CSF Anti-Aβ autoantibodies as novel biomarker for cerebral amyloid angiopathy-related inflammation: Implications for amyloid-related imaging abnormalities (ARIA) during passive immunization in Alzheimer’s disease

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Background: The data emerged from the two phase3 bapineuzumab trials provided valuable insights into its mechanism of action and the need of biomarkers in trial safety, highlighting the APOEε4 and dose-related development of Amyloid-Related Imaging Abnormalities (ARIA) as the most notable adverse event. Similar MRI abnormalities have been recently shown both in a human spontaneous model of ARIA, represented by Cerebral Amyloid Angiopathy-related inflammation (CAA-ri), and in immunized PDAPP mice, suggesting that anti-Aβ antibody and vasogenic edema are linked to a transient vascular leakage at the sites of major vascular Aβ clearance.

Methods: World-wide case-control study in 150 patients from the iCAβ Network. By a novel ultra-sensitive technique, we evaluated anti-Aβ autoantibody concentration in the CSF of CAA-ri, CAA, AD, MS and healthy-control. All patients undertaken T2*/SWI and FLAIR MRI analyses. 15/45 CAA-ri underwent brain biopsy for pathological confirmation. Aβ40, Aβ42, tau, P-181 tau and APOE4 were investigated.

Results: In CAA-ri, a higher amount of anti-Aβ autoantibodies is accompanied by massive drainage of Aβ from brain and vascular deposits into the soluble forms, followed by a reduction of both autoantibodies and neurodegenerative markers after remission. An increased concentration of autoantibodies in APOε4 carriers has been also observed in AD. Diagnostic cut-off for autoantibodies has been determined.

Conclusions: ARIA may represent a transient event preceding the downstream beneficial Aβ-clearance effects of treatment, where increased CSF anti-Aβ antibodies may cause a shift in CAA accumulation and increased vascular permeability. CSF anti-Aβ autoantibody test as biomarkers for the CAA-related consequences of treatment could mark an important advance for the current ongoing clinical trials in AD, both for patient enrichment and ARIA safety, opening also a new scenario for CAA therapy.

Biography

Fabrizio Piazza is a Researcher at the University of Milano-Bicocca. He graduated in Pharmaceutical Biotechnology at the University of Milan in 2005, and he got the International PhD in Translational and Molecular Medicine in 2008. From 2009 to 2011 he moved to Boston-USA, as Postdoc Associate at Tufts University. From 2012 is the Coordinator of the inflammatory Cerebral Amyloid Angiopathy and Alzheimer’s disease biomarkers International Network (iCAβ), leading neurobiological researches applied to neurodegenerative, neuroimmunological and cerebrovascular disorders. In 2013, he received the Alzheimer’s disease and Parkinson’s disease Faculty Award (ADPD International Conference) and the Perusini Award from the Italian Society of Neurology-Dementia for outstanding researches on AD and CAA. He is inventor of a patent application for the ultra sensible evaluation of Abeta antibodies and endothelial damage in human CSF.

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