DISTINCTIVE OLIGOMERIC PROFILE OF THE RECESSIVE A673V APP MUTATION

M.L. Moro¹, M. Catania¹, G. Di Fede¹, F. Moda¹, A.R. Višcomi², L. Colombo³, A. Uggetti¹, G. Giaccone¹, M. Morbin¹, M. Salmona¹, F. Tagliavini¹

¹Division of Neurology and Neuropathology, U.O.Neurology 5, Carlo Besta National Neurological Institute, Milan, ²Dept. Biochemistry and Molecular Biology, University of Parma, Parma, ³Dept. Molecular Biochemistry and Pharmacology, Istituto di Ricerche Farmacologiche “Mario Negri”, Milan, Italy

Introduction: Accumulation of soluble and globular oligomers of amyloid beta peptides (Aβ) in distinct cellular and extracellular compartments is a central feature of Alzheimer’s disease (AD). Consequently, Aβ oligomerization and compartmentalization represent relevant biochemical aspects in the pathogenesis of sporadic and genetic AD. Recently, we identified a homozygous Amyloid Precursor Protein (APP) mutation (A673V) in a patient with severe, early-onset dementia and a distinctive neuropathological profile.

Aims: Since the A673V mutation enhances Aβ fibrilization in vitro, we considered primary to further characterize the amyloidogenic pathway induced by this genetic defect.

Methods: Synthetic Aβ peptides with and without the A-to-V substitution (Aβ-MUT and Aβ-WT) were aggregated in vitro and the Aβ assemblies separated by SDS-PAGE. Furthermore, we compared the content of Aβ aggregates in distinct cellular and extracellular compartments of brain tissue from the patient with the mutation, sporadic AD cases and age-matched controls. The Aβ40 and Aβ42 composition of the aggregates was analyzed by two color-Western blot.

Results: Synthetic Aβ-MUT peptides showed higher production of oligomers than Aβ-WT. Remarkable levels of multi-assembled forms characterized the SDS (membrane-associated) and formic acid soluble brain fractions of the patient with the A673V mutation. The amount of Aβ40 and Aβ42 also diverged from sporadic AD for striking prevalence of Aβ40 multi-assembled forms.

Conclusion: These results suggest that the peculiar neuropathological profile of A673V mutation is associated with a specific Aβ oligomeric profile. Further characterization of this mutation may contribute to understand the mechanisms of Aβ deposition in AD.