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Dementia-2014: CSF Anti-Aβ Autoantibodies as novel biomarker for cerebral amyloid angioplasty-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 APOE?4 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. Anti-Aβ40, Aβ42, tau, P-181 tau and APOE4 were investigated. Results: In CAA-ri, a higher amount of Anti-Aβ Autoantibodies are accompanied by massive drainage of A? 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 APO?4 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 A?-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.

Biomarkers for the stratification, follow-up and monitoring of the safe and effective therapeutic response of amyloid-beta (Aβ) disease-modifying therapies (DMT) represent a research priority in Alzheimer's disease (AD).

Immunotherapy trials, in particular, have underlined the urgent need of safety biomarkers to avoid, or at least enable the early detection of the severe side effects of treatment termed amyloid-related imaging abnormalities (ARIA) (2). There are two types of ARIA: ARIA-E, characterized by the magnetic resonance imaging (MRI) evidence of vasogenic edema (VE) and/or sulcal effusion on fluid-attenuated inversion recovery (FLAIR), as hallmarks of inflammation at the level of the affected vessels; and ARIA-H, characterized by signal of hemosiderin deposits involving microhemorrhages (MHs) and superficial siderosis on T2*-weighted gradient echo (T2*-GRE) or susceptibility-weighted imaging (SWI), as hallmarks of cerebral amyloid angiopathy.

Even if the acronym ARIA was initially referred to specifically describe the MRI abnormalities of bapineuzumab, the first monoclonal antibody employed in clinical trial, the term is currently used to define the clinical–radiological side effects subsequently reported with almost all the immunotherapy strategies testes.

Today, no early biomarker able to predict the incipient occurrence of an ARIA has been already included in clinical trials. However, the current FDA guidelines for enrolling patients in studies assessing DMT require MRI evaluation, recommending excluding patients with ≥5 MHs and with any evidence of superficial siderosis or prior parenchymal hemorrhage.

Nevertheless, MHs on MRI are relatively non-specific, reflecting a variety of pathologic conditions. MRI could thus be particularly helpful for the detection of the acute/subacute course of ARIA, but it could fail to predict patients at high risk to develop incipient occurrence of these events, both at the baseline and during the therapeutic follow-up. The ARIA issue recently generated increasing interest after the very promising data for the Phase 1b study of aducanumab.

This drug demonstrated a statistically significant cognitive improvement in patients with prodromal or mild AD, together with a dose- and time-dependent reduction of deposited Aβ on amyloid-PET. Aducanumab, however, revealed an incidence of immunotherapy-related ARIA in the 55% of patients, particularly in the high-dose and APOEϵ4 carriers arm, associated with a 35% of ARIA drop-outs due to the development of these side effects

The recent discovery that ARIA-like events in CAA-related inflammation (CAA-ri) are mediated by increased anti-Aβ autoantibodies in the CSF, has sensibly increased the understanding of the etiological mechanisms of ARIA. CAA-ri has thus been proposed as a human spontaneous model of the drug-induced ARIA in AD.

Foot Note: This work is partly presented at 2nd International Conference on Alzheimer's Disease and Dementia, September 23-25, 2014 | Valencia Convention Centre, Spain