

•COMMENTARY•

More is Needed before Alzheimer's Disease can be Conquered

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German Neurologist Alois Alzheimer first reported the autopsy results of a fifty year old female patient named Auguste Deter in 1907. The patient presented with classic cognitive and behavioral disorder. The autopsy results showed two abnormal pathological changes: neurofibrillary tangles (NFTs) and senile plaques (SPs). In 1924 Divery found that SPs consisted of amyloid using Congo red staining. In 1984, Glenner and Wong purified a 4.2 kDa β -amyloid ($A\beta$) from a patient with Alzheimer's disease (AD) with cerebral amyloid angiopathy (CAA). The sequencing analysis showed $A\beta$ was a peptide containing 39-43 amino-acids, moreover $A\beta_{40}$ and $A\beta_{42}$ were main types.^[1] Hardy and Selkoe proposed the amyloid cascade hypothesis in later years. Amyloid precursor protein (APP) severing disorder lead to over expression or less clearance of $A\beta$, and then $A\beta$ became aggregated. In particular, $A\beta_{42}$ accumulation caused synaptic degeneration, inflammation, oxidative stress, NFTs, neuron loss, and so on.^[2] Not long afterwards, several massive, multidimensional, long-term clinical studies showed a relationship between $A\beta$ deposition in the brain and dementia using demic biomarker analysis.^[3,4]

On the one hand, this may show why $A\beta$ -target strategies in AD drug development were always unsuccessful, but many pharmaceutical factories and labs still insisted on studying AD drugs because over the past 20 years of research a foundation for the pathological mechanism of AD has been established. Although its not necessary to completely start over, it is clear $A\beta$ -targeting drugs are not the final answer. In addition to what other researchers have reported in detail there are other ideas to consider. First, the neurophysiological and neurotoxic effects of $A\beta$ soluble monomer, oligomer and insoluble amyloid plaques are not clear. We have less knowledge about the clinical benefits of indiscriminate removal in passive

immunotherapy. Second, $A\beta$ deposit in the brain begins ten years before clinical symptoms of dementia begin to appear This progress can also be observed in normal aged brains. Does $A\beta$ have a dramatic increase in AD brains compared to non-cognitive impairment (NCI)? Or are AD brain neurons more sensitive to $A\beta$, which leads to neural impairment and irreversible neuron apoptosis? We lack evidence for both of these questions. Third, although $A\beta$ and Tau are two individual pathological processes in AD, more and more results have shown relationships between them. However, almost all studies to this point have concentrated on either $A\beta$ or Tau, and few clinical studies have combined both of them as a target for treatment. Fourth, genetic and environmental factors, which cause $A\beta$ or Tau overexpression, may accelerate neuron aging. It is synchronous between $A\beta$ deposition, Tau hyperphosphorylation and neural synapse degeneration, hypocyto metabolism, cytothesis impairment. Clearance of $A\beta$ or Tau cannot reverse neuron aging.

While several clinical tests have been unsuccessful we should continue in our efforts to conquer AD. At the same time, it is necessary to realize the complexity of the brain and brain diseases. Aging also plays an important role. Therefore it will be difficult to make a great breakthrough in the treatment of AD if our methods are only from a disease perspective.

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