Iatrogenic CAA-ri supported by ARIA-E, raised CSF anti-Aβ autoantibodies and sTREM2 after COVID-19 vaccination

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Background

Cerebral amyloid angiopathy–related inflammation (CAA-ri) is a rare autoimmune encephalopathy associated with spontaneous amyloid-related imaging abnormalities suggestive of vasogenic edema (ARIA-E) that are thought to reflect downstream autoantibody (aAbs) immune reaction effects on β-amyloid (Aβ) clearance pathways and microglial reactivity in patients with comorbid CAA and Alzheimer disease (AD) .
A potential association between CAA-ri and SARS-CoV2 vaccination has been recently suggested in 3 different case reports. However, the diagnosis in these cases has never been supported by biomarkers-based evidence.
Here, we first provide biomarkers-based evidence for two patients who developed CAA-ri associated with ARIA-E and raised CSF concentrations of aAbs and sTREM2 early after administration of two different vaccines against SARS CoV-2.

Aim

To describe two cases of severe iatrogenic CAA-ri, supported by clinical, MRI, and CSF biomarkers evidence, after 24h and 48h exposure to SARS-CoV-2 vaccine.

Methods

Longitudinal CSF testing for aAbs (F. Piazza patented assay), ATN biomarkers of AD (Lumipulse G, Innogenteics) and sTREM2 (Innotest, Innogenetics). MRI images findings for ARIA-E on FLAIR T2*sequences.
Clinicoradiological diagnostic criteria for CAA-ri according to Auriel et al. JAMA Neurol 2016.

Results

Case 1

A 77 years-old male presented to the emergency room with confusion and fever that started 48 hours after he received first vaccination dose against SARS CoV-2 with Tozinameran. One week before, the patient was discharged from neurosurgery ward for a right temporo-occipital spontaneous ICH. He has past medical history of arterial hypertension, coronary artery disease and right parietal ICH (8 years before). Brain CT showed normal evolution of the previous ICH. The search for serum SARS COV-2 antibodies was positive (48.9 kAU/L, nv <1).
Two days after, he had focal-onset refractory status epilepticus. Repeated CT scan showed diffuse sulcal subarachnoid haemorrhage and MRI revealed ARIA-E in the right occipital-parietal regions and left parietal lobe, diffuse multiple subcortical and cortical microbleeds and cSS.
CSF tests showed lymphocytic pleocytosis (122/uL), elevated proteins (1.23 g/L), mirror pattern oligoclonal bands, (QAlb 28, normal values <9), and negative microbiology. CSF testing for biomarkers of the AD continuum gave an A+T-N- profile for prodromal/preclinical AD. ApoE genotyping resulted E3/E4.
CSF biomarker testing showed markedly elevated concentrations of aAbs (1.98ug/mL) according to current literature levels reported in CAA-ri, and 529.77 pg/mL of sTREM2, a specific biomarkers of microglial reactivity.
After two weeks, a second LP showed normal CSF and BBB integrity (QAlb 9.96). Although reduced, the CSF concentration of aAbs was still high (0.91ug/mL) and sTREM2 increased by 43% (759.05 pg/mL). SARS-CoV-2 IgGs against spike protein were found in both CSF samples.
The patient died for aspiration pneumonia 20 days later.

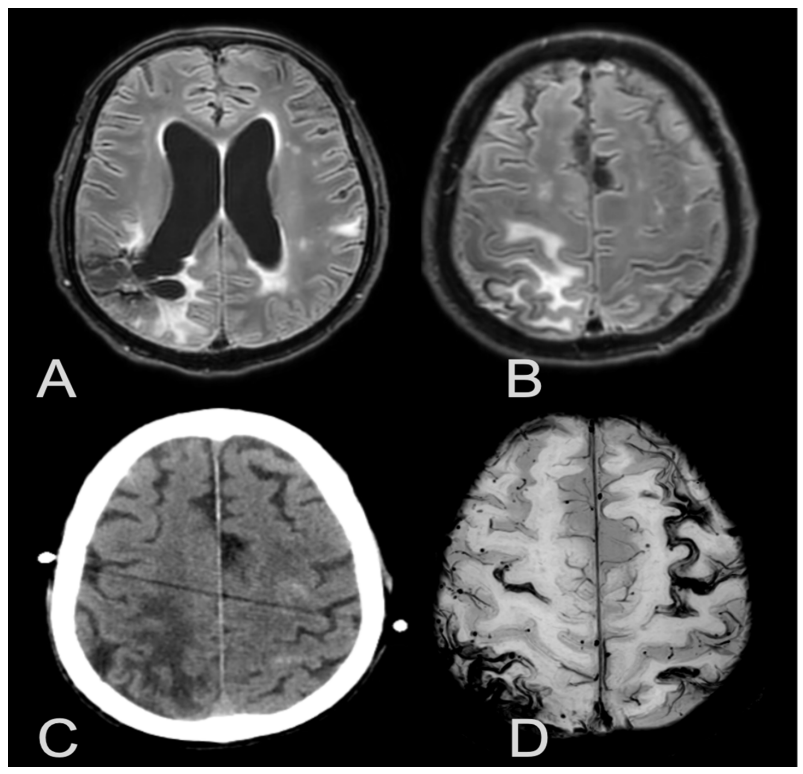

Figure 1. MRI-FLAIR sequence showing ARIA-E in the right and left parietal lobe (**A** and **B**); SWI showing diffuse bilateral cortical siderosis with subcortical microbleeds (**D**). In **C**, CT shows sulcal subarachnoid haemorrhages.

Case 2

A 73 years-old woman was admitted to the emergency room because of abrupt onset of slurred speech and inadequate behavior after 24h she received first dose of AZD1222 vaccine against SARS-CoV2. She had past medical history of memory complaints in the previous 12 months. CT scan showed a small ICH in the left posterior temporal lobe with cortical involvement.
Four days after, brain MRI showed a cluster of microbleeds in the left temporal and occipital lobes, with one macrobleed corresponding to the CT hyperintensity, and ARIA-E with corresponding enhancement in post-gadolinium contrast FLAIR acquisitions.
Blood and CSF tests were unremarkable and infectious or systemic causes excluded. Testing for CSF biomarkers of the AD continuum gave an A+T+N+ biomarker profile for AD. ApoE genotype was E3/E3. The CSF concentration of aAbs was high (0.56ug/mL), sTREM2 resulted 4580.71 pg/mL.
2.5 months after admission, a second LP showed still high/slightly increased concentrations of aAbs (0.78ug/mL) and -39% (3277.01 pg/mL) of sTREM2, suggesting a potential non-biological resolution of the immune/inflammatory response.
The patient completed the vaccination cycle using a different vaccine without further events.

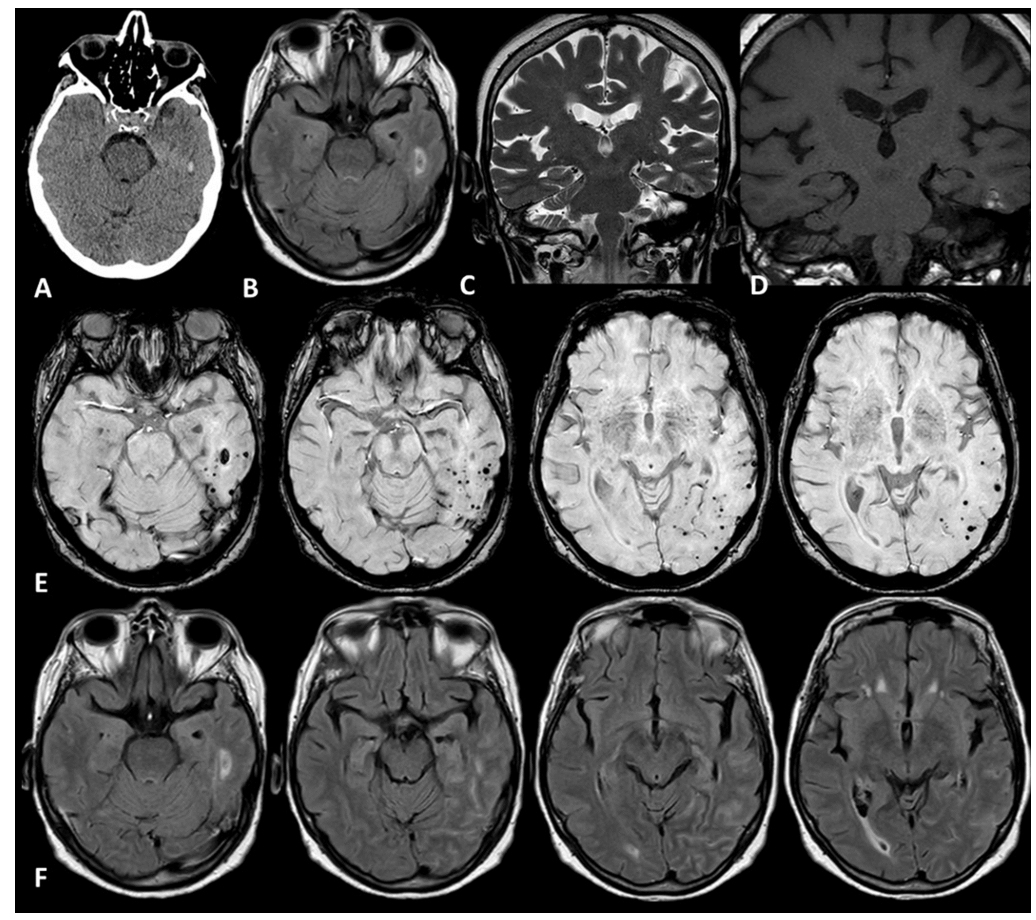

Figure 2. Neuroradiological investigations at the baseline, showing the small left temporal ICH on NCCT (**A**) and the MRI findings (**B-F**).**B** shows the axial FLAIR slice corresponding to CT on **A**; **C** and **D** show the coronal T1W and T2W slice, respectively, corresponding to the level of the left temporal ICH. **E** highlights the hemorrhagic burden in SWI. **F** shows the sequential slices of post-contrast FLAIR.

Conclusions

We provided first biomarker-based evidence for probable acute-onset iatrogenic CAA-ri after anti-SARS-CoV2 vaccination. We suggest the immune response elicited by vaccination triggered an aAbs-mediated immune reactivity to overcome the threshold for CAA-ri. Main findings supporting our hypothesis are: (i) the temporal association of SARS COV-2 vaccination with the manifestation of acute CAA-ri symptoms and both ARIA-E and CAA on MRI; (ii) the high titre of anti-spike antibodies in the CSF, which support a CNS immune-mediated inflammatory involvement; (iii) the raised CSF concentration of aAbs and sTREM2 at presentation, that support the acute-onset CAA-ri nature of ARIA-E, in line with current evidence; (*iv)* the coexisting CAA and AD background disease pathology, currently recognized as the main risk factor for CAA-ri and ARIA. Although a coincidental relationship between COVID-19 vaccination and CAA-ri cannot be excluded, our data adds provocative supporting evidence for reconsidering ARIA-E as iatrogenic CAA-ri calling for future studies aimed at validating the potential of aAbs testing to attribute the specific immune/inflammatory nature of ARIA-E and the effectiveness of corticosteroids during immunotherapy and vaccination of AD and CAA.

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