide followed by four octapeptide repeats between codons 51 and 91 of *PRNP*, or point mutations in the C-terminal portion of the protein.

Phenotypes can be highly variable even in patients with the same mutation and within a family. Some of these cases have been transmitted to other species but many have not,

Table 10.1 MRI-CJD consortium criteria for sporadic Creutzfeldt–Jakob disease

I Clinical signs (with a symptom duration of less than 2 years) Dementia Cerebellar or visual Pyramidal or extrapyramidal Akinetic mutism
II Tests Periodic sharp wave complexes on the EEG 14–3-3 protein detection in the CSF High-signal abnormalities in caudate nucleus and putamen or at least two cortical regions (temporal, parietal, or occipital) either in diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) MRI
Probable CJD Two out of I and at least one out of II
Possible CJD Two out of I and duration less than 2 years

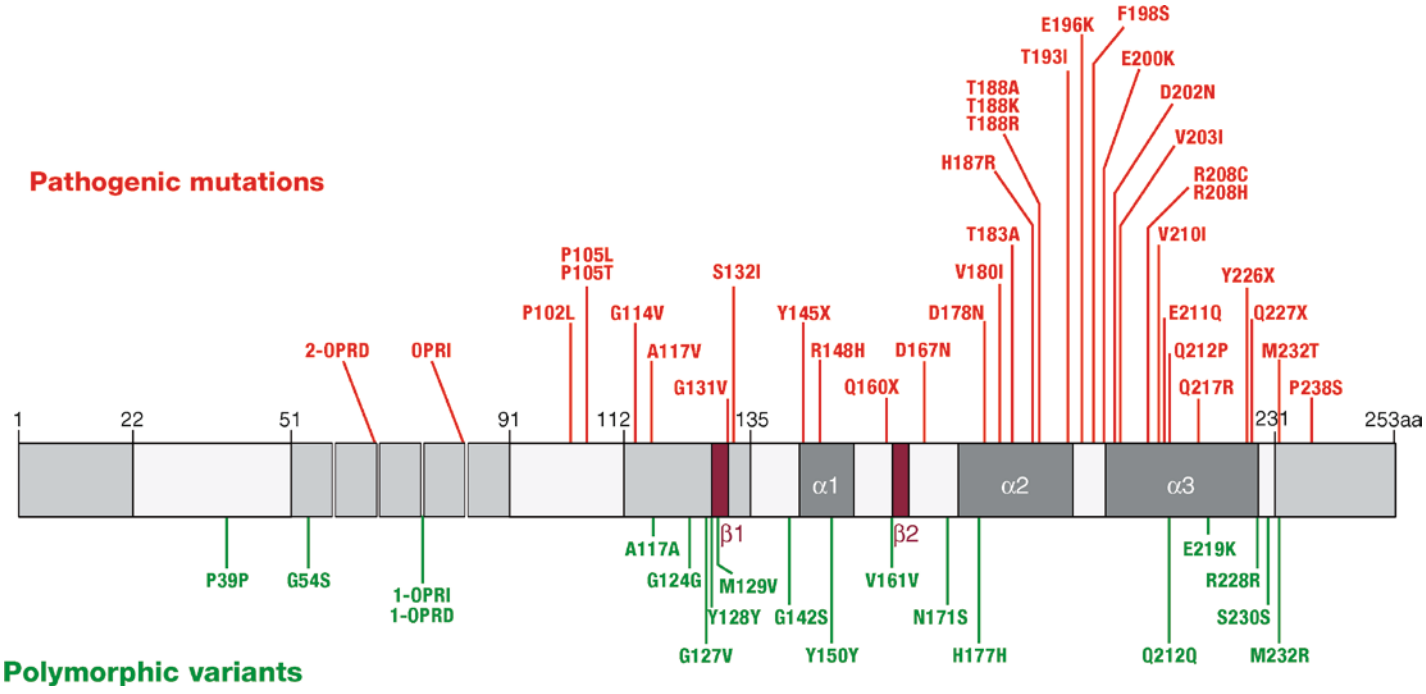


Fig. 10.2 Pathogenic mutations (*red above*) and polymorphic changes (*green below*) in the prion protein gene are shown on this schematic. The *central grey bar* also illustrates the secondary structural features of the prion protein

particularly those reported from a single family. Failure of transmission in experimental situations does not necessarily mean that transmission will not occur given the appropriate route of inoculation and genetic background of the recipient. A summary of the mutations so far described is shown in Table 10.2.

Table 10.2 In this table, the mean age (years) of onset, range of ages, and clinical features of IPD mutations are shown. Modification by codon 129 and transmission to laboratory animals is also shown where known. In the table, Gerstmann–Sträussler–Scheinker syndrome (GSS) is used to refer to the clinical combination of a slowly progressive ataxia, spasticity and later dementia, rather than the pathological phenotype, which is not known in all cases

PRNP mutation	Median onset	Range	Clinical features	Modification by codon 129 genotype	Transmission of disease to laboratory animals
P102L	50	25–70	GSS, CJD, psychiatric presentations, heterogenous	Possible	Yes
P105L	45	38–50	GSS, spastic paraparesis	Not known	Not known
G114V	22	18–27 in one family	GSS, neuropsychiatric and extrapyramidal signs prominent	Not known	Not known
A117V	40	20–64	GSS with early cognitive, neuropsychiatric, extrapyramidal features	Not known	No
G131V	42		GSS	Not known	Not known
Y145X	38		Alzheimer-like dementia	Not known	No
R148H	72	63–82	CJD	Not known	Not known
Q160X	40	32–48	Unspecified dementia	Not known	Not known
D178N	50	20–72	FFI, CJD	Possible	Yes
V180I	74	58–81	CJD	Not known	Not known
T183A	45	37–49	Prominent behavioral abnormalities, one patient with dementia, and no additional signs	Not known	Not known
H187R	32	20–53	Early onset with personality disorder in one family	Not known	Not known
T188A	82		CJD	Not known	Not known
T188K	59		CJD	Not known	Not known
E196K	69		CJD	Not known	Not known
F198S	56	40–71	GSS	Yes	Not known
E200K	58	33–78	CJD	Yes	Yes

Table 10.2 (continued)

PRNP mutation	Median onset	Range	Clinical features	Modification by codon 129 genotype	Transmission of disease to laboratory animals
D202N	73		Dementia	Not known	Not known
V203I	69		CJD	Not known	Not known
R208H	59	58–60	CJD	Not known	Not known
V210I	58	54–68	CJD	Not known	Not known
E211Q	69		CJD	Not known	Not known
Q212P	60		Ataxia, no dementia	Not known	Not known
Q217R	64	62–66	CJD, frontotemporal dementia	Not known	Not known
4-OPRI	62	56–82	CJD	Not known	Not known
5-OPRI	45	26–61	GSS, CJD, Alzheimer-like, variable, some with prominent extrapyramidal signs	Yes	Not known
6-OPRI	34	20–53	GSS, CJD, variable, personality and psychiatric features, and extrapyramidal signs	Yes	Yes
7-OPRI	29	23–35	GSS, CJD, variable, personality and psychiatric features	Not known	Yes
8-OPRI	38	21–55	GSS, CJD, variable, personality and psychiatric features	Not known	Yes
9-OPRI	44	34–54	GSS	Not known	Not known
2-OPRD			CJD	Not known	Not known

Octapeptide Repeat Insertion Mutations (OPRI)

In the United Kingdom, a number of families with 6-OPRI have been described. The largest group of over 100 patients has a 144 bp insertion (6-OPRI). These patients have a mean age of onset of symptoms of 35 (20–53) years and mean age at death of 45 (30–65) years. Interestingly, those with methionine homozygosity at codon 129 have an earlier onset (by about 10 years) than heterozygotes, although the duration of the illness is similar between genotypes. Younger patients have a slightly longer course. Typically, patients present with cortical cognitive deficits encompassing acalculia, language dysfunction, apraxia, and memory impairment together with frontal behavioral disturbance. There is some evidence that scholastic achievement is poor before overt clinical signs are apparent. Similarly, work history often shows a progressive decline before the diagnosis is established. Physical signs include ataxia, corticospinal, and extrapyramidal features. Myoclonus occurs but seizures are rare. The phenotype is variable within families suggesting genetic or other factors, additional to codon 129, play an important part in the clinical picture.

A number of different 5-OPRI mutations are described, including at least three families from the United Kingdom, South Africa, and Northern Ireland. The phenotypic variation is probably greater in this group than with any other mutation. The age of onset ranges from the third to the seventh decade and the duration from of the illness from 4 months to 15 years. Some patients are indistinguishable from sCJD but most have a slower dementing disorder mistaken for Alzheimer's disease, only later accompanied by apraxia, ataxia, and sometimes myoclonus. Additional features include pyramidal signs in many, and, less commonly, extrapyramidal features.

Seven, eight, and nine octapeptide repeat insertions have been described, all with pathological evidence of prion disease. A 7-OPRI mutation has been reported in a number of families characterized by multiple system involvement in young people (23–35 years) The disease usually has a prolonged course (10–13 years) with exception of a recently described Dutch family with a late-onset and shorter course. A similar clinical picture is seen in three families with 8-OPRI; the disease is of variable duration extending up to 13 years. A single case of 9-OPRI insertion in a 54-year-old English woman with dementia, rigidity, and myoclonus lasting about 5 years has been described; there was no convincing family history of a similar illness.

Occasionally, patients with a clinical phenotype typical of sCJD have other octapeptide repeat mutations, but the exact significance of these mutations in this group is unclear in many. Those involving one, two, or three additional repeats may be coincidental findings, as these have been found in healthy control populations. Four repeat insertions have been reported more frequently associated with a late-onset, short duration course with an absence of family history and so are often mistaken for sCJD.

There are only two reports of a deletion in the repeat region (2-OPRD) in patients with CJD; this has not been found in controls and is probably causal of disease. A 1-OPRD is a relatively uncommon polymorphism of the healthy population and is therefore not causal of disease.

Point Mutations

A large number of point mutations have been described. Some show marked ethnogeographic clustering. Some of the more prevalent mutations in Europe are described here.

P102L (Gerstmann–Straussler–Scheinker Disease)

In the UK, the most frequent point mutation is P102L, which usually presents as the archetypal Gerstmann–Sträussler–Scheinker disease. Ataxia is the commonest symptom with cognitive decline, leg weakness, and lower limb pain, especially burning discomfort, occurring later. Additional features include psychiatric symptoms and pyramidal and extrapryramidal signs in a minority. Myoclonus is uncommon. A particularly striking feature is the presence, on clinical testing, of a neuropathy especially marked in the lower limbs, although it is unclear whether the spinothalamic impairment is peripheral or central in origin. Occasional CJD-like atypical patients are seen.

Many of the patients reside in southern or mid-England and may well have a common ancestor dating back before the seventeenth century. The age of onset is 27–66 (mean 51) years and death occurred from 33 to 69 (mean 55) years. Again, those who were homozygous for methionine at codon 129 had an earlier age of onset (mean 47 years) than heterozygotes but the range of durations of the illness is wide and may be independent of codon 129.

P105L

Originally, described in Japanese families, this condition occurs more widely. Age of onset is in the fourth to fifth decade with a duration of about 5 years. All have dementia and some a spastic paraparesis. There are plaques in the cerebral cortex but not in the cerebellum.

A117V

This mutation was first described in France and subsequently has been reported from a number of countries. Parkinsonian features are frequent with dementia and there is a severe loss of ability to speak but with relative preservation of understanding. The age of onset is variable between 20 and 64 years and a duration of several years. Amyloid plaques are plentiful and there is often associated tau pathology. There is one large UK family under the care of the National Prion Clinic.

Y145X

Ghetti and colleagues described a 38-year-old Japanese woman with progressive dementia evolving over 12 years, who had extensive amyloid deposition in the CNS parenchyma and leptomeningeal blood vessels, sparing the white matter, associated with marked tau pathology. Genetic analysis showed a mutation at codon 145 and heterozygosity at 129. Western blotting revealed a 7.5 kDa band. The exact nosology of this condition remains unclear.

D178N (Including Familial Fatal Insomnia)

Fatal familial insomnia, due to a mutation most frequently on the 129 methionine allele, was the first described in Italians but occurs extensively. Onset is between 36 and 62 (mean 51) years and duration wide varying between 1 and 6 (mean 2.5) years. Insomnia is the cardinal feature of the disease often preceded by lack of attentiveness. The insomnia may be masked by apparent excessive day time sleeping as a result of lack of nocturnal somnolence. This is soon accompanied by autonomic symptoms such hypertension, excessive sweating, evening pyrexia, salivation, and impotence. Later hallucinations

occur, often related to dreams, and the patients may have limb movements related to the dreaming. As the disease progresses ataxia, pyramidal signs and myoclonus occurs in many patients.

Usually, but not exclusively, 178N on a valine 129 allele is a rare cause of a CJD type picture. These patients present with memory impairment often at a younger age than sCJD, and a more prolonged course and have no periodic complexes on EEG.

E200K

This is common in localized populations, e.g., in Eastern Europe, North Africa, and Chile, but is less common in the UK. E200K patients are on average slightly younger than sCJD subjects but there is great variation. They are indistinguishable from the sCJD apart from some having a peripheral neuropathy of mixed axonal and demyelinating type and seizures are more common than in sCJD. There are rare reports of this mutation being on the valine allele where the patients are reported to have a longer course and more ataxia.

V210I

This is the commonest form of IPD in Italy but also described in other countries. The phenotype is like sCJD but with a mean age of onset at 55 years.

Other Point Mutations

A number of other point mutations have been described often in a single family. These patients may present a clinical phenotype of sCJD (R148H), Alzheimer's disease (G131V, F198S), frontotemporal dementia (T183A), early onset dementia (Q160X), rapidly progressive dementia (E196K), or psychiatric symptoms (G114V). The significance of other mutations is less certain because of lack of pathological confirmation or inconsistent occurrence of morbidity in carriers within a family (various substitutions at codon 188).

Genetic Counseling and Presymptomatic Testing

PRNP analysis allows unequivocal diagnosis in patients with inherited prion disease. This has also allowed presymptomatic testing of unaffected, but at-risk, family members, as well as antenatal testing following appropriate genetic counseling. The effect of codon 129 genotype on the age of onset of disease associated with some mutations also means it is possible to determine within a family whether a carrier of a mutation will have an early or late onset of disease. Most of the well-recognized pathogenic *PRNP* mutations appear fully penetrant; however, experience with some mutations is extremely limited. In families with the E200K mutation, there are examples of elderly unaffected gene carriers who appear to have escaped the disease.

Variant CJD (vCJD)

In late 1995, two cases of sporadic CJD were reported in the UK in teenagers. Only four cases of sporadic CJD had previously been recorded in teenagers, and none of these cases occurred in the UK. In addition, both were unusual in having kuru-type plaques at autopsy. Soon afterwards, a third very young sporadic CJD case occurred. These cases caused considerable concern and the possibility was raised that they were BSE-related. By March 1996, further extremely young-onset cases were apparent and review of the histology of these cases showed a remarkably consistent and unique pattern. These cases were named "new variant" CJD.

Review of neuropathological archives failed to demonstrate such cases. The statistical probability of such cases occurring by chance was vanishingly small and ascertainment bias seemed unlikely as an explanation. It was clear that a new risk factor for CJD had emerged and appeared to be specific to the UK. The UK Government Spongiform Encephalopathy Advisory Committee (SEAC) concluded that, while there was no direct evidence for a link with BSE, exposure to specified bovine offal prior to the ban on its inclusion in human foodstuffs in 1989, was the most likely explanation. A case of vCJD was soon after reported in France. Direct experimental evidence that vCJD is caused by BSE was provided by molecular analysis of human prion strains and transmission studies in transgenic and wild-type mice.

The striking feature of vCJD is the young age of the patients. The mean age of onset is 29 (range 16–74) years and the mean duration 14 months. Surprisingly, the average age of onset has not progressively increased with time; the reason for this is unknown. Presentation of vCJD is with behavioral and psychiatric disturbances and, in some cases, sensory disturbance. Initial referral is often to a psychiatrist because of depression, anxiety, withdrawal, and behavioral change. Suicidal ideation is, however, infrequent and response to antidepressants poor. Delusions, which are complex and unsustained, are common. Other features include emotional lability, aggression, insomnia, and auditory and visual hallucinations. Dysesthesia, or pain in the limbs or face, which was persistent rather than intermittent and unrelated to anxiety levels is a frequent early feature, sometimes prompting referral to a rheumatologist. A minority of cases have early memory loss or gait ataxia but, in most cases, such overt neurological features are not apparent until some months later. Typically, a progressive cerebellar syndrome then develops with gait and limb ataxia followed by dementia and progression to akinetic mutism. Myoclonus is frequent, and may be preceded by chorea. Cortical blindness develops in a minority of patients in late disease. Upgaze paresis, an uncommon feature of classical CJD, has been noted in some patients.

There remain concerns that extensive human infection may have resulted from the widespread dietary exposure to BSE prions. Cattle BSE was subsequently reported, albeit at much lower levels than in the UK, in most member states of the EU, Switzerland, USA, Canada, and Japan. Fortunately, the number of recognized cases of vCJD (~170) in the UK has been relatively small and the incidence has been falling for some years. Patients have been identified in a number of other counties, notably France and including Ireland, Italy, USA, Canada, and Hong Kong. However, the number of healthy but infected individuals is unknown. Human prion disease incubation periods, as evidenced by kuru, are known to span decades. While estimates based on mathematical modeling and clinically recognized

vCJD suggest the total epidemic will be small key uncertainties, notably with respect to major genetic effects on incubation periods suggest the need for caution: such models cannot estimate the number of infected individuals and it is these that are most relevant to assessing risks of secondary transmission. Also, the possibility of subclinical carrier states of prion infection in humans, as recognized in several animal models, must also be considered.

An attempt to estimate prevalence of vCJD prion infection in the UK by anonymous screen of archival – largely appendix – tissue, necessarily using a method of unknown sensitivity, found three positives in around 12,000 samples and estimated prevalence of 237 per million (95% CI 49–692 per million). This was followed by a larger UK study screening discarded tonsil tissue, which found no positives and suggested a lower prevalence but which was still statistically consistent with the earlier study. Further UK studies to attempt to better estimate prevalence of infection are planned.

The risk of secondary transmission via medical and surgical procedures is unquantifiable at present. As discussed below, vCJD appears transmissible by blood transfusion; also prions are known to be resistant to conventional sterilization and indeed iatrogenic transmission from neurosurgical instruments has long been documented. The wider tissue distribution of infectivity in vCJD, unknown prevalence of clinically silent infection, together with the recent experimental demonstration of the avid adherence to, and ease of transmission from, surgical steel surfaces highlight these concerns. Studies in transgenic mouse models of human susceptibility to BSE prion infection suggest that BSE may also induce propagation of a prion strain indistinguishable from the commonest type of sporadic CJD, in addition to that causing variant CJD. Other novel human prion disease phenotypes may be anticipated in alternative *PRNP* genotypes exposed to BSE prions.

No *PRNP* mutations are present in vCJD and gene analysis is important to exclude pathogenic mutations, as inherited prion disease presents in this age group and a family history is not always apparent. The codon 129 genotype has uniformly been homozygous for methionine at *PRNP* codon 129 to date in clinical cases with the exception of a recent case thought clinically to be vCJD in an MV heterozygote, although neither tonsil biopsy (see below) nor autopsy was performed.

Clear antemortem tissue-based diagnosis of vCJD can now be made by tonsil biopsy with detection of characteristic PrP immunostaining and PrP^{Sc} type. It has long been recognized that prion replication, in experimentally infected animals, is first detectable in the lymphoreticular system, considerably earlier than the onset of neurological symptoms. Importantly, PrP^{Sc} is only detectable in tonsil in vCJD, and not other forms of human prion disease studied. The PrP^{Sc} type detected on Western blot in vCJD tonsil has a characteristic pattern designated type 4 (see below). A positive tonsil biopsy obviates the need for brain biopsy, which may otherwise be considered in such a clinical context to exclude alternative, potentially treatable diagnoses. To date, tonsil biopsy has proved 100% specific and sensitive for vCJD diagnosis and is well tolerated.

Iatrogenic CJD (iCJD)

CJD can be transmitted within a species and across species by experimental techniques such as intracerebral administration of infected brain and other tissues. There is often considerable resistance to transmission between species. However, as discussed above, there have been

examples of accidental transmission between humans and even between another species and man (e.g., vCJD). We will now discuss intraspecific transmission in man in more detail.

While there have been a handful of intraspecific transmissions in man from neurosurgery (five cases), cortical electroencephalography (two cases), and corneal transplants (two cases), two major causes of iatrogenic CJD have been identified, viz: dural grafts and administration of contaminated human growth hormone to children. In addition, recently, transmission of vCJD by blood transfusion has been reported. Of particular interest is the fact that those few cases who developed CJD from intracerebral invasive procedures, had a clinical picture similar to sCJD with predominantly cortical features while those receiving growth hormone systemically or dural grafts, with no intracerebral surgery, develop an initial ataxic illness with cerebellar features.

Dural Graft Associated CJD

There have been 196 cases of CJD following dural grafting mostly (123 updated in 2008 to 132) from Japan. The majority of these cases received grafts produced from a single company before 1987. The first case was recorded in 1978 in the USA, although the epidemic started later (1985). There is good evidence that the incidence is falling from a peak of about 20 cases in 1997 to three cases in 2005. The mean incubation period is 11 years (range 1.4–23 years). The initial symptoms are most frequently a cerebellar syndrome, especially ataxia of gait, rather than cerebral cortical symptoms although these features ultimately occur in most cases. There is no correlation between the site of the graft and the clinical picture. There are no good data on duration of disease but, in general, it is measured in months. As with most other types of CJD, there is an excess of patients with homozygosity at codon 129, methionine being disproportionately represented. In a recent paper from Japan, where MM homozygosity at codon 129 is almost universal, there is evidence of at least two different pathologies occurring with equal frequency, one with and one without plaques. The first has a slower clinical evolution than the latter.

Growth Hormone Associated CJD

Growth hormone administration to children has resulted in a number of cases of CJD. All the cases have received hormones from pooled cadaver pituitary glands, a manufacturing process that ceased in 1985, when recombinant material became available. In the manufacturing process, many hundreds or thousands of pituitaries were pooled, thereby greatly increasing the chance of contamination from an infected cadaver.

The total number of cases recorded by 2006 was 194 with the majority occurring in France (107), UK (51), and USA (26). The primary diagnosis requiring hormone replacement was idiopathic growth hormone deficiency or post surgery for hypothalamic or pituitary tumors in most cases. In the UK population, the relative risk of getting iCJD from growth hormone injection was maximal at 9–10 years of age and the lifetime risk to recipients about 3.5%. The mean incubation period worldwide, assuming a midpoint of administration as the time of infection, is 15 years (range 4–36 years). In the UK, analysis of the products used suggests that one (Wilhelmi) was that most likely implicated although the

data are not conclusive. The methods of preparation differed with different products worldwide, but which of the various steps in these processes resulted in persistence of infective prions is not clear, a situation reminiscent of the situation in cattle supplementary feed manufacture and transmission of BSE.

As growth hormone was only administered in children, the mean age of these patients is younger than for any other form of CJD except vCJD and, rarely, IPD. Patients typically present with an ataxia and subsequently develop some cortical features. The disease evolves over a period of months, death typically occurring within 12–18 months. Homozygosity at codon 129 is over represented in these cases but interestingly, 129VV comprises the majority of the UK cases whilst in the USA and France, it is 129MM. The reason for this is unclear but a plausible explanation is that in the UK a 129VV infected donor contaminated the product whereas in the other countries it was 129MM, a more frequent phenotype in the general population.

Blood Transfusion Associated vCJD

There have been concerns that vCJD could be transmitted by blood transfusion. In sheep scrapie, which also has an extensive distribution of prions throughout the lymphoreticular system, transmission has been demonstrated. Surveillance of blood transfusion records linking these to the CJD registry revealed a case of vCJD in a patient who had received a transfusion just over 3 years before developing vCJD, the blood having come from an asymptomatic person who 4 months later developed vCJD. Two more cases have now been identified (one unpublished), in which a recipient of blood products from asymptomatic donors who later developed vCJD. One had received a large volume of red blood cells, platelets, and FFP for a colectomy 6 years before becoming symptomatic and the donor had developed symptoms 20 months after donation. In these two cases, the donor was the same.

Two additional cases of transmission of prions, but who did not have symptoms of vCJD, are known. One was an elderly patient who received blood from a donor who subsequently developed vCJD. She only had PrP^{Sc} detectable in the lymphoreticular system and died of an unrelated cause. The other was a patient with hemophilia who had received multiple transfusions of blood products, none of which was known to come from vCJD donor, who was shown to have PrP^{Sc} in the lymphoreticular tissue but not the CNS. Interestingly, the three vCJD cases were all 129MM as were the donors, but the cases of asymptomatic infection the patients were both 129MV. At present, there are only a small number of persons thought to be at risk from transfusion sourced from patients who subsequently developed vCJD. However, as the true prevalence of prion infection in the community is unknown, it is not possible to give an accurate assessment of the risk of a single or multiple transfusions of blood or blood products.

Secondary Prophylaxis After Accidental Exposure

Certain occupational groups are at risk of exposure to human prions, for instance neurosurgeons and other operating theatre staff, pathologists and morticians, histology

technicians, as well as an increasing number of laboratory workers. Because of the prolonged incubation periods to prions following administration to sites other than the CNS, which is associated with clinically silent prion replication in the lymphoreticular tissue, treatments inhibiting prion replication in lymphoid organs may represent a viable strategy for rational secondary prophylaxis after accidental exposure. A preliminary suggested regimen is a short course of immunosuppression with oral corticosteroids in individuals with significant accidental exposure to human prions. There is hope that progress in the understanding of the peripheral pathogenesis will identify the precise cell types and molecules involved in colonization of the organism by prions. The ultimate goal will be to target the rate-limiting steps in prion spread with much more focused pharmacological approaches, which may eventually prove useful in preventing disease even after iatrogenic and alimentary exposure. A proof of principle of immunoprophylaxis by passive immunization using anti-PrP monoclonals has already been demonstrated in mouse models.

Kuru

Kuru is a fatal, predominantly ataxic disease, confined to a remote region of Papua New Guinea. First recognized at the turn of the twentieth century, it was clearly defined by Alpers in the 1950s and subsequently shown by Gajdusek to be transmissible to other primates by intracerebral inoculation and later to other animals.

Kuru predominantly affected women and children. The disease was transmitted at cannibalistic feasts where tissues with the greatest concentration of prions, viz: brain, were preferentially eaten by the children and females, the males older than 7 years predominantly consuming muscle. The disease is a progressive ataxia and subsequent dementia developing over 1–2 years, the patient ultimately becoming moribund. There is often a prodrome of headache.

Banning cannibalistic practices has resulted in a dramatic decline in the prevalence of kuru although a few cases may still occur. Interestingly, while the early cases were predominantly 129MM and 129VV, in the most recent examples, heterozygotes are the majority, some with extremely long incubation times (over 50 years). Some elderly women who attended cannibalistic feasts, but did not get kuru, possess a novel genetic resistance factor, G127V, unique to the Fore people of the region.

Investigations

Neuropsychology

Full cognitive assessment, which is a fundamental part of the neurological assessment, cannot be made by the clinician seeing the patient for the first time. It is important to obtain full assessment as soon as possible with a neuropsychologist to determine the nature of the cognitive defects. Repeated assessments to document change are important in trials of

therapy bearing in mind that there can be a learning component if repeated too frequently. As was found in the PRION-1 trial, none of the instruments used in dementia trials is ideally suited for these cases as they often take too long to administer, omit certain cognitive assessments, give too much emphasis on others, or are not sensitive to advanced stages of disease.

Computed Tomography

Computed tomography (CT) scanning is an insensitive modality for diagnosis in CJD. Atrophy is apparent in some cases, but this is usually a late feature. The greatest generalized atrophy is seen in CJD patients surviving several years. GSS patients (P102L mutation) have focal cerebellar atrophy in some cases. Enhancement does not occur.

Magnetic Resonance Imaging

MRI is the most useful modality of imaging in CJD. High signal return from grey matter is characteristic of CJD except some cases of inherited prion disease (IPD) and is usually most apparent on diffusion-weighted images, less so on FLAIR, and least on T2-weighted images but this is not an invariable rule. Diffusion-weighted imaging (DWI) can be done at various *b*-values, which conventionally is 1,000 s/mm^2 but in some cases, a 3,000 s/mm^2 protocol is better. Apparent diffusion coefficient (ADC) maps should be calculated to confirm true restricted diffusion and remove T2-weighted "shine through." Enhancement with gadolinium does not occur in any type of CJD.

The distribution of the abnormal signal varies between different types of CJD. In sCJD, there is usually high signal return from the basal ganglia, typically the caudate and anterior putamen. This may be asymmetrical. In addition, thalamic signal is often abnormal and can be focal. In some patients, the lateral complex returns high signal while in others, the medial nuclei are more affected. The abnormality can include the posterior complex but, invariably, the thalamic signal is less intense than that from the caudate nuclei. Cortical "ribboning" is found in many patients usually, but not invariably, in addition to the basal ganglia abnormality (Fig. 10.3). This is best seen on DWI and ADC maps. The distribution can be focal involving any part of the cortex; care must be taken in determining abnormality in areas of allocortex, particularly the anterior cingulate and insula with 3T scanning and with frontal cortex adjacent to the frontal sinuses. Nevertheless, the cingulate abnormality often extends caudally and can be the sole abnormal cortical region. The cortical signal abnormality is usually asymmetrical. In a few patients, cortical ribboning is the only abnormality. In many patients, the body and tail of the hippocampus also returns high signal.

Little is known about the progression of abnormal signal on serial MRI, but it does become more extensive with time and the signal characteristics change. Whether spread is directly to adjacent cortex, through the corpus callosum or randomly through other mechanisms has not been determined. It appears that the greatest restriction is in tissues with most spongiform change while gliosis decreases it; the signal can therefore lessen with time in some areas and increase in others.

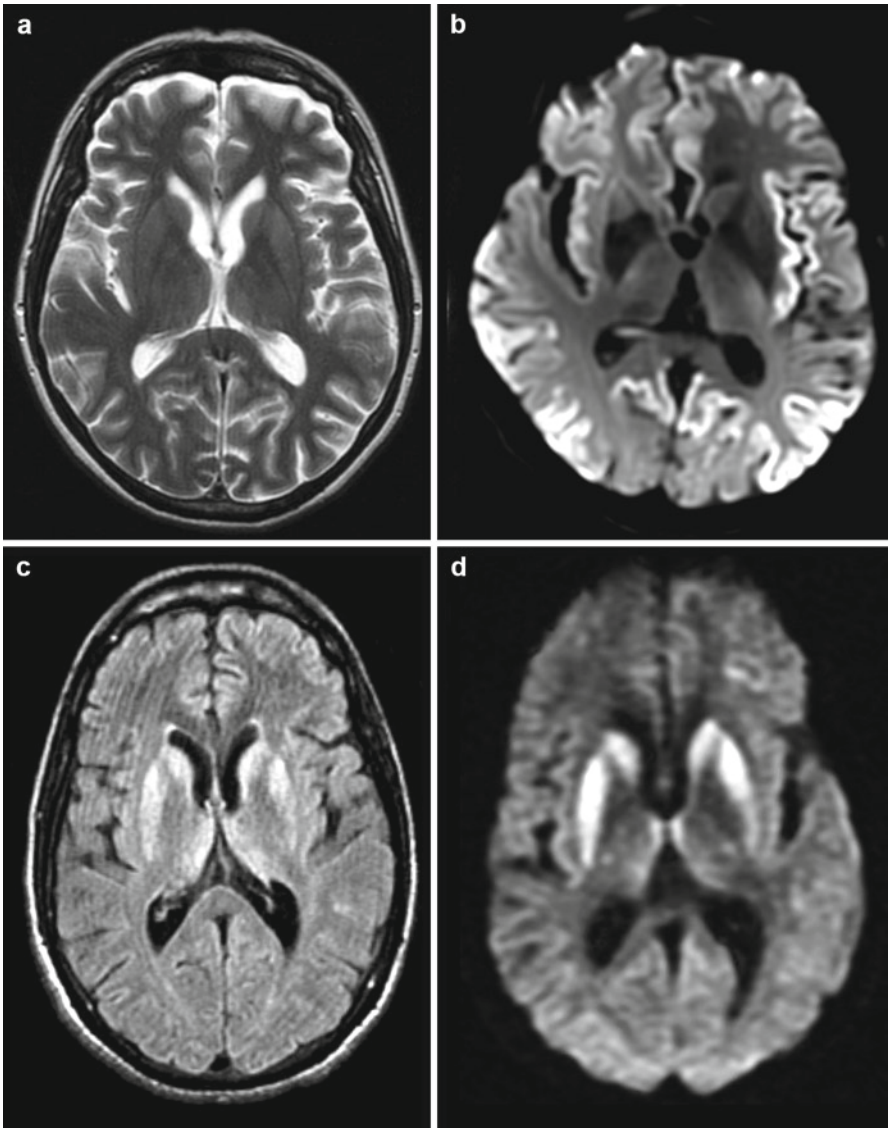


Fig. 10.3 (**a**) T2-weighted axial MRI in sCJD showing subtlety of increased cortical signal. (**b**) Diffusion-weighted imaging (DWI) showing cortical ribbon in sCJD. (**c**) FLAIR images in sCJD. (**d**) DWI showing high signal in the caudate, putamen, and less so from the thalamus in sCJD. (**e**) FLAIR images in iCJD showing cortical, caudate, putamen, and thalamic high signal. (**f**) FLAIR images showing pulvinar sign in vCJD

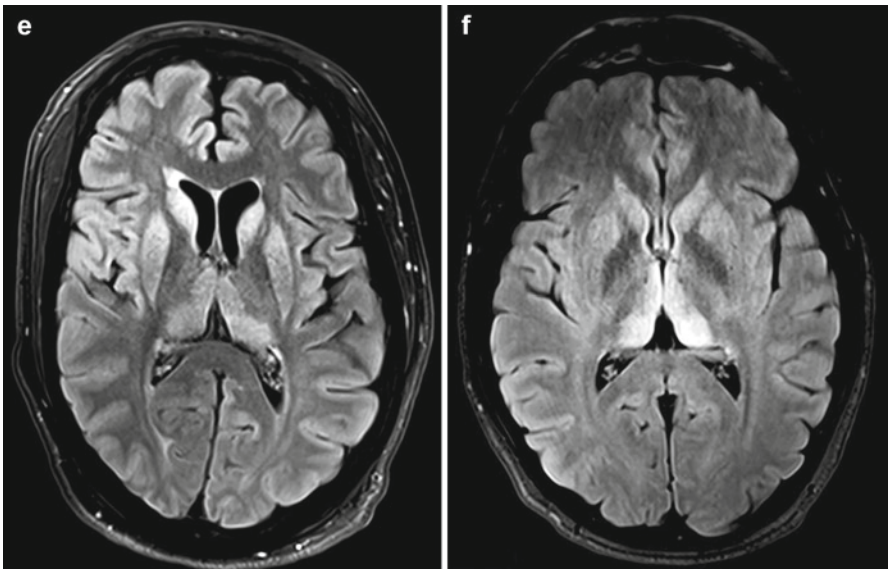


Fig. 10.3 (continued)

In vCJD, about 90% of patients in a prospective series have high signal return from the pulvinar and medial areas of the thalamus, particularly adjacent to the ventricle, the so-called "hockey stick" sign (Fig. 10.3). This is most apparent on DWI in the majority of cases. However, it is unclear when this sign develops and it is not infrequent that the initial scan is reported as normal but becomes clearly abnormal over a few months. Whether all patients ultimately develop the sign is unknown as serial scanning has not been undertaken in sufficient numbers of patients. In addition, the amygdala often gives high signal return on FLAIR and DWI, which is most apparent in the cortical nucleus and its anterior–medial extension. Images obtained at b3000 result in more obvious abnormalities in the pulvinar; interestingly, this is not a reflection of restricted diffusion but due to lengthening of T2, a finding consistent with extensive gliosis rather than spongiform change in this region.

IPD cases, in general, show no significant signal abnormality apart from those with a clinical phenotype that is similar to sCJD, when the imaging may also show abnormalities in keeping with this diagnosis. Recently, an E200K patient had a scan with pulvinar sign. Atrophy of either the cerebral cortex or cerebellum is the only consistent feature in IPD. Interestingly, abnormal signal return from the cerebellum does not occur. There are no series of patients with spinal cord imaging.

Additional experimental imaging techniques such magnetic transfer ratios (MTR), short echo time proton magnetic resonance spectroscopy (H^{1-} MRS) and cortical thickness mapping may well be useful in diagnosis and, particularly, monitoring disease progression. MTR are reduced in the deep nuclei and cortical grey matter in a variety of types of CJD, and from experiments on autopsy specimens of vCJD cases, this appears to be related to spongiform change rather than gliosis. There appears to be a good correlation between cognitive and neurological function and the reduction in MTR. H^{1-} MRS demonstrates

increased myo-inositol to creatine (MI/Cr) ratios and decreased N-acetylcysteine to creatine (NAA/Cr) ratios in the basal ganglia and thalamus in patients with inherited prion diseases. Observed increases in MI/Cr over time in the basal ganglia may prove useful as in monitoring disease activity. Cortical thickness mapping can measure the amount of grey matter in different areas of the cerebral cortex. This has been used to show a striking difference between patients with the 6-OPRI, mutation who have widespread diminution of cortical thickness, compared to those with P102L mutation and this correlates with the psychometric deficits. Further developments of sectional imaging will no doubt improve sensitivity and specificity for the diagnosis of CJD.

Electroencephalography

The EEG is abnormal in the majority of symptomatic patients with CJD. The most common abnormality is slowing of the background rhythm with predominant theta waves and loss of the normal alpha rhythm in many.

In sCJD, a characteristic abnormality is repetitive (>5) bi- or triphasic periodic complexes occurring at 0.5–2 s intervals with <0.5 s variability between complexes and distributed widely over the cortex. They occur in up to 73% of patients with the codon 129MM genotype at some time during the evolution of the disease. However, the sensitivity declines if only a single EEG is obtained. The prevalence of periodic complexes increases with the age of the patient but decreases with disease duration. This abnormality occurs most frequently if myoclonus is present and there is phase locking between the complexes and the myoclonic jerks in many where the myoclonus is of cortical origin. This can be seen in the raw record if an electrode is placed over the affected part although back averaging may be required convincingly to demonstrate this phenomenon.

Periodic complexes are less frequent in sCJD patients with other polymorphisms at codon 129, especially valine homozygotes. The specificity of such complexes is fairly high but they do occur with a wide range of pathologies, including those that mimic CJD such as metabolic disorders, especially hepatic coma, other neurodegenerative diseases and encephalitides, as well as stroke and tumors, conditions less likely to be confused clinically with CJD.

Epilepsy occurs in patients with sCJD and is said to be more common in some inherited types of CJD (E200K). It is uncommon in other forms of prion diseases. The majority of fits are major generalized convulsions. The EEG shows the typical changes associated with major convulsions if obtained during a fit and decreased activity post ictally. It may be difficult to separate periodic complexes from epileptic activity. Intravenous diazepines may help to distinguish the two with epileptic activity typically responding, but this technique does not unequivocally distinguish between the two types of discharge.

Nerve Conduction Studies

Peripheral nervous system involvement is not common in prion diseases. However, some of the inherited diseases do have abnormalities. The E200K mutation is also associated

with a mixed axonal and demyelinating neuropathy in some cases. P102L patients also have clinical evidence of loss of thermal sensation on objective testing, but this could well be centrally determined as peripheral nerve conduction and threshold tracking are normal.

Occasionally, there is evidence of lower motor neuron destruction with fasciculation, fibrillation, and small compound muscle action potentials. It is unclear how often this occurs, and in which patients, but it does appear to be rare.

Cerebrospinal Fluid Examination

In all types of prion disease, the CSF typically has a normal cell count of 0–2 cells/mm^3. A pleocytosis suggests an alternative diagnosis, particularly an inflammatory disorder. Total protein level is usually normal or only modestly elevated, and there is no evidence of intrathecal immunoglobulin synthesis.

The 14–3-3 proteins comprise a large family of intracellular proteins found in all eukaryotic cells, and constitute about 1% of the total protein content of brain neurons. They are found in the CSF in a variety of conditions where there is rapid and extensive neuronal destruction. They are detected using a qualitative assay, giving a positive, negative, or "weak positive" result. The 14–3-3 assay is included in the World Health Organization's diagnostic criteria for sporadic CJD (sCJD). The assay is typically positive in classical, rapidly progressive sCJD, with a sensitivity of 90–95% for the MM1 subtype. However, it is less sensitive for longer duration cases, for younger patients, and for the acquired and the more slowly progressive inherited prion diseases. It is positive in only about 40% of cases of variant CJD.

Interestingly, successive studies over the years have tended to show a reducing sensitivity of the 14–3-3 assay for CJD. This may well be related to the increasing recognition and inclusion of cases with atypical, more slowly progressive clinical features leading to more "false-negative" results in recent studies. There is some evidence that the 14–3-3 assay is more sensitive when performed at later stages of disease. It has therefore been suggested that in cases where there is continuing diagnostic uncertainty, there may be a role for repeating the assay at a later stage if the first is negative. However, in practice, this is often superseded by a decision either to obtain a definitive tissue diagnosis, or that further investigations are no longer appropriate.

The overall specificity of the 14–3-3 assay for prion disease is quite low, at around 70–80%. In patients with clinically suspected CJD, false-positive results occur most commonly when the final diagnosis is inflammatory or malignancy (including CNS tumors and paraneoplastic syndromes). Other causes of a positive result include recent stroke, infective encephalitis, and subacute sclerosing panencephalitis (SSPE), but these diagnoses can usually be ruled out clinically or on the basis of other tests. A raised CSF cell count has been shown to be highly significantly associated with an increased false-positive rate, and should always prompt investigation for other causes. The specificity is not high enough for the test to have a role in screening unselected patients with dementia for prion disease.

S100b comprise a large family of calcium-binding cytoplasmic proteins found in glia in the CNS, as well as widely outside the CNS. They are detected using a quantitative assay.

Their levels are raised in the CSF in a large number of destructive diseases of the nervous system where there is extensive gliosis, including CJD. As with the 14–3-3 proteins, they are more likely to be raised in rapidly progressive disease, where sensitivity is around 90%. However, the specificity is even lower than for 14–3-3, and in practice, they rarely add any further useful diagnostic information.

Tau is a microtubule-associated protein, which is found in increased levels in the CSF when there is destruction of neurons. In some disease states, the Tau protein becomes hyperphosphorylated. The levels of total Tau and hyperphosphorylated Tau can be measured using quantitative assays. The total Tau (T-Tau) level in the CSF is elevated in a wide variety of degenerative CNS disorders, including Alzheimer's disease. It is increasingly used, in combination with CSF $A\beta(beta)_{42}$, as a diagnostic marker for Alzheimer's disease. In sCJD, it can be elevated to a much higher level than in the more common slowly evolving degenerative disorders. If a high threshold is used, the sensitivity is again high for rapidly progressive CJD, and the specificity seems to be similar to that of the 14–3-3 assay. It has been suggested that CSF levels of hyperphosphorylated Tau (P-Tau) are particularly elevated in variant CJD (vCJD), such that the ratio of P-Tau to T-Tau is higher in vCJD than sCJD. This may have a role in helping to distinguish between these two conditions.

Various other proteins have been considered as CSF markers for CJD, including neuron-specific enolase, prostaglandins, and interleukins. However, these are less sensitive and specific than those above, and have little clinical utility. The limited data available on $A\beta(beta)_{42}$ in CJD suggest that it has little diagnostic significance.

Tissue Diagnosis

The only way to obtain a definite diagnosis of CJD, other than the inherited forms, is to obtain tissue. In sCJD, brain biopsy or autopsy are required. In vCJD, the lymphoreticular tissue is involved early in the evolution of the disorder. In the experience of the National Prion Clinic, tonsillar biopsy is diagnostic in all cases with symptomatic vCJD. It is not known when the tonsillar tissue first becomes involved, but based on extrapolation from animal studies, it is probably relatively early in the incubation period.

Pathology

sCJD

Macroscopically, the cerebral hemispheres in sCJD are often of normal appearance although atrophy occurs in long-standing cases.

The characteristic microscopic features of sCJD on hematoxylin and eosin staining are spongiform degeneration of the cerebral cortex, neuronal loss, and gliosis associated with amyloid deposition in some cases (Fig. 10.4). Spongiform change begins in the dendrites, especially the presynaptic zones, and expands to form vacuoles in the neuropil. Typically, the vacuoles are 2–20 μm but can expand into much larger structures. The vacuoles have

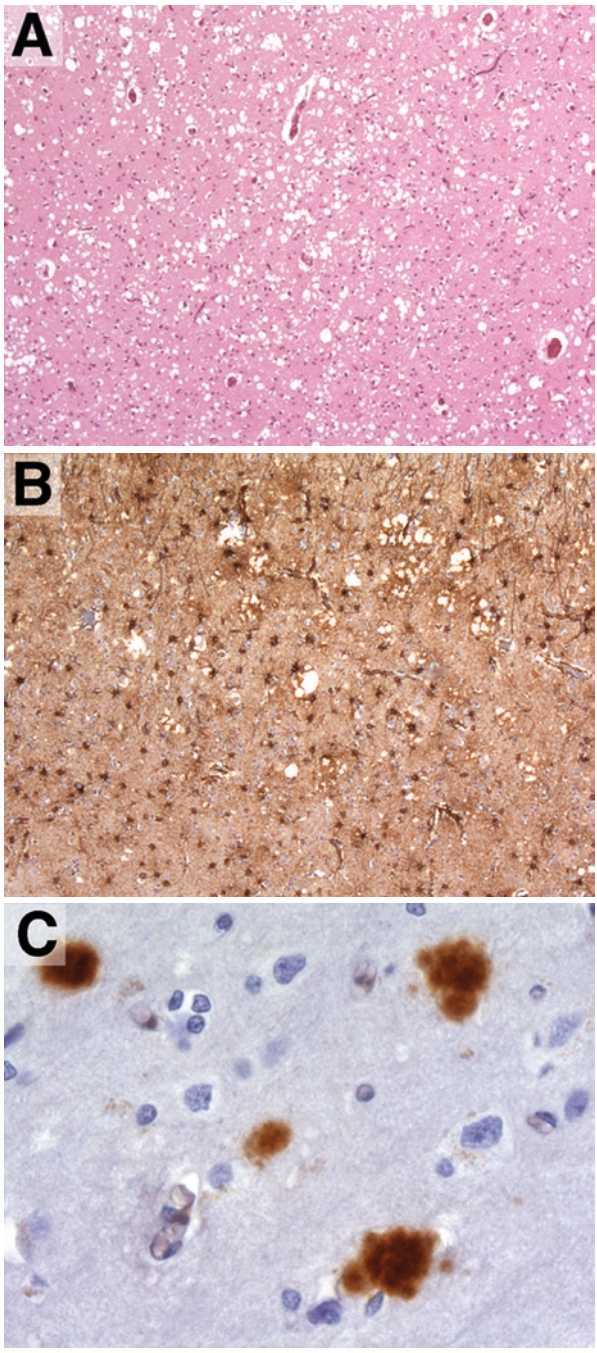


Fig. 10.4 Examples of prion pathology. (**a**) Spongiform change in sCJD (H&E). (**b**) Gliosis and spongiform change in sCJD (GFAP). (**c**) Prominent plaques in kuru (ICSM35). (**d**) Perineuronal PrP staining in sCJD (ICSM35). (**e**) Perivacuolar PrP staining in sCJD (ICSM35). (**f**) Synpatic PrP staining in sCJD (ICSM35). (**g**) and (**h**) Florid plaques in vCJD (H&E, ICSM35). (**i**) PrP deposition in follicular dendritic cells in a tonsillar biopsy specimen in vCJD (ICSM35) (Courtesy of Professor Sebastian Brandner, UCL Institute of Neurology)

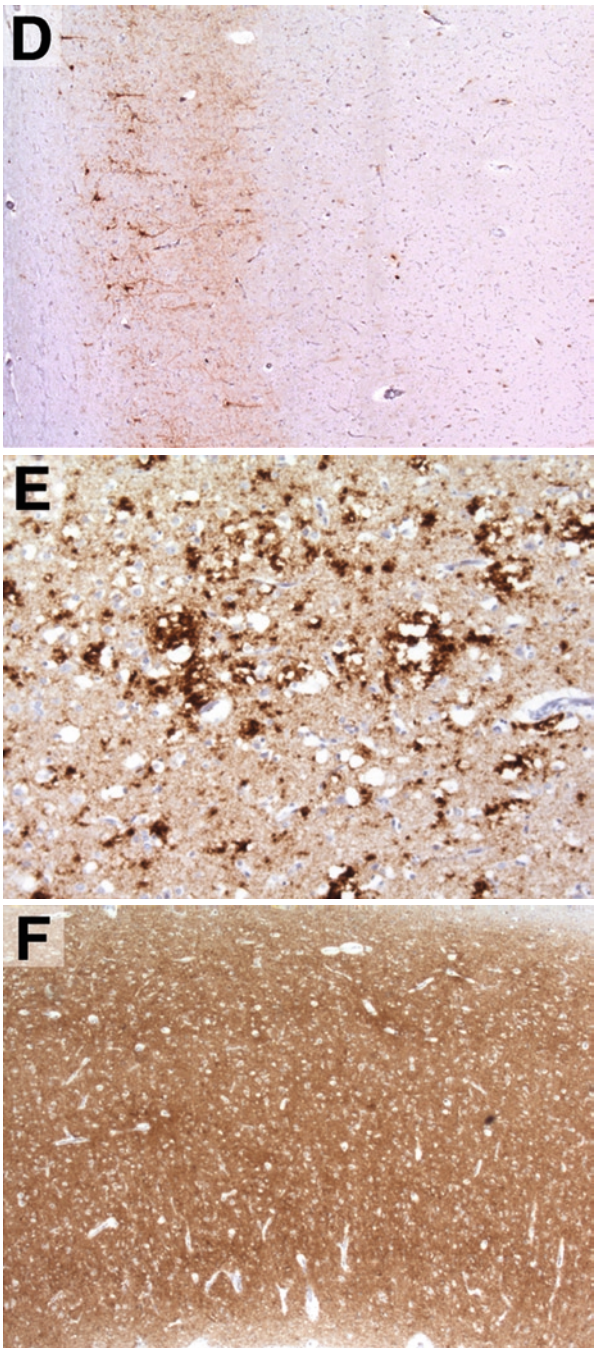
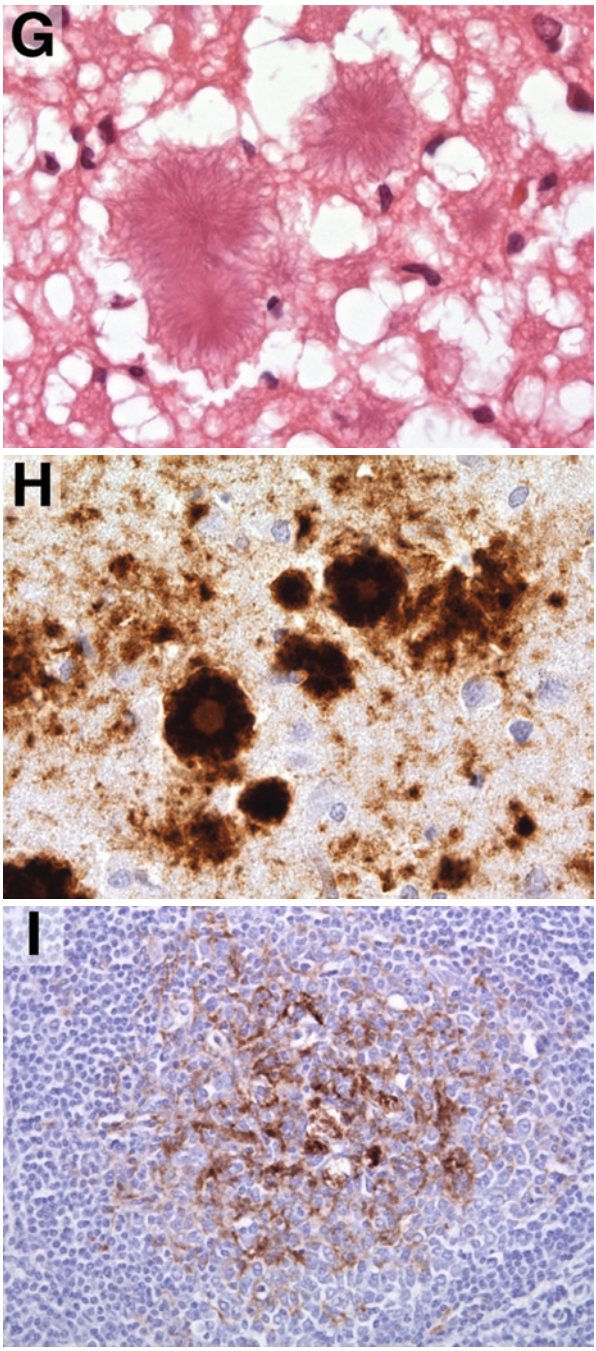


Fig. 10.4 (continued)

Fig. 10.4 (continued)



numerous membranous fragments in them on electron microscopy. The cortical layers four and five are most affected in the typical case with additional pathology in the basal ganglia, thalamus, and cerebellum. There may be substantial neuronal loss that increases with time and may vary considerably between different brain regions.

Understanding the microscopic pathology has been greatly enhanced by the development of specific PrP stains, which particularity visualize the synaptic depositions of abnormal PrP, which is undetectable in H&E stains. Non-plaque deposition occurs in all cases of sCJD. The deposits can be granular synaptic, perineuronal decorating the neurons, or perivacuolar; the type of deposition depends on the subtype of sCJD and usually one type dominates (Fig. 10.4). In some cases, there are so-called mini-plaques, which occur particularly in iCJD.

PrP immunostains also demonstrate amyloid plaques better, and can show other abnormalities not apparent on routine stains. In sCJD, they occur in about 10% of patients; they are very small, have a dense core with a fibrillary halo, and may assume a substantial size when they form plaques similar to those found in kuru (Fig. 10.4).

Tau inclusions are common. and they co-localize with prion amyloid. The morphology of Tau deposits is different to that seen in Alzheimer's disease. In the latter, the deposits are thread-like, whereas in CJD they form minute rods.

The pathology in the spinal cord and nerve roots is less well documented. Few autopsy studies have been done in sCJD, but these do show scanty deposits of PrPsc in the dorsal root ganglia in some cases.

Pathology in Other Forms of CJD

In addition to varying degrees of cerebral cortical atrophy, cerebellar atrophy occurs in kuru, iCJD, vCJD, and Gerstmann–Sträussler–Scheinker syndrome (GSS) and there is striking thalamic atrophy in the insomnias. The distribution of pathology is dependent on the type of CJD. In vCJD and the insomnias, thalamic damage is most prominent while in Gerstmann–Sträussler–Scheinker disease (P102L), the cerebellum is most involved. Neuronal loss and gliosis occur in a similar distribution. It should be emphasized that these changes are variable between patients even in those with the same phenotype. Interestingly, spongiform change is not found in some inherited forms of CJD.

Some inherited disorders such as GSS (P102L) have numerous plaques in the forebrain and the cerebellum, which have a multicentric appearance while those patients with the 6-OPRI mutation have a pathognomonic linear arrangement in the cerebellum perpendicular to the cerebellar surface. In contrast, patients with fatal familial insomnia have no amyloid plaques, but only diffuse, dense amyloid deposits, resembling primitive plaques. vCJD patients have numerous large florid plaques with a characteristic pattern of fibrillary structure surrounded by spongiform change (Fig. 10.4).

Tau inclusions occur in all types of CJD and are particularly prominent in the vicinity of amyloid plaques in vCJD in spite of the young age of the patients. They co-localize with prion deposition as in sCJD and have a similar morphology.

Information on spinal cord and spinal root pathology is sparse. In iCJD with P102L mutation, there is loss of fibers in the corticospinal, spinocerebellar and gracile tracts.

Patients carrying the E200K mutation sometimes have a mixed axonal and demyelinating sensorimotor neuropathy.

There are a group of vascular prionopathies, of which the Y145X mutation is the best described, in which there is no spongiform change in the CNS but marked cerebral atrophy associated with features of a tauopathy. The striking feature is deposition of prions in the medium-sized arterial walls of the brain and meninges.

While the pathology in sCJD, the insomnias, inherited disease, and some of the iatrogenic disease (growth hormone and dural implantation), the abnormalities are confined to the CNS including the spinal cord, this is not the case with vCJD or kuru. These diseases have systemic pathology, notably in the lymphoreticular system, including the spleen, and in this respect are similar to cervid chronic wasting disease (CWD), ovine and caprine scrapie, and to a lesser extent BSE. Prion staining is positive early in the course of the disease in animals and precedes the encephalopathy, a situation that almost certainly applies to man. The deposition in the lymphatic tissue is the basis of tonsil biopsy for diagnosis in vCJD where all definite cases have been positive (Fig. 10.4).

Molecular Classification

Since the advent of prion protein gene (*PRNP*) analysis and prion protein analysis by Western blotting, a molecular classification of sporadic CJD has emerged. Although the subdivision of sCJD in this way is of interest from a research perspective, to date, it has little clinical relevance. Nevertheless, some new facts have emerged. A polymorphic genetic variant at *PRNP* codon 129, between methionine and valine is one factor that is particularly important in determining the PrP^{Sc} type. Second, two classifications have been developed in which the genotype at codon 129 is combined with prion protein electrophoretic pattern on Western blot after partial digestion with protease, viz, that of Parchi and colleagues, or the London (MRC Prion Unit). The patterns of PrP staining after Western blot (Fig. 10.5) are different because of differential protease cleavage and differing predominance of three glycosylation states. The situation is further complicated by the sensitivity of Western blot protocols to changes in the experimental conditions and the frequent coexistence of types when multiple brain areas are examined.

As a starting point in the following discussion, the London classification will be used and this is compared to the Parchi typing. In general, homozygosity at codon 129 causes a more aggressive disease. Type 1 patients, who are 129MM, tend to have the classical CJD phenotype with a mean age of 55–60 years and survival of weeks. Type 2 patients who are 129MM differ in that the course of the disease is usually longer (a few months) and they are younger with a mean age of onset of about 50 years, although ascertainment may be an influence here. In the Parchi classification, there is no distinction between London types 1 and 2, thus giving a wider range of age and duration in their type MM1.

The most frequent type of sCJD in the London series is type 2 MM, comprising some 45% of all cases, while about 16% were type 1 MM. The number of homozygotic VV cases is smaller in all series, making accurate description of the clinical picture less reliable. Nevertheless, type 2 VV and type 3 VV (type VV2 Parchi) tend to have aggressive

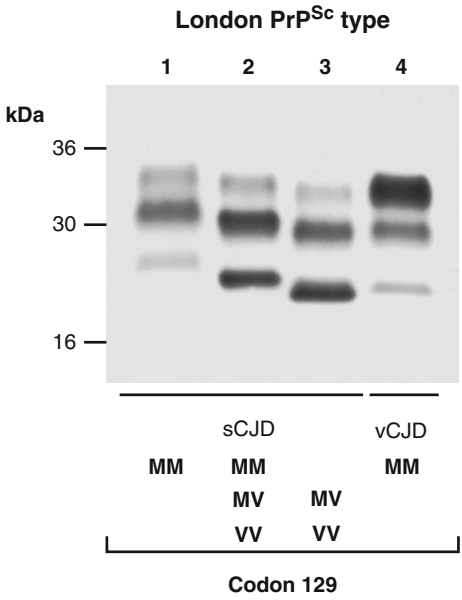


Fig. 10.5 Western blot of four patient brain samples prepared by homogenization in phosphate buffered saline, partial protease digestion using proteinase K, and immunoblotting. Three PrP immunoreactive bands are seen related to three glycosylation states (un-, mono-, and diglycosylated). Types 1–3, distinguished by molecular weight, are seen in sCJD with restriction to certain codon 129 genotypes (*below*). Type 4, distinguished from sporadic types by the predominance of the diglycosylated (*top*) band, is exclusively seen in vCJD

disease. Certain rare forms of sCJD appear to be most distinct from the others. Having MV at codon 129 causes a less aggressive disease in general, with longer survival, and the patients can initially mimic other neurodegenerative disease such as the frontotemporal dementias or have a marked apraxia at onset, and little or no myoclonus.

One final, but very rare, form of sCJD is sporadic fatal insomnia, a condition that is associated with autonomic features. The cases are classified as Parchi MM2 (thalamic) type. vCJD has a unique Western blot appearance termed type 4, with a predominance of the diglycosylated band (Fig 10.5).

However, despite what is dogmatically stated above, there remains considerable doubt about the significance of these classifications. Proteinase digestion of PrP^{Sc} with proteinase K interrogates a small part of the protein towards the N-terminus, cutting at around glycine 82 and serine 97, and tells us little about the conformation towards the carboxyl end. The precise pattern produced is dependent upon the conditions of digestion, antibodies applied, and assumes uniform distribution of a single isomer of PrP^{Sc}. In the 129MM group, 40% of the patients have two isoforms present by some estimates, and presumably greater heterogeneity will emerge when more sophisticated analytical systems have been developed.

Development of a molecular classification for human prion disease may have implications for epidemiological research into the causes of sporadic CJD, whose etiology remains obscure. Spontaneous conversion of PrP^{C} to PrP^{Sc} as a rare stochastic event, or somatic mutation of *PRNP*, resulting in expression of a pathogenic PrP mutant, are plausible explanations for sporadic CJD. However, other causes, for at least some cases, including environmental exposure to human prions, or exposure to animal prions may also be important. In this regard, the number of prion strains causing sheep scrapie has yet to be established and epidemiological data cannot exclude this as a cause of a minority of cases. As future research

begins to provide a more precise understanding of the origins of human prion disease, this will facilitate reanalysis of epidemiological data, and is likely to reveal important risk factors that might have been obscured by analyzing sporadic CJD as a single entity.

Therapy

There is no therapy that has been shown convincingly to alter the course of any form of prion disease. One trial of flupertine, in which a placebo was also given, claimed a beneficial effect on certain clinical scores but not mortality; this trial was small and of borderline statistical significance. The largest trial to date was PRION-1, a patient preference trial, in which quinacrine had no significant effect on survival or any clinical assessment variables. There have been a number of anecdotal reports concerning tetracycline derivatives claiming benefit but none is convincing. The glycosaminoglycan pentosan administered intraventricularly to animal models of prion disease has been shown to have a small beneficial effect. It has been given to a small number of patients with a variety of types of CJD and long survival has been described in some vCJD patients. However, confounding factors such as parenteral feeding and aggressive management of coincident infection may partially or completely account for this increased survival.

Administration of monoclonal antibodies or small molecules, which interfere with conversion of PrP^{c} to PrP^{Sc} have been studied in trials in mouse models of CJD and show some benefit if given prophylactically during the incubation period after intraperitoneal injection of prions.

Some types of symptomatic therapy have been beneficial. This particularly applies to myoclonus (levetiracetam, valproate, and clonazepam), aggression (risperidone), agitation (diazepines), and hallucinations (centrally acting anticholinesterases). Other symptoms such as insomnia and rigidity are usually resistant to treatment with the standard agents. Supportive therapy, including various forms of parenteral nutrition and vigorous treatment of intercurrent infections may prolong survival but have little effect on quality of life measures.

Good nursing care in conjunction with symptomatic therapy and liaison with carers and relatives is mandatory in these diseases.

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Medical Mimics of Neurodegenerative Diseases

11

Lewis P. Rowland and Orla Hardiman

Abstract Mimic syndromes may differ from a neurodegenerative condition not only in natural history with periods of stability or even spontaneous improvement, but also because the mimic may be treatable. Careful attention to history and clinical examination are required to ensure that important clues to a mimic syndrome are not overlooked. Atypical features, failure to progress, or the development of new or atypical signs should trigger a full reevaluation and a search for a mimic syndrome.

Keywords Motor neuropathy • Reversible cognitive impairment • Conversion disorder • Autoimmune disease • Parkinsonism

Introduction

In this chapter, we consider syndromes that resemble neurodegenerative disorders but differ in some essential way. It is important to recognize these mimic syndromes, which may differ from a neurodegenerative condition not only in natural history with periods of stability or even spontaneous improvement, but also because the mimic may be treatable. Clinical examination and judicious use of ancillary studies, as described in each chapter of this book, usually exclude the mimic syndrome, as described in the pages that follow.

Mimics of Amyotrophic Lateral Sclerosis (ALS)

Benign Fasciculation

Blexrud et al. introduced this term in 1993, identifying the benign future of 121 people with fasciculation with no other abnormality on examination or in electrodiagnostic studies. Follow-up by telephone 2–32 years after this diagnosis, not one of the 121 patients had

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developed symptomatic ALS. As indicated by Eisen and Stewart in 1994, in response to that report, however, fasciculation may be the first manifestation of ALS. Blexrud et al. responded that those patients usually have "weakness or incoordination" in addition to the visible twitching and, additionally, other EMG abnormalities are usually present by that time. Others, including de Carvalho and Swash, reported similar cases in 2004. Bruyn et al. described a patient who had PLS for 27 years before lower motor neuron signs appeared.

Multifocal Motor Neuropathy with Conduction Block

Another important consideration in the differential diagnosis of ALS is multifocal motor neuropathy with conduction block (MMNCB).

ALS is only rarely reversible spontaneously and almost always progresses inexorably to death, regardless of therapy. Neither ALS nor MMNCB responds to corticosteroid therapy or plasmapheresis. In contrast, however, MMNCB improves with intravenous immunoglobulin therapy (IVIG) in doses of 400 mg/kg body weight over 5 days. Efficacy has been proven in four randomized controlled trials but there is no consensus about dosage or frequency of treatments to maintain the original improvement. Benefit may be seen within a week of the first series of treatments, and lasting for a variable number of weeks before symptoms recur. Disability may be severe, but the disease is only rarely fatal.

Demonstration of conduction block in nerve conduction studies is the sine qua non for the diagnosis. Antibodies against GM1 are found in up to 80% of cases. Clinical clues to the presence of MMNCB include onset before age 50, men affected three times more often than women, hands affected more than legs and bulbar innervated muscles spared, stuttering course and distribution of weakness suggesting mononeuropathy multiplex, more weakness than atrophy, visible fasciculations in about half the patients, and no cutaneous sensory loss. Tendon reflexes are usually absent but are active in some cases. Hoffmann and Babinski signs are rarely seen. The CSF protein content is usually normal or only slightly elevated up to 80 mg/dL (in contrast to the values near or above 100 mg/dL seen in chronic inflammatory demyelinating polyneuropathy).

Multifocal Acquired Motor Axonopathy

Conduction block is not present in all patients who have the clinical features of motor neuropathy. These patients also respond well to IVIG therapy. In other words, this disorder is a clinical look-alike for MMNCB but lacks the defining physiological characteristics in nerve conduction studies. Moreover, an axonal motor neuropathy is difficult to differentiate from a disease of the cell body itself, i.e., the progressive muscular atrophy (PMA) form of motor neuron disease, although multifocal acquired motor axonopathy (MAMA) is more likely to be subacute than PMA, which is slowly progressive.

Brachial Amyotrophic Diplegia (BAD)

The term brachial amyotrophic diplegia (BAD) has been used to describe a slowly progressive lower motor neuron disorder affecting proximal arm muscles. The wasted arms

hang limply at the sides giving the person the appearance of "a man in a barrel." Another moniker is the "flail arm syndrome." In most cases, there is no obvious cause but reports have implicated HIV or HTLV-1 infection. In one case, an axial view of the cervical spinal cord showed high signal in the anterior horns of the gray matter. Sjögren syndrome was held responsible for one patient with BAD who improved with combination therapy that included prednisone, plasmapheresis, and IVIG.

Cervical Spondylotic Myelopathy

The clinical manifestations of cervical spondylotic myelopathy can rarely mimic ALS. Observations from the Irish and Scottish Registers of ALS suggest that cervical spondylotic myelopathy is more likely to show slowly progressive wasting of the arms and hands plus spastic diplegia. However, there have been few documented reports of visible fasciculation. Also, the rate of progression is slower than in ALS, and the condition may be more symmetric than in ALS. Key clinical features identified by the Irish and Scottish Registers that raised the possibility of cervical myelopathy included the presence of upper motor signs caudal to lower motor signs, early bladder involvement, the absence of bulbar involvement and the relatively slow progression. Neuroimaging is helpful in making the diagnosis. However, some people over the age of 40 have spondylosis with cord compression and may even show high signal within the cord, but they are asymptomatic. Also, 5–10% of people with documented ALS have had cervical decompressive operations without benefit.

Misdiagnosing ALS as cervical myelopathy is more common than the converse.

HIV-Associated ALS

Brachial diplegia has been reported in HIV-positive patients. In 2006, Verma and Berger raised doubts about the possibility that HIV might cause ALS because HIV is not a neurotropic virus and because, in comparison with HIV-negative ALS patients, the reported HIV-infected patients were younger, the course of ALS was more rapid, had atypical features and, perhaps most important, the ALS improved in some of those treated with HAART for the HIV infection. On the other hand, about half of the treated HIV-infected patients succumbed to ALS. They concluded that "the causal relationship remains uncertain." Primary lateral sclerosis may also appear with HIV infections, but is rare.

Other Causes of Reversible Motor Neuron Disease

Motor neuron diseases usually progress inexorably to death. However, cases of complete resolution of sporadic motor neuron diseases with upper and lower motor neuron signs have been reported. The underlying pathology is unclear and such cases are extremely rare: no spontaneous resolutions of ALS have been noted among over 1400 population-based cases collected by the Irish ALS Register over 16 years. West Nile virus infections can cause a reversible poliomyelitis that differs from the others in having a much more acute course. Electrical injury, HTLV-1 infection, and lead intoxication can also cause reversible motor neuron syndromes.

Reversible Causes of Cognitive Decline

Delirium

This term implies an "acute impairment of cognition with a fluctuating course," including a change in the level of consciousness. Impaired cognition, the acute and transient course, and also the many evident causes of delirium including metabolic, infectious and toxic, differentiate this cerebral dysfunction from both neurodegeneration and from dementia.

However, patients with an underlying dementia are more susceptible to delirium in the context of infection, metabolic changes, or drugs (see also Chaps. 3, 4, 5, and 12).

Mild Cognitive Impairment

Alzheimer disease (AD) classically presents with both subjective and caregiver reports of memory dysfunction, which is subacute in onset but progressive. The condition tends to evolve with the pathological recruitment of other networks including the dorsolateral prefrontal cortex, causing executive dysfunction, and language networks, causing word finding problems. In clinical practice, most physicians deal regularly with patients with subjective complaints in any or all these domains, the majority of whom do not have a neurodegenerative disorder. In many cases, depression, anxiety, or psychosocial stress can play a significant role. The lack of objective concern in family and caregivers and the performance on standardized delayed word recall testing are usually enough to reassure. Nevertheless, there are some patients with mild subjective symptoms, without any negative effective on work or social performance who score poorly on testing and may have what we call "mild cognitive impairment" (MCI). This condition is believed to be in excess of what might be expected with normal aging and is a risk factor for the development of clinical dementia. The exact risk is unclear but about 80% of MCI patients progress eventually to AD (see also Chap. 3). The remaining 20% either remain stable or may even improve, two features that point toward a mimic syndrome rather than a neurodegenerative one. The mechanisms underpinning stable or improving MCI are unclear.

Drug-Induced Encephalopathy

Medications are listed as the most common cause of reversible "dementia" but some drug effects must also include obtundation in addition to cognitive decline. That would be defined as delirium rather than dementia. Common causal drugs include anticholinergics, tricyclic antidepressants, antipsychotics, bismuth (in the form of bismuth subsalicylate, available as an over-the-counter medication), bromides, antihistamines, antiepileptics, benztropine, and lithium (see Table 11.1).

The evaluation of a patient with cognitive impairment should therefore include the medication history, including a complete review of all over-the-counter medications.

Table 11.1 Common drugs that can cause cognitive impairment

Drug	Effect
Amitriptyline	Anticholinergic properties: sedation, confusion, delirium, or hallucinations
Anticholinergics	Sedation, confusion, delirium, or hallucinations
Anticonvulsants	Confusion, sedation, elevated ammonia
Valproate Levetiracetam	Confusion, hallucinations
Antihistamines	Anticholinergic properties: sedation, confusion, delirium, or hallucinations
Antipsychotics	Confusion, sedation
Antispasmodics (GI)	Anticholinergic properties: confusion, delirium, or hallucinations
Baclofen	Hallucinations, impaired memory, catatonia, mania
Barbiturates	Drowsiness, lethargy, depression, severe CNS depression
Long-acting benzodiazepines	Sedation, drowsiness, ataxia, fatigue, confusion, weakness, dizziness, vertigo, syncope, psychological changes
Bismuth subsalicylate	Encephalopathy resembling dementia, encephalopathy resembling CJD
Chlorpropamide	Hypoglycemia, which can result in altered mental state (confusion, amnesia, coma)
Digitalis	Headache, fatigue, malaise, drowsiness, and depression
H2 receptor antagonists	Confusion, hallucinations, agitation
Indomethacin	Headache, dizziness, vertigo, somnolence, depression, fatigue
Lithium	Confusion, sedation, movement disorder
Methyldopa	May exacerbate depression
Muscle relaxants	Anticholinergic properties, weakness, confusion, delirium, or hallucinations
Pentazocine	Confusion, hallucinations, dizziness, lightheadedness, euphoria, and sedation
Reserpine	Depression, sedation

Epilepsy

Nonconvulsive status epilepticus or clusters of nonconvulsive seizures may be focal onset or be part of a generalized epileptic syndrome. Occasionally, the only clinical manifestation may be altered mental status that appears more like delirium than dementia. Some patients, however, especially the elderly, may maintain such vigilance that the patient merely appears cognitively impaired. This has been called “epileptic pseudodementia” a

rare disorder that can be diagnosed only in the presence of unequivocal prolonged epileptiform discharges in the electroencephalogram (EEG) of the cognitively impaired patient. Treatment is that for other forms of nonconvulsive status but as the term epileptic pseudodementia implies a prolonged course, the prognosis for eventual recovery is poor.

Subdural Hematoma

Chronic subdural hematoma is the most frequent type of intracranial hemorrhage and may occur in the elderly following minor trauma. Patients may show a slow decline in cognitive function with confusion, impaired memory, headache, and motor deficits or aphasia. Chronic subdural hematoma should therefore be considered in the differential dementia of cognitive impairment. Diagnosis is by neuroimaging, and treatment is surgical evacuation.

Sleep Apnea

Sleep apnea can be associated with memory loss. Patients may present with symptoms suggestive on cognitive decline, and can account for up to 8% of patients attending a young onset dementia clinic. Symptoms include daytime somnolence, snoring, and morning headache. The reversible cognitive decline is thought to relate to sleep deprivation and nocturnal hypoxemia. Diagnosis is made by overnight polysomnography with oxygen saturation monitoring. Treatment is with noninvasive ventilation using a continuous positive air way pressure (CPAP) device.

Neuropsychiatric Conditions Associated with Reversible Cognitive Decline

Depression

Depressive pseudodementia has been defined as a reversible cognitive impairment of the type seen in dementia. It is associated with delusions and a history of affective illness.

There are few studies of the frequency of depressive pseudodementia, although rates as high as 18% have been reported in specialist dementia referral centers.

Patients with cognitive impairment and concomitant depression should be treated aggressively with antidepressants. However, clinically depressed patients with signs of pseudodementia are at higher risk of developing irreversible dementia in 2 or more years. This suggests that depression with reversible cognitive impairment could be a prodromal phase for dementia rather than a risk factor, and that patients with depressive pseudodementia should be followed closely.

The prevalence of depression in people with Parkinson disease varies in different reports from 20% to 80% and often starts before the motor signs appear (see also Chap. 5). This problem of diagnosis is compounded because some syndromes are common in both conditions: bradykinesia, bradyphrenia, sleep and autonomic disorders, anorexia and weight loss, apathy, and loss of libido. However, the fundamental signs of parkinsonism

(include tremor, cogwheel rigidity, loss of dexterity, deterioration of handwriting, frequent falls, or loss of postural control) are not seen in patients with depression.

Severe depression may also mimic a predominantly apathetic presentation of FTD; cognitive testing should help distinguish the two with dysexecutive features much more prominent in the dementia (see also Chap. 6).

Catatonia

This complex neuropsychiatric syndrome may be seen with either a primary psychiatric disorder or with a general medical condition. Catatonia may mimic other neurodegenerative conditions including FTD and Parkinson disease (Table 11.2). The acute onset of catatonia, with alternating agitation, stupor, and dysautonomia may respond to high-dose lorazepam or electroconvulsive therapy.

Conversion Disorder

Conversion disorder is characterized by loss or alteration of physical function that suggests a physical disorder, but that has a psychological basis. Although conversion disorders are more likely to occur in younger patients – onset is unusual after 35 years of age, symptoms can mimic neurodegenerative disease. Common psychogenic mimic symptoms include limb paralysis, diverse movement disorders, gait disturbances, blindness, and deafness. The patient's behavior seems inappropriately accepting of or indifferent to the serious physical symptoms.

The *Diagnostic and Statistical Manual of Mental Disorders* (*DSM IV*) lists six criteria that must be filled for the diagnosis of conversion disorder (Table 11.3). All neurological and medical causes must be excluded.

Late Onset Psychiatric Disease

Late-onset psychiatric disease may mimic frontotemporal dementia.

Table 11.2 Abnormal signs in catatonia

Motor	Speech and language	Behavioral	Autonomic	Laboratory
Akinesia Bradykinesia Parkinsonism Tremor Stupor Primitive Reflexes Upgoing Plantars Oculomotor signs Tics	Mutism Aphasia Palilalia	Agitation Impaired judgment Impaired insight	Hypertension Pyrexia Diaphoresis Insomnia Tachycardia	Leukocytosis Elevated creatine kinase (CPK) Abnormal EEG

Table 11.3 *DSM IV* criteria for conversion disorder

- Patient has one or more symptom affecting voluntary, motor, or sensory function that suggests a neurological or medical condition.
- Psychological factors are associated with the symptom or deficit.
- Symptom or deficit is not intentionally produced, but is maintained by secondary gain.
- Symptom or deficit cannot be fully explained by a general medical condition, by direct effects of a substance, or as a culturally sanctioned behavior or experience.
- Symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning, or warrants medical explanation.
- Symptom or deficit is not limited to pain or sexual dysfunction, and is not better accounted for by another mental disorder.

Of the three main clinical syndromes of FTD (see Chap. 6), the behavioral variant FTD (bv-FTD), is the one most likely to be confused with a mimic disorder, the others having a more characteristic language dysfunction (semantic dementia). Detailed neuropsychological testing is helpful in distinguishing organic disease from a late-onset psychiatric disorder.

Nutritional Causes of Reversible Cognitive Decline

Wernicke Encephalopathy

This is the result of thiamine deficiency, usually with other nutritional deprivations and often in the context of alcohol abuse. In addition to the cognitive disorder, the full syndrome includes ophthalmoparesis and ataxia. It is also seen with dialysis, after bariatric surgery or prolonged intravenous administration of glucose.

Pellagra

Vitamin B3 deficiency (niacin deficiency) is manifest by dementia, rash, and diarrhea. If unrecognized and untreated, it may be fatal.

Both Wernicke syndrome and pellagra differ from neurodegeneration syndromes in younger age at onset, more acute onset, more rapid progression, and reversibility with replacement therapy.

B12 Deficiency

Whether B12 deficiency causes a dementia-like disorder has been controversial, but it seems to be standard practice to test blood levels routinely and, if values are low, to administer the missing cobalamin. The neurological syndrome ("combined system disease") that accompanies pernicious anemia results from both myelopathy and sensorimotor polyneuropathy. Severity of the disorder is related to duration of symptoms before treat-

ment. Symptoms may include ataxia of gait, distal paresthesias, dementia, psychosis, or visual loss. Many individuals with B12 deficiency are asymptomatic these days but some have one or more comorbid autoimmune diseases. Tendon reflexes may be increased or decreased and upper motor neuron signs may be evident. Distal sensory loss and impaired perception of limb position may be found.

Almost all patients improve with treatment and, in about half, recovery is complete. Dementia has been reversed by treatment even when B12 levels are still in the low normal range.

Toxic Exposures

Many heavy metals, pesticides, solvents, and gasses can lead to neurological deficits that can mimic a neurodegenerative process. For example, manganese toxicity can induce a parkinsonian syndrome, lead and arsenic toxicity can induce an encephalopathy, and chronic inhalation of low-dose elemental mercury is associated with ataxia and cognitive impairment.

The most common toxic exposure is to ethanol. Alcohol abuse is associated with a wide range of neuropsychiatric syndromes including cerebellar degeneration, Wernicke-Korsakoff syndrome, and alcohol-related dementia. Although the concept of a dementia that is directly related to alcohol abuse remains controversial, in the United States, it is estimated that alcohol-related dementia accounts for up to 20% of admissions to state psychiatric facilities. The mechanism of alcohol-associated cognitive decline is poorly understood, and there are no established treatment protocols other than abstinence with psychosocial supports.

Acute exposure to carbon monoxide is one of the most common causes of poisoning requiring admission to hospital. In the United States, the incidence of suspected carbon monoxide poisoning is approximately 1/10,000 per annum. Acute intoxication can lead to encephalopathy and coma. Up to 50% of individuals with carbon monoxide poisoning subsequently develop neurologic, neurobehavioral, or cognitive sequelae. Some patients experience a progressive course, with development of a persistent akinetic-mute state. Other patients experience a delayed relapse after an initial recovery period of approximately 3 weeks. Those with the delayed relapsing course can develop a parkinsonian state with behavioral and cognitive impairment. Brain MRI reveals multiple lesions in the subcortical white matter and basal ganglia, mostly in the globus pallidus, and to a lesser extent in putamen, and caudate.

Diagnosis should be suspected if the partial pressure of blood oxygen is low, in the presence of apparently normal oxygen saturation. Treatment is with hyperbaric oxygen.

Endocrine Causes of Reversible Cognitive Decline

Thyroid Disease

Clinical hypothyroidism may cause cognitive impairment, which can be reversed if treated early. There are no long-term cognitive sequelae in treated hypothyroidism.

Hyperthyroidism can cause tremulousness, chorea, and encephalopathy. Symptoms resolve with treatment.

Hashimoto Encephalopathy

Encephalopathy in people with high levels of antibodies to thyroid antigens (thyroperoxidase and thyroid microsomal proteins) has long been considered a specific syndrome, one likely to respond to prednisone therapy, and called "Hashimoto encephalopathy." Most of the cases with this neurologic syndrome have had Hashimoto thyroiditis. Other autoimmune thyroid diseases have also been described, mainly Graves disease. The pathogenesis of this encephalopathy is still unknown and largely debated. Cerebral symptoms include stroke-like episodes, coma, seizures, subacute cognitive decline, and hallucinations. However, high serum levels of the same thyroid antibodies may be found in many asymptomatic people. Moreover, it has not been proven that the antibodies cause the symptoms (or how they might do so) and steroid therapy may fail in 50% of otherwise typical cases.

The occipital cortex may be especially vulnerable and the "posterior reversible encephalopathy syndrome" (PRES) is sometimes seen with Hashimoto encephalopathy. Some authors have advocated brain biopsy as an important diagnostic test, primarily to exclude Creutzfeldt–Jakob disease.

In 1999, Caselli et al. proposed a more formal name, but the simpler eponym, honoring Hashimoto, has not disappeared. The syndrome is subacute in onset and course, another difference from the chronic features of neurodegeneration.

Paraneoplastic Causes of Cognitive Decline

Cognitive impairment is sometimes seen in patients with malignant tumors, especially small cell lung cancer, lymphoma, thymoma, or testicular cancer (Table 11.4). The complex paraneoplastic syndromes include disordered sleep patterns, hallucinations, behavioral anomalies, orthostatic hypotension, and the Morvan syndrome (neuromyotonia, hypersalivation, hyperhidrosis, and insomnia). The clinical picture is that of limbic encephalitis with manifestations that evolve in days or weeks.

Other features that distinguish these syndromes are imaging abnormalities in the temporal lobes, noninfective CSF pleocytosis, and presence of serum antibodies to the Hu antigen, anti-Ma, and (in the Morvan syndrome) anti-voltage-gated potassium channels (VGKC), as well as other antigens.

Non-paraneoplastic Autoimmune Syndromes

Antibodies to VGKC have been found in several reversible conditions without an underlying neoplasm, but the critical antigen and target of the antibodies is the synaptic protein leucine-rich glioma-inactivated 1 (LGI1). The ensuing condition is an autoimmune synaptic encephalopathy. The clinical features of the associated limbic encephalitis may

Table 11.4 Paraneoplastic neurological syndromes

Antibody	Tumor	CNS syndrome
Hu	Small cell lung carcinoma	Encephalomyelitis, paraneoplastic cerebellar degeneration, limbic encephalitis
CV2 (CRMP 5)	Small cell lung carcinoma, thymoma	Encephalomyelitis, chorea, cerebellar degeneration limbic encephalitis
Amphiphysin	Breast, small cell lung carcinoma	Stiff person syndrome, encephalomyelitis
Ri	Breast, small cell lung carcinoma	Brainstem encephalitis, cerebellar degeneration, opsoclonus myoclonus
Yo	Breast, ovary	Paraneoplastic cerebellar degeneration
Ma2	Testicular	Limbic encephalitis, brainstem encephalitis
Voltage-gated potassium channel	Small cell lung cancer, thymoma	Limbic encephalitis, Morvan syndrome, Creutzfeldt-Jacob-like syndrome
NMDA receptor	Ovarian teratoma	Encephalitis with catatonia, dystonia, psychiatric symptoms
AMPA receptor	Small cell lung carcinoma, thymoma	Limbic encephalitis, psychosis
GABA B receptor	Small cell lung carcinoma	Limbic encephalitis
Glycine receptor	Lung carcinoma	Encephalomyelitis, stiff person syndrome

be the subacute onset of episodic memory impairment, disorientation, and agitation. Movement disorders may also occur, and some patients have hyponatremia.

Treatment with prednisone, intravenous immunoglobulins, or plasmapheresis leads to improvement of about 80% of patients with VGKC antibodies. Although these findings suggest autoimmunity, it is not clear how these or other antibodies damage the brain.

Mimics of Parkinson Disease

Tauopathies, Dementia, and Parkinsonism

Neurodegeneration may cause parkinsonian disorders that can be divided into two major categories based on postmortem histological findings. First, are the synucleinopathies, which include Parkinson disease dementia (PDD), dementia with Lewy bodies, and multiple system atrophy. Disorders in the second group are "tauopathies," including progressive supranuclear palsy and corticobasal degeneration, as well as AD and FTLD. Both categories are multisystem syndromes and both include clinical manifestations of parkinsonism in combination with dementia, oculomotor abnormalities, and other basal ganglia signs (Table 11.5). Therefore, parkinsonism can result from other mimic conditions (see also Chaps. 3, 5, 6 and 9).

Table 11.5 Classification of parkinsonian dementia syndromes

Etiology	Clinical manifestations
Degenerative	
PDD	Parkinsonism precedes dementia
DLB	Visual hallucinations, fluctuating mental state; variable parkinsonism; REM sleep disorder; neuroleptic sensitivity; falls
PSP	Impaired balance, bulbar signs, down-gaze limited
CBD	Dementia with limb apraxia, myoclonus, parkinsonism
MSA cerebellar (OPCA)	Brainstem signs; cerebellar atrophy; oculomotor disorders
MSA parkinsonism	Parkinsonism; autonomic disorders (urinary incontinence; orthostatic hypotension; cerebellar signs)
Prion disorders	Rapidly progressing dementia, ataxia, PRES
Secondary parkinsonism	
Drug-induced	Neuroleptics; metaclopramide, promethazine, valproate
Vascular	Subcortical infarcts, white matter lesions
NPH	Magnetic gait, urinary incontinence, dementia
Hereditable metabolic disorders	
Wilson disease	Abnormal copper metabolism, hepatic failure, Kayser-Fleischer rings
Hallervorden-Spatz (neurodegeneration with brain iron accumulation, NBIA)	Iron deposits in basal ganglia; familial or sporadic with parkinsonism, dystonia, dementia
Basal ganglia calcification (Fahr disease)	Familial, autosomal dominant or recessive dementia with parkinsonism

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CBD corticobasal degeneration, *CBS* corticobasal syndrome, *DLB* dementia with Lewy bodies, *PDD* Parkinson disease dementia, *MSA* multiple system atrophy, *NPH* normal pressure hydrocephalus, *OPCA* olivopontocerebellar syndrome, *PRES* posterior reversible encephalopathy syndrome, *PSP* progressive supranuclear palsy, *REM* rapid eye movement

Drug-Induced Parkinsonism

Fifty years ago, reserpine was found to cause parkinsonian symptoms and signs, an observation leading to the discovery that dopamine content in the brain is depleted in Parkinson disease. Tetrabenazine administration also depletes dopamine and can also cause parkinsonism. Later came the antipsychotic neuroleptics, which act by a different mechanism, blocking receptors for dopamine and also inducing parkinsonism. Some neuroleptic drugs were first thought to cause fewer extrapyramidal disorders and were therefore called "atypical" but that view was proven wrong with continued experience (Table 11.6).

The neuroleptic drugs include haloperidol, chlorpromazine, and metoclopramide. Other pathophysiological mechanisms seem to be involved in the parkinsonian syndromes ascribed to fluoxetine, lithium, amiodarone, or valproic acid (Table 11.4). Mild parkinsonism is sometimes tolerated for the beneficial antipsychotic effects of quetiapine, olanzapine, and risperidone.

Table 11.6 Drugs that can mimic Parkinson disease

- Neuroleptics
- Reserpine
- Tetrabenazine
- Methyldopa
- Alpha methyltyrosine
- Lithium
- Diazoxide
- Physostigmine
- Metoclopramide
- Trazodone
- Meperidine
- Cimetidine
- Cinnarizine
- Flunarizine

Table 11.7 Differentiation of parkinsonian disorders

	Idiopathic Parkinson disease	Drug-induced parkinsonism
Exposure to neuroleptics	No	Yes
Age at onset	>50	<50
Natural history	Progressive	Resolves after discontinuation of neuroleptic
Tremor	4–6 Hz, supination, pronation	Action/postural
Distribution	Asymmetric	Symmetric

Drug-induced parkinsonism can mimic Parkinson disease in all major features including rigidity, bradykinesia, tremor, and postural abnormalities. Bradykinesia is the most common symptom. The condition can be distinguished from idiopathic Parkinson disease by the history of drug exposure in the context of symptom-onset, age at onset, duration of symptoms, the nature of the tremor (pill-rolling tremor is rare in drug-induced parkinsonism), the presence of symmetry (Parkinson disease tends to be asymmetric), and response to anticholinergics (Table 11.7). Neuroleptic-induced parkinsonism usually improves when the offending drug is discontinued, but recovery may take several weeks.

Sometimes, persistent parkinsonism after withdrawal of the offending drug proves to be the onset of true Parkinson disease (see also Chap 5).

Street Drugs and Frozen Addicts

In 1984, Langston and associates described the appearance of parkinsonism in men who were using a home-brewed version of meperidine. The contaminant that proved to be causal was N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The parkinsonian

features were comparable to those seen in PD and were partially responsive to levodopa but seemed permanent. Animal models of PD have been created with MPTP and 5-hydroxytryptophan. Ephedrone (methcathinone) is another intoxicant that can cause parkinsonism in opiate addicts.

Vascular Parkinsonism

Whether cerebrovascular disease can cause parkinsonism is a question that does not go away. Critics point out that both conditions are relatively common and affect elderly people. Even by chance, the presence of either disorder is probably a risk factor for the other. Nevertheless, vascular parkinsonism and Parkinson disease differ in clinical manifestations

Vascular parkinsonism is less likely to include the pill-rolling tremor, and is more likely to affect the lower body, with postural instability, freezing, and falling, as well as hyperactive tendon reflexes with Hoffmann and Babinski signs. These patients are more likely to have had a history of stroke, are more likely to have stroke risk factors (hypertension, smoking, diabetes, hyperlipidemia, heart disease) and are much less likely to benefit from levodopa therapy (Table 11.8).

This debate involved two of neurology's leaders. In a multi-authored 1954 book on parkinsonism, the editor (Lewis J. Doshay) asked Houston Merritt to write the preface. He

Table 11.8 Clinical features of patients with vascular parkinsonism (VP) and Parkinson disease (PD)

Features	VP ($n=69$)	PD ($n+277$)	*P*
Tremor	23 (33.3)	220 (79.4)	<.00001
Gait	62 (89.9)	108 (40.0)	<.00001
Asymmetric involvement	35 (50.7)	225 (81.2)	<.00001
Upper body predominant	3 (4.3)	119 (43.0)	<.00001
Lower body predominant	41 (59.4)	27 (9.7)	<.00001
Postural instability	50 (72.5)	56 (20.2)	<.00001
Falling	32 (46.4)	29 (10.5)	<.00001
Rigidity	37 (53.6)	172 (62.1)	<.01
Response to the use of levodopa	17 (24.6)	204 (73.6)	<.00001
Dementia	31 (45.0)	28 (10.7)	<.00001
Corticospinal findings	19 (27.5)	3 (1.1)	<.00001
Incontinence	13 (18.8)	5 (1.8)	<.00001
Pseudobulbar affect	7 (10.1)	7 (2.5)	<.05

From Winnikates and Jankovic (1999). Used with permission

VP vascular parkinsonism, *PD* Parkinson disease

Values are number (percentage)

opined: "It is also possible that degeneration of the basal ganglia, as a result of arteriosclerosis, can produce the characteristic symptoms, but the pathological evidence for such a relationship is not unequivocal. In addition, there are few satisfactory criteria for the establishment of the clinical entity of arteriosclerotic parkinsonism." Merritt attributed the disorder to "unknown cause" or "so-called idiopathic parkinsonism." A few pages later, Denny-Brown wrote a section entitled "Arteriosclerotic Parkinsonism." Neither author referred to the other.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) is the main problem in differential diagnosis of vascular parkinsonism; bradykinesia is seen in almost half of NPH patients and frank parkinsonism has been reported in up to 11% of those patients. The clinical syndrome is the triad of dementia, ataxia, and urinary incontinence. Numerous imaging tests have been advocated to improve prediction of a good response to diverting the outflow of CSF. If CSF drainage and shunting help relieve NPH, the parkinsonism may also improve.

Binswanger Disease (Subcortical Vascular Cognitive Impairment, Leukoaraiosis)

Vladimir Hachinski, the modern authority on this syndrome, concluded that the eponym should not be used. With John Bowler, he writes that "Binswanger" has become a popular term in the era of modern imaging to describe asymptomatic changes seen in MRI or CT. However, they prefer the word "leukoaraiosis" for that asymptomatic condition. A dictionary definition of leukoaraiosis is, "Decreased vascular density, especially in deep white matter in the brain, on MRI or CT; may be caused by demyelination, gliosis, or decreased perfusion." Bowler and Hachinski describe MRI changes of "extensive deep white matter lesions sparing subcortical U-fibers and corpus callosum." That is, the disorder is defined by the MRI appearance of diffuse high signal in the white matter. It is often seen in asymptomatic people but may be seen with dementia or parkinsonism. Cognitive impairment is seen more often than the vascular parkinsonism described above. Despite admonitions from respected authorities, the eponym honoring Binswanger is still used for the combination of dementia with imaging evidence of "subcortical vascular cognitive impairment" (see also Chap. 4).

Hepatolenticular Degeneration (Wilson Disease) and Other Hereditary Movement Disorders

According to a literature review by Lorincz, parkinsonism is seen in about 17% of patients with Wilson disease, with onset of symptoms at about age 20. Liver failure is usually evident and cerebellar tremor is seen more often than parkinsonism (mean 36%) so the correct diagnosis is usually evident. Pfeiffer, however, was skeptical about any association of parkinsonism with Wilson disease. Similarly, juvenile parkinsonism may be seen with

mutations of other movement disorder genes, including Huntington disease, dentatorubropallidoluysian atrophy, Hallervorden-Spatz disease, and neuronal intranuclear inclusion disease as well as mutations of mitochondrial DNA.

Idiopathic Basal Ganglia Calcification (Fahr Syndrome)

Once again, experts disparage use of the eponym in reviewing this syndrome. Yet, once again, the eponym continues to be used. The disease is defined by the imaging abnormalities that show widespread intracranial calcification of the basal ganglia, with or without concomitant hypoparathyroidism, and clinically manifest by dementia, parkinsonism, or both. In some families, inheritance seems to be autosomal dominant. Calcific deposits are sometimes seen with other diffuse cerebral disorders.

Pantothenate Kinase–Associated Neurodegeneration (PKAN) (Hallervorden-Spatz Disease)

Most often, this is a disease of children but symptom-onset occurs after age 10 in about 25% of affected people. Inheritance is autosomal recessive and caused by mutations in *PANK2*, which leads to iron deposition in the basal ganglia. Symptoms include dystonia, dysarthria, pigmentary retinopathy, and lower body parkinsonism. Orobuccolingual dystonia may cause mutilating tongue biting. Upper motor neuron signs may be seen. MRI shows the eye-of-the-tiger sign, a central hyperintensity surrounded by hypointensity on T2 images of the globus pallidus.

Conclusion

Careful attention to history and clinical examination is required to ensure that important clues to a mimic syndrome are not overlooked. Atypical features should be assiduously assessed and pursued. Systemic signs may point to an underlying neoplasm, raising the possibility of a paraneoplastic disorder. A history of poor sleep and loud snoring may reveal a diagnosis of sleep apnea.

Routine hematological and biochemical tests should be performed in all cases, as should CSF analysis and detailed neuroimaging. Heavy metal screening may be useful in those with occupational exposures. EEG can be helpful in differentiating clinical syndromes, for example, the preservation of alpha rhythm in the FTDs and its early disintegration in AD (Chaps. 3 and 6); or the presence of epileptiform changes in a patient with epilepsy associated amnesia. Nerve conduction studies can identify evidence of conduction block in patients with multifocal motor neuropathy (Chap. 7).

The course of mimic syndromes often differs from true neurodegenerative disease, and perhaps the most important diagnostic test is careful clinical evaluation over time. Patients should be reviewed regularly.

Failure to progress or the development of new or atypical signs should trigger a full reevaluation. And during each clinician review, the clinician should pose the question, "Could this be a mimic syndrome?"

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Managing Neuropsychiatric Symptoms of Neurodegenerative Diseases

12

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Abstract Many neurodegenerative conditions are associated with neuropsychiatric symptoms. The origin of these symptoms is complex, and includes neuroanatomical, neurochemical, psychological, and social factors. Management of neuropsychiatric symptoms in neurologic disease is challenging, as there is a dearth of evidence-based data. This chapter explores the neurobiology of the most common neuropsychiatric symptoms encountered in clinical practice, and outlines current approaches toward their pharmacological and behavioral management.

Keywords Dementia • Alzheimer's disease • Parkinson's disease • Neuropsychiatry • Neuropharmacology

Introduction

A review of the worldwide incidence of dementia has estimated that a new case is diagnosed every 7 seconds. Worldwide, 25 million suffer from dementia with 3–7 million cases of dementia in the U.S. alone. Dementia is a costly disease. A global estimate of the annual cost of dementia is US$315.4 billion. The number of dementia patients is estimated to double in the next decade. Although the direct costs of dementia care are often emphasized, one also needs to be concerned about the toll that caring takes on providers. Most people with dementia are still cared for at home by family members. The physical, psychosocial, and financial burdens of the caregiver need to be taken into consideration as well. The disease burden and cost of caring are heightened even more when the patient suffers from neuropsychiatric symptoms associated with dementia. It is with these points in mind that this chapter was written. Our goal is to help the clinician and caregiver identify the neuropsychiatric symptoms associated with dementia and cognitive decline, offer treatment plans to address them, and if no cure is available, provide strategies for symptomatic

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relief with available drugs, keeping in mind the benefits and risks of use. Finally, we consider caregivers and caregiver burden and examine how dementia impacts the quality of life of all involved in the system of care.

Behavioral and Psychological Symptoms of Dementia

Behavioral and psychological symptoms of dementia (BPSD) represent a heterogenous group of behaviors and psychiatric symptoms occurring in patients with different types of dementia. More than 50% of individuals with dementia suffer BPSD, with 90% of patients experiencing at least one symptom of BPSD at some point in their disease. BPSD increases the risk for injury to oneself and others, necessitating acute interventions. Symptoms are distressing for patients and their caregivers, and are often the reason for placement into residential care. The development of BPSD is associated with a more rapid rate of cognitive decline, greater impairment in activities of daily living, and diminished quality of life.

Although the origin of BPSD remains unclear and seems to be different across cultures and countries, symptoms are often due to multiple etiologies. These include neuroanatomical (e.g., limbic or frontal network degenerations), neurochemical (e.g., deficiencies in various neurotransmitters), psychological (e.g., premorbid personality), and social (e.g., caregiver factors and changes in the environment). Dysregulation of cholinergic function correlates with memory problems, and deficits in serotonin, noradrenalin, and GABAergic transmitters have been associated with depression, anxiety, and aggression. In addition, symptoms often co-occur and may share the same neuroanatomical correlates, although the underlying pathology may differ. For example, apathy and disinhibition in AD are both associated with frontal lobe dysfunction, while visual hallucinations and Capgras misidentification delusions, common in dementia with Lewy bodies (DLB), are associated with a reduction in function and metabolism of the posterior visual cortices.

During the last few years, the field has advanced to recognize the importance of BPSD, correctly diagnose it, and promptly treat it as part of the dementia syndrome. For example, there has been growing awareness of disinhibition, and lack of personal concern and insight in frontotemporal degeneration (FTD); visual hallucinations, mental status fluctuations, and sleep disturbances in DLB; apathy, anxiety, and depression in early stages Alzheimer's disease (AD), and delusions, hallucinations, and agitation in late stage of the disease. In FTD and DLB, for instance, the behavioral problems may precede the cognitive ones by years.

Although specialists in the field are getting a better grasp of the neuropsychiatric problem, most patients with dementia are still managed within primary care systems that must deal with challenging medical and psychiatric issues. The behavioral and psychological presentations of patients increase utilization of medical services and cost of care, complicate clinical management of other comorbid diseases, especially involving cardiovascular or infectious processes, delirium, or falls, and cause family members to experience excessive anxiety, depression, sleep problems, and fatigue. Unfortunately, dementia-related symptoms often are under-recognized by primary care physicians. Patients may end up receiving medications, such as anticholinergics, with potentially negative side effects.

Comorbid processes associated with alterations in mental status may not be identified and instead treated with neuroleptics.

Improving the care for such vulnerable patients requires supporting the primary care system with resources. This includes dementia care managers, access to and coordination with interdisciplinary dementia specialists, a feasible dementia screening process, and a thorough diagnostic work-up that considers the etiology of the dementia, after the exclusion of other causes, such as drug-induced delirium, pain, or infection.

When facing BPSD, care planning should involve psychosocial treatments for both the patient and family. Although BPSD may respond to environmental and psychosocial interventions, pharmacotherapy is often required for more severe presentations. Below, we will review these issues in detail.

Dementing Illnesses

BPSD are a manifestation of dementing illnesses. Any type of dementia affects multiple domains, and impairs, if not debilitates, social functioning and quality of life. The list of dementing illnesses is very long (Table 12.1). Since much of this book is devoted to elucidating the different dementing syndromes, only a few examples will be highlighted here. The main purpose of this section is to provide a broader context in which to consider BPSD.

Table 12.1 Causes of dementia

Neurodegenerative
Alzheimer's disease
Frontotemporal degeneration
Dementia with Lewy bodies
Huntington disease
Corticobasal degeneration
Progressive supranuclear palsy
Multisystem atrophy
Argyrophilic brain disease
Wilson disease
Hallevorden–Spatz disease
Mitochondrial diseases
Kuf disease
Metachromatic leukodsytrophy
Adrenoleukodystrophy
Vascular
Vascular dementia
Hypoxic/ischemic injury
Post-CABG
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

(continued)

Table 12.1 (continued)

Inflammatory/infectious
Multiple sclerosis
Syphilis
Lyme
HIV
Creutzfeldt–Jakob disease
Primary CNS vasculitis
Vasculitis secondary to other autoimmune disorders (i.e., lupus)
Sarcoid
Chronic meningitis (i.e., tuberculosis, cryptococcus, etc.)
Viral encephalitis (i.e., HSV)
Whipple disease
Systemic lupus erythematosus
Sjögren syndrome
Metabolic/toxins
Hypothyroid
Vitamin B_{12}
Thiamine deficiency (Wernicke–Korsakoff)
Niacin deficiency (pellagra)
Vitamin E deficiency
Uremia/dialysis dementia
Addison/Cushing
Chronic hepatic encephalopathy
Heavy metals
Alcohol
Neoplastic
Tumor (depends on location)
Paraneoplastic limbic encephalitis (anti-Hu)
Acute and chronic sequelae of brain radiation (acute and subacute encephalopathy, radiation necrosis, diffuse late brain injury)
Chemotherapy
Lymphomatoid granulomatosis

Adapted from Daffner and Wolk (2010)

This list is not exhaustive, as any brain injury can result in dementia depending on location. Some diseases could be under multiple categories

CNS central nervous system, *HSV* herpes simplex virus, *CABG* coronary artery bypass graft, *HIV* human immunodeficiency virus

Alzheimer's disease is the most common degenerative dementia and causes a progressive decline in cognitive and functional status. Episodic memory deficits are the predominant initial complaints in most cases. However, deficits in attention, visuospatial processing, naming/language, and executive functions may be present. Over the course of the illness, non-memory cognitive domains become progressively more involved and patients often deteriorate to the point in which they can no longer perform their activities of daily living,

recognize family members, and maintain continence. The main pathologic findings of AD are amyloid plaques (an extracellular accumulation of Aβ[beta]), neurofibrillary tangles (intracellular, paired helical structures composed of hyperphosphorylated tau), synaptic loss, and neuronal death. There is reduction in the availability of acetylcholine (ACh), which is associated with memory and other cognitive deficits. Other neurotransmitter systems also are disrupted.

Mild cognitive impairment (MCI) is believed to reflect the transition between normal aging and dementia, in particular AD. Originally, MCI was defined in terms of relatively isolated memory deficits in the setting of preserved general cognitive and functional abilities. More recent formulations have categorized the syndrome into amnestic and non-amnestic subtypes, and specified the number of domains involved (single and multiple-domain). The neuropsychiatric aspects of MCI have only recently begun to receive attention. In studies involving specialty memory clinics, patients have tended to convert from MCI to AD at a rate of 10–15% per year compared to the 1–2% conversion of age-matched controls. However, in epidemiological studies, the rates of conversion are lower, and 20–40% of patients may eventually "revert to normal" on subsequent evaluations. At autopsy, many patients who were diagnosed with amnestic-MCI have had neurofibrillary tangles in the hippocampus and entorhinal cortex, with variable findings of amyloid plaques in the neocortex. These findings are felt to be consistent with the idea that MCI often represents a transitional period to AD.

Behavioral variant frontotemporal dementia (bv-FTD) is the most frequent form of the set of syndromes under the general rubric of frontotemporal lobar degeneration. Bv-FTD is the second most common cause of neurodegenerative dementia in the presenile years. Patients with bv-FTD exhibit salient changes in personality and behavior that can range from apathy to disinhibition. Patients frequently are inappropriate and lack insight and empathy. Tests of frontal executive function often are impaired (with relative sparing of memory storage and visuospatial function), but may not be abnormal when the disease is primarily limited to the medial aspects of frontal lobes, sparing dorsolateral cortices.

Pathologically, tauopathies and TDP-43 proteinopathies make up approximately 60% of cases of FTD. Tauopathies are associated with accumulation of the microtubule-associated protein tau, and includes Pick's disease, corticobasal syndrome, and progressive supranuclear palsy. In bv-FTD, pathology has an early anatomical predilection for medial frontal regions of the brain, including the frontoinsular and orbitofrontal cortices, which likely accounts for the prominent changes in personality and behavior. Neurochemically, deficiencies have been found in the serotonin and dopamine systems, with relative sparing of the cholinergic and NE systems.

DLB appears to be the second most common form of neurodegenerative dementia in older patients, with Lewy body pathology found in up to 35% of dementia cases. DLB presents with fluctuations in cognition, visual hallucinations, and mild extrapyramidal features. The hallucinations tend to be well formed (e.g., animals or people). Cognitive impairments most often involve the realms of executive function, attention, speed of processing, and visuospatial abilities. Memory is disrupted at the level of encoding and retrieval, and tends to be less severe than in AD. REM sleep behavior disorder and depression are relatively common. The clinical overlap with Parkinson's disease-associated dementia (PDD) is considerable and differentiating one from the other often is arbitrary.

Pathologically, cortical Lewy bodies (spheric, intracytoplasmic, eosinophilic, neuronal inclusions containing α[alpha]-synuclein, and ubiquitin proteins) are found in these patients. The temporal cortex and limbic structures are prominently involved. In addition, Alzheimer pathology often is observed in these patients, with 60% or more reaching pathologic criteria for AD. Neurochemically, cholinergic deficits are more pronounced in DLB than AD, which may explain why cholinesterase inhibitors tend to have a greater therapeutic benefit in DLB.

Vascular dementia (VaD) often is cited as the second most common form of dementia, with estimates varying from 10% to more than 33%. Vascular dementia represents the clinical end-product of vascular injury to the brain from a range of etiologies, including leukoariosis, small-vessel infarcts, multiple cortical strokes, or a single, strategically placed stroke. Multiple lacunar infarcts or significant white matter disease (Binswanger disease) can lead to apathy, frontal networks impairment, and corticospinal and bulbar signs. Large-vessel strokes result in syndromes specific to the site of the lesion, such as amnesia, aphasia, agnosia, etc. The coexistence of vascular injury and AD pathology is extremely common (greater than 50% of cases diagnosed with vascular dementia). Often, such cases are labeled as a "mixed dementia." Particularly pertinent is the observation that vascular events seem to hasten the onset and increase the severity of clinical AD, which makes it very difficult to accurately estimate the actual prevalence of vascular dementia. Not surprisingly, the risk factors for vascular dementia are believed to be the same as those for stroke and include hypertension, diabetes, high cholesterol, and atherosclerosis.

Spectrum of Neuropsychiatric Symptoms in Neurodegenerative Diseases

Before tackling subgroups of neuropsychiatric and behavioral symptom, we would like to point out disagreement that currently is encountered in the literature. For example, can BPSD be divided into syndromes that cluster as psychosis, agitation, and mood disorders? Should clinicians group together disparate symptoms if patients present with many different ones that have various underlying etiologies? An important issue is that clinicians and nursing home providers often lack formal screening batteries to appropriately identify the symptoms. Regardless of where one stands on these debates, there is clear evidence that BPSD increases the rate of institutionalization and the cost of care. The study of BPSD has been challenging, as researchers have had difficulty quantifying behavior in trials. Dividing by subtypes of dementia has had limited benefit. For example, research comparing AD and VaD has found that behavioral dysregulation did not differ by subtype of dementia but rather by severity of the disease process.

Below, we list the most common neuropsychiatric symptoms in neurodegenerative diseases that are often captured in the Neuropsychiatric Inventory (NPI). Particular emphasis is placed on the underlying neuroanatomy and neurochemistry that correlates with symptoms.

Delusions are extremely common in patients with AD, with up to 73% of patients developing them. They also occur in patients with DLB, VaD, and PDD. The most common

delusion is that people are stealing things. Delusions of abandonment and sexual infidelity are also common. Delusions are frequently accompanied by physical aggression.

Hallucinations occur commonly in dementia. It is most often seen in DLB and PPD and less commonly in AD (late in the course). Hallucinations may predict a rapid rate of decline, and have been correlated with severity of dementia and aggression.

Neurobiology of Psychosis

Farber and colleagues have found an association between psychosis in AD and increased tangles in the middle frontal, superior temporal, and inferior parietal areas, even after accounting for DLB and Lewy body pathology, which earlier studies had not done. Neurochemically, a significant decrease of serotonin in hippocampus, hyperactivity of dopamine, and intact norepinephrine in substantia nigra were implicated.

Agitation is commonly observed in AD and FTD. Agitation in these diseases manifests as restlessness, pacing, being fidgety, increases in motor activities, and abnormal vocalizations. It is the most common symptom in AD that is accompanied by aggression. Aggression is expressed as verbal insults, shouting, hitting, and throwing things. Needless to say, both agitation and aggression necessitate an increase in personal care assistance, and at least at their onset, should prompt a complete metabolic and structural work-up to rule out any acute reversible causes (Table 12.2).

Aggression/rage reactions and irritability are complex behaviors that most frequently lead to an assessment by physicians. Aggressive symptoms can be divided into physically aggressive symptoms such as hitting, biting, punching, grabbing, and kicking, or verbally aggressive symptoms such as yelling, cursing, and anger outbursts. Aggression is associated with FTD and greater dementia severity in general, as seen in late stage AD and DLB. It can be influenced by environmental and physical factors such as pain or change in locations, to name a few. Aggression is associated with increased use of psychotropics, increased caregiver burden, and increased likelihood of being transferred to nursing homes. A large epidemiological study of community dwellers and nursing home residents reported by Lyketsos and colleagues found that 23.7% of dementia patients are considered agitated or aggressive. “Rage Reaction” can also occur in patients with dementia. They present as a sudden emotional/physical response. This behavior can be explosive and unpredictable.

Table 12.2 Behavior as a form of communication about underlying processes: BPSD and its common mimickers

1. Review possible physical contributions (e.g., pain and infections)
2. Rule out delirium
3. Check for dehydration
4. Look at the patient’s medication list (for drug–drug interactions and anticholinergic side effects)
5. Look for contributing environmental factors (noise, change of caregivers, etc.)
6. Consider psychiatric diseases such as depression and anxiety
7. Sleep difficulties
8. Consider un-witnessed falls and ensuing fracture or hematoma

Neurobiology of Agitation and Aggression

Greater agitation in AD correlates with tangles in bilateral orbitofrontal and left anterior cingulate cortex. Chemically, disruption of serotonin systems appears to be relevant, as symptoms partially respond to SSRIs that are used as a first-line treatment to target aggression, followed by neuroleptics to counter disruption in the dopaminergic system.

Depressed mood with various intensities occurs in 30–40% of patients with dementia. It is one of the most common BPSD symptoms and may develop at any stage of the disease. Depression is comorbid with AD, DLB, VaD, PDD, and corticobasal degeneration. Recently, these symptoms have become of greater interest to clinicians and researchers. Depression was found to alter function, often preceding MCI and heralding the switch to dementia. Some studies have even supported the association of biomarkers such as Troponin and S100β with depression, while others reported up to 1/3 patients with dementia and BPSD had depression. A high association has been found between depression in dementia and symptoms of irritability, disinhibition, agitation, and anxiety.

Neurobiology of Depression

Some studies have reported a decrease in noradrenaline (NA) in the locus coeruleus in depressed patients with AD, whereas others have found increased NA activity, perhaps to compensate for dysfunction elsewhere in the nervous system. Loss of dorsal raphe nuclei also has been implicated. Finally, the superior frontal regions have been anatomically implicated in depression.

Anxiety occurs often in AD, PD, and VaD. Anxiety is rarely studied alone in medication trials for neurodegenerative diseases. It is usually coupled with depression, and together forms the affective dyad in BPSD. Anxiety often is associated with irritability, aggression, agitation, and pathological crying. It has been challenging to quantify anxiety as a single variable. Refusal to bathe and attend to dental and physical symptoms have been attributed to anxiety. Repetitive sentences with senseless content also may be a sign of anxiety.

Neurobiology of Anxiety

The pathophysiologic origins of anxiety are unclear. It has been linked to the causes of depression. More studies are needed to pinpoint the neurobiology of this common symptom in BPSD.

Euphoria is medically recognized as a state of exaggerated sense of elation and well-being. An overexcited and elated mood could be a marker of frontal dysfunction and is often a sign of FTD. The affective disorders of BPSD are generally nonspecific and can mimic hypomanic and manic states. Euphoria often precedes memory deterioration in FTD, for example. Once dementia has progressed, the identification of a hypomanic component becomes more difficult, as mental deterioration predominates.

Apathy is commonly seen in AD, VaD, progressive supranuclear palsy (PSP) and FTD. The term apathy is being used with increasing frequency in both neurology and psychiatry. However, its definition varies. Some consider it a symptom of other major psychiatric disorders, whereas others view it as a syndrome of its own. Apathy often is considered a disorder involving motivation rather than mood. It has been characterized by reduced goal-directed behavior (in domains of cognition, emotional expression, and self-generated voluntary purposeful behavior). There is strong evidence that apathy is a common finding in AD. The MMSE and other brief cognitive screens do not measure apathy. Clinically, there can be a co-occurrence of apathy and agitation, or apathy and depression. In some studies, apathy is cited as the most common BPSD symptom in AD. For example, a study by Craig and colleagues enrolled 435 patients with AD and concluded that apathy and indifference were the most frequent symptoms at 76%, followed by aberrant motor behavior (65%), appetite changes in 64%, and irritability in 63%, a frequency similar to agitation/aggression. Apathy has been shown to be associated with a decline in activities of daily living (ADLs) and to be a potential predictor of MCI patients who will develop dementia. Although current data have been obtained from randomized controlled trials (RCTs) that did not investigate apathy per se, it has been readily noted that apathy/indifference are moderately distressing to caregivers. Treatment with cholinesterase inhibitors and/or psychosocial interventions are the only available modalities for treating apathy in AD that have been shown to have some efficacy. Medications will be discussed in more detail in subsequent sections.

Neurobiology of Apathy

Symptoms of apathy in AD correlate with higher neuronal loss and increased tangles in frontal areas. Similar patterns are seen with the accumulation of Lewy bodies in those cortical regions. Neurochemically, multiple transmitters have been implicated, including reduction in NA, dopamine, and acetylcholine. Neuroimaging studies of apathy in Alzheimer's disease have demonstrated atrophy and hypoperfusion of anterior cingulate and orbitofrontal cortex.

Sleep disturbances are often found in early stages of DLB, with REM disorders and disrupted sleep–wake cycles, although they may occur in other dementias, especially with increasing severity of disease.

Appetite and eating disturbances are often seen in FTD. Hyper-orality and "craving for sweets" may herald the disease. Patients may choke on what they are eating as they cannot gauge the quantity of food they put in their mouth. Sense of satiety appears to be lost, as is the capacity for the appropriate experience of disgust. Disturbance of satiety and disgust have been linked to dysfunction of the frontoinsular cortex.

Other Symptoms

- Behaviors such as chanting, pacing, and repetitive tapping may be symptoms of underlying anxiety or may occur alone.
- Wandering is one of the common and troublesome symptoms of BPSD, with a prevalence rate of up to 53%. Wandering can be seen as aimless walking, trying to leave the

house, leaving the premises to go to unfamiliar and sometimes dangerous areas, and shadowing the caregiver.
- Delirium in patients with BPSD can exacerbate symptoms. Delirium itself can lead to BPSD and needs to be ruled out as a cause of alterations in behavior. Often, this behavioral change comes abruptly. Of note, the higher risk factors for the development of delirium include advancing age, cognitive impairment, and dementia.
- Misidentification syndromes as seen in Capgras (i.e., a familiar person becomes an imposture) and Fregoli (i.e., people are dressed up as others) often are seen in DLB and FTD. The response of patients to the delusions may lead to aggressive behavior.

Assessment and Testing of Presence/Absence of Neuropsychiatric Symptoms

Although neuroimaging, functional imaging, and CSF markers are readily available and are used to help diagnose different types of neurodegenerative disorders, clinicians continue to rely heavily on quantifying deficits using neuropsychological testing and standardized behavioral scales. More than 30 scales are available for use to measure BPSD. Some of the most commonly used are:

- Cohen-Mansfield Agitation Inventory (CMAI) examines 29 types of agitated behaviors.
- Neuropsychiatric Inventory (NPI) and its version for Nursing Homes (NPI-NH) assess 12 behavioral issues.
- Behavioral Pathology in AD (BEHAVE-AD) scale is structured around the psychiatric interview and assesses 25 abnormal behaviors in seven different domains of psychosis, affective disorders, aggressiveness, and diurnal rhythm changes.
- Cornell Scale for Depression in Dementia (CSDD) was developed to assess signs and symptoms of major depression in patients with dementia during the week preceding the interview. Because some of these patients may give unreliable reports, the CSDD requires an interview with an informant.
- Apathy scale includes 14 items on initiation, motivation, and goal-directed behaviors that are rated by the patient's relative or care provider.

BPSD and Activity of Daily Living (ADL)

There is little correlation between the severity of cognitive dysfunction and BPSD, leading researchers to think that they are the manifestations of two different underlying phenomena. BPSD may be prominent in patients with MCI (mostly amnestic type), especially when symptoms involve depression and apathy. Visual hallucinations, disinhibition, and agitation are prominent in FTD and DLB and often occur before a decline in cognitive function.

In contrast to the relationship between cognitive impairment and behavioral symptoms, BPSD and ADLs are highly correlated. As planning and organizational skills necessitate higher executive function, dysfunction in the frontal network system often alters ADLs and induces behavioral symptoms.

In addition, while assessing a patient with BPSD, care should be taken to examine the interaction between the specific brain disease, the patient, and the environment with which he/she is interacting. The clinical analysis of people with dementia necessitates that providers look into all the contributing dimensions of the disease state, and consider both pharmacological and non-pharmacological interventions.

Treatment

Management of dementia should focus on the maintenance of function and independence for the person with the disease. Current symptomatic treatments for dementia have only modest efficacy. An international group of caregivers, organizations, and professionals with expertise in dementia developed a consensus statement that recommended that medication trials should state clear, predefined diagnostic and severity criteria and outcome measures (e.g., functional and executive capacity). It was suggested that to be complete, health economic measures should be incorporated as secondary outcomes in all future Phase III trials, with analysis of cost-effectiveness and clinical outcome. Although current drugs for AD may reduce the amount of family caregiver time required, the treatment may have a negative impact on the time spent with patients, and reduce their opportunity for connectedness crucial for their well-being. As the population of older adults grows across the world, their empowerment may impact the political establishment and lead to a change in the economics of treatment in dementia. One example is increased caution about the use of psychotropics, and more stringent regulations with black box warnings and documentation of side effects and duration of treatment (Table 12.3).

Table 12.3 Questions to ask before starting a medication

- What is the targeted behavior to be treated?
- Is a drug really necessary?
- Have alternative non-pharmacological methods been tried?
- Was informed consent sought? (If patient is not capable of providing consent, was caregiver asked?)
- Which drug to use?
- What is its lowest therapeutic dose?
- When will the treatment plan be reassessed?
- Are side effects checked for and treatment plan adjusted accordingly?
- Is this the most cost-effective choice?

Neuroleptics

Several neuroleptics have been investigated in older adults with psychosis, and studies have shown some benefit in a select group of patients, but with various side effects and risks, including increased mortality and cardiovascular and cerebrovascular events. Neuroleptic use is common in both community-dwelling older adults and nursing home residents to address symptoms of psychosis and/or BPSD. In community-dwelling adults aged 40–64, living in the United States, an average of 620,000 individuals annually were found to be prescribed neuroleptics during the 8 year study period (51.9% typical neuroleptics and 50.4% atypical neuroleptics). That number increases in the 65 and older population, where approximately one million individuals per year are prescribed atypical antipsychotics. In the United Kingdom, almost 18% of older adults in contact with a mental health provider were found to be prescribed neuroleptics, mostly atypical neuroleptics.

Neuroleptics that have been used with some degree of efficacy in the treatment of BPSD include haloperidol, risperidone, quetiapine, olanzapine, and aripiprazole. To our knowledge, there have been no RCTs of clozapine for treatment of BPSD, but there are limited data on its use in schizophrenia in older adults.

However, one should note that many side effects were related to the use of these medications, ranging from additional cognitive decline to heart disease, cerebrovascular events, and increased mortality with both typical and atypical antipsychotics, particularly in patients with dementia.

Superiority of one neuroleptic over another has not been demonstrated in trials of risperidone vs. olanzapine, risperidone vs. quetiapine, and quetiapine vs. haloperidol. Moreover, other trials have failed to show superiority of the studied neuroleptic compared to placebo, including randomized trials of quetiapine. In the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) trial, a 12 week multicenter, randomized, placebo-controlled trial investigating the efficacy of olanzapine, quetiapine, and risperidone in AD patients with BPSD, there was no significant difference between patients treated with an atypical neuroleptic and placebo in terms of clinical response. For patients with dementia and parkinsonism, quetiapine was without demonstrable benefit. Similarly, a 1 year prospective study did not find any difference in BPSD incidence among users and nonusers of psychotropic medications (an antipsychotic, antidepressant, or anxiolytic). Additional trials for treatment of BPSD have varied largely in terms of number of patients. Also, the relatively brief duration of some trials may not reflect long-term risks and benefits. Taken together, the currently available data suggest that while there is some benefit of neuroleptics for the treatment of BPSD, the evidence is by no means conclusive, and considering the substantial risks and side effects associated with their use, neuroleptics should be limited to severe psychosis or behavioral disorders that could lead to harm to self or others when non-pharmacologic measures have failed. The need for their continued use should be assessed regularly and plans discussed with the patient (when possible) and family.

Cholinesterase Inhibitors

Cholinesterase inhibitors (ChEI) and memantine are alternative treatments to neuroleptics. They tend to stabilize cognition and may have a positive influence on the NPI. Cholinergic systems, among other neurotransmitters in the brain, appear to contribute to different behav-

iors, such as psychosis, depression, agitation, and personality changes. ChEIs have been shown to produce secondary benefits in BPSD. More than 30 RCTs have been published that included information about the treatment of BPSD by ChEIs over a period of 6–12 months. The medications are generally well tolerated. Gastrointestinal symptoms include nausea, vomiting, and diarrhea and were the most common symptoms. Bradycardia and syncope need to be closely monitored. The pooled evidence suggests sustained benefits for anxiety, depression, and apathy, but no benefit for agitation and aggression over 24 weeks of the study. Efficacy may vary among agents and differ across individual patients. There has been scant investigation employing head-to-head trials. The greatest number of studies indicating positive effects have been reported for donepezil. Drug benefits were easier to demonstrate for moderate-to-severe BPSD compared with mild-to-moderate symptoms.

Galantamine is a specific reversible ChEI. It also works on nicotinic receptors to potentiate cholinergic neurotransmission. There is some evidence demonstrating that galantamine has positive effects on ADLs and behavior. A 2001 Cochrane data analysis noted seven RCTs for galantamine addressing these issues.

Most of the studies done with rivastigmine were open-label studies, with behavior as secondary endpoint. They showed efficacy in treating behavioral disturbances in patients with a wide range of dementias, including AD, VaD, FTD, mixed dementia, DLB, PDD, and schizophrenia with dementia.

In summary, additional research is needed to more definitely establish the efficacy of CHEIs on BPSD. They appear to be more beneficial for anxiety, depression, and apathy than for agitation and aggression.

Memantine

Individual studies, meta-analysis, and pooled analysis showed benefit from the use of memantine to target irritability, lability, agitation, aggression, and psychosis over 3–6 months. It is well tolerated and so far has been a promising treatment, but studies are still needed in patients with moderate-to-severe agitation. A Cochrane review indicated little effect of memantine for symptoms in VaD and failed to show any benefit in PDD and DLB.

Antiepileptic Drugs

Anticonvulsants and mood stabilizers (carbamazepine, valproic acid, gabapentin, lamotrigine, topiramate, oxcarbazepine) have been studied in the treatment of BPSD and "noncognitive" symptoms of dementia. Current data are insufficient to recommend them for routine treatment of BPSD.

Among these medications, only carbamazepine has demonstrated efficacy in the treatment of BPSD in controlled studies. Significant adverse events were reported in the elderly (sedation, hyponatremia, cardiac toxicity). Because carbamazepine is a strong enzymatic inducer, it has been associated with a higher incidence of drug–drug interactions.

A number of open-label studies and case reports yielded promising results with valproic acid for the treatment of BPSD. However, five controlled studies published failed to demonstrate that it was a useful treatment modality for BPSD. More studies need to be conducted on the role of valproic acid in preventing or treating BPSD.

Evidence that gabapentin treats BPSD is still very preliminary. The drug is well tolerated when used for this purpose, but no controlled study has been conducted to prove its efficacy, despite case reports and open-label studies showing encouraging results. There are two case reports in which gabapentin was used in the context of agitation in DLB, but did not work in other types of dementia. At this time, the off-label use of gabapentin cannot be recommended for the treatment of BPSD.

Concerning lamotrigine, two recent case reports seem to indicate some efficacy in BPSD. Furthermore, lamotrigine appears to have neuroprotective effects. Caution should be used when it is given concomitantly with valproic acid.

Topiramate has shown promising results in one open study in BPSD. However, given its potential negative side effects on cognition, it cannot be recommended for routine use.

No clinical study has been published studying oxcarbazepine to support its efficacy in the treatment of BPSD. This drug is better tolerated than carbamazepine, but can induce severe and more frequent hyponatremia.

Antidepressants

Depression, anxiety, apathy, and agitation may have an underlying neurobiological profile that would make the use of antidepressants in BPSD a reasonable choice.

The evidence for SSRIs is encouraging but still at an early stage. Large RCTs of long duration are needed. In a small placebo-controlled trial reported by Mendez, Citalopram was more efficacious for the treatment of BPSD than placebo. Sertraline showed significant benefits for agitation and remains the drug of choice in treating behavior dyscontrol related to FTD.

A meta-analysis on trazodone failed to show sufficient efficacy. However, of note, in bv-FTD, one RCT by Liebert and colleagues in 2004 indicated that trazodone improved neuropsychiatric symptoms. Side effects were frequent, especially sedation.

Although antidepressants that augment NE (TCAs) have been used to target apathy, depression, and anxiety, their anticholinergic side effect profile tends not to make them feasible. To date, the probability that the noradrenergic system has a role to play in BPSD has led to the use of B-Blockers to address aggression and agitation in patients with dementia. Their efficacy remains to be determined. Other antidepressants with putative effects on NA have not been studied in BPSD (e.g., venlafaxine, bupropion). Mirtazapine has been used successfully in one case report by Raji and Brady.

Benzodiazepines

Benzodiazepines are to be used only on an as-needed basis and for severe agitation over short periods of time. As previously discussed, patients can develop paradoxical reactions, become more agitated, and have worsening of cognitive symptoms.

In summary, pharmacotherapy for the treatment of BPSD has substantial limitations. Several factors should be taken into account. First, whenever feasible, a non-pharmacological

approach is recommended as first choice. Second, to date, most studies in the literature are the ones that show positive effects. Negative trials may be less likely to be published. Third, given the inclusion/exclusion criteria of clinical trials, most have tended to enroll "better behaved" patients, making it difficult to evaluate the treatment effect in the most troubled patients with BPSD. Fourth, agitation and aggression often coexist with depression and psychosis. Fifth, biomarkers are needed, especially concerning pathologies (vascular and others) in which we know so little and where response to treatment has been very limited. Behaviors with a poor response to drugs include:

- Wandering
- Pacing
- Attempting to leave
- Disruptive vocalizations
- Pathological laughing and crying
- Incontinence
- Failure to bathe

Finally, the authors concur with the adage "start low, go slow" (Table 12.4). Moreover, it is wise to assess treatment frequently over time, monitor side effects (Table 12.5), avoid

Table 12.4 Drug dose schedule

Drug	Dose range	Schedule
Haloperidol	0.5[a]–2 mg	Once daily
Risperidone	0.5[a]–2 mg	Once daily
Clozapine	6.25[a]–100	Once or twice daily
Olanzapine	2.5[a]–10	Once daily
Quetiapine	25[a]–100	Divided dose
Lorazepam	0.5[a]–2.0	Divided dose
Oxazepam	10[a]–30 mg	HS
CBZ	300–800 mg/day	Twice daily
VPA	125[a]–1,000 mg	Divided dose up to q.i.d.
Trazodone	25–300 mg/day	HS
Citalopram	10–60 mg	Once daily
Paroxetine	10[a]–30 mg	Once daily
Fluoxetine	10[a]–30 mg	Once daily
Sertraline	25[a]–100 mg	Once daily
Nortriptyline	10[a]–60 mg	Once daily
Mirtazapine	7.5[a]–45 mg	HS

HS at bedtime

[a]Starting dose

Table 12.5 Medication side effects

	EPS	Postural ↓ BP	Antichol.	Sedation	Bone marrow	Cognition	LFTs	Weight
Typical neuroleptics	+	+	+	+	−	↓		
Atypical neuroleptics	−	−	+	+	−	↓	+/−	↑↑
CBZ	−	−	−	+	+	?	+	0
VPA	−	−	−	+	−	?	↑	↑
Trazodone	−	+	+	+	−	?	−	−
TCA	−	+	+	+	−	+/−	−	↑
SSRI	−	−	Confusion/ restless	Insomnia	−	?	(↓N/A)	↓/↑

EPS extrapyramidal signs, *LFTs* liver function tests, *CBZ* carbamazepine, *VPA* valproic acid, *TCA* tricyclic antidepressant, *SSRI* selective serotonin reuptake inhibitors

Table 12.6 Drugs to avoid

1. Those causing orthostatic hypotension and anticholinergic effects:
   (a) Typical low-potency antipsychotics: chlorpromazine
   (b) TCA : amitryptiline
   (c) Anticholinergic drugs: benztropine
2. Those causing EPS:
   (a) High-potency antipsychotics
3. Those causing paradoxical agitation reaction:
   (a) Benzodiazepine
   (b) Antipsychotics in DLB

drugs that are known to cause side effects (Table 12.6), and engage family members and caregivers in the treatment of the patient.

Non-Drug Approaches

Livingston and colleagues reviewed more than 160 studies examining the impact of psychotherapy, including brief psychosocial therapy (later investigated in the CALM-AD trial), music therapy, aromatherapy use, light therapy, and education of nurses and family members. Some psychosocial interventions appear to have specific therapeutic properties, over and above those due to the benefits of participating in a clinical trial. Their effects were mostly small to moderate with a short duration of action. They work when implemented systematically by a seasoned staff. For example, learning the ABC Model (Antecedents, Behaviors, Consequences) was useful to reduce unwanted behaviors (Table 12.7). Also,

Table 12.7 Charting behaviors before starting a drug

Use of **A**ntecedents-**B**ehavior-**C**onsequences (A-B-C) method may help identify temporary patterns of behavioral decompensation. Although this method may be helpful early in the disease process, it may lose its efficacy as the disease progresses in severity. Nonetheless, it is easy to implement and may curtail the use of powerful medications for a while.
1. Date and time behavior occurred
2. Antecedents (What was the trigger?)
3. Behavior (What happened?)
4. Consequence (What was the response?)

Adapted from Proulx (1989)

when the "unmet needs" paradigm is addressed, some negative behaviors were ameliorated. The unmet needs point to the fact that people have inappropriate behavior when their emotional and physical needs are not met. The "stress threshold model" views dementia as a reduced capacity to cope with stress, leading to more behavioral outbursts.

Project ACT is a RCT designed to test the effectiveness of a non-pharmacological home-based intervention to reduce BPSD and caregiver distress. It targeted 272 diverse family caregivers who provided in-home care to persons with moderate stage dementia with one or more behavioral disturbances. Services involved nurses and occupational therapists visiting families over 13 visits and working with family members to identify and resolve triggers to behaviors (miscommunication, complex commands, high and unrealistic expectations). The study found that teaching caregivers coping strategies, either individually or in a group, improved caregiver level of stress and psychological well-being. Selwood and colleagues found excellent evidence for the efficacy of therapy centered on the patient's behavior to lessen caregiver burden and help with BPSD in patients both immediately and for up to 32 months.

Similarly, Mittleman and colleagues conducted a RCT of usual care vs. an enhanced social work counseling and support intervention (six sessions of individual and family counseling, support group participation, and continuous availability of telephone counseling, as needed). They found that over the 9.5-year study period, the intervention for spouse–caregivers was associated with a 28.3% reduction in the rate of nursing home placement of the patients with dementia (median difference between groups in time to nursing home placement was 557 days). Improvements in caregivers' satisfaction with social support, symptoms of depression, and response to patient behavior problems accounted for 61.2% of the beneficial impact of the intervention.

Multidimensional Treatment of Patients with BPSD: A Better Quality of Life

The best way to address disorders as complex as BPSD is to take the problem as a whole and understand the burden it creates on the patients, their caregivers, and their treatment team. Biomedical, psychological, and social aspects of BPSD should be

considered in the context of maintaining as good a quality of life as possible that emphasizes respect and dignity to the elders. It should aim to make patients comfortable, sparing as much as possible the patient and his/her system of care from disease burden, ageism, and pain. There are high levels of stress, distress, and psychological illness in family caregivers of individuals with dementia. Practitioners are well advised to identify these signals and work hard to alleviate them. Discussion about end-of-life care should be addressed early in the process and the wishes of the patient made clear, when possible, before cognitive decline precludes meaningful and thoughtful decision-making.

Conclusion

In summary, neuropsychiatric and behavioral symptoms are extremely common in dementia. They cause considerable suffering and distress to patients and their caregivers. Quality of life is undermined and there is a greater probability of nursing home placement. There has been increased investigation and understanding of some of the neurobiological mechanisms underlying these disorders, augmenting the likelihood of developing more effective treatment interventions. Awareness of the nature of BPSD has grown, which can facilitate a more systematic approach to the identification, evaluation, and treatment of neuropsychiatric impairments. Social and behavioral interventions can be effective tools and are associated with fewer "side effects" than medication.

Pharmacologic treatment of depression, anxiety, and cognitive impairments has been shown to have a modest beneficial impact on the lives of patients. In general, neuroleptic medications should only be used to manage severe behavioral disorders or psychosis in patients for whom less risky interventions have failed. Under such circumstances, patients need to be closely monitored to determine if treatment is yielding benefits and to assess ongoing risks. Clearly, the armamentarium available to treat BPSD needs to grow. Investment in ongoing research is necessary to discover more effective interventions for these devastating symptoms.

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Symptomatic Management and Palliative Care in Neurodegenerative Disease

13

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Abstract In the absence of effective disease-modifying drugs, the emphasis in all of the neurodegenerative diseases is on symptom management and maintenance of quality of life for the patient and carer. Palliative care enhances quality of life for patients and family members by addressing medical symptoms and individual psychological, social, and spiritual needs. Emphasis is placed on patient autonomy and dignity. Patients are encouraged to generate advance directives. Formal international guidelines for active palliative management of the common neurodegenerative diseases remain to be established.

Keywords End of life • Quality of life • Carer burden • Symptomatic management • Advance directive

Introduction

Palliative care uses a team approach to enhance quality of life for patients and family members. The aim is symptomatic management of late-stage illness focusing on relief of suffering and maintenance of dignity and respect for patient autonomy, regardless of the underlying diagnosis. In addition to medical management, palliative care addresses individual psychological, social, and spiritual needs. The palliative approach relies heavily on a dynamic partnership between the patient, carers, and the multidisciplinary clinical team. Patient- and family centered coordination of care is achieved by clear communication, advance care planning, and candid discussion of the expected disease trajectory.

Specialist palliative care has traditionally been associated with the symptomatic management of advanced neoplastic disorders. In recent years, however, specialist palliative care gradually expanded into the management of progressive nonmalignant conditions such as neurodegenerative conditions, chronic obstructive pulmonary disease, HIV, and renal and cardiac failure.

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The involvement of local palliative services in nonmalignant conditions varies from country to country. Limitations in access to palliative care are primarily due to financial barriers, lack of comprehensive guidelines, and referral patterns of different medical specialties.

In the absence of effective disease-modifying drugs, the emphasis in all of the neurodegenerative diseases is on symptom management and maintenance of quality of life for the patient and carer. Several studies are currently underway to demonstrate the effectiveness of palliative care intervention in neurological disease with respect to alleviation of symptoms and improvement in quality of life. Early involvement of palliative care as part of the multidisciplinary approach can be very effective in achieving these aims.

Amyotrophic lateral sclerosis (ALS) has often been regarded as a model condition for integration of specialist palliative care into the management of a progressive neurological disease. This is a function of the complex symptoms, progressive nature, and short life expectancy of the disease. However, few comprehensive guidelines exist for the integration of palliative care into the management of neurological disorders like ALS, and the timing and triggers for specialist palliative care intervention remain poorly defined.

Other neurodegenerative conditions including Parkinson's disease, Huntington's disease, and Alzheimer's disease, would also benefit from a specialist palliative care approach. Parkinson's disease has a high incidence and a progressive course with significant impact on activities of daily living and quality of life. Huntington's disease requires multidimensional support across physical, cognitive, and social domains. The dementias also require a complex integrated approach across medical, social, and existential domains. A holistic approach toward the management of these and other progressive diseases is best achieved using a palliative-care-based approach.

Several palliative guidelines in neurodegenerative conditions are currently under development. Most proposed frameworks envisage a dynamic, consultation-based, episodic model of specialist palliative care intervention in neurodegenerative conditions, where palliative services are involved early in the course of the disease.

Neurodegeneration is a rapidly changing field of medicine and represents an important interface between several medical specialties. The development of effective neuropalliative frameworks will provide an optimal environment for the care of patients with advanced neurological conditions, benefiting patient and carers, and providing an integrated approach involving all members of the multidisciplinary team. In this chapter, we discuss the role of palliative medicine in the most common neurodegenerative conditions.

Existing Frameworks and Current Initiatives in Palliative Neurology

A number of international frameworks have extended specialist palliative care into the management of nonmalignant conditions (Table 13.1).

The Gold Standards Framework was developed in 2000 as a community-based, primary-care-centered U.K. program. It focuses primarily on continuity, coordination of care, and symptom control as well as carer support. The program is based on the identification of the patient's individual palliative needs and preferences, and on planning their care

Table 13.1 International frameworks for palliative care in neurology

International initiatives in palliative medicine for nonmalignant conditions				
Name of the program	Country	Year	Stage	Focus
Gold Standards Framework	UK	2000	Audited and implemented	Community-based service, carer Support
PEACE – Palliative Excellence in Alzheimer's Care Efforts	US	2003	Audited and implemented	Patients with dementia, advance planning, death at desired location
Liverpool Care Pathway (Version 12)	UK	2009	Audited and implemented	Holistic approach to physical, psychological, social, and spiritual care
Preferred Priorities for Care	UK	2004	Audited and implemented	Discussion and respect of patient preferences
Neurological Care Pathway	UK	2007	Audited and implemented	Management algorithm with indicators to advance care planning and specialist palliative care referral
Neurology Taskforce of the EAPC	EU	2009	Under development	Palliative guidelines for ALS, HD, AD, PD
Guidelines for a Palliative approach in Residential Aged Care	Australia	2006	Audited and implemented	Evidence-based palliative guidelines for elderly patients in residential units
Respecting Patient Choices Program	Australia	2005	Piloted	A comprehensive advance care planning program
My Home Life	UK	2007	Development	Support for staff working in care homes

regardless of the diagnosis. The principle aim is to reduce hospital admissions, enabling more patients to die where they choose (Table 13.2).

PEACE – Palliative Excellence in Alzheimer's Care Efforts is an American program that aims to extend high-quality palliative care to people with Alzheimer's disease and their families. This model has been developed at the University of Chicago and the Hospice of Michigan to provide patient-centered care and family support. This initiative emphasizes advance planning and a palliative care approach from the time of diagnosis of dementia. Preliminary results of the PEACE program have demonstrated that implementation of the program is more likely to respect patient preferences, to ensure that patients die in their desired locations, that adequate pain control in achieved, and that patients and families are more likely to express satisfaction with the quality of care.

The Liverpool Care Pathway for the dying patient (LCP) was originally developed for patients with malignant conditions, and has been adapted to other conditions. It identifies physical, psychological, social, and spiritual care as main domains of care. The aim is to improve care over the last few days of life – identifying those who are imminently dying, withdrawing unnecessary treatment, ensuring appropriate treatment is in place to control symptoms, and supporting patient, family, and professionals.

Table 13.2 A selection of online, Internet-based resources on palliative care and symptomatic management

Online resources on palliative care in neurology	
Palliative medicine	
The European Association for Palliative Care (EAPC)	http://www.eapcnet.org/
The National Council for Palliative Care (UK)	www.ncpc.org.uk
American Academy of Hospice and Palliative Medicine	http://www.aahpm.org/index.html
PEACE – Palliative Excellence in Alzheimer's Care Efforts (US)	http://www.promotingexcellence.org/chicago/index.html
Preferred Priorities for Care (UK)	http://www.endoflifecareforadults.nhs.uk/eolc/CS310.htm
Respecting Patient Choices Program (AUS)	http://www.respectingpatientchoices.org.au/
Gold Standards Framework(UK)	http://www.goldstandardsframework.nhs.uk/
National Hospice and Palliative Care Organization (US)	http://www.nhpco.org/templates/1/homepage.cfm
Liverpool Care Pathway (UK)	http://www.mcpcil.org.uk/liverpool-care-pathway/index.htm
Quality of Life Research Unit of the University of Toronto	http://www.utoronto.ca/qol/index.html
Motor neuron disease	
ALS America, (ALSA), US	www.alsa.org
MND Association, (MNDA), UK	www.mndassociation.org
ALS Society of Canada	www.als.ca
ALS Forums	http://www.alsforums.com/
World Federation Of Neurology Research Group	http://www.wfnals.org/
The Irish Motor Neuron Disease Research Foundation	www.mnd.ie
Huntington's disease	
Huntington's Disease Association (UK)	http://www.hda.org.uk/
Huntington's Disease Society of America	http://www.hdsa.org/
Australian Huntington's Disease Association	http://www.ahda.asn.au/
International Huntington Association (IHA)	http://www.huntington-assoc.com/
Huntington Society of Canada	http://www.huntingtonsociety.ca/english/index.asp

Table 13.2 (continued)

Parkinson's disease	
Parkinson's Disease Society (UK)	http://www.parkinsons.org.uk/
American Parkinson Disease Association	http://www.apdaparkinson.org/userND/index.asp
"We Move" Foundation	http://www.wemove.org/
National Parkinson Foundation (US)	www.parkinson.org
European Parkinson's Disease Association (EPDA)	http://www.epda.eu.com/
Parkinson's Disease Foundation (US)	http://www.pdf.org/
Parkinson's Australia	http://www.parkinsons.org.au/index.htm
Parkinson Society Canada	www.parkinson.ca
Cure PSP (US)	http://www.psp.org/
Alzheimer's Disease	
Alzheimer's Foundation of America	http://www.alzfdn.org/
Alzheimer's Society (UK)	http://alzheimers.org.uk/
Alzheimer's Australia	www.alzheimers.org.au
Alzheimer Society of Ireland	http://www.alzheimer.ie/
Alzheimer Society of Canada	http://www.alzheimer.ca/english/index.php

Preferred Priorities for Care (formerly Preferred Place of Care or PPC) is a U.K. initiative that promotes a discussion of preferred place of care and death. The patient-held document of the PPC has two key questions: "Where would you like to be cared for in the future?" and "What are your preferences and priorities for your future care?" This document is designed to enhance clear communication of the patient's preferences and is recommended by the National Institute for Health and Clinical Excellence (NICE) guidance in the United Kingdom.

In the United Kingdom, the National Council for Palliative Care set up the Neurological Conditions Policy Group in 2004 to assess the palliative care needs of people with neurological conditions, to evaluate good practice examples, and to identify service models. Based on a large survey (the First National Survey of Palliative Care, Neurology and Rehabilitation Services), the group developed the *Neurological Care Pathway*. This pathway describes specific indicators for referral and brings forward the concept of neuropalliative rehabilitation.

An Australian initiative, "*Guidelines for a Palliative Approach in Residential Aged Care*" is a set of evidence-based guidelines, developed to answer the specific palliative care needs of older people in residential care facilities in Australia. This program has been funded by the Australian government and adopts a multifaceted, holistic, palliative

approach to nonmalignant symptoms of elderly people. These comprehensive recommendations address the physical, social, cultural, and spiritual needs of patients as well as advance care planning, dignity, and family support.

Assessment Scales

Underreporting of pain and discomfort and inability to recall symptoms is a well-known problem of treating patients with long-term conditions and, in particular, for those with impaired cognition.

A comprehensive assessment and review of symptoms is the initial step following referral to specialist palliative services. A number of validated tools are available for baseline evaluation. Some of them had been optimized for elderly people and have a role in neuropalliative assessments.

The Memorial Symptom Assessment Scale (MSAS) is a scale used to assess 32 physical and psychological symptoms in three different dimensions: intensity, frequency, and distress.

The Rotterdam Symptom Checklist (RSCL) is another tool that measures both psychological and physical aspects of quality of life. These instruments, despite being recognized as highly sensitive, are too lengthy to be administered routinely in progressive neurological conditions.

The Edmonton Symptom Assessment Scale (*ESAS*) is patient-rated symptom visual analogue scale that may be particularly useful in patients with neurodegeneration (Table 13.3).

Careful assessment of symptoms, including listening to the patient, family, and carers can ensure that appropriate treatment is provided to alleviate distress. Severe cognitive impairment increases reliance on the carers' views and in such situations, a standardized assessment system such as the Disability Distress Assessment Tool can be helpful.

Table 13.3 Domains of the supplemented Edmonton symptom assessment scale (ESAS)

Symptoms are rated from 0 to 10 on a numerical scale:
1. Limited activity
2. Fatigue
3. Physical discomfort
4. Shortness of breath
5. Pain
6. Lack of well-being
7. Problems with appetite
8. Feelings of depression
9. Anxiety
10. Nausea
11. Difficulty sleeping
12. Weakness
13. Dizziness
14. Difficulty thinking
15. Constipation

The *Disability Distress Assessment Tool* (DisDAT) was developed in 2001 to identify distress in people with severe communication difficulties. The design of DisDAT is based on the observation that patients have their own "vocabulary" of distress signs and behaviors and that these cues may not be specific to the cause of the distress. The scale allows carers, both family and professional, to describe the individual's usual content cues to enable distress cues to be identified more clearly. The assessment tool uses a so-called "Distress Passport" – a summary of signs and behaviors when patient is content and when distressed. Assessment takes appearance, vocal signs, habits, mannerisms, and posture into consideration. Validation studies of DisDAT have confirmed that it is sensitive to the task of identifying distress and that it is easy to use.

Decision Making and Planning in Neurodegenerative Disease

During the progression of neurological disease, there may be many decisions regarding care preferences, for instance decisions about specific interventions such as gastrostomy placement, respiratory support, or end-of-life care. It is crucial to enable patients and their families to be closely involved in these decisions and to be able to express their autonomy – the informed preference or consent to whatever we do or what is done to us. This will include enabling people with neurological disease to have:

- Knowledge about the disease and the symptoms and issues they face
- Information about the decision
- A choice of options, clearly presented without bias
- Opportunity to discuss and consider decisions

Many people with neurological disease will face cognitive decline – most obviously in Huntington's disease, multiple sclerosis, Parkinson's disease, and the various forms of dementia described in this volume including ALS. To assess if these patients are able to make an autonomous decision may be difficult, as they must be able to:

- Communicate and understand the decision
- Understand the relevant information
- Appreciate the situation and its consequences
- Manipulate the information

As cognitive loss occurs, the capacity of the person may be affected and there is a need to ensure that the person has the capacity to make this decision. In England and Wales, the Mental Capacity Act stresses that it is essential to facilitate the person's decision-making ability as far as possible and every decision will be discrete and specific – patients should not be assumed to have lost capacity for all decision making. There is an imperative on all professionals to allow decisions to be made by the person themselves, if at all possible.

In many countries, advance directives are allowed – allowing the person to express their wishes for their future care while they are able to express them clearly. There is

evidence that patients with neurological disease do wish to express their wishes but the discussions may be difficult and complex. The legal validity will vary from country to country but the overall aim, to allow the patient to express their wishes, will usually be respected.

In England and Wales, there are three main ways of advance planning:

- An *advance statement* – made by the person while competent – expresses their overall wishes. While not legally binding, the advance statement must be taken into consideration by the decision-makers when the patient has lost capacity.
- An *advance decision to refuse treatment* defines specific treatments in specific circumstances. The advance decision is legally binding and should be adhered to if the patient loses capacity and the issues defined become relevant.
- A *lasting power of attorney* defines a proxy (an attorney or family member) to make decisions on the patient's behalf if they lose capacity themselves. This may be for financial and personal and medical care issues.

The principles of advance care planning are similar in most jurisdictions, although there may be some variations from country to country in the application. And while the discussion of the patient's wishes may be difficult, it allows the patients to retain autonomy and involvement in their care, even when their condition is advanced and they are unable to make the decisions themselves.

Quality of Life in Neurodegenerative Disease

Quality of life (QoL) is a concept of emotional, physical, and social well-being within the individual's specific medical, social, and cultural context. QoL has been defined by a number of organizations and universities. The clear description of the different aspects (domains) of quality of life is necessary for the design of comprehensive and sensitive assessment tools. These instruments are indispensible for auditing the effectiveness of medical and palliative interventions. Numerous QoL rating scales have been developed and validated. Many of these instruments are health-related and have been optimized for specific medical conditions. Regardless of the type of rating instrument used, the emphasis is on the individual's subjective perception of his or her well being in the given cultural, social, and medical circumstances.

Quality of life has been defined the World Health Organization Quality of Life Group in 1996 as: "… the individual's perceptions of their position in life in the context of the culture and value system where they live, and in relation to their goals, expectations, standards, and concerns. It is a broad-ranging concept, incorporating in a complex way a person's physical health, psychological state, level of independence, social relationships, personal beliefs, and relationship to salient features of the environment."

The WHO identifies six major domains of QoL:

1. Physical domain (pain and discomfort, energy and fatigue, sexual activity, sleep and rest, sensory functions)

2. Psychological domain (positive feelings, thinking, learning, memory and concentration, self-esteem, bodily image and appearance, negative feelings)
3. Level of independence (mobility, activities of daily living, dependence on medicinal substances and medical aids, dependence on non-medicinal substances, communication capacity, work capacity)
4. Social relationships (personal relationships, social support, activities as provider/supporter)
5. Environment (freedom, physical safety and security, home environment, work satisfaction, financial resources, health and social care accessibility and quality, opportunities for acquiring new information and skills, participation in and opportunities for recreation and leisure activities, physical environment (pollution/noise/traffic/climate), transport)
6. Personal beliefs/spirituality

Based on the above domains, the WHO developed its own QoL assessment tools, The WHOQOL-100 and the WHOQOL-BREF instruments.

The University of Toronto's Quality of Life Research Unit defines quality of life as "The degree to which a person enjoys the important possibilities of his or her life." This research group proposed a conceptual framework around three life domains: being, belonging, becoming. This model further divides the domains into three subdomains. *Being*: physical being, psychological being, spiritual being. *Belonging*: physical belonging, social belonging, community belonging. *Becoming*: practical becoming, leisure becoming, growth becoming. The definition of subdomains allows a systematic approach to the assessment of QoL. This research group approaches QoL by the enjoyment and the meaning attached to the above subdomains. This framework defines a quality environment as one that:

- Provides for basic needs (shelter, food, social interactions)
- Provides control (decision making)
- Provides opportunities within the individual's potential

The assessment tool proposed by this group is the Quality of Life Profile (QOLP), a 54-item instrument rating importance, enjoyment, control, and opportunities within the above domains.

Given the inexorable course of neurodegenerative disease, preservation of QoL is a key therapeutic concept. Several QoL-related studies in ALS demonstrated that QoL is independent from physical disability and is frequently a function of complex social factors.

Measurement of QoL in neurodegenerative disease raises a number of specific challenges due to the combination of cognitive and physical disabilities. Generic instruments such as the SF-36 Health Survey or the Sickness Impact Profile have a limited role in the assessment of quality of life neurodegenerative conditions. A number of disease-specific instruments have been developed to overcome the amnesic, communication, and cognitive difficulties associated with neurodegenerative conditions (Table 13.4). Many of these rating scales are observational and use composite scores from patients and carers.

Table 13.4 A selection of quality-of-life assessment instruments in neurodegenerative disease

Alzheimer's Disease-Related Quality of Life (ADRQL)	Optimized for AD, 47 items in 5 domains: social interaction, awareness of self, feelings and mood, enjoyment of activities, response to surroundings
The Cornell-Brown Scale for Quality of Life in Dementia (CBS)	Incorporation of caregivers' perspective
Dementia Care Mapping (DCM)	Observational assessment tool developed to be used in residential care for patients with moderate-to-severe disability
Parkinson's Disease Quality of Life (PDQL Questionnaire)	37 item questionnaire; four subscales: parkinsonian symptoms, systemic symptoms, emotional functioning, and social functioning
Quality of Life in Late-Stage Dementia (QUALID Scale)	Observational scale for late-stage dementia, brief, used in residential care
Psychological Well-Being in Cognitively Impaired Persons (PWB-CIP)	11 item, observer-rated assessment instrument
Dementia Quality of Life questionnaire (D-QOL)	29 item scale in 5 domains: positive affect, negative affect, feelings of belonging, self-esteem, sense of aesthetics
Quality of Life-Alzheimer's Disease (QOL-AD)	Composite scores from patient and caregiver responses on a 13-item scale
Schedule for the Evaluation of Individualized Quality of Life-Direct Weighting (SEIQoL-DW)	A brief instrument used extensively in ALS research. Respondents identify the areas of life, which are most important to their QoL, then rate their level of functioning or satisfaction with each
McGill QoL Questionnaire (MQOL)	A 20-item scale frequently used in ALS, 5 domains: physical well-being, physical symptoms, existential well-being, psychological symptoms, and support

Palliative Care of Individual Neurodegenerative Diseases

Amyotrophic Lateral Sclerosis

ALS is a relentlessly progressive and presently incurable neurodegenerative condition. See Chap. 7 for a detailed discussion of ALS. ALS causes muscle weakness, disability, and death with a median survival of 3–5 years. ALS is regarded by many as an excellent model for palliative care intervention in neurology.

There is consensus in the international literature that optimal ALS management should adopt a multidisciplinary (MDT) approach. The EFNS task force on management of ALS recommends that a palliative care approach should be adopted from the time of diagnosis. Palliative care should be based in the local community and advance directives should be discussed early and revisited regularly. The referral criteria for specialist inpatient palliative care have been well defined in ALS (Table 13.5).

Table 13.5 Referral criteria for inpatient palliative care in ALS

Consensus criteria for hospice referral of ALS patients by the ALS peer workgroup
1. FVC <60% predicted (or rapid decline in FVC (more than 20%) over 2–3 months), or
2. Clinical signs or clinical symptoms of respiratory insufficiency, or
3. Respiratory weakness requiring noninvasive positive pressure ventilation (NIPPV), or
4. Nutritional decline requiring enteral feeding, or
5. Severe pain or psychosocial distress requiring intensive palliative care interventions (including opioid medication), or
6. Rapidly progressive (over 2–3 months) paralysis in two body regions

ALS is now increasingly recognized to be a complex multisystem disorder with prominent nonmotor manifestations, including a broad range of neuropsychological and behavioral deficits. Currently, there is limited recognition of the impact of cognitive impairment on the disease management in ALS.

The presence of cognitive and behavioral impairment in ALS has serious implications for the patient and caregivers. Survival is significantly shorter among ALS patients with frontotemporal dementia (ALS-FTD). ALS patients with cognitive impairment are at higher risk of falls, choking episodes, and injuries. They show poorer compliance with walking aids, feeding tubes, and noninvasive ventilation (NIV). Cognitive impairment also affects the ability of this patient group to make important financial and legal decisions and the ability to competently engage in end-of-life decisions.

Early signs of respiratory insufficiency may include morning headaches, daytime somnolence, or orthopnea. Initiation of noninvasive positive pressure ventilation (NIPPV) is discussed in detail in Chap. 7. Common initial complaints with NIPPV, such as leaks, abdominal bloating, and facial discomfort, can be easily managed. Reversible causes of shortness of breath such as infections, pulmonary embolus, or bronchospasm should also be considered when assessing dyspnea. Yearly influenza vaccinations and polyvalent pneumococcal vaccine is recommended. Discussion about tracheostomy and invasive ventilation should take place early.

Abnormal arterial blood gas findings develop late in ALS, and hypercapnia carries a very poor prognosis. To avoid arterial sampling, noninvasive blood gas measurement or venous blood can be used, where raised venous bicarbonate and low chloride levels are adverse prognostic markers. For dyspnea despite NIPPV, a combination of opiates and benzodiazepines are used. Opioids (e.g., morphine) can be administered orally, through feeding tubes, transdermally, or via continuous subcutaneous infusion by a portable syringe driver. Changing the route of administration requires expertise in dose conversions and coexisting renal and liver disease needs to be taken into account depending on the type of opiate.

There is no evidence that morphine use shortens life in ALS. It has been established that doses of morphine used in ALS are significantly lower than those used in cancer-related pain syndromes. Opiates are effective in the management of pain, nocturnal discomfort, and dyspnea long before the terminal phase of ALS.

Anxiolytics, such as oral or sublingual lorazepam or midazolam by injection or continuous subcutaneous infusion, are widely used in combination with opiates to reduce anxiety and distress associated with dyspnea.

The routine use of supplemental oxygen is not recommended in ALS as it may reduce the respiratory drive leading to carbon dioxide retention and headaches.

Sialorrhea can be treated with oral medications such as amitriptyline or a transdermal hyoscine hydrobromide patch, botulinum toxin A injection into the salivary glands, or salivary gland radiotherapy.

Thick mucous secretions of the airways are difficult to manage when the coughing effort is insufficient. Physiotherapy, manually assisted coughing techniques, modified postural drainage, and mechanical insufflation−exsufflation devices (e.g., CoughAssist®, Phillips Healthcare, Andover MA, USA, and Best, The Netherlands) can be helpful.

Psychological and existential factors contribute greatly to the QoL of patients with ALS. The prevalence of depression varies in different studies. Both serotonin-specific reuptake inhibitors (SSRI) and tricyclic antidepressants can be used, but amitriptyline is often the preferred choice if sialorrhea, insomnia, or pseudobulbar affect coexist.

Pseudobulbar affect is a consequence of corticobulbar degeneration and has been treated traditionally with amitriptyline or fluvoxamine. There is now evidence that dextromethorphan combined with quinidine is beneficial.

Spasticity is caused by upper motor neuron degeneration and is described as stiffness and slowness of voluntary movements by the patients. Spasticity may cause significant discomfort and pain and lead to the impaired coordination of the affected limb. Pharmacological treatment options include baclofen and tizanidine. Physiotherapy with passive movements is encouraged to maintain full range of motion and to avoid contractures. Reduction of the spasticity of the lower limbs may reduce mobility; therefore, careful assessment by an experienced physiotherapist is essential. Cramps are common complaints in ALS and can be managed by quinine sulfate. However, potential adverse effects of quinine include cardiac arrhythmias (QT prolongation), agranulocytosis, or thrombocytopenia. Tinnitus is often seen in higher doses. Alternatively, phenytoin or carbamazepine can be used.

Sleep problems might arise from dyspnea, anxiety, depression, or difficulty in changing position due to weakness. The identification of the cause of the sleep disturbance is crucial prior to treatment. Nocturnal oximetry should be considered if respiratory failure is suspected and NIV may be appropriate (see also Chap. 7). Pharmacological options include zopiclone, flurazepam, and chloral hydrate. Of those who tolerate NIV while hospitalized, a significant proportion (50% in one study) do not persevere following discharge. Factors that adversely affect the ability of patients to tolerate NIPPV include the presence of bulbar symptoms with increased secretions, the ability to manually adjust the mask, and the presence of cognitive impairment.

Invasive mechanical ventilation, implying the use of a tracheostomy or endotracheal tube, may be considered in patients who cannot tolerate NIV. Invasive mechanical ventilation has the advantage of bypassing the upper airway and of prolonging life indefinitely, notwithstanding the progression of the disease. However, while the use of tracheostomy may extend life, there are many ethical issues to be considered. Formal and candid discussions about the relative merits and demerits of full mechanical ventilation should take place in a planned manner, and in a comfortable and quiet setting. The conversation should include a senior neurologist, the patient, and a close family member. The discussion should take place when the patient is relatively stable. This is because mechanical ventilation is

occasionally undertaken as an emergency procedure in the context of sudden respiratory deterioration, without prior discussion with the patient or family. This is a situation that is to be avoided at all costs.

A clear plan for management of respiratory failure should be established, taking into account the fact that routine use of invasive mechanical ventilation at home may be prohibitively expensive in many European health care systems. Moreover, patients contemplating full mechanical ventilation should be aware of the risk of losing all methods of conventional communication, including eye movements, and that they may effectively become "locked in." In the absence of advanced technology such as brain–computer interface, the wishes of these patients who have become anarthric and incapable of communicating may be difficult to assess. It is therefore desirable that the patient's wishes are made known prior to the loss of communication, and a decision to withdraw ventilation be made according to the patient's advance directive.

In the more likely event that patients and carers decline full mechanical ventilation, the patient and family should be provided with assurances that palliative care strategies can control symptoms in the terminal phase of the illness.

In those who have undergone tracheostomy and who are permanently using full mechanical ventilation, withdrawal poses a number of medical, legal, and ethical problems. While it is well recognized by ethicists that patients who are receiving mechanical ventilation have the right to discontinue their respiratory support, the realization of this right may produce legal, ethical, and religious concerns that are culturally based for some individuals.

A decision by the patient to withdraw mechanical ventilation should be acted upon in a manner that causes the patient minimal discomfort. Protocols should exist to this effect in each intensive care unit.

Supplemental oxygen and positive end-expiratory pressure should be initially discontinued. The T-tube is then converted to spontaneous breathing.

The patient may require a sedative/hypnotic or opiate preoperatively and during each stage of withdrawal and should then be supported using standards of palliative care as outlined above.

New Palliative Models of Care in ALS

The course and rate of progression of ALS varies greatly from person to person. Because of the heterogeneous combination of complaints and different disease trajectories in ALS, there are no simple, stepwise management algorithms as might be the case in other progressive conditions. Optimal management requires the expertise of a large multidisciplinary team with experience in ALS management. While these teams tend to be based in larger centers, most patients are cared for in the community. A management strategy that incorporates hospital-based multidisciplinary care with community-based intervention in a "hub and spoke" model is most effective.

A flexible model of care with evidence-based palliative interventions at specific trigger points in various clinical domains has been proposed. This framework gives specific guidance to primary care and medical physicians when specialist palliative care referral should

Palliative Framework				
Domain of functioning	**Diagnostic phase**	**Mild–Moderate disability**	**Severe disability**	**Terminal phase**
Cognition				
Gross motor function				
Fine motor function				
Swallowing				
Communication				
Breathing				
Psycho-social carer burden				

Fig. 13.1 The structure of palliative care intervention matrix in amyotrophic lateral sclerosis (ALS)

take place, depending on symptom severity. This model envisages episodic, consultation-based specialist palliative care involvement in ALS management. It is presented as a matrix of clinical and chronological domains. The clinical domains include cognition, gross motor function, fine motor function, swallowing, communication, breathing, and psychosocial domains, with specific possible interventions ranging from simple management strategies to referral to specialist palliative care services. Chronological domains include the diagnostic phase, mild-to-moderate disability, severe disability, and the terminal stage (Fig. 13.1). Triggers for palliative care intervention include changes in the domains listed in Table 13.6.

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative condition inherited as an autosomal dominant disease. See Chap. 8 for a detailed discussion of Huntington's disease. HD is characterized by choreiform movements, psychiatric problems, and dementia. Without disease-modifying or neuroprotective treatments, the mainstay of therapy is supportive from the diagnosis and aims at optimizing QoL.

A number of palliative challenges are specific to the management of HD (Table 13.7). Presymptomatic genetic screening can identify individuals who are fully aware of the devastating course of the disease. Attempted suicide or psychiatric hospitalization is not uncommon after predictive testing for HD and intensive support is required at the time of testing.

Optimal care should adopt a multidisciplinary approach. As is the case for all neurodegenerative conditions where cognitive decline is a feature, end-of-life issues and patients' preferences regarding location of care, feeding tubes, resuscitation, and other advance directives need to be discussed early, prior to the development of significant cognitive and

Table 13.6 Domains of palliative care intervention in amyotrophic lateral sclerosis

Domains of care	Management issues	Examples	Possible intervention
Physical care	Respiratory symptoms	Orthopnea, dyspnea, respiratory insufficiency	Assessment: SNIP, overnight oximetry, early morning ABG Noninvasive ventilation (NIV)
		Infections, thick secretions	Influenza vaccinations, manually assisted coughing techniques, modified postural drainage, humidification, mechanical insufflation–exsufflation devices, high-frequency chest wall oscillation, antibiotics
		Respiratory distress	Opiates and anxiolytics
	Cognitive deficits	Early verbal fluency deficits, language deficits, dysexecutive syndromes	Early identification, referral to neuropsychological assessment
	Behavioral dysfunction	Disinhibition, apathy, impaired insight and safety awareness	Carer support
	Dysphagia	Nutrition and hydration	Speech and language therapy assessment
		Aspiration, malnutrition	Compensatory swallowing maneuvers
		Weight loss	RIG/PEG placement prior to respiratory compromise
			Dietetics: high protein, high calorie diet, oral nutritional supplementation, carer education
	Dysarthria	Impaired communication	Speech therapy Augmentative and alternative communication (AAC) devices
	Fatigue	Lethargy, influenced by mood	SSRIs or TCAs
	Sialorrhea	Oropharyngeal secretions, drooling	Amitriptyline, transdermal hyoscine hydrobromide patch, salivary gland botulinum toxin A injection, salivary gland radiotherapy
	Musculoskeletal discomfort	Spasticity	Baclofen, tizanidine, physiotherapy
		Cramps	Quinine sulfate
		Pain: postural or joint e.g., shoulder pain – adhesive capsulitis	Analgesics, physiotherapy, steroid injection of affected shoulder

(continued)

Table 13.6 (continued)

Domains of care	Management issues	Examples	Possible intervention
	Pseudobulbar affect	Outbursts of tearfulness or laughter	Amitriptyline Dextromethorphan combined with quinidine
	Sleep disturbances	Postural discomfort, anxiety	Zopiclone
	Muscle weakness and functional decline	Loss of independence in activities of daily living	*Occupational therapy*: Education of adaptive techniques, access and home modifications, assistive technology and equipments, driving assessments *Physiotherapy*: orthotics, walking aids, collars, exercise
	Dependent Edema of hands and feet	Secondary to reduced muscle pump activity in the weak limb	Positioning
	Constipation	Rare, medication/immobility related	Hydration, lactulose
Psychosocial care	Psychological distress	Denial, anger, anxiety, helplessness, fatigue, depression, hopelessness, fears of death and dying	Psychosocial assessment, empowerment, discussion of coping strategies, acknowledgement of loss, support groups, counseling
	Social interventions	Financial advice by experienced social worker Carer support	Disability benefits, allowances, pensions, carer's allowance if applicable Home care teams, respite
Advance care planning	End-of-life decisions	Place of death preferences, management preferences (feeding tubes, tracheotomy, resuscitation, etc.)	Advance directives/statement Advance decisions to refuse treatment Lasting power of attorney
Spiritual care	Existential questions	Faith, hope, vocation, acceptance	Spiritual and pastoral care
Bereavement	Anticipatory grief, grief	Bereavement, continuing bonds	Acknowledgement of grief, bereavement support

Table 13.7 Domains of palliative care intervention in Huntington's disease

Domains of care	Management issues	Examples	Possible intervention
Physical care	Movement disorders	Chorea	Only treat if troublesome, e.g., tetrabenazine
		Gait impairment	Physiotherapy
		Rigidity, bradykinesia, severe akinesia is rare	Poor evidence for dopaminergic therapy
	Psychiatric problems	Psychosis, agitation, irritability, dysphoria	Quetiapine, calm predictable environment
		Depression, wish to suicide	Screen for suicidal thoughts, TCAs, or SSRIs
	Progressive cognitive decline, dementia	Executive dysfunction, loss of insight, poor judgment, memory loss	Family support, counseling for carers, regular respite
	Skin care	Pressure ulceration	Airflow mattresses
	Respiratory distress	Infections, exhaustion	Opiates, benzodiazepines
Supportive care	Dysphagia	Weight loss	Feeding tubes, dietetics
	Gait and balance problems	Falls	Physiotherapy, occupational therapy
Psychosocial care	Psychological issues	Presymptomatic genetic screening	Pretest guidance, psychological support
	Social aspects	Financial issues, legal issues	Driving restriction, support groups, home care
Advance care planning	Patient preferences	Site of care, medical interventions, guardianship, resuscitation	Early discussion of advance directives prior to cognitive impairment
Spiritual care	Existential questions	Spiritual distress, faith, hope, vocation, acceptance	Individualized spiritual support for patient and family
Bereavement	Anticipatory grief, grief	Continuing bonds	Acknowledgement of grief, bereavement support

motor deficits. Speech therapy and dietetics are effective in managing initial weight loss; physiotherapy assessments are beneficial to prevent falls.

In later stages of the condition, chorea may become disabling. The involuntary movements may be aggravated by stress or anxiety. Tetrabenazine and atypical neuroleptics have been used for the treatment of involuntary movements, but they frequently have a negative impact on cognition and parkinsonism. For the management of psychiatric symptoms such as agitation and psychosis, quetiapine is recommended. Depression can be managed with SSRIs or tricyclic antidepressants and screening for suicidal thoughts is important. Cholinesterase inhibitors have been used for the treatment of dementia, but no

clear improvement has been demonstrated in HD. In the terminal phase, patients succumb to respiratory weakness and infection, and in the agonal stages, supportive palliation of symptoms is arguably more appropriate than aggressive antimicrobial treatment.

The multifaceted symptoms associated with HD can be challenging both for patients and for carers, and regular respite can be beneficial, as can counseling and support for carers.

Palliative Care in Dementia Syndromes

While the underlying pathology and the early presentation of the various dementia syndromes are very different, as the disease progresses, they lead to similar challenges in management. See Chaps. 4 and 6 for detailed discussion of vascular and frontotemporal dementias. Carers of advanced dementia patients face similar ethical and professional dilemmas with regards to feeding tubes, resuscitation, behavioral symptoms, and infections regardless of the type of dementia (Table 13.8).

Dementia syndromes share common symptoms for effective palliative care intervention. As with other conditions, the focus of palliative care in dementia is to enhance comfort, dignity, and QoL.

Behavioral disturbances include wandering, psychosis, depression, agitation, and sleep disorders. Wandering and getting lost are major concerns for families. Paranoid delusions can be particularly distressing for caregivers. When assessing disruptive behavior or agitation, it is important to rule out infection, full bladder, pain, pressure areas, unrelieved constipation, or perception of restraint. Olanzepine, risperidone, and quetiapine are used for symptomatic management. Although small dose of parenteral haloperidol for emergency management or severe agitation have proven safe, the switch to oral preparations for prolonged use often leads to the development of drug-induced parkinsonism, especially in patients who have dementia with Lewy bodies (DLB) disease and may be exquisitely sensitive to antipsychotic medication. The evidence for increased stroke risk associated with atypical antipsychotics is conflicting and has not been confirmed by large studies.

Eating difficulties and food refusal might arise from apraxia, dislike of institutional food, lack of perception of hunger, or swallowing difficulty. There is consensus that feeding tubes provide little benefit in advanced dementia and that they do not promote the healing of pressure ulcers, improve functional status, or increase survival. Feeding tubes may actually increase the risk of pneumonia, sinus and middle ear infections, and cellulitis. The need for restraints to prevent tube removal, the pleasure of eating, and contact with caregivers during feeding are other arguments against feeding tubes.

Several studies demonstrated the high number of inappropriate referrals of patients with dementia to the emergency room or acute hospitals. The benefits and risks of transfer to an acute hospital should be discussed with family and staff. Available data suggest little benefit from transferring a patient with advanced dementia to an acute hospital from home or a nursing home. Even elderly patients with no cognitive deficits are at high risk of developing confusion, incontinence, or depression on hospital admission. Frequent medical complications include deep venous thrombosis, pulmonary embolism, atrial fibrillation, myocardial infarction, and urinary tract infections in this patient group. Routine invasive procedures on hospital admissions such as x-rays, arterial blood gas sampling, intravenous

Table 13.8 Domains of palliative care intervention in advanced dementia

Domains of care	Management issues	Examples	Possible intervention
Physical care	Infections	Asymptomatic bacteriuria	No evidence of benefit from antibiotics
		Fever, pneumonia	Antipyretics and analgesia
	Psychiatric problems	Psychosis, wandering, agitation, irritability, dysphoria, paranoid delusions	Rule out infection, constipation, pain, urinary retention, pressure ulcers, trial of atypical neuroleptics, provision of a familiar, calm, predictable environment
	Terminal respiratory distress	Infections, exhaustion	Opiates, benzodiazepines
Supportive care	Dysphagia	Weight loss	Risks of feeding tubes, pleasure of eating
	Gait and balance problems	Falls	Physiotherapy, occupational therapy
	Skin care	Pressure ulceration	Prevention, airflow mattresses
Psychosocial care	Psychological issues	Distress from changing site of care	Continuity of care, providing a familiar environment
	Social aspects	Financial issues, legal issues	Driving restriction, support groups, respite, home care
Advance care planning	Patient preferences	Site of care, proxy decision making, guardianship, medical interventions, feeding tubes, resuscitation, management of infections and cardiac events, transfer to acute hospital/ER	Early discussion of advance directives addressing the risks and benefits of specific management issues
Spiritual care	Existential questions	Spiritual distress, faith, hope, vocation, acceptance	Individualized spiritual support for patient and family
Bereavement	Anticipatory grief, grief	Continuing bonds of carers and family	Acknowledgement of grief, bereavement support, pastoral Care

cannulation, and Foley catheter placement might be inappropriate and are not keeping with the comfort-centered management of patients with advanced dementia.

In the terminal phase of dementia, the most frequent symptoms are dyspnea, pain, fever, oral thrush, and constipation, all of which can be managed effectively in the community or residential care.

Cardiopulmonary resuscitation (CPR) is unlikely to be successful in advanced dementia. Data from CPR attempts in nursing home show reduced success rate in the presence of

dementia. CPR is traumatic and causes significant distress to the families and caregivers. CPR might thus be inappropriate in late-stage dementia. Discussion around CPR should take place between the patient, staff, clinicians, and the caregivers. Decisions should be clearly documented and respected.

The use of antibiotics in advanced dementia has an extensive literature. There is no evidence for treating asymptomatic bacteriuria and studies showed it does not reduce the incidence of urinary incontinence. Antimicrobial therapy should be reserved for symptomatic bacteriuria associated with fever, dysuria, pain, or new-onset incontinence.

Despite being effective in the treatment of an isolated episode of infection, the use of antibiotics in recurrent infections does not prolong survival in the terminal stages of dementia. Inappropriate antibiotic use in long-term care facilities contributes to high rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) infections as well as *Clostridium difficile* colitis. Invasive procedures such as arterial blood gas sampling, IV cannulation, and collection of blood cultures are often inappropriate and intensive comfort measures with analgesics and antipyretics should be considered.

In summary, the goals of care should be established early with the patient and carers and revisited as the condition progresses. The risks and benefits of specific interventions such as transfer to an acute hospital, resuscitation, feeding tube placement, and antimicrobial therapy should be addressed.

Parkinson's Disease and Related Conditions

Parkinson's disease (PD) (see Chap. 5 for a detailed discussion.) and Parkinson-related conditions such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD) (discussed in Chap. 9) are more common than ALS and have a longer course. No disease-modifying or effective neuroprotective agents are currently available for PD. Disease trajectory is frequently divided into the supportive phase, the phase of transition, and the terminal phase (Table 13.9).

Distressing motor symptoms include bradykinesia, muscle rigidity, dystonia, fear of falling, and tremor, which increasingly interfere with daily activities. Physiotherapy is the mainstay of non-pharmacologic therapy to improve balance and confidence and preventing falls. Pharmacological management of Parkinson-related movement disorder is described in Chap. 9. Painful dyskinesias and dystonias are distressing for patients and carers and require aggressive management. More frequent and lower doses of carbidopa/levodopa might improve motor fluctuations. Controlled release preparations and adding a dopamine agonist or amantadine are other considerations.

Autonomic dysfunction such as orthostatic hypotension might require reduction of levodopa or the use of compression stockings, increased sodium intake, improved hydration, or fludrocortisone therapy. Increased sweating, delayed gastric emptying, constipation, sialorrhea, urinary urge incontinence, and erectile dysfunction are also part of the dysautonomic spectrum of Parkinson-related disorders.

Progressive dysphagia is due to rigidity and hypokinesis and the gradual involvement of the dorsal motor nucleus of the vagus in the disease process. There is no evidence to

Table 13.9 Domains of palliative care intervention in Parkinson's disease (PD)

Domains of care	Management issues	Examples	Possible intervention
Physical care	Movement disorders	Motor fluctuations (MF)	Reduction of levodopa administration intervals, addition of COMT inhibitors, dopamine agonist
		Dyskinesias	Reduction of levodopa dose if possible, amantadine
		Delay of the "on" response	Avoidance of high protein meals when taking Levodopa
		Early morning "off" period dystonia	Nocturnal sustained release levodopa or middle-of-the-night levodopa
		Acute akinesia	Investigate for systemic infection, fractures, acute medical problems
	Non-pharmacologic interventions	Non-pharmacologic management of gait impairment, progressive rigidity and akinesia	Physiotherapy: stretching and strengthening exercises, water aerobic exercises, balance training, treadmill training with body weight support, cued exercises
		Weight loss	Dietetics: high fiber diet, adequate hydration
		Hypophonia, dysarthria	Speech therapy
	Autonomic dysfunction	Orthostatic hypotension	L-dopa reduction, fludrocortisone therapy, compression stockings, increased salt intake
		Delayed gastric emptying	Hydration, low-fat diet, domperidone, avoidance of metoclopramide
		Constipation	Dietary changes, hydration, lactulose
	Psychiatric problems	Psychosis and hallucinations	Dose reduction of antiparkinsonian drugs if possible, quetiapine, clozapine
		Depression	Selective serotonin reuptake inhibitors (NOTE interaction with Selegiline)

(continued)

Table 13.9 (continued)

Domains of care	Management issues	Examples	Possible intervention
	Fatigue, sleep disorders	Excessive daytime sleepiness (EDS)	Improved sleep hygiene, coffee
		Restless legs syndrome (RLS)	Valproic acid, gabapentin, low-dose nocturnal dopamine agonists
		Rapid eye movement behavior disorder (RBD)	Clonazepam (0.25–1.5 mg), melatonin (3–12 mg)
	Progressive cognitive decline, dementia	Executive dysfunction (planning and attention deficits in particular), visuospatial deficits, amnestic features	Cholinesterase inhibitors; rivastigmine or donepezil (might worsen nausea and tremor), memantine (might cause hallucinations)
Psychosocial care	Social support	Carer support	Addressing social and economic concerns, support groups
Advance care planning	Patient preferences	Site of care, medical interventions, guardianship, resuscitation	Early discussion of advance directives prior to cognitive impairment
Spiritual care	Existential questions	Spiritual distress	Individualized spiritual support for patient and family
Bereavement		Anticipatory grief, grief, continuing bonds	Acknowledgement of grief, bereavement support

suggest a survival or QoL benefit by feeding tube placement in advanced parkinsonism. This remains an individual decision following discussion with the patient and caregivers.

Depression, panic attacks, and anxiety are frequent psychological features of parkinsonism. There are conflicting data on the effectiveness of SSRIs versus tricyclic antidepressants in the management of depression associated with Parkinson's disease. SSRIs are frequently preferred because of their more favorable side effect profile. While a concern of many specialists, large studies failed to demonstrate that SSRIs worsen motor symptoms in PD. More recently, amitryptyline has shown to be of benefit for depression in Parkinson's disease.

Psychosis, hallucinations, and delusions are common in Parkinson-related disorders. Dose reduction of antiparkinsonian medications often helps. If hallucinations are causing distress, it is recommended that anticholinergic drugs should be withdrawn first, followed by amantadine, (COMT) inhibitors, and dopamine agonists if necessary. Stopping levodopa treatment is not usually an option, but dose reduction might be attempted. Low doses of atypical neuroleptics can be beneficial without worsening the motor symptoms significantly.

Fatigue is a frequent complaint in parkinsonism, but pharmacological treatment, such as methylphenidate is rarely successful.

Daytime sleepiness and complex sleep disorders are often associated with advanced PD. Restless legs syndrome (RLS) might respond to low-dose dopamine agonists before bedtime and valproic acid, gabapentin, and benzodiazepines are also used. Rapid eye movement (REM) behavior disorder (RBD) is often an early symptom of PD, manifesting in complex active behavior during REM sleep. Most dopaminergic drugs as well as anticholinergics worsen RBD.

Cognitive dysfunction is very common in this patient group and different from the neuropsychological features of Alzheimer's disease. It often manifests as executive dysfunction and visuospatial impairments, and the initial verbal memory impairment is less prominent. Cholinesterase inhibitors (CIs) are used with moderate success. The potential benefit of CIs has to be weighed against worsening tremor and nausea. There is some suggestion that memantine is effective in PD, but hallucinations might worsen.

Atypical Parkinsonian Disorders

The term "atypical parkinsonian disorders" encompasses a group of conditions that have Parkinson-like symptoms but do not respond to the usual antiparkinsonian drugs. These syndromes frequently present with distinguishing symptoms that are seldom seen in PD. They are also referred to as Parkinson-plus disorders and have distinctive neuropathological characteristics. The most common diseases of this group include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), dementia with Lewy bodies (DLB), and multiple systems atrophy (MSA). See also Chap. 9. Despite these conditions being rapidly progressive, there is now evidence that quality of life can be preserved with high-quality palliative care. This is especially true in PSP and MSA.

In contrast to the relatively longer life expectancy of patients suffering from PD, the median survival is only 6 years in PSP, 9.5 years in MSA, 7 years in CBD, and 9 years in DLB. Although these conditions do share similar features, the presentation and therapeutic challenges are very different. For example, neuroleptic sensitivity is highly specific to DLB and presents with impaired consciousness and severe acute parkinsonism regardless

Table 13.10 Domains of palliative care intervention in atypical Parkinsonian disorders

Domains of care	Management issues	Examples	Possible intervention
Physical care	Movement disorders	Rigidity, bradykinesia. Note: severe akinesia is rare	Limited evidence for dopaminergic therapy
		Gait impairment	Physiotherapy
		Frequent falls	Amitriptyline, rasagiline, safety measures (helmets etc.)
	Psychiatric problems	Psychosis, agitation, irritability, dysphoria	Quetiapine, clozapine, provision of a calm predictable environment
		Depression	Screen for suicidal thoughts, TCAs, or SSRIs
	Progressive cognitive decline, dementia	Executive dysfunction, loss of insight, poor judgment, memory loss	No benefit from cholinesterase inhibitors
Supportive care	Dysphagia	Weight loss	Dietetics
	Skin care	Pressure ulceration	Airflow mattresses
Psychosocial care	Psychological issues	Distress from changing site of care	Continuity of care, providing a familiar environment
	Social aspects	Financial issues, legal issues	Driving assessments, support groups, home care, respite
Advance care planning	Patient preferences	Site of care, medical interventions, guardianship, resuscitation	Early discussion of advance directives prior to cognitive impairment
Spiritual care	Existential questions	Spiritual distress	Individualized spiritual support for patient and family
Bereavement	Anticipatory grief, grief	Continuing bonds	Acknowledgement of grief, bereavement support, pastoral – spiritual care

of the dose administered. Anticholinergic agents and tricyclic antidepressants should be avoided in the presence of orthostatic hypotension and benzodiazepines frequently cause paradoxical agitation in DLB.

Atypical parkinsonian disorders are not traditionally managed by palliative care teams. However, as there are no disease-modifying agents and the wide spectrum of symptoms have a significant impact on QoL of the patients and families, palliative intervention has a lot to offer in the management of these conditions (Table 13.10).

Symptomatic Management of Atypical Parkinsonian Disorders

Motor symptoms are often the presenting symptoms and dopaminergic agents may offer temporary relief. The most commonly used drugs are carbidopa/levodopa, amantadine, imipramine,

and selegiline. Zolpidem has been reported to improve eye movements in PSP, but benefit is transient and sedation is likely. As the antiparkinsonian medications become ineffective over time, they can be gradually discontinued. Effective symptomatic pharmacological management of these disorders may be limited to only a few months. As the patient becomes more and more disabled and persistent neuropsychiatric problems develop, the priority of care shifts to preservation of QoL through effective symptom control.

Neck and back pain is very common in atypical parkinsonian disorders. As in PD, it arises from stiffness, rigidity, or dystonic spasms. If botulinum toxin treatment fails, analgesics should be prescribed according to the WHO ladder. This is an algorithm based in the management of cancer pain, and is based on the premise that the correct drug should be administered in the correct dose at the correct time. Drugs are administered in the following order: nonopioids (aspirin and paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain. Anxiety can be managed with additional drugs. To maintain freedom from pain, drugs should be given "by the clock," rather than "on demand."

Falls occur frequently in PSP and MSA and can cause serious injuries. In PSP, amitriptyline or rasagiline might reduce the frequency of falls in the early stages of the disease. Occupational therapists often suggest helmets and other safety devices such as transfer belts or grab bars to prevent or buffer falls. Despite these measures, insight and safety awareness becomes a problem as cognitive deficits develop.

Myoclonus might be present in PSP, CBD, and MSA, and treatment usually requires benzodiazepines (e.g., clonazepam) or levetiracetam. Blepharospasm or eyelid apraxia may benefit from botulinum toxin A injections.

Dysautonomic symptoms are a hallmark of MSA but occur across the whole spectrum of parkinsonian syndromes. Treatment of orthostatic dysfunction might require reduction of levodopa, fluid and salt repletion, vasoconstrictors, fludrocortisone, or midodrine. Urgency and urinary incontinence can be treated with oxybutinin or tolterodine. Urinary tract infections should be identified early. Occasionally, intermittent catheterization might be necessary. Erectile dysfunction might precede the onset of these conditions by years.

Dysphagia and dysarthria are caused by extensive medullar neuronal loss and involvement of the corticobulbar pathways in the disease process. Oropharyngeal dystonia and impaired reflexes put patients at risk of choking and aspiration. Similarly to ALS, assessment by a speech and language therapist is essential. Feeding tube placement should be considered on case by case bases, depending on the stage of the disease and respecting patient preferences. Feeding tube options include percutaneous radiologically inserted gastrostomy tubes and endoscopically inserted (PEG) feeding tubes. Whilst in ALS there is evidence that RIG tubes should be the preferred choice, in dementia and parkinsonian syndromes decisions in favor of RIG over PEG frequently depends on tolerance of sedation and local policies.

Personality and mood changes are common in each of these disorders and are characteristic clinical features of DLB. The cognitive domains affected initially in DLB are executive function, attention, and visuospatial function as opposed to the amnestic deficits of AD. Cognitive changes in MSA are less likely and occur later in the course of the disease. In PSP and CBD, patients gradually develop subcortical dementia, characterized by mental slowing, language deficits, impaired memory, apathy, and irritability. Cholinergic

deficits are thought to underlie the cognitive impairment of PSP, but trials of cholinergic agonists and cholinesterase inhibitors have failed to show improvement. Impulsive behavior might be treated with SSRIs, and amitriptyline can also be effective if the anticholinergic effects are acceptable.

Sleep disorders such as insomnia, daytime somnolence, sleep apnea, and RLS are not uncommon in atypical parkinsonism and can be managed effectively. Rapid eye movement behavior disorder (RBD) or rapid eye movement sleep behavior is a prominent feature of DLB that describes complex motor manifestations of vivid dreams. DLB patients with RBD might harm themselves or their partners. Treatment options include bedtime clonazepam and melatonin.

Patient Groups, Support Groups, Organizations

A number of Internet-based databases are available for health care professionals, patients, and caregivers (Table 13.1). These sites have been developed and maintained by patient groups, research and clinical centers, governmental organizations, and universities. Many of these sites include high quality, evidence-based, up-to-date information on the management of late-stage neurological conditions. Discussion forums provide an invaluable source of information for patients, carers, and researchers worldwide. Contributions from patients and their families can be a source of inspiration and provide valuable insight into the experiences and concerns of those affected by these conditions.

Conclusions

In the management of neurodegenerative conditions, the goals and emphasis of care, whether it is maintenance of function, prolongation of life, or maintenance of comfort, should be discussed early and clearly so that management strategies can be tailored accordingly. In advanced neurological conditions, clinical decisions should be made with patient comfort, autonomy, dignity, and QoL in mind.

Specialist palliative care intervention in neurodegeneration is a dynamically developing field of medicine. Several guidelines are currently under development or auditing. This is an exhilarating field of mutual learning and cooperation between rehabilitation medicine, neurology, geriatrics, and specialist palliative care.

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