Abstract

It is accepted that fibrillar aggregated tau is the best histopathological correlate of the onset and progression of dementia. Tau protein was long regarded as an intracellular protein with several functions inside of cells. New evidence suggests tau secretion into the extracellular space. It is plausible that both intracellular and extracellular forms of tau protein contribute to AD neurodegeneration. The truncated/fragmented forms of tau protein are prone to self-aggregate and form soluble oligomers which are now considered the toxic agents that spread the pathology in AD and other tauopathies. In addition, immunologic abnormalities including defective immune regulation and autoimmunity have been demonstrated in AD patients. Therefore, we have studied the role of various extracellular forms of tau protein and antibodies against them in AD.

Firstly, we showed that antibodies isolated from intravenous IgG (IVIG, product Flebogamma) and plasma of older cognitively healthy persons (controls) were reactive with pathological soluble aggregates (oligomers) of tau protein present in the brain of AD patients. On the contrary, isolated antibodies from the plasma of AD patients revealed reactivity with lower molecular weight (LMW, monomeric) tau forms found in brain tissue. Moreover, the antibodies from control subjects showed strong binding to the fragment of tau (155-421 aa). Thus, our findings with the hypothesis of peripheral sink in mind may indicate the participation of blood antibodies in clearance of the aggregated and truncated tau structures from the brain without the need to cross the blood-brain barrier. However, the levels of anti-tau antibodies itself have not proved as suitable biomarkers of AD.

Secondly, we have found tau oligomers in sera of controls and their levels correlated with aging. On the contrary, the serum tau oligomers in the group of patients with mild cognitive impairment due to AD were lowered in comparison to control subjects. This result may be related to elevated serum levels of tau-reactive antibodies found in this study and/or to impaired clearance of tau protein from interstitium to blood and consequent accumulation of tau aggregates in the brain. By western blot, we found that serum of AD patients contained stable higher molecular weight (HMW) oligomers while in the serum of controls the HMW oligomers were unstable and dissociated into LMW oligomers. We suppose extracellular tau proteins are cleared from the brain to the periphery where are subjected to degradation. In some cases as for the AD pathology, this clearance pathway could fail, thus contribute to form oligomers and spread the pathology.