Extended Abstract Journal of Alzheimer's & Dementia
2021
Vol.4 No.4

Advances in determination of Alzheimers amyloid peptide

Maotian Xu & Yintang Zhang

Shangqiu Normal University, China

Alzheimer???s disease (AD), the most common type of dementia in the elderly, is a progressive and devastating neurodegenerative disease causing memory loss, impaired thinking and other symptoms. ?-amyloid peptide (A?) indicates a biomarker for an AD in cerebrospinal fluid, blood, plasma and serum. Therefore, it is important to determine the A? concentration for early diagnosis and treatment of AD. In this study, micellar electrokinetic capillary chromatography (MEKC) combined with an online preconcentration method sweeping was established to determine A?1-42. Electrophoresis was carried out at a constant voltage of 5 kV in an uncoated fused-silica capillary. The 15 mmol/L borate buffer containing 20 mmol/L sodium dodecyl sulfate (SDS) with pH 9.3 was used as the running buffer. The samples were injected into the capillary by applying a pressure of 50 mbar for 60s. Under the optimal conditions, the detection limit of A?1-42 was as low as 0.08 ?mol/L. The recoveries of the normal addition method in real human serum sample analysis were found to be between 89.2% and 98.5%. The relative standard deviation (RSD) of the determination was less than 6%.

The two hallmark pathologies required for a diagnosis of Alzheimer's disease (AD) are the extracellular plaque deposits of the β-amyloid peptide (Aβ) and the flame-shaped neurofibrillary tangles of the microtubule binding protein tau. Familial early onset forms of AD are associated with mutations either in the precursor protein for Aβ (the β-amyloid precursor protein, APP) or in presenilin-1 (PS1) or presenilin-2 (PS2). Either PS1 or PS2 can be the catalytic subunit of γ-secretase, which is the final endoprotease in the pathway that generates the peptide. Despite this genetic evidence and the demonstrated involvement of Aβ in inducing synaptic dysfunction, disrupting neural connectivity, and association with neuronal death in a brain region-specific manner, the amounts and distribution of Aβ deposition are only weakly correlated with the clinical expression of the disease.

Development of a disease stage classification for AD has not been a simple process, nor is there complete consensus with the system(s) that are in place. Definitive staging of disease state remains a judgment call decided in clinicopathological conferences between clinicians, neuropsychologists, and pathologists. A major deficiency in the staging system is that it can only be approximately applied in the living subject. Since AD pathology is determined at autopsy, a clinical diagnosis of probable AD has to be used instead. The lack of an in-life diagnostic test greatly hampers research efforts on disease mechanisms, and is a particular problem for clinical trials as it introduces additional heterogeneity into the subject population. Therapeutics cannot be properly tested if they need to be administered before the disease progresses past a certain stage, especially if this stage is nebulous or the patient population is poorly defined.

Why Aβ deposition is only weakly related to the degree of dementia has been an enduring puzzle in the AD field. While potential floor or ceiling effects in the amount of Aβ deposition could contribute, there is also the possibility that Aβ exerts its major effects early by triggering a cascade of processes that, once begun, proceed independently of Aβ. Some support for this argument might be found in the human Aβ immunization trial (AN-1792). Although the numbers of individuals to come to autopsy is still very small, the brain Aβ deposition in these cases was far lower than might be expected based on historical levels for a given clinical stage. In spite of this markedly lower amount of Aβ, presumably caused by the immunotherapy, the subjects continued to decline cognitively to an end stage dementia that was clinically indistinguishable from untreated AD. This is not iron-clad proof that the removal of Aβ succeeded, since we have no way of knowing the pre-treatment amyloid load, and the number of cases is too small for a true cross sectional comparison. It is tempting to speculate that the implication of these results is that Aβ acts as a trigger for a degenerative process that continues even if it is removed.

It is not clear what the mechanism might be for this continued degeneration, although a continued accumulation of misfolded hyperphosphorylated tau, leading directly to further neuron loss, is perhaps the most likely candidate. However, this is a difficult hypothesis to test because it requires the reliable identification of subjects with AD at a very early, preclinical stage, a feat that is currently not possible even with the most sensitive and dependable means of diagnosing the disease.

Another possible explanation is that a specific form or forms of Aβ are responsible for the massive neuronal death that accompanies the disease. The tools used to quantify Aβ are not able to distinguish the disease-related Aβ from less relevant forms which weaken the correlation with clinical stage. An analogy of this situation is found in prion diseases in which the same protein sequence can assume multiple disease-causing conformations, each causing neurodegeneration in a distinct distribution of brain regions resulting in different clinical presentations [4, 5]. In this review we suggest that Aβ is also polymorphic, producing conformational form(s) or specific pool(s) of Aβ that are disease-relevant while others are less so. Progress is being made in methods and systems to delineate these relevant forms, which will allow testing of this hypothesis.