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Short communication

Neurodegeneration in tauopathies and synucleinopathies

C. Foguem [a,b], B. Kamsu-Foguem [c,*]

[a] Epernay Hospital Centre, 137, rue de l'Hôpital Auban-Moët, BP 137, 51205 Epernay, France
[b] Center for Food and Taste sciences (CSGA), UMR 6265 CNRS, UMR 1324 INRA, University of Burgundy, 9E, boulevard Jeanne-d'Arc, 21000 Dijon, France
[c] Laboratory of Production Engineering (LGP), EA 1905, ENIT-INPT University of Toulouse, 47, avenue d'Azereix, BP 1629, 65016 Tarbes cedex, France

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ABSTRACT

While increasing life expectancy is a major achievement, the global aging of societies raises a number of medical issues, such as the development of age-related disorders, including neurodegenerative diseases. The three main disease groups constituting the majority of neurodegenerative diseases are tauopathies, alpha-synucleinopathies and diseases due to repetitions of glutamine (including Huntington's disease). In each neurodegenerative disease, the accumulation of one or more aggregated proteins has been identified as the molecular signature of the disease (as seen, for example, in Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, amyotrophic lateral sclerosis and frontotemporal dementia). The etiology of neurodegenerative diseases is often multifactorial, and the known risk factors include, in addition to genetic polymorphisms and age, some other possible causes, such as certain immune and metabolic conditions, endocrine pathologies, gender, socioeconomic or professional status, oxidative stress or inflammation, vitamin deficiencies and environmental factors (chemical exposure, metals). However, innovative strategies to elaborate suitable diagnostic and therapeutic approaches (aiming to at least delay or possibly even reverse disease progression) require further knowledge of the genetic and adaptive immunological characteristics of neurodegenerative diseases.

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1. Introduction

In every neurodegenerative disease, the accumulation of one or more aggregated proteins has been identified as the molecular signature of the disease [as seen in, for example, Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD)] [1]. The proteins that accumulate in the central nervous system of patients with such diseases were initially identified by the purification of polypeptides from the brains of affected humans and animals [2]. It is currently assumed that the basic mechanism of cell death in degenerative diseases is related to a rather restricted number of processes in which oxidative stress

* Corresponding author.
E-mail address: bernard.kamsu-foguem@enit.fr (B. Kamsu-Foguem).
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could play a central role, resulting in protein dysfunction and aggregation, which may be signs of differential clinical expressions [3].

The identification of specific mutations in certain genes is oriented towards certain proteins and pathways currently considered critical in the pathogenesis of the most prominent neurodegenerative diseases (Table 1). These include mutations of precursor proteins: amyloid beta (Aβ or Abeta) causes AD; alpha-synuclein leads to PD or DLB; and microtubule-associated protein tau (MAPT) causes FTD with parkinsonism. These aberrant misfolded proteins occurred initially in specific brain areas and were secondarily found in wider areas of the brain as the neurodegenerative disease symptoms worsened or the disease entered its later stages (Figs. 1 and 2) [4,5].

Furthermore, the prion concept explains how a disease can manifest as hereditary, sporadic or infectious. In addition, the common feature of prion diseases (sporadic, dominant inheritance, acquired through infection) is that they involve aberrant metabolism of prion protein. An important feature that distinguishes prion viruses is the two isoforms of prion protein (PrP) encoded by a chromosomal gene. In humans, the *PrP* gene is designated *PRNP* and is located in the short arm of chromosome 20.

Table 1 – Intraneuronal filamentous inclusions in neurodegenerative diseases.

Disease	Filamentous inclusions	Main component
Alzheimer's disease	Neurofibrillary tangles (lesions)	Tau protein
Pick's disease (type of frontotemporal dementia)	Pick bodies	Tau protein
FTDP-17	Neurofibrillary lesions, glial fibrillary lesions	Tau protein
Progressive supranuclear palsy (PSP)	Neurofibrillary lesions, glial fibrillary lesions	Tau protein
Corticobasal degeneration (CBD)	Neurofibrillary lesions, glial fibrillary lesions	Tau protein
Parkinson's disease	Lewy bodies and neurites	Alpha-synuclein
Dementia with Lewy bodies (DLB)	Lewy bodies and neurites	Alpha-synuclein
Multiple system atrophy (MSA)	Neuronal and glial inclusions	Alpha-synuclein
Huntington's disease	Intranuclear inclusions, dystrophic neurites	PolyQ repeat expansion in huntingtin protein
Spinocerebellar ataxia type 1 (SCA1)	Intranuclear inclusions	PolyQ repeat expansion in ataxia type 1 protein
Spinocerebellar ataxia type 3 (SCA3)	Intranuclear inclusions	PolyQ repeat expansion in ataxia type 3 protein
Spinocerebellar ataxia type 7 (SCA7)	Intranuclear inclusions	PolyQ repeat expansion in ataxia type 7 protein
DRPLA, or Naito–Oyanagi disease	Intranuclear inclusions	PolyQ repeat expansion in ataxia type 1 protein
Spinal and bulbar muscular atrophy (SBMA)	Intranuclear inclusions	PolyQ repeat expansion in androgen receptor

FTDP-17: frontotemporal dementia and parkinsonism linked to chromosome 17; PolyQ: polyglutamine; DRPLA: dentatorubral-pallidoluysian atrophy.

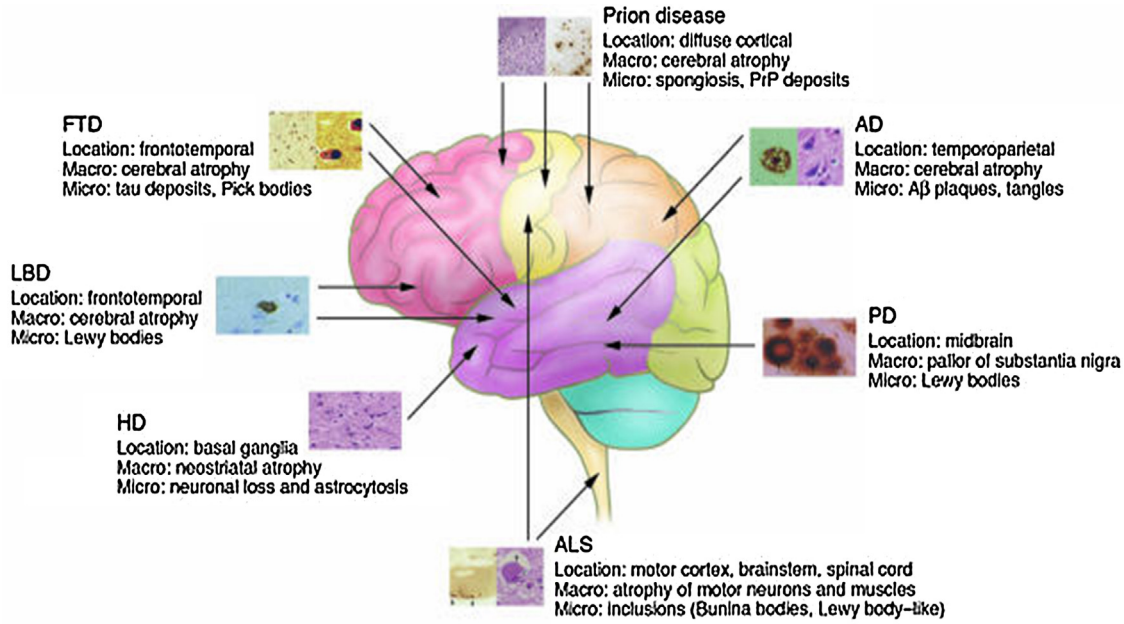

Fig. 1 – Brain anatomical locations of primary macro- and microscopic changes (misfolded proteins) are characteristic of particular neurodegenerative diseases. PrP: prion protein; FTD: frontotemporal dementia; AD: Alzheimer's disease; LBD: Lewy body dementia (including Parkinson disease dementia, PDD and dementia with Lewy bodies, DLB); PD: Parkinson's disease; HD: Huntington's disease; ALS: amyotrophic lateral sclerosis. From Bertram and Tanzi [4].

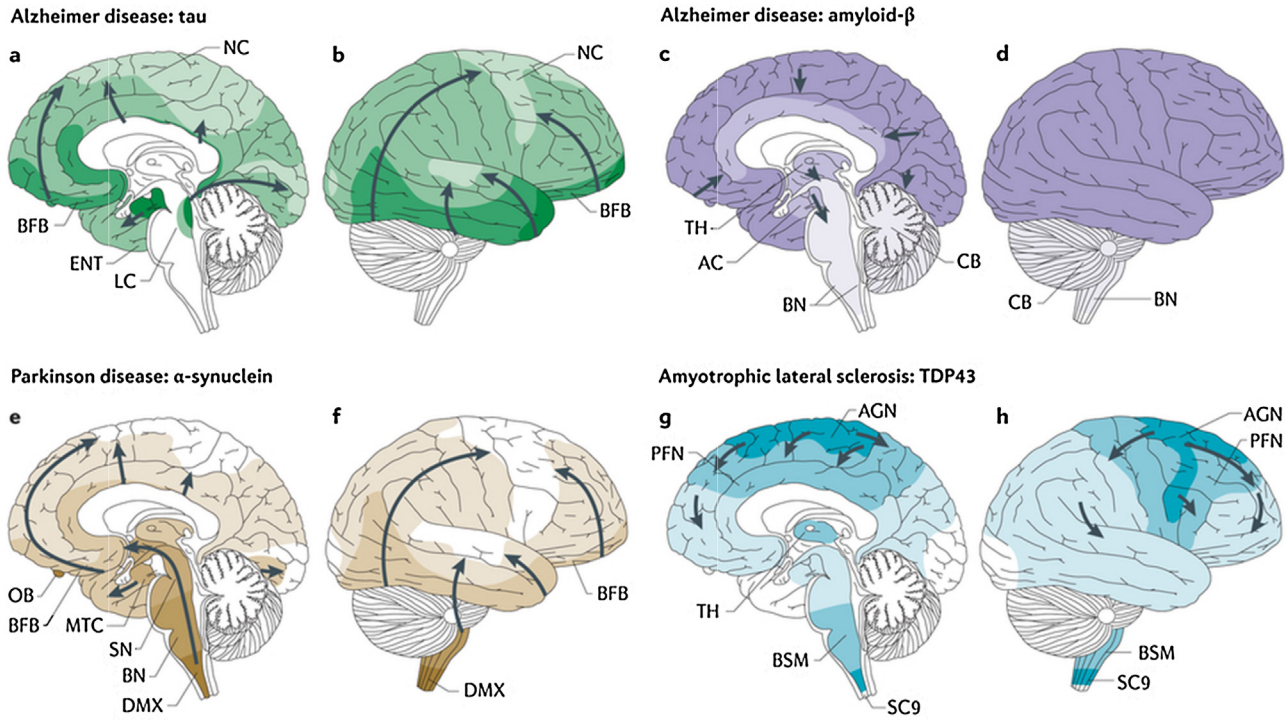

Fig. 2 – Sequential topographical dissemination of non-prion proteins in neurodegenerative diseases. Pathology is first detected in areas shown in darker colours and then in regions shown in lighter colours. (a and b) In Alzheimer's disease (AD), tau aggregates develop initially in the locus ceruleus (LC), then in transentorhinal and entorhinal regions, and finally in the hippocampal formation and wide areas of neocortex (NC). (c and d) In contrast to tau pathology, amyloid-β deposits in AD are first seen in NC and then in allocortical, diencephalic and basal ganglia structures (caudal direction), brainstem, and sometimes cerebellum (CB). (e and f) Progression of α-synuclein immunoreactive Lewy body/neurite pathology in Parkinson's disease follows an ascending pattern from brainstem to telencephalon. Earliest lesions are in the olfactory bulb (OB) and dorsal motor nucleus of the vagus nerve (DMX) in the medulla oblongata. (g and h) In amyotrophic lateral sclerosis with a low burden of TAR DNA-binding protein 43 (TDP43) pathology, TDP43 inclusions are seen initially in the agranular motor cortex (AGN), brainstem motor nuclei of cranial nerves XII–X, VII and V, and α-motor neurons in the spinal cord. AC: allocortex; BFB: basal forebrain; BN: brainstem nuclei; BSM: brainstem somatomotor nuclei; ENT: entorhinal cortex; MTC: mesiotemporal cortex; PFN: prefrontal neocortex; SC9: spinal cord gray-matter lamina IX; SN: substantia nigra; TH: thalamus. Reprinted from Brettschneider et al. [5] and Braak et al. [16].

2. Filamentous inclusions in neurodegenerative diseases

The three main disease groups constituting the majority of neurodegenerative diseases are the tauopathies, alpha-synucleinopathies and diseases due to repetitions of glutamine (including Huntington's disease; Table 1).

Tauopathies (including AD, FTD and progressive supranuclear palsy) and alpha-synucleinopathies [comprising mainly PD, DLB and multiple system atrophy (MSA)] represent the majority of late-onset neurodegenerative diseases in humans. Amyloidopathies, tauopathies and synucleinopathies share common pathological features in terms of structural, aggregatory and spreading properties (the pathophysiological molecular mechanisms leading to cellular toxicity) [6]. The factors that generate tauopathy and its extension within areas of the brain are not well known; amyloid precursor protein (*APP*) gene dysfunction is the best candidate so far, as revealed by genetic studies [7]. The development of intracellular filamentous inclusions could bring a risk of acute or chronic toxicity, leading to injury or damage to brain cells [8].

3. Etiology of neurodegenerative diseases

Another feature observed in the most common neurodegenerative diseases is the dichotomy between familial (rare) and non-familial forms (most common; Table 2). These are also frequently described as 'sporadic' or 'idiopathic', although there is a growing body of evidence suggesting that a large proportion of these cases are also strongly influenced by genetic factors. The genetics behind these diseases has been labeled 'complex', in contrast to the classical Mendelian genetics dubbed 'simplex' (single mode or single inheritance), due to the involvement of numerous genes that are likely to have complex interactions with each other and with non-genetic variables as well (Fig. 3). The genetics considered complex would be governed by common deoxyribonucleic

Table 2 – Etiological frequency (sporadic, genetic and infectious) of neurodegenerative pathologies.

Diseases	Etiological frequency (%)		
	Sporadic	Genetic	Infectious
Prion disease	85	> 10	< 1
Alzheimer's disease	90	10	
Parkinson's disease	95	< 5	
Frontotemporal dementia	90	10	
Pick's disease	95	< 5	
Progressive supranuclear palsy (PSP)	95	< 5	
Amyotrophic lateral sclerosis (ALS)	90	10	
Huntington's disease (HD)		100	
Spinocerebellar ataxia (SCA)		100	

acid (DNA) variants, such as single nucleotide polymorphisms, which significantly increase the risk of disease, yet are insufficient to effectively cause a disorder or specific disease.

Innovative strategies to elaborate suitable therapeutic approaches (aiming to at least delay and possibly even reverse disease progression) require knowledge of the genetic and adaptive immunological characteristics of these neurodegenerative diseases. Genetic evidence supports the idea that multiple neurodegenerative pathways lead to mild cognitive impairment and that the eventual conversion to dementia, principally of the AD subtype, is essentially due to the AD pathway(s) [9].

The etiology of neurodegenerative diseases is often multifactorial, although these chronic diseases share two main characteristics:

- neuronal loss in motor, sensory or cognitive systems, generating mental and motor decline;
- a strong association between metabolic changes and neurodegeneration (for example, disruption of the link between the peripheral organs governing energy metabolism and the cognitive and neural systems) [10].

The known risk factors for neurodegenerative diseases include, in addition to genetic polymorphisms and age, other possible causes such as certain endocrine pathologies, gender, socioeconomic or professional status, oxidative stress or inflammation, vitamin deficiencies [especially of vitamin B9 (folic acid) and vitamin B12], immune and metabolic conditions, and environmental factors (such as chemical exposure and heavy metals; Fig. 3). Indeed, some studies have revealed correlations between chronic pesticide exposures in occupational settings and the development of neurological disorders [11]. In addition, epigenetic regulation of gene expression and environmental modulation are factors that may play a key role in the onset and course of common neurological conditions, including AD, PD, Huntington's disease (HD) and multiple sclerosis (MS) [12]. The immune system also has an important role in neurodegenerative disorders: while there are undoubtedly maladaptive components of neural inflammation that serve to spread a neurotoxic environment that can encourage neuropathogenic lesions, there is also the opportunity to use adaptive and beneficial microglial/monocyte phenotypes to enable beneficial neuroimmune responses in some neurodegenerative diseases (such as AD and PD) [13].

4. Discussion

The degenerative processes in brain cells are considered 'primary' when no causal factor can be identified, and 'secondary' when triggering factors are demonstrated (inflammatory factors, or toxic, metabolic or traumatic events). These triggering factors of neurodegenerative pathologies are still mostly unknown, making a timely and accurate diagnosis difficult to achieve during antemortem assessment of these diseases [1]. Although in certain cases, the diagnosis made by a clinician can be confirmed postmortem by pathological examination, it is generally accepted that diagnostic errors may be identified from the patient's postmortem anatomical pathological findings. In many situations, there are difficulties in diagnosis, as some neurodegenerative diseases have many signs and symptoms in common. The diagnosis of DLB is particularly difficult as some of its symptoms can be found in other neurodegenerative diseases, such as PD and AD, thereby often leading to its misdiagnosis.

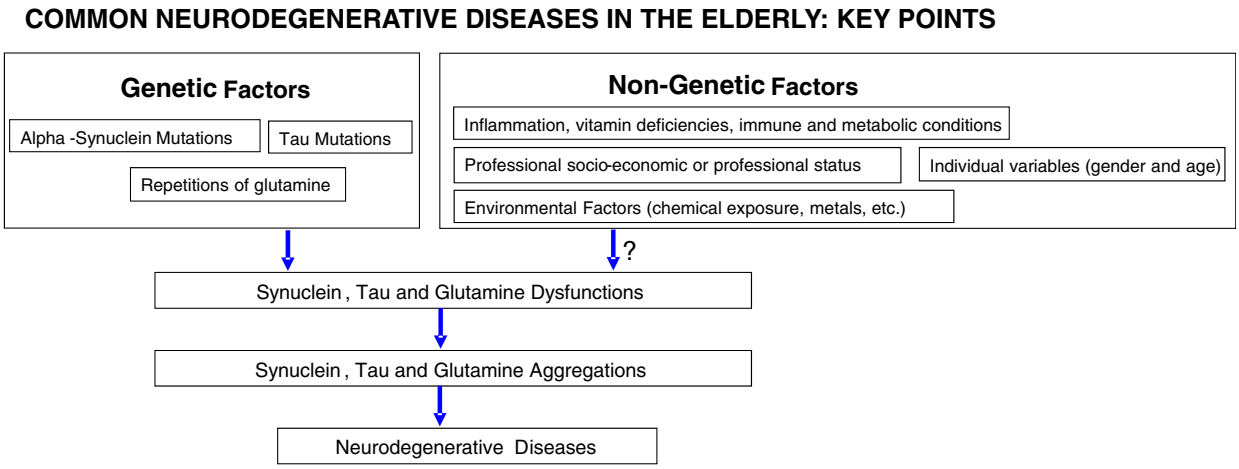

Fig. 3 – Spectrum of risk predisposing to common neurodegenerative diseases. This regrouping distinguishes genetic predisposition from non-genetic factors.

AD is the most common neurodegenerative disease, affecting 20 to 25 million people worldwide, and is the fourth leading cause of death in industrialized countries. Its prevalence rate is around 7% in those aged $\geq$ 65, with the doubling of risk for every 5 years after age 65. Some studies of AD suggest that the gene encoding spondin 1 (*SPON1*) may be associated with the differential rate of cognitive decline in AD patients [14,15].

PD is the second most common neurodegenerative disease associated with intraneuronal filamentous inclusions made up of aggregated alpha-synuclein in Lewy bodies and dystrophic neurites. It affects between six and seven million people around the world. Some rare familial forms of PD are caused by mutations of the gene for alpha-synuclein [8].

DLB is the second most common neurodegenerative dementia after AD, and the second most common synucleinopathy after PD, FTD represents 5–10% of all dementias, including Pick's disease. These disorders are related to mutations of the tau gene in familial FTD and parkinsonism linked to chromosome 17 (FTDP-17). For most of these diseases, the definitive diagnosis can only be made by pathological examination of brain tissue.

The primary neurodegenerative diseases that lead to a dementia syndrome have a number of common characteristics and constitute a consistent set of features:

- the neurodegenerative process is slow and can take 20 years before the onset of its first clinical manifestations, making it difficult to precisely date the beginning of the disease or even the start of the first clinical signs;
- the brain damage is irreversible, so the clinical signs persist over time;
- the symptomatology and all clinical signs of the dementia are important;
- the course of the illness trends towards a loss of independence.

5. Conclusion

There is accumulating evidence that most neurodegenerative diseases are due to deposits of aberrantly misfolded and aggregated brain proteins. Pathologies with a primary degenerative process mainly include AD, PD, DLB, ALS, HD, FTD and prion diseases. AD is characterized by degeneration of neuronal cells due to filamentous neuronal inclusions, comprising the microtubule-associated protein tau in a hyperphosphorylated state; tau is the key constituent of neurofibrillary tangles and has a synergistic relationship with APP dysfunction.

The pathological accumulation of alpha-synuclein and Lewy bodies in the brains of PD patients (as postulated by Braak et al.) [16] could lead to the development of a predictable six-stage sequence of lesions, based on a stepwise pathological progression starting from the medullary nuclei and olfactory cortex. Implementation of such a staging strategy to categorize the degree of pathology in PD might then influence the patient's final diagnosis [16,17]. However, it has been shown that, in certain rare cases, there is no relationship between the Braak stage and clinical severity of PD [18].

The clinical syndrome of DLB seems to be directly related to Lewy body pathology and is often inversely related to the pathological lesions associated with AD. Thus, DLB neuropathological criteria could be useful for making a precise diagnosis. In particular, a visual semi-quantitative analysis could be used to differentiate DLB from PD in the brain: lesions in the latter have a distribution predominantly in the brainstem whereas, in the former, the distribution and frequency of Lewy bodies are likely be diffused throughout the neocortex. Imaging of the dopaminergic system using ^{123}I-fluoropropyl-2-beta-carbomethoxy-3-beta(4-iodophenyl)-nortropane (FP-CIT) single-photon emission computed tomography (SPECT) may represent an accurate method for differentiating DLB from other dementia syndromes [19].

Filamentous inclusions of tau protein have been identified in the brains of patients with FTD, and especially Pick's disease. This has been revealed to be due to mutations in the tau gene in familial forms of FTD, thus providing a direct link between tau protein dysfunction and dementia severity [8].

Finally, in MSA, which is less common than the other neurodegenerative pathologies and often confused with PD at the clinical level, the accumulation of misfolded alpha-synuclein has been described, as well as multiple forms of neural degeneration similar to those found in PD and DLB [20].

In future, the development of strategies to elaborate new potentially therapeutic approaches and of further research aimed at the discovery of novel drugs for neurodegenerative diseases will require greater knowledge of the innate and adaptive immunological aspects of neurodegenerative diseases (such as those found in PD, AD and ALS) [21,22].

Ethical approval

The authors agree with ethical approval and informed written consent.

Disclosure of interest

The authors declare that they have no competing interest.

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