

# CURRENT CONCEPTS OF NEURODEGENERATIVE DISEASES

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## ABSTRACT

Neurodegenerative diseases (NDDs) are described as disorders with selective loss of neurons and distinct involvement of functional systems defining clinical presentation. Extensive studies demonstrated that proteins with altered physicochemical properties are deposited in the human brain in NDDs. The present review focuses on predominantly sporadic disorders in adulthood. Major concepts of NDDs can be summarised as follows: 1) molecular pathologic classification of NDDs is protein-based; 2) the proteinopathy concept underpins the role of protein processing systems; 3) seeding of pathological proteins supports the theory of prion-like spreading; 4) the clinical symptoms are determined by the system affected and do not unequivocally reflect the molecular pathological background; 5) overlapping of NDDs may be more the rule than the exception. Accordingly, NDD-related proteins and their biochemical modifications can be used as biomarkers and may be targeted for therapy. However, due to the high number of combinations of different proteinopathies a personalised therapy strategy may be warranted.

Keywords: Biomarker, concomitant pathology, neurodegenerative disease, prion-like, proteinopathy.

## INTRODUCTION

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, many studies have demonstrated that proteins with altered physicochemical properties are deposited in the human brain in NDDs. Furthermore, not only neurons but glial cells also accumulate these proteins. Involvement of proteins has led to the definition of the concept of conformational diseases.<sup>1</sup> According to this, the structural conformation of a physiological protein changes, which results in an altered function or potentially toxic intra or extra-cellular accumulation. Mutations in the encoding genes are linked to hereditary forms of disease. Molecular pathological, genetic, and biochemical studies have led to reclassification of several disorders, and opened completely new

avenues for biomarker development or therapeutic strategies.<sup>2</sup> This review aims to summarise the major developments in this field with an emphasis mainly on sporadic disorders of adulthood. It must be noted that further neurological disorders are associated with neuronal degeneration, including mainly hereditary metabolic diseases and others such as multiple sclerosis or those with immune-mediated (autoimmune) aetiology; however, these are beyond the scope of the present review.

## MAJOR CONCEPTS OF NDD AND THEIR IMPLICATIONS

### 1. Classification of NDDs is Protein-Based

A nosological classification of NDDs is based on clinical presentation, anatomical regions and cell types affected, conformationally altered proteins involved in the pathogenetic process, and aetiology if known (i.e. genetic variations or acquired pathways of prion diseases).<sup>2</sup>

In most cases, there is an overlap and convergence of the clinical symptoms in the course of the disease. Thus, clinical classification is helpful mostly when early clinical symptoms are evaluated. The major clinical features of NDDs correlate with the anatomical involvement as follows:

a) Cognitive decline, dementia, behavioural disturbances, and alterations in high-order brain functions. The most important anatomical regions involved are the hippocampus, entorhinal cortex, limbic system, and neocortical areas. In focal cortical symptoms, focal degeneration of the frontal, temporal, parietal, or the occipital lobe may be seen. A subtype of dementia is frontotemporal dementia (FTD), which is associated with degeneration of the frontal and temporal lobes (frontotemporal lobar degeneration [FTLD]). It is important to distinguish rapid (prion) diseases and slowly progressive forms of cognitive decline.

b) Movement disorders and other motor features. The most important anatomical regions involved are the basal ganglia, thalamus, brainstem nuclei, cerebellar cortex and nuclei, motor cortical areas, and lower motor neurons.

c) Combinations of these symptoms may be observed in some disease forms early during the clinical course and in many cases during the progression.

The neuropathological classification is based on the following:

a) Evaluation of the anatomical distribution of neuronal loss and reactive astrogliosis, and additional histological features such as spongiform change of the neuropil or vascular lesions.

b) Evaluation of protein deposits in the nervous system; these can be deposited intracellularly and extracellularly, and are analysed by immunohistochemistry and eventually by biochemistry.

The following proteins are associated with the majority of sporadic and genetic adult-onset NDDs:<sup>2</sup>

a) The microtubule-associated protein tau (MAPT) is important for the assembly and stabilisation of microtubules. The *Tau* (*MAPT*) gene maps to chromosome 17q21.2.

b) Amyloid- $\beta$  ( $A\beta$ ), which derives from the amyloid precursor protein (APP). The *APP* gene maps to

chromosome 21q21.3. Among others, further genes with relevance to the pathogenesis of Alzheimer's disease (AD) and familial disorders include presenilin-1 (*PSEN1*) (chromosome 14q24.3) and *PSEN2* (chromosome 1q31-42).

c)  $\alpha$ -Synuclein is a 140-amino acid (aa) protein that belongs to a family of abundant brain proteins ( $\alpha$ ,  $\beta$ , and  $\gamma$ -synuclein). The  $\alpha$ -synuclein gene locates to chromosome 4.

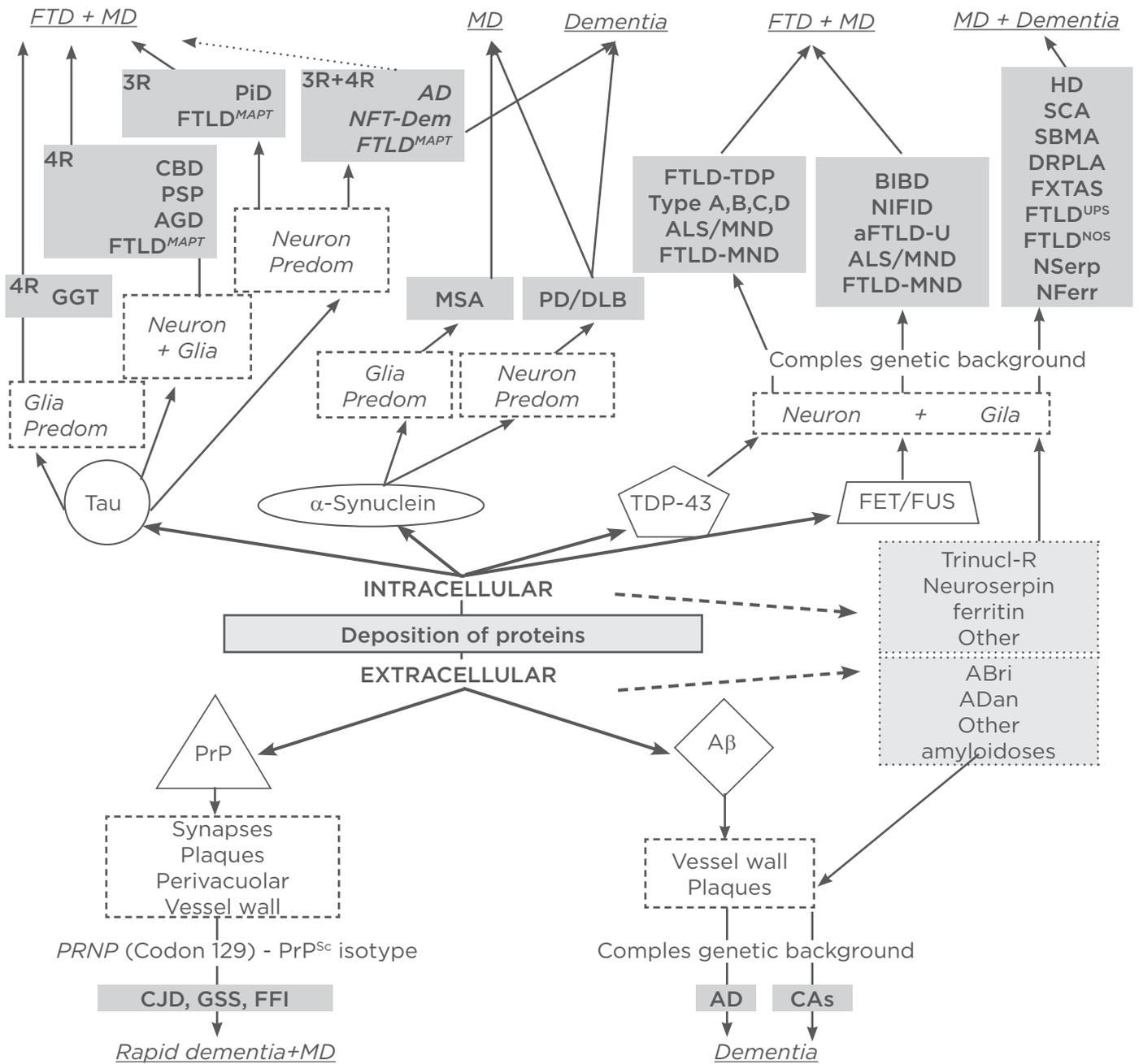
d) Prion protein (PrP) is a 253-aa protein central in the pathogenesis of prion diseases or transmissible spongiform encephalopathies. The encoding gene of PrP (*PRNP*) locates to chromosome 20.

e) Transactive response (TAR) DNA-binding protein 43 (TDP-43) is a highly conserved 414-aa nuclear protein. TDP-43 is encoded by the *TDP* (*TARDBP*) gene on chromosome 1p36.22. Among others, further most relevant genes for TDP-43 proteinopathy include progranulin (*GRN*; chromosome 17q21.32) and C9orf72 (chromosome 9p21).

f) 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).<sup>3</sup>

There are more forms of genetic NDDs with abnormal protein inclusions, comprising proteins encoded by genes linked to neurological trinucleotide repeat disorders such as Huntington's disease, some forms of spinocerebellar ataxias, and spinal and bulbar muscular atrophy. Further rare, inherited disorders associated with proteins and genes include neuroserpin or ferritin-related NDDs where the molecular genetic defect resides in the ferritin light polypeptide gene. 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 *BRI<sub>2</sub>* gene. There are further, mostly hereditary, NDD forms, such as spinocerebellar ataxias or degenerations of basal ganglia and brainstem, where protein deposits have not yet been discovered. These are mostly related to complex metabolic (e.g. mitochondrial, ion channel, etc) alterations requiring further characterisation.

From a diagnostic aspect, for the neuropathologists a further step is to evaluate the cell-specific subcellular localisations of the following:<sup>4</sup>



**Figure 1: Algorithm for the classification of sporadic neurodegenerative disorders.**

FTD: frontotemporal dementia; MD: movement disorder and other motor symptoms; PiD: Pick's disease; FTLD<sup>MAPT</sup>: frontotemporal lobar degeneration, linked to chromosome 17 caused by mutations in the MAPT (tau) gene; AD: Alzheimer's disease; NFT-Dem: neurofibrillary tangle-dementia; HD: Huntington's disease; SCA: spinocerebellar ataxia; CBD: corticobasal degeneration; SBMA: spinal and bulbar muscular atrophy; PSP: progressive supranuclear palsy; TDP: TAR-DNA binding protein; BIBD: basophilic inclusion body disease; DRPLA: dentatorubropallidoluysian atrophy; AGD: argyrophilic grain disease; NIFID: neuronal intermediate filament inclusion body disease; FXTAS: fragile X-associated tremor/ataxia syndrome; FTLD<sup>UPS</sup>: FTLD with inclusions immunoreactive for the ubiquitin-proteasome system; FTLD<sup>NOS</sup>: FTLD not otherwise specified; NSerp: neuroserpinopathy; NFerr: hereditary ferritinopathy; ALS: amyotrophic lateral sclerosis; MND: motor neuron disease; aFTLD-U: atypical FTLD with ubiquitin inclusions; Glia predom: the inclusions are predominantly in glial cells; Neuron predom: the inclusions are predominantly in neurons GGT: globular glial tauopathies; MSA: multiple system atrophy; PD: Parkinson's disease; DLB: dementia with Lewy bodies; TDP-43: TAR-DNA binding protein-43; FUS: fused in sarcoma; PrP: Prion protein; CJD: Creutzfeldt-Jakob disease; GSS: Gerstmann-Sträussler-Scheinker disease; FFI: fatal familial insomnia; CA: cerebral amyloidosis.

Adapted from Kovacs et al.<sup>2</sup>

a) Extracellular deposits comprise deposits with immunoreactivity for A $\beta$  or PrP. It is of diagnostic importance that disease-associated PrP deposits also in a synaptic pattern.

b) Major proteins that deposit intracellularly include tau,  $\alpha$ -synuclein, TDP-43, and FET proteins; furthermore, those associated with trinucleotide repeat disorders or rare hereditary diseases.

Further stratification is needed to distinguish cell-types (neurons, astrocytes, or oligodendroglia) and subcellular localisations (cell-process, cytoplasm, nucleus). These are influenced by genetic variations and may associate with different biochemical signatures. Current molecular pathological classification is summarised in [Figure 1](#), and the list of most important diseases is shown in [Table 1](#).

## 2. The Proteinopathy Concept Underpins the Role of Protein Processing Systems

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 (ALP).<sup>5</sup> Chaperones and stress response proteins are in close relation to protein processing systems. Widespread molecular pathological and biochemical studies revealed that there are modifications of proteins intrinsic to disease (e.g. phosphorylated, nitrated, oligomers, proteinase-resistant, with or without amyloid characteristics; cleavage products).<sup>2</sup> The pathological conformers are also called misfolded proteins and are associated with the disruption of the homeostasis of the endoplasmic reticulum (ER). ER stress and upregulation of related pathways are called the unfolded protein response.<sup>6</sup> The common role of the protein processing systems in all NDDs renders these systems as general targets for therapeutic approaches. Further changes, which are out of the scope of this review, include pathways of energetic dysregulation (i.e. oxidative stress and mitochondrial instability), molecular damage (i.e. lipid peroxidation, DNA oxidation), metabolic changes (i.e. alterations of cholesterol metabolism), or dysregulation of ion homeostasis and adaptation, such as anti-inflammatory cytokines, microglial activation, anti-apoptotic, or antioxidant processes.<sup>7</sup> It needs to be clarified whether the altered proteins lead to neuronal damage (if yes, which modification like oligomer formation etc.) or whether their deposition is merely a reaction of the sick cells.

## 3. Seeding of Pathological Proteins: The Concept of Prion-Like Spreading

The proteinopathy concept serves as a basis for the theory of prion-like spreading of disease-associated proteins.<sup>8</sup> This stems from the observations that, in prion diseases, the disease-associated PrP spreads in the nervous system. Recent findings implicate disease-associated protein seeds as an essential element in the initiation and expansion of aggregated proteins in diverse NDDs.<sup>9</sup> Although human-to-human transmissibility has been proven only for prion diseases, several other NDDs were suggested to be associated with the prion-like spreading of the specific protein characterising it. It must be noted that in NDDs the spreading of disease alterations seems to be more selective than in prion diseases. There are no epidemiological evidences, which would suggest a similar transmissibility for Parkinson's disease (PD) or AD. However, this issue needs great caution and attention in the near future to react adequately on the public health level should any further evidence arise.

The notion of prion-like spreading was supported by the neuropathological observations in human brains that protein deposition of  $\alpha$ -synuclein in PD and tau in AD follows a hierarchical path defined as stages of disease.<sup>10,11</sup> Moreover, subjects with PD who had long-term survival of transplanted foetal mesencephalic dopaminergic neurons developed  $\alpha$ -synuclein-positive Lewy bodies in grafted neurons, suggesting that the disease can propagate from host to graft cells.<sup>12</sup> Importantly,  $\alpha$ -synuclein pathology is increasingly detected in peripheral tissue,<sup>13</sup> thus, spreading from the periphery could also be suggested. Analogously, five phases of A $\beta$  deposition as AD-related pathology has been reported.<sup>14</sup> A similar concept of hierarchical spreading in the brain has been suggested for TDP-43 in amyotrophic lateral sclerosis (motor neuron disease) and FTLN with TDP-43 protein deposition.<sup>15,16</sup> Cell culture and animal experimental models have provided variable support for this prion-like theory.<sup>8</sup> It is also suggested that the considerable variability of NDDs is due to different 'strains'.<sup>8</sup>

These findings have implications for developing therapeutic strategies halting the spreading of protein deposits. It must be emphasised that vaccinations should aim to distinguish disease-associated from physiological forms of proteins to avoid unexpected complications by interacting with the normal forms of proteins.

**Table 1: Overview of neurodegenerative diseases according to major proteins deposited.**

1) In some forms of motor neuron disease (with/without FTLD) only FUS (and not FET) immunoreactive deposits are seen.

2) Globular glial tauopathies: recent studies have highlighted a group of 4-repeat (4R) tauopathies that are characterised neuropathologically by widespread, globular glial inclusions. Clinically these patients present with frontotemporal dementia with or without motor neuron disease and additionally extrapyramidal features.<sup>30</sup>

3) For spinocerebellar ataxias \* indicates that only where inclusions were described are listed here.

Proteinopathy	Protein	Disease / Subtype
Alzheimer's Disease-related	Tau, A $\beta$	Alzheimer's disease
Tauopathy	Tau	Pick's disease Corticobasal degeneration Progressive supranuclear palsy Neurofibrillary tangle-dementia Argyrophilic grain disease FTLD <sup>MAPT</sup> (FTDP-17T) Globular glial tauopathies
TDP-43 proteinopathy	TDP-43	FTLD-TDP: Type A-D MND FTLD-MND
FET(FUS)-proteinopathy	FET / FUS	FTLD-FET: aFTLD-U, NIFID, BIBD FUS: MND FTLD-MND
$\alpha$ -Synucleinopathy	$\alpha$ -Synuclein	Parkinson's disease Dementia with Lewy bodies Multiple system atrophy
Prion disease	Prion protein	Sporadic CJD Variably protease sensitive prionopathy Iatrogenic CJD (acquired) Variant CJD (acquired) Kuru (acquired) Genetic CJD, Gerstmann-Sträussler-Scheinker disease Fatal familial insomnia Prion protein-cerebral amyloid angiopathy
Trinucleotide repeat disorders	Huntington ataxin 1, 2, 3, 7, CACNA1A, TBP Frataxin Atrophin-1	Huntington's disease  (SCA 1, 2, 3, 6, 7, 17)*  Friedreich ataxia DRPLA
Other forms	Ferritin Tau, $\alpha$ -Synuclein Neuroserpin ABri, ADan	Hereditary ferritinopathy Neurodegeneration with brain iron accumulation Neuroserpinopathy Further hereditary amyloidoses

FTLD: frontotemporal lobar degeneration; FTLD<sup>MAPT</sup>/FTDP-17T: frontotemporal dementia and parkinsonism linked to chromosome 17 caused by mutations in the *MAPT* (tau) gene; TDP-43: TAR-DNA binding protein-43; MND: motor neuron disease; FUS: fused in sarcoma; aFTLD-U: atypical FTLD with ubiquitin inclusions; NIFID: neuronal intermediate filament inclusion body disease; BIBD: basophilic inclusion body disease; CJD: Creutzfeldt-Jakob disease; TBP: TATA-binding protein; SCA: spinocerebellar ataxia; DRPLA: dentatorubropallidoluysian atrophy; FET: fluoro-ethyl-tyrosine.

#### 4. Clinico-Neuropathological Correlations

Different disorders can affect the same anatomical regions. During the progression of disease, further anatomical regions will be affected, leading to complex constellations of symptoms, possibly hampering the correct diagnosis. The following examples can be mentioned:

a) Corticobasal syndrome. This can associate with corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP)-type tau pathology but also with TDP-43 proteinopathy and AD-related pathology.

b) PSP clinical syndrome (Steele-Richardson-Olszewski syndrome) can associate with CBD and PSP-type tau pathology but also with TDP-43 proteinopathy or even with prion disease.

c) CBD-type tau pathology can associate with FTD, moreover PSP-type tau pathology can associate with a spectrum of clinical syndromes apart from the classical Steele-Richardson-Olszewski syndrome, such as Dopa responsive Parkinsonism, pure akinaesia with freezing, or - mainly in the elderly - with cognitive decline and hypokinaesia.

d) FTD (including behavioural variant, or semantic dementia or progressive aphasia) with or without motor neuron disease can be associated with tau, TDP-43, or FET (FUS) proteinopathy or with the frontal variant of AD.

Thus, the clinical symptoms are determined by the system affected and do not unequivocally reflect the molecular pathologic background.

#### 5. Concomitant Neuropathological Alterations

The term 'mixed or concomitant' pathologies in NDD means that in addition to the hallmark lesions of a NDD entity, further pathological alterations can be observed in the same brain. The term 'mixed pathology' has been earlier used when describing accompanying vascular pathology. Later, Lewy body pathology was also mentioned as concomitant pathology. However, deposition of multiple neurodegeneration-related proteins, in addition to co-occurrence of non-neurodegenerative pathology (vascular, metabolic, etc.), is a frequent event.<sup>17</sup> In fact, overlapping of NDDs may be more the rule than the exception, particularly in the elderly. Our recent community-based neuropathology study on 233 individuals is proof of this concept since we detected a large variety of proteinopathies

with different combinations<sup>18</sup> reflecting the biological variability and arguing against simplified classifications. The high number of combinations reflects the different aetiologies showing overlapping pathogenetic pathways and is influenced also by the genetic background of patients and by other common diseases such as vascular or metabolic disorders. This suggests that in addition to therapeutic targeting of neurodegeneration, prevention and supplementary treatment of co-morbidities such as diabetes, alcohol consumption, hypertension, and previous stroke could be useful in a considerable fraction of patients.

These findings might have implications on: 1) therapy strategies aiming to target single pathological proteins in the brains of elderly individuals with dementia; 2) for the stratification of patients for a biomarker of genomic research.

This concept is supported by observations in genetic forms of NDDs where various proteins may show pathological deposits in the same brain.<sup>19-21</sup> Complex constellations of clinical symptoms (movement disorders and cognitive decline) may associate with the accompanying presence of diverse neurodegenerative disorders.

The term concomitant NDD indicates that the classical neuropathological features in an anatomical distribution defining a disease entity are seen in the brain together with the full features of another disease entity. The most frequent disease entities that overlap with others are AD and PD-related pathologies; these are reported as practically associated with all other types of NDD.

The term 'concomitant neurodegenerative pathologies restricted to certain anatomical regions' means that there are morphological features of a disorder fulfilling the criteria of its entity, but there are further neurodegenerative pathologies restricted to certain anatomical regions. Here TDP-43 and  $\alpha$ -synuclein need to be mentioned, but deposition of A $\beta$  and tau may also show different patterns when compared to the disease entity showing their deposition as a primary feature. Some important examples are as follows:

a) When appearing as a concomitant pathology, TDP-43 immunoreactivity usually involves the hippocampus, amygdala, and temporal cortex, and only rarely subcortical structures. This pattern can be seen in AD or in dementia with Lewy bodies

or argyrophilic grain disease (AGD) (up to 30-40%), rarely in PSP and CBD,<sup>22,23</sup> and is unusual in multiple system atrophy,<sup>24</sup> sporadic Creutzfeldt-Jakob disease,<sup>25</sup> or Pick's disease.<sup>26</sup>

b) Presence of Lewy bodies, mostly restricted to the brainstem, may be observed in various disorders. A peculiar constellation is when the NDD is associated with  $\alpha$ -synuclein deposition restricted to the amygdala and olfactory bulb. This is seen in up to 20-30% of AD patients.<sup>27</sup>

c) Coexistence of AD pathology and A $\beta$  deposition is not infrequent in NDDs. One reason for unusual amounts of A $\beta$  in another disease may be influenced by the apolipoprotein  $\epsilon$  (apoE) genotype.<sup>28</sup> Deposition patterns of A $\beta$  in PD, in particular in those showing dementia, seems to differ and may involve the striatum more than as expected only by aging.<sup>29</sup>

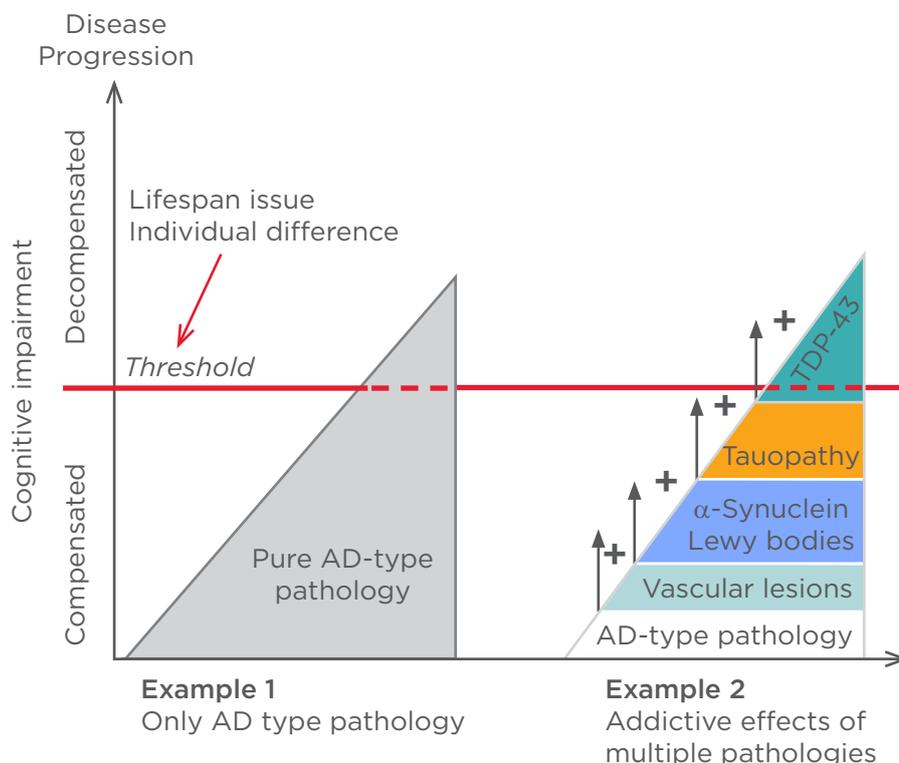
d) Among the sporadic tauopathies, PSP-type pathology and early stages of AGD-type pathology may be found in several other diseases restricted to certain anatomical regions.

For the clinical and neuropathological diagnostic practice, understanding the concept of 'lowering the threshold' for a clinical symptom is important. For example, the threshold of cognitive impairment, which shows inter-individual variability, could be reached by a prominent amount of AD-related changes (i.e. only plaques and tangles) but could not be reached by the concomitant presence of neuropathological alterations that, by themselves, are not sufficient to cause dementia (Figure 2).

## SUMMARY AND CONCLUSIONS

### Why is the Protein-Based Classification Important for Clinicians?

- These proteins and their biochemical modifications can be potentially detected in body fluids or potentially visualised in positron emission tomography imaging.
- The subcellular distribution of the pathological proteins can influence how these proteins reach the body fluids (i.e. different from an extracellular



**Figure 2: The concept of 'lowering the threshold' for a clinical symptom (i.e. cognitive impairment). The threshold shows inter-individual variability. This threshold can be reached by Alzheimer's disease (AD)-related neuropathological alterations (example 1), but can be reached by the concomitant presence of neuropathological alterations (example 2).**

AD: Alzheimer's disease; TDP-43: TAR-DNA binding protein-43.

Adapted from Kovacs et al.<sup>18</sup>

protein deposit than from an intracellular inclusion including glia or neurons).

- These proteins may be targeted for therapy (elimination of diseased-forms) or halting prion-like spreading. It must be clarified which modifications of proteins have relevance to be targeted for therapy.
- Targeting the protein processing systems may help to maintain the healthy homeostasis of proteins.

### What are the Perspectives for the Future?

Detection of a panel of neurodegeneration-related proteins and their modifications ('protein coding of NDDs') together with markers, which reflect the dynamics of disease (i.e. neuroinflammatory or signalling factors) in body fluids combined

with neuroradiological approaches and genetic screening of disease-modifying gene variations, can lead to personalised diagnosis or better prediction of prognosis.<sup>2</sup> If these concepts are validated, accepted, and implemented into the daily practice, the patients with NDDs would most benefit from discussing the cases in a multidisciplinary setting, analogously to tumour boards in oncology: the clinician, the neuroradiologist together with the neurochemist, clinical neuropathologist, and neurogeneticist will try to provide an individualised interpretation of diagnostic markers. This makes more sense if there are therapies to offer, or at least to provide a better prediction of the prognosis. Finally, it should be emphasised that, without continuous neuropathological studies, this approach loses its sense due to the need for permanent quality feedback.

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