RECESSIVE A673V APP MUTATION: CENTRAL ROLE OF MUTANT AB1-40 IN OLIGOMERIZATION AND AMYLOIDOGENESIS

G. Di Fede1, M. Catania1, M.L. Moro1, R. Ghidoni2, V. Albertini2, G. Giaccone1, M. Morbin1, A. Uggetti1, F. Moda1, M. Salmona3, F. Tagliavini1

1Neurology V - Neuropathology, Fondazione IRCCS “Carlo Besta” National Neurological Institute, Milan, 2Proteomics Unit, IRCCS “Centro S.Giovanni di Dio-Fatebenefratelli”, Brescia, 3Department of Molecular Biochemistry and Pharmacology, Istituto di Ricerche Farmacologiche “Mario Negri”, Milan, Italy

Introduction: The A673V mutation in the Amyloid-beta (Aβ) Precursor Protein (APP) gene causes early-onset Alzheimer's disease (AD) in the homozygous state while heterozygous carriers are not affected since the interaction between A2V-mutated and wild-type Aβ hinders amyloidogenesis. Neuropathological examination of an A673V homozygous patient revealed unprecedented amyloid-related changes with high content of Aβ40 in senile plaques suggesting that the A673V mutation leads to a previously unrecognized amyloidogenic pathway.

Aims: To assess the effects of the A673V mutation on APP processing and Aβ assembly and topology in brain tissue and CSF.

Methods: An immunoproteomic analysis of Aβ using Western blot, ELISA and SELDI-TOF MS was carried out on different brain tissue fractions and CSF samples obtained at different disease stages from a patient carrying the homozygous A673V mutation.

Results: A reduction of A2V-mutated Aβ peptides and relative maintenance of Aβ10/11-40 N-truncated forms lacking the mutant residue were observed in patient's CSF. Levels of the most common CSF Aβ peptides strongly decreased along disease progression except for Aβ10-40 that became the most abundant isofrom in the advanced stages. A distinctive oligomeric profile with predominant involvement of Aβ1-40, and a peculiar distribution of Aβ species (i.e., segregation of amyloid peptides in the TRITON-soluble fraction and marked increase of aggregated Aβ in both SDS-soluble and formic acid extracts) were found in the brain of the A673V homozygous patient.

Conclusions: These results suggest that the A2V mutation remarkably enhances the aggregation properties of Aβ1-40 which is the most abundant Aβ species, strongly boosting amyloidogenesis.