Anti-amyloid-β immunotherapy-related vasculitis

Rudy Castellani MD

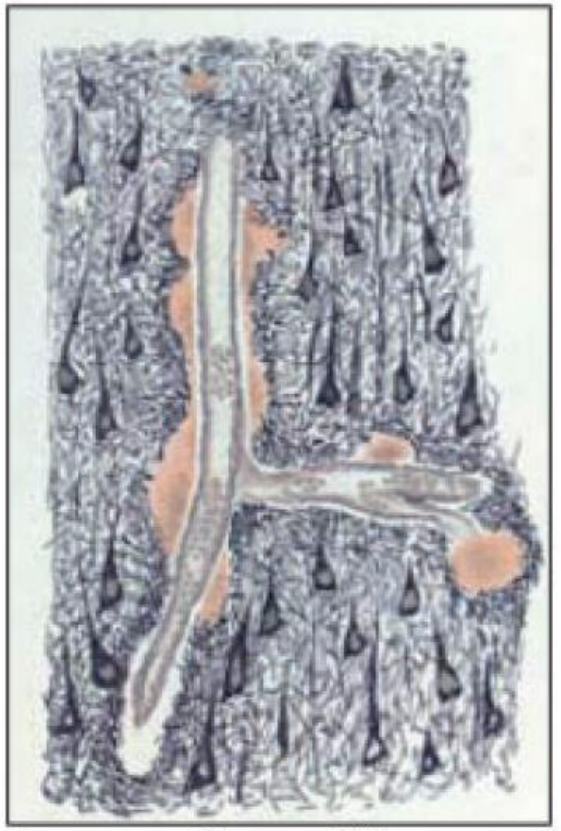
Northwestern University Feinberg School of Medicine

Disclosures

- No financial or other conflicts of interest
- Presentation reflects the opinions of the speaker
- The speaker does not represent any institution or organization

Cerebral amyloid angiopathy

- 1909 - Oppenheim
  - Metachromasia
- 1910 - Fischer
- 1927 – Divry
  - Congo red

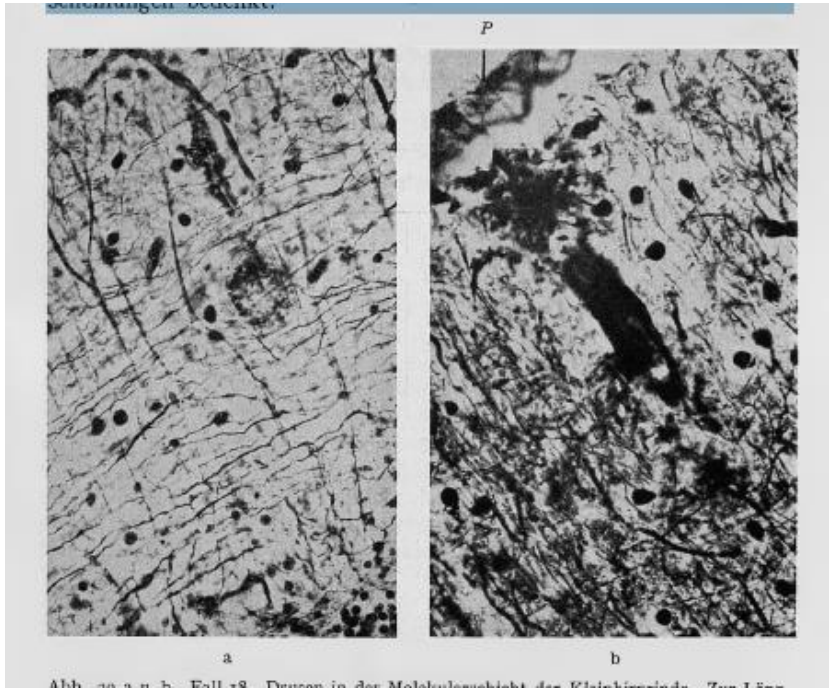


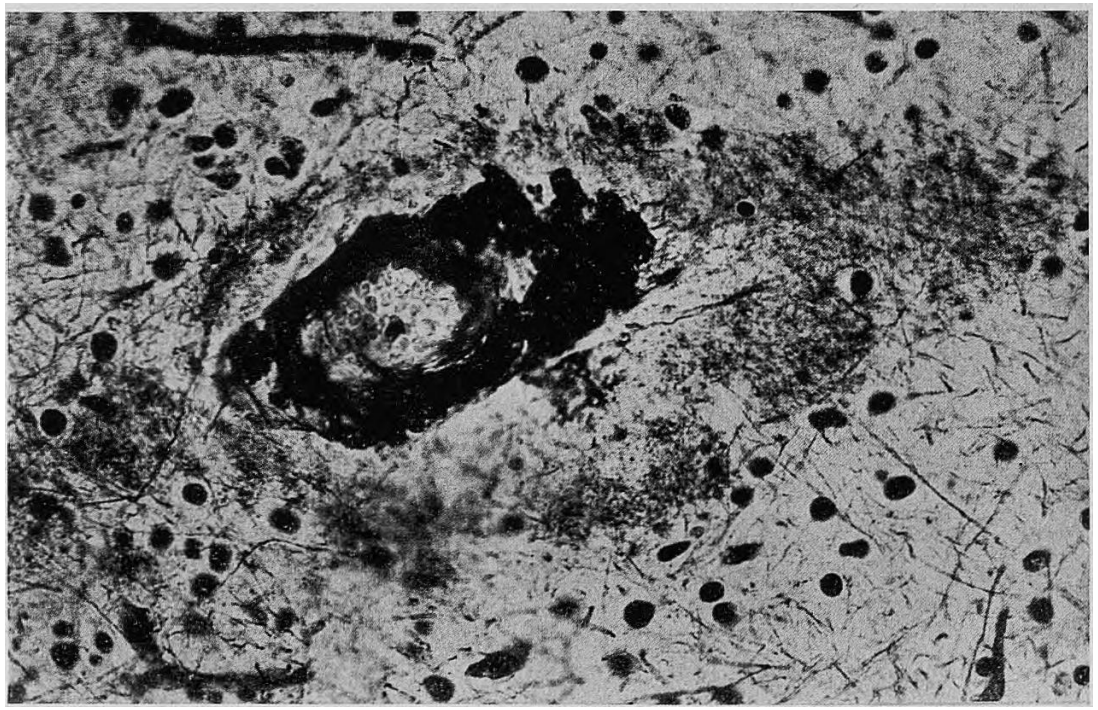
Stage VI

Fischer O. Die presbyophrene Demenz, deren anatomische Grundlage und klinische Abgrenzung. Z ges Neurol Psychiat 1910; 3: 371–471.

Goedert M. Brain 2009;132(Pt 4):1102-11. DOI: 10.1093/brain/awn256.

- Gellerstadt, 1933
  - “perivascular plaque deposition in the occipital cortex”





Gellerstedt N. Zur Kenntnis der hirnveranderungen bei der normalen altersinvolution. Uppsala: Almqvist & Wiksells Boktryckeri-A.-. 1933.

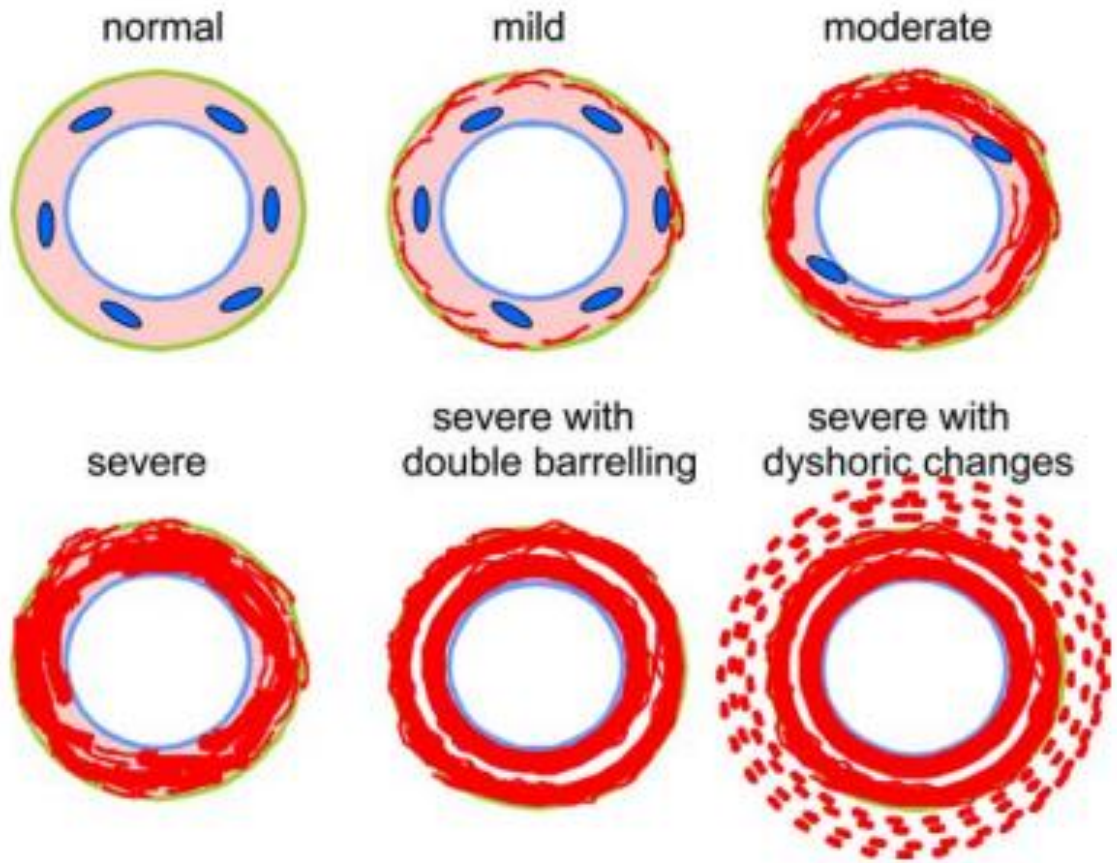
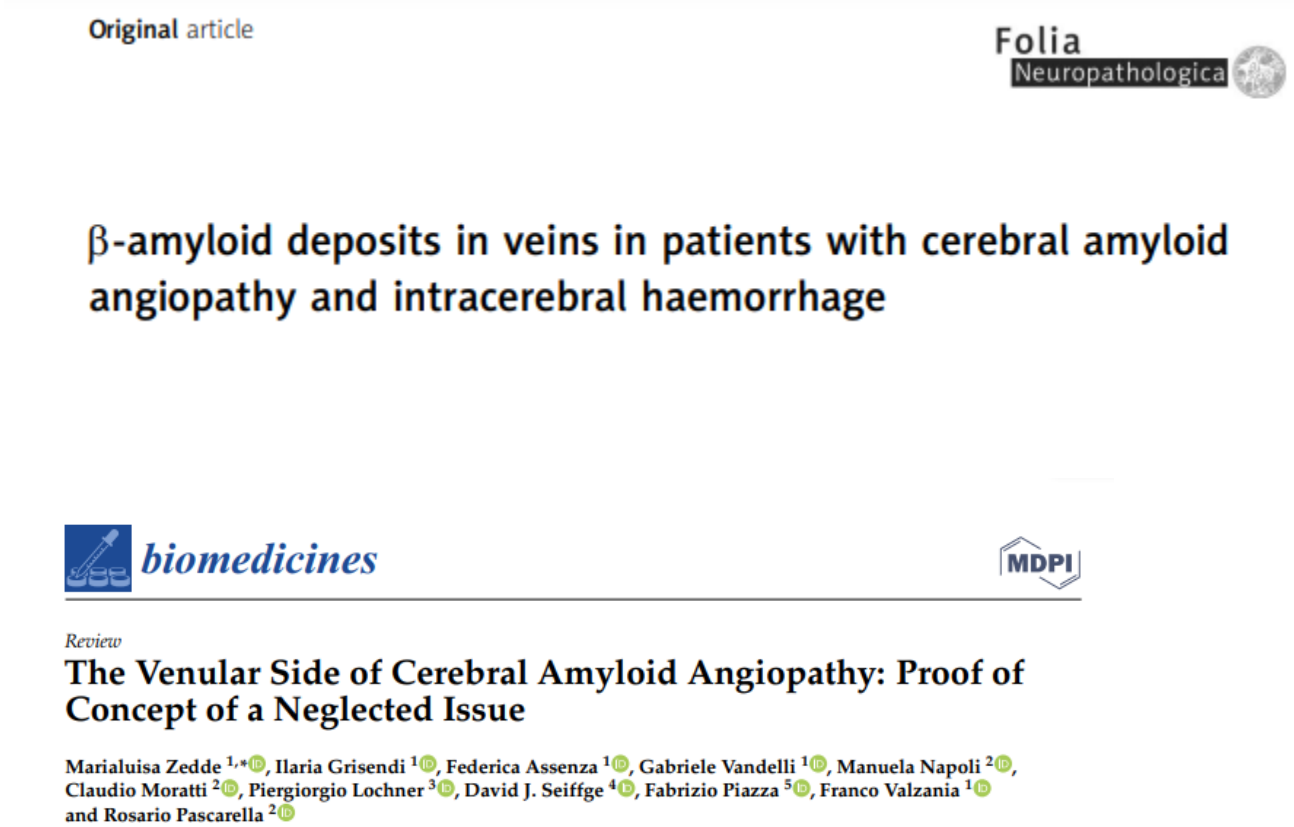


Fig. 1 Progression of CAA: mild, Aβ depositions in abluminal portions of the blood vessel wall; moderate, abundant Aβ depositions in all layers of the blood vessel wall with loss of smooth muscle cells; severe, blood vessel wall replaced by Aβ depositions, additional double barrelling and/or dyshoric changes may be present (for dyshoric changes see section Morphology of CAA) (*CAA* cerebral amyloid angiopathy, *Aβ* β-amyloid peptide)

Attems, J Acta Neuropathol (2005) 110: 345–359
DOI 10.1007/s00401-005-1074-9

Vessels affected by CAA

- Arteries
- Arterioles
- Capillaries
- Venules
- Veins



Original article

Folia Neuropathologica

β-amyloid deposits in veins in patients with cerebral amyloid angiopathy and intracerebral haemorrhage

biomedicines

MDPI

Review

The Venular Side of Cerebral Amyloid Angiopathy: Proof of Concept of a Neglected Issue

Marialuisa Zedde [1,*], Ilaria Grisendi [1], Federica Assenza [1], Gabriele Vandelli [1], Manuela Napoli [2], Claudio Moratti [2], Piergiorgio Lochner [3], David J. Seiffge [4], Fabrizio Piazza [5], Franco Valzania [1] and Rosario Pascarella [2]

Scholz W. Studien zur Pathologie der Hirngefasse 11. Die dru-sige Entartung der Hirnarterien und -capillaren. (Eine Form se-niler Gefisserkrankung). **Z Gesamte Neurol Psychiatr 1938;162:694-71**

“drusige Entartung”

“Glandular degeneration”

› Monatsschr Psychiatr Neurol. 1950 Nov-Dec;120(5-6):352-7.

[An apparently dyshoric and topical angiopathy]

[Article in Undetermined language]

F MOREL

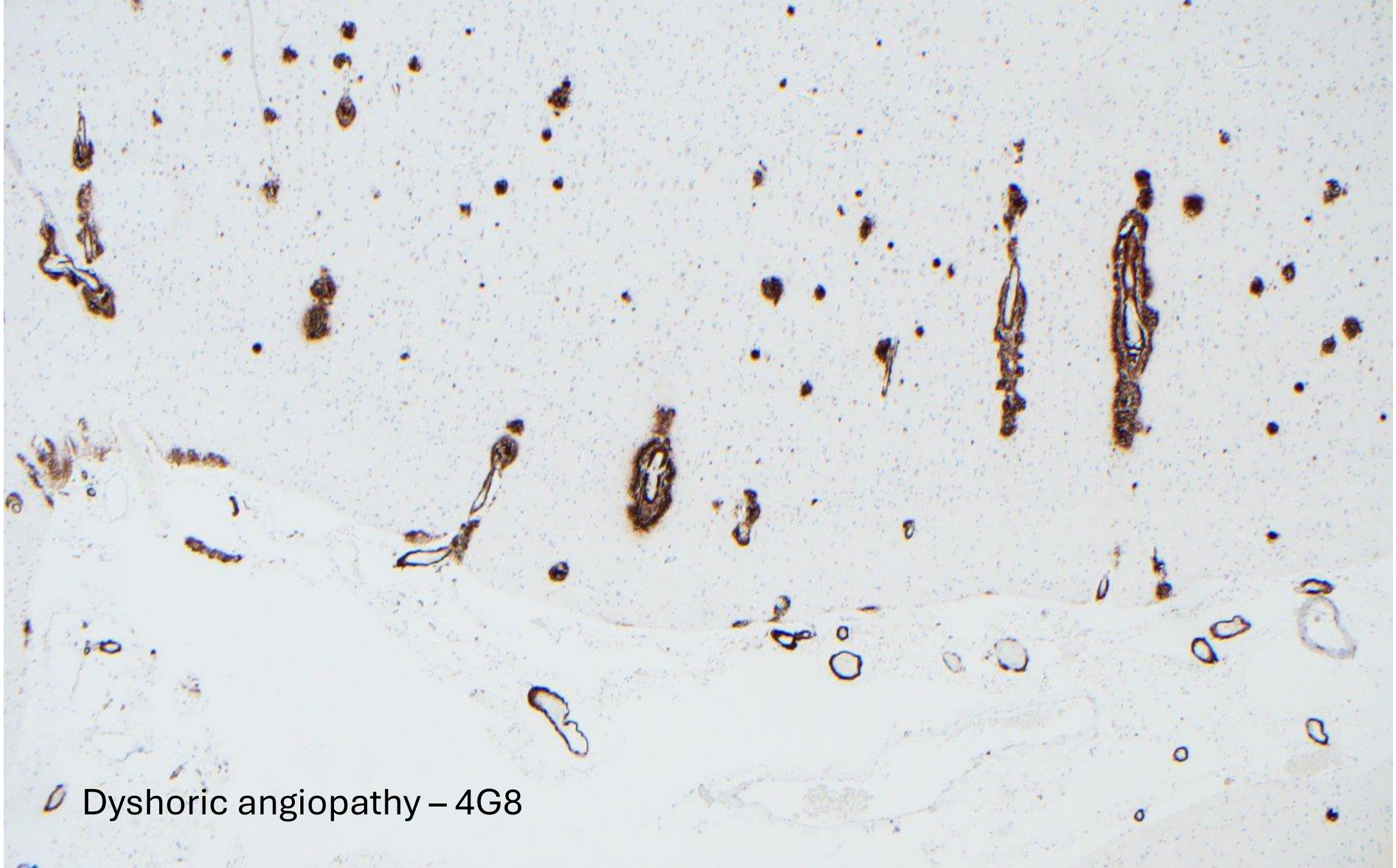
PMID: 14806299

› Monatsschr Psychiatr Neurol. 1954 Oct;128(4):219-56.

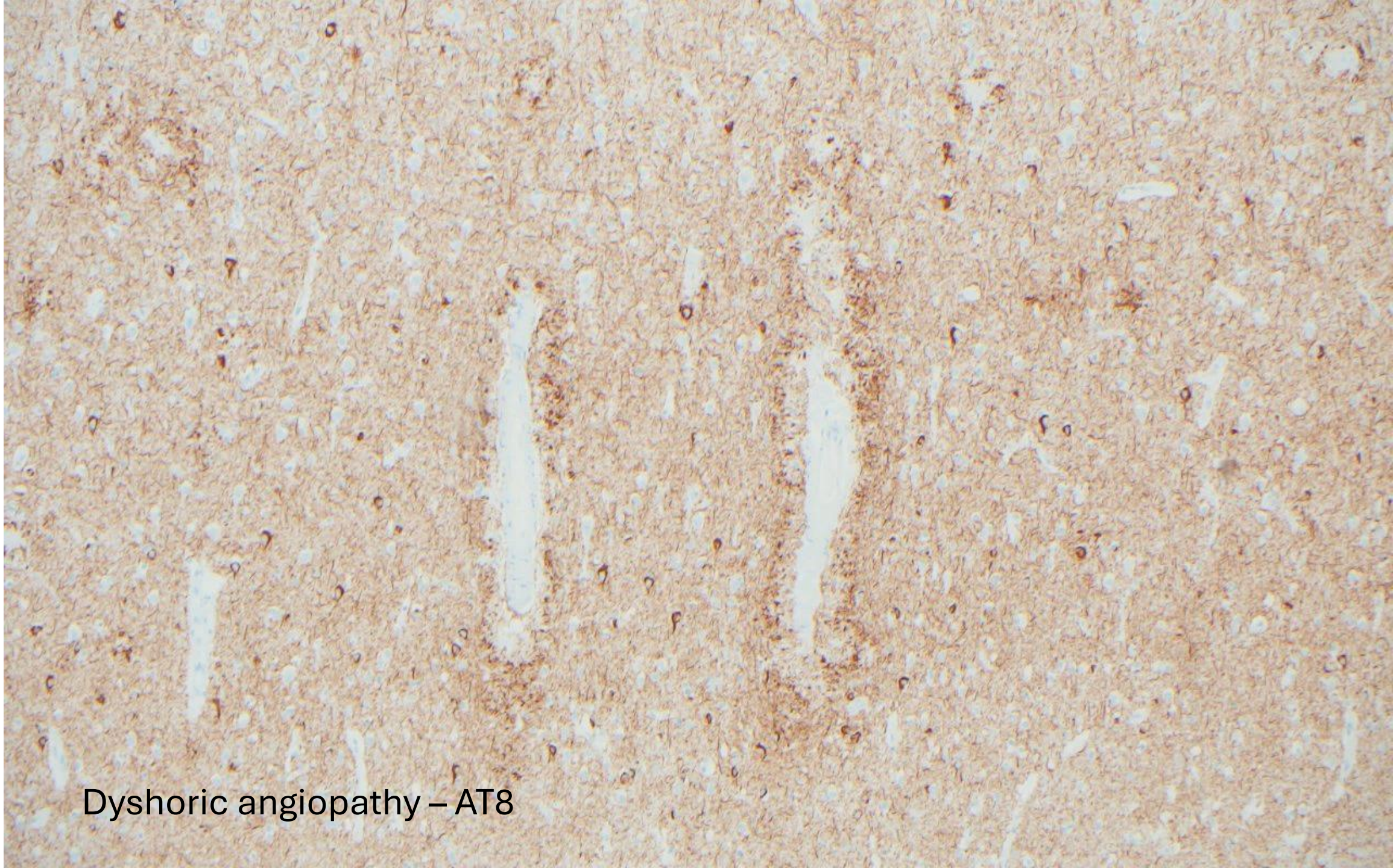
[A particular type of senile angiopathy of the central nervous system: congophilic angiopathy, topography and frequency]

[Article in French]

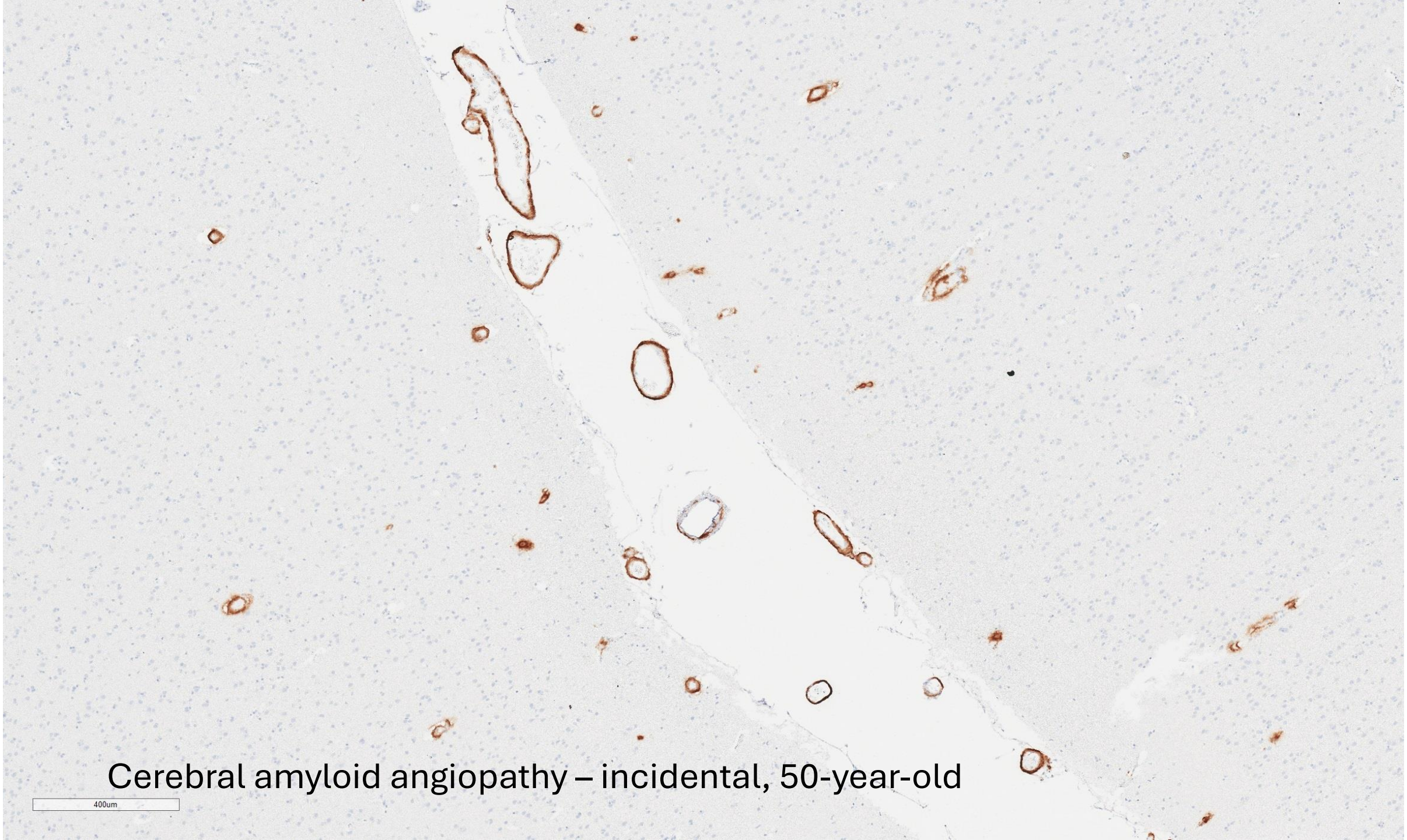
S PANTELAKIS



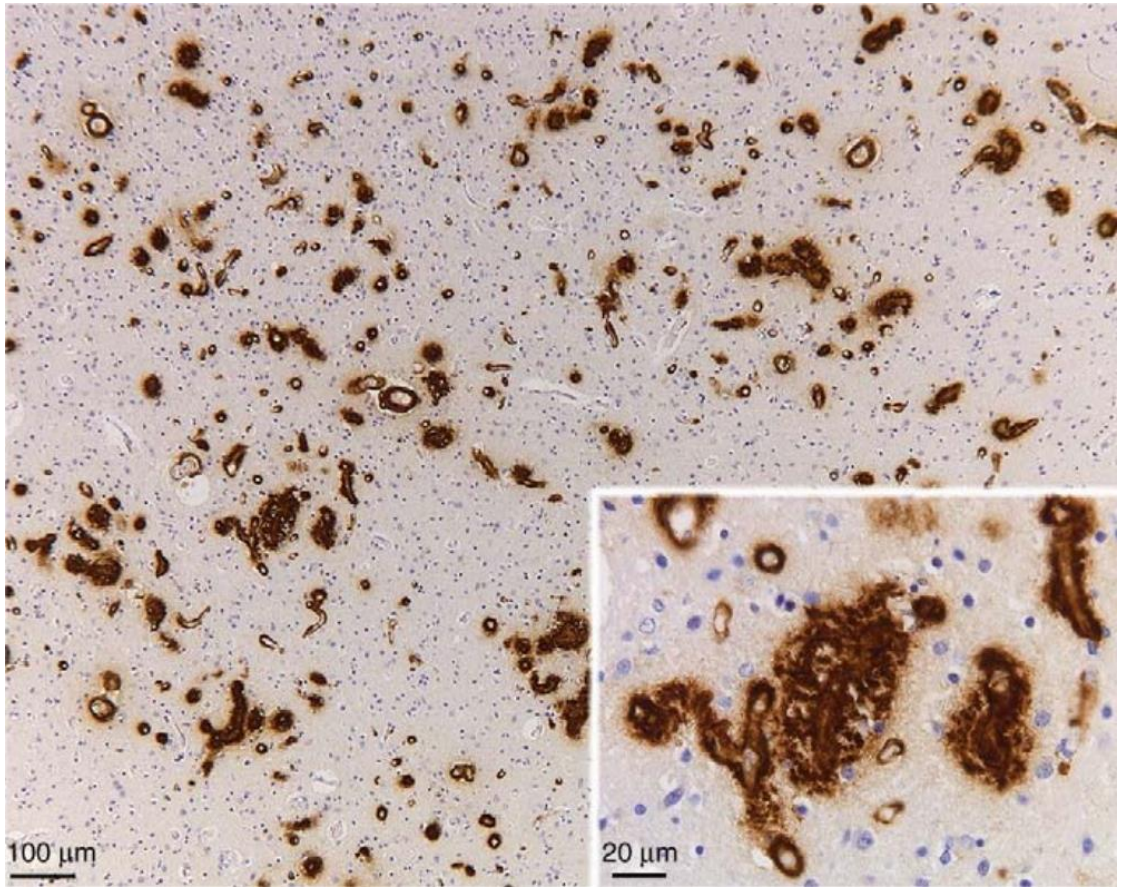
Dyshoric angiopathy – 4G8



Dyshoric angiopathy – AT8



Cerebral amyloid angiopathy – incidental, 50-year-old



Journal of the Neurological Sciences 295 (2010) 131–134

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Short Communication

Dyshoric capillary cerebral amyloid angiopathy mimicking Creutzfeldt–Jakob disease

L.S.M. Eurelings [a], E. Richard [a,*], A. Carrano [b], P. Eikelenboom [a], W.A. van Gool [a], A.J.M. Rozemuller [b,c]

[a] Academic Medical Center, University of Amsterdam, dept of Neurology, H2-225, PO box 22660, 1100 DD Amsterdam, The Netherlands
[b] VU University Medical Center, dept of Neuropathology, Amsterdam, The Netherlands
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Journal of Neuropathology and Experimental Neurology

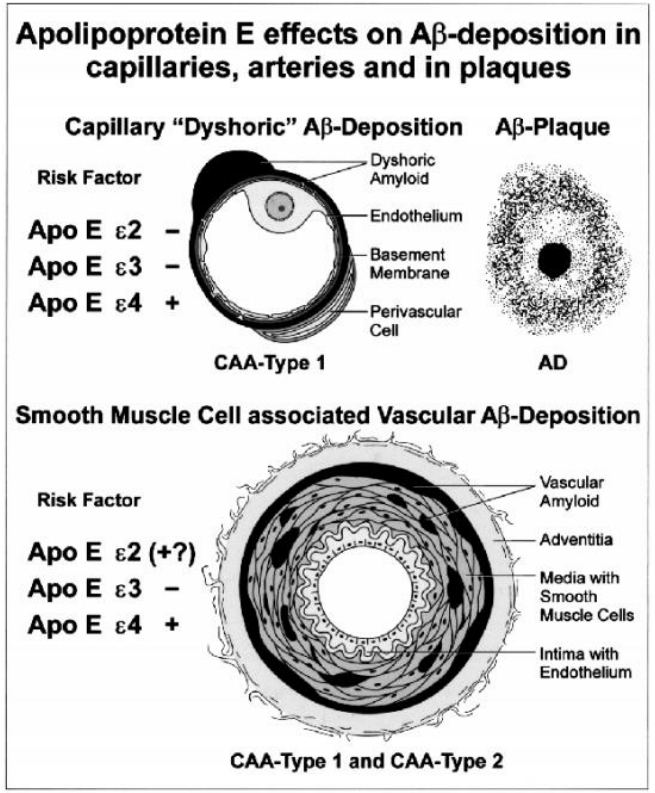
Vol. 61, No. 3
March, 2002
pp. 282–293

Two Types of Sporadic Cerebral Amyloid Angiopathy

DIETMAR RUDOLF THAL, MD, ESTIFANOS GHEBREMEDHIN, MD, UDO RÜB, MD, HARUYASU YAMAGUCHI, MD, PHD, KELLY DEL TREDICI, PHD, AND HEIKO BRAAK, MD

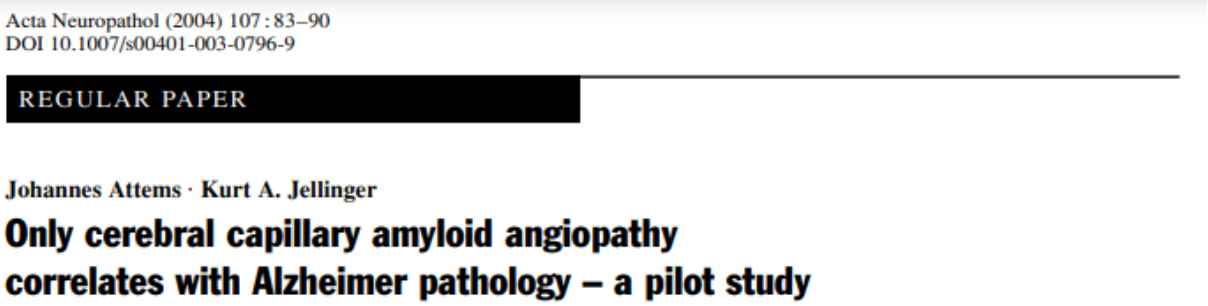
- CAA-Type 1 - leptomeningeal and cortical arteries and veins, **and capillaries**
  - ***APOE* ε4**
  - Not *APOE* ε2
  - **"Dyshoric"**

- CAA-Type 2 - leptomeningeal arteries and veins as well as in cortical arteries and veins
  - *APOE* ε2
  - **Not *APOE* ε4**



Capillary CAA and dementia?

- Boyle et al. Neurology® 2015;85:1930–1936
  - “The associations of CAA with cognitive outcomes were **not** driven by the presence of capillary involvement”

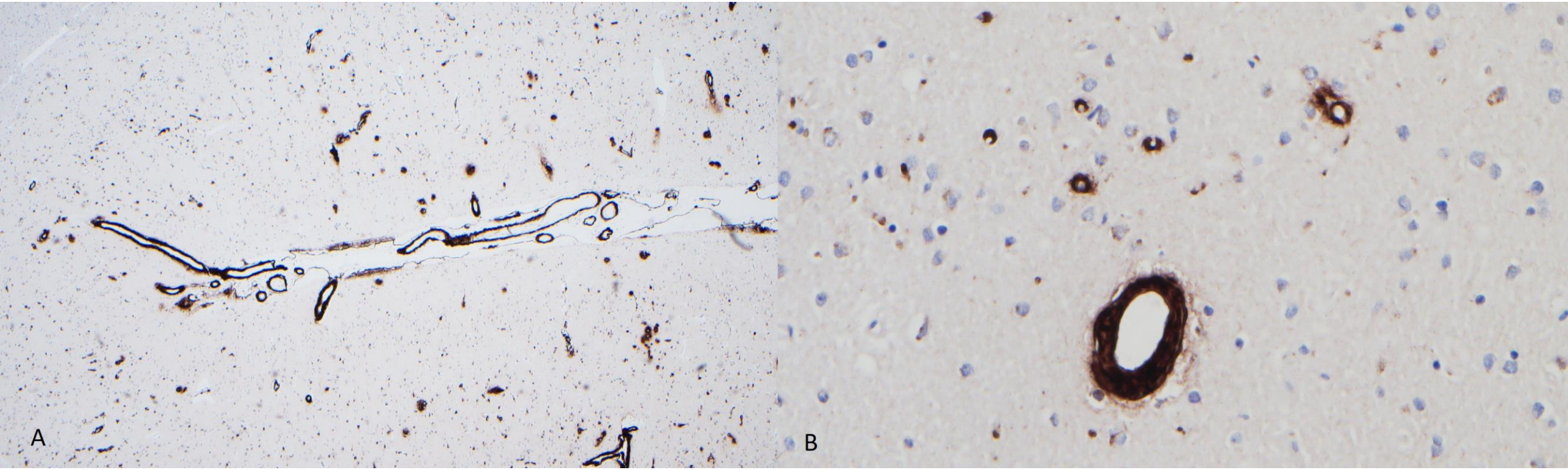


Acta Neuropathol (2004) 107 : 83–90
DOI 10.1007/s00401-003-0796-9

REGULAR PAPER

Johannes Attems · Kurt A. Jellinger

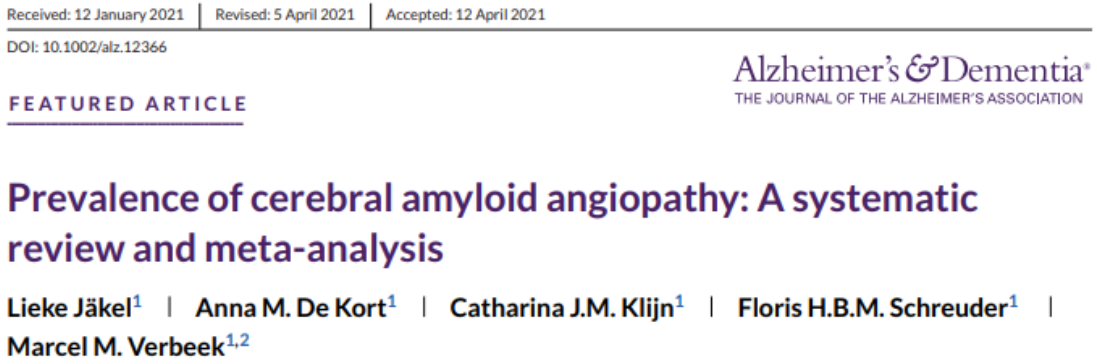
Only cerebral capillary amyloid angiopathy correlates with Alzheimer pathology – a pilot study



Capillary cerebral amyloid angiopathy – 84-year-old with dementia (no neuritic plaques)

Prevalence of CAA in Alzheimer's disease

- Moderate to severe CAA in AD
  - 48 % if based on pathology
  - 22% if based on lobar microbleeds (MRI)
- Moderate to severe CAA in elderly general population
  - 23%



Received: 12 January 2021 | Revised: 5 April 2021 | Accepted: 12 April 2021

DOI: 10.1002/alz.12366

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Prevalence of cerebral amyloid angiopathy: A systematic review and meta-analysis

Lieke Jäkel[1] | Anna M. De Kort[1] | Catharina J.M. Klijn[1] | Floris H.B.M. Schreuder[1] | Marcel M. Verbeek[1,2]

Prevalence of CAA in Alzheimer's disease

- Any CAA?
  - "At least a minimal degree of amyloid angiopathy was found in **every brain** showing histopathological abnormalities of AD."

Clinically Diagnosed Alzheimer's Disease: Autopsy Results in 150 Cases

C. L. Joachim, MD,*† J. H. Morris, BM, BCh, DPhil,* and D. J. Selkoe, MD†

One hundred fifty autopsy brains from patients with clinically diagnosed Alzheimer's disease (AD) were examined pathologically. The brains were received consecutively over a 3-year period from numerous sources as part of a research program in which one brain half was frozen for biochemical studies and the other half was fixed in formalin. One hundred thirty-one (87%) of the 150 cases fulfilled histological criteria for AD, with or without additional findings, such as Parkinson's disease or stroke. At least a minimal degree of amyloid angiopathy was found in every brain showing histopathological abnormalities of AD. Twenty-three (18%) of the 131 AD brains had Lewy bodies in neurons of the substantia nigra. Thirteen of the 19 non-AD cases were diagnosed as other neurodegenerative disorders. In only 2 cases was no histological correlate for the patient's dementia found. We conclude that (1) the many physicians who diagnosed these cases did so highly accurately; (2) degenerative changes in the substantia nigra were more common in patients with AD than has been reported for the general aged population; (3) amyloid angiopathy was a constant accompaniment of AD, although its severity varied widely; (4) vascular dementia was rarely clinically misdiagnosed as AD; (5) neuropathological findings were insufficient to account for the clinical syndrome of dementia in less than 2% of cases; (6) the histological criteria established by the National Institutes of Health/American Association of Retired Persons Research Workshop on the Diagnosis of Alzheimer's Disease worked well in assessing this large series.

Joachim CL, Morris JH, Selkoe DJ. Clinically diagnosed Alzheimer's disease: autopsy results in 150 cases. Ann Neurol 1988;24:50–56

From: **Clinical Predictors of Severe Cerebral Amyloid Angiopathy and Influence of APOE Genotype in Persons With Pathologically Verified Alzheimer Disease**

JAMA Neurol. 2014;71(7):878-883. doi:10.1001/jamaneurol.2014.681

Table 1. Distribution of *APOE* Genotypes in the Study Population Relative to the Presence or Absence of Severe CAA[a]

APOE Genotype	No. (%)	
	Severe CAA (n = 165)	No CAA (n = 194)
ε3/ε3	54 (34.2)	104 (65.8)
ε3/ε4	53 (45.7)	63 (54.3)
ε2/ε3	4 (36.4)	7 (63.6)
ε4/ε4	47 (73.4)	17 (26.6)
ε2/ε4	7 (70.0)	3 (30.0)

Abbreviation: CAA, cerebral amyloid angiopathy.

[a] $\chi^2_4 = 31.03$; $P < .001$.

(AD patients with “severe CAA”)

Published in final edited form as:
Lancet Neurol. 2022 August ; 21(8): 714–725. doi:10.1016/S1474-4422(22)00208-3.

The Boston Criteria v2.0 for cerebral amyloid angiopathy: A multicentre MRI-neuropathology diagnostic accuracy study

A full list of authors and affiliations appears at the end of the article.

Definite – post-mortem examination
Probable – Clinical data and pathologic tissue
Probable – Clinical data and MRI (lobar hemorrhagic lesions)

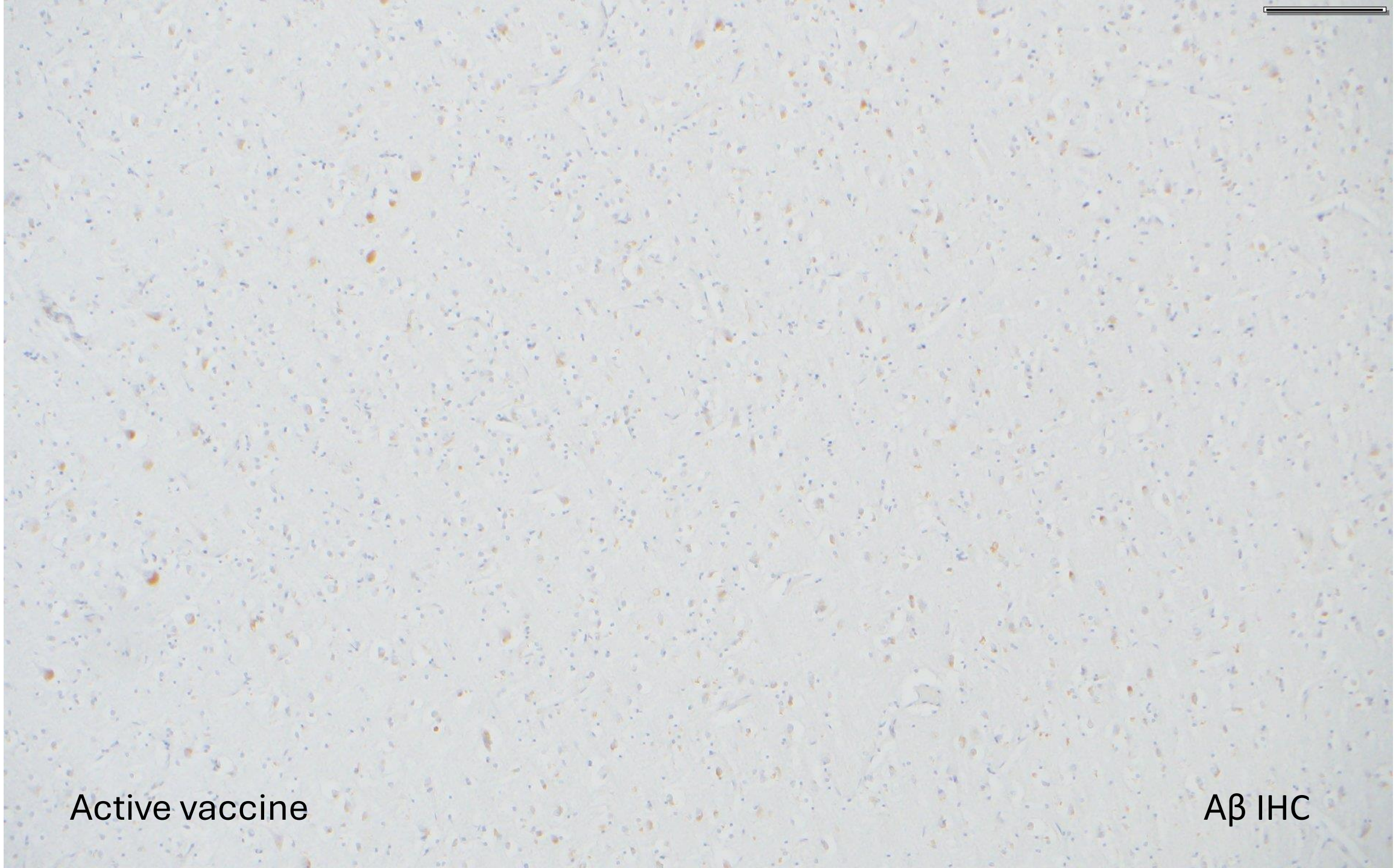
nature medicine

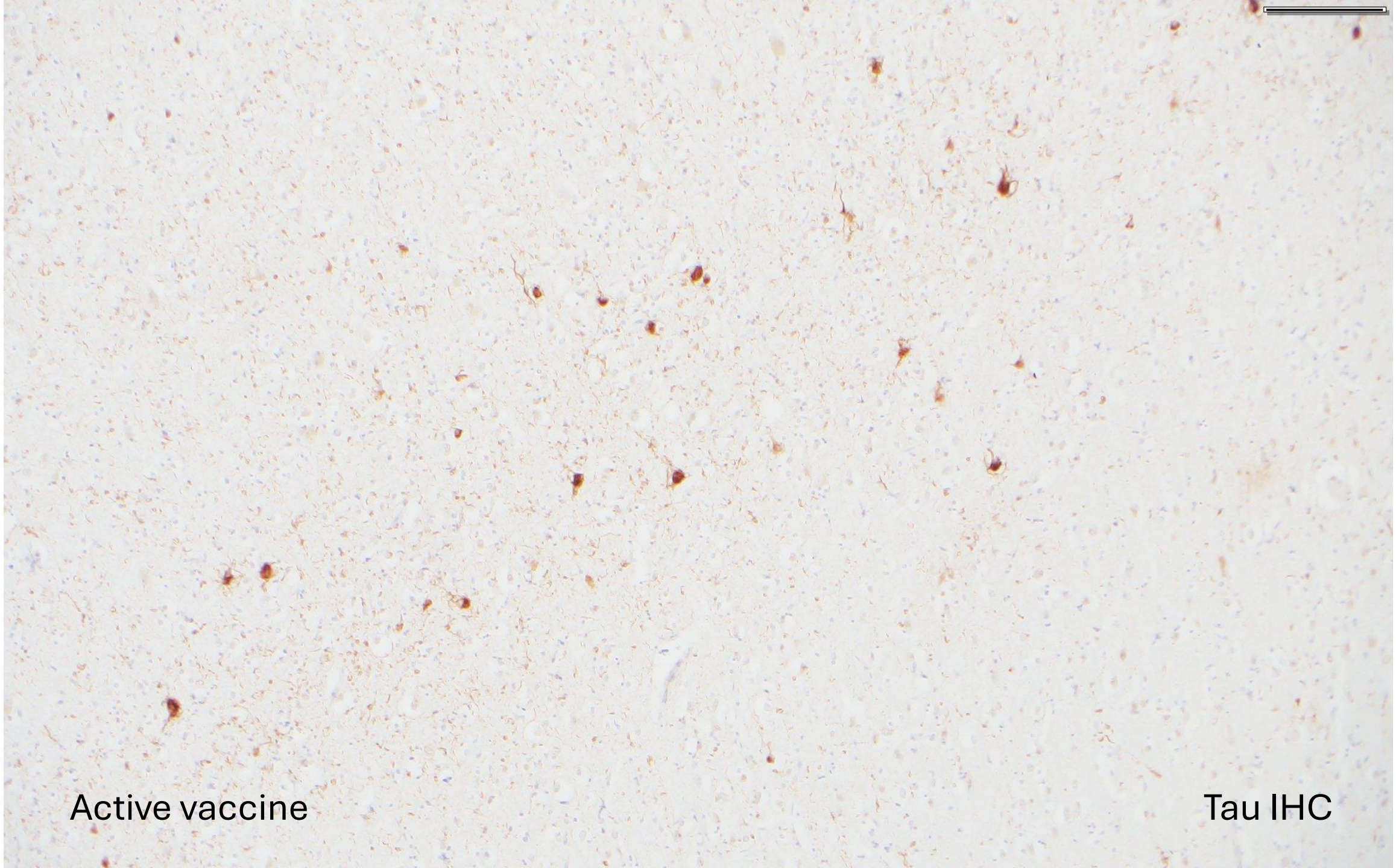
Article

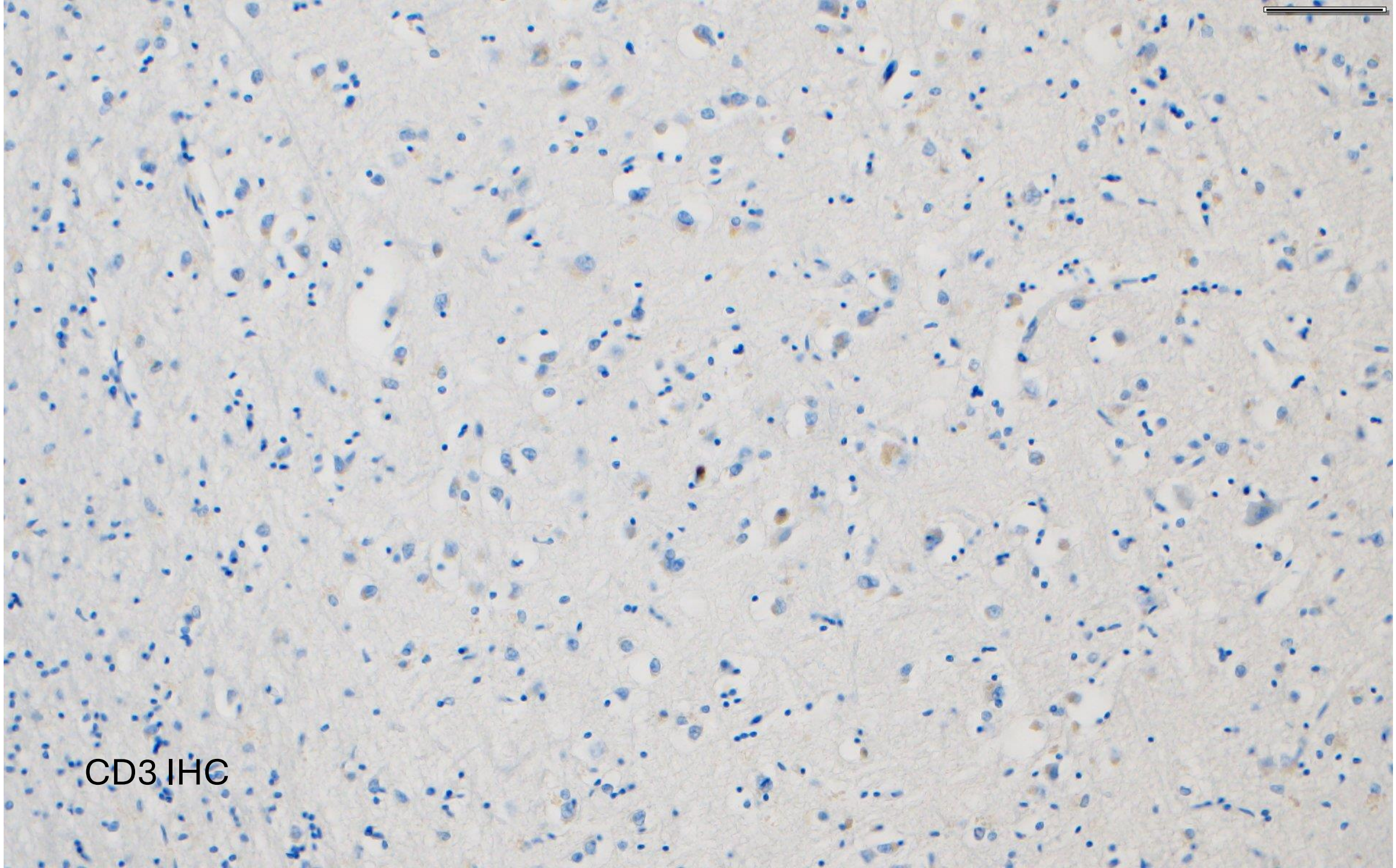
https://doi.org/10.1038/s41591-025-03574-1

Microglial mechanisms drive amyloid-β clearance in immunized patients with Alzheimer's disease

Lynn van Olst[1,2], Brooke Simonton[1,2], Alex J. Edwards[1,2], Anne V. Forsyth[1,2], Jake Boles[1,2], Pouya Jamshidi[3], Thomas Watson[1,2], Nate Shepard[2], Talia Krainc[2], Benney MR Argue[1,2], Ziyang Zhang[1,2], Joshua Kuruvilla[1,2], Lily Camp[1,2], Mengwei Li[4], Hang Xu[4], Jeanette L. Norman[5], Joshua Cahan[1,2], Robert Vassar[2,6], Jinmiao Chen[4,7,8], Rudolph J. Castellani[3], James AR Nicoll[5,9], Delphine Boche[5] & David Gate[1,2] ✉


Active vaccine
Aβ IHC


Active vaccine
Tau IHC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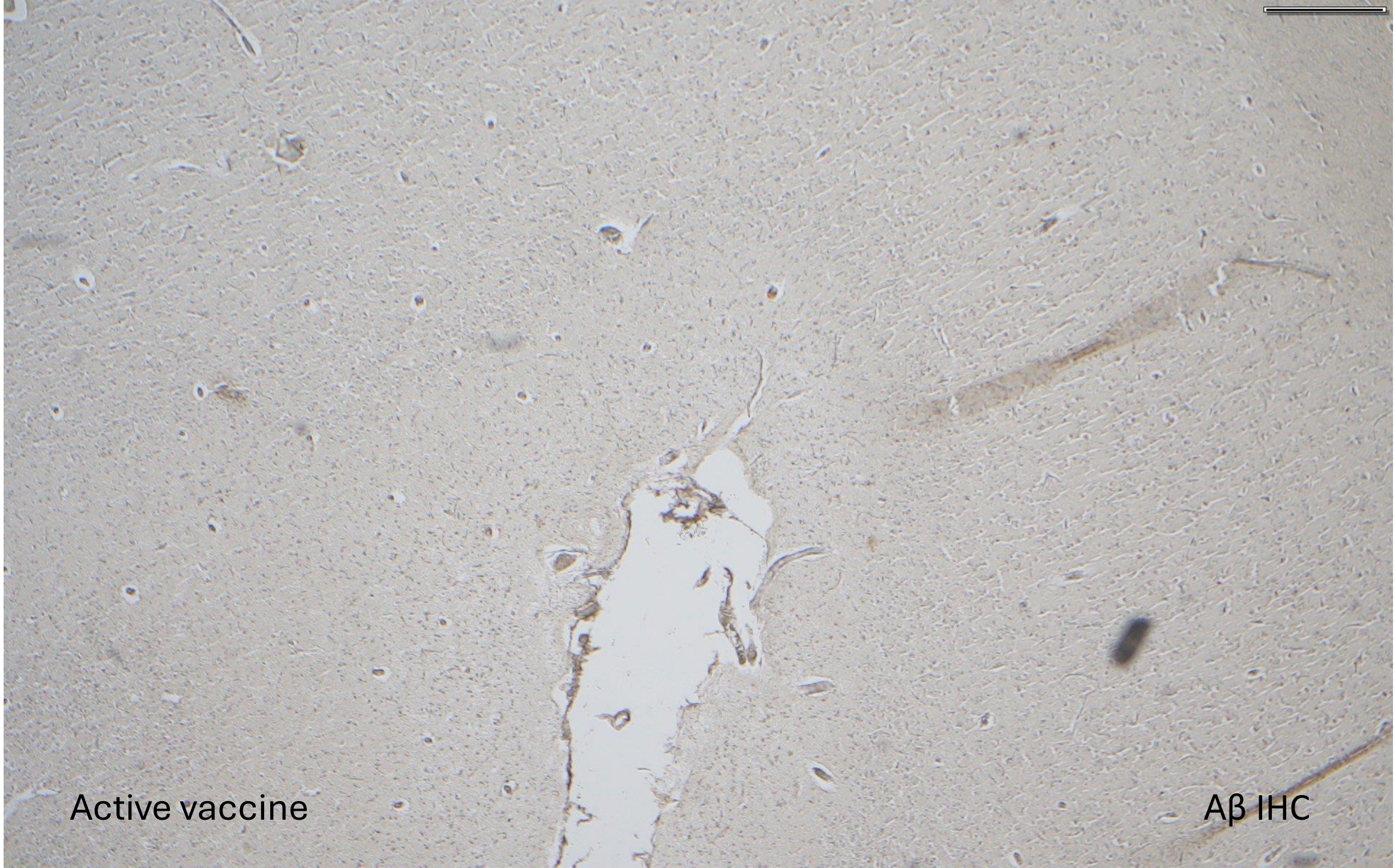
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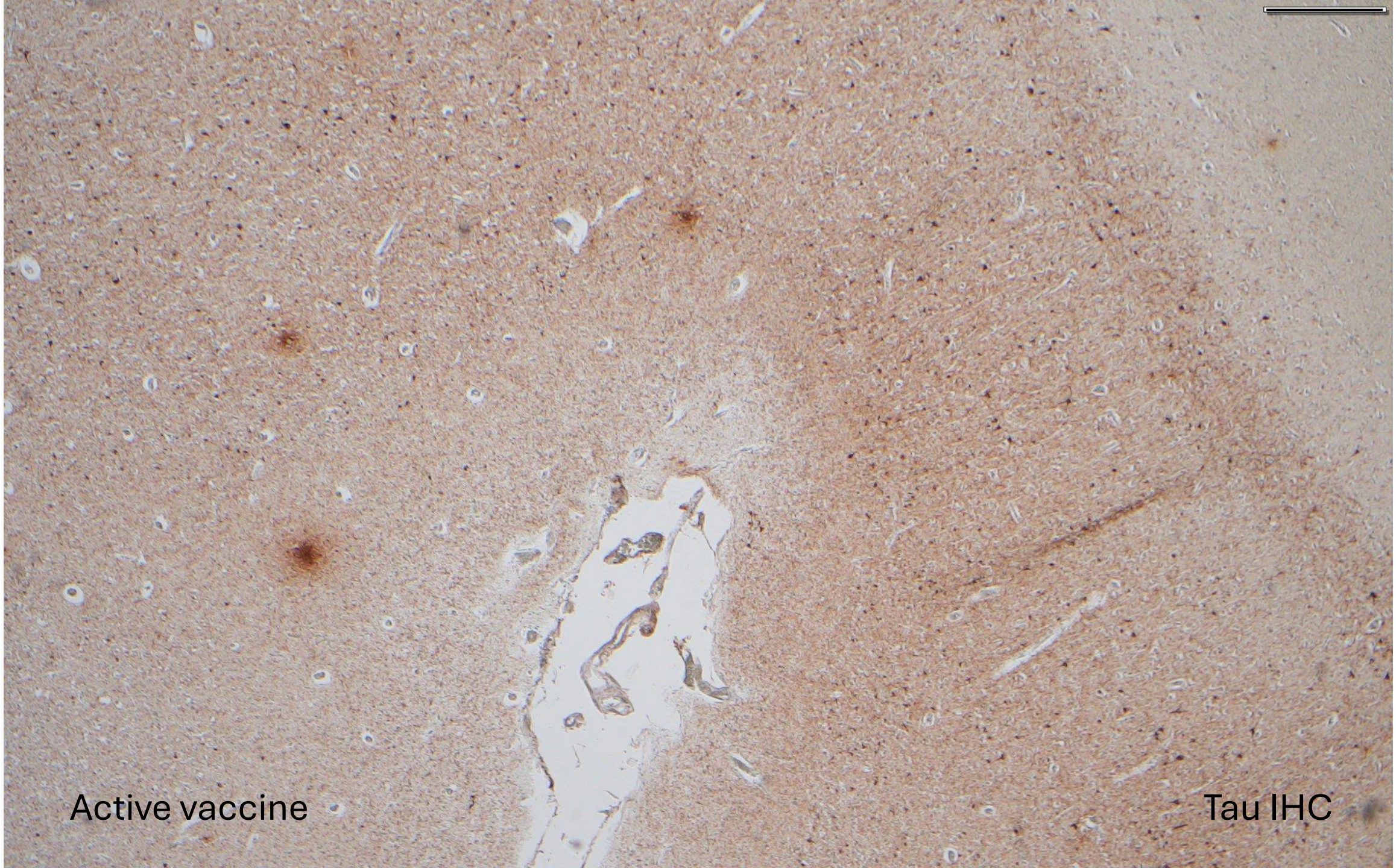
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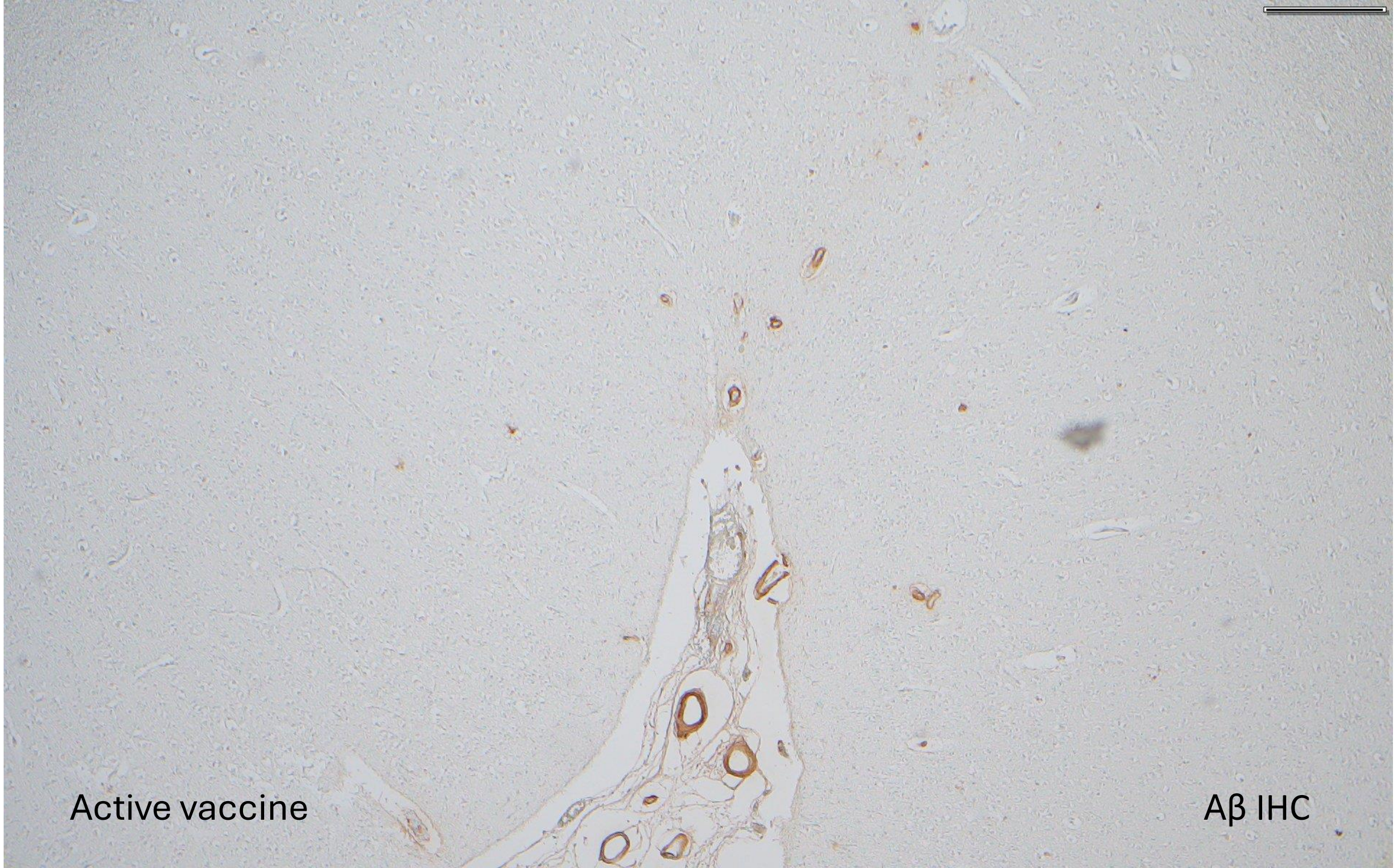
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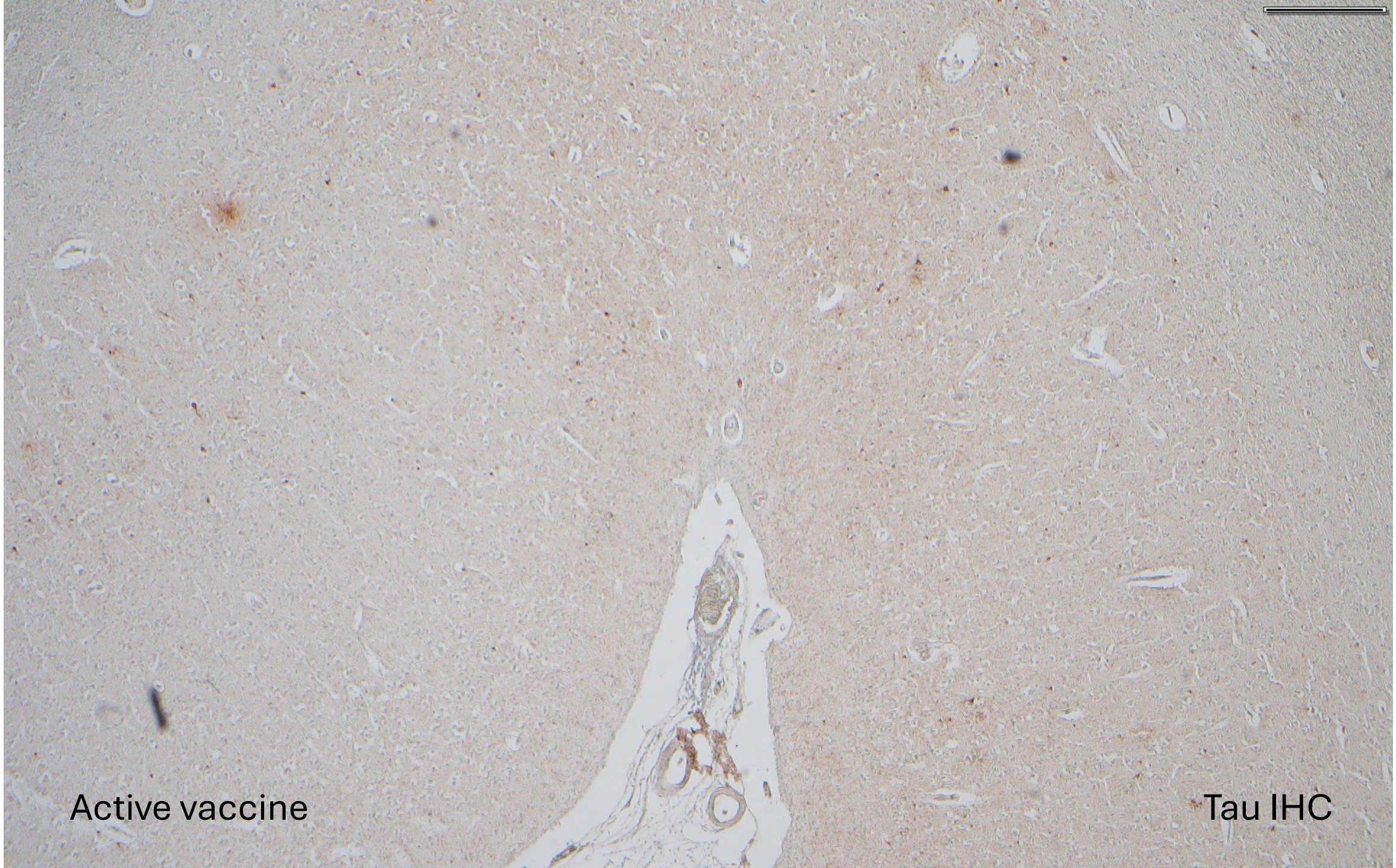
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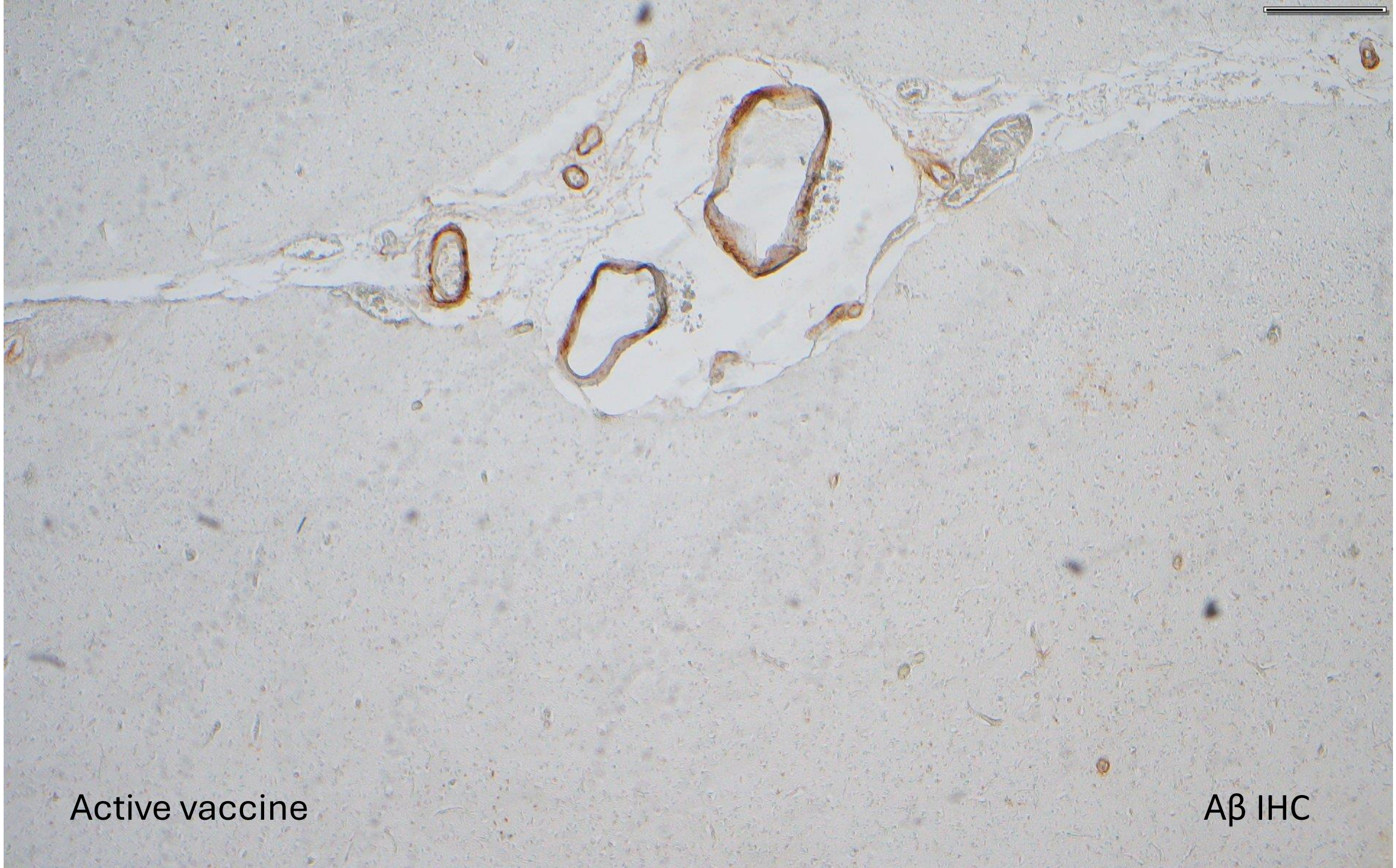
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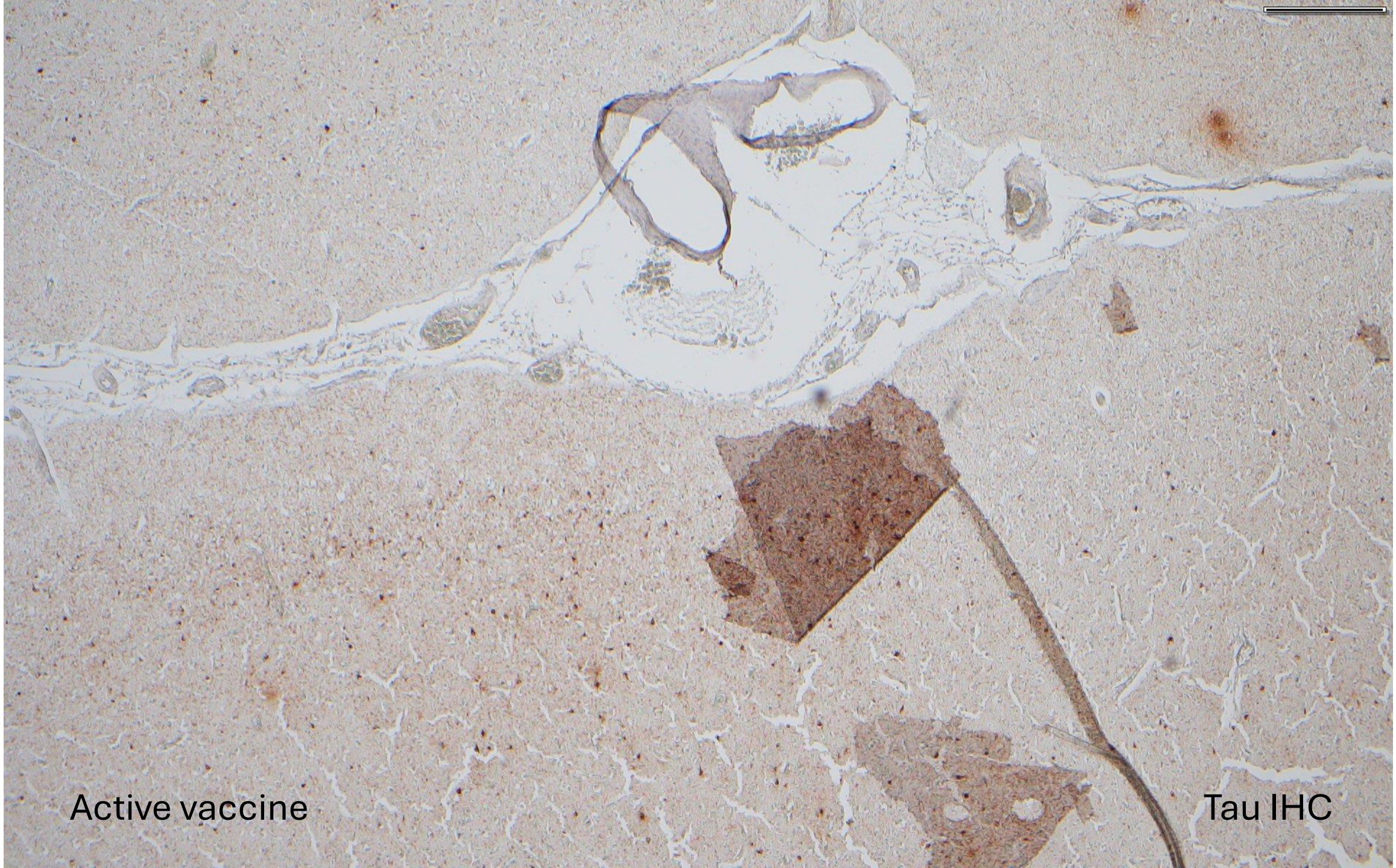
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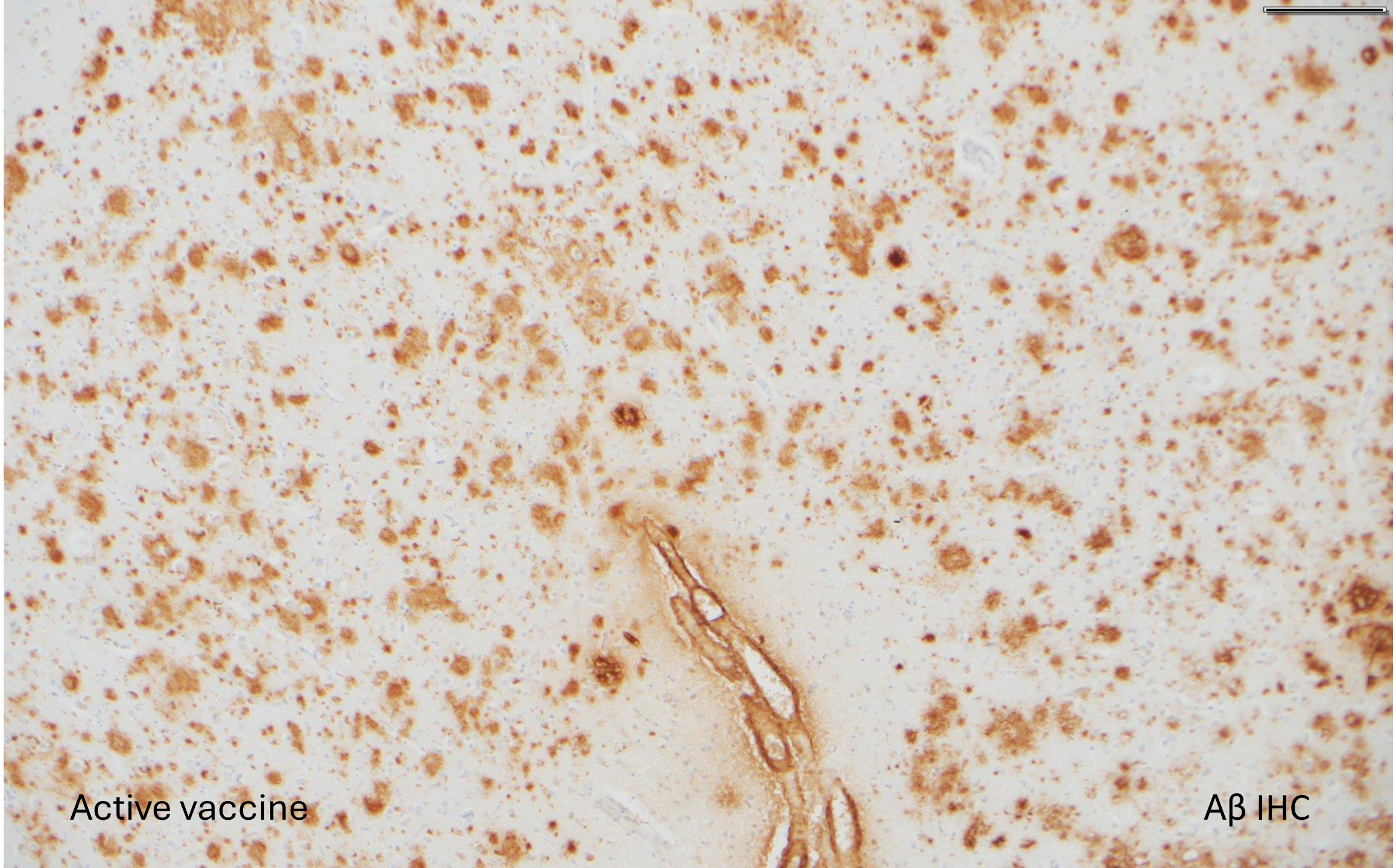
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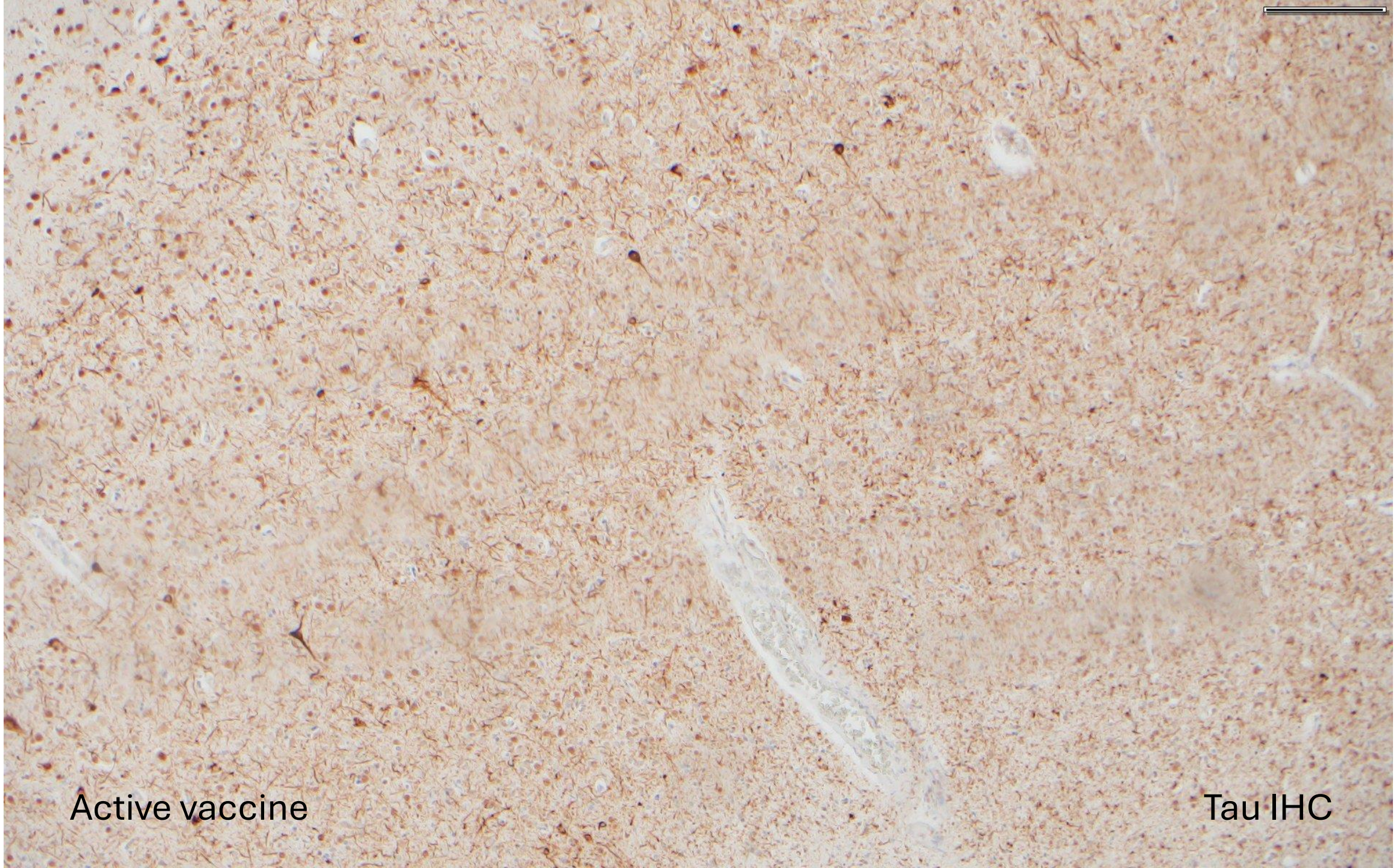

Active vaccine
Tau IHC

“Although at the time of entry of the trial all participants satisfied the criteria for mild/moderate dementia, 19/22 were assessed as having severe dementia prior to death (Table 1), notably ***including all five patients with near complete clearance of plaques from the brain***”

Nicoll JAR, Buckland GR, Harrison CH, Page A, Harris S, Love S, Neal JW, Holmes C, Boche D: Persistent neuropathological effects 14 years following amyloid-beta immunization in Alzheimer's disease. ***Brain 2019***, 142:2113-26.

…”the cognitive function of all the immunized AD patients had continued to decline and reached a terminal end stage dementia (MMSE = 0) prior to death. ***This includes two patients in whom there was virtually complete clearance of Aβ plaques from the brain”***

Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JA: Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. ***Lancet 2008***, 372:216-23.

Acta Neuropathologica (2022) 144:143–153
https://doi.org/10.1007/s00401-022-02433-4

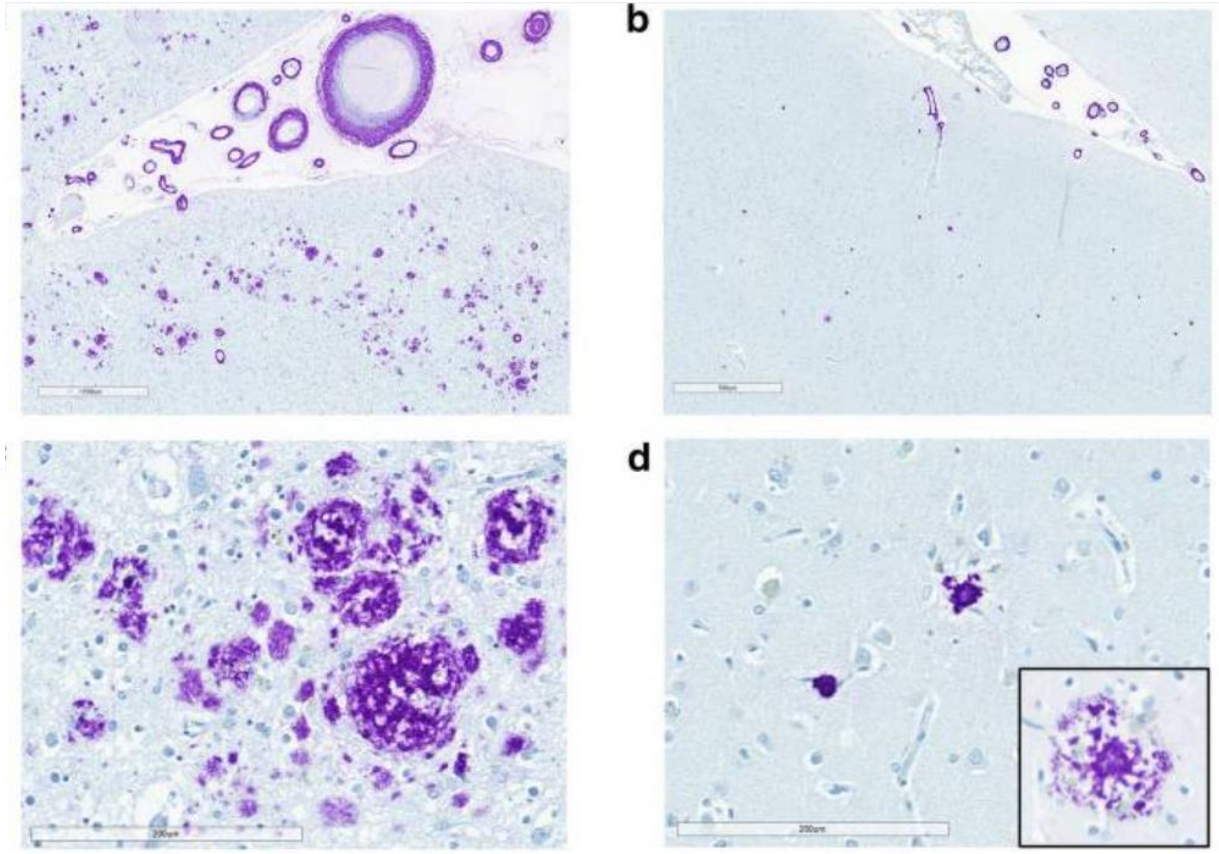
CASE REPORT

Alzheimer disease neuropathology in a patient previously treated with aducanumab

Edward D. Plowey[1] · Thierry Bussiere[1] · Raj Rajagovindan[1] · Jennifer Sebalusky[1] · Stefan Hamann[1] · Christian von Hehn[1] · Carmen Castrillo-Viguera[1] · Alfred Sandrock[1] · Samantha Budd Haeberlein[1] · Christopher H. van Dyck[3] · Anita Huttner[2]

Received: 27 January 2022 / Revised: 5 May 2022 / Accepted: 5 May 2022 / Published online: 17 May 2022

MMSE = 14/30 at start
32 monthly doses
Last dose 4 months before death



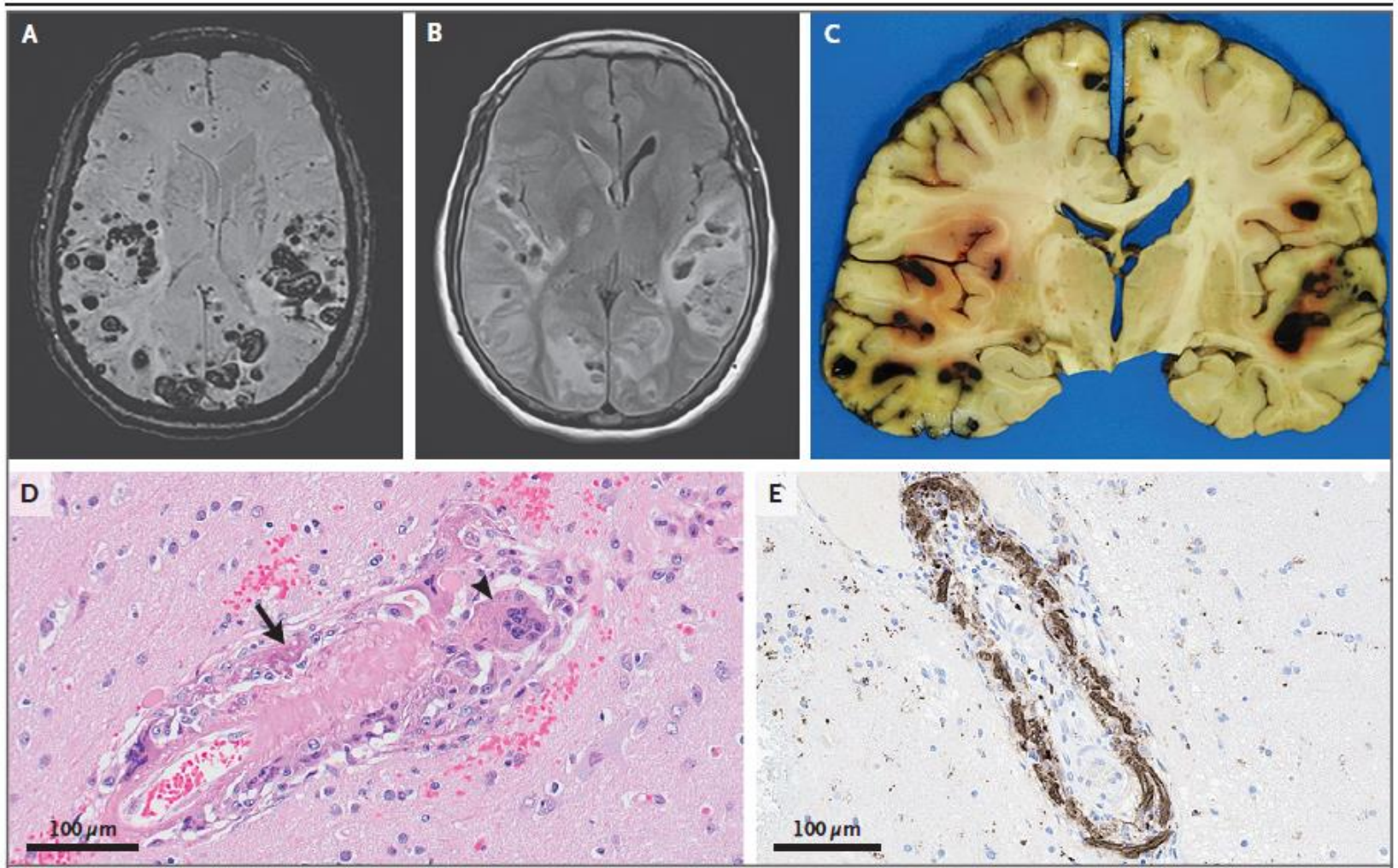


Figure 1. MRI and Neuropathological Findings.

Panel A shows a magnetic resonance imaging (MRI) susceptibility-weighted sequence in which extensive multifocal cortical intraparenchymal hemorrhages are visible. Panel B shows an MRI T2 fluid-attenuated inversion recovery (FLAIR) sequence in which extensive cerebral cortical and subcortical edema is seen in association with multifocal hemorrhages, as well as a right thalamocapsular acute ischemic infarct. Panel C shows a coronal section of the formalin-fixed cerebral hemispheres in which numerous cortical intracerebral hemorrhages are present. Panel D shows a representative hematoxylin and eosin–stained section of the left parietal cortex, in which a blood vessel with probable amyloid angiopathy and histiocytic infiltration of the blood-vessel wall is visible. Multinucleated histiocytes (arrowhead) and focal fibrinoid degeneration (arrow) are present. Panel E shows amyloid-β immunohistochemical staining of a cortical blood vessel affected by cerebral amyloid angiopathy. The vascular amyloid is fragmented, and the blood-vessel wall shows infiltration by lymphocytes and histiocytes.

The New England Journal of Medicine NEJM Evidence NEJM AI NEJM Catalyst

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke

Published January 4, 2023 | N Engl J Med 2023;388:478-479
DOI: 10.1056/NEJMc2215148 | VOL. 388 NO. 5 | Copyright © 2023

Journal of Alzheimer's Disease 93 (2023) 803–813
DOI 10.3233/JAD-221305
IOS Press

Neuropathology of Anti-Amyloid-β Immunotherapy: A Case Report

Rudolph J. Castellani[a,*], Elisheva D. Shanes[a], Matthew McCord[a], Nicholas J. Reish[c], Margaret E. Flanagan[b], M-Marsel Mesulam[c,d] and Pouya Jamshidi[a]
[a]*Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*
[b]*Department of Pathology, University of Texas, San Antonio, San Antonio, TX, USA*
[c]*Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*
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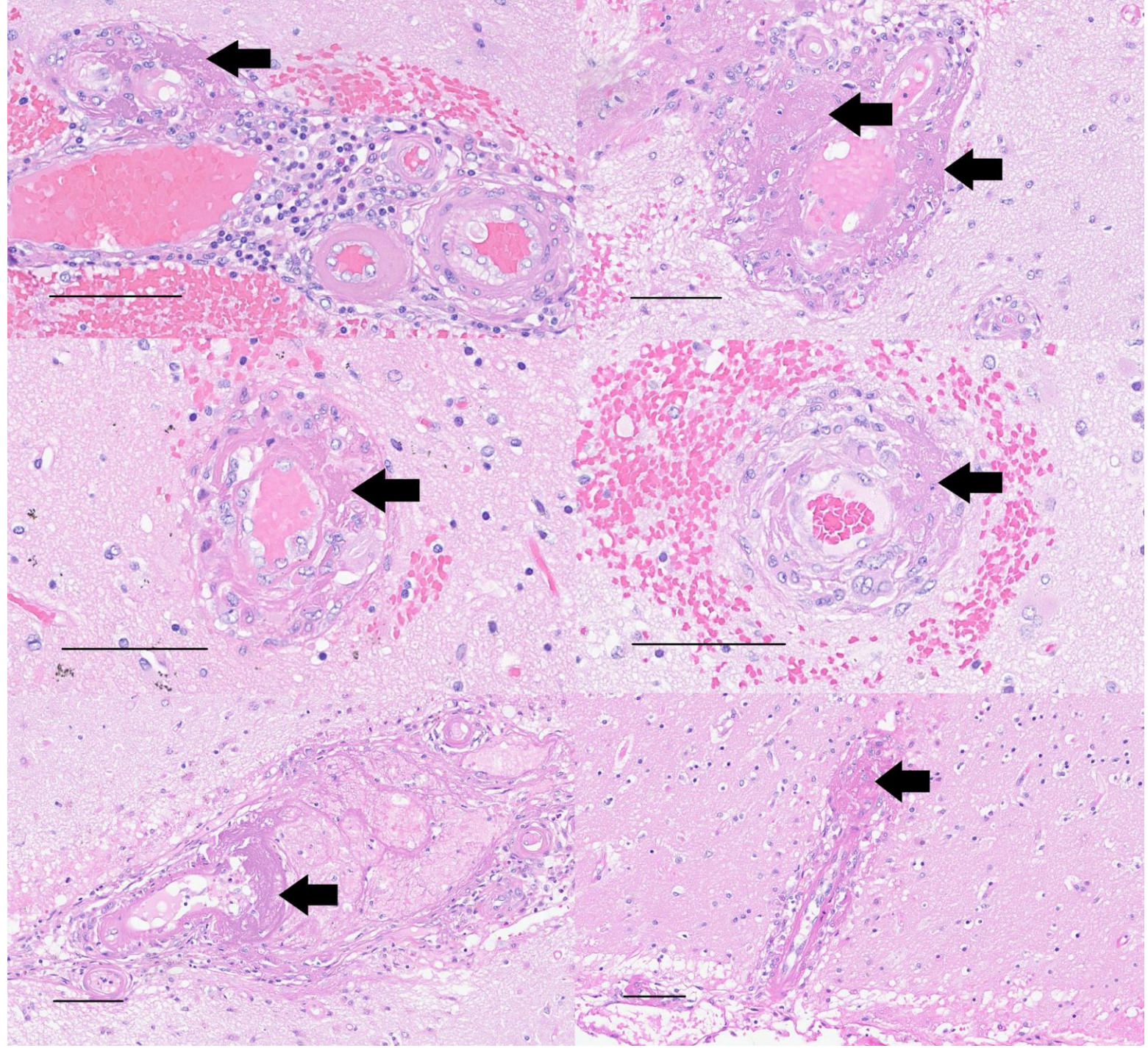
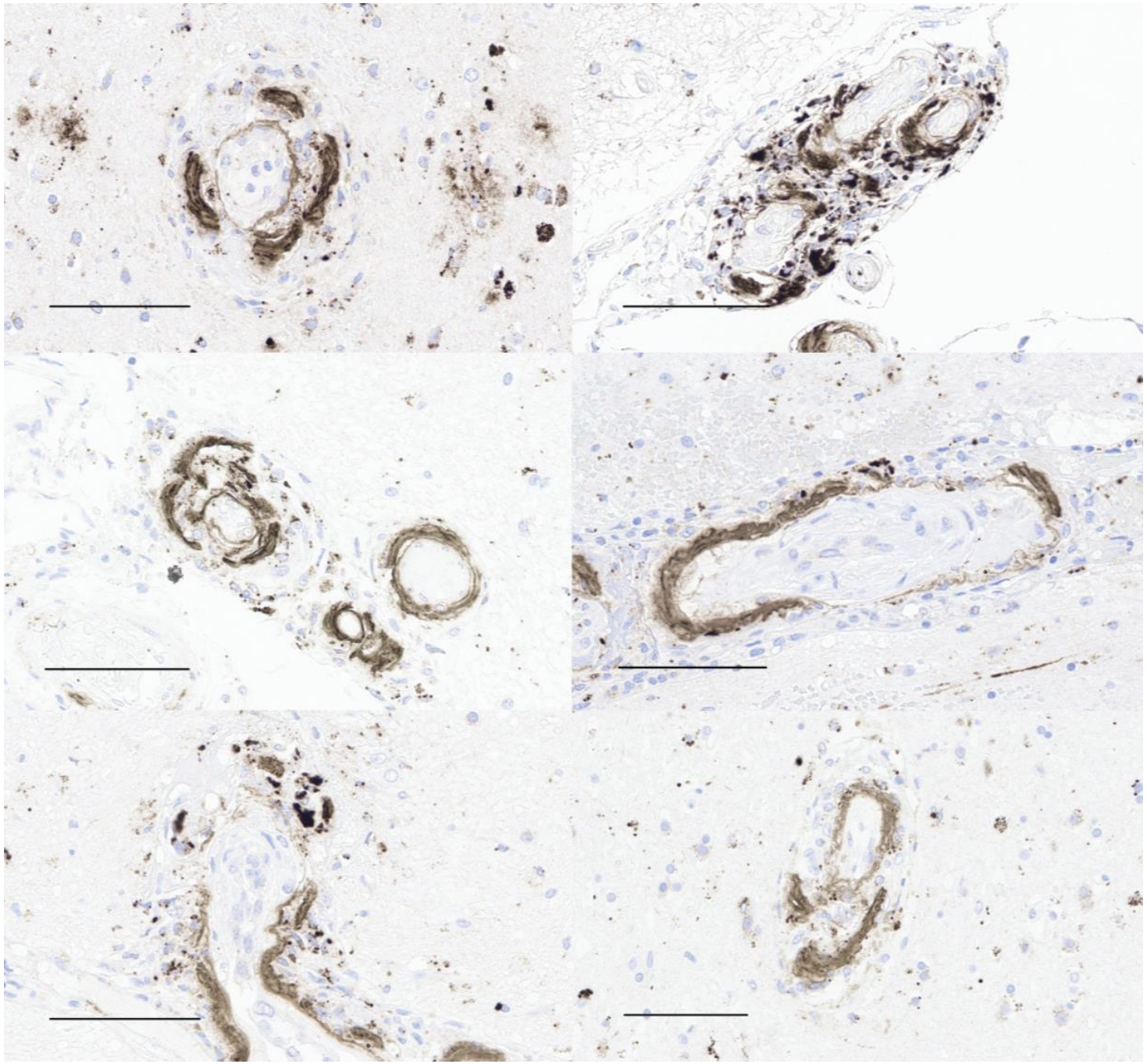


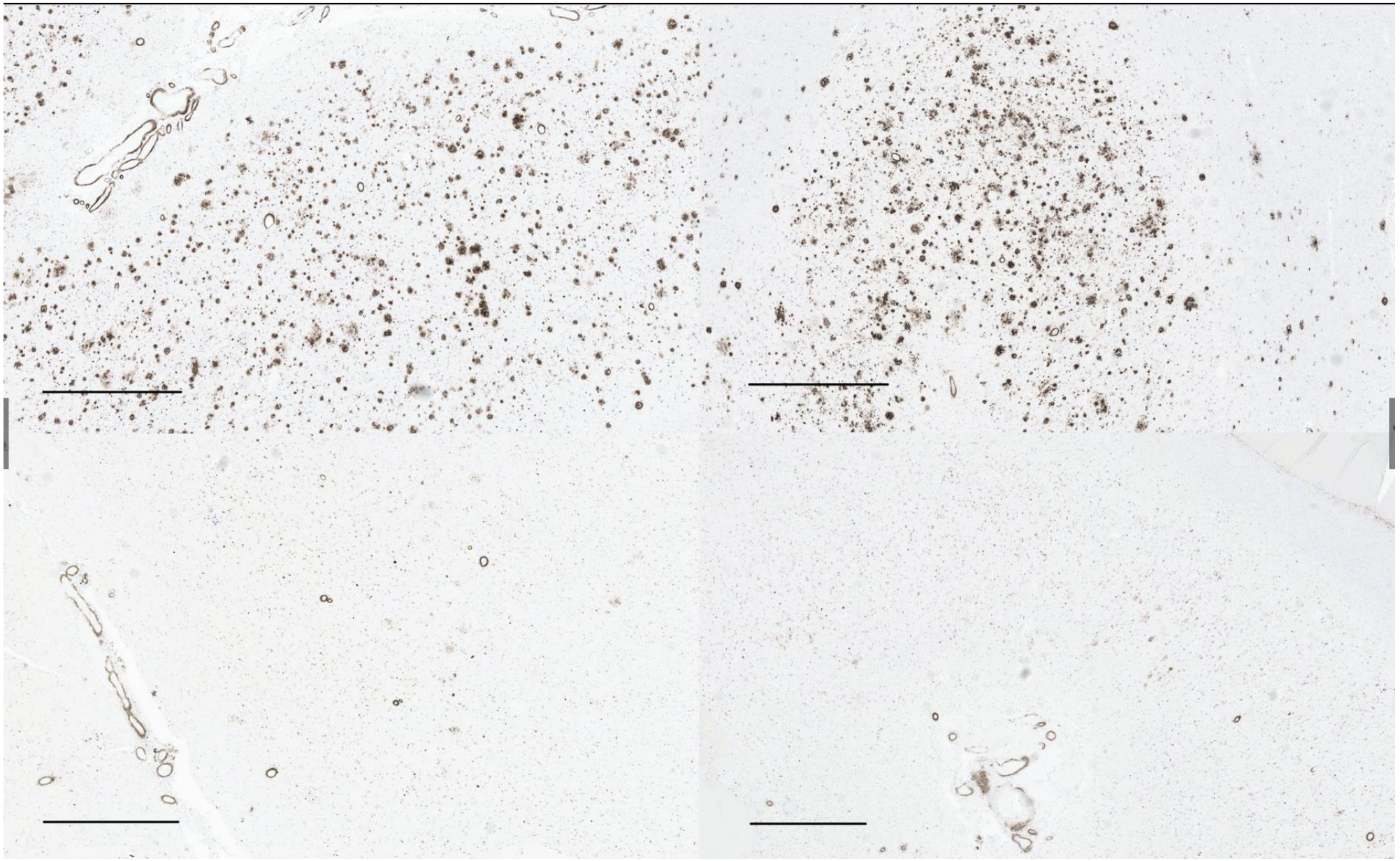
4G8



Middle frontal

4G8

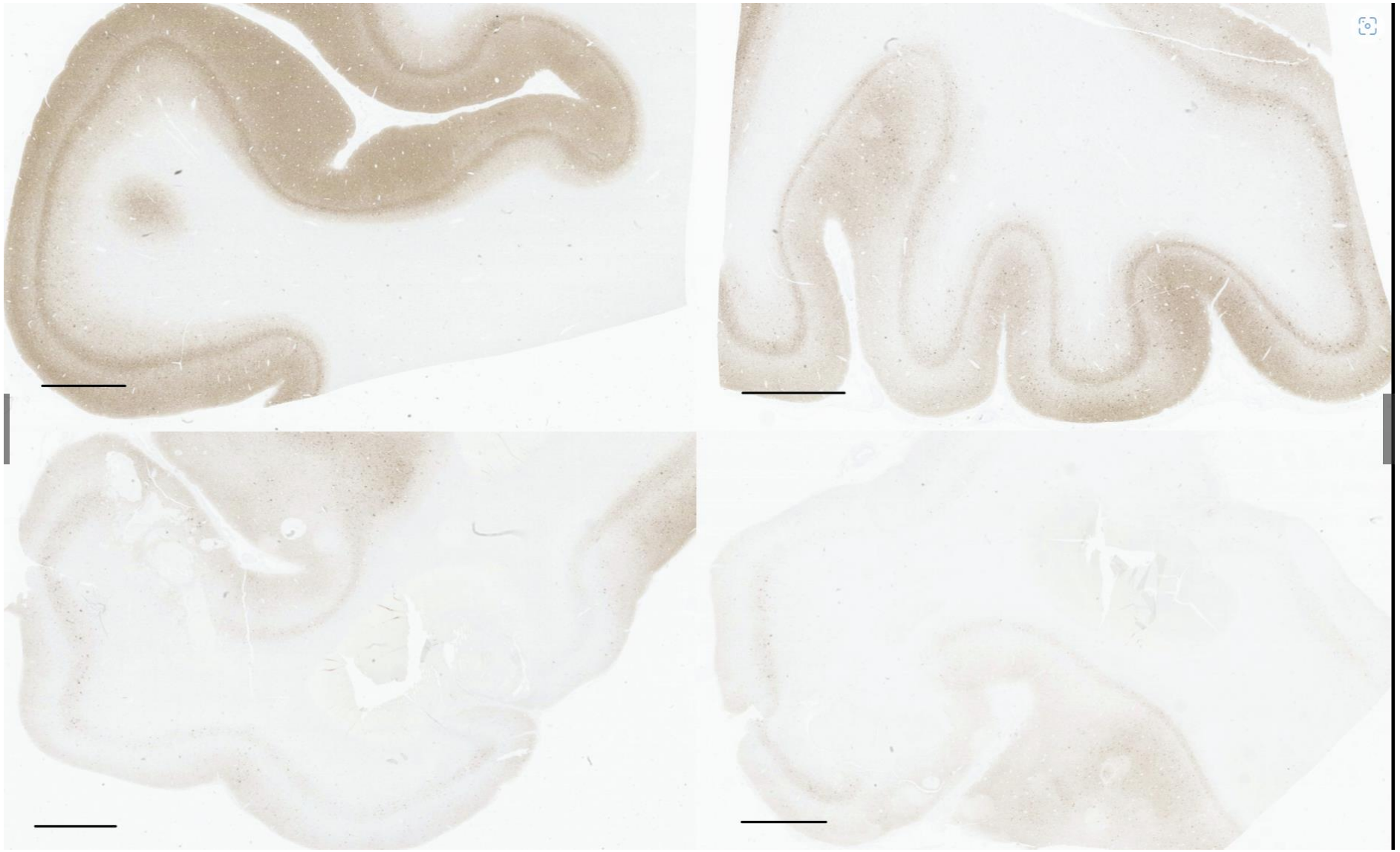
Superior temporal

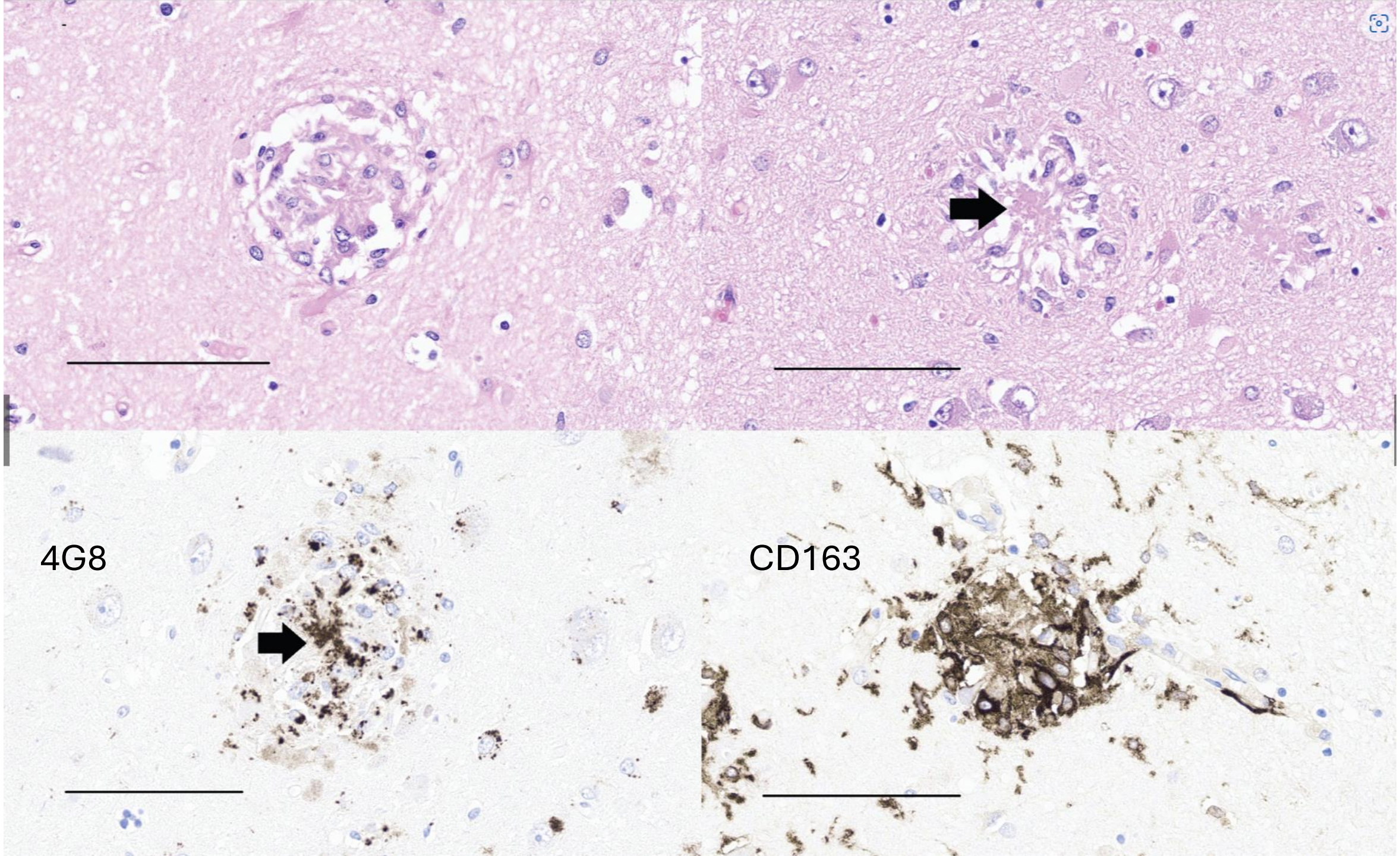


Middle frontal

AT8

Superior temporal




4G8
CD163

nature communications

Article

https://doi.org/10.1038/s41467-023-43933-5

Fatal iatrogenic cerebral β-amyloid-related arteritis in a woman treated with lecanemab for Alzheimer's disease

Received: 26 April 2023

Accepted: 24 November 2023

Published online: 12 December 2023

Check for updates

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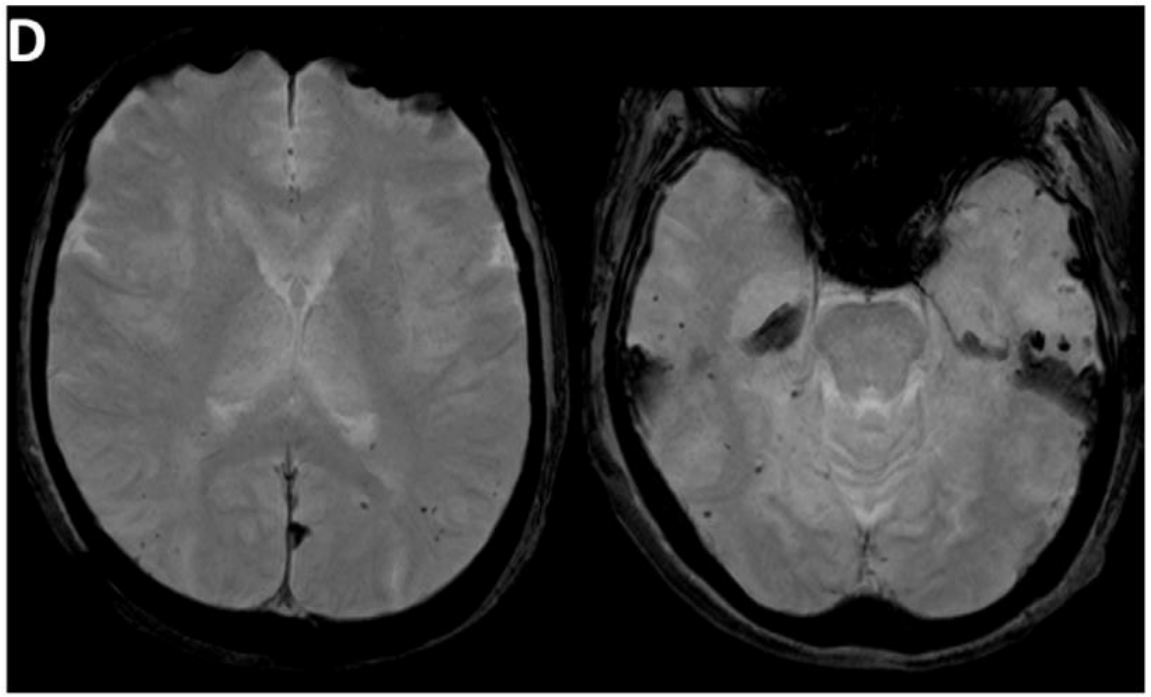
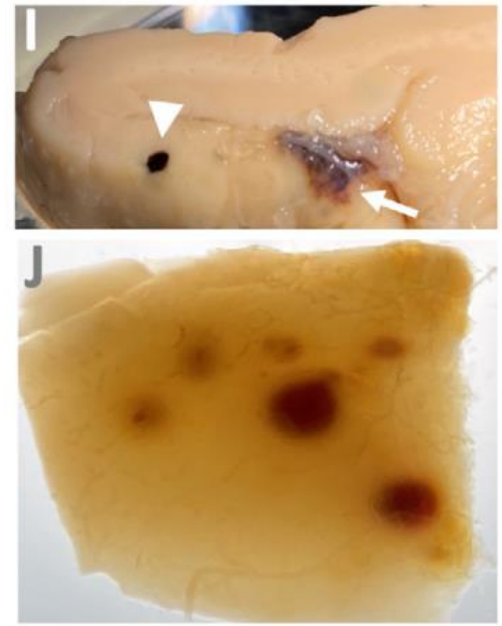
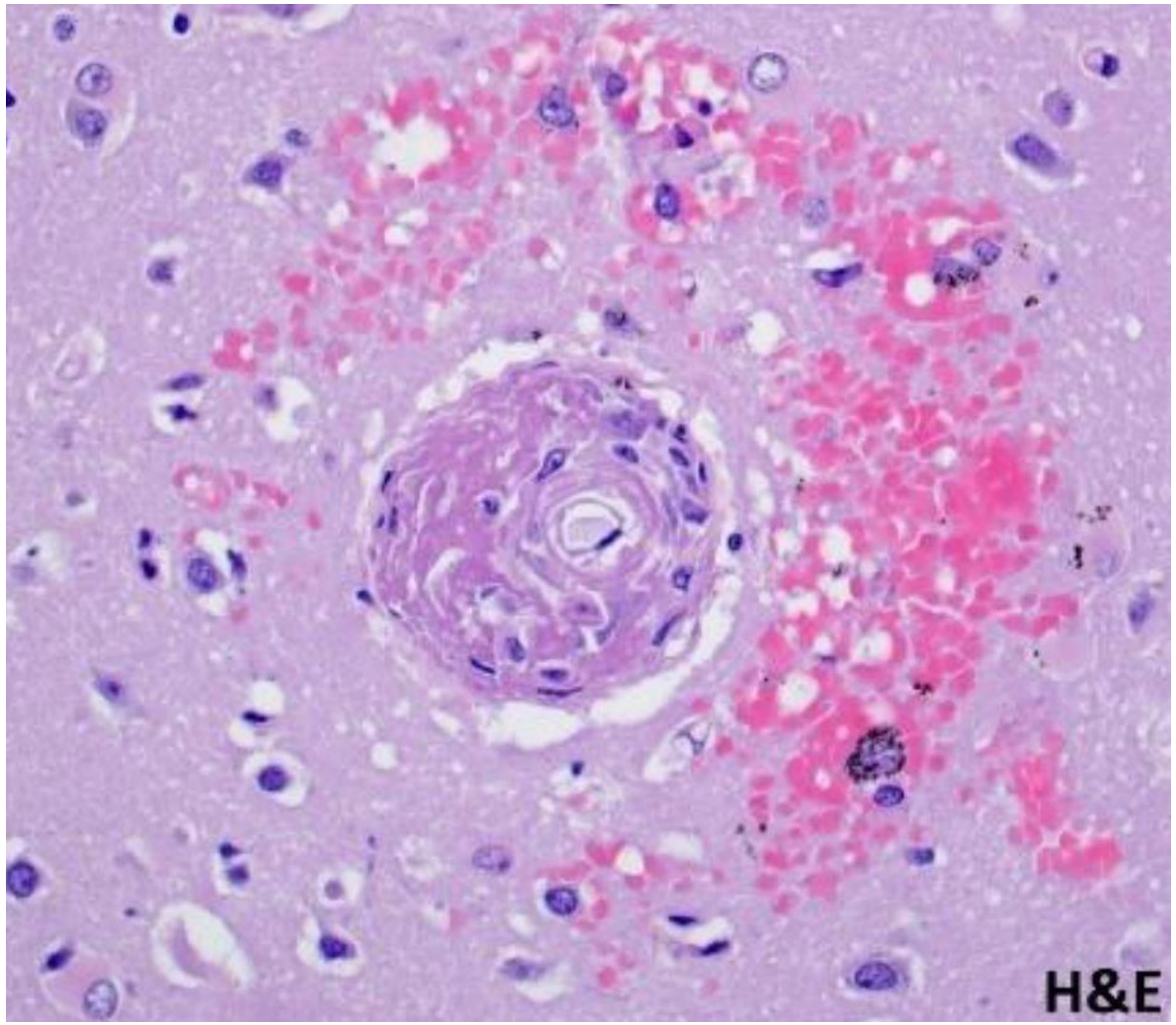




3 doses, identical vascular pathology



Solopova et al. Fatal iatrogenic cerebral β-amyloid-related arteritis in a woman treated with lecanemab for Alzheimer's disease. Nature Communications 2023;14:8220, 1-8. https://doi.org/10.1038/s41467-023-43933-5

Journal of Neuropathology & Experimental Neurology, 2024, 1–3
https://doi.org/10.1093/jnen/nlae068
Letter to the Editor

OXFORD

Letter to the Editor

Cerebral amyloid-β-related angiitis and iatrogenic cerebral amyloid angiopathy-related vasculitis: implications for amyloid-related imaging abnormalities

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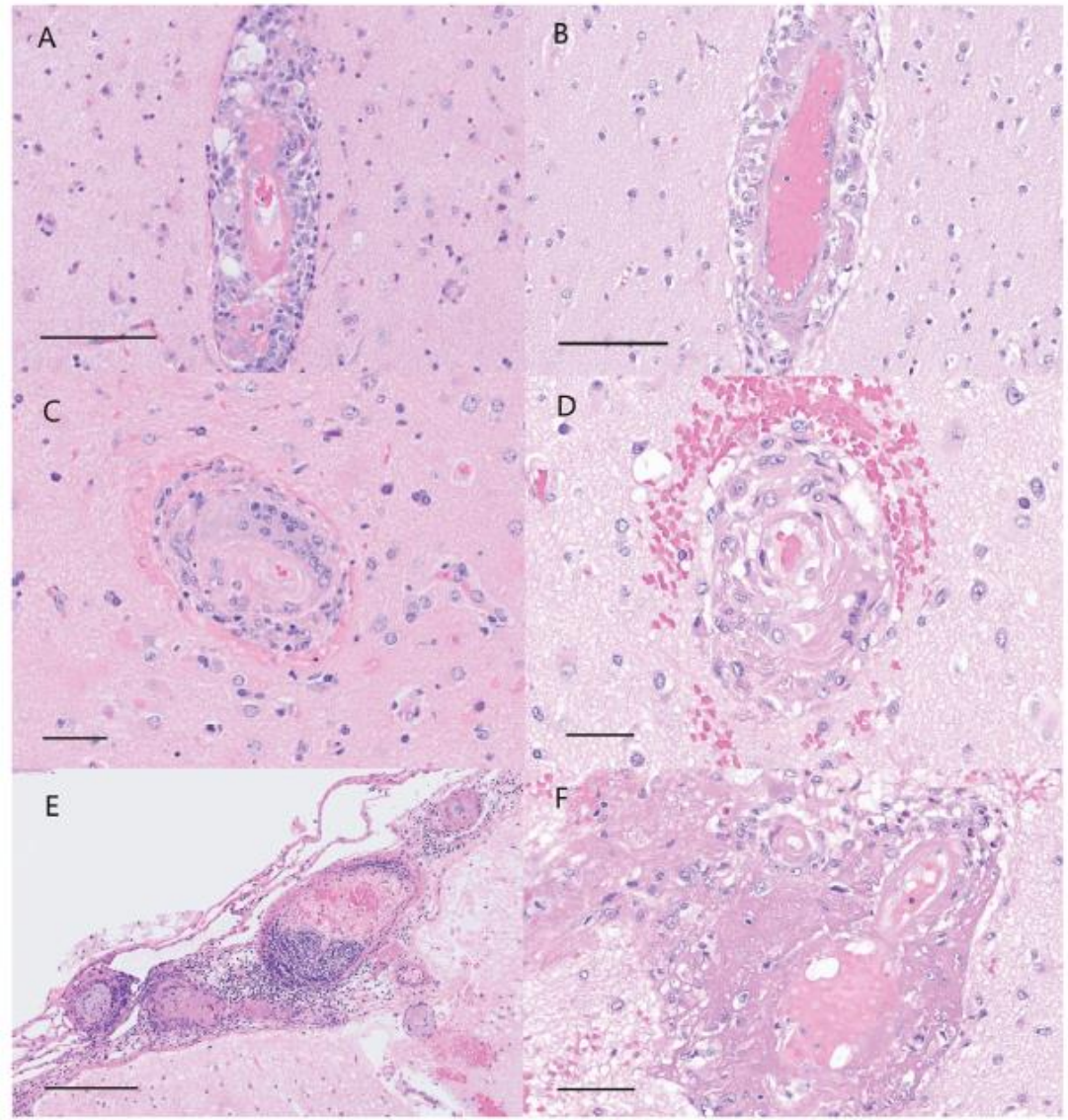
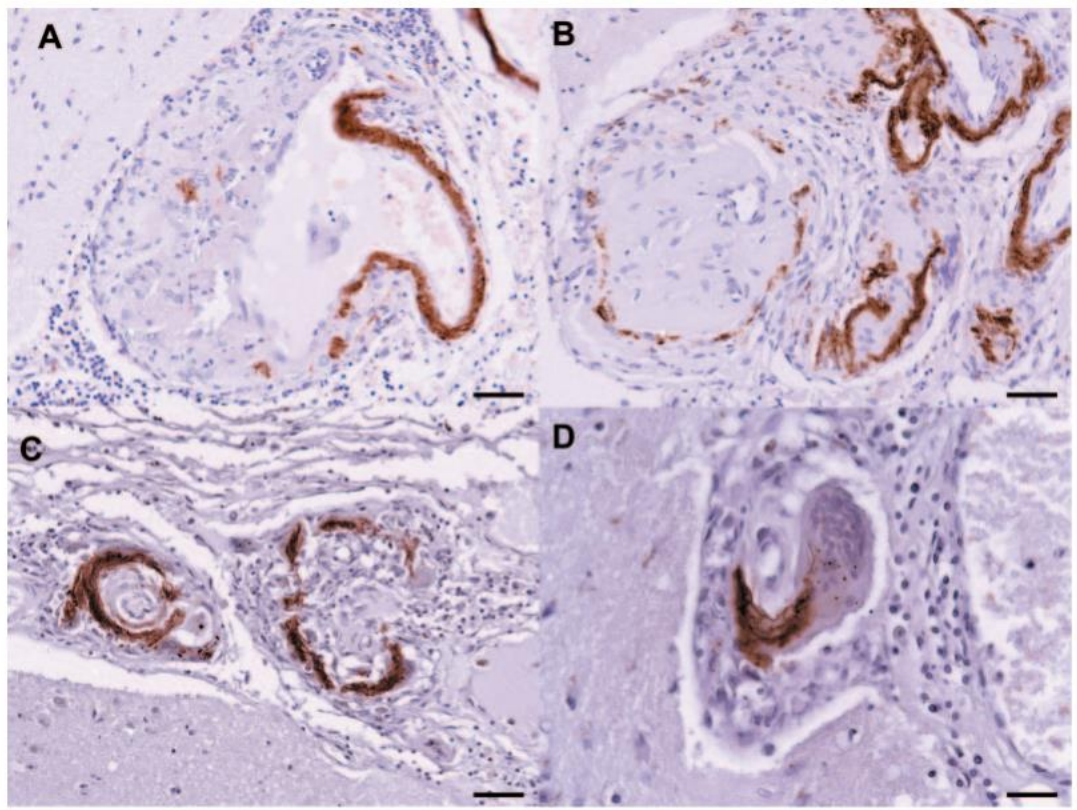


doi:10.1093/brain/awh379 *Brain* (2005), **128**, 500–515

Aβ-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy

Neil J. Scolding,[1] Fady Joseph,[1] Patricia A. Kirby,[9] Ingrid Mazanti,[3] Françoise Gray,[10] Jacqueline Mikol,[10] David Ellison,[4] David A. Hilton,[6] Timothy L. Williams,[5] James M. MacKenzie,[7] John H. Xuereb[8] and Seth Love[2]



ARTICLES

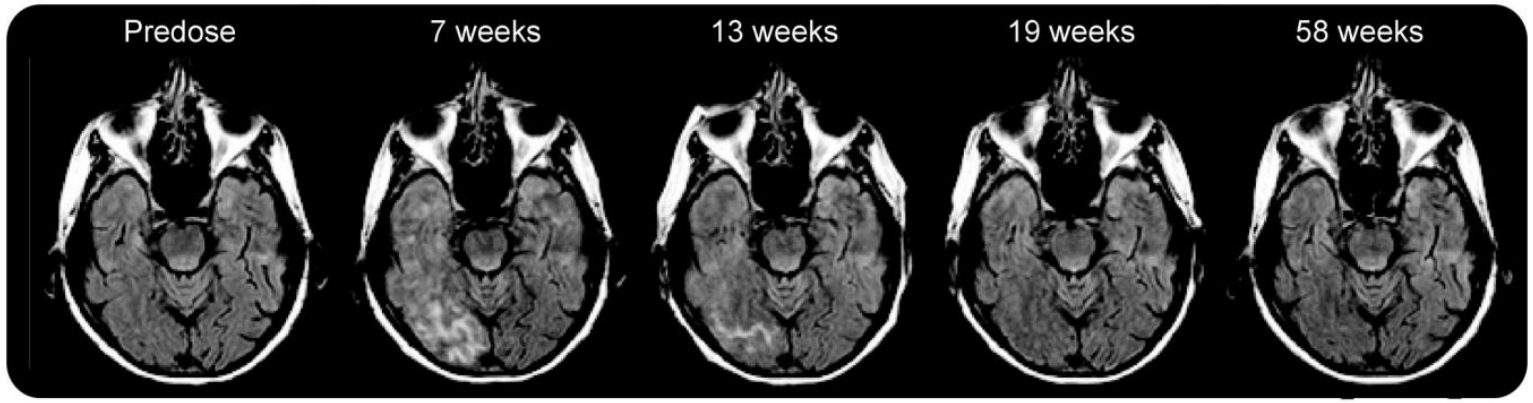
A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease

S. Salloway, MD, MS
R. Sperling, MD, MMSc
S. Gilman, MD, FRCP
N.C. Fox, MD, FRCP

ABSTRACT

Background: Bapineuzumab, a humanized anti-amyloid-beta (Aβ) monoclonal antibody for the potential treatment of Alzheimer disease (AD), was evaluated in a multiple ascending dose, safety, and efficacy study in mild to moderate AD.

Figure 3 Serial MRI scans (fluid-attenuated inversion recovery) in a patient with vasogenic edema (VE)



This 69-year-old woman is an *APOE* ϵ4 homozygote who was treated with bapineuzumab 1.0 mg/kg IV. She remained asymptomatic despite the appearance of multiple areas of VE evident on the MRI. The VE was apparent on MRI by 7 weeks after her first infusion and resolved by 19 weeks. The patient was redosed at 0.5 mg/kg of bapineuzumab IV and followed for over 2 years without recurrence of VE.

NIH Public Access
Author Manuscript
Alzheimers Dement. Author manuscript; available in PMC 2013 June 26.

Published in final edited form as:
Alzheimers Dement. 2011 July ; 7(4): 367–385. doi:10.1016/j.jalz.2011.05.2351.

Amyloid Related Imaging Abnormalities (ARIA) in Amyloid Modifying Therapeutic Trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup

Reisa A. Sperling[a,‡,*], **Clifford R. Jack**[b,*], **Sandra E. Black**[c], **Matthew P. Frosch**[d], **Steven M. Greenberg**[e], **Bradley T. Hyman**[f], **Philip Scheltens**[g], **Maria C. Carrillo**[h], **William Thies**[h], **Martin M. Bednar**[i], **Ronald S. Black**[j], **H. Robert Brashear**[k], **Michael Grundman**[l], **Eric R. Siemers**[m], **Howard H. Feldman**[n,*], and **Rachel J. Schindler**[o,*]

The relationship to dose level in the bapineuzumab studies suggests that ARIA may be related to increased clearance of parenchymal plaque with **transient increase in vascular amyloid**. This hypothesis is supported by the published autopsy results from the AN-1792 (active immunization) trial [52, 53]. It remains unclear whether rapid movement of amyloid from parenchymal plaques into perivascular space might result in a "drainage back up" leading to excess fluid shifts. It is also possible that movement of amyloid into cerebral vessel walls might result in increased vascular friability and increased permeability. This mechanism might also relate to increased incident mH, if the vessel wall integrity is sufficiently impaired to permit small amounts of red blood cell passage.

Neuropathology of human Alzheimer disease after immunization with amyloid-β peptide: a case report

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Published online 17 March 2003; doi:10.1038/nm840

Nature medicine 2003;9(4):448-452

The persistence of amyloid in the walls of blood vessels (CAA), despite its removal from plaques, was also observed in studies of PDAPP mice4 . The vascular amyloid deposits, which comprise predominantly Aβ40 (unlike plaques, which are predominantly Aβ42), may be more stable, more rapidly replenished or less accessible, for example to Aβ-specific antibody or phagocytes4 . **A further possibility is that efflux of Aβ from the brain through perivascular drainage pathways** may be stimulated by the immunotherapy and contribute to CAA11. Whatever the mechanism, this relative persistence of vascular Aβ may be relevant to the observation that CAA-related hemorrhage in APP transgenic mice was increased by one Aβ-specific antibody12

doi:10.1093/brain/awn261 *Brain* (2008), **131**, 3299–3310

Consequence of Aβ immunization on the vasculature of human Alzheimer's disease brain

D. Boche,[1] E. Zotova,[1] R. O. Weller,[1] S. Love,[2] J. W. Neal,[3] R. M. Pickering,[4] D. Wilkinson,[5] C. Holmes[1,5] and J. A. R. Nicoll[1,6]

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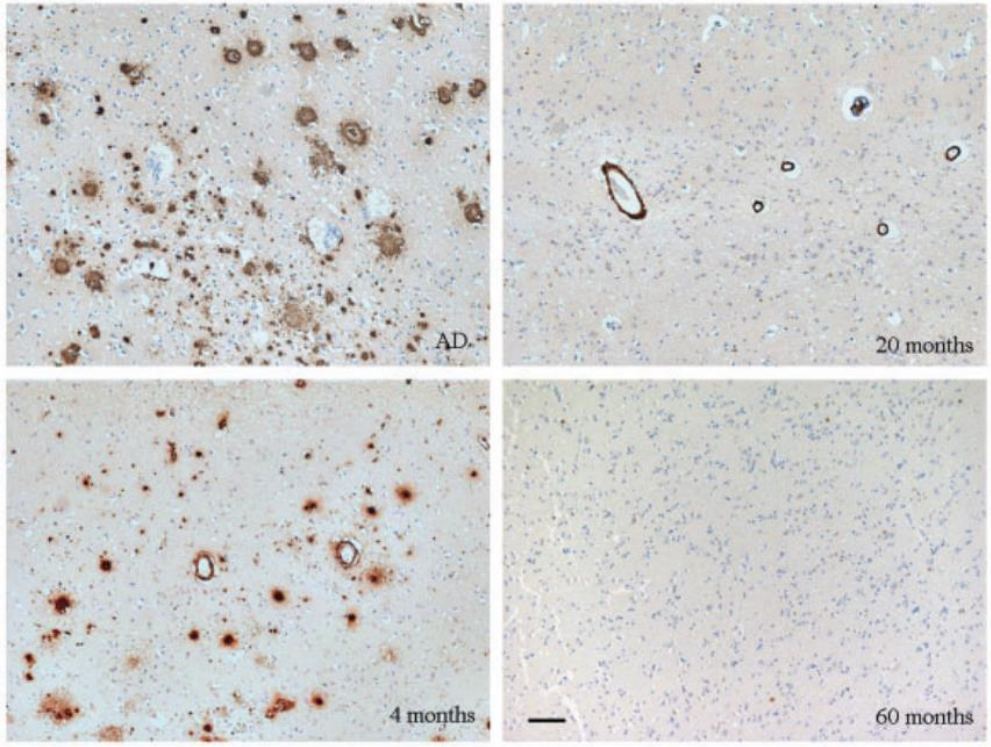

Quantification of parenchymal Ab42 and vascular Ab42 in Alzheimer's disease and immunized Alzheimer's disease cases.The immunized Alzheimer's disease group **shows a significantly lower load of parenchymal Ab42 (P = 0.020) and a significantly higher level of vascular Ab42 (P < 0.001**)

9 immunized, 11 controls

Vasculitis – say it

- …a central role for cerebral amyloid angiopathy — a condition characterized by cerebrovascular Aβ deposits — as a key component, either as a direct target for antibody-mediated inflammation ***or as recipient of Aβ mobilized from plaques in the Alzheimer brain parenchyma.***


nature reviews neurology
https://doi.org/10.1038/s41582-024-01053-8
Review article
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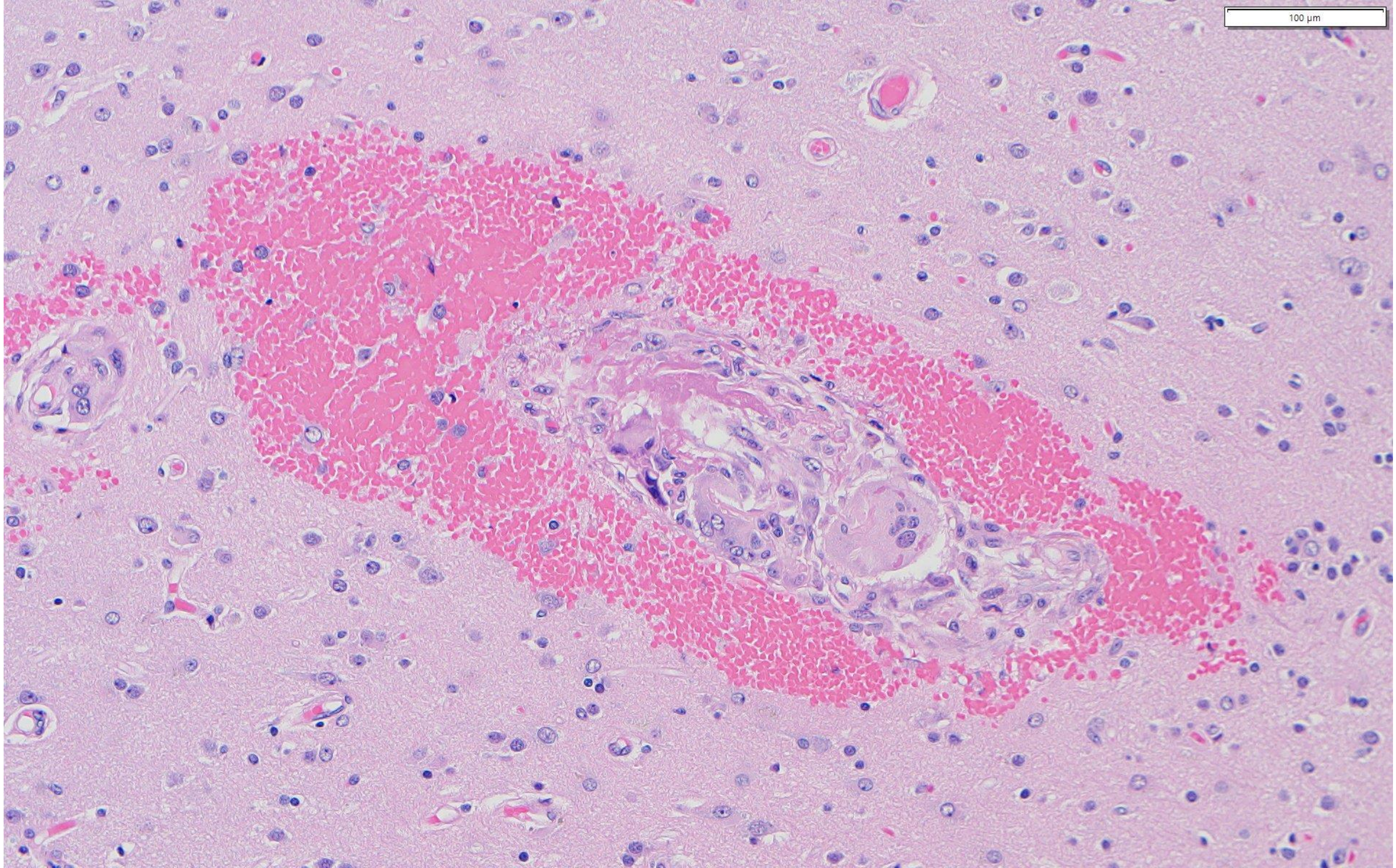
Amyloid-related imaging abnormalities: manifestations, metrics and mechanisms

Steven M. Greenberg[1], Francesco Bax[1,2] & Susanne J. van Veluw[1]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Conclusions

- Anti-Amyloid-β immunotherapy causes a ***necrotizing vasculitis***
  - Attacks ***insoluble*** amyloid-β
  - Likely microglial and ***myeloid*** clearance mechanisms
- ***Necrotizing vasculitis likely comprises the substrate for "ARIA"*** in most cases
- The notion of "perivascular clearance" of amyloid-β as the basis for "ARIA" should be retired
- Should tPA be an absolute contraindication?