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Chapter 21

Concepts and classification of neurodegenerative diseases

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Abstract

Neurodegenerative diseases are disorders characterized by progressive loss of neurons associated with deposition of proteins showing altered physicochemical properties in the brain and in peripheral organs. Molecular classification of neurodegenerative disease is protein-based. This emphasizes the role of protein-processing systems in the pathogenesis. The most frequent proteins involved in the pathogenesis of neurodegenerative diseases are amyloid-β, prion protein, tau, α-synuclein, TAR-DNA-binding protein 43 kDa, and fused-in sarcoma protein. There are further proteins associated mostly with hereditary disorders such as proteins encoded by genes linked to trinucleotide repeat disorders, neuroserpin, ferritin, and familial cerebral amyloidoses. The clinical presentations are defined by the distinct involvement of functional systems and do not necessarily indicate the molecular pathologic background. Seeding of pathologic proteins and hierarchic involvement of anatomic regions is commonly seen in neurodegenerative diseases. Overlap of neurodegenerative diseases and combinations of different disorders is frequent. Translation of neuropathologic categories of neurodegenerative diseases into in vivo detectable biomarkers is only partly achieved but intensive research is performed to reach this goal.

FUNDAMENTALS OF NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are characterized by progressive dysfunction and loss of neurons. Involvement of functional systems differs between disorders and is associated with a wide spectrum of clinical presentations. An important feature is the deposition of proteins with altered physicochemical properties, also known as misfolded proteins. The concept of conformational diseases implies that the structural conformation of a physiologic protein changes, resulting in an altered function or potentially toxic intra- or extracellular accumulation (Carrell and Lomas, 1997). Most, but not all, of the neurodegenerative disorders are characterized by protein deposits. For example, in hereditary spastic paraplegia or some forms of spinocerebellar ataxia there are no specific protein inclusions detected with current methods. Mutations in the encoding genes of these proteins lead to familial diseases.

Based on the proteinopathy concept, studies emphasized the role of the unfolded protein response (Cornejo and Hetz, 2013) and protein elimination pathways, such as the ubiquitin-proteasome system and the autophagy-lysosome pathway (Nijholt et al., 2011), chaperones, and stress response proteins. In addition, interaction with molecular damage, dysregulation of energetic and ion homeostasis, metabolic changes, and adaptation are crucial aspects of the pathogenesis (von Bernhardi and Eugenin, 2012). A novel concept, referred to as prion-like spreading, suggests that the proteins associated with neurodegenerative diseases spread in the nervous system. The template-directed protein misfolding, similarities in cell-to-cell propagation of pathologic proteins, and deposition of proteins that seem to follow anatomic pathways suggest overlap with the pathogenesis of prion diseases (Brettschneider et al., 2015).

For neurodegenerative diseases cell culture and animal experimental models have been used to demonstrate

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that cells can take up pathologic proteins and eventually pass them to further cells (Guo and Lee, 2014). Human-to-human transmissibility and public health relevance are however different for prion diseases and nonprion neurodegenerative diseases, such as Alzheimer and Parkinson disease.

The term propagon was introduced to fine-tune the terminology of spread of pathologic proteins and disease transmission (Eisele and Duyckaerts, 2016). Four conceptual levels have been proposed – molecular, tissue, systemic, and infectious propagons – which also reflect the experimental approach used to demonstrate the spread (Eisele and Duyckaerts, 2016). The highest level, called infectious propagons, has been defined as "proteins that transmit pathological conformation between individuals." In prion diseases the whole clinicopathologic phenotype and the pathologic conformer of the prion protein can be transmitted (hence the term transmissible spongiform encephalopathy). Under very unusual circumstances transmission of amyloid-β (Aβ) has been shown through human grafted dura mater containing pathologic Aβ (Kovacs et al., 2016). Therefore, a further level could be defined as phenotype propagon to further distinguish the transmissibility properties of prion diseases as compared to other neurodegenerative conditions (Kovacs et al., 2016). In addition to the pathogenic spread of proteins, the classic selective vulnerability hypothesis is discussed (Walsh and Selkoe, 2016). This suggests that protein aggregation is initiated in a subset of neurons that are vulnerable to certain adverse conditions (Walsh and Selkoe, 2016).

CONCEPTS OF DISEASE CLASSIFICATION

Classification of neurodegenerative diseases is based on the following (Kovacs, 2014, 2015):

1. clinical symptoms determined by the anatomic region showing neuronal dysfunction
2. proteins showing various biochemical modifications and accumulating in neurons or glial cells (intracellular), or in extracellular locations.

Accordingly, anatomic, cellular, and protein vulnerability patterns can be defined in neurodegenerative conditions (Kovacs et al., 2013; Kovacs, 2016).

ANATOMIC INVOLVEMENT AND CLINICAL SYMPTOMS

Clinical classification is helpful when focusing on the early symptoms (Table 21.1). Combinations of clinical manifestations may be occasionally observed as an early feature and frequently during the progression of disease. The following groups of clinical manifestations are distinguished:

1. Cognitive decline, dementia, and alterations in high-order brain functions. Anatomic structures involved comprise the hippocampus, entorhinal cortex, limbic system, and neocortical areas. Frontotemporal dementia is associated with the degeneration of the frontal and temporal lobes (frontotemporal lobar degeneration: FTLD).
2. Movement disorders include hyperkinetic and hypokinetic movement disorders, symptoms related to cerebellar dysfunction or involvement of the upper and lower motor neurons. The most important anatomic regions involved in movement disorders are the basal ganglia, thalamus, brainstem nuclei, cerebellar cortex and nuclei, motor cortical areas, and lower motor neurons of the spinal cord.

MOLECULAR PATHOLOGIC CLASSIFICATION

In addition to the neuronal loss in different anatomic regions, histopathologic features must be described. The whole spectrum of protein deposits can only be seen using immunohistochemistry. The diagnostic approach focuses on the distinction of synaptic, intracellular, and extracellular protein accumulations. It is important to distinguish the subcellular location of the intracellular deposits – whether they are nuclear, cytoplasmic, or neuritic (axonal or dendrites), or in cellular processes (i.e., for astrocytes). For the disease classification currently not all protein deposit morphologies are taken into account. This is due to the fact that many new antibodies have been developed and the diagnostic criteria are not updated to include novel immunostaining patterns. Biochemistry and genetic analysis is often required as a complementary examination to immunohistochemistry. For subtyping of diseases mostly morphologic criteria are used. There are a few exceptions where biochemical modifications or even a gene polymorphism are also considered for subtyping (Kovacs, 2016). Importantly, for all neurodegenerative proteinopathies there are hereditary forms described, thus genetic analysis and detailed family history are recommended for the full characterization of a disorder.

The following proteins are associated with the majority of sporadic and genetic adult-onset neurodegenerative diseases (Kovacs et al., 2010):

1. the microtubule-associated protein tau encoded by a single gene (*MAPT*) on chromosome 17q21
2. Aβ, which is cleaved from a large transmembrane precursor protein (amyloid precursor protein or APP).

Table 21.1

Major dementia and movement disorder syndromes/subtypes[a]

Alzheimer dementia			
	Amnestic		
	Nonamnestic		
		Frontal-variant	
		Corticobasal syndrome	
		Posterior cortical atrophy	
		Logopenic progressive aphasia	
Dementia with Lewy bodies			
Frontotemporal dementia			
	Behavioral-variant FTD (bvFTD)		
	Primary progressive aphasia (PPA)		
		Nonfluent/agrammatic-variant PPA (naPPA)	
		Semantic-variant PPA (svPPA)	
		Logopenic-variant PPA (lvPPA)	
Corticobasal syndrome (CBS)			
Progressive supranuclear palsy (PSP)-related syndromes			
	PSP syndrome (Richardson)		
	PSP parkinsonism		
	PSP with pure akinesia with gait freezing		
	PSP with progressive apraxia of speech		
Rapidly progressive dementia			
Hypokinetic movement disorder			
	Bradykinesia, hypokinesia, akinesia		
	Rigidity		
	Rigid-akinetic syndromes		
	Freezing		
	Stiff muscles		
Hyperkinetic movement disorder			
	Tremor		
	Myoclonus		
	Chorea		
	Ballism		
	Athetosis		
	Tics, stereotypies		
	Startle syndrome		
	Restless legs		
	Ataxia, dysmetria		
	Akathisia		

[a]List of clinical symptoms and their subtypes frequently associated with neurodegenerative proteinopathies. Note that the nomenclature of some of these clinical syndromes overlaps with neuropathologic terminology, exemplified by dementia with Lewy bodies or progressive supranuclear palsy.

The *APP* gene has been mapped to the centromeric region of chromosome 21q21.3

3. α-synuclein, which is encoded by a single gene (*SNCA*) on chromosome 4
4. prion protein (PrP), which is a 253-amino acid protein encoded by the gene of PrP (*PRNP*) located to chromosome 20
5. transactive response (TAR) DNA-binding protein 43 (TDP-43), a highly conserved nuclear protein, encoded by the *TARDBP* gene on chromosome 1
6. FET proteins, which include the fused-in sarcoma (FUS), Ewing sarcoma RNA-binding protein 1 (EWSR1), and TATA-binding protein-associated factor 15 (TAF15) (Neumann et al., 2011). The most examined is FUS, which is a 526-amino acid-long protein encoded by a gene on chromosome 16
7. there are further proteins associated mostly with hereditary disorders. These include, for example, proteins encoded by genes linked to neurologic trinucleotide repeat disorders, neuroserpin, ferritin-related neurodegenerative diseases, and familial cerebral amyloidoses.

Neurodegenerative disease groups are named according to the major protein showing deposits in the nervous

system. Accordingly, we distinguish tauopathies, α-synucleinopathies, TDP-43 proteinopathies, FUS/FET proteinopathies, prion diseases, trinucleotide repeat diseases, neuroserpinopathy, ferritinopathy, and cerebral amyloidoses (Table 21.2). This nomenclature overlaps with clinicopathologic descriptions, like the grouping of FTLD (see Chapters 25 and 26). Alzheimer disease is usually discussed separately since it shows pathologic accumulation of Aβ and tau together.

An excess of biochemical modifications of these proteins has been described for neurodegenerative conditions (Kovacs, 2016). These are important to understand the pathogenesis of neurodegenerative conditions or to develop biomarkers. For neuropathology, the most important step is to evaluate the localization and distribution of proteins (Kovacs and Budka, 2010). Extracellular or vascular deposits comprise deposits with immunoreactivity for Aβ or PrP. In addition, disease-associated PrP shows a synaptic pattern of deposition. Proteins that deposit intracellularly include tau, α-synuclein, TDP-43, FUS/FET proteins, furthermore, those associated with trinucleotide repeat disorders or rare hereditary diseases. Regarding the distribution of proteins it is of great importance that many protein deposits show a hierarchic involvement of brain regions, which has important implications for clinicopathologic correlation, since early and late stages or phases of certain diseases can be distinguished.

In summary, evaluation of the most frequent neurodegenerative conditions requires differentiation based on extra- or intracellular predominance of protein deposits (Table 21.3) and evaluation of stages and phases in a growing number of disorders.

THE CONCEPT OF MULTIPROTEINOPATHIES

Neurodegenerative proteinopathies show frequent co-occurrence (Kovacs et al., 2008; Rahimi and Kovacs, 2014). Accordingly, in addition to the hallmark lesions of a disease entity, further pathologic alterations can be observed in the same brain (see Chapter 35). Indeed, in the aging brain a large variety of proteinopathies with different combinations can be seen, which makes the translation of disease subtyping into clinically easily interpretable biomarkers difficult (Kovacs et al., 2013). The threshold of cognitive impairment could be reached by a prominent amount of a single disease but by the concomitant presence of neuropathologic alterations that alone are not sufficient to cause dementia (Kovacs et al., 2013; Kovacs, 2014). This multiproteinopathy is seen associated with several gene mutations (e.g., *βAPP* mutation Aβ, tau, and also with α-synuclein pathology or *PRNP* mutations with tau or α-synuclein pathology).

OVERVIEW OF THE SECTION ON NEURODEGENERATIVE DISEASES

The present section on neurodegenerative diseases follows this classification and provides detailed description on the neuropathology of Alzheimer disease, alpha-synucleinopathies, tauopathies, FTLD with TDP-43 or FUS/FET proteinopathies, trinucleotide repeat disorders, and prion diseases. It provides an overview of the complexity of the genetic background. Some conditions, like those associated with brain iron accumulation, including ferritinopathy, postencephalitic disorders, head trauma, or others observed in restricted geographic areas (e.g., parkinsonism–dementia complex of Guam) are associated with various spectra of proteinopathy lesions reminiscent of, or overlapping with, the features of major neurodegenerative disease entities. Hereditary cerebral amyloid angiopathies are discussed in Chapter 7.

Further rare inherited disorders not discussed in detail include those associated with pathologic accumulation of neuroserpin. This is a serine protease inhibitor, mainly expressed in the central nervous system; the encoding gene is mapped to chromosome 3q26 (Davis et al., 1999a, b). The clinical phenotype of neuroserpinopathies includes progressive myoclonus epilepsy, focal or generalized seizures, dysarthria, tremors, and dementia; neuroserpin inclusion bodies are present in the neuronal cytoplasm and processes but not in the nucleus (Davis et al., 1999a, b; Takao et al., 2000; Gourfinkel-An et al., 2007; Hagen et al., 2011).

Some disorders exhibit inclusions, which are immunoreactive for a variety of proteins, such as intranuclear inclusion body disease (INIBD). INIBD is a neurodegenerative disorder mostly documented as an infantile or juvenile fatal condition, but rarely reported in adults as well (Takahashi-Fujigasaki, 2003). It is characterized by eosinophilic nuclear inclusions that are immunoreactive for ubiquitin, but also for some neurodegeneration-related proteins, such as FUS or optineurin (Woulfe et al., 2010; Nakamura et al., 2014). Inclusions are seen in neuronal as well as glial cells and peripheral organs (Liu et al., 2008; Mori et al., 2012).

PERSPECTIVES

The proteinopathy concept has changed our approach to the diagnosis of neurodegenerative conditions. In particular, these proteins or their biochemical modifications can potentially be detected in body fluids or visualized with neuroimaging methods. The different subcellular distribution of proteins has an impact on the pathways by which these reach the body fluids to be detected as

Table 21.2

Summary of most relevant modifications of neurodegeneration related proteins with remarks (see also Kovacs, 2016)

Disease group	Protein	Disease type	Subtypes
AD	Tau, Aβ	AD	
Tauopathy	Tau	FTLD-tau/primary tauopathies	PiD GGT CBD PSP AGD NFT-dementia/PART FTDP-17 T
TDP-43 proteinopathy	TDP-43	FTLD-TDP	Type A–D
		MND-TDP	
		FTLD-MND-TDP	
FUS (FET)-proteinopathy	FUS / FET	FTLD-FUS (FET)	aFTLD-U NIFID BIBD
		MND-FUS	
α-Synucleinopathy	α-Synuclein	PD DLB MSA	
Prion disease	PrP	CJD	Sporadic CJD Genetic CJD Iatrogenic CJD Variant CJD
		Kuru GSS FFI PrP-CAA	
Prionopathy		VPSPr	
Trinucleotide repeat disorder	Huntingtin	HD	
	Ataxin 1, 2, 3, 7, CACNA1A, TBP	SCA 1, 2, 3, 6, 7, 17	
	Atrophin-1	DRPLA	
	FMRP	FXTAS	
	ARP	SBMA	
	Frataxin	Friedreich ataxia (no inclusion)	
Other forms	Ferritin	Hereditary ferritinopathy	
	Neuroserpin	Neuroserpinopathy	
	ABri, Adan, gelsolin, cytostatin, transthyretin, Aβ	Hereditary amyloidoses/CAA	
	Only UPS	FTLD-UPS	
	Not determined	FTLD-ni	
	Tau, α-synuclein	NBIA	
	Tau, α-synuclein, TDP-43	Various genetic and sporadic diseases ("secondary" proteinopathy forms)	

AD, Alzheimer disease; aFTLD-U, atypical FTLD with ubiquitinated inclusions; AGD, argyrophilic grain disease; ARP, androgen receptor protein; BIBD, basophilic inclusion body disease; CAA, cerebral amyloid angiopathy; CACNA1A, α1A subunit of the P/Q-type voltage-gated calcium channel; CBD, corticobasal degeneration; CJD, Creutzfeldt–Jakob disease; DLB, dementia with Lewy bodies; DRPLA, dentatorubral-pallidoluysian atrophy; FTDP-17 T, frontotemporal dementia and parkinsonism linked to chromosome 17 caused by mutations in the *MAPT* (tau) gene; FFI, fatal familial insomnia; FMRP, fragile X mental retardation protein; FTLD, frontotemporal lobar degeneration; FTLD-ni, FTLD no inclusion specified; FTLD-UPS, FTLD with inclusions immunoreactive only for the components of the ubiquitine proteasome system; FXTAS, fragile X-associated tremor and ataxia syndrome; GGT, globular glial tauopathy; GSS, Gerstmann–Sträussler–Scheinker disease; HD, Huntington disease; MND, motor neurone disease; MSA, multiple system atrophy; NBIA, neurodegeneration with brain iron accumulation; NFT, neurofibrillary tangle type; NIFID, neurofilament intermediate filament inclusion disease; PART, primary age-related tauopathy; PD, Parkinson disease; PiD, Pick disease; PrP, prion protein; PSP, progressive supranuclear palsy; SBMA, spinal and bulbar muscular atrophy; SCA, spinocerebellar ataxia; SCA6, cytoplasmic aggregates; TBP, TATA-box binding protein (SCA17); VPSPr, variably protease-sensitive prionopathy.

Table 21.3

Overview of protein deposition patterns in neurodegenerative proteinopathies

	Intracellular deposition			Extracellular	Synapse	Vessel
Protein	**Neuron**	**Astroglia**	**Oligodendroglia**			
Aβ	(–/+)	(+)	–	+	–	+
Prion protein	(+)	(+)	–	+	+	+
α-Synuclein	+	(+)	+	–	–	–
Tau	+	+	+	–	–	–
TDP–43	+	–	(+)	–	–	
FUS	+	–	(+)	–	–	–
Cerebral amyloid angiopathy proteins	–	–	–	+	–	+
TRD proteins	+	–	–	–	–	–
Neuroserpin	+	–	–	–	–	–
Ferritin	+	+	–	+	–	+

+ indicates present; – indicates not present; –/+ indicates that it is reported inconsistently; + in brackets indicate that it is present but not appreciated for subtyping of diseases; TRD, trinucleotide repeat disorder.

biomarkers. This is why neuropathologists subtype disorders in such detail. The concept of seeding and spreading of proteins raises the possibility that these may be targeted for therapy. However, it must be emphasized that pure proteinopathies are less frequent than combined ones. Accordingly, the protein-processing systems might be targeted for therapy to help to maintain the healthy homeostasis of cells and protect the physiologic forms of neurodegeneration-associated proteins. The high number of combinations of diseases implies that detection of a panel of neurodegeneration-related proteins and their modifications ("protein coding of neuodegenerative diseases") together with markers, which reflect the dynamics of disease (i.e., neuroinflammatory or signaling factors) in body fluids combined with neuroradiologic approaches and genetic screening of disease-modifying gene variations can lead to personalized diagnosis or better prediction of prognosis (Kovacs et al., 2010). The most beneficial for patients and their relatives would be to discuss clinical cases during the in vivo diagnostic procedure in a multidisciplinary setting together with the clinician, neuroradiologist, geneticist, biomarker expert, and neuropathologist.

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