

The use of neuropathology in Alzheimer's disease

Mini review

Alzheimer's disease (AD) has been historically defined by protein accumulation around critical areas of the brain, i.e. hippocampus.¹ The hippocampus is a relatively small brain structure located within the limbic system.¹ Functionally, this particular structure has been correlated with cognitive functions such as learning, memory and spatial navigation.² In line with this reasoning and thinking in terms of brain disease development, is not difficult to imagine hippocampal damage associated with pathologies like AD.^{1,3} Here two proteins are the major players circumscribing the pathological development of AD: amyloid beta ($A\beta$) and tau proteins.^{3,4} Although the exact or the mayor mechanism of protein deposition remains under extensive study, the reality is that we do not know how or why these proteins elicit the accumulation process. However, we need to acknowledge that several pieces of evidence are clues of the putative mechanism. Evidence in support of the case for $A\beta$: we know that gene mutation in the amyloid precursor protein generates a 42 amino acid peptide that is susceptible to extracellular aggregation during the course of AD development.⁵ This peptide is the main component of the extracellular $A\beta$ plaque (Figure 1, black arrows). In addition, we know that the $A\beta$ plaque presents preferentially a spherical shape that can be clearly observed around the limbic area (Figure 1, black arrows). Unfortunately and despite this remarkable finding, the gene mutation corresponding as causal mechanism only accounts for the hereditary form of AD.⁶ In this regard, the second and most predominant form of AD is sporadic, and for this particular type, the mechanism remains unknown.⁶ We need to mention that the sporadic form of AD accounts for more than 95 percent of the cases.⁶

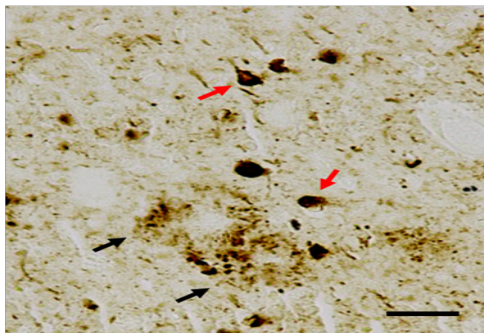


Figure 1 Phosphorylation of tau protein is a signature of Alzheimer's diseases. Phosphorylation at sites Ser^{396/404} labelled by PHF-1 are clearly seen in the tau aggregates (red arrows), but importantly, this event is also present in the formation of the $A\beta$ aggregates (black arrows). Scale bar 50 μ m.

Evidence in support of the case for tau protein; of note, remains far more complex and under extensive study.^{3,6} What we know is that tau protein is susceptible of suffering several posttranslational modifications such as conformational shifts, cleavages and several phosphorylation events.^{1,3} The current hypothesis holds that a combination of those events prompts the tau protein to an aggregation state. Thus giving rise to the neurofibrillary tangle (NFT), which normally adopts a flame like shape (Figure 1, red arrows). Important

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to note that opposite to the $A\beta$ plaque which is an extracellular protein deposit, the NFTs are intracellular protein aggregates.^{1,3} In agreement with previous published data, we have observed that the NFTs are mainly comprised of phosphorylase tau protein.³

Clearly, both aggregates are related to the AD pathological development; however the main question is how do the aggregates can affect the hippocampal function? Although the answer is far from simple, one thing is clear; both structures can affect the homeostasis of neuronal function. In one hand the $A\beta$ plaque locates preferentially in the proximity of synaptic terminals with the capacity of modifying the neuronal responses.^{4,7} On the other hand the extensive tau accumulation within the neuron takes all the intracellular space that ultimately leads to neuronal death (Figure 1). Despite this data, we cannot definitively name either of these structures as the cause of the disease. In fact, the chronology of events remains under extensive study. In this vein, we found that phosphorylation of tau protein is an early event that can function as an early stage developmental biomarker in tau pathologies such as Pick disease, Down syndrome and AD.^{8,9} More recently, by using transgenic mouse models, we have found that abnormally phosphorylase tau protein is actually present before any signs of $A\beta$ peptides (in preparation). This data is extremely important if we take into consideration that $A\beta$ has traditionally been suggested as the effector of tau alterations.¹⁰ This data opens a new perspective in terms of chronology and pathology effectors. In addition, our data could offer an explanation of the current failure for therapeutic strategies directed against $A\beta$ proteins.¹⁰ Most likely, we are working with agents directed against the wrong therapeutic target, although this remains to be proven.¹⁰

Overall, it is clear that both structures, the $A\beta$ plaques and the NFTs, are intimately related to AD and several associated brain pathologies such as hereditary cerebral hemorrhage with amyloidosis Dutch type, vascular dementia, Pick disease, Down syndrome and Parkinson's disease.^{3,8,9,11} However, only the neuropathological studies will provide a differential diagnosis between brain diseases.

As a consequence, they remain as the most accurate predictors of neurodegeneration stage.

Financial & competing interest's disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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Conflict of interest

The author declares no conflict of interest.

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