Anti-Amyloid Beta Immunotherapy-Related Vasculitis

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Case-Based Questions (please see page 3 for answers)

1.	A 75-year patient with cognitive impairment is treated with intravenous anti-amyloid therapy. The patient develops word finding difficulties and confusion after 3 doses, and is found to have "ARIA-H" by MRI. Which of the following is the most likely explanation for the clinical presentation and imaging findings?	
	a.	Demyelination
	b.	Intracerebral hematoma
	c.	Lewy body dementia
	d.	Necrotizing histiocytic vasculitis
	e.	Vascular territory ischemic infarct (large vessel occlusion)

2.	Which of the following is true?	
	a.	APOE e4 alleles confers a relative resistance to cerebral amyloid angiopathy
	b.	Boston criteria for cerebral amyloid angiopathy are highly sensitive for the identification of cerebral amyloid angiopathy in living patients
	c.	Cerebral amyloid angiopathy can be diagnosed by clinical history and MRI in most cases
	d.	Cerebral amyloid angiopathy is "severe" in most patients with Alzheimer's disease
	e.	Patients with homozygous APOE e3/e3 may have cerebral amyloid angiopathy

3.	Which of the following is true?	
	a.	Anti-amyloid antibodies are specific for soluble amyloid-beta
	b.	Anti-amyloid therapy has been shown to stabilize cognitive function in patients with Alzheimer's disease
	c.	Glymphatic clearance of amyloid-beta has been demonstrated in humans who have received anti-amyloid beta treatment
	d.	Myeloid-derived macrophages are not involved in amyloid clearance in patients treated with anti-amyloid immunotherapy
	e.	Target-engagement has been demonstrated in patients treated with anti-amyloid antibodies

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Correct Answers and Rationales

Question 1 Correct Answer and Rationale: **D. Necrotizing histiocytic vasculitis**

Rationale: Anti-amyloid agents do not distinguish between amyloid plaque pathology and cerebral amyloid angiopathy. The presence of hemorrhage in this scenario most likely reflects a therapy-mediated attack on cerebral amyloid angiopathy, which has been shown in case reports to be associated with necrotizing histiocytic vasculitis. Intracerebral hematoma would be unusual, and the imaging does not support this diagnosis. The presentation is not consistent with Lewy body dementia. ARIA differs from large vessel occlusion-associated ischemic infarct.

Question 2 Correct Answer and Rationale: **E. Patients with homozygous APOE e3/e3 may have cerebral amyloid angiopathy**

Rationale: Although APOE e4 confers a relative risk for cerebral amyloid angiopathy, e3 alleles including homozygous e3/e3 are common in patients with cerebral amyloid angiopathy because of the high frequency of the e3 allele in the population. Boston Criteria are not highly sensitive, which is the primary shortfall of these criteria. Most individuals with cerebral amyloid angiopathy cannot be diagnosed by clinical presentation and neuroimaging. Alzheimer's disease-associated cerebral amyloid angiopathy is common but would not be assessed as "severe" according to various criteria (Love et al, Vonsattel et al) in most cases.

Question 3 Correct Answer and Rationale: **E. Target-engagement has been demonstrated in patients treated with anti-amyloid antibodies**

Rationale: Autopsy data suggest that insoluble amyloid-beta is targeted with anti-amyloid agents. Such agents do not stabilize cognitive function. Preliminary studies suggest a possible reduced rate of cognitive deterioration. Mechanisms of clearance of amyloid-beta are unclear but may involve the hematogenous route. Target engagement has been demonstrated with evidence of plaque clearing at autopsy, reduction in PET signal, and reduced levels of AD biomarkers.