



## Neuropathology and Underlying Mechanisms of Cerebral Amyloid Angiopathy



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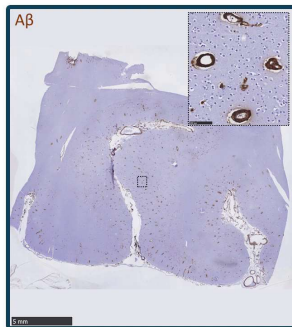
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## Cerebral Amyloid Angiopathy (CAA)

- Leading cause of hemorrhagic stroke and dementia in older individuals
- Common cerebral small vessel disease
- Characterized by the accumulation of amyloid  $\beta$  ( $A\beta$ ) in the walls of cortical and pial surface vessels



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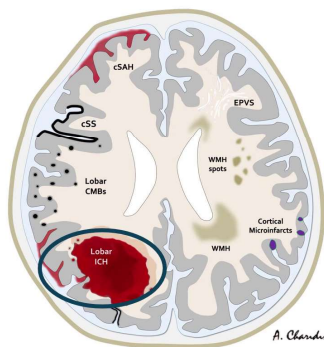
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## Cerebral Amyloid Angiopathy (CAA)



A. Charidimou

Courtesy of Dr. Andreas Charidimou

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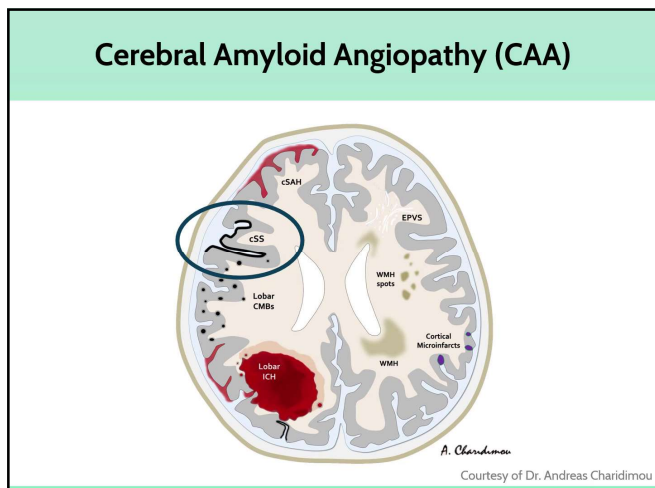
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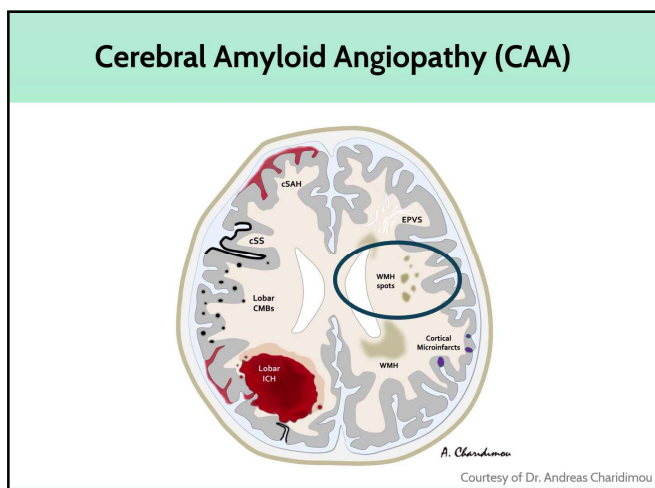
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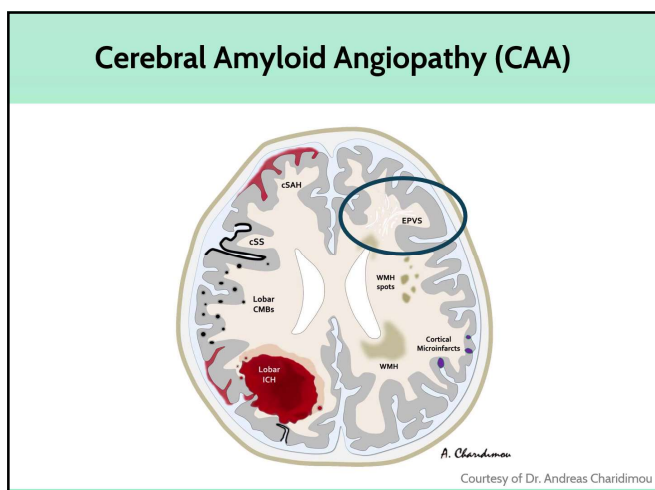
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### CAA progression

Vonsattel Grading System

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4

100 μm 100 μm 100 μm 250 μm 250 μm  
100 μm 100 μm 100 μm 250 μm 250 μm

Kozberg M.G., et al., *Brain Commun.* 2022;26:4(5):fcac245  
Vonsattel J.P., et al., *Ann Neurol.* 1991;30(5):637–649

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CAA progression

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CAA progression

Vonsattel Grading System

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**CAA progression**

**Vonsattel Grading System**

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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**CAA progression**

**Vonsattel Grading System**

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**CAA progression**

**Vonsattel Grading System**

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### Cortical microinfarcts (CMI)

The diagram on the left shows a cross-section of the brain with various pathologies labeled: cSAH, EPVS, WMH spots, Lobar CMBs, and Lobar ICH. A blue circle highlights 'Cortical Microinfarcts'. The MRI scan on the right is a FLAIR image showing a cortical microinfarct as a small white spot in the cortex, indicated by a white arrow. A dashed box on the MRI scan indicates the area shown in the diagram.

van Veluw S.J., et al., *J Cereb Blood Flow Metab.* 2013;33(3):322-329

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### Brain sample of an ischemic lesion

The image shows a coronal section of a brain specimen. A red box highlights a pale, wedge-shaped area of infarction. A magnified view of this area shows a well-demarcated, pale, and swollen area of brain tissue, characteristic of an acute ischemic stroke.

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### Histopathology of a CMI

The left micrograph shows a hematoxylin and eosin (H&E) stained section of a cortical microinfarct. The right micrograph shows an immunohistochemical stain for amyloid-beta (Aβ), highlighting the presence of amyloid plaques within the infarcted area.

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### Enlarged perivascular spaces (EPVS)

Perosa V., et al., Acta Neuropathol. 2022;143(3):331-348

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### Brain sample of an EPVS

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### Histopathology of an EPVS

Retrograde A $\beta$  accumulation

H&E

A $\beta$

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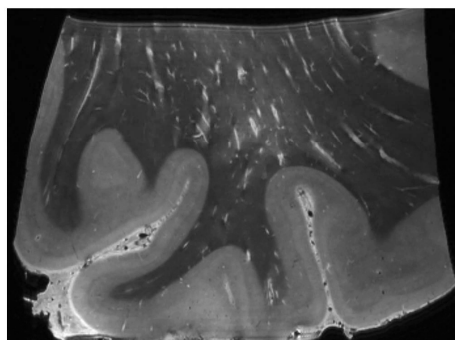
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## High-resolution image of a patient with EPVS



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Perosa V., et al., *Acta Neuropathol.* 2022;143(3):331-348

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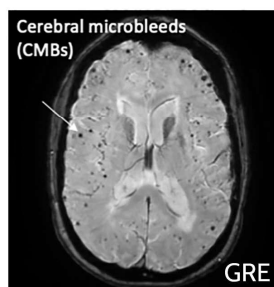
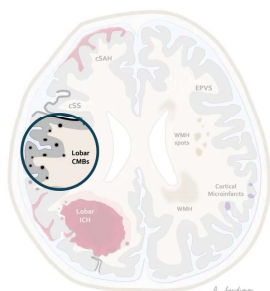
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## Cerebral microbleeds (CMB)

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Kozberg M.G., et al., *Int J Stroke.* 2021;16(4):356-369

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## Pathology of a CMB

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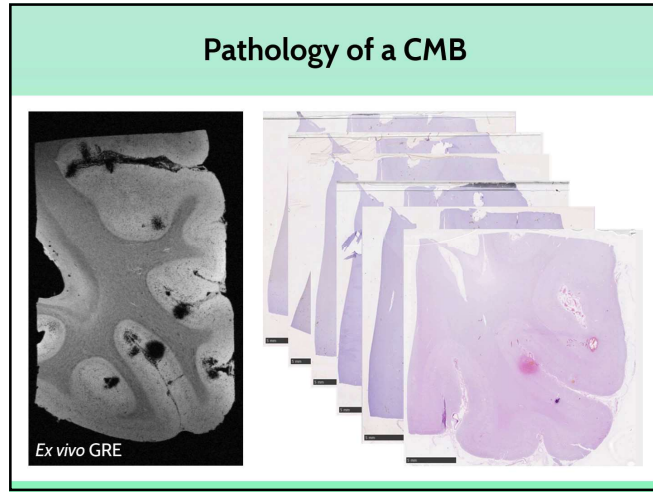
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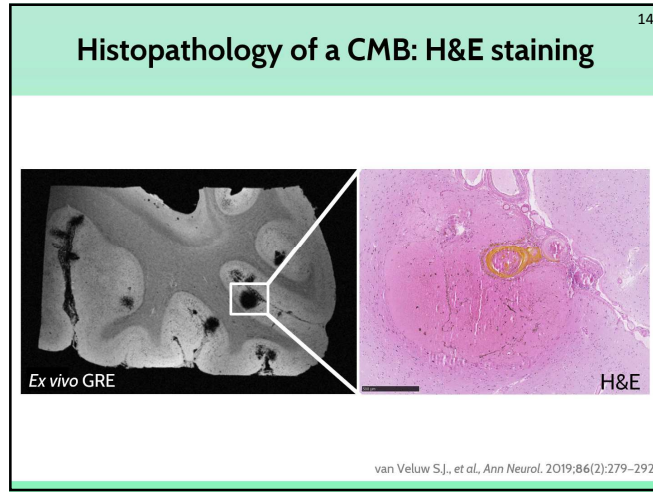
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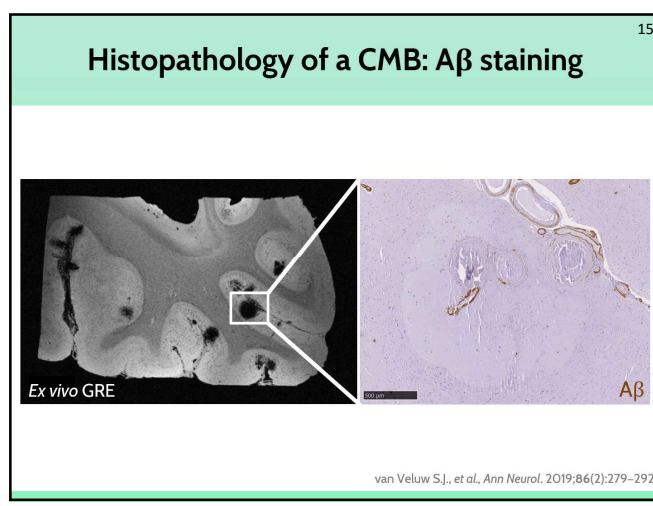
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## Vascular remodeling

Vascular remodeling plays a role in hemorrhage formation in CAA

Evidence of multiple vessels that are grade 4-type vessels in the same area as the microhemorrhages

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## Vascular remodeling

250 µm H&E

Aβ

Fibrin(ogen)

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## Cortical superficial siderosis (cSS)

CSAM

cSS

EPVS

Lobar CMBs

Lobar ICH

WMH

Cortical Microinfarcts

WMH

Focal cortical superficial siderosis (cSS)

SWI

Kozberg M.G., et al., *Int J Stroke*. 2021;16(4):356–369

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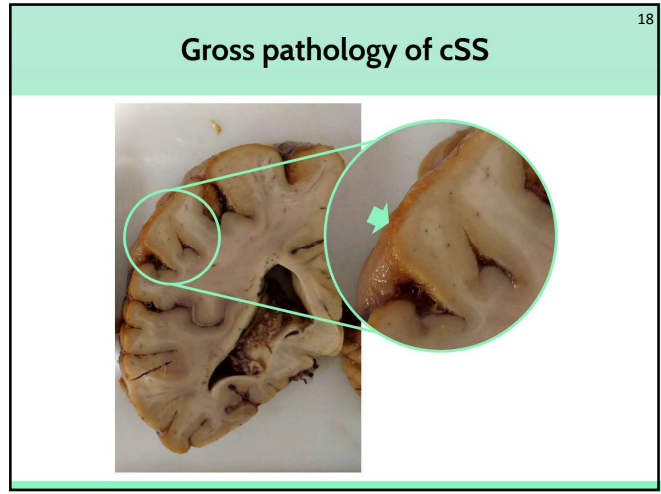
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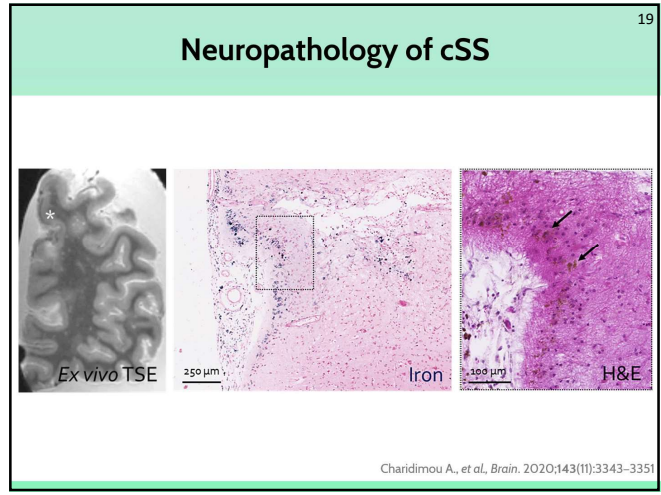
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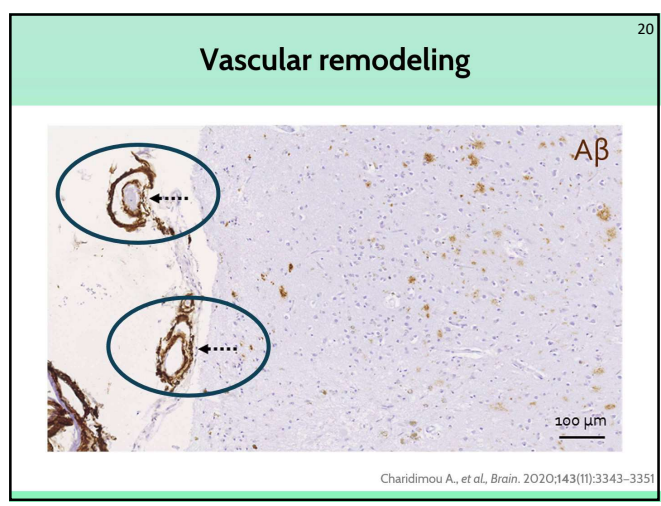
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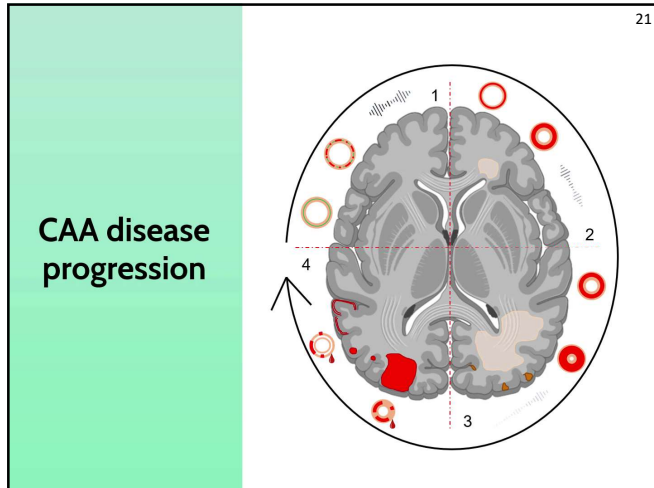
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### Acknowledgments

<p><b>Van Veluw lab</b></p> <ul style="list-style-type: none"><li>• Mariel Kozberg</li><li>• Leon Munting</li><li>• Orla Bonnar</li><li>• Valentina Perosa</li><li>• Hilde van den Brink</li><li>• Maria Clara Zanon Zotin</li><li>• Corinne Auger</li><li>• Lee Maresco</li><li>• Maarten van den Berg</li></ul>	<p><b>Mass General Hospital</b></p> <ul style="list-style-type: none"><li>• Steven Greenberg</li><li>• Anand Viswanathan</li><li>• Edip Guroi</li><li>• Matthew Frosch</li><li>• Andre van der Kouwe</li><li>• Bruce Fischl</li><li>• Brad Hyman</li><li>• Brian Bacskai</li><li>• Rachel Bennett</li></ul>
<p><b>Alumni</b></p> <ul style="list-style-type: none"><li>• Nazanin Makinejad</li><li>• Whitney Freeze</li><li>• Ashley Scherlek</li><li>• Irvin Yi</li></ul>	<p><b>Our brain donors and their families</b></p> <p><b>Funding sources</b> NIH/NIA (ROO AGO59893, R21 AGO70363), NIH/NINDS (RF1 NS110054), Alzheimer's Association, American Heart Association, BrightFocus Foundation, Netherlands Organization for Scientific Research, Alzheimer Nederland</p>

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