Association of Microglial Activation With Spontaneous ARIA-E and CSF Levels of Anti-Aβ Autoantibodies

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Study Question
Is amyloid-related imaging abnormalities–edema/exudate (ARIA-E) associated with increased anti β-amyloid (Aβ) autoantibodies (Abs) inducing microglial activation?

What Is Known and What This Paper Adds
Ex vivo evidence suggests that Aβ-lowering monoclonal antibodies might promote microglial activation. The direct association between microglial activation and ARIA-E in cerebral amyloid angiopathy (CAA) and patients with Alzheimer disease (AD) with ascertained high levels of Abs has never been demonstrated in vivo. The results of this study show that there is a specific regional and temporal association between the radiographic severity of ARIA-E and the presence of focal peaks of microglial activation in the context of increased concentrations of Abs in the CSF.

Methods
We describe the findings in 4 patients monitored longitudinally from the (sub)acute presentation of ARIA-E (inpatients hospital setting) to posttreatment follow-up with corticosteroids. ARIA-E was diagnosed by clinical presentation, CSF testing, and MRI findings, according to current criteria. Multimodal and multiparametric MRI images were rated for CAA, CAA-related inflammation, and ARIA-E magnitude and severity according to validated scoring systems and criteria. CSF testing for Abs, Aβ42/40, tau, and p-tau was assessed to define the biomarker profile in the AD continuum and 11C-PK11195 PET to quantify microglial activation.

Results and Study Limitation
At (sub)acute presentation, we found focal peaks of microglial activation having a greater spatial colocalization with ARIA-E images compared with chronic age-related white matter change (ARWMC) imaging abnormalities. The radiographic severity of ARIA-E and the magnitude of the associated microglial activation was greater in patients with AD and concomitant severe CAA pathology, as measured with CSF and MRI biomarkers, compared with patients with CAA only. CSF levels of anti-Aβ Abs at ARIA-E presentation were high in all patients and markedly decreased at posttreatment follow-up, in parallel with clinical resolution of acute symptoms, reduced radiographic severity, and a marked reduction of microglial activation associated with ARIA-E compared with ARWMC. Our results highlight CSF testing for anti-Aβ Abs as a promising companion diagnostic biomarker to guide treatment and monitoring decisions in the immunotherapy of AD.

Limitations of this study include the low number of cases and the lack of Aβ-PET or neuropathology data, which precluded any further analysis on the specific association between ARIA-E and microglial activation in the focal removal of parenchymal Aβ and an increased vascular deposition of Aβ in the form of CAA.

Study Funding and Competing Interests
The Alzheimer Association funded this study. Some authors report additional competing interests. Go to Neurology.org/N for full disclosures.
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