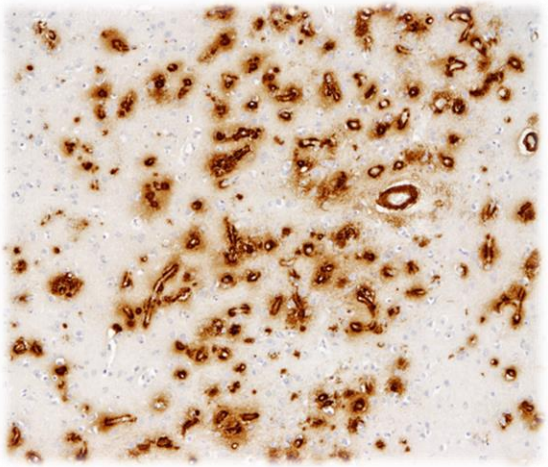
ASOCIACIÓN MADRILEÑA DE NEUROLOGÍA

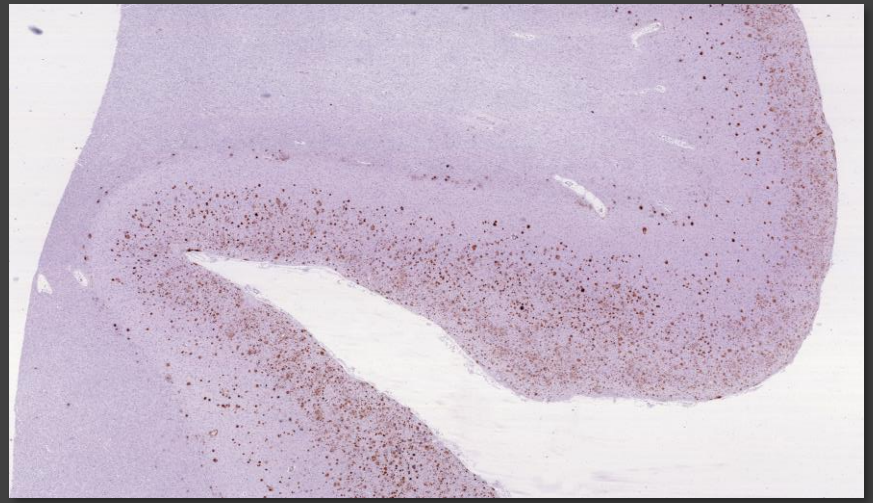
XXI REUNIÓN ANUAL DE LA ASOCIACIÓN MADRILEÑA DE NEUROLOGÍA (AMN)

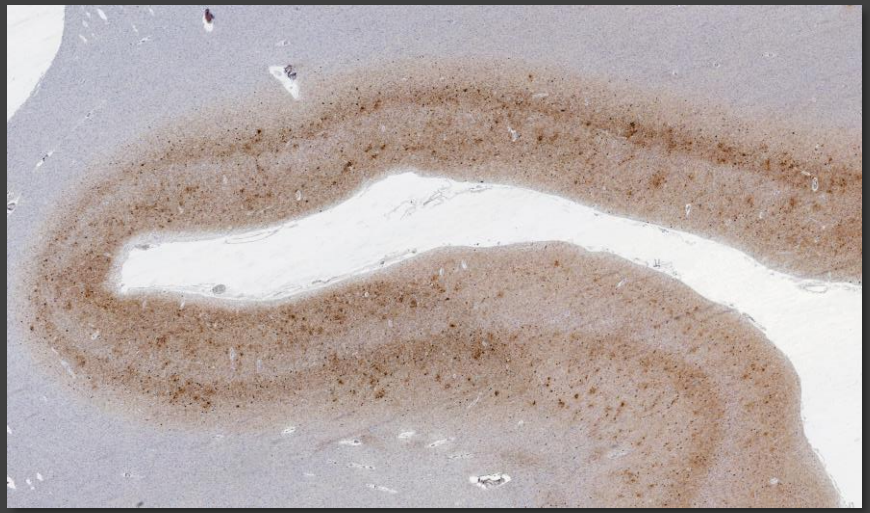
5 Y 6 OCTUBRE 2023
HOTEL SANTO DOMINGO
MADRID

PATOLOGÍA DE LA PROTEÍNA BETA-AMILOIDE: MÁS ALLÁ DE LAS PLACAS

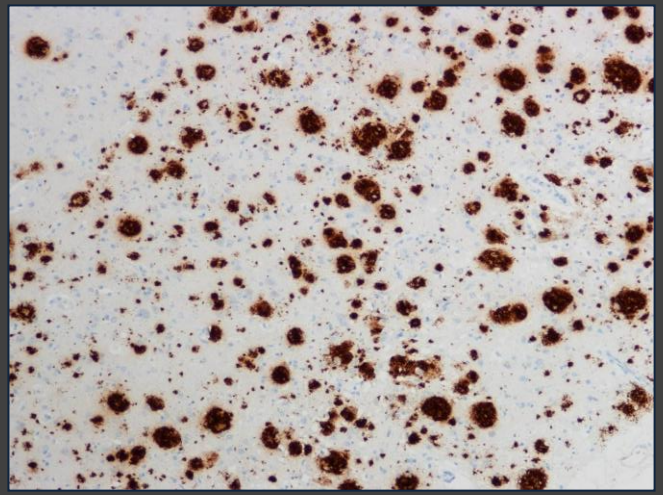


Alberto Rábano
Banco de Tejidos CIEN
Fundación CIEN, ISCIII

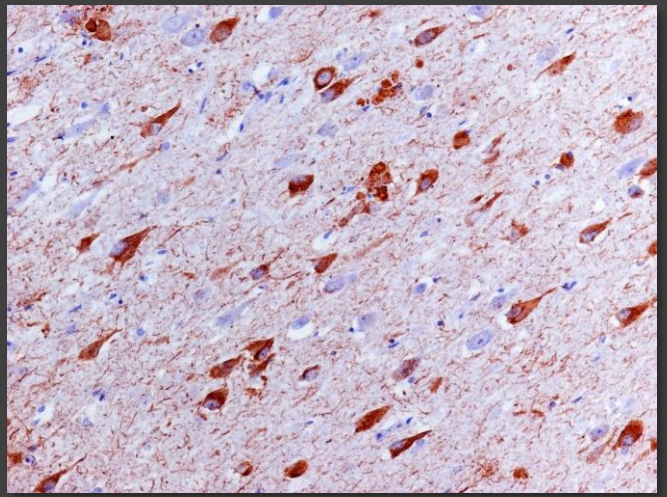




Aβ



Tau



100 años de investigación en la enfermedad de Alzheimer

1976		Cholinergic deficit described
1983	Huntington's genetic linkage	Sequence of Aβ from Alzheimer's amyloid angiopathy
1984		Sequence of Aβ from Down's syndrome from amyloid angiopathy
1985	Cloning of the prion gene	Sequence of Aβ from plaques
1986		Tau as major component of tangles
1987		Cloning of APP and localization to chromosome 21
1989	Mutations in prion gene in CJD/GSS	
1990	Mutations in APP cause HCHWA-D; prion mutations cause neurodegeneration in mice	Alzheimer's disease genetically heterogeneous
1991		APP mutations in Alzheimer's; a descriptive system of cataloguing the neuropathology determined
1993		ApoE4 associated with Alzheimer's; cholinergic therapy approved for AD
1994		APP mutations increase Aβ42
1995		APP transgenic mice made with plaque pathology; presenilins cloned as loci for early onset Alzheimer's
1996		Presenilin mutations shown to alter APP processing

1906

2006

J Hardy, 2006

Table 1. A Summary of the History of Research into Alzheimer's Disease and Related Disorders

Year	Related Developments	Alzheimer's Disease
1902	Improved silver stains	
1906		Alzheimer's case history of Auguste D.
1910		Alzheimer's Disease named
1922	Lewy body described	
1932		First hereditary case described
1962	L-dopa therapy in Parkinson's	
1963/4		Ultrastructure of plaque and tangle by electron microscopy
1968		Recognition of prevalence of disease in the elderly
1976		Cholinergic deficit described
1983	Huntington's genetic linkage	Sequence of Aβ from Alzheimer's amyloid angiopathy
1984		Sequence of Aβ from Down's syndrome from amyloid angiopathy
1985	Cloning of the prion gene	Sequence of Aβ from plaques
1986		Tau as major component of tangles
1987		Cloning of APP and localization to chromosome 21
1989	Mutations in prion gene in CJD/GSS	
1990	Mutations in APP cause HCHWA-D; prion mutations cause neurodegeneration in mice	Alzheimer's disease genetically heterogeneous
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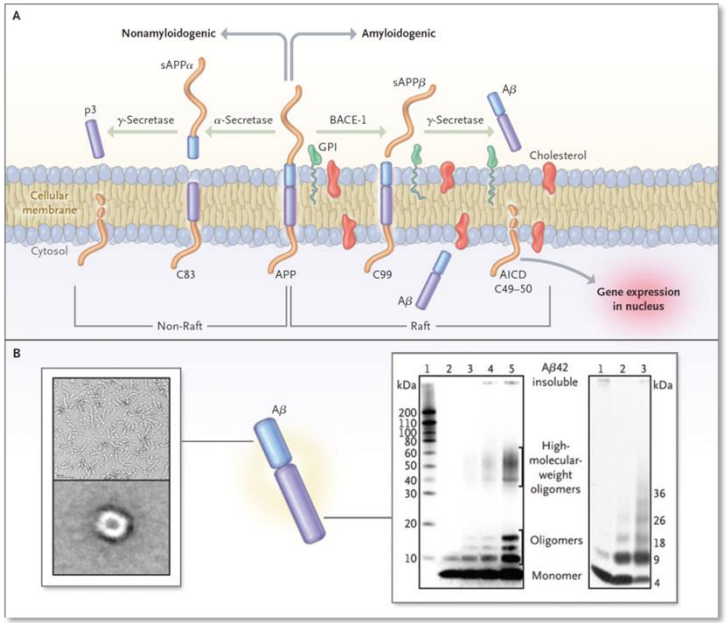
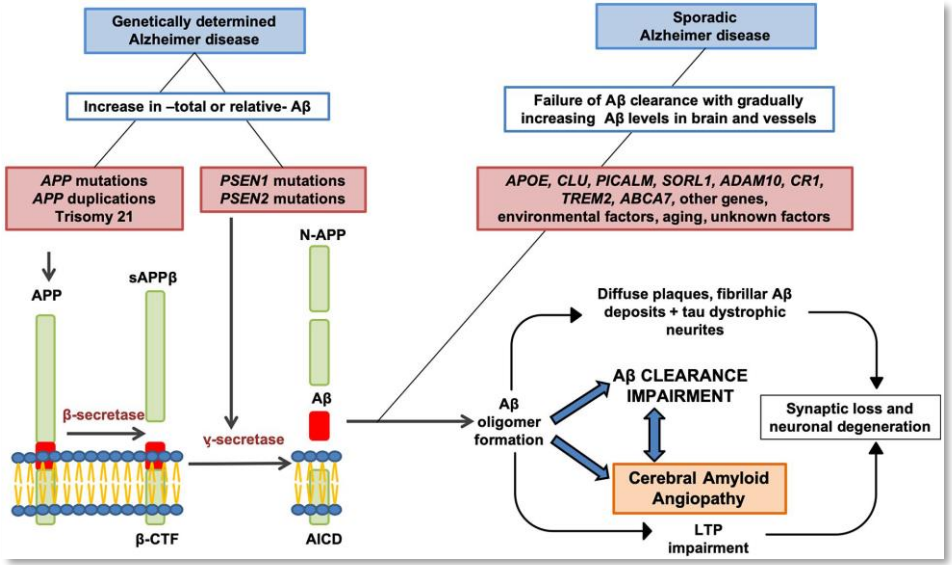
1993		ApoE4 associated with Alzheimer's; cholinergic therapy approved for AD
1994		APP mutations increase Aβ42
1995		APP transgenic mice made with plaque pathology; presenilins cloned as loci for early onset Alzheimer's
1996		Presenilin mutations shown to alter APP processing
1997	Synuclein mutations identified in PD; Synuclein identified as major component of Lewy bodies	
1998	Tau mutations identified in FTDP-17	Presenilins identified as γ-secretase
1999		BACE cloned; Aβ immunization in mice reduces amyloid pathology
2000	Mice with tangles made using FTDP-17 mutations	
2001		Mice with plaques and tangles made
2003		Aβ vaccine trials halted because of side effects

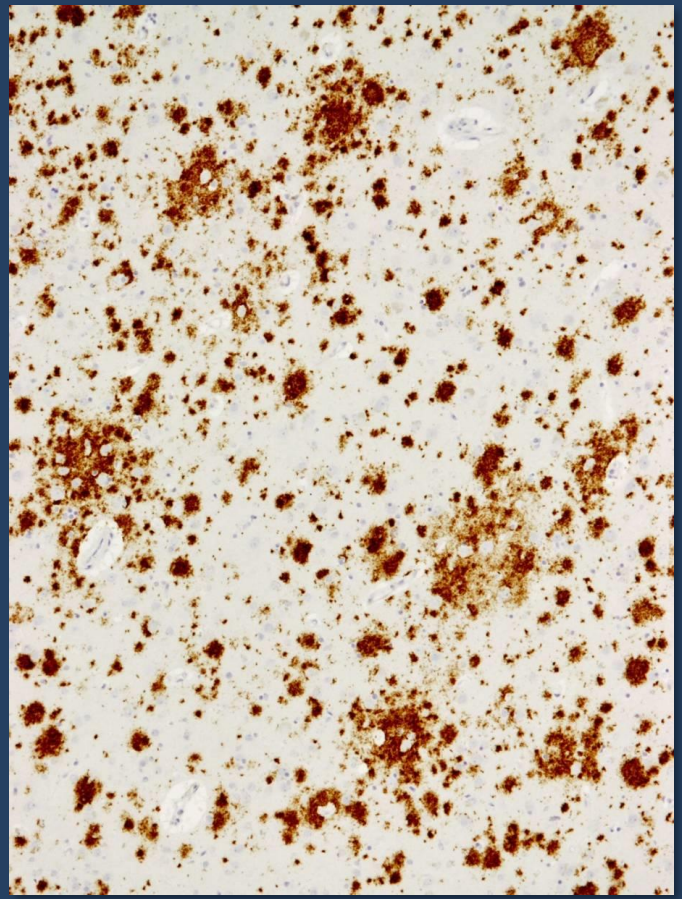


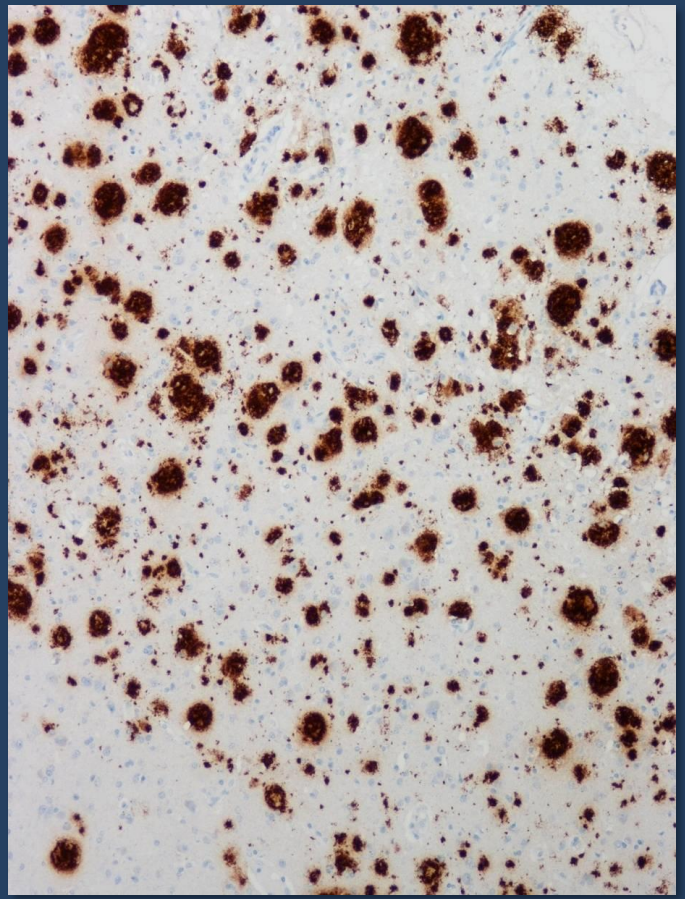
Querfurth & LaFerla, 2010



Carmona-Iragui M *et al*., 2019

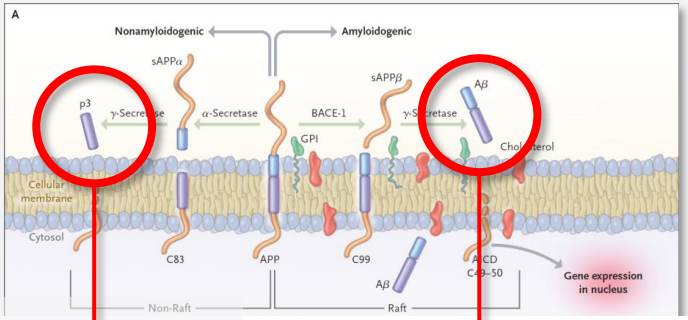
Placas difusas





Placas focales

Inmunotinción β-amiloide

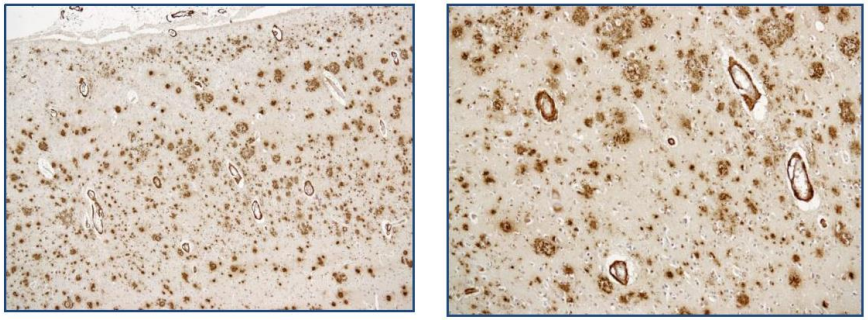


Current Alzheimer Research, 2005, 2, 409-417 409

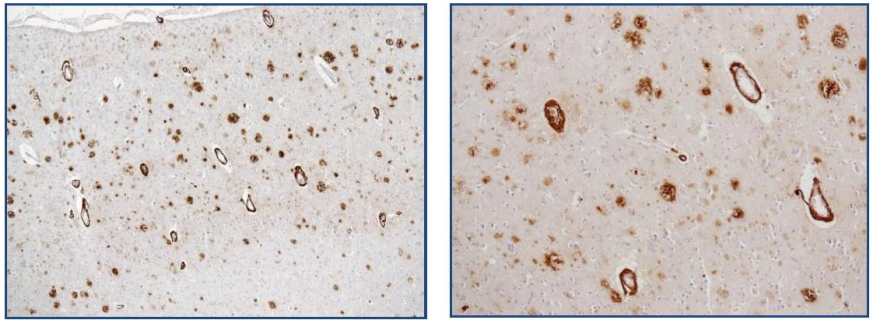
Diversity of Senile Plaques in Alzheimer's Disease as Revealed by a New Monoclonal Antibody that Recognizes an Internal Sequence of the Aβ Peptide

Alberto Rábano[1,*], Adolfo Jiménez-Huete[2], Boris Acevedo[3], Miguel Calero[4], Jorge Ghiso[5], Israel Valdés[4], Jorge Gavilondo[4], Blas Frangione[5] and Enrique Méndez[2]

C42



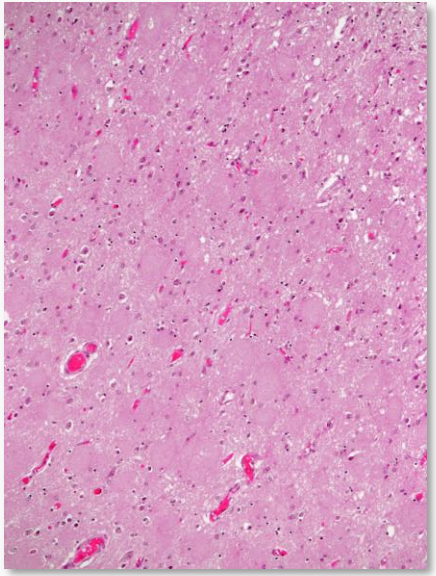
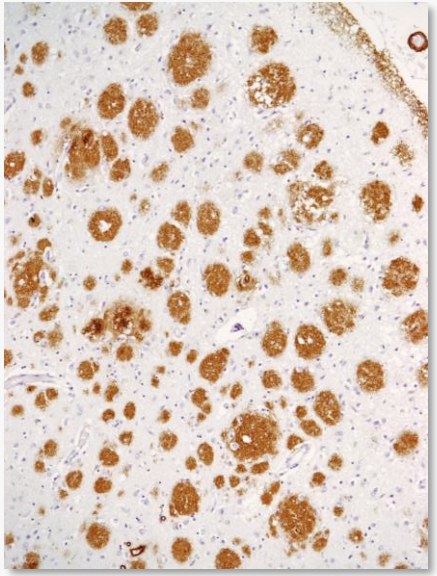
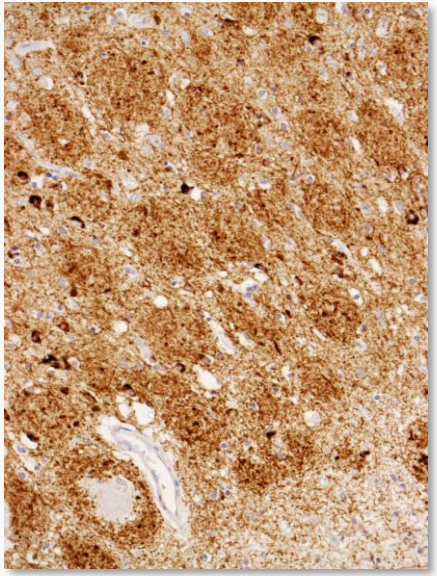
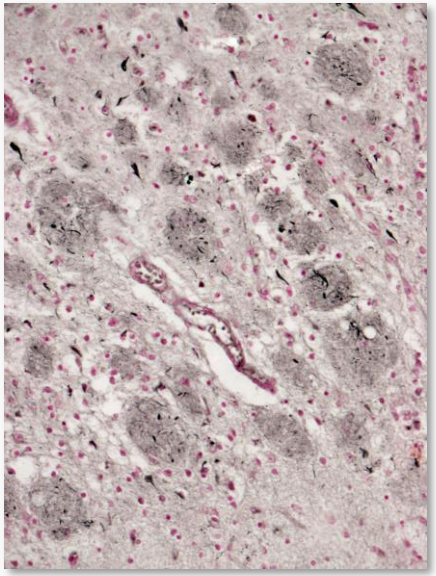
EM5



Péptidos de β-amiloide

Más allá de las placas clásicas…

placas algodonosas

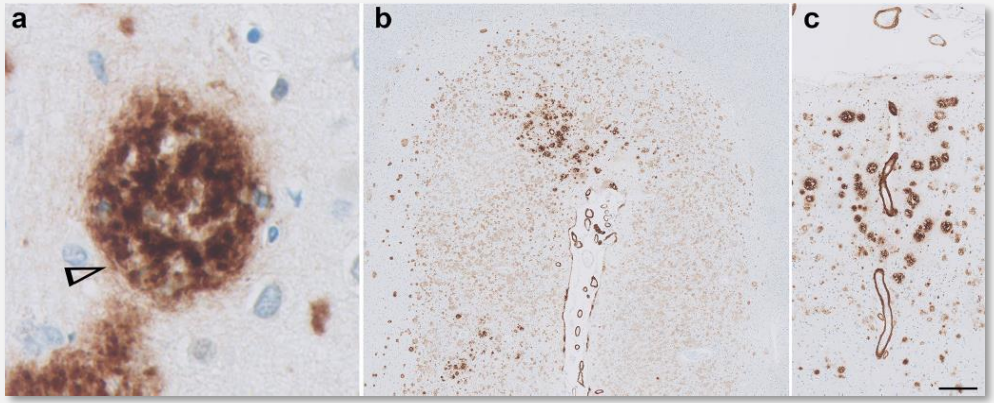
Pro264Leu en el exón 8 de PSEN1.

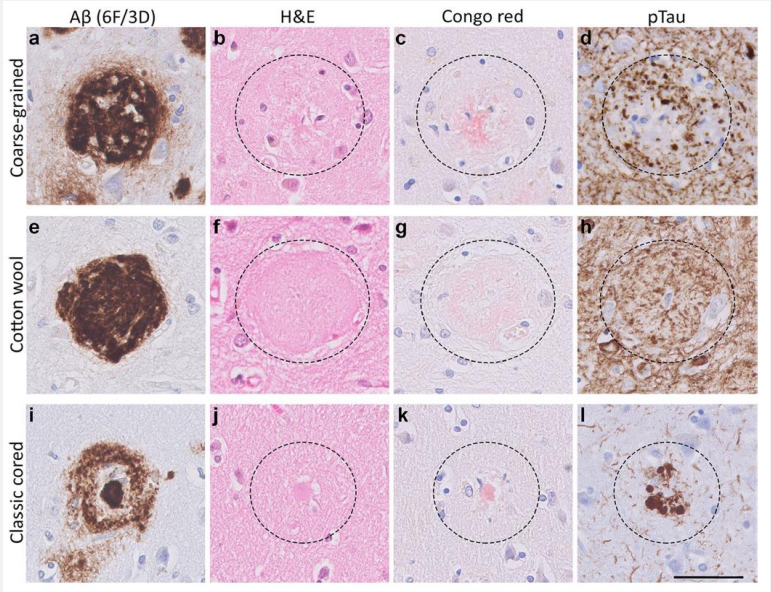
Acta Neuropathologica (2020) 140:811–830
https://doi.org/10.1007/s00401-020-02198-8

ORIGINAL PAPER

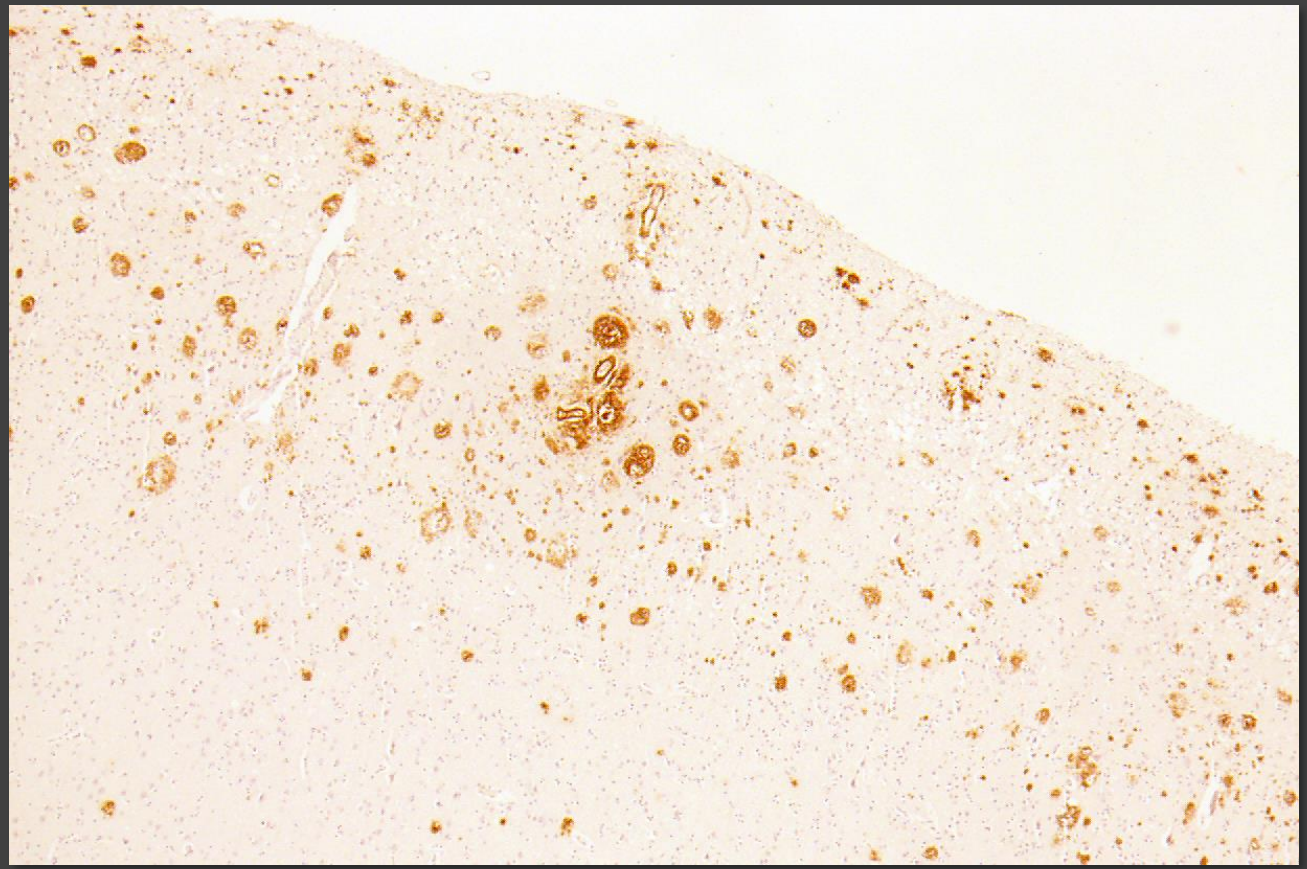
The coarse-grained plaque: a divergent Aβ plaque-type in early-onset Alzheimer's disease

Baayla D. C. Boon[1,2] · Marjolein Bulk[3] · Allert J. Jonker[4] · Tjado H. J. Morrema[2] · Emma van den Berg[4] · Marko Popovic[5] · Jochen Walter[6] · Sathish Kumar[6] · Sven J. van der Lee[1,7] · Henne Holstege[1,7] · Xiaoyue Zhu[8] · William E. Van Nostrand[8] · Remco Natté[9] · Louise van der Weerd[3,10] · Femke H. Bouwman[1] · Wilma D. J. van de Berg[4] · Annemieke J. M. Rozemuller[2] · Jeroen J. M. Hoozemans[2]





Hombre,
ADNC de alta probabilidad de EA,
Inicio clínico con 54 años.



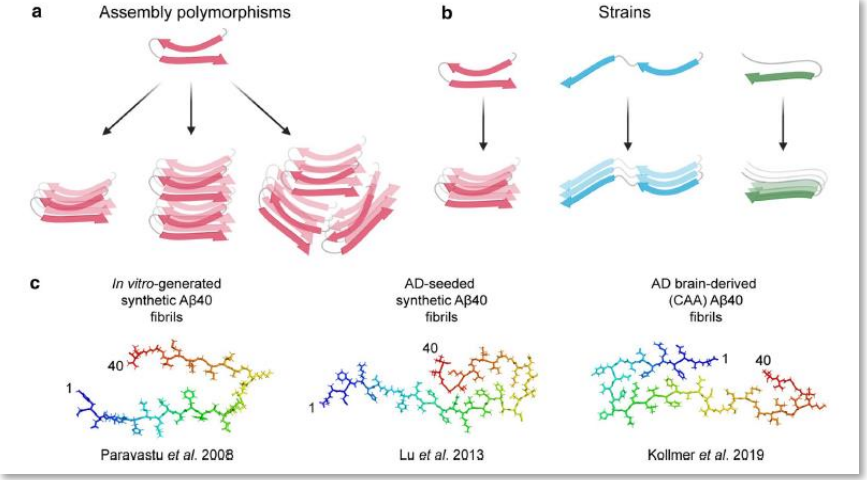
Acta Neuropathologica
https://doi.org/10.1007/s00401-020-02201-2

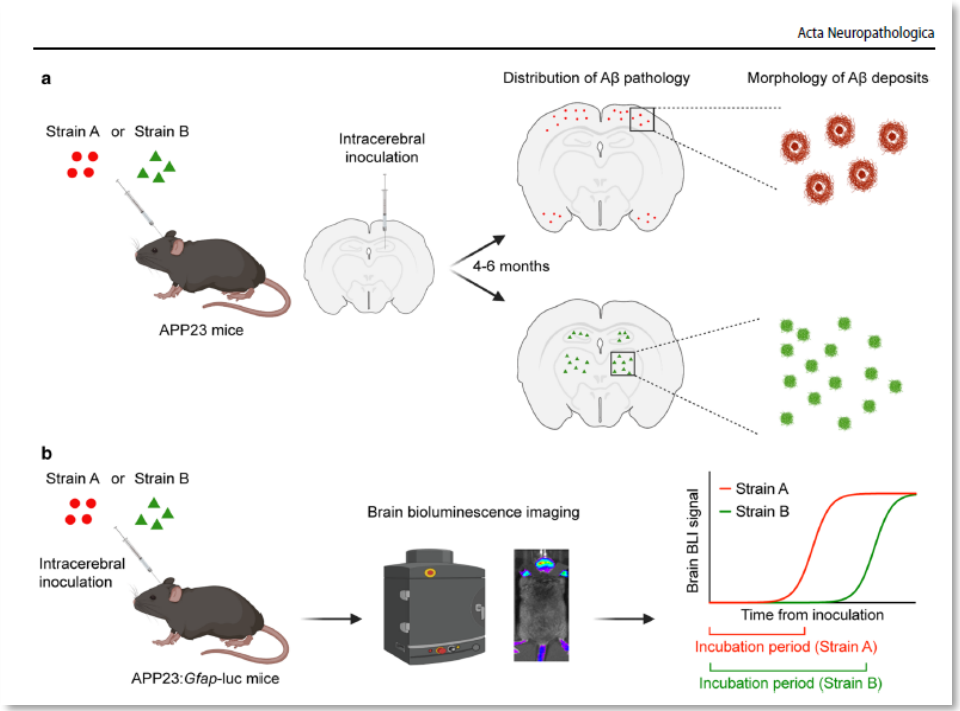
REVIEW

The existence of Aβ strains and their potential for driving phenotypic heterogeneity in Alzheimer's disease

Heather H. C. Lau[1,2] · Martin Ingelsson[1,2,3] · Joel C. Watts[1,2]

Received: 24 June 2020 / Revised: 23 July 2020 / Accepted: 24 July 2020





Acta Neuropathol (2012) 123:1–11
DOI 10.1007/s00401-011-0910-3

CONSENSUS PAPER

National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach

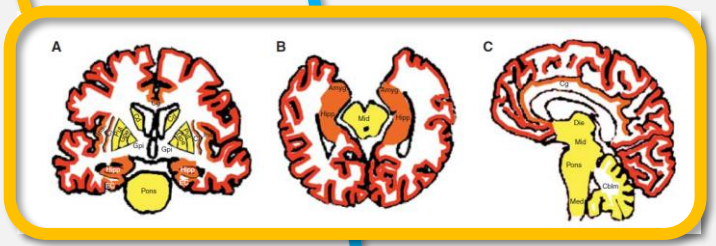
Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman

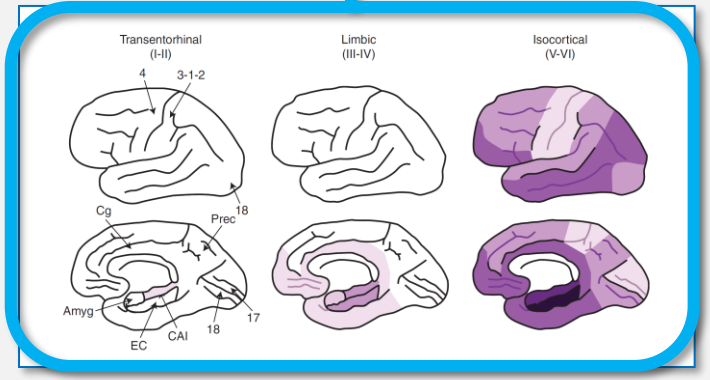
Table 2 "ABC" score for AD neuropathologic change

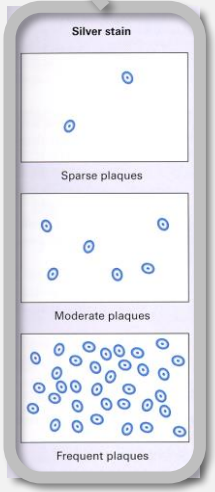
"A"	Thal Phase for Aβ plaques [57]	"B"	Braak and Braak NFT stage [14,15]	"C"	CERAD neuritic plaque score [41]
0	0	0	None	0	None
1	1 or 2	1	I or II	1	Sparse
2	3	2	III or IV	2	Moderate
3	4 or 5	3	V or VI	3	Frequent

Table 3 "ABC" score for level of AD neuropathologic change

AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High







Alzheimer's disease neuropathological change: A1 B2 C3

Más allá de la enfermedad de Alzheimer…

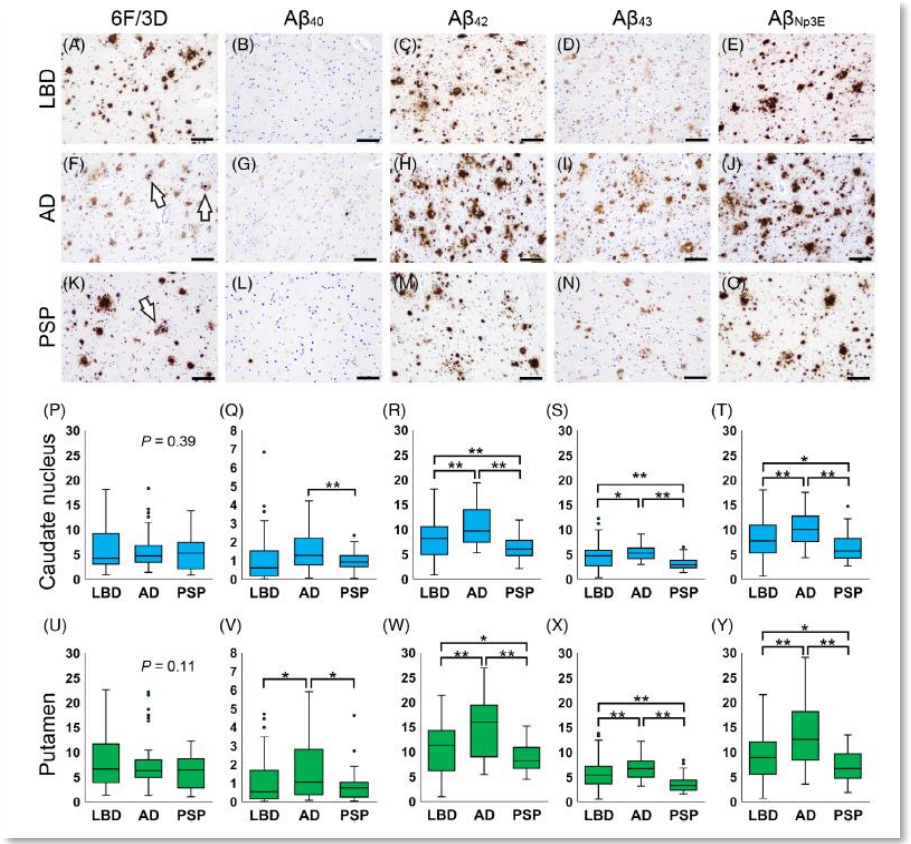
Received: 14 July 2023 | Accepted: 18 August 2023
DOI: 10.1111/bpa.13210

RESEARCH ARTICLE

Brain Pathology

The molecular spectrum of amyloid-beta (Aβ) in neurodegenerative diseases beyond Alzheimer's disease

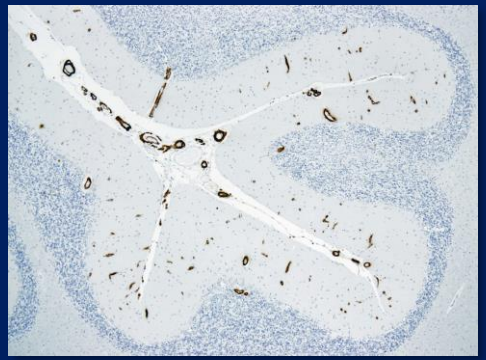
Shojiro Ichimata[1,2,3] | Koji Yoshida[1,2,3] | Jun Li[1] | Ekaterina Rogaeva[1] | Anthony E. Lang[1,4] | Gabor G. Kovacs[1,2,4,5]

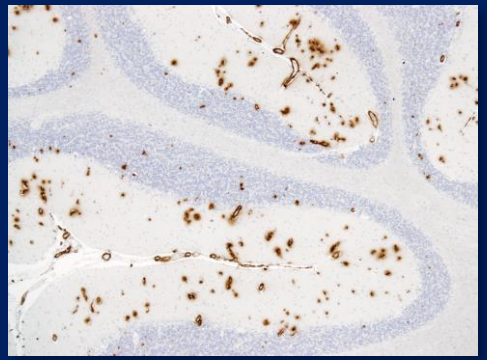


Más allá de las placas…

…la angiopatía amiloide cerebral (AAC)

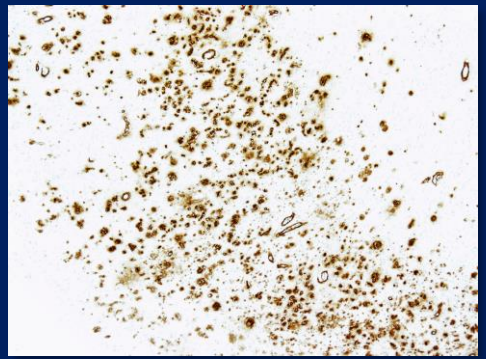
AAC de tipo 2

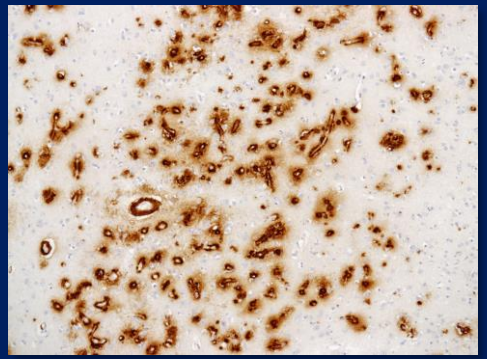




Córtex cerebeloso

AAC de tipo 1





Isocórtex

Acumulación progresiva de β-amiloide en las arterias leptomeníngeas, arteriolas penetrantes y capilares.

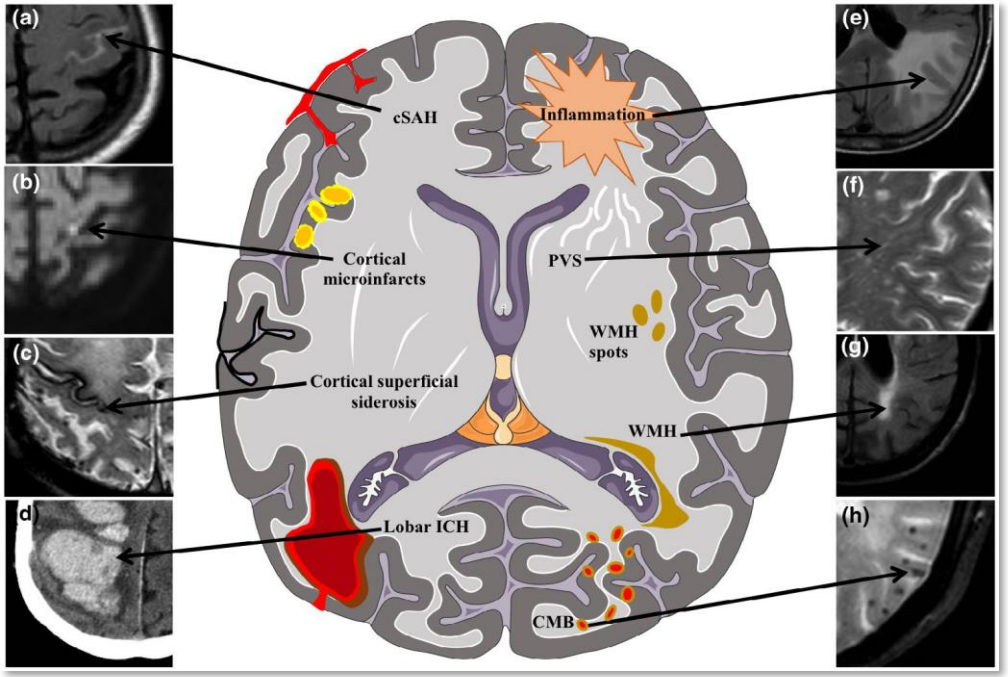
Presente en 20-40% de personas mayores sin demencia y en 50-60% de los pacientes con demencia.

Se asocia a marcadores de enfermedad de pequeño vaso en RM, y entre ellas las mxhemorargias lobares son altamente predictivas de AAC.

AAC es una causa principal de hemorragia lobar intracerebral espontánea.

AAC contribuye de forma independiente al deterioro cognitivo.

Se presenta como enfermedad esporádica, genética y yatrogénica. (ApoE como gen de riesgo)



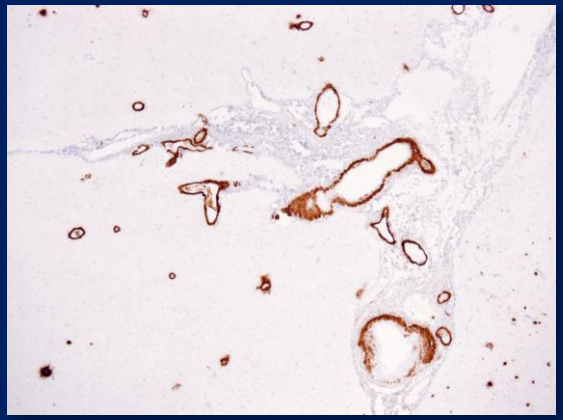
- Hemorragia subaracnoidea atraumática de la convexidad
- Microinfartos corticales
- Siderosis cortical superficial
- Hemorragia intracerebral lobar
- Reacción inflamatoria
- Espacios perivasculares dilatados
- Hiperintensidades en la sustancia blanca
- Microhemorragias córtico-subcorticales

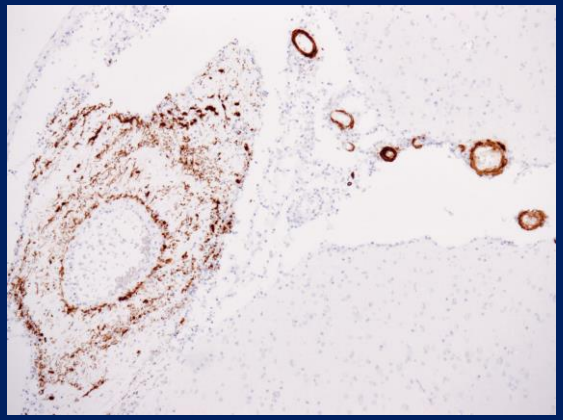
Carmona-Iragui M *et al*., 2019

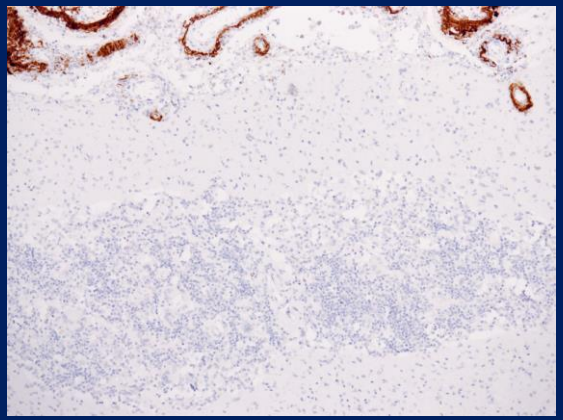
Mujer de 62 años.

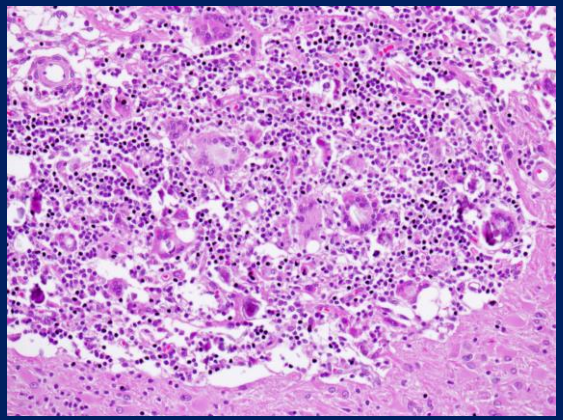
Crisis comiciales generalizadas.

RM: Lesión en lóbulo temporal derecho, ínsula, compatible con neoplasia vs. esclerosis mesial.









doi:10.1093/brain/aww214 BRAIN 2016: Page 1 of 13 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment

Olivia A. Skrobot,[1] Johannes Attems,[2] Margaret Esiri,[3] Tibor Hortobágyi,[4,5] James W. Ironside,[6] Rajesh N. Kalaria,[2] Andrew King,[7] George A. Lammie,[8] David Mann,[9] James Neal,[10] Yoav Ben-Shlomo,[11] Patrick G. Kehoe[1] and Seth Love[1]

Escala de AAC (0 – 4)

Escala de arterioloesclerosis (0 – 4)

Low Moderate High

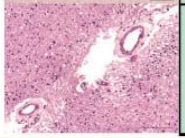
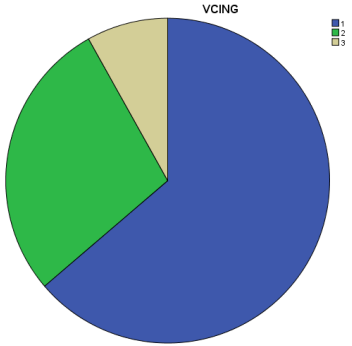
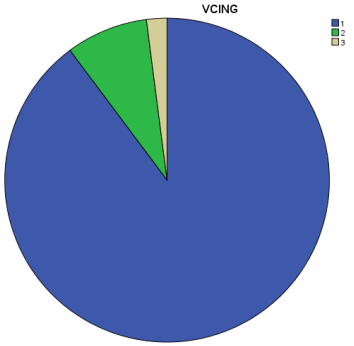
Likelihood that cerebral vascular disease contributed to cognitive impairment		Low (<50%)			Moderate (50-80%)		High (>80%)		
One or more large (> 10 mm) subcortical cerebral infarcts		-	-	-	+	-	+	+	+
Moderate or severe occipital leptomeningeal CAA		-	+	-	-	+	+	-	+
Moderate or severe occipital white matter arteriolosclerosis		-	-	+	-	+	-	+	+

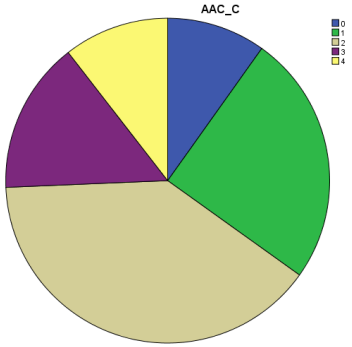
Figure 1 VCING model estimating the likelihood that cerebrovascular disease contributed to cognitive impairment. Combinations of the three main determinants—at least one large (>10 mm diameter) infarct, moderate/severe occipital leptomeningeal CAA, and moderate/severe arteriolosclerosis in the occipital white matter—are used to assign a low, intermediate or high likelihood that cerebrovascular disease contributed to cognitive impairment in an individual case. Scale bars in the *top*, *middle* and *bottom* photomicrographs represent 1 mm, 250 μm and 100 μm, respectively.

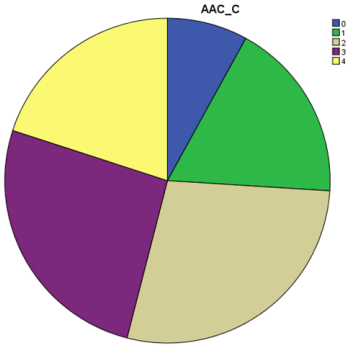
VCING (probabilidad baja, media o alta)





Escala de AAC (0 – 4)





Cohorte CAV-CAFRS (LOAD) (n = 167)

Cohorte EOAD (n = 58)

LETTER
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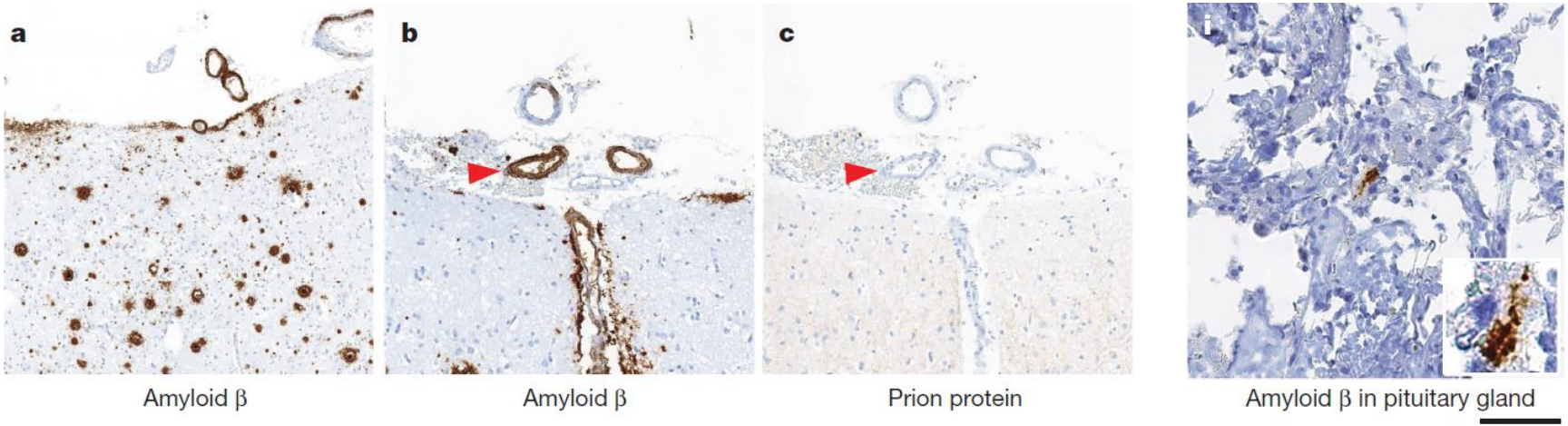
doi:10.1038/nature15369

Evidence for human transmission of amyloid-β pathology and cerebral amyloid angiopathy

Zane Jaunmuktane[1], Simon Mead[2,3,4], Matthew Ellis[3], Jonathan D. F. Wadsworth[2,3], Andrew J. Nicoll[2,3], Joanna Kenny[2,4], Francesca Launchbury[3], Jacqueline Linehan[2], Angela Richard-Loendt[3], A. Sarah Walker[5], Peter Rudge[2,4], John Collinge[2,3,4] & Sebastian Brandner[1,2,3]

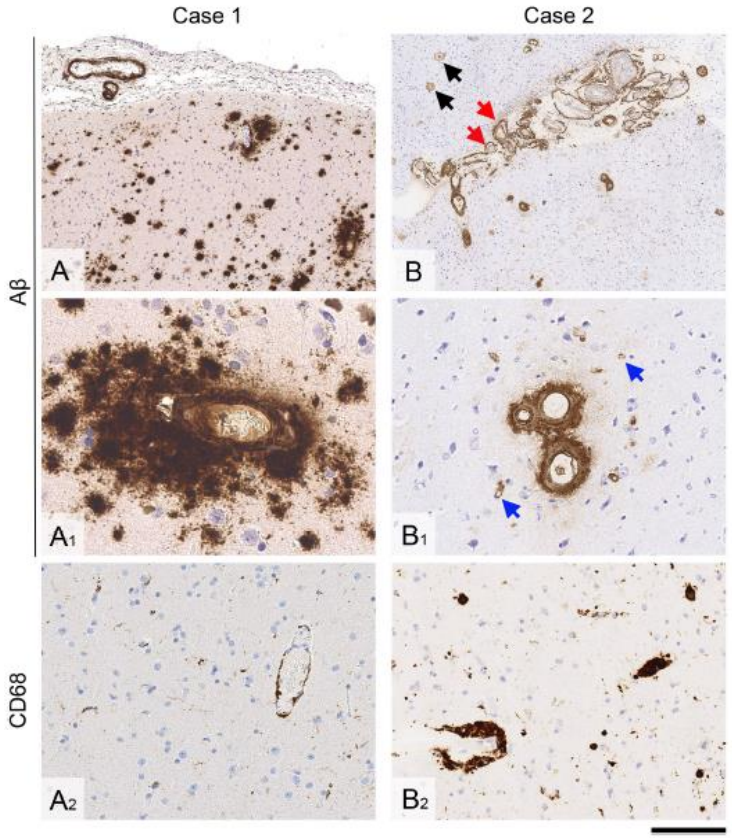
ition but do not co-localize with Aβ deposits. While there is no suggestion that Alzheimer's disease is a contagious disease and no supportive evidence from epidemiological studies that Alzheimer's disease is transmissible, notably by blood transfusion[28,29], our findings should prompt consideration of whether other known iatrogenic routes of prion transmission, including surgical instruments and blood products, may also be relevant to Aβ and other proteopathic seeds seen in neurodegenerative diseases. Aβ seeds are known, like prions, to adhere to metal surfaces and to resist formaldehyde inactivation and conventional hospital sterilisation[30].



Amyloid β | Amyloid β | Prion protein | Amyloid β in pituitary gland

Early Onset Cerebral Amyloid Angiopathy following Childhood Exposure to Cadaveric Dura

Gargi Banerjee, MRCP [1], Matthew E. Adams, FRCR,[2] Zane Jaunmuktane, FRCPath,[3,4] G. Alistair Lammie, FRCPath,[5] Ben Turner, MD,[6] Mushtaq Wani, FRCP,[7] Inder M. S. Sawhney, DM,[7] Henry Houlden, PhD,[3] Simon Mead, PhD,[8,9] Sebastian Brandner, MD, FRCPath,[4,10] and David J. Werring, FRCP[1]

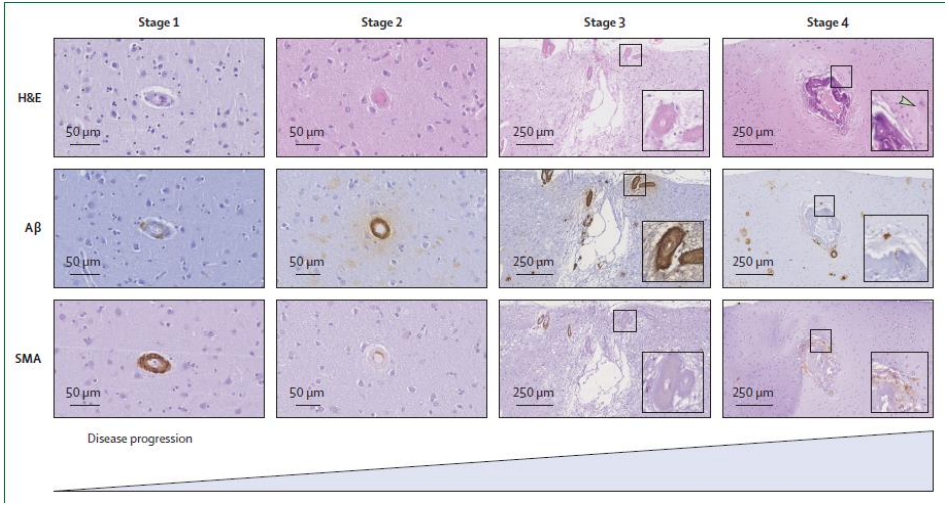


Caso 1: hombre de 48 a., neurocirugía a los 11 a.

Caso 2: hombre de 39 a., cirugía carotídea a los 11 a.

Progression of cerebral amyloid angiopathy: a pathophysiological framework

Emma A Koemans, Jasmeer P Chhatwal*, Susanne J van Veluw*, Ellis S van Etten, Matthias J P van Osch, Marianne A A van Walderveen, Hamid R Sohrabi, Mariel G Kozberg, Zahra Shirzadi, Gisela M Terwindt, Mark A van Buchem, Eric E Smith, David J Werring, Ralph N Martins, Marieke J H Wermer*, Steven M Greenberg**



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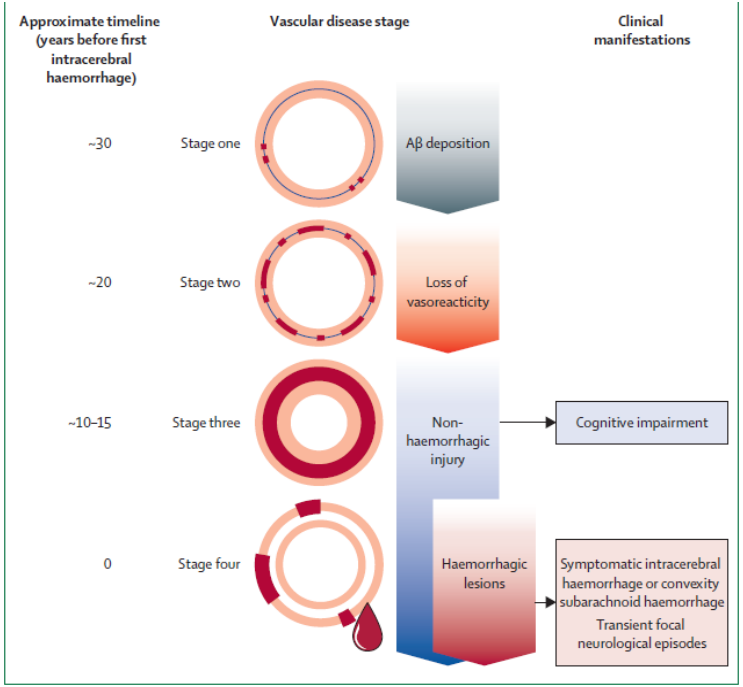

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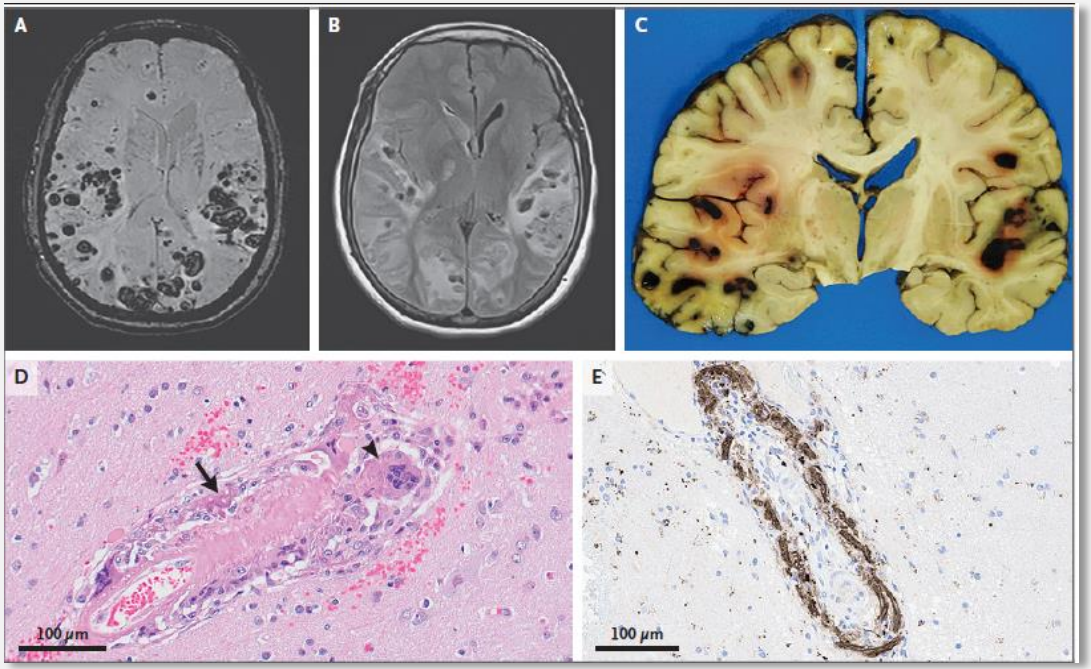
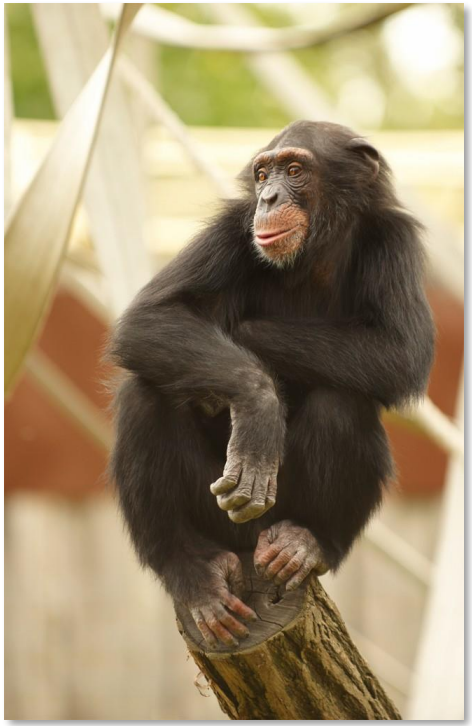
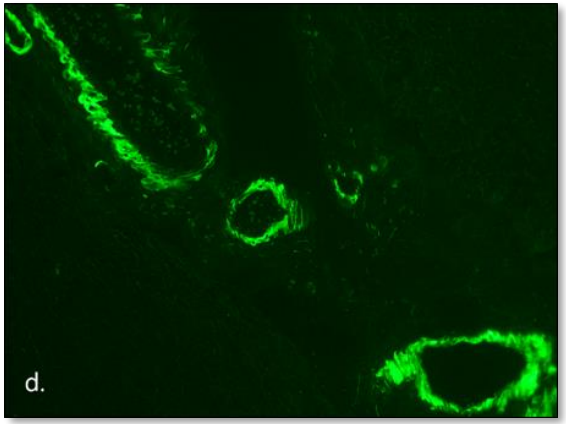
Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke

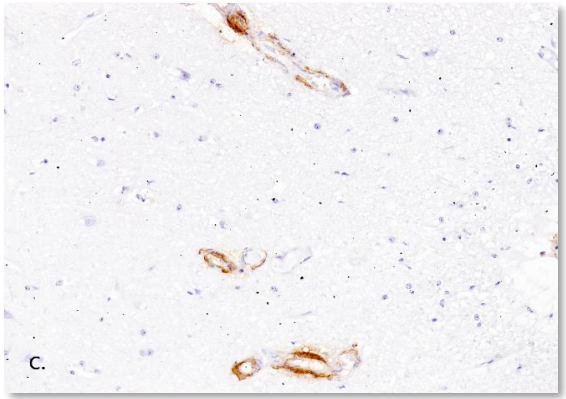
N ENGL J MED 388;5 NEJM.ORG FEBRUARY 2, 2023







Tioflavina S



Inmunotinción para β-amiloide

¡Gracias!

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