CURSO NACIONAL DE NEURORRADIOLOGÍA

S.E.N.R Sociedad Española de Neurorradiología

Radiología en la Patología Neurodegenerativa, Desmielinizante e Infecciosa del SNC

15 y 16 de febrero de 2024 | MADRID

Sede: CINESA. C/ Fuencarral 136

Complicaciones de las nuevas terapias en patología neurodegenerativa: evaluación neurorradiológica

Dr. Pablo Domínguez

Clínica Universidad de Navarra

No tengo conflictos de interés

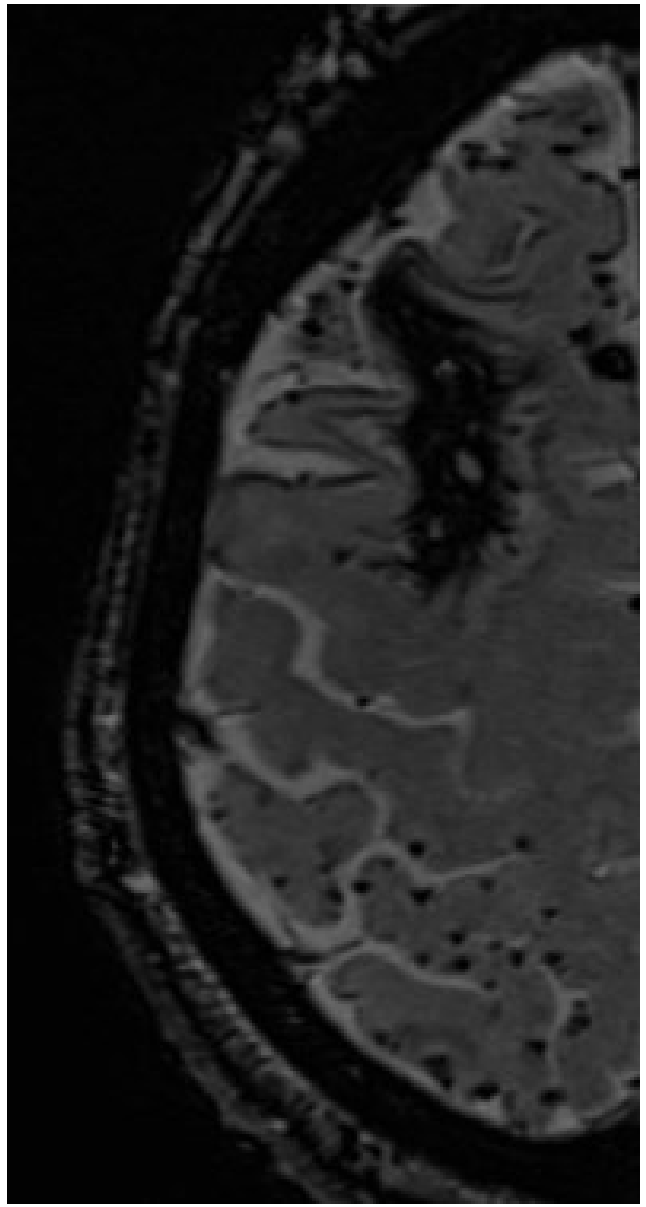
Introducción

Angiopatía amiloide cerebral

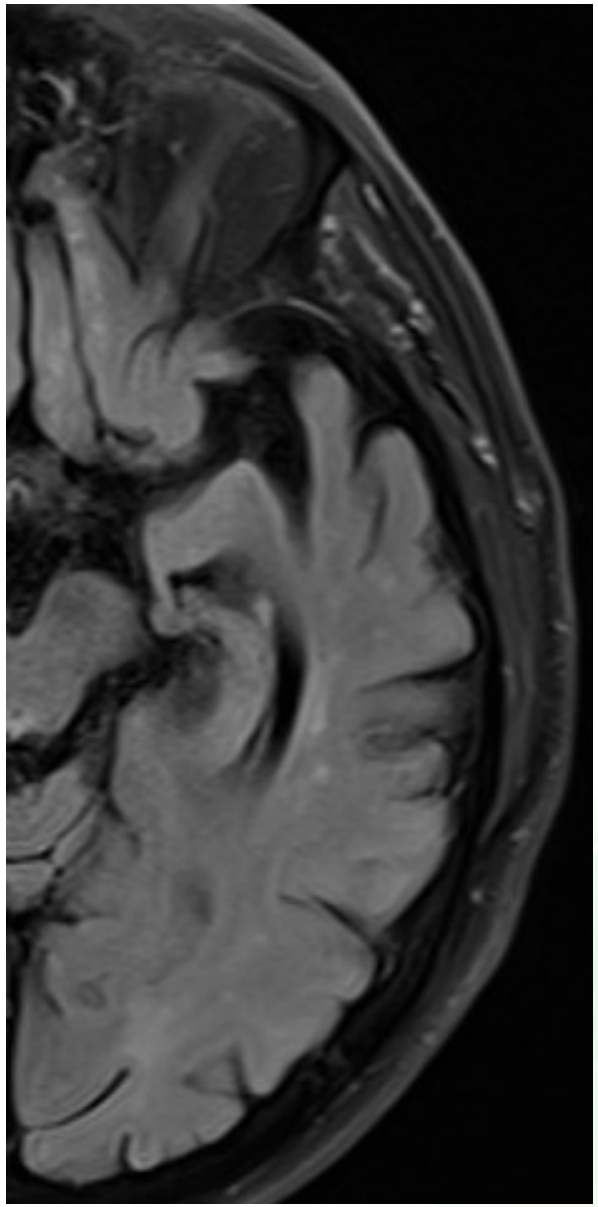
Angiopatía amiloide inflamatoria

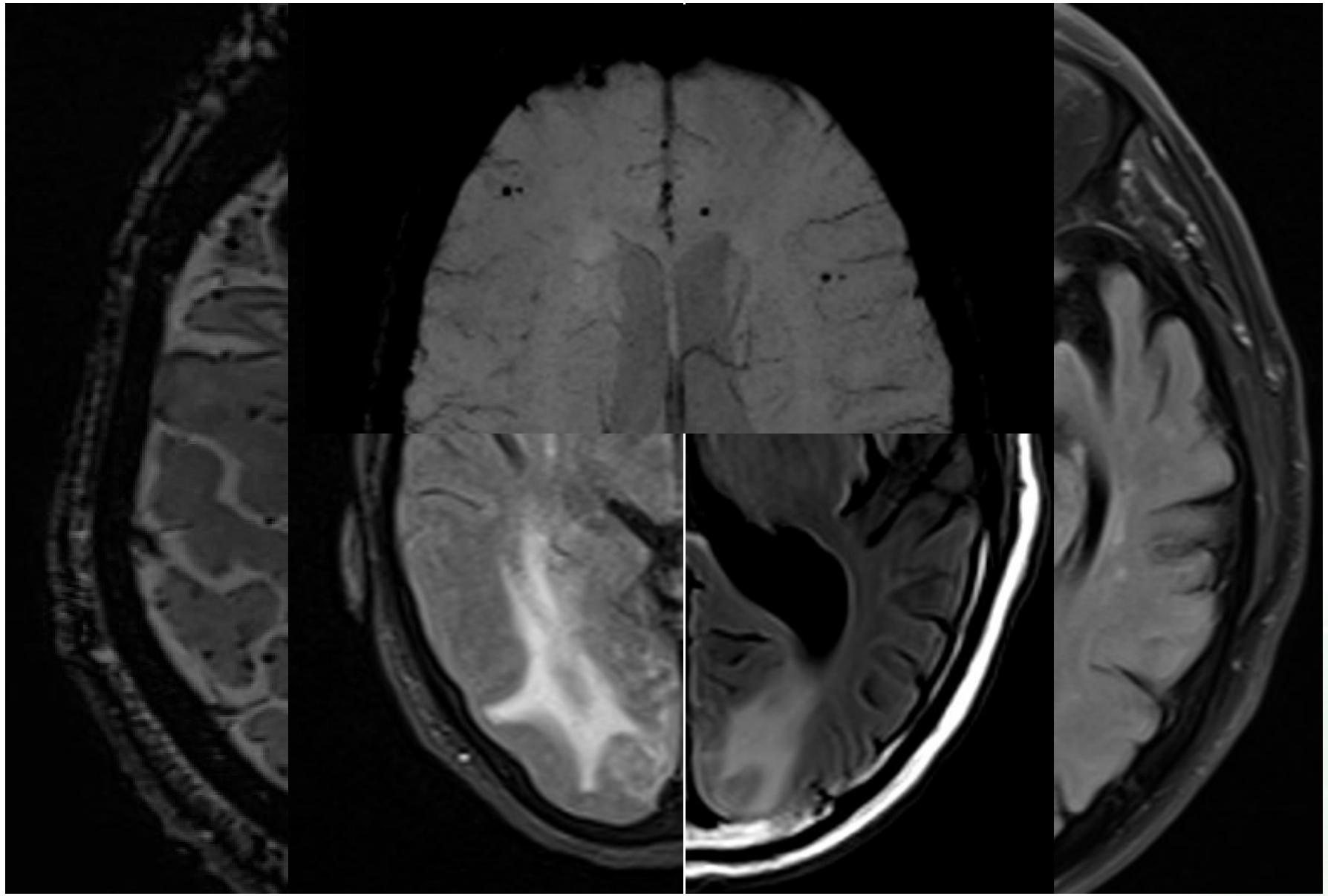
Enfermedad de Alzheimer

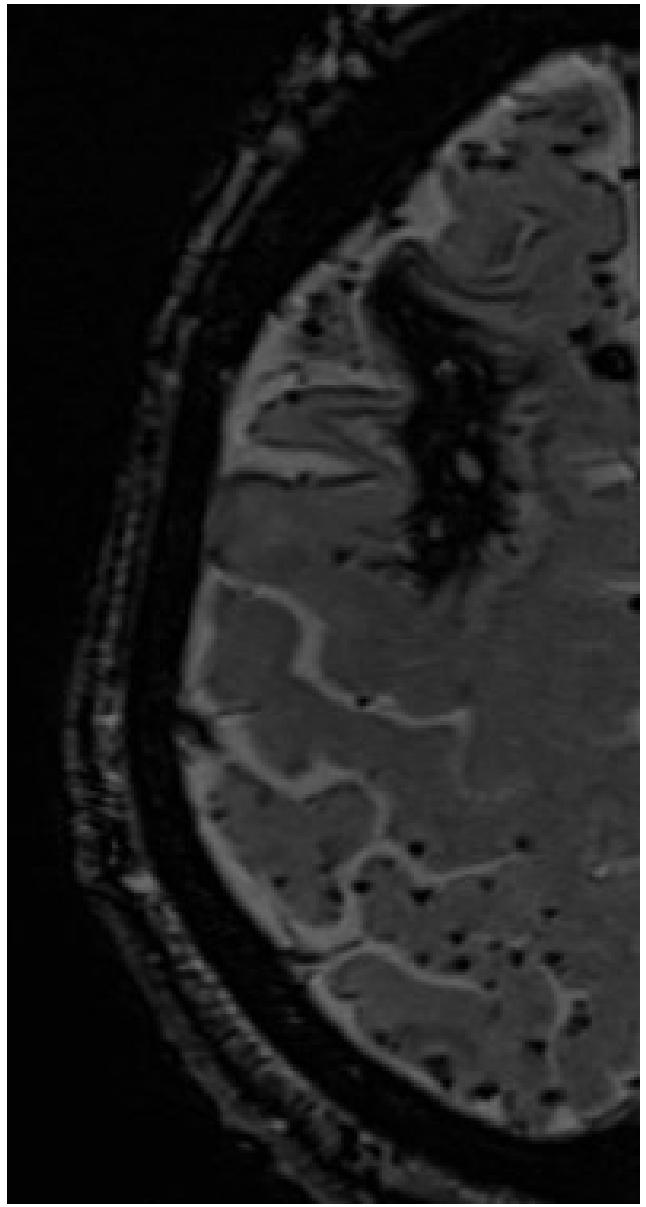
Complicaciones de las nuevas terapias contra el β-amiloide (ARIA)



AAC vs EA

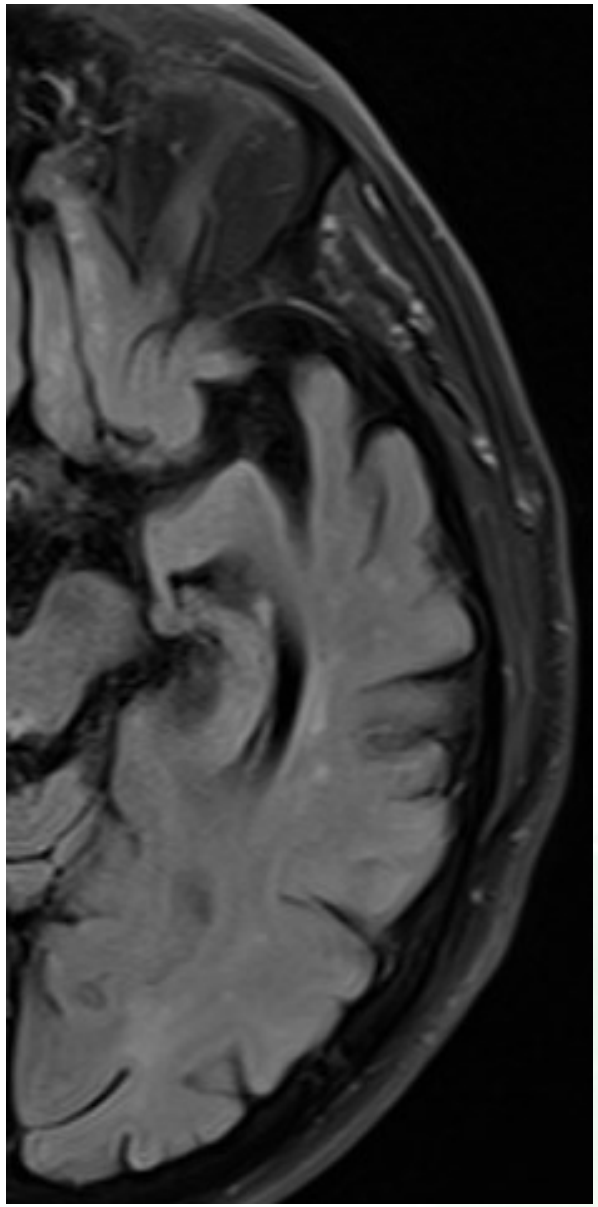




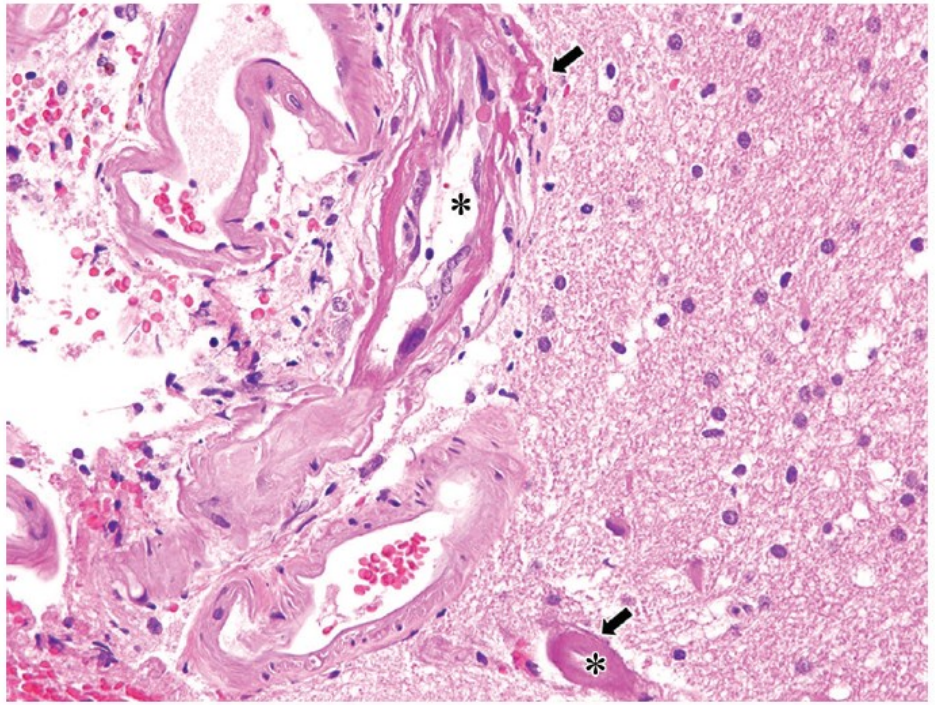


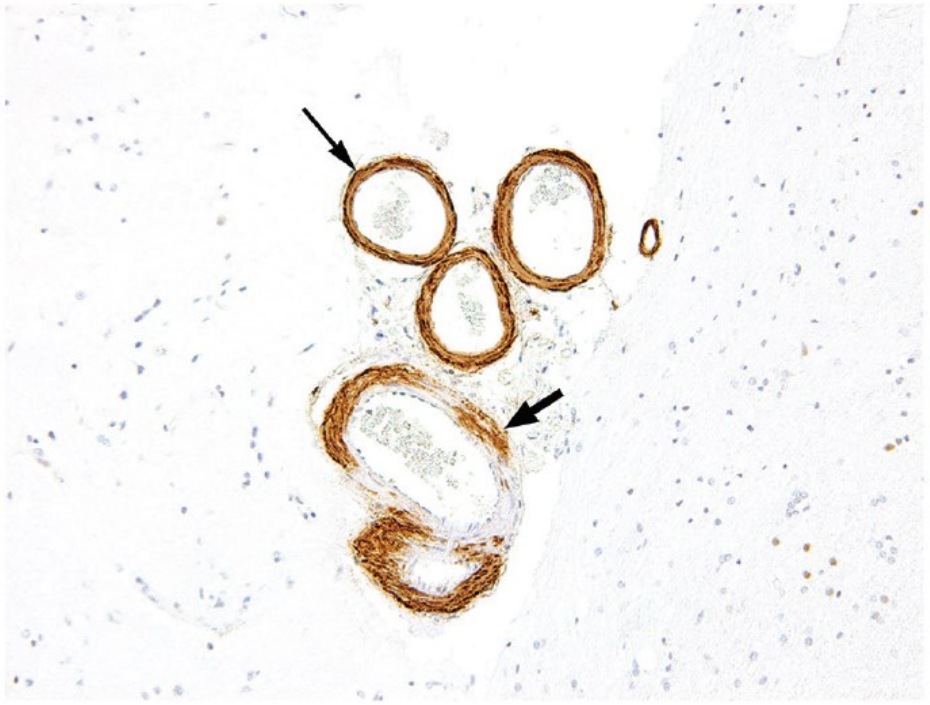
AAC vs EA

βA-40	βA-42
Pared vascular	Matriz extraclr

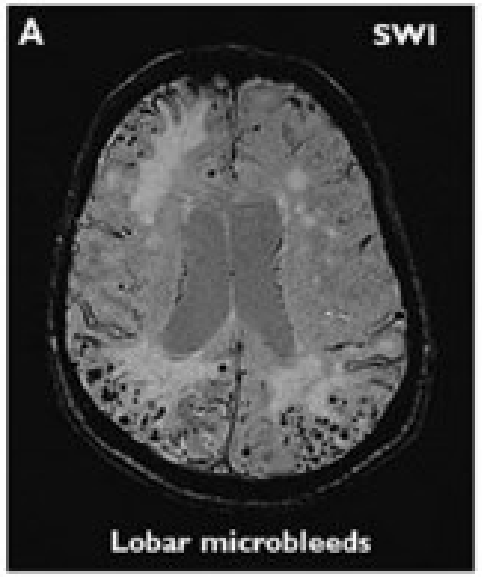


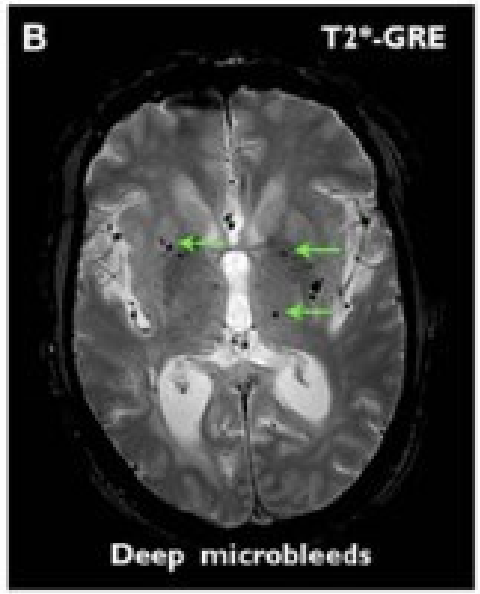
Angiopatía amiloide cerebral (AAC)

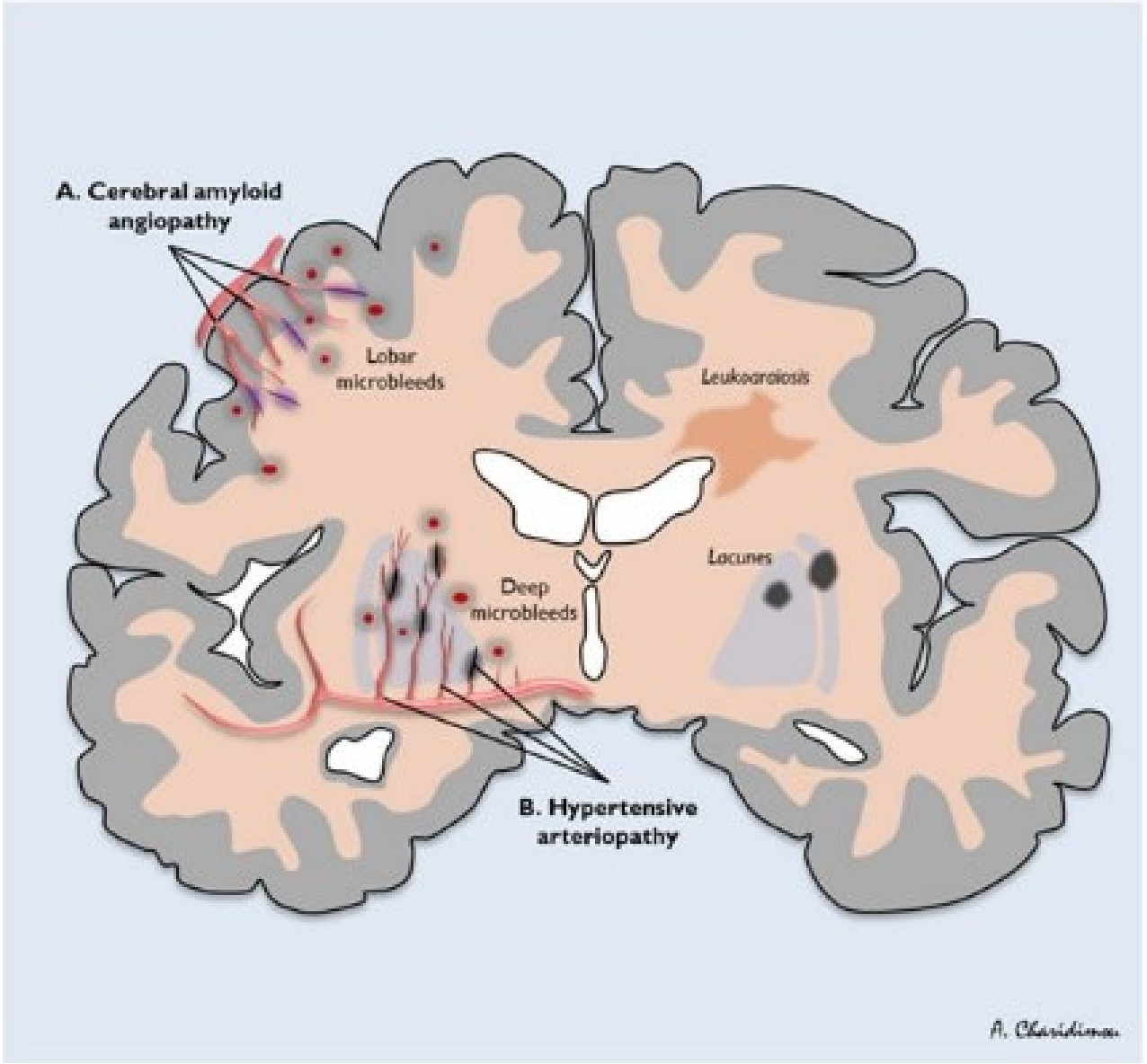




Miller-Thomas MM et al. RadioGraphics 2016; 36:1147–1163



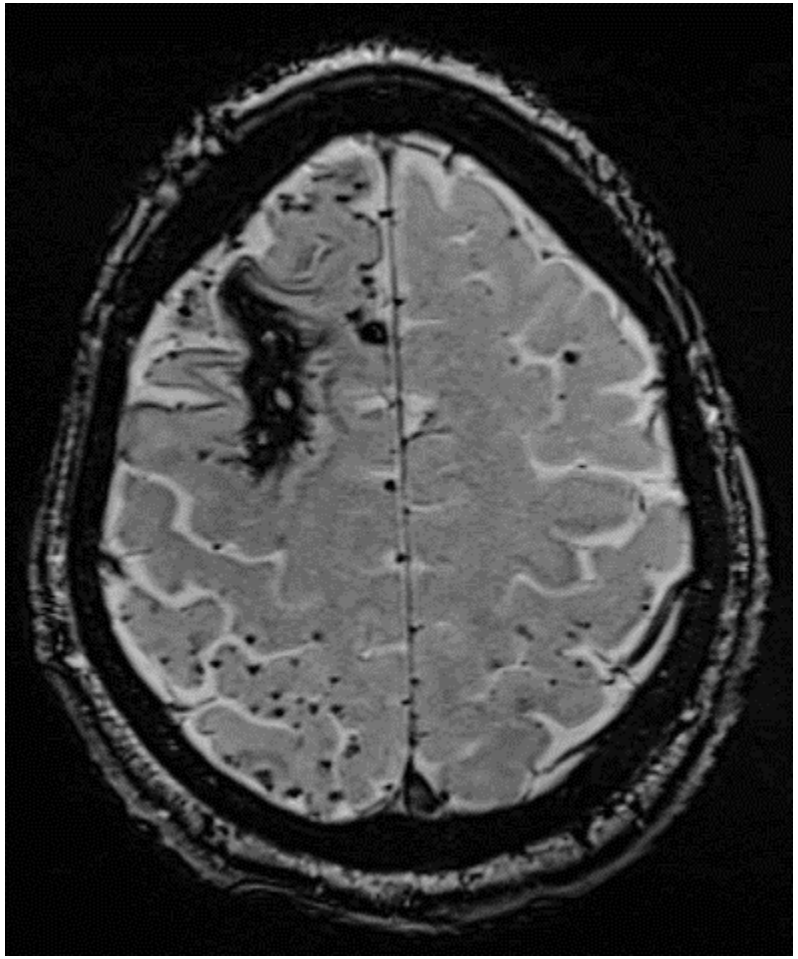


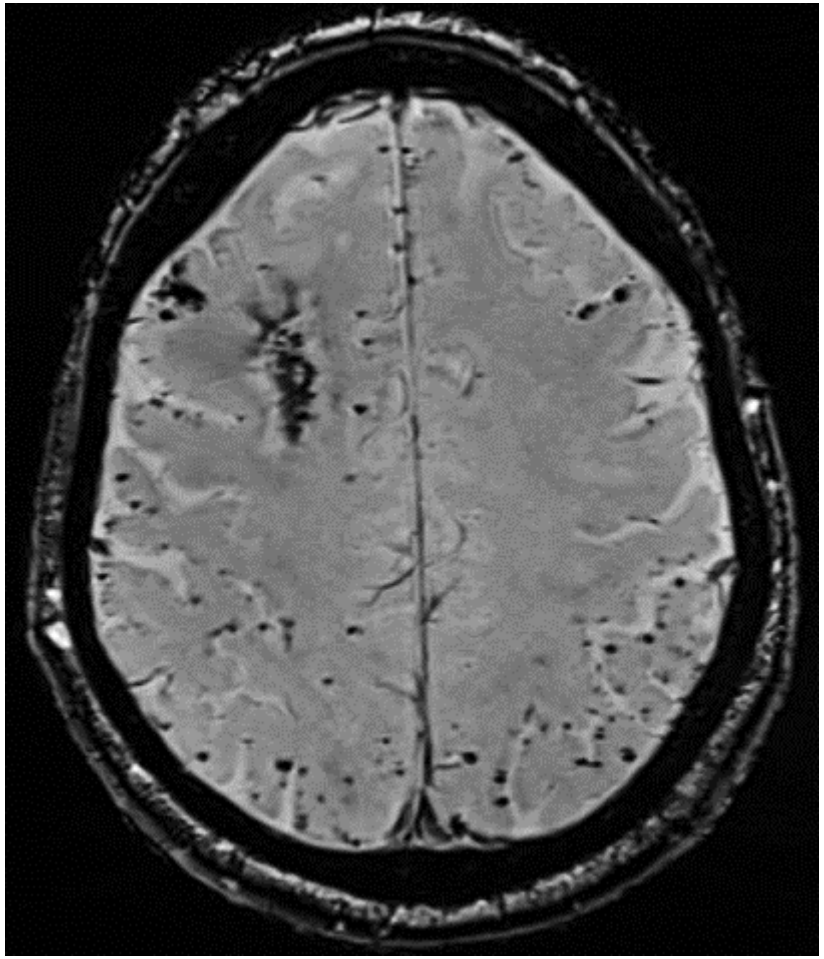


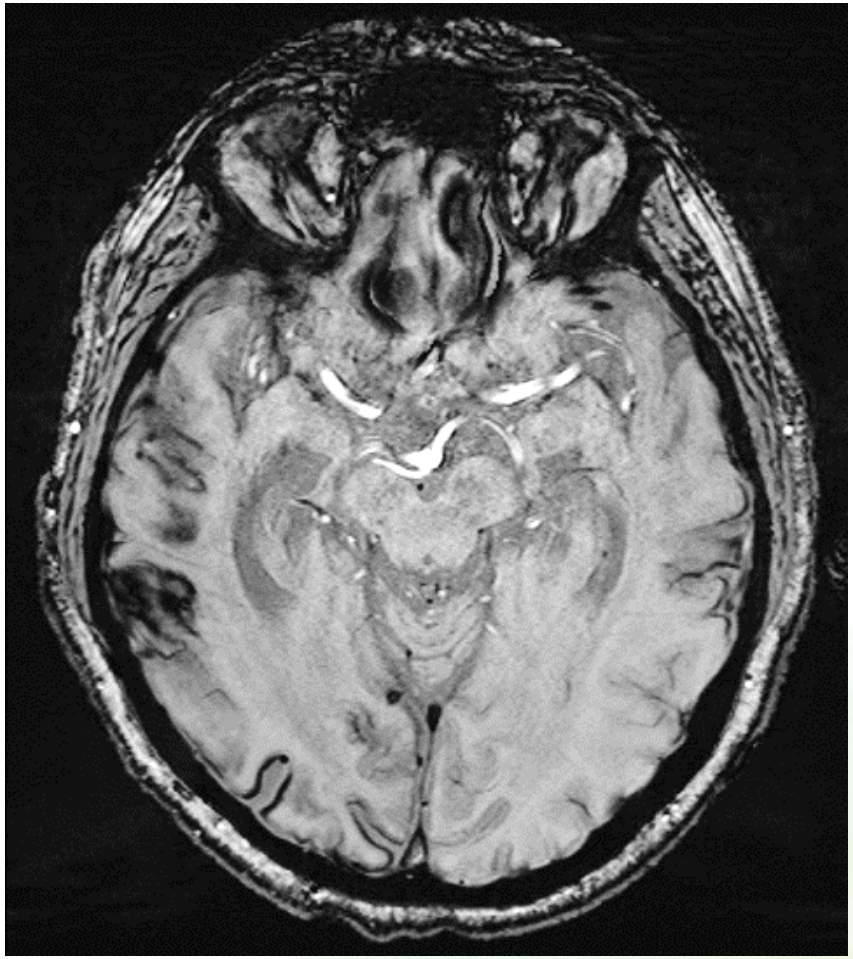
- Hematomas lobares, microhemorragias periféricas y HSA/siderosis superficial como orientadores a AAC.

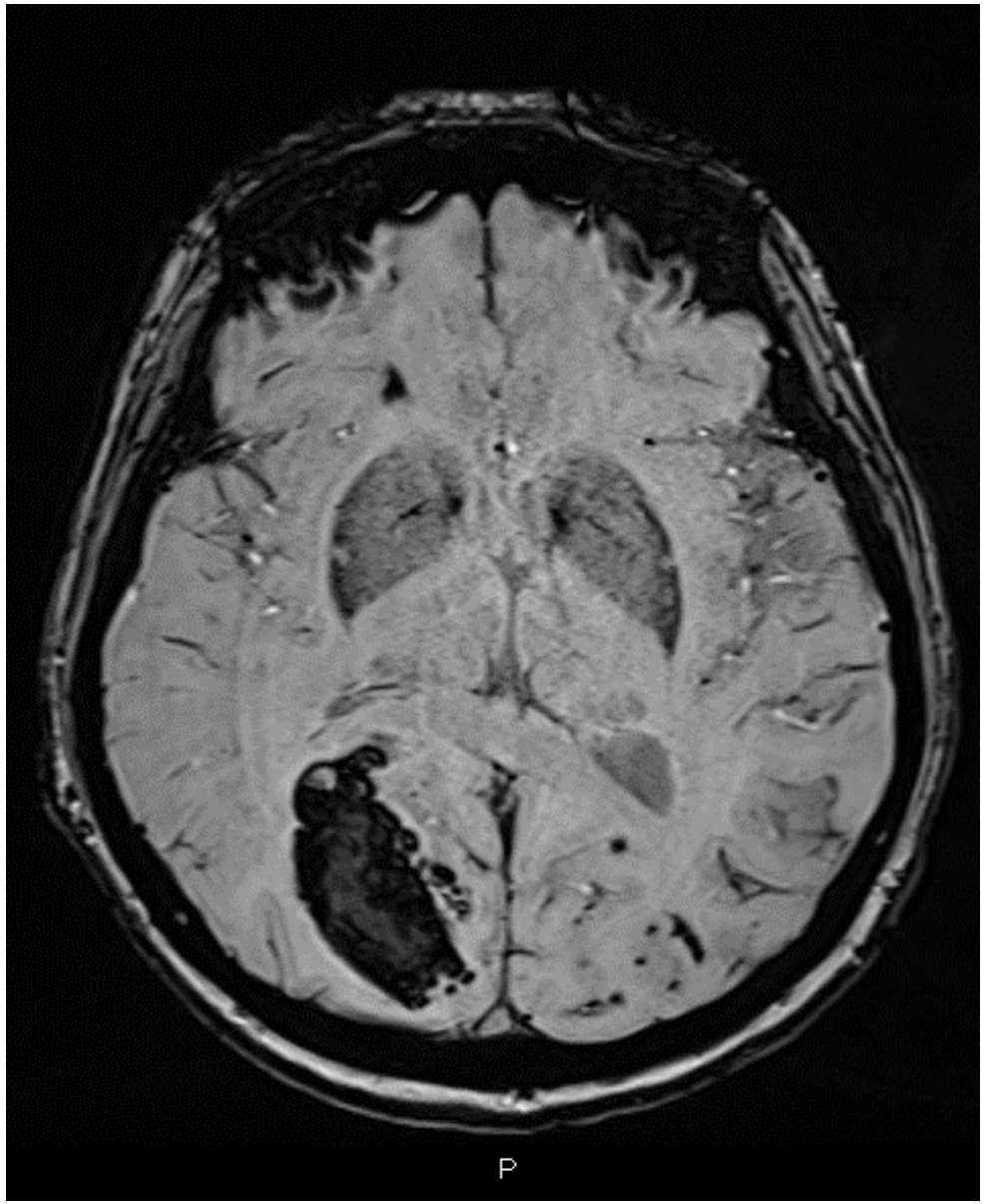
- Hematomas profundos y microhemorragias centrales sin HSA/siderosis superficial como marcadores de EHC.

Charidimou A et al Frontiers in neurology (2012) 3. 133. 10.3389/fneur.2012.00133.





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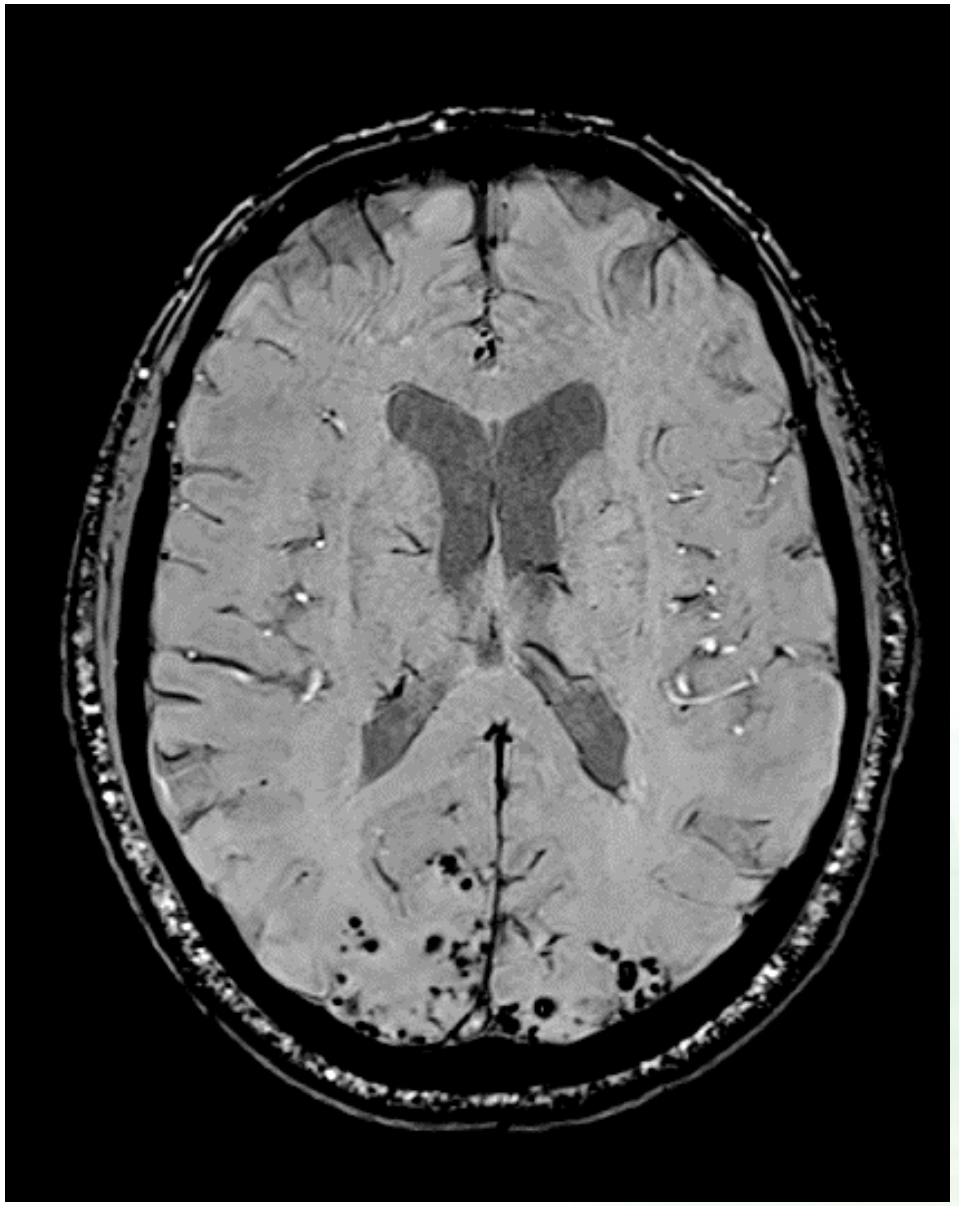
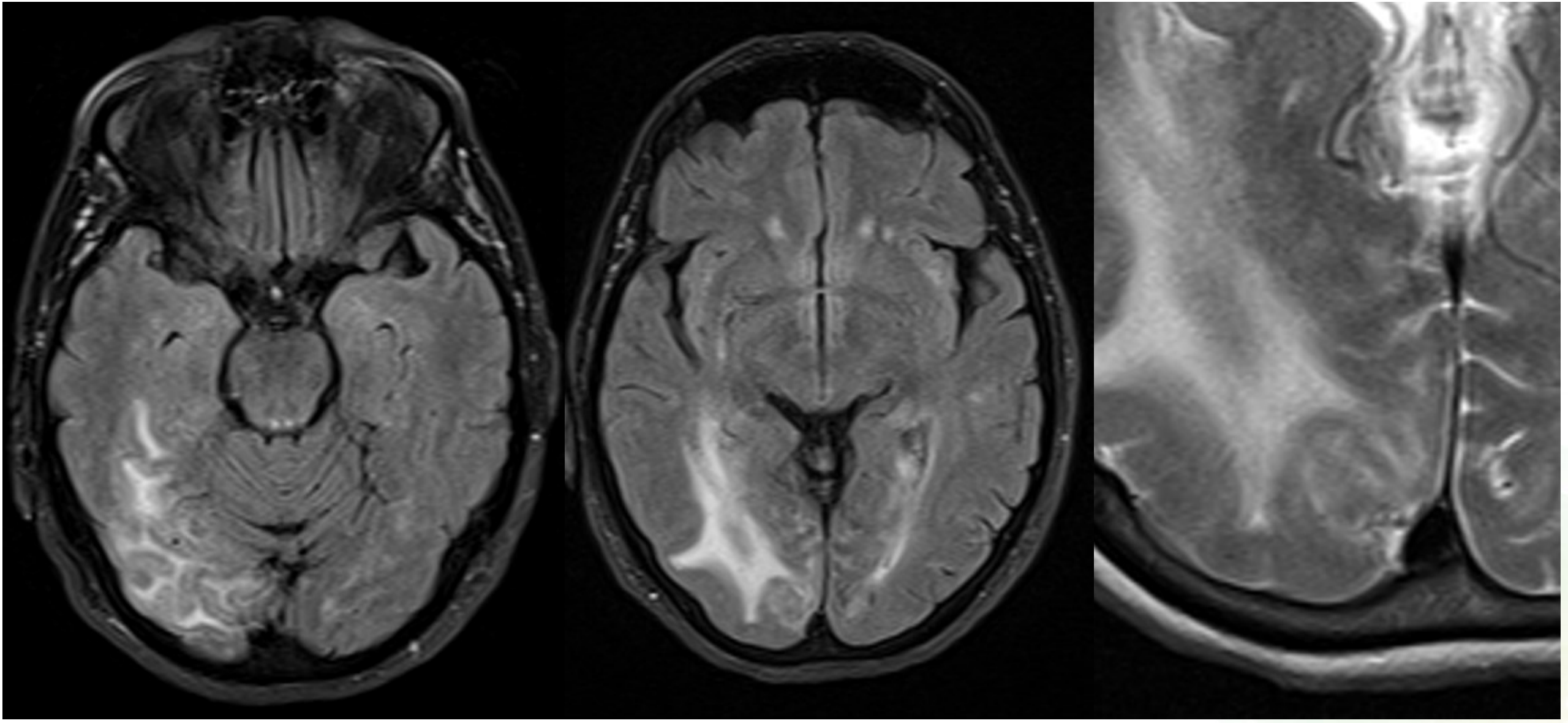


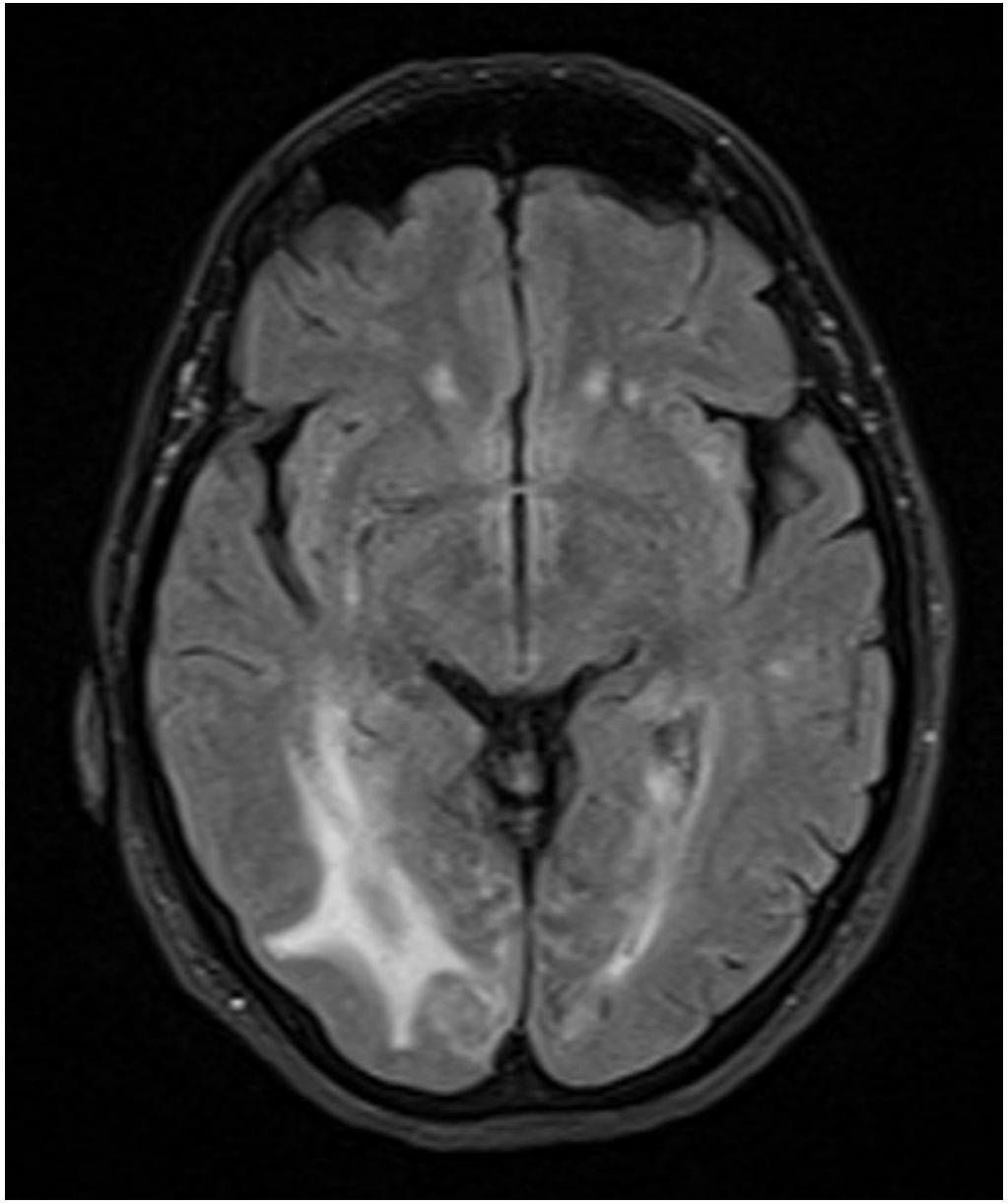
Angiopatía amiloide cerebral inflamatoria (AACi)

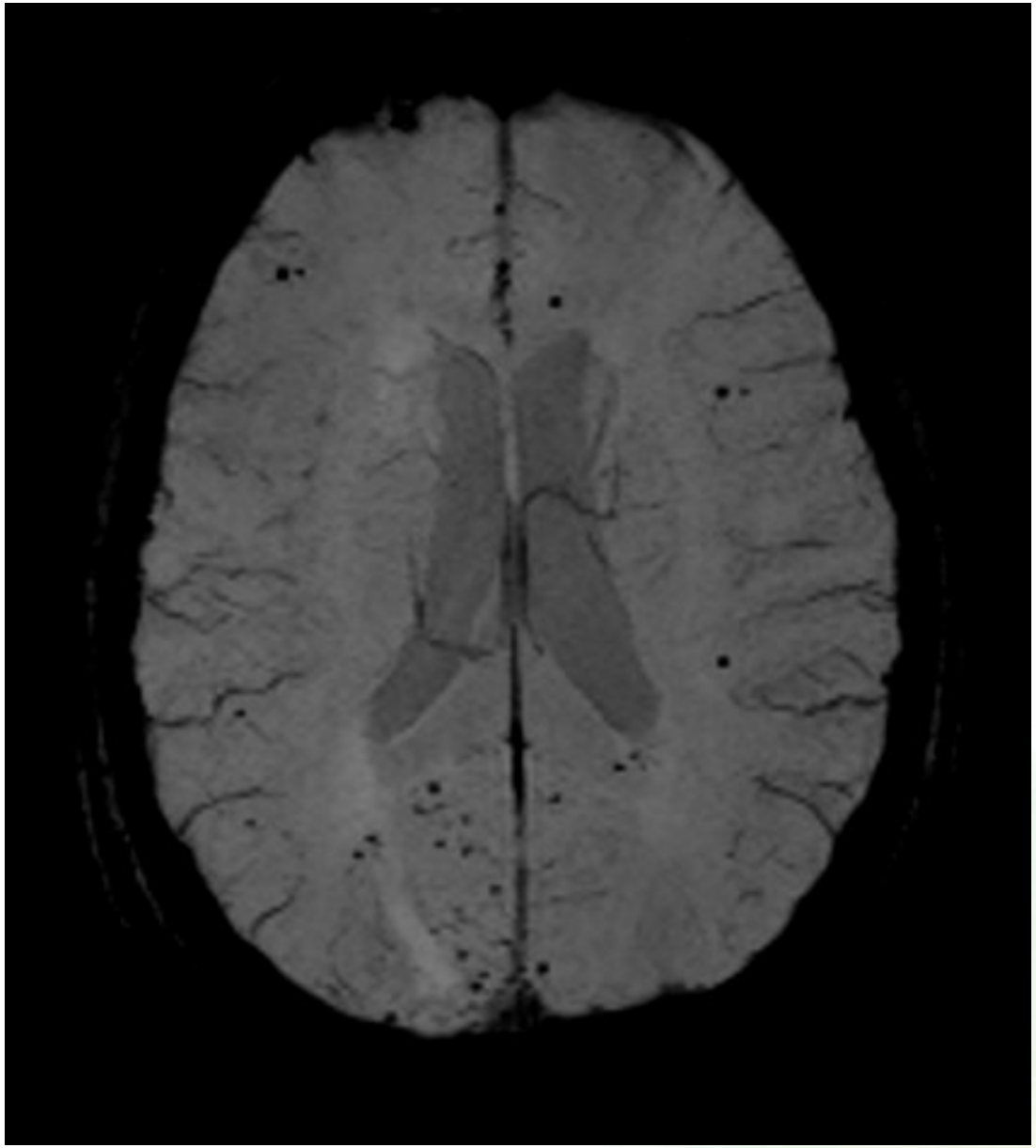
Autoinmunidad contra βA que produce reacción inflamatoria focal con edema y posibles microhemorragias sobre un AAC de base.

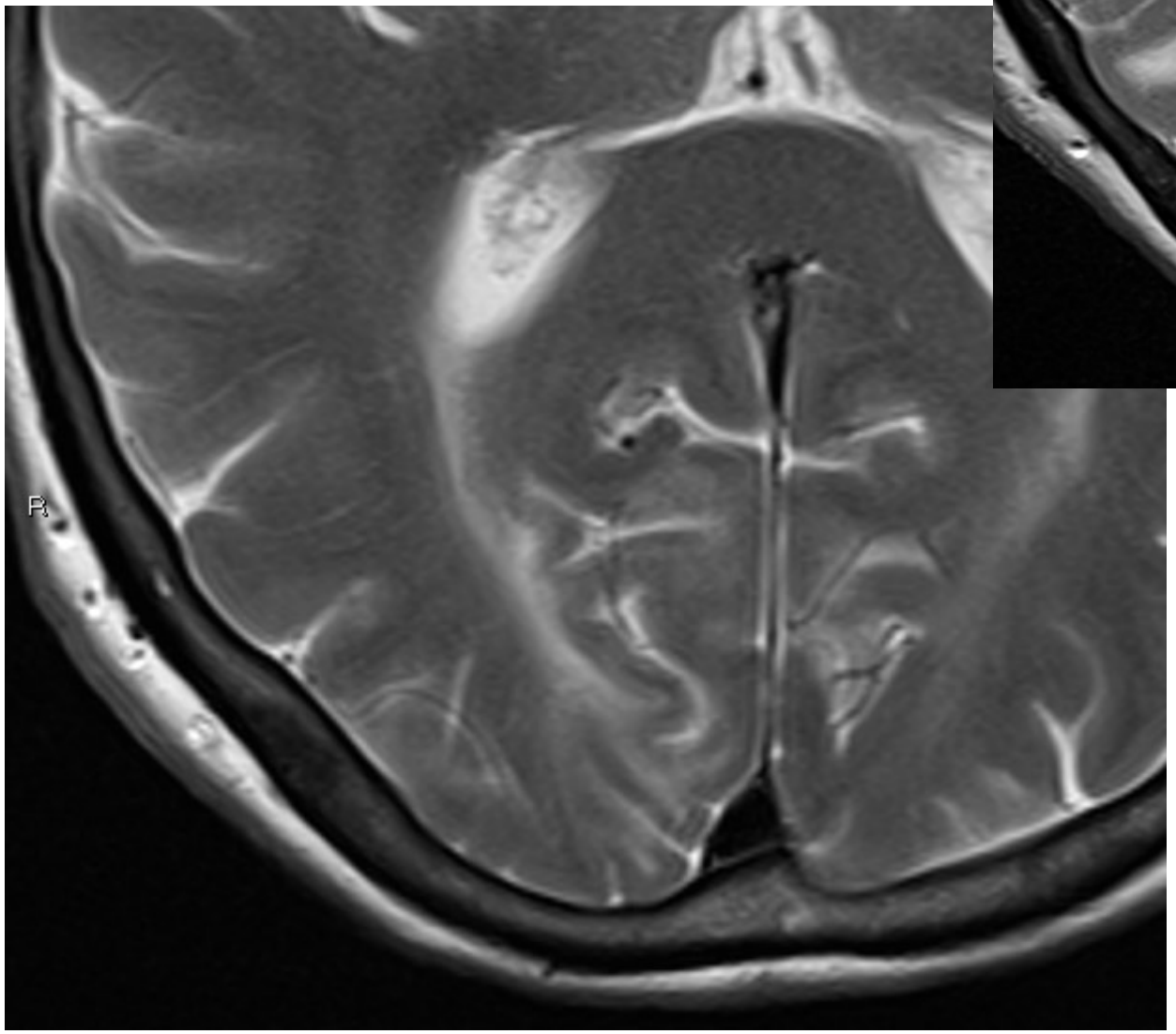
Dx AP

Criterios “probable” y “posible” incluyen hallazgos radiológicos.





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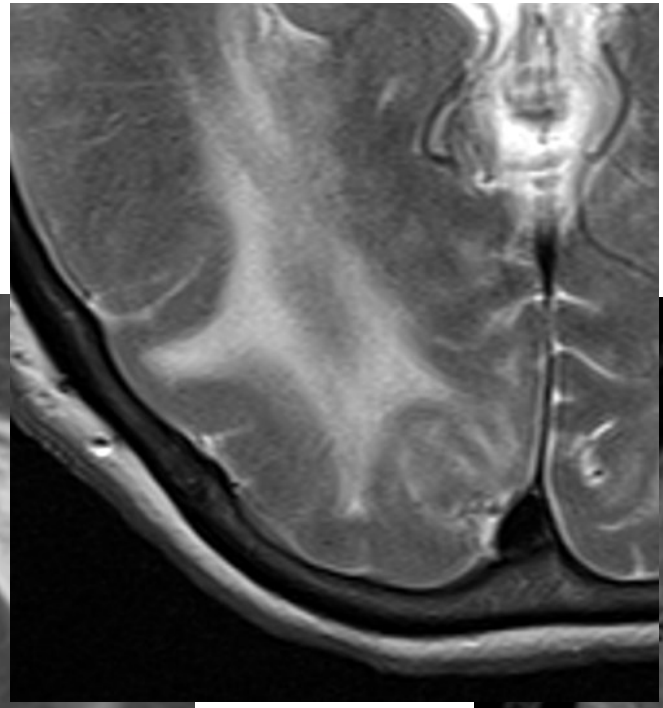
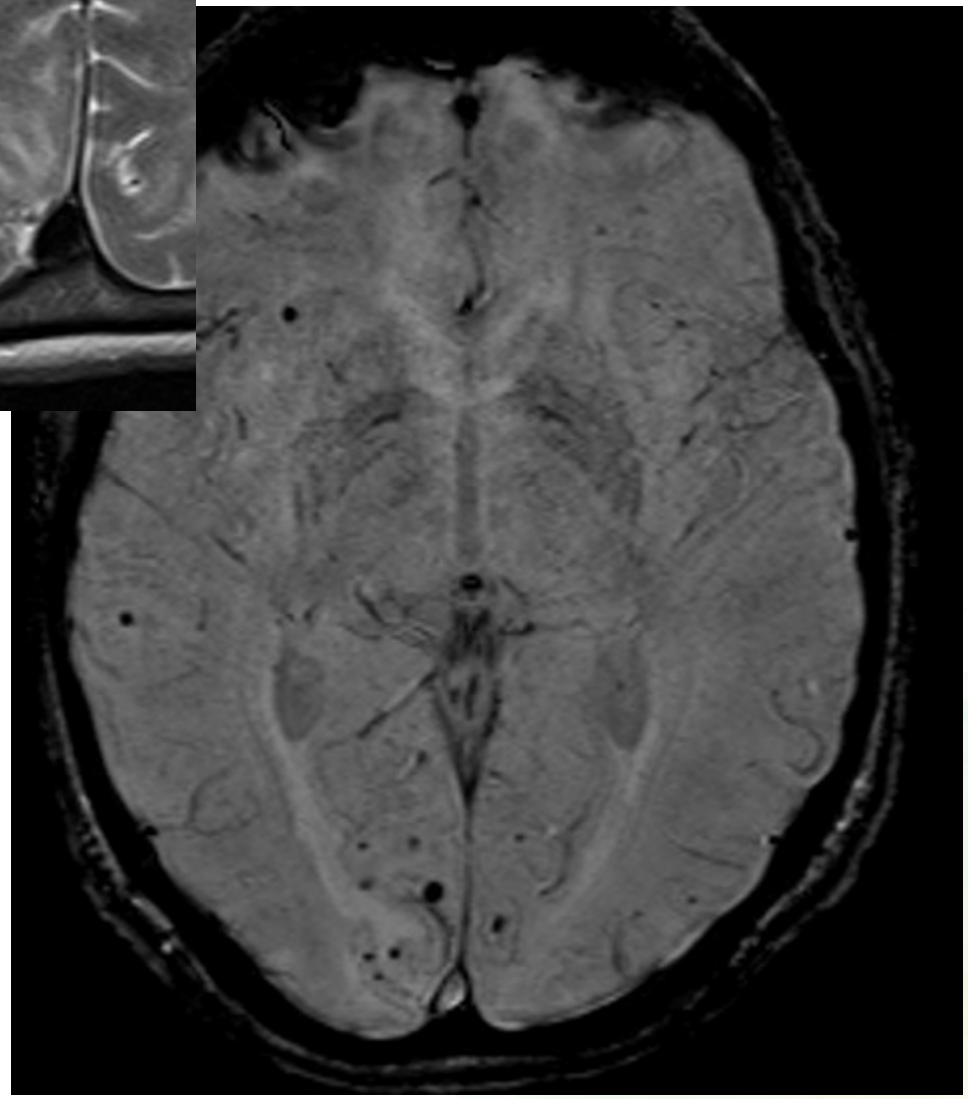




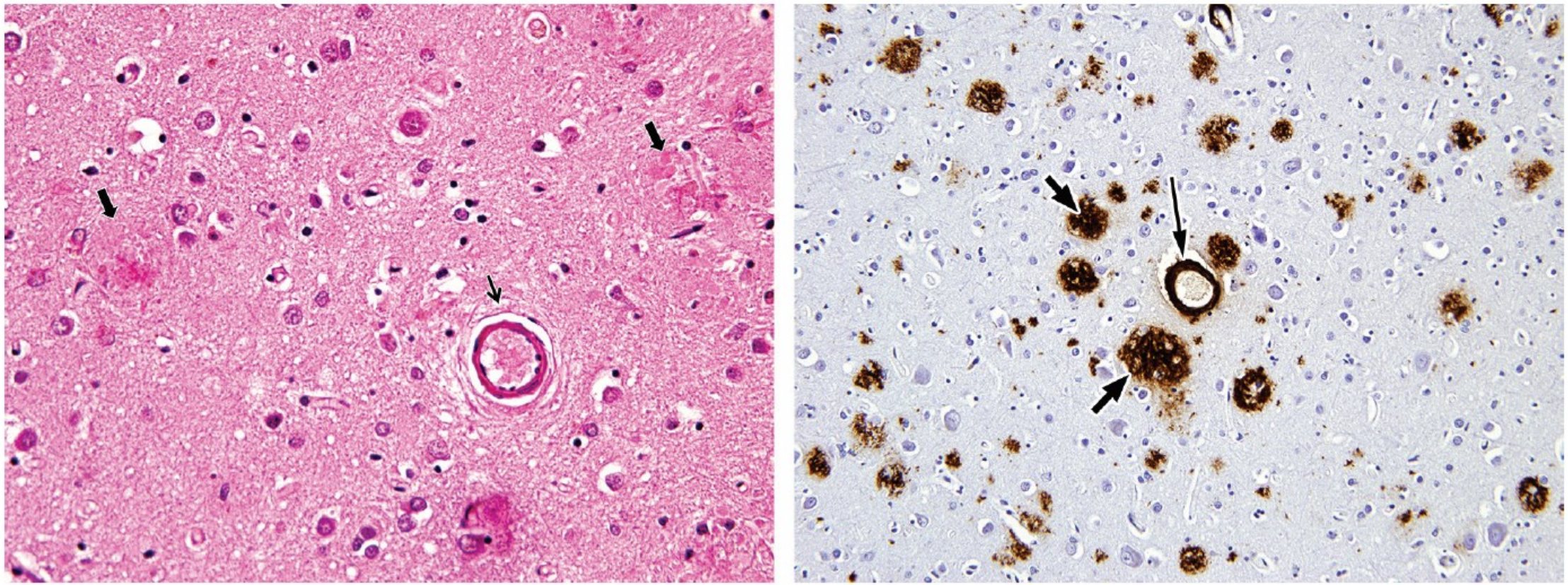
Alteraciones en imagen por los nuevos tratamientos contra el βA en la enfermedad de Alzheimer

Enfermedad de Alzheimer

Tipo más frecuente de demencia.

Personas mayores de 65 años en general.

Se considera que el depósito de **βA es el principal responsable** de la disfunción sináptica y degeneración neuronal (“cascada”).



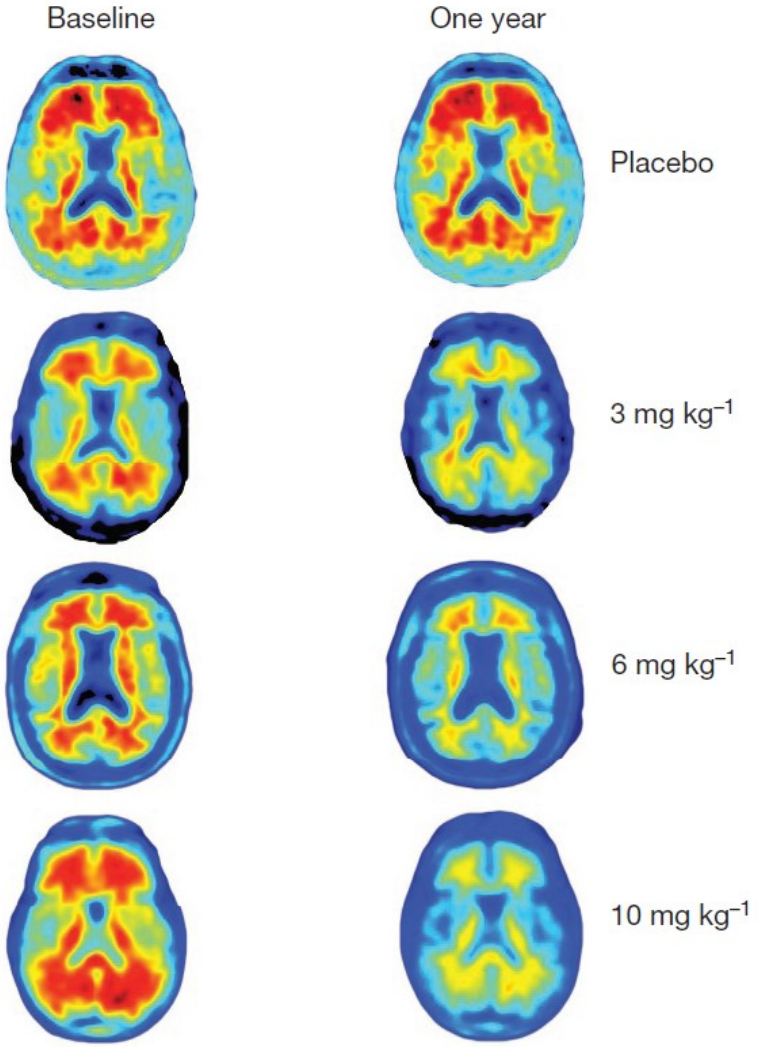
a. b.

Figure 1. Pathologic changes in a patient with AD. **(a)** Photomicrograph of frontal cortex specimen shows Aβ plaques (large arrows) typical of AD. Coexistent CAA characterized by a hyalinized vessel with intramural Aβ (small arrow) is commonly found with pathologic results typical of AD. (Hematoxylin-eosin [H-E] stain; original magnification, ×400.) **(b)** Photomicrograph of frontal cortex specimen stained with an antibody to Aβ shows dark brown stain corresponding to scattered round Aβ plaques (short arrows) and ringlike Aβ deposition (long arrow) in the vessel wall. Vascular intramural deposition of Aβ characteristic of CAA pathologic results may coexist with typical pathologic findings of AD. (10D5 immunohistochemical stain; original magnification, ×200.)

Enfermedad de Alzheimer

RM o TC útil para excluir causas tratables de demencia o para identificar patrones que puedan orientar hacia el tipo de demencia.

MN para determinar depósito patológico de amiloide o Tau.



Sevigny J et al. Nature (2016) 537:50–6

Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen based on visual impression and SUVR change relative to average one-year response for each treatment group ($n = 40$, 32, 30 and 32, respectively). Axial slice shows anatomical regions in posterior brain putatively related to AD pathology. SUVR, standard uptake value ratio.

EA en fase prodrómica o de DCL con confirmación por PET o LCR A+ T+

ARIA

ARIA, por las siglas en inglés de “Alteraciones de Imagen Relacionadas con el Amiloide”.

ARIA-E y ARIA-H.

Se considera que tiene que ver con mayor daño vascular por el lavado de βA cerebral y de la propia pared vascular y/o un componente inflamatorio transitorio.

Similitud con AAC/AACi. Preferencia por lóbulos **occipitales**.

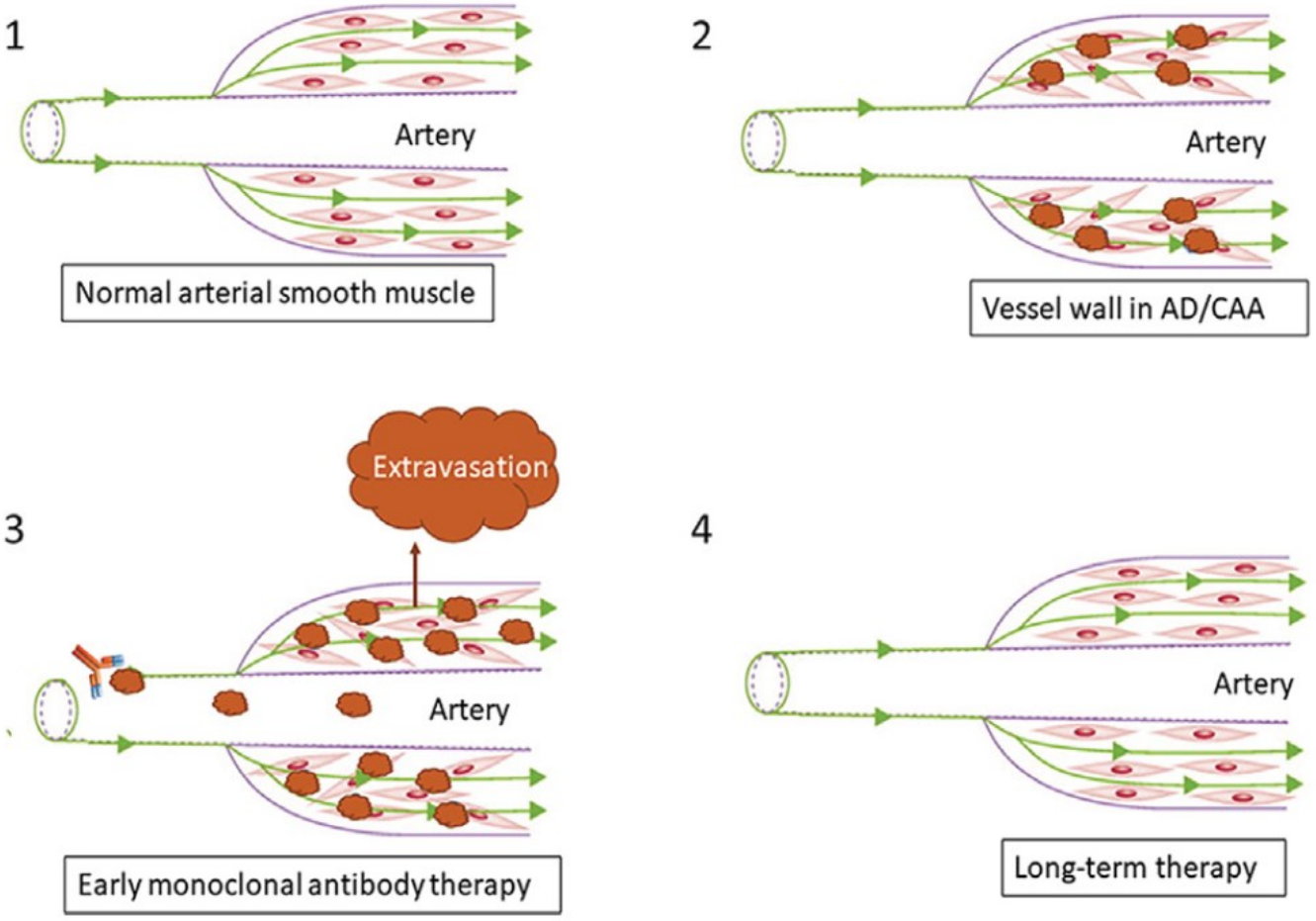


Figure 5. Pathophysiology of ARIA. Increased parenchymal Aβ accumulation with reduced perivascular clearance along with Aβ deposition within the vessel wall is seen in AD and CAA, resulting in disruption of arterial smooth muscle *(1, 2)*. After anti-Aβ therapy initiation, vessels with preexisting amyloid vascular pathologic conditions become more susceptible to vascular extravasation events, resulting in ARIA-E (leakage of proteinaceous fluid) and ARIA-H (leakage of blood products) *(3)*. Long-term therapy results in clearance of vessel wall amyloid buildup with reorganization of arterial smooth muscle *(4)*.

Agarwal A et al.RadioGraphics 2023; 43(9):e230009
https://doi.org/10.1148/rg.230009

ARIA

Frecuentes (20-40%), pero **casi siempre leves y asintomáticas, con resolución espontánea**.

Solo 1 de cada 200 pacientes tratados desarrolla ARIA graves, pero puede provocar marcado deterioro cognitivo o incluso ser mortal.

Si síntomas sobre todo cefalea, ocasional encefalopatía y clínica visual o caídas.

ARIA

Múltiples ensayos en marcha con múltiples fármacos.

Dos de ellos ya aprobados en EEUU, uno de los cuales podría aprobarse en Europa **en los próximos meses**.

Siendo los ARIA el principal riesgo de estos tratamientos y **pudiendo condicionar la interrupción del mismo**, cobra un enorme papel la valoración radiológica.

ARIA-E

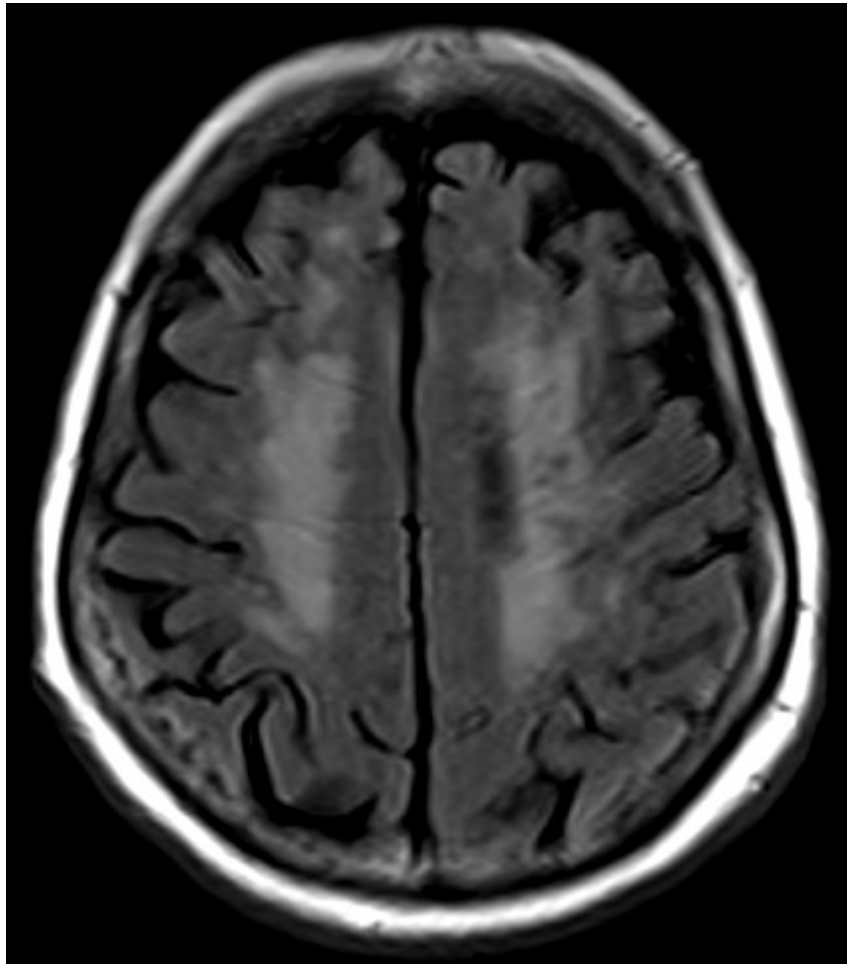
Por “edema” o “efusión”. La más frecuente (35%), sore todo en primeros 6 meses y **occipital**. 80% asintomáticas.

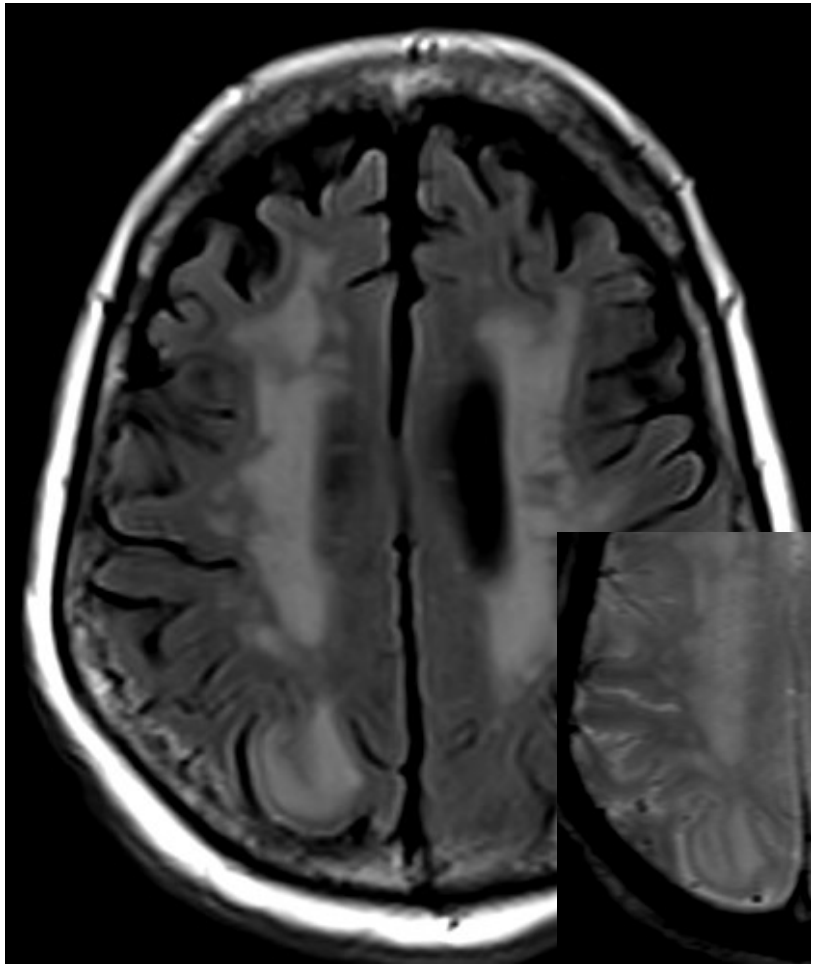
T2-FLAIR: áreas de HI de señal parenquimatosas de nueva aparición y/o áreas de HI de señal en surcos corticales de la convexidad.

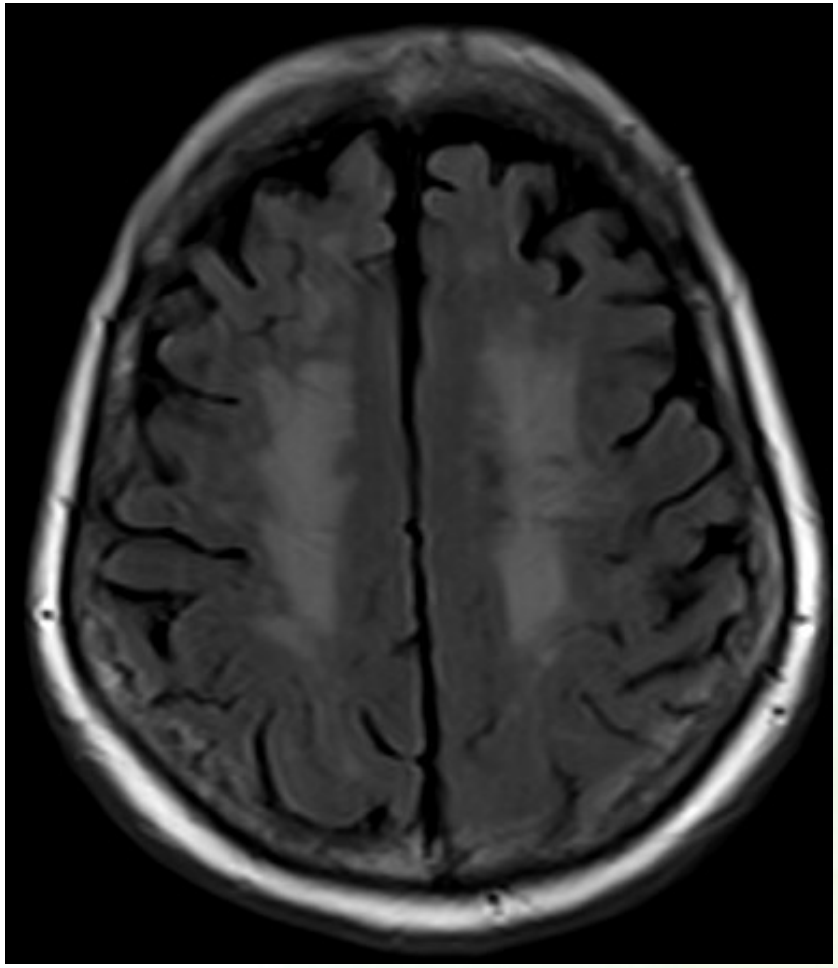
Similar a AACi o PRES pero la enorme mayoría se resuelve espontáneamente en el seguimiento. No restrictivas en difusión

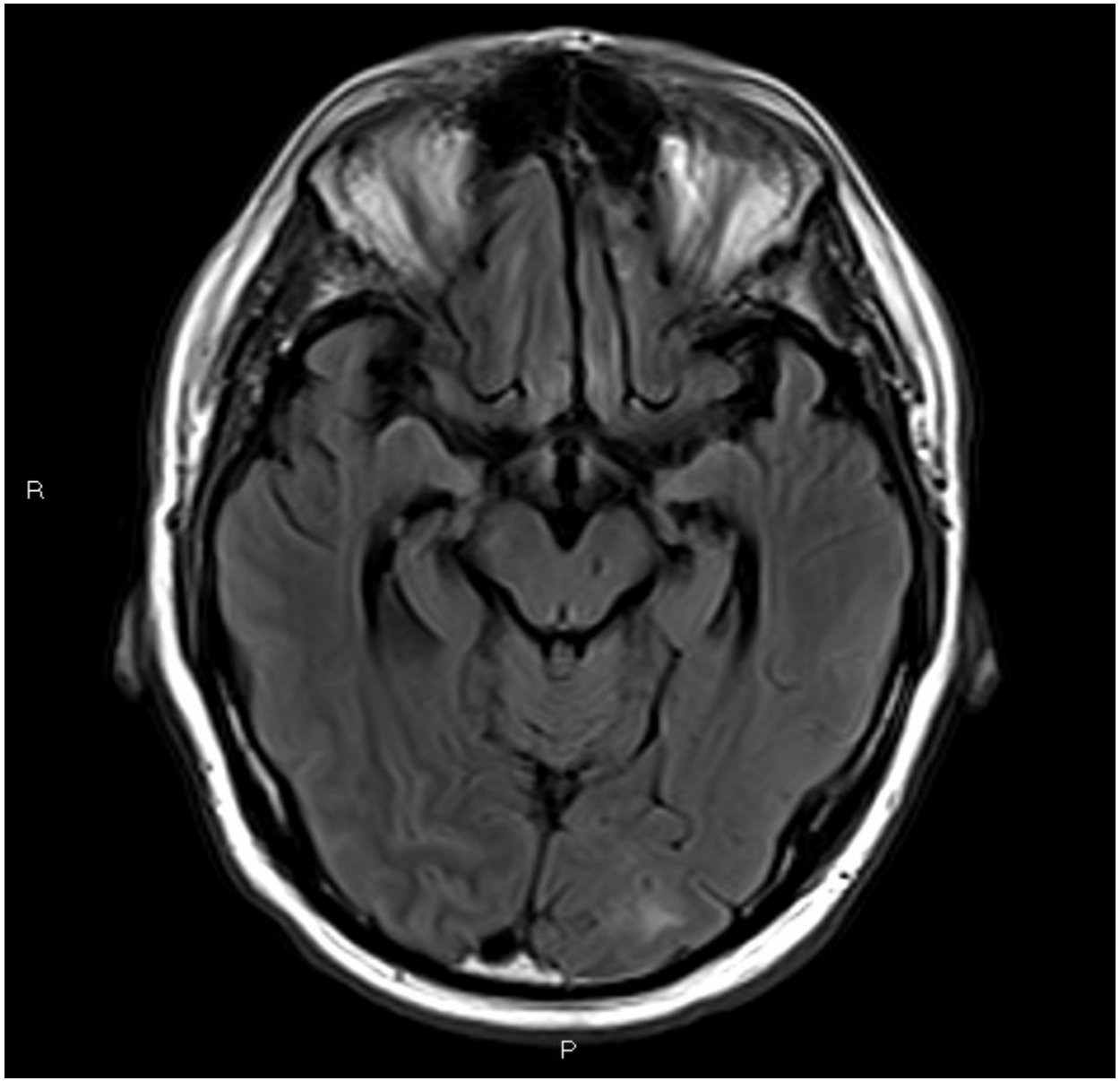
A los 5 meses

Al mes





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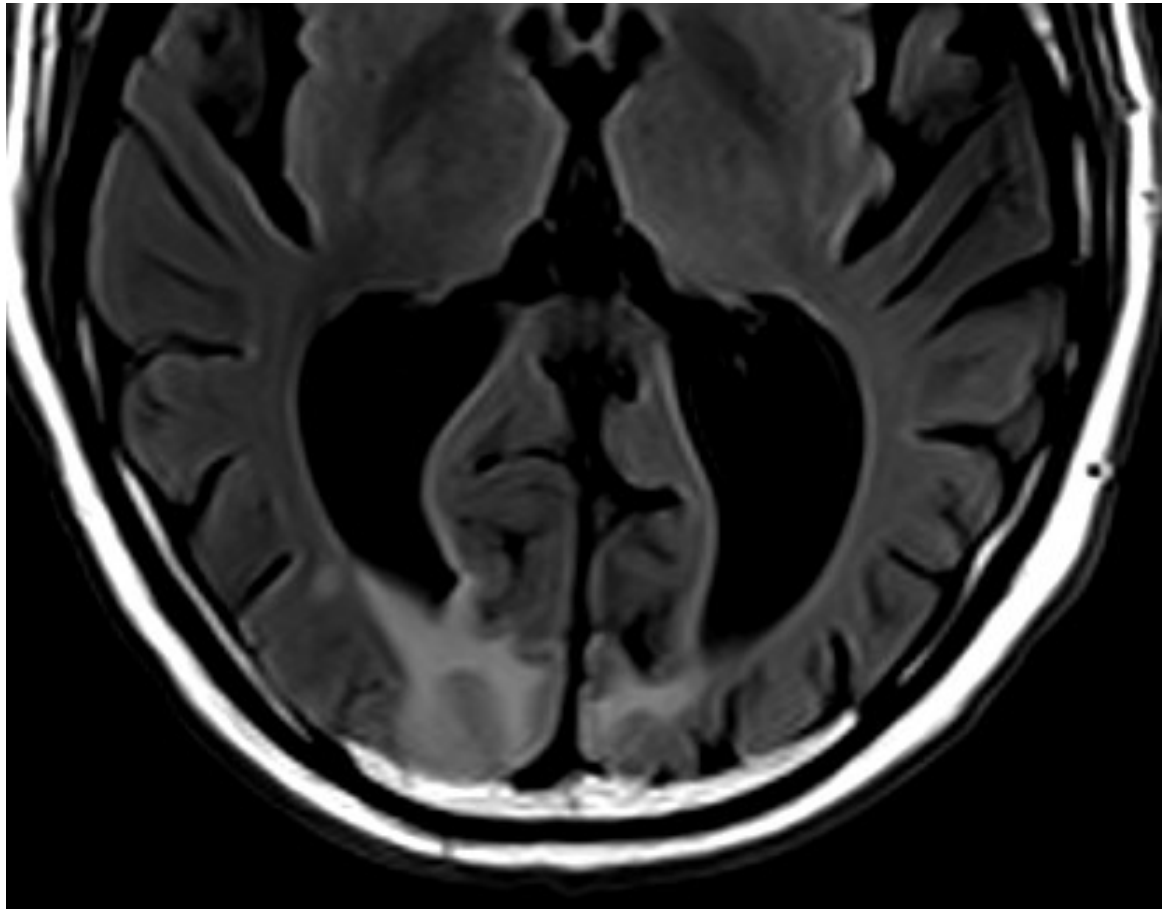
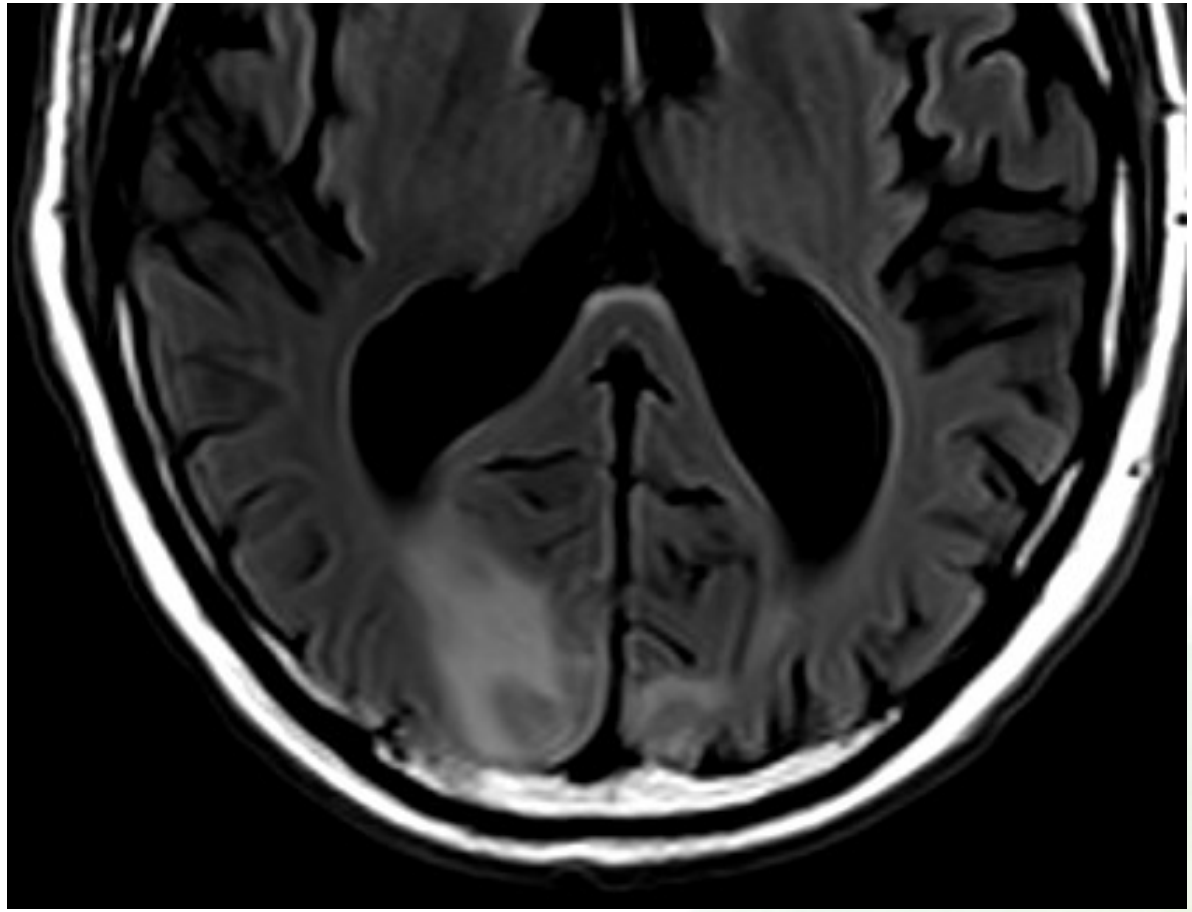
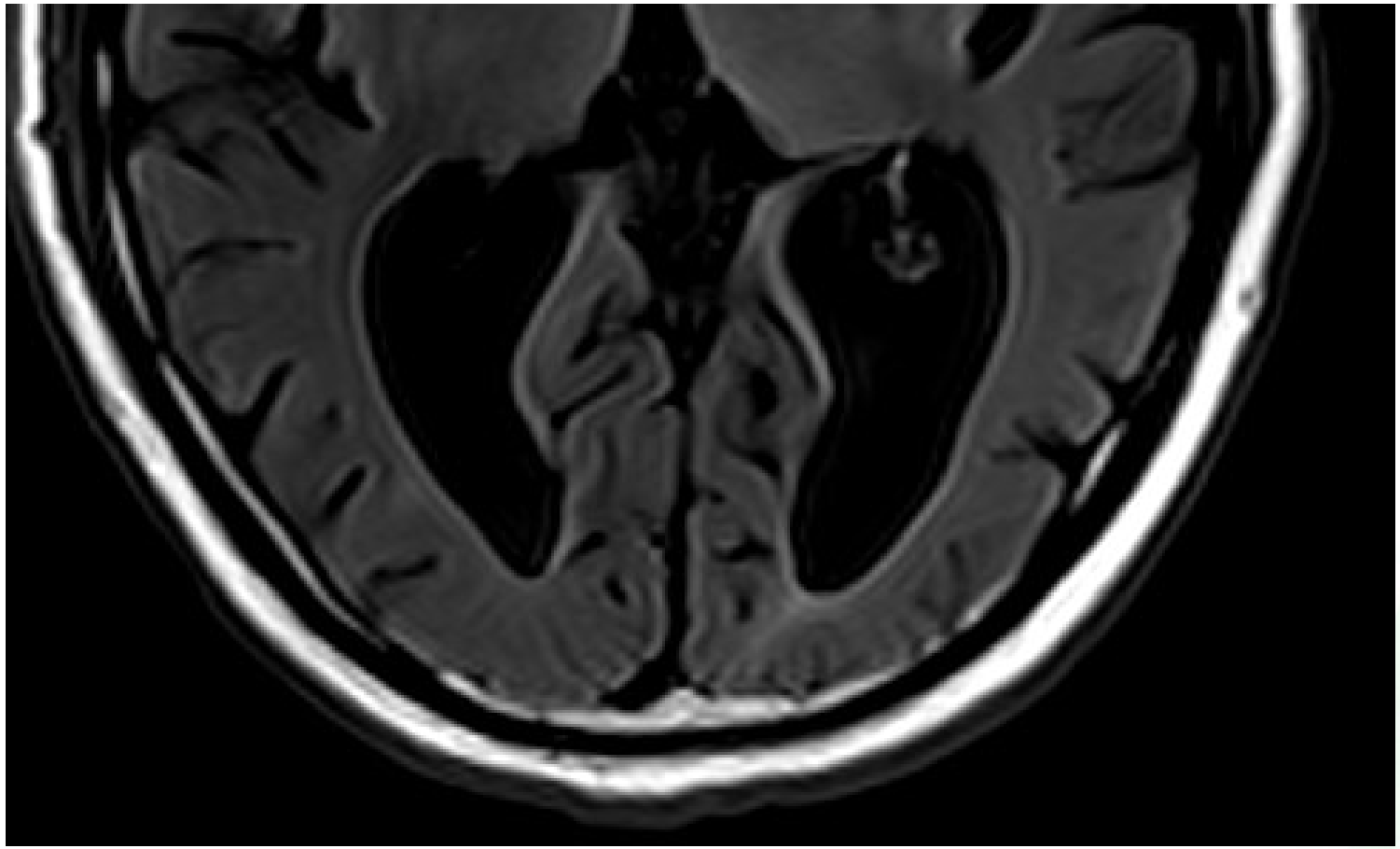
P

A los 30 meses del ARIA-E previo





2 meses después

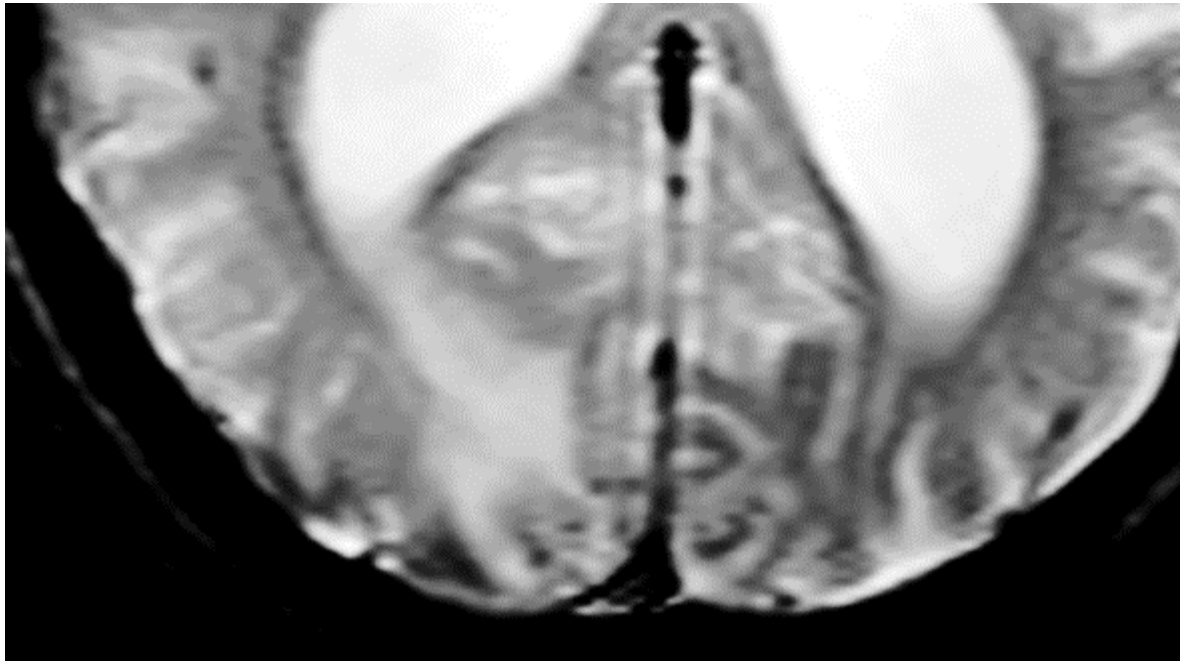


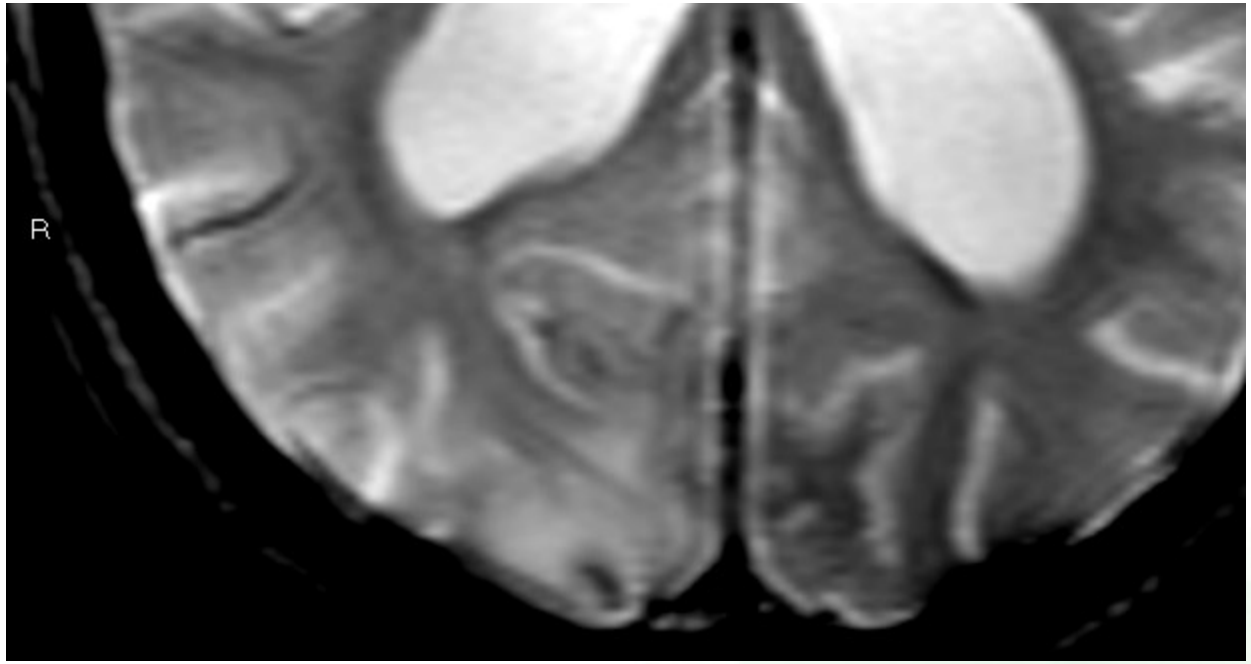
ARIA-H

De “Hemorragia”. 20%.

T2*: bien microhemorragias (lo más frecuente) o bien focos de siderosis superficial. Raro macrohemorragias (>10 mm en T2*)

Pueden asociarse (o no) a ARIA-E en localización o tiempo

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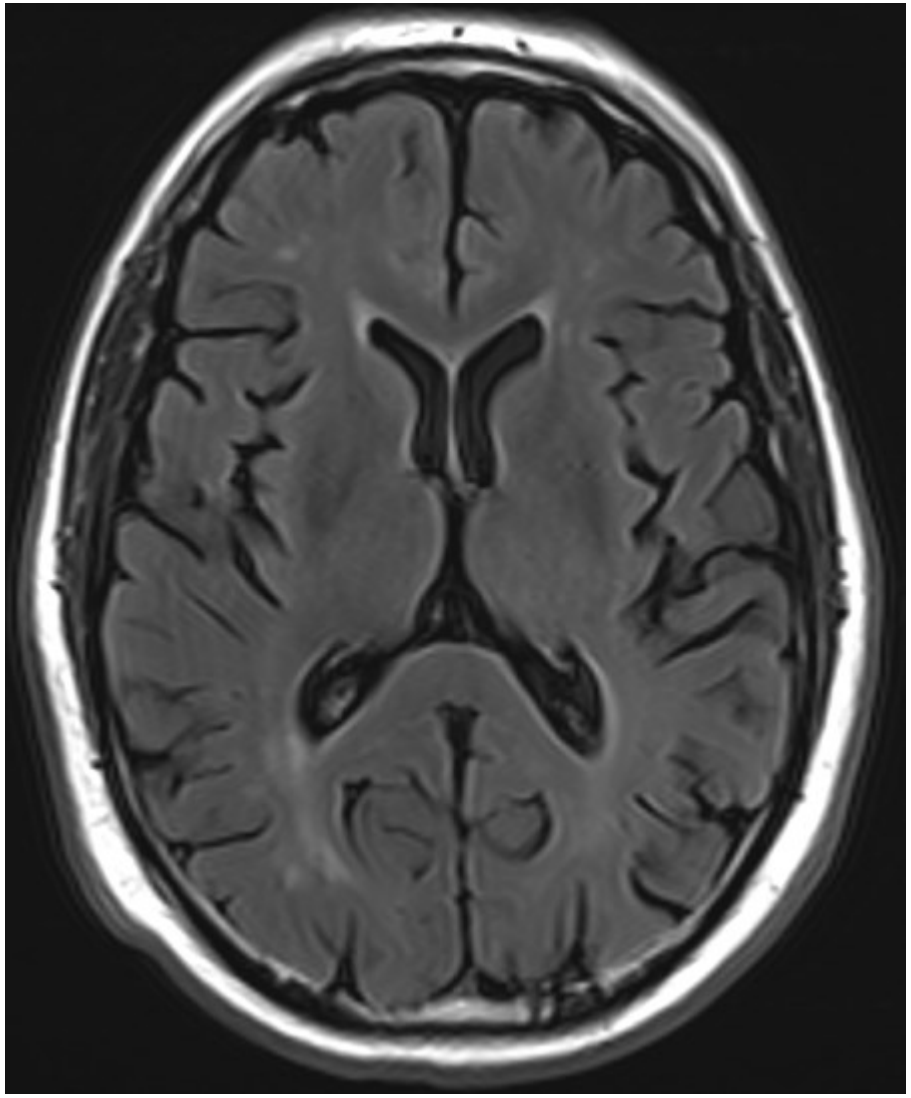

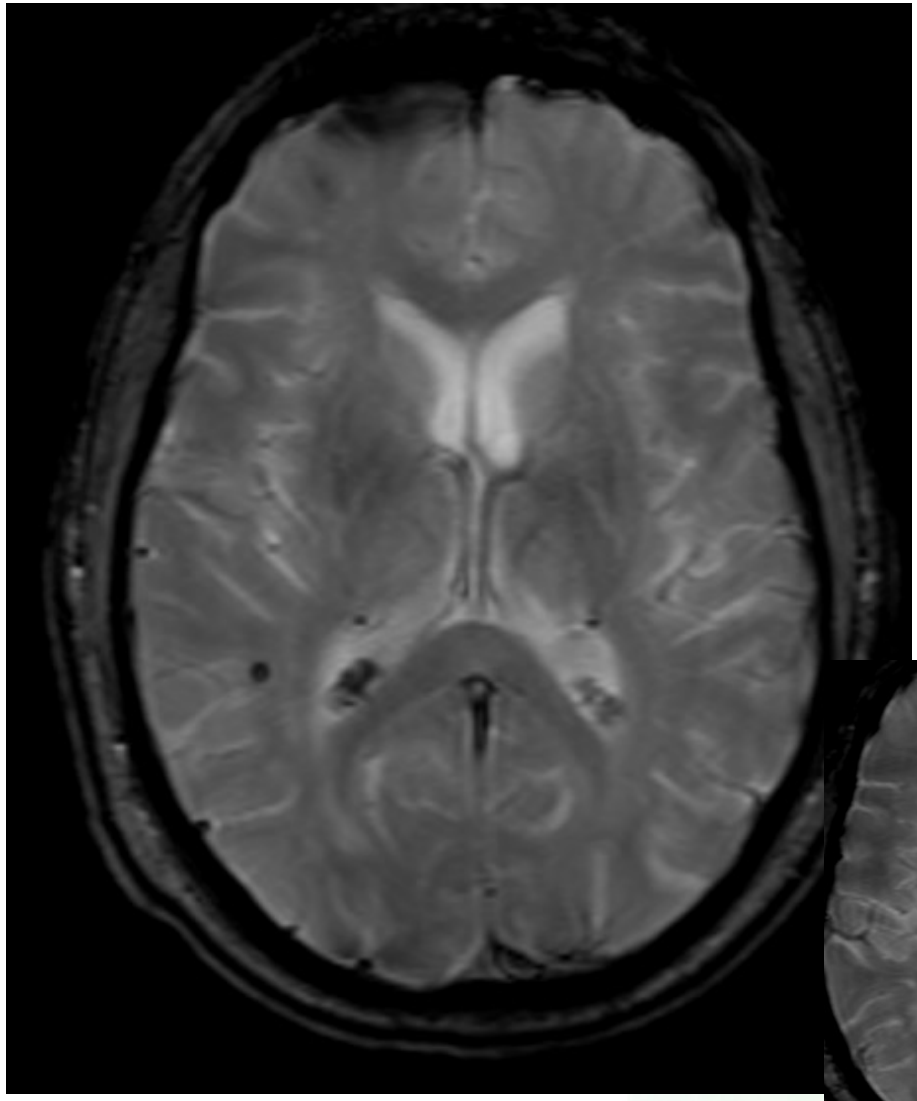

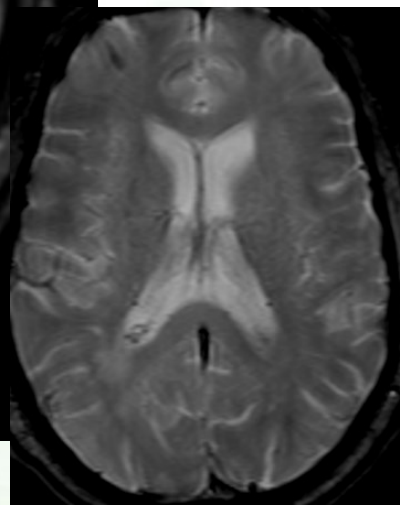

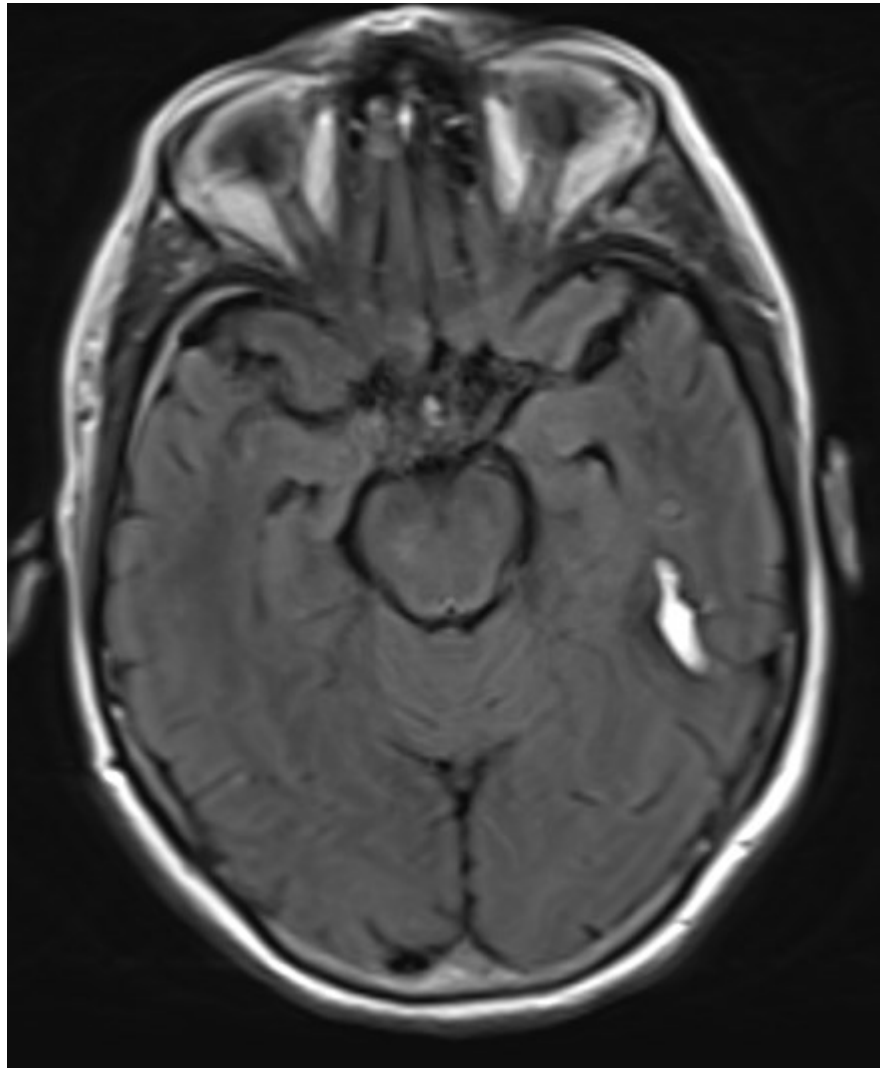

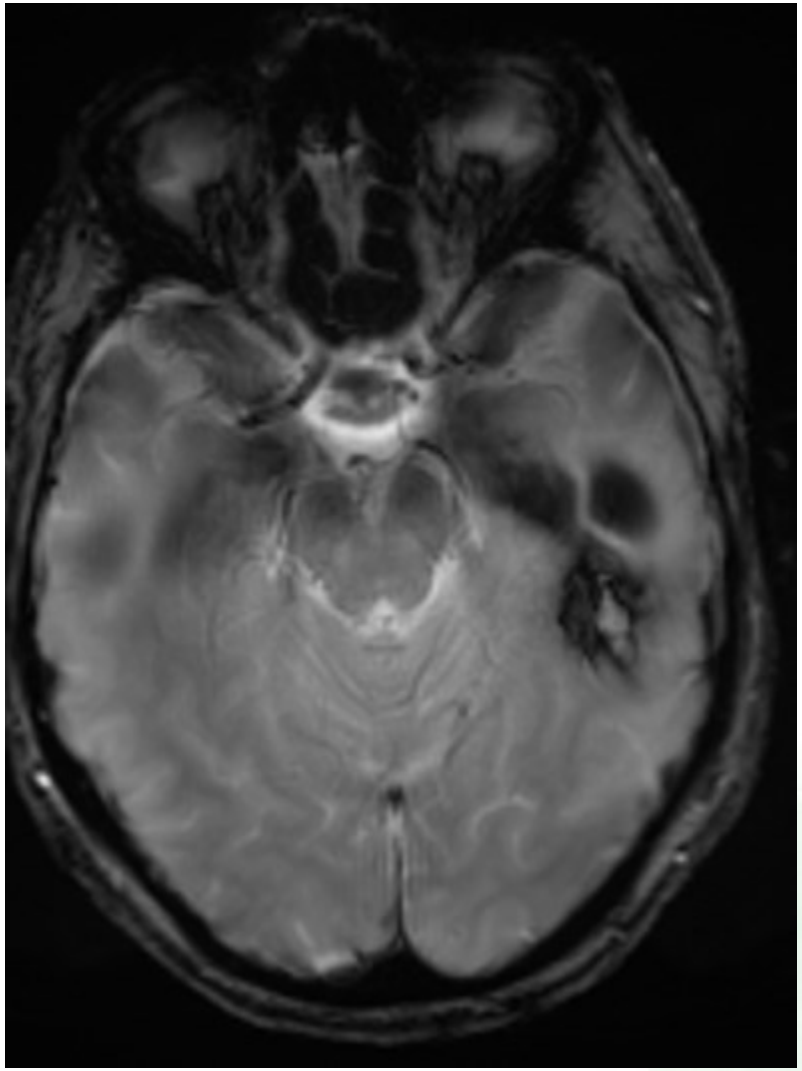

TABLE 1 | Safety and efficacy of second-generation anti-amyloid monoclonal antibodies.

	Aducanumab (2)	Lecanemab (3, 4)	Donanemab (5)	Gantenerumab (6)
CNS amyloid clearance	+	+	+	+
Clinical stabilization	+/–	+	+	?
Tau reduction	+	+	?	+
Estimated ARIA-E incidence at the highest dose (%)	42	9.9	27.5	13.5
Estimated ARIA-H incidence at the highest dose (%)	Same as placebo	5.6	30.5	16.2

ARIA (–E/–H), Amyloid-related imaging abnormalities (–edema/–hemorrhagic); [+] indicates that the drug is associated with the variable in the row; ? not known.

Withington CG, Turner RS. Front. Neurol. 13:862369. doi: 10.3389/fneur.2022.862369

May 03, 2022; 98 (18 Supplement) MONDAY, APRIL 4

Defining a Standardized MRI Acquisition Protocol to Be Proposed to ICARE AD Sites for ARIA Monitoring (N3.001)

Tammie L. S. Benzinger, Frederik Barkhof, Alex Rovira, Tobias Kober, Christopher T. Whitlow, Michael Smith, Christina Marsica Grassi, Elizabeth Fisher

J Prev Alz Dis 2022;2(9):221-230
Published online April 5, 2022, http://dx.doi.org/10.14283/jpad.2022.34

Special Article

Aducanumab: Appropriate Use Recommendations Update

J. Cummings[1], G.D. Rabinovici[2], A. Atri[3], P. Aisen[4], L.G. Apostolova[5], S. Hendrix[6], M. Sabbagh[7], D. Selkoe[8], M. Weiner[9], S. Salloway[10], For the Alzheimer's Disease and Related Disorders Therapeutics Working Group

Table 2: ARIA severity grading[a]

	Radiographic Severity		
	Mild	**Moderate**	**Severe**
ARIA-E (sulcal and/or cortical/subcortical FLAIR hyperintensity)	1 Location < 5 cm	1 Location 5–10 cm OR >1 Location each <10 cm	1 more location > 10 cm
ARIA-H (microhemorrhage)	≤4	5–9	≥10
ARIA-H (superficial siderosis)	1 Focal area	2 Focal areas	>2 Focal areas

[a] ARIA is graded on the basis of treatment-emergent events. For ARIA-H, this count includes cumulative new microhemorrhages or regions of siderosis compared with the baseline, pretreatment examination.

Cogswell et al. AJNR Am J Neuroradiol 43:E19–E35
10.3174/ajnr.A7586

Clinical symptom severity	ARIA-E severity			ARIA-H severity		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Asymptomatic	C	S	S	C	S	D
Mild	S	S	S	S	S	D
Moderate	S	S	S	S	S	D
Severe	S	S	S	S	S	D
Serious (other)	S	S	S	S	S	D
Serious	D	D	D	D	D	D

FIG 10. Patient management based on ARIA severity and clinical symptoms. ARIA-H management rules are the same for each severity of microhemorrhages and superficial siderosis. C (green) indicates continue dosing at current dose and schedule; S (yellow), suspend dosing; resume dosing at same dose once ARIA-E resolved or ARIA-H stable and clinical symptoms resolve; D (red), discontinue dosing; Serious (other), medical event unrelated to anti-amyloid therapy.

Cogswell et al. AJNR Am J Neuroradiol 43:E19–E35
10.3174/ajnr.A7586

T2*

NO SWI (puede hacerse adicionalmente)

FLAIR

2D de hasta 5 mm o 3D

Difusión

T1 3D

Para un mismo paciente tratar de realizar siempre el mismo protocolo en el mismo equipo

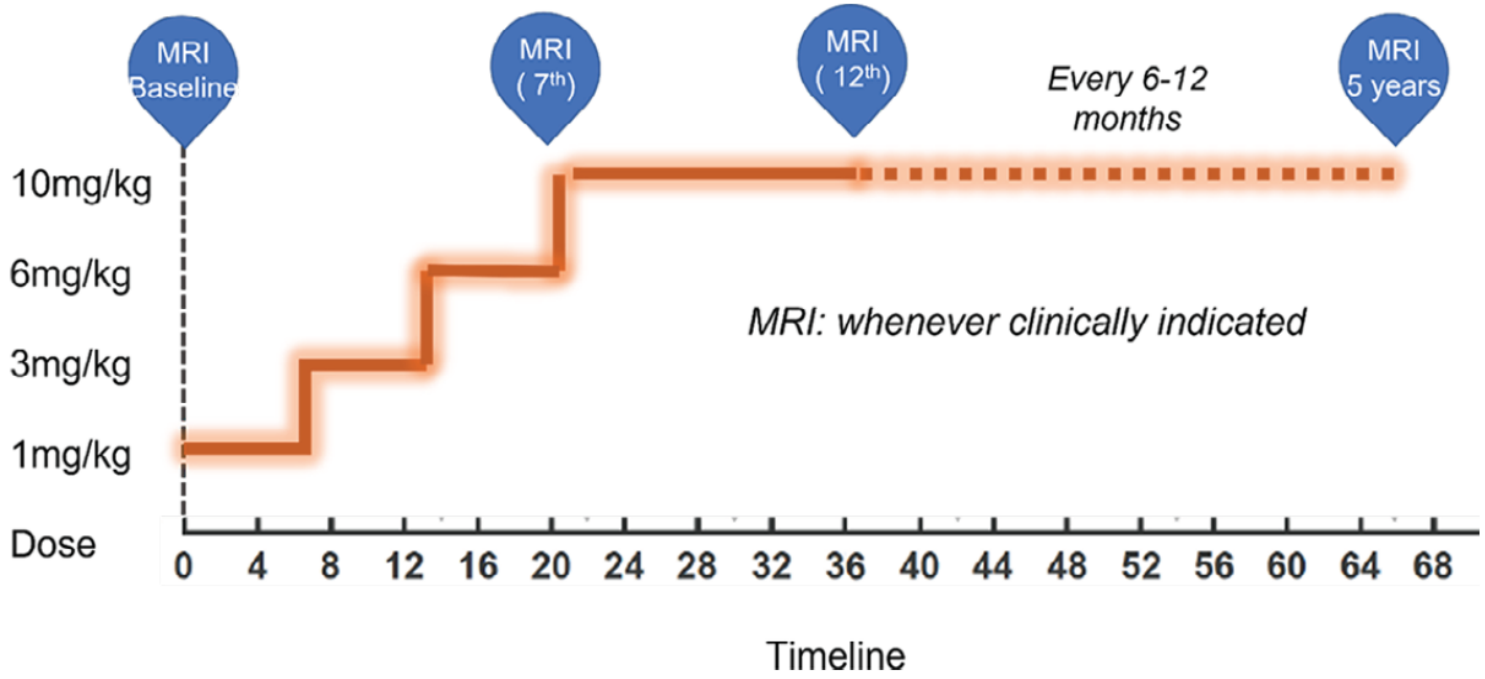

Figure 6. Dose titration chart and timeline (in weeks) for ARIA monitoring MRI. Current guidelines recommend starting at a low dose of 1 mg/kg for the first two infusions, moving to 3 mg/kg for the third and fourth infusions, 6 mg/kg for the fifth and sixth infusions, and finally to the optimum target dosage of 10 mg/kg from beyond the seventh infusion, usually achieved over a period of 20–24 weeks. MRI should be performed within 12 months before initiation of therapy and before the seventh (10 mg/kg dose) and 12th infusions for aducanumab, for up to 5 years. For *ApoE4* carriers, it is recommended to undergo MRI at the fifth (6 mg/kg), seventh (10 mg/kg), 10th, and 12th infusions. MRI should also be performed for any new signs or symptoms suggestive of ARIA or any other clinical indication.

Agarwal A et al. RadioGraphics 2023; 43(9):e230009
https://doi.org/10.1148/rg.230009

RM "obligatorias"

- ✓ **Inclusión***
- ✓ **Seguimiento** según protocolo, habitualmente 2-3 durante la escalada de dosis y cada 6-12 meses en el seguimiento.

RM adicionales

- ➢ Si síntomas
- ➢ Si ARIA previo

* Importante **conocer los criterios de exclusión de cada fármaco,** aunque en general similares.

La **contraindicación para RM será contraindicación para tratamiento**.

RM de inclusión/screening:

- Excluir otras causas de demencia
- Identificar posibles criterios de exclusión por riesgo aumentado de ARIA-H como AAC, un foco hemorrágico agudo o subagudo, hemorragia macroscópica, mas de 4 microhemorragias, infarto > 1,5 cm, siderosis superficial o leucoaraiosis extensa.

Conclusiones

Papel **FUNDAMENTAL DE LA RM** en la inclusión y sobre todo en el seguimiento.

Importancia de conocer la presentación de ARIA y su clasificación rigurosa dado que puede suponer la interrupción temporal o definitiva del tratamiento.

Si se aprueba un fármaco en Europa, conocer los **criterios de exclusión** y evaluar de manera rigurosa una posible contraindicación para RM por implantes. Idealmente protocolo consensuado (SENR) e informe estructurado que garantice reproducibilidad de los hallazgos.

Potencial avalancha de solicitudes de RM.

¡Muchas gracias!

Pablo Domínguez
pdaniel@unav.es

Clínica Universidad de Navarra