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# Neurodegenerative lesions: Seeding and spreading

## *Les lésions neurodégénératives: initiation et propagation*

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ABSTRACT

Accumulation of specific proteins has replaced loss of specific populations of neurons in the definition of most neurodegenerative diseases. In some cases, the amino-acid sequence of the protein that accumulates is altered by a mutation in the gene that codes for it but most generally, the primary structure is normal. Much evidence from human neuropathology has been collected over the years indicating that the progression of the lesions in such neurodegenerative diseases as Alzheimer's disease, Parkinson's disease and progressive supranuclear palsy follow the neuroanatomical connections. More recently, injection of aggregates of the specific proteins in the brain of experimental animals has been attempted in various experimental settings. Brain homogenates containing Aβ aggregates induce the early development of Aβ deposits in APP transgenic mice. Brain homogenates from various human tauopathies induce tau aggregates in transgenic mice expressing normal human tau. Finally, synthetic preformed fibrils of alpha-synuclein initiate the development of alpha-synuclein accumulation resembling Parkinson's disease in wild-type mice. Experiments in cell cultures suggest that the protein has to be in some specific state of oligomerization or fibrillation to be endocytosed and transported by the neuron. These data suggest that the protein that accumulates in a specific disease is initially misfolded and that this misfolding contaminates normal protein in a prion-like manner – in some cases through the neuronal connections.

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RÉSUMÉ

L'accumulation de protéines spécifiques a remplacé la mort de populations neuronales spécifiques dans la définition de la plupart des maladies neurodégénératives. Dans certains cas, la séquence des acides aminés qui constituent la protéine est altérée du fait d'une mutation dans le gène qui la code, mais de façon plus générale, sa structure primaire est normale. De nombreuses données descriptives provenant de la neuropathologie humaine ont été collectées au cours des années indiquant que la progression des lésions dans des affections comme la maladie d'Alzheimer, de Parkinson, ou la paralysie supranucléaire progressive, suit les voies de connexion nerveuse. Plus récemment, des injections d'agrégats

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Touffe astrocytaire
Plaque astrocytaire
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Corps de Lewy

de protéines spécifiques dans le cerveau d'animaux d'expérience ont été réalisées dans des conditions expérimentales variées. Des homogénats cérébraux contenant des dépôts de peptide Aβ induisent de développement accéléré de dépôts d'Aβ chez une souris transgénique APP. Des homogénats cérébraux provenant de différentes tauopathies humaines induisent l'apparition d'agrégats de tau chez des souris transgéniques qui expriment une tau humaine normale. Enfin, des fibrilles synthétiques préformées d'alpha-synucléine déclenchent, chez des souris sauvages, une accumulation d'alpha-synucléine ressemblant à celle qui est observée dans la maladie de Parkinson. Les études in vitro suggèrent que la protéine doit être dans un état particulier d'oligomérisation ou de fibrillation pour être endocytée ou transportée par le neurone. Selon les hypothèses actuelles, la protéine qui s'accumule dans une maladie donnée est initialement mal repliée; ce repliement anormal « contamine » la protéine normale au cours d'un processus qui rappelle celui qui a été décrit dans les maladies à prions. L'observation des cas humains et l'expérimentation indiquent que cette propagation s'effectue dans certaines maladies neurodégénératives comme la maladie d'Alzheimer ou la maladie de Parkinson par les connexions nerveuses.

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## 1. Neurodegeneration, aggregates and inclusions

Accumulation of specific proteins tends to replace death of specific populations of neurons in the operational definitions of neurodegenerative diseases. The protein, specific for each disorder, accumulates in insoluble aggregates in which molecules are held together as oligo- or polymers by non-covalent bonds. Aggregates are visible with light microscopy as ''inclusions'' (Fig. 1). Some inclusions may be seen after haematein-eosin stain (the Lewy body is a good example), when other ones are apparent only after immunohistochemistry using an adequate antibody (for instance the nuclear inclusions of polyglutamine diseases). Immunohistochemistry is now the tool of the pathologist studying neurodegenerative diseases. Immunohistochemistry relies on antibodies that bind with a high affinity to the antigens to be detected. But antibodies are, in their vast majority, directed against peptides or proteins. In other words, the pathology of neurodegenerative diseases is currently observed with an instrument massively biased toward the observation of proteins. That limitation has to be kept in mind.

### 1.1. *Aggregation and misfolding*

How do inclusions form? If their formation was directly related to an increased production of the protein that composes it or to a faulty clearance due, for instance, to an enzymatic deficit, accumulation should take place as soon as the protein is produced as in storage diseases. The neurodegenerative disease should declare at an early age and the accumulation be visible in young patients and steadily increase with age. In most of the cases, however, the inclusions are visible only in old people and in some disorders, their number seems to decrease with the severity of the disease (see for instance Lewy bodies in the substantia nigra).

The proteins that accumulate in most neurodegenerative diseases fall into two categories: either they are mutated and the mutation favors their aggregation or their sequence is normal and the aggregation is related to a process that has been named misfolding. In the first category are placed the polyglutamine diseases in which at least the part of the protein that includes the polyglutamine stretch forms intranuclear inclusions. Glutamine rich sequences are known to be aggregation-prone (Plumley and Dannenberg, 2010). In the second category, the amino-acid sequence of the protein that aggregates is normal. This is the case for Aβ and tau in AD, alpha-synuclein in Parkinson disease and dementia with Lewy bodies, or tau in Pick disease, progressive supranuclear palsy (PSP) and cortico-basal degeneration (CBD) – with the rare exceptions of a few specific mutations. The inclusion could be the mere consequence of an increase in the concentration of the accumulated protein. The inclusion may however be isolated from the cell medium or the extracellular space and remain individualized. The cohesion of the aggregated proteins has thus become independent from the concentration of the protein in the medium where the inclusion was formed. How can a protein which may have a normal amino-acids sequence, becomes insoluble and aggregates? That question was raised in the 1960th when biochemists were looking for ''the'' amyloid substance that accumulated in various organs, in familial or sporadic diseases, with very diverse clinical syndromes. It was found that ''the'' amyloid substance was actually not unique. Proteins of various types could produce the characteristic fibrils – with a uniform aspect at electron microscopy (Cohen and Calkins, 1959). The analysis by X-ray diffraction revealed, in all cases, a cross-beta sheet structure (Eanes and Glenner, 1968; Glenner, 1980) that indicated that the peptides were aligned and formed sheets. Proteins, in such a conformation, gain a high affinity for the Congo red stain which shows green birefringence when viewed by polarized microscopy (Glenner et al., 1972). Although, the mechanisms remain poorly understood, several factors may be involved in the aggregation of proteins with a normal primary sequence: the protein may be altered by a post-translational modification. Tau hyperphosphorylation could be such a modification favoring aggregation (for review see Noble et al., 2013). The balance between isoforms could also be an important factor: in the human, the ratio between

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