Chapter 1

Introduction

Classification of neurodegenerative diseases

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Definition and current concepts of neurodegenerative diseases

Neurodegenerative diseases (NDDs) are traditionally defined as disorders with selective loss of neurons and distinct involvement of functional systems defining clinical presentation. Comprehensive biochemical, genetic and molecular pathological examinations have expanded this definition. During the last century, the application of different silver staining techniques has demonstrated that argyrophilic intra- and extracellular (i.e. plaques) structures are associated with many forms of neurodegenerative diseases. This suggested that proteins with altered physicochemical properties are deposited in the human brain in neurodegenerative diseases. In addition, as well as neurons, glial cells also accumulate these proteins. The involvement of proteins has led to the definition of the concept of *conformational diseases* [1]. According to this, the structural conformation of a physiological protein changes, which results in an altered function or potentially toxic intra- or extracellular accumulation. Mutations in the encoding genes are linked to hereditary forms of disease. The pathological protein conformers are also called *misfolded proteins*. Disruption of the homeostasis of the endoplasmic reticulum leads to the misfolding of proteins. Endoplasmic reticulum stress and upregulation of several signaling pathways are called the *unfolded protein response* [2]. The two major elimination pathways, which control the quality of cellular components and maintain cell homeostasis, are the *ubiquitin–proteasome system* (UPS) and the *autophagy–lysosome pathway* [3]. Chaperones and stress-response proteins are in close relation to protein-processing systems, which have a central role in the pathogenesis of neurodegenerative diseases. Widespread molecular pathological and biochemical studies have revealed that there are modifications of proteins intrinsic to disease (species that are, for example, phosphorylated or nitrated, oligomers, proteinase resistant, with or without amyloid characteristics, or cleavage products) [4].

These concepts are reflected during the neuropathological examination: the objective is to evaluate the proteins, their modifications and whether they are ubiquitinated and show amyloid staining properties or not. It is important to clarify that the term "amyloid" can refer to a specific staining property or to the definition that protein aggregates are composed of highly ordered stacks of β-sheet-rich fibrils. The amyloid staining property means that a particular structure shows apple-green birefringence under polarized light when stained with Congo red dye. However, not all protein deposits visible by immunohistochemical methods show the amyloid staining property, even though they are composed of proteins rich in β-sheets. Thus, immunohistochemistry detects many more pathological protein deposits than can be seen with Congo red staining alone. Similarly, not all protein deposits are ubiquitinated; in fact, there is a kind of maturation of cellular inclusions within the cells.

The proteinopathy concept serves as a basis for the theory of *prion-like spreading* of disease-associated proteins [5]. This stems from the observations that, in prion diseases, the disease-associated prion protein (PrP) spreads in the nervous system. Although human-to-human transmissibility has been proven only for prion diseases, several other neurodegenerative diseases are suggested to associate with the

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Table 1.1 Current concepts of neurodegenerative diseases.

A common feature of neurodegenerative diseases is the deposition of β-sheet-rich protein aggregates
Molecular classification of neurodegenerative diseases is protein based
The concept of conformational disease underpins the role of protein-processing systems
• Unfolded protein response • Ubiquitin–proteasome system • Autophagy–lysosome pathway
There are modifications of neurodegenerative disease-related proteins intrinsic to disease
• Phosphorylated forms • Nitrated forms • Oligomers • Protease-resistant forms • Protein cleavage products
Protein deposits in the brain show "maturation"
• From non-ubiquitinated/non-argyrophilic to ubiquitinated/argyrophilic structures • Protein deposits with or without amyloid staining properties (birefringence in Congo red staining)
The appearance of protein deposits in anatomical regions of the brain shows a hierarchy
• Basis for the theory of prion-like cell-to-cell spreading of misfolded proteins • Definition of stages or phases of protein deposition
Neuronal loss is associated with a plethora of pathogenic pathways
• Apoptosis • Cell-cycle disturbance • Molecular damage (i.e. lipid peroxidation, DNA oxidation) • Energetic dysregulation (i.e. oxidative stress and mitochondrial instability) • Metabolic changes (i.e. alterations of cholesterol metabolism) • Dysregulation of ion homeostasis • Dysregulation of adaptation such as anti-inflammatory cytokines, microglial activation and anti-apoptotic or antioxidant processes
Neuronal vulnerability shows selectivity in early phases of disease
• Detection of focal atrophy (neuroradiology) • Basis for early symptomatic therapy
Neurodegenerative diseases associate with tissue reactions detectable during the neuropathological evaluation
• Neuronal loss • Synaptic degeneration, dendritic atrophy, axonal degeneration and transport failure • Reactive astrogliosis • Reactive microgliosis • Neuronal alterations (ballooned cells, inclusion bodies) • Extracellular plaques • Lack of relevant inflammatory cell infiltration • Other (e.g. spongiform change of the neuropil)
There is considerable overlap in the accumulation of different proteins in neurodegenerative diseases

prion-like spreading of the specific protein characterizing it. This notion is supported by the neuropathological observations in human brains that protein deposition of α-synuclein in Parkinson's disease and tau in Alzheimer's disease follows a hierarchical path defined as stages of disease [6, 7]. A similar concept was suggested for the transactive-response (TAR) DNA-binding protein 43 (TDP-43) in amyotrophic lateral sclerosis and frontotemporal lobar degeneration (FTLD) with TDP-43 protein deposition [8, 9]. Analogously, phases of amyloid-β (Aβ) in Alzheimer's disease have also been reported [10]. Cell-culture and animal experimental models have provided variable support for this theory [5]. It is also suggested that the considerable variability of neurodegenerative diseases is due to different "strains" of each type of disease protein [5].

In summary, comprehensive experimental and neuropathological evidence suggests that neurodegenerative diseases share common pathways of a complex pathogenic scenario, including mitochondrial dysfunction, compromised stress responses, synaptic rearrangements and altered protein expression. The current concepts of neurodegenerative diseases are summarized in Table 1.1.

Classification of neurodegenerative diseases: basic concepts

A nosological classification of neurodegenerative diseases is based on clinical presentation, anatomical regions and cell types affected, conformationally altered proteins involved in the pathogenic process, and etiology if known, such as genetic aberrations or acquired pathways of transmissible disorders (prion diseases) [4].

Clinical–anatomical classification

The clinical symptoms are determined by the system affected and do not unequivocally reflect the molecular pathological background. In most cases, there is an overlap and convergence of the symptoms in the course of the disease. Thus, clinical classification is helpful mostly when early clinical symptoms are evaluated. The major clinical features of neurodegenerative disorders are as follows (for details, see Chapters 2 and 3, this volume):

1. *Cognitive decline, dementia and alteration in high-order brain functions.* The most important

anatomical regions involved are the hippocampus, entorhinal cortex, limbic system (amygdala, olfactory cortices, anterior cingulate cortex, subcortical structures) and neocortical areas. In focal cortical symptoms, focal degeneration of the frontal, temporal, parietal or occipital lobe may be seen. A subtype of dementia is frontotemporal dementia, which is associated with degeneration of the frontal and temporal lobes (FTLD). These patients present with either behavioral or speech disorders. It is very important to distinguish rapid and slowly progressive forms of cognitive decline; this has relevance in raising the suspicion of transmissible spongiform encephalopathies (prion diseases).

2. *Movement disorders.* The most important anatomical regions involved are the basal ganglia, thalamus, brainstem nuclei, cerebellar cortex and nuclei, motor cortical areas and lower motor neurons of the spinal cord. Clinically, they are associated with so-called hypokinetic or akinetic/rigid symptoms such as Parkinson syndrome; with hyperkinetic movement disorders like chorea, dystonia, ballismus, athetosis, tremor, tics and myoclonus; with ataxic movement disorders; or with upper and lower motor neuron symptoms.
3. *Combinations* of these symptoms may be observed in some disease forms early during the clinical course and in many cases during the progression.

Neuropathological classification

The neuropathological classification is based on the following:

1. Evaluation of the anatomical distribution of neuronal loss and reactive astrogliosis, and additional histological features like spongiform change of the neuropil in prion disease, or vascular lesions. These changes are seen with conventional staining techniques.
2. Evaluation of protein deposits in the nervous system: these can be deposited intracellularly and extracellularly and are analyzed by immunohistochemistry. It is always important to examine those anatomical regions that have a relation to the major or earliest clinical symptoms.

Due to the fact that the UPS is central in the pathogenesis of neurodegenerative diseases, the role of ubiquitin immunohistochemistry is of particular interest in diagnostic neuropathology. Ubiquitin is a small stress-induced protein that participates in the degradation of short-lived and damaged proteins and is found in diverse filamentous inclusions of neurodegenerative diseases. In addition, the ubiquitin-binding protein 62/sequestosome 1, a cytosolic 62 kDa protein (p62), is also a common component of various inclusions [11]. During the formation of inclusions, ubiquitination is seen in later phases within the cells [12, 13]. Early protein deposits (called pre-aggregates or pre-inclusions) are detectable only with specific antibodies raised against the specific disordered protein.

Proteins with relevance for the classification of neurodegenerative diseases

The following proteins are associated with the majority of sporadic and genetic adult-onset neurodegenerative diseases [4]:

- The microtubule-associated protein tau (MAPT), which is important for the assembly and stabilization of microtubules. The *Tau* (*MAPT*) gene maps to chromosome 17q21.2.
- Aβ, which derives from the amyloid-β precursor protein (AβPP). The sequence length of AβPP is 770 aa. The *AβPP* gene has been mapped to the centromeric region of chromosome 21q21.3.
- α-Synuclein, which is a 140 aa protein that belongs to a family of abundant brain proteins (α-, β- and γ-synuclein). The gene encoding α-synuclein gene locates to chromosome 4.
- PrP, which is a 253 aa protein. PrP is central to prion diseases or transmissible spongiform encephalopathies. The gene encoding PrP (*PRNP*) locates to chromosome 20.
- TDP-43, which is a 414 aa nuclear protein. This is a highly conserved protein expressed in non-central nervous system (CNS) tissues as well. TDP-43 is encoded by the *TARDBP* gene on chromosome 1p36.22.
- FET proteins, which include the fused-in-sarcoma (FUS), Ewing's sarcoma RNA-binding protein 1 (EWSR1) and TATA-binding protein-associated factor 15 (TAF15) proteins [14].

There are more forms of genetic neurodegenerative diseases with abnormal protein inclusions, comprising proteins encoded by genes linked to neurological

trinucleotide repeat disorders. Their basis is the expansion of unstable trinucleotide repeats that account for disorders ranging from developmental childhood disorders to late-onset diseases such as Huntington's disease and inherited ataxias. Further rare inherited disorders associated with proteins include neuroserpinopathy, associated with a serine protease inhibitor expressed mainly in the CNS; the encoding gene is mapped to chromosome 3q26. In ferritin-related neurodegenerative diseases, the molecular genetic defect resides in the ferritin light polypeptide (*FTL*) gene located on chromosome 19. In familial British and Danish dementias with deposition of amyloid proteins in the extracellular spaces of the brain and in blood vessels, the molecular genetic defect is a mutation in the *BRI2* gene (chromosome 13). There are also further rare forms of cerebral amyloid angiopathies.

Based on the most important proteins related to neurodegenerative disorders listed above, diseases are also classified as tauopathies (Chapter 8), α-synucleinopathies (Chapter 9), prion diseases (Chapter 10), trinucleotide repeat disorders (Chapter 11) and TDP-43 or FUS (or FET) proteinopathies (Chapter 12). The most frequent neurodegenerative disease, Alzheimer's disease (Chapter 7), is not strictly included in these groups but is defined by both Aβ plaques and intracellular tau deposits in the form of neurofibrillary tangles. In addition, there are further disease forms that do not completely fit into these categories (Chapters 13–16) and further ones that need to be examined more to define their major molecular pathology.

In addition to the aforementioned proteins that are linked to specific diseases, it is important to mention that many other proteins may be found within inclusions and proteinaceous deposits; however, these are not structural elements of abnormal fibrils, but are proteins binding to them.

Synthesis

An algorithm for the molecular pathological classification of neurodegenerative diseases is presented in Figure 1.1. The following points must be considered when characterizing neurodegenerative diseases:

- The starting point for the neuropathological diagnosis and disease classification includes the collection of clinical information.
- Evaluation of atrophy during neuroimaging investigations and postmortem macroscopic inspection of the brain may suggest vulnerable areas where neuronal loss predominates.
- The next step is the detailed microscopic anatomical mapping of neuronal loss and reactive astrogliosis. Other types of pathologies, such as vascular lesions (Chapter 17), can considerably influence the clinical presentation; these must also be mapped and interpreted. This requires knowledge of strategic anatomical regions, including segregated circuits linking the subcortical and cortical structures (functional cortico–subcortico–cortical loops). Affection of the stations of these circuits may lead to similar symptoms.
- This is followed by the mapping of protein deposits: an immunohistochemical screening for these can be done using anti-ubiquitin/p62 antibodies; however, the full spectrum will be seen only when using protein-specific antibodies. Disease-associated proteins are deposited either intra- or extracellularly (Table 1.2); a further step is to evaluate the cell-specific subcellular localizations of these.
  - Extracellular deposits comprise deposits with immunoreactivity for Aβ or PrP or further amyloid proteins. It is of diagnostic importance that disease-associated PrP is also deposited in a synaptic pattern.
  - Major proteins that deposit intracellularly include tau, α-synuclein, TDP-43 and FET proteins, as well as those associated with trinucleotide repeat disorders or rare hereditary diseases.
  - Pathological tau, α-synuclein, TDP-43 and FET proteins may deposit in neuronal processes (dendrite or axon) or the cytoplasm, whereas TDP-43 and FET protein aggregates, as well as α-synuclein (in multiple system atrophy), may be seen in the neuronal nucleus. In addition, nuclear inclusions are characteristic features of trinucleotide repeat disorders.
  - Glial cells also show a variety of inclusions; astrocytes are mainly involved in tauopathies, while in oligodendroglial cells tau, α-synuclein, TDP-43 or FET proteins may form cytoplasmic inclusions.
  - It must be noted that Aβ and PrP immunodeposits may be seen intracellularly; however, description of these localizations is not of primary importance for the neuropathological diagnosis but is required to understand the pathogenesis of these disorders. On the other hand, tau, α-synuclein, TDP-43 and FET inclusions can be seen extracellularly or in synaptic localizations. For example, inclusions can

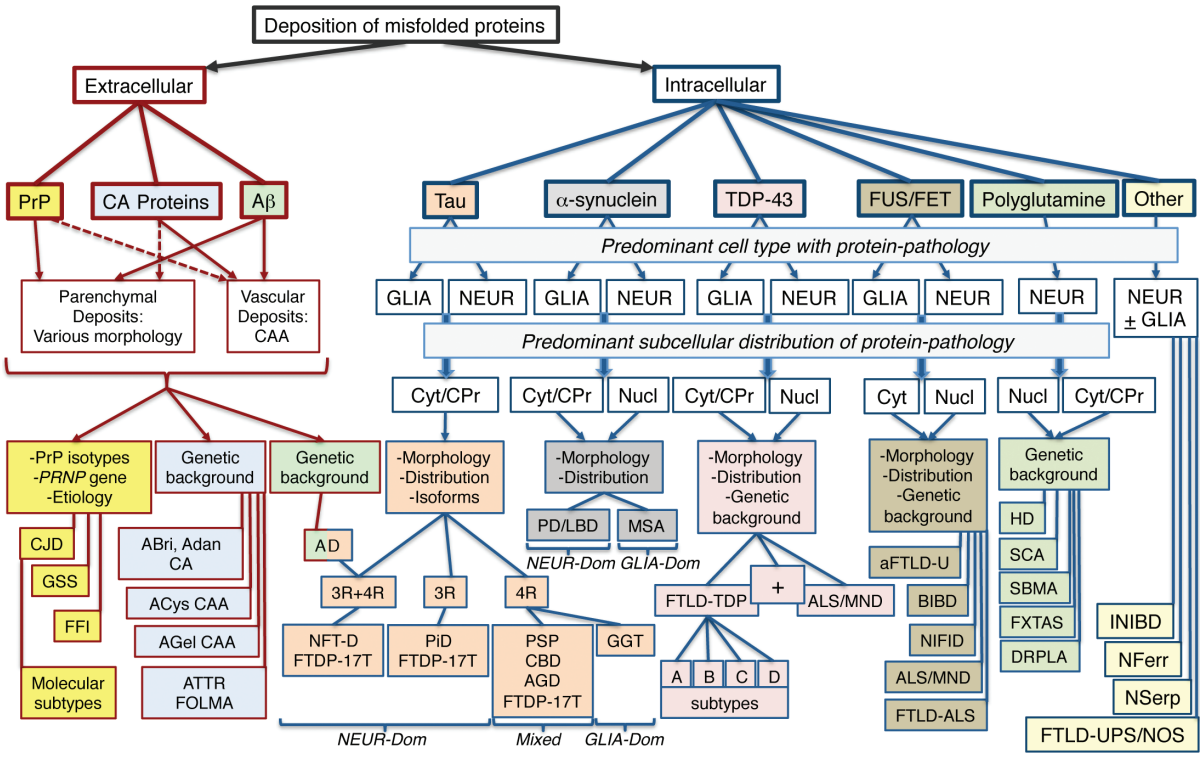

Figure 1.1 Algorithm for the classification of neurodegenerative disorders (adapted from Kovacs *et al.* [4]). Aβ, amyloid β; Abri and ADan, amyloidoses related to familial British dementia and familial Danish dementia; ACys, amyloidosis related to cystatin C amyloid; AD, Alzheimer's disease; AGD, argyrophilic grain disease; AGel, amyloidosis related to gelsolin amyloid; ATTR, amyloidosis associated with transthyretin amyloid; ALS, amyotrophic lateral sclerosis; BIBD, basophilic inclusion-body disease; CA, cerebral amyloidosis; CAA, sporadic cerebral amyloid angiopathy; CBD, corticobasal degeneration; CJD, Creutzfeldt–Jakob disease; Cyt, cytoplasm; CPr, cell process (i.e. dendrite, axon, glial process); DRPLA, dentatorubropallidoluysian atrophy; FFI, fatal familial insomnia; FOLMA, familial oculoleptomeningeal amyloidosis; FTLD, frontotemporal lobar degeneration; aFTLD-U, atypical FTLD with ubiquitinated inclusions; FTLD-UPS, FTLD with inclusions immunoreactive only for the components of the ubiquitine proteasome system; FTLD-NOS, FTLD not otherwise specified; FTDP-17T, frontotemporal dementia and parkinsonism linked to chromosome 17 caused by mutations in the *MAPT* (tau) gene; FXTAS, fragile X-associated tremor and ataxia syndrome (here also astroglial inclusions); FUS/FET, fused-in-sarcoma (FET family); GLIA-Dom, glia-dominant, thus the inclusions are predominatly in glial cells; GGT, globular glial tauopathies; GSS, Gerstmann–Sträussler–Scheinker disease; HD, Huntington's disease; INIBD, intranuclear inclusion-body diseases; LBD, Lewy body disease/dementia with Lewy bodies; MND, motor neuron disease; MSA, multiple system atrophy; NEUR, neuron; NEUR-Dom, neuron-dominant, thus the inclusions are predominatly in neurons; NFerr, neuroferritinopathy; NFT-D, neurofibrillary tangle-predominant dementia; NIFID, neurofilament intermediate filament inclusion disease; NSerp, neuroserpinopathy; Nucl, nucleus; PD, Parkinson's disease; PiD, Pick's disease; PrP, prion protein; PSP, progressive supranuclear palsy; 3R and 4R, tau isoforms with three or four repeats; SCA, spinocerebellar ataxia; SBMA, spinal and bulbar muscular atrophy; TDP, TAR DNA-binding protein-43. Trinucleotide R, trinucleotide repeat expansion disorder: refers to genetic disorder and is associated with different proteins. The "+" between FTLD-TDP and ALS/MND indicates combined phenotypes (ALS-FTLD/MND). Note: (i) Friedreich's ataxia is also a trinucleotide repeat disease but the inclusion-body pathology is not primary. (ii) Nuclear deposition of α-synuclein is seen in MSA. (iii) Intranuclear inclusion-body disease (INIBD) is a neurodegenerative disorder mostly documented as an infantile or juvenile fatal condition, while in adults it is thought to be very rare. It is characterized by eosinophilic nuclear inclusions that are immunoreactive for ubiquitin and ubiquitin-related proteins in neuronal but also in glial cells. Interestingly, these inclusions can be immunolabeled with antibodies against FUS [15].

be observed without visibly belonging to a cell; this happens when the neuron "dies away" and the protein aggregates remain in that place.

- Further rare disorders to be considered include neuroserpinopathy, ferritinopathy, intranuclear inclusion-body disease, disorders where inclusions are immunoreactive only for the UPS (e.g. FTLD-UPS) or diseases where no specific inclusion can be detected (e.g. FTLD-NOS, not otherwise specified). Some conditions like those associated with brain iron accumulation, postencephalitic disorders, head trauma or others observed in restricted geographical areas (e.g. parkinsonism–dementia complex of Guam)

Table 1.2 List of extra- and intracellular protein depositions associated with major forms of neurodegenerative diseases.

Protein	Extracellular	Morphology of deposit
Aβ	Focal	With or without dense core; includes the classic neuritic plaques
	Stellate	Mostly related to astrocytes
	Diffuse	Fleecy, lake-like and subpial
	Vascular	With or without amyloid features; check vessel type
	Unusual	Cotton wool plaques, inflammatory plaques
PrP	Fine/diffuse	Diffuse/synaptic
	Fine or coarse	Perineuronal
	Fine or coarse	Axonal
	Coarse/focal	Patchy perivacuolar
	Focal	Plaque-like PrP deposit without amyloid characteristic
	Focal	Amyloid plaque (micro, multicentric, kuru-type, florid)
	Vascular	With or without amyloid features
Protein	**Intracellular**	**Morphology of deposit**
Tau	Neuron – cytoplasm	Neurofibrillary tangle
		Diffuse cytoplasmic granular IR ("pretangle")
		Spherical/globular inclusion
		Other forms
	Neuron – process	Threads (axons)
		Neurites (periplaque)
		Grains (dendrites)
	Astrocyte	Tufted
		Astrocytic plaque
		Other (ramified, thorny, bush-like, globular astroglial inclusion)
	Oligodendroglia	Coiled body
		Globular oligodendroglial inclusion
α-Synuclein	Neuron – cytoplasm	Spherical inclusion (Lewy body) or pale body
		Granular cytoplasmic IR (diffuse or as small aggregates)
	Neuron – nucleus	Immunoreactive deposit without well-defined shape (MSA)
	Neuron – process	Thin and thick (Lewy) neurites
	Astrocyte	Star or crescent shaped (PD/DLB)
	Oligodendroglia	Globular/conical/crescent-shaped inclusion (MSA)
		Thin coiled-body-like or circular (PD or LBD)
TDP-43	Neuron – cytoplasm	Granular, dash-like
		Compact round or skein-like inclusions
	Neuron – nucleus	Round, rod, or lentiform ("cat-eye") inclusions
	Neuron – process	Thin and thick neurites
	Oligodendroglia	Coiled-body-like, semicircular, small flame shaped or round
FUS/FET	Neuron – cytoplasm	Compact round, spherical, skein-like inclusions
		Basophilic inclusions
	Neuron – nucleus	Round, vermiform, ring-like
	Oligodendroglia	Round or thin

Adapted from Kovacs & Budka [16].
DLB, dementia with Lewy bodies; IR, immunoreactivity; MSA, multiple system atrophy; PD, Parkinson's disease.

associate with various spectrums of proteinopathy lesions reminiscent of, or overlapping with, the features of major neurodegenerative disease entities.

- Finding one proteinopathy does not exclude the presence of further ones (Chapter 18). There is considerable overlap in the accumulation of different aggregated proteins. Moreover, several pathologies may co-exist in the same brain and may confound disease classification.

The present book follows the current protein-based molecular pathologic classification of neurodegenerative diseases. The aim is to provide a practical support for the complex and interactive task, which associates the clinical symptomatology with the neuroradiological findings, the anatomical distribution of neuronal loss, and extra- and intracellular deposits composed of abnormal protein conformers. Biochemical examination of these proteins provides further information that may specify morphologically

distinct disease forms. Such a complex clinical–morphological–biochemical approach that relates specific clinical phenotypes to atrophy patterns and proteinopathy forms may serve as a basis for developing in vivo diagnostic biomarkers and also as a rationale for developing therapies. This emphasizes the importance of the neuropathological examination. The neuropathological report should contain the diagnosis according to current definitions, including staging and description of disease phases. Moreover, detailed anatomical mapping of protein deposits in a tabularized form is helpful for future comparative studies aiming to stratify the patients based on multidisciplinary investigations. There is an increased need for neuropathological examinations for brain banks; the neuropathologist must be aware of ethical, health and safety considerations (Chapter 4), sampling approaches (Chapter 5) and the available modern molecular methods (Chapter 6). It must be noted that further neurological disorders are associated with neuronal degeneration, including mainly hereditary metabolic diseases where protein deposits have not been discovered and others like multiple sclerosis or those with an immune-mediated (autoimmune) etiology; however, these are beyond the scope of this book.

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Chapter 2

Clinical aspects of dementia

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Dementia

Dementia is a non-specific syndrome that is characterized by a state of cognitive impairment and is often associated with memory, language, behavioral and motor disturbances. In general, a diagnosis of dementia requires that cognitive impairment is severe enough to affect an individual's functioning in daily life. A global study estimated that, in 2010, the worldwide prevalence of dementia was 35.6 million people. This number is expected to double every 20 years [1]. Dementia can be divided into both static and progressive forms. A static dementia can result from a wide variety of causes including brain injury, congenital defect or a toxic-metabolic/hypoxic event. Progressive etiologies of dementia are dominated by the neurodegenerative causes, especially in the older population. Mild cognitive impairment is distinguished from dementia by preserved functioning in daily life and often precedes neurodegenerative forms of dementia. Less common causes including infectious, autoimmune, paraneoplastic or toxic-metabolic often have a more subacute course. In this chapter, the major forms of neurodegenerative dementia syndromes will be detailed, along with the relevant clinical symptoms, diagnostic evaluation and neuroimaging.

Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia in the older population and thus has enormous individual, family and social consequences [2]. The disease can be divided into two categories with respect to age of first clinical symptoms: early onset and late onset. Early onset, or symptoms beginning before the age of 60–65 years, represents 6–7% of all cases. The vast majority of AD cases present as late onset – at ages older than 60–65 years.

Approximately 75% of AD is sporadic, with the remainder being inherited, less than 5% in an autosomal-dominant fashion [3, 4]. Late-onset AD has a significant genetic component, felt to be inherited through several alleles across different loci. Nine loci have recently been identified that are associated with late-onset AD [5–9]. Apolipoprotein E (*APOE*) is the major susceptibility gene for AD and can be associated with both early and late onset [10]. There are three alleles of *APOE* (E2, E3 and E4), of which *APOE4* confers the highest risk of developing AD [4]. Most autosomal-dominant AD presents with early-onset dementia; however, the majority of early-onset cases are sporadic. There have been three genes implicated in the autosomal-dominant transmission of AD: amyloid-β precursor protein, presenilin 1 and presenilin 2, all of which result in almost complete penetrance. These genes account for up to 82% of autosomal-dominant inheritance of AD.

In 1984, the first clinical criteria for the diagnosis of AD dementia were published [11]. These criteria served as the basis for a clinical diagnosis of probable AD dementia in extensive clinical trials and research studies. With increased knowledge about the disease, as well as diagnostic testing, the criteria required revision, and this was accomplished through the National Institute on Aging and the Alzheimer's Association. The new criteria were published in 2011 [12]. Dementia is defined as cognitive impairment that impacts at least two domains including acquiring and remembering new information, reasoning and handling of complex tasks, visuospatial abilities, language functions, personality and behavior. These deficits need to

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Table 2.1 National Institute on Aging/Alzheimer's Association diagnostic criteria for diagnosis of Alzheimer's disease (AD) dementia [12].

Probable AD dementia
Meets criteria for dementia
Insidious onset, gradual onset over months to years
Clear history of cognitive worsening
Initial prominent symptoms are one of the following:

- Amnestic
- Non-amnestic
  - Language dysfunction
  - Visuospatial dysfunction
  - Executive dysfunction

No evidence of another etiology of cognitive impairment including: vascular dementia, dementia with Lewy bodies, behavioral-variant frontotemporal dementia, primary progressive aphasia, or other entity (disease process, medication) significantly impacting cognition.

Possible AD dementia
Meets criteria for dementia
Atypical course (sudden onset or insufficient history for cognitive decline) *or*
Mixed etiologies:

- Concomitant cerebrovascular disease (temporally-related strokes, severe leukoaraiosis) *or*
- Features of dementia with Lewy bodies *or*
- Disease process or medication potentially impacting cognition

Pathophysiologically proven AD dementia
Meets criteria for AD dementia by clinical and cognitive criteria *and*
Pathological evidence of AD

interfere with the ability to function in usual activities and should represent a decline in previous functioning [12]. This history should be obtained from both the patient and an informant who can provide reliable collateral, and neuropsychological testing should be completed for the best assessment of a cognitive profile.

Table 2.1 details the 2011 diagnostic criteria for probable, possible and neuropathologically proven AD.

The certainty of probable AD is increased with evidence of genetic mutations associated with AD and a cerebrospinal fluid (CSF) biomarker profile consistent with AD.

There are two major presentations of AD, amnestic and non-amnestic. In most cases, the presentation is that of the amnestic version where the predominant deficits are impairment in learning and recall of recently learned information, with other domains of cognition being less affected [12]. Non-amnestic forms of AD include corticobasal syndrome (CBS), frontal-variant AD, posterior cortical atrophy and logopenic progressive aphasia [13]. In these presentations, impairments in other domains of cognition predominate and other neurological symptoms and signs are uniquely present. They can often be indistinguishable from other types of neurodegenerative disorders.

Features of CBS reflect dysfunction in the frontal and parietal lobes, as well as the basal ganglia. Asymmetric rigidity and akinesia, apraxia, cortical sensory deficits, myoclonus and alien limb phenomenon can all be seen. Cognitive impairment can also be present [14]. Up to 50% of CBS cases can be attributed to AD [15]. Details of CBS are further delineated in the section "Corticobasal degeneration" below.

Frontal-variant AD can be clinically indistinguishable from behavioral-variant frontotemporal dementia. A detailed description of behavioral-variant frontotemporal dementia follows in the "Frontotemporal dementia" section below. Predominant symptoms include executive dysfunction, attentional impairment and behavioral issues such as impulsivity and disinhibition. Concomitant symptoms of memory and visuospatial impairment early in the clinical course would suggest AD as opposed to behavioral-variant frontotemporal dementia [13].

Posterior cortical atrophy typically presents in younger patients with progressive visuospatial dysfunction and relative sparing of other domains such as memory, executive function and language. Posterior cortical atrophy can be divided into two main presentations, and often there is a clinical overlap between the two. Both the dorsal occipitoparietal region (the "where" visual pathway) and the ventral occipitotemporal region (the "what" visual pathway) can be affected by AD. Dorsal occipitoparietal dysfunction is more common and produces a Balint syndrome (simultagnosia, optic ataxia and oculomotor ataxia), dressing apraxia and Gerstmann syndrome. Complete Balint and Gerstmann syndromes are rare, and the most common element of each is simultagnosia and alcalculia, respectively. Ventral occipitotemporal dysfunction instead results in visuospatial phenomena such as apperceptive visual agnosia, prosopagnosia, achromatopsia and alexia [13, 16]. Posterior cortical atrophy is usually secondary to AD. In a 2004 study, seven out of nine patients with posterior cortical atrophy syndrome had AD pathology, with Brodmann areas 17 and 18 preferentially affected [16, 17].

The logopenic variant of primary progressive aphasia (lvPPA) represents another atypical presentation of AD and the most recently described primary progressive aphasia (PPA). Logopenic progressive aphasia presents with slow speech, word-finding pauses and impaired repetition of sentences with intact single-word repetition, grammar and relatively spared single-word comprehension. Phonological paraphasias are characteristic in this disorder [13, 18]. Impairment of sentence repetition is felt to be secondary to a deficit in working memory, which causes difficulty with storing incoming verbal information [18]. AD is felt to be the underlying cause for at least half of all lvPPA. Microhemorrhages as a result of concomitant amyloid angiopathy with AD can often be seen on imaging and in a recent study occurred in one-third of cases [19]. For further details of lvPPA, refer to the section "Primary progressive aphasia" below.

Structural magnetic resonance imaging (MRI), especially volumetric MRI, has been researched extensively in the field of AD. The hippocampus, entorhinal cortex and regional gray matter show atrophy disproportionate to that of the whole brain in both AD dementia and mild cognitive impairment due to AD. Atrophy occurs secondary to dendritic and neuronal losses [20]. Atrophy has been shown to begin at the entorhinal cortex and then progress to the hippocampus, amygdala and parahippocampus. The entire medial temporal neocortex is the next to be affected, followed by the entire neocortex, usually in a symmetrical fashion [20]. This atrophy progression is consistent with histopathological studies upon which the Braak and Braak staging is based, which showed the sequential regional involvement of neurofibrillary tangles [20, 21]. MRI has been shown to display changes in hippocampal volume even before the onset of cognitive symptoms. There is a 10% reduction in hippocampal volume at least 3 years prior to a diagnosis of AD dementia [20]. Cortical thinning is also shown, especially in the heteromodal regions, including the posterior cingulate, precuneus, lateral parietal, temporal and frontal regions [22]. The atypical presentations of AD have structural MRI changes anatomically consistent with their individual presentations, with left temporal atrophy in language variants and typically right more than left posterior cortical atrophy in visual variants [13, 20]. Functional MRI, while rarely used in clinical practice, has provided an insightful tool in the study of AD and generally shows the integrated synaptic activity of neurons due to changes in blood flow, blood volume and the blood oxyhemoglobin/deoxyhemoglobin ratio. In AD, there is decreased hippocampal activity with the encoding of new information. Interestingly, mesial temporal lobe structures in those with mild cognitive impairment or who are genetically at risk of developing AD actually show increased activity, and this is thought to be a compensatory mechanism prior to subsequent cognitive decline [20].

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) studies, which reflect synaptic activity, can be an important biomarker in assessing regional dysfunction consistent with AD, even before clinical symptoms are present. Glucose metabolism is first reduced in the precuneus, posterior cingulate and parietotemporal cortex before the whole brain is affected. Hypometabolism in these regions can sometimes be seen before clinical decline can be detected. In later stages of AD, frontal regions can also preferentially show hypometabolism [23]. Often, early in the course of the disease, there is an asymmetry. Primary cortices can be affected with advanced disease [20]. There have not been specific patterns noted that distinguish between normal, mild cognitive impairment and AD. However, specific patterns of hypometabolism can be seen with lvPPA (Figure 2.1) and with posterior cortical atrophy (Figure 2.2).

The ability to directly image amyloid in vivo has become possible through radiotracer positron emission tomography (PET) scans. An individual radiotracer contains a histopathological stain, which binds to the fibrillar form of Aβ and is then visualized through the PET scan. The first amyloid PET imaging was performed with ^{11}C-based Pittsburgh compound B (^{11}C-PIB), and the majority of research involving amyloid PET imaging has been conducted using this tracer. However, ^{11}C-PIB has a short half-life of 20 min, which limits its use. Other tracers with longer half-lives have been developed, using ^{18}F including ^{18}F-flutemetamol, ^{18}F-florbetaben and ^{18}F-florbetapir [22, 24]. Amyloid burden via ^{18}F-florbetapir imaging was recently shown to correlate well with the pathological findings at autopsy in individuals who were scanned shortly before their death [24]. If amyloid PET imaging shows minimal or absent amyloid burden, the probability that cognitive impairment is secondary to AD is very low. However, moderate to severe amyloid burden through amyloid PET imaging does not necessarily mean that cognitive impairment is due to AD