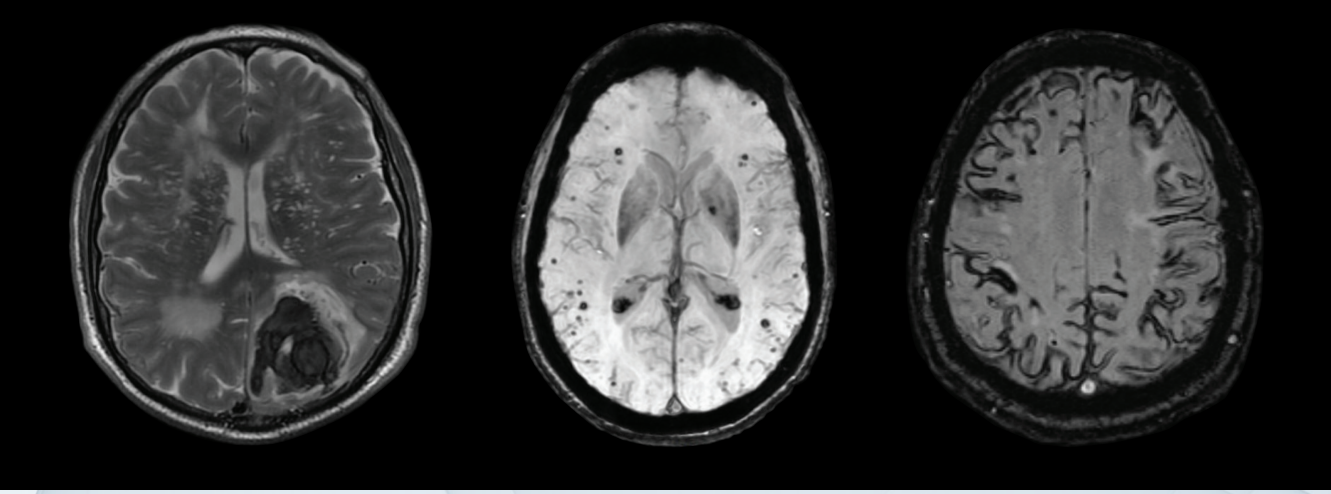

DOCTORAL THESIS

Doctoral Program in Neuroscience
Universitat de València, UV

NEUROPSYCHOLOGICAL AND NEUROIMAGING MARKERS IN CEREBRAL AMYLOID ANGIOPATHY:

A CROSS-SECTIONAL POPULATION-BASED STUDY

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Valencia, March 2024

Front cover figures: Magnetic resonance images of structural changes resulting from cerebral amyloid angiopathy. First image represents a lobar hemorrhage with enlarged perivascular spaces – one of the ischemic hallmarks of this disease; Second image illustrates multiple cerebral microbleeds – one of the hemorrhagic hallmarks of this condition. Finally, the third image displays disseminated cortical superficial siderosis.

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Doctoral Program in Neuroscience (3142)

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VNIVERSITAT DE VALÈNCIA Escola de Doctorat

CERTIFICATE OF ACADEMIC DIRECTION

Dr. Aida Lago Martin, specialist in Neurology at Hospital Universitari i Politècnic La Fe, Dr. Raúl Espert, lecturer of neuropsychology at the Psychology Faculty's Psychobiology Department at Universitat de València and Neuropsychologist at Hospital Clínico de Valencia and Dr. Marien Gadea Doménech, lecturer at the Psychology Faculty's Psychobiology Department at Universitat de València

CERTIFY:

That the doctoral thesis presented by Cristina Giménez Paños, with the title "Neuropsychological and Neuroimaging Markers in Cerebral Amyloid Angiopathy: A Cross-Sectional Population-Based Study" to qualify for Doctor in Neuroscience for the Universitat de València has been carried out under our direction and has been examined to ensure that it meets all the requirements to be presented and defended before the corresponding Thesis Committee.

Valencia, January 10th, 2024

Director of the thesis	Co-director and thesis tutor	Co-director of the thesis
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El trabajo de investigación que se expone a continuación es fruto de años de dedicación y trabajo con pacientes con angiopatía amiloide cerebral. Nace de la observación clínica de una condición a veces poco entendida y desconocida para los neuropsicólogos y con el objetivo firme de avanzar en su conocimiento. Además, no solo constituye la culminación de mi etapa de formación como neuropsicóloga e investigadora, sino que el hecho de haber llegado hasta aquí es el resultado de muchas enseñanzas vitales de quienes a continuación me gustaría agradecer.

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"Nothing is safe from the human need for knowledge and research: the more hidden it is, the greater the interest in unveiling it",

Lucien Briet (1860-1921)

"Nada queda al margen del afán investigador y de la necesidad de conocimiento del ser humano: cuanto más oculto esté, mayor será el interés por desvelarlo",

Lucien Briet (1860-1921)

Scientific Production

Some of the results presented in this thesis have been previously presented at national and international conferences:

1. **Title of the paper:** Lobar hematoma associated with amyloid angiopathy: in search of a specific neuropsychological profile. Cross-sectional study.
   Name of the congress: LXXII Annual Meeting of the Spanish Society of Neurology.
   Corresponding author: Yes
   City of celebration: Seville, Andalusia, Spain
   Celebration year: 2019
   Authors: Cristina Giménez Paños; José Ignacio Tembl Ferrairó; Gerardo Fortea Cabo; Lluís Morales Caba; Raúl Espert Tortajada; Marien Gadea Doménech; Miguel Baquero Toledano; Aida Lago Martín.

2. **Title of the paper:** Cognitive profile after intracerebral hemorrhage associated with cerebral amyloid angiopathy.
   Name of the congress: XII National Congress of Neuropsychology (FANPSE)
   City of celebration: Seville, Andalusia, Spain
   Celebration year: 2020
   Authors: Cristina Giménez Paños; José Ignacio Tembl Ferrairó; Gerardo Fortea Cabo; Lluís Morales Caba; Raúl Espert Tortajada; Marien Gadea Doménech; Miguel Baquero Toledano; Aida Lago Martín.

3. **Title of the paper:** Cognitive function following an intracerebral hemorrhage associated with cerebral amyloid angiopathy.
   Name of the congress: ESO-WSO 2020 Virtual Conference
   Celebration year: 2020
   Authors: Giménez-Paños, Cristina; Tembl-Ferrairó, José; Fortea Cabo, Gerardo; Morales Caba, Lluís; Espert Tortajada, Raúl; Gadea-Domenech, Marien; Baquero Toleado, Miguel; Lago-Martín, Aida.

4. **Title of the paper:** Computed tomography for the characterization of lobar hemorrhages in a hospital series of cerebral amyloid angiopathy.
   Name of the congress: LXXIII Reunión Anual de la Sociedad Española de Neurología
   Celebration year: 2021
   Authors: Tembl Ferrairó, José; Giménez-Paños, Cristina; Fortea Cabo, Gerardo; Vielba Gómez, Isabel, Morales Caba, Luís; Escudero Martínez, Irene; Salom Sanvalero, Juan B.; Más Estellés, Fernando; Aparici Robles, Fernando.

5. **Title of the paper:** Analyzing long-term neuropsychological outcomes of patients with intracerebral hemorrhage associated with amyloid angiopathy: a cross-sectional study.
   Name of the congress: LXXV Reunión Anual de la Sociedad Española de Neurología
   Celebration year: 2023
   Authors: Giménez-Paños, Cristina; Tembl Ferrairó, José Ignacio; Oltra Cucarella, Javier: Gadea Doménech, Marien; Espert Tortajada, Raúl; Lago Martín, Aida.

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

A:	AAC	Angiopatía Amiloide Cerebral
	Aβ	Amyloid-Beta Protein
	AD	Alzheimer's Disease
	AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
	AHA	American Heart Association
	APoE ε4	Apolipoprotein E
	ASA	American Stroke Association
B:	BADL's	Basic Activities of Daily Living
	BBB	Blood-Brain Barrier
	BDRS	Blessed Dementia Rating Scale
	BG	Basal Ganglia
	Bi	Barthel Index
C:	CAA	Cerebral Amyloid Angiopathy
	CAARI	Cerebral Amyloid Angiopathy – Related Inflammation
	CNS	Central Nervous System
	cMBs	Cortical Microbleeds
	cMIs	Cortical Microinfarcts
	cSAH	Cortical Subarachnoid Hemorrhage
	CSF	Cerebrospinal Fluid
	cSS	Cortical Superficial Siderosis
	CSO	Centrum Semiovale

	CT	Computed Tomography
	COWAT	Controlled Oral Word Association Test
D:	DALYs	Disability-Adjusted Life Years
	DM	Diabetes Mellitus
	DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
E:	EF	Executive Function
	EPVS	Enlarged Perivascular Spaces
F:	FHS	Framingham Heart Study
	FLAIR	Fluid-Attenuated Inversion Recovery
	FLPs	Finger-Like Projections
G:	GCA	Global Cortical Atrophy
	GCS	Glasgow Coma Scale
	GCP	Good Clinical Practice
H:	HIV	Human Immunodeficiency Virus
	HCHWA-I	Hereditary Cerebral Hemorrhage with Amyloidosis in Icelandic patients
	HCHWA-D	Hereditary Cerebral Hemorrhage with Amyloidosis in Dutch patients
I:	IADLs	Instrumental Activities of Daily Living
	iCAA	Iatrogenic Cerebral Amyloid Angiopathy
	ICH	Intracerebral Hemorrhage
	ICF	Inform Consent Form

	IDER	Inventario Depresión Estado-Rasgo
	IIS	Instituto de Investigación Sanitaria
	INHERIT	**IN**tracerebral **HE**mo**R**rhage p**R**ospect**I**ve S**T**udy
	INE	National Institute of Statistics
	IQ	Intelligence Quotient
	IQCODE	Informant Questionnaire on Cognitive Decline
J:	JLO	Judgement of Line Orientation
L:	LBi	Lawton and Brody Index
M:	MBI	Mild Behavioral Impairment
	MCI	Mild Cognitive Impairment
	MEC	Mini Examen Cognoscitivo
	MMSE	Mini Mental State Examination
	MND	Major Neurocognitive Disorder
	MoCA	Montreal Cognitive Assessment
	MRI	Magnetic Resonance Imaging
	mRS	Modified Rankin Scale
	MTA	Medial Temporal Lobe Atrophy
N:	NIDDM	Noninsulin-Dependent Diabetes Mellitus
	NIHSS	National Institute Health Stroke Scale
P:	PsyS	Psychiatric Symptoms
	PSCI	Post-Stroke Cognitive Impairment
	PSD	Post-Stroke Dementia

	PWV	Pulse Wave Velocity
R:	ROCFT	Rey-Osterrieth Complex Figure Test
S:	SAH	Subarachnoid Hemorrhage
	SAE	Subarachnoid extension
	SDMT	Symbol Digits Modalities Test
	STAI	State-Trait Anxiety Inventory
	STRIVE	Standards for Reporting Vascular Changes on nEuroimaging
	SVD	Small Vessel Disease
	SWI	Susceptibility Weighted Imaging
T:	TAVEC	Test Aprendizaje Verbal España-Complutense
	TIA	Transient Ischemic Attack
	TFNEs	Transient Focal Neurological Episodes
	ToL	Tower of London
V:	VaD	Vascular Dementia
	VAS-COG	Vascular Behavioral and Cognitive Disorders
	VICCS	Vascular Impairment of Cognition Classification Consensus Study
	VOSP	Visual Objects and Space Perception Test
	VPI	Velocidad de Procesamiento de la Información
W:	WAT	Word Accentuation Test

WHO	World Health Organization
WMHs	White Matter Hyperintensities

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CONTENTS

AN OVERVIEW

Due to the uncommon nature of hemorrhagic stroke, slow and uneven progress has been made in understanding the neurological mechanism responsible for the disease, as well as in identifying and describing the clinical, imaging, and neuropsychological phenotypes that characterize the condition.

The present thesis contributes to our understanding of the key aspects of cerebral amyloid angiopathy (CAA). This was achieved by studying subjects with lobar intracerebral hemorrhage (ICH) caused by sporadic CAA from a clinical, neuropsychological and neuroimaging perspective. In order to boost the use of efficient surrogate markers for CAA, we sought to strengthen the correlations between clinical manifestations, cognitive function and imaging parameters.

The current volume is divided into six sections. Chapters in Section 2 discuss epidemiological and neuropsychological research related to Mild Cognitive Impairment (MCI), Alzheimer's disease (AD), and Vascular dementia (VaD). Also, it highlights the effects of cardiovascular risk factors on cognition, brain structure, and risk of all-cause dementia or AD. Moreover, it describes the most prevalent clinical presentation of cerebral small vessel disease (SVD). The hypothesis and objectives of this thesis are presented in the third chapter.

In chapter 4, we provide a detailed study of a single center cohort of subjects with a lobar ICH. This kind of hemorrhage is the most common clinical manifestation of CAA. Clinical data, magnetic resonance imaging (MRI) studies and neuropsychological assessment were evaluated.
Chapter 5 addresses the main principal results to better understand this highly defined cohort by describing in detail its clinical, cognitive, emotional, functional, and imaging characteristics. Moreover, a relationship is also explained between image markers and cognitive performance.
Finally, chapters 6 and 7 provides a general discussion, final remarks, implications for clinical practice and future perspectives regarding the thesis.

Essentially, in this thesis, we study sporadic ICH-CAA from a translation perspective using neuropsychology and neuroimaging techniques. It is our hope that this volume will stimulate multimodal approach with new ideas which is crucial to gaining new insights into disease process and better identification establishing more accurate diagnostic tools.

ABSTRACT

English summary

Dementia is an acquired disorder that is characterized by a decline in cognition involving one or more cognitive domains (i.e., attention, executive function, processing speed, language, memory). In contrast, mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia in which there are objective cognitive impairments but no decline in overall level of function. While specific subtle changes in cognition can occur in normal aging, MCI can also be a precursor of dementia. Dementia may have more than one cause, particularly as the condition progresses and especially in older persons.

One of the most common causes of cognitive impairment is cerebral amyloid angiopathy (CAA), which is a small vessel disease (SVD) characterized by progressive amyloid beta (Aß)-peptide deposits within small-to medium-size blood vessels of the brain and leptomeninges. In the elderly, spontaneous intracerebral hemorrhage (ICH) is the most dramatic and immediately life-threatening sign of CAA. CAA is a risk factor for the development of dementia in previous studies. Even though cognitive impairment has been observed clinically in CAA, little is known about the frequency, severity, and comprehensive cognitive profile of patients clinically diagnosed with CAA after a lobar ICH.

We hypothesize that a proportion of patients with ICH-CAA may present with cognitive alterations (defined as an in impairment of <1 SD relative to the reference group in 2 cognitive domains) similar to that of SVD vascular cognitive impairment (VCI). In addition, individuals with a greater burden of small vessel disease are more likely to experience moderate to severe cognitive impairment. The main aim of this study is to determine the neuropsychological profile of this cohort. Secondary aim includes to determine the association of cognitive domains with various cerebral SVD markers in this population.

Patients with a diagnosis of lobar and/or cortical ICH associated to CAA, based on the modified Boston criteria, were selected from the INHERIT (**IN**tracerebral **HE**mo**R**rhage p**R**ospect**I**ve S**t**udy) database. Demographic and clinical data were collected, and a comprehensive neuropsychological assessment and a 1.5T and 3T brain magnetic resonance (MRI) was performed between 2016-2021 on patients ≥ 55 years old.

We have seen from our neuropsychological study that, overall, at a median delay of 15 months after the ICH, no process or subprocess were impaired in the cognitive assessment. However, the processes in which they have the lowest performance are processing speed with a *t* score of 42 ± 1.47 (mean ± standard deviation), followed by memory (44 ± 1.61) and planning (44 ± 1.97).

None of the patients in our cohort had symptoms of depression. On both, the state (Depression total state: t=49, SD=11,24; Dysthymia State: t=43, SD=13.56 and Euthymia State: t=52, SD=11.29) and the trait scale (Depression total trait: t=44, SD=9.96; Dysthymia Trait: t= 40, SD=10.22; Euthymia Trait: t= 45, SD 11.61), patients scored appropriately. The results of this analysis indicate that none of the patients in our cohort had depression symptoms. Similar results were observed with anxiety, with an appropriate severity (Anxiety State: t=51, SD=11.79) and frequency (Anxiety Trait: t=45, SD=8.27) level. In this population, no antidepressants and anxiolytic medications were prescribed.

Finally, among the 24 long-term survivors, 18 (75%) were independent (mRs 0-2) and 4 (17%) were dependent (mRs= 3) presenting a good ability to carry out basic activities of daily living (Bi = 98.60) as well as instrumental activities of daily living (LBi = 6.56).

Despite our cohort's adequate performance on all tests included in the cognitive assessment battery, we found strong associations between putative biomarkers of parenchymal CAA and cognitive domains. MTA was strongly associated with: Attention: p=0.002; adjusted R^2= 31; Planning: p= 0.006; adjusted R^2= 26; Verbal fluency: p=0.001; adjusted R^2= 35); Language: p=0.001; adjusted R^2= 36; Memory: p=0.003; adjusted R^2= 29; Visuospatial: p=0.005; adjusted R^2= 26; Visuoconstruction: p=0.006; adjusted R^2= 26). Also, significant correlation was found between SVD total score and Verbal fluency p=0.032; adjusted R^2= 15; Memory p=0.013; adjusted R^2= 21; Visuoperception: p=0.0548; adjusted R^2= 11; Visuospatial: p=0.037; adjusted R^2= 14. Regarding the CAA total score, we found significant correlations with Memory: p=0.018; adjusted R^2= 19; and Visuoperception: p=0.0326; adjusted R^2= 15. As for GCA, we only found that it correlated significantly with Visuoperception: p=0.0221; adjusted R^2= 17. In contrast, ICH volume was not significantly correlated with any cognitive process.

In conclusion, lobar ICH survivors have adequate cognitive and functional performance 15 months after the index event. Moreover, they do not present affective symptoms. However, we found that hippocampal atrophy (MTA) – an imaging marker traditionally associated with neurodegenerative disorders and memory impairment – is intimately related to potential future impairment in a wide range of cognitive processes.

Spanish summary

La demencia es un trastorno adquirido que se caracteriza por una disminución de la cognición que implica uno o más procesos cognitivos (atención, funciones ejecutivas, velocidad de procesamiento, lenguaje, memoria, etc.). Por otra parte, el deterioro cognitivo leve (DCL) es un estado intermedio entre la cognición normal y la demencia en la cual existen alteraciones cognitivas objetivas, pero no existe una disminución del nivel general de funcionamiento. Si bien pueden producirse cambios específicos en la cognición en el envejecimiento normal, el DCL también puede ser un precursor de la demencia. La demencia puede tener más de una casusa, especialmente a medida que la enfermedad avanza sobre todo en personas mayores.

Una de las causas más comunes de deterioro cognitivo es la angiopatía amiloide cerebral (AAC), la cual es una enfermedad de pequeño vaso caracterizada por el acúmulo de la proteína beta-amiloide dentro de los vasos sanguíneo de tamaño pequeño del cerebro y en las leptomeninges. En la población mayor, la hemorragia intracerebral (HIC) espontánea es el signo más dramático y potencialmente mortal. Se ha evidenciado que la AAC es un factor de riesgo para el desarrollo de demencia. Aunque se ha observado clínicamente deterioro cognitivo en pacientes con AAC, poco se sabe sobre la frecuencia, la gravedad y el perfil cognitivo de los pacientes diagnosticados con esta condición después de debutar con una HIC lobar.

Nuestra hipótesis es que una proporción de pacientes con HIC-AAC puede presentar alteraciones cognitivas (definidas como un deterioro de >1 DT en relación con el grupo de referencia en 2 procesos cognitivos) similares a las del deterioro cognitivo vascular. Además, los sujetos con mayor carga de enfermedad de pequeño vaso tienen más probabilidades de experimentar deterioro cognitivo moderado-grave. El objetivo principal de este estudio es determinar el perfil neuropsicológico de esta cohorte. El objetivo secundario incluye determinar la asociación entre los procesos cognitivos y los marcadores de enfermedad de pequeño vaso en resonancia magnética en esta población.

Se seleccionaron pacientes con diagnóstico de HIC lobar y/o cortical asociada a AAC, según los criterios de Boston modificados, de la base de datos INHERIT (Intracerebral HemoRrhage pRospectIve Study). Se recopilaron datos demográficos y clínicos, y se realizó una evaluación neuropsicológica integral y una resonancia magnética (RM) cerebral de 1.5 teslas (1.5T) y 3 teslas (3T) a pacientes ≥ 55 años entre 2016 y 2021.

De nuestro estudio neuropsicológico se desprende que, en general, con una mediana de 15 meses entre la realización de la evaluación y el evento índice, ninguno de los procesos y subprocesos evaluados presentaba alteraciones. Sin embargo, los procesos en los que presentaban un rendimiento más bajo son la velocidad de procesamiento de la información (VPI), con una puntuación t de 42 ± 1,47 (media ± desviación típica), seguida de la memoria (44 ± 1,61) y la planificación (44 ± 1,97).

Ninguno de los pacientes de nuestra cohorte presentaba síntomas de depresión. Tanto en la escala de estado (estado total de depresión: t=49, DT=11,24; estado distimia: t=43, DT=13,56 y estado eutimia: t=52, DT=11,29) como en la de rasgo (rasgo total de depresión: t=44, DT=9,96; rasgo distimia: t=40, DT=10,22; rasgo eutimia: t=45, DT=11,61), los pacientes puntuaron adecuadamente. Los resultados de este análisis indican que ninguno de los pacientes de nuestra cohorte presentaba síntomas de depresión. Se observaron resultados similares con la ansiedad, con un nivel adecuado de gravedad (Estado de Ansiedad: t=51, DT=11,79) y frecuencia (Rasgo de Ansiedad: t=45, DT=8,27). En esta población no se prescribieron antidepresivos ni ansiolíticos.

Finalmente, entre los 24 supervivientes, 18 (75%) eran independientes (mRs= 0-2) y 4 (17%) eran relativamente dependientes (mRs= 3) presentando una buena capacidad para realizar las actividades básicas de la vida diaria (Bi = 98,60) así como las actividades instrumentales de la vida diaria (LBi = 6,56).

A pesar del rendimiento adecuado de nuestra cohorte en todas las pruebas incluidas en la batería de evaluación cognitiva, encontramos fuertes asociaciones entre biomarcadores putativos de AAC parenquimatosa y procesos cognitivos. La atrofia del hipocampo se asoció fuertemente con: Atención: p=0,002; R^2 ajustado= 31; Planificación: p= 0,006; R^2 ajustado= 26; Fluidez verbal: p=0,001; R^2 ajustado= 35); Lenguaje: p=0,001; R^2 ajustado= 36; Memoria: p=0,003; R^2 ajustado= 29; Visuoespacial: p=0,005; R^2 ajustado= 26; Visuoconstrucción: p=0,006; R^2 ajustado= 26). Asimismo, se halló una correlación significativa entre la puntuación total de la escala de enfermedad de pequeño vaso (SVD total score) y la Fluidez verbal p=0,032; R^2 ajustado= 15; Memoria p=0,013; R^2 ajustado= 21; Visuopercepción: p=0,0548; R^2 ajustado= 11; Visuoespacial: p=0,037; R^2 ajustado= 14. En cuanto a la puntuación total en la escala de angiopatía amiloide cerebral (CAA total score), encontramos correlaciones significativas con Memoria: p=0,018; R^2 ajustado= 19; y Visopercepción: p=0,0326; R^2 ajustado= 15. En cuanto a la atrofia cerebral global (ACG), sólo encontramos que se correlacionaba significativamente con Visuopercepción: p=0,0221; R^2 ajustado= 17. En cambio, el volumen de la HIC no se correlacionó significativamente con ningún proceso cognitivo.

En conclusión, los supervivientes de HIC lobar tienen un rendimiento cognitivo y funcional adecuado 15 meses después del evento índice. Además, no presentan síntomas afectivos. Sin embargo, observamos que la atrofia del hipocampo (ATM) -un marcador de imagen tradicionalmente asociado con trastornos neurodegenerativos y con el deterioro de la memoria- está íntimamente relacionado con posibles alteraciones futuras en una amplia gama de procesos cognitivos.

Valencian summary

La demència és un trastorn adquirit que es caracteritza per una disminució de la cognició que implica un o més dominis cognitius (atenció, funcions executives, velocitat de processament de la informació, llenguatge, memòria, etc.). D'altra banda, el deteriorament cognitiu lleu (DCL) és un estat intermedi entre la cognició normal i la demència en el qual hi ha deficiències cognitives objectives però no hi ha una disminució del nivell general de funcionament. Si bé es poden produïr canvis subtils específics en la cognició en l'envelliment normal, el DCL també pot ser un precursor de la demència. La demència pot tenir més d'una causa, especialment a mesura que la malaltia avança i sobretot en persones grans.

Una de les causes més comunes de deteriorament cognitiu és l'Angiopatia Amiloide Cerebral (AAC), que és una malaltia de petits vasos caracteritzada per dipòsits progressius de pèptids beta amiloide dins dels vasos sanguinis de mida petita i mitjana del cervell i les leptomeninges. En la gent gran, l'hemorràgia intracerebral (HIC) espontània és el signe més dramàtic i que posa inmediatament en perill al subjecte. S'ha evidenciat que l'AAC és un factor de risc per al desenvolupament de la demència. Tot i que s'ha observat clínicament un deteriorament cognitiu a l'AAC se sap poc sobre la freqüència, la gravetat i el perfil cognitiu complet dels pacients diagnosticats clínicament d'AAC després d'una HIC lobar.

La nostra hipòtesi és que una proporció de pacients amb HIC-AAC pot presentar alteracions cognitives (definides com un deteriorament de > 1 DT en relació amb el grup de referència en 2 processos cognitius) similars als del deteriorament cognitiu vascular. A més, els subjectes amb més càrrega de malaltita de petit vas cerebral tenen més probabilitats d'experimentar deteriorament cognitiu moderat-greu. L'objectiu principal d'aquest estudi és determinar el perfil neuropsicològic d'aquesta cohort. L'objectiu secundari inclou determinar l'associació entre els processos cognitius i marcadors de malaltia de petit vas en aquesta població.

Es van seleccionar pacients amb diagnòstic de HIC lobar i/o cortical associada a AAC, segons els criteris de Boston modificats, de la base de dades INHERIT (Intracerebral HemoRrhage pRospectIve Study). Es van recopilar dades demogràfiques i clíniques, i es va realitzar una avaluació neuropsicològica integral i una ressonància magnética (RM) cerebral de 1.5 tesles (1.5T) i 3 tesles (3T) a pacients ≥ 55 anys entre 2016 i 2021.

Del nostre estudi neuropsicològic es desprèn que, en general, amb una mitjana de 15 mesos per a la realització de l'avaluació després de l'esdeveniment índex, cap dels processos i els subprocesos avaluats presentaven alteracions. Tot i això, els procesos en que presentaven un rendiment més baix son la velocitat de processament, amb una puntuació t de 42 ± 1,47 (mitjana ± desviació típica), seguida de la memoria (44 ± 1,61) i la planificació (44 ± 1,97).

Cap dels pacients de la nostra cohort presentava símptomes de depressió. Tant a l'escala d'estat (estat total de depressió: t=49, DT=11,24; estat de distímia: t=43, DT=13,56 i estat d'eutimia: t=52, DT=11,29) com en la de tret (tret total de depressió: t=44, DT=9,96; tret de distimia: t=40, DT=10,22; tret d'eutimia: t=45, DT=11,61), els pacients van puntuar adequadament. Els resultats d'aquesta anàlisi indiquen que cap dels pacients de la nostra cohort no presentava símptomes de depressió. Es van observar resultats similars amb l'ansietat amb un nivell adequat d'ansietat (Estat d'ansietat: t=51, DT=11,79) i frequüència (Tret d'ansietat: t=45, DT=8,27). En aquesta població no es van prescriure antidepressius ni ansiolítics.

Finalment, entre els 24 supervivents, 18 (75%) eren independents (mRs=0-2) i 4 (17%) eren relativamente dependents (mRs=3) presentant una bona capacitat per fer les activitats bàsiques de la vida diària (Bi= 98, 60) així com les activitats instrumentals de la vida diària (LBi=6,56).

Malgrat el rendimient adequat de la nostra cohort en totes les proves incloses a la batería d'avaluació cognitiva, trobem fortes asociaciones entre biomarcadors putatius d'AAC parenquimatosa i processos cognitius. L'atròfia de l'hipocamp es va associar fortament amb: Atenció: p=0,002; R^2 ajustat= 31; Planificació: p= 0,006; R^2 ajustat= 26; Fluïdesa verbal: p=0,001; R^2 ajustado= 35); Llenguatge: p=0,001; R^2 ajustat= 36; Memòria: p=0,003; R^2 ajustat= 29; Visuoespacial: p=0,005; R^2 ajustat= 26; Visuoconstrucció: p=0,006; R^2 ajustat= 26). Així mateix, es va trobar una correlació signitifactiva entre la puntuació total de ll'escala de petit vas (SVD total score) i la fluïdesa verbal p=0,032; R^2 ajustat= 15; Memòria p=0,013; R^2 ajustat= 21; Visuopercepción: p=0,0548; R^2 ajustat= 11; Funció visoespacial: p=0,037; R^2 ajustat= 14. Quant a la puntuació total de l'escala d'AAC (CAA total score), trobem correlacions significatives amb Memòria: p=0,018; R^2 ajustat= 19; i Visopercepció: p=0,0326; R^2 ajustat= 15. Quant l'atròfia cerebral global (ACG), només vàrem trobar que es correlacionava significativament amb Visuopercepció: p=0,0221; R^2 ajustat= 17. En canvi, el volum de la HIC no es va correlacionar significativament amb cap procés cognitiu.

En conclusió, els supervivents de HIC lobar tenen un rendiment cognitiu i funcional adequat 15 mesos després de l'esdeveniment índex. A més, no presenten símptomes afectius. Tot i això, observem que l'atròfia de l'hipocamp – un marcador d'imatge tradicionalment associat amb trastorns degeneratius i amb el deteriorament de la memòria – está íntimament relatzionat amb possibles alteraciones futures en una àmplia gamma de procesos cognitius.

GETTING STARTED: THE INTRODUCTION

1.1. The Neurocognitive Disorder: Epidemiology, Etiology, and Classification

Advances in medicine, improved access to health systems, reduced infant mortality, increased levels of social well-being and quality of life, promotion of the importance of physical exercise, and increased knowledge and access to healthy diets are leading to an increase in the world's population along with an increase in life expectancy.

Figure 1. Percentage of Population Aged 65 Years or Older in Spain 1900-2068[1]

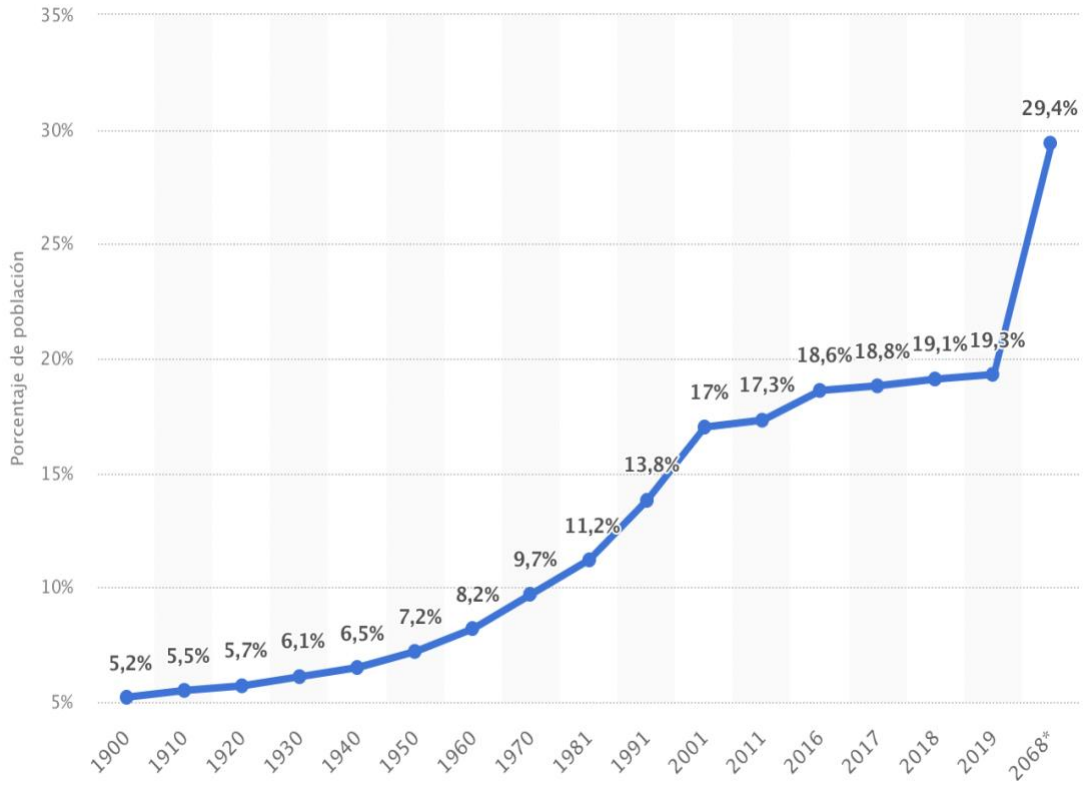


Figure 1 presents the evolution of the percentage of the population in Spain aged 65 and over from 1900 to 2019, as well as projections up to the year 2068. Between the years 1900 and 2019, the percentage of inhabitants aged 65 years or older increased by approximately 12 points.

As a result of this change in the population curve, social, clinical, and scientific efforts have been devoted to advancing healthy aging and quality of life since the increase in life expectancy leads to an increase in age-related pathologies.

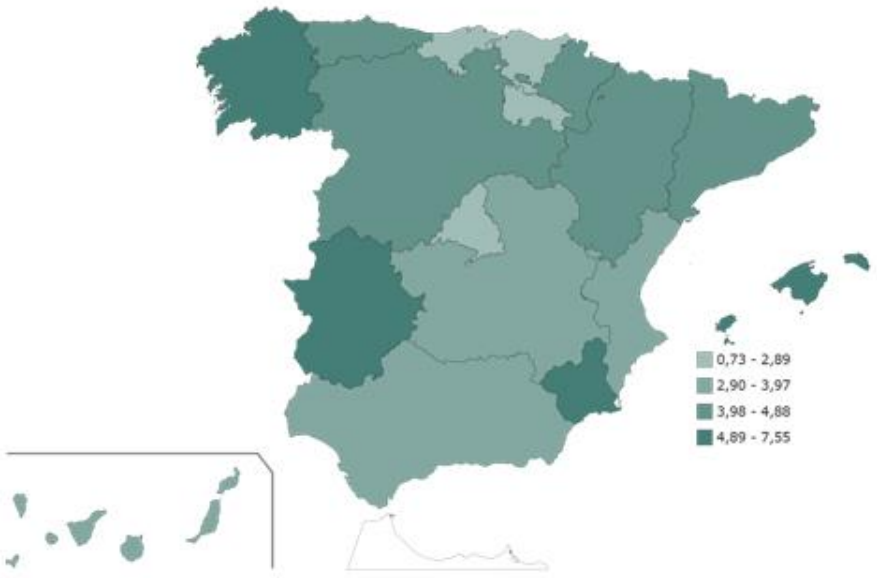
Since the aging population is growing faster than ever, there is a sharp rise in the incidence of multiple diseases, including cardiovascular disease, cancer, and neurodegenerative disorders, including dementia such as AD[2].

It should be noted that dementia is not a disease, but rather a collection of symptoms that are caused by many clinical circumstances and/or underlying causes. In general, it involves difficulties in reasoning, memory, and attention, which affect patients' ability to be independent. It is important to emphasize that the process of healthy aging is often associated with normal changes in the structure and functioning of the brain, and in the ability to process information, pay attention, cognitive flexibility, as well as have good visual-spatial skills and memory[3].

A distinction needs to be made between pathological deterioration and biological, cognitive, and functional changes resulting from healthy aging.

According to the World Health Organization (WHO), dementia is the seventh leading cause of death among all diseases and a major cause of disability and dependency among older people. People living with dementia, as well as their carers, families, and society at large, are affected by the physical, psychological, social, and economic consequences of dementia. The lack of awareness and understanding of dementia often leads to stigmatization and a lack of access to diagnosis and care. Worldwide, around 55 million people have dementia, with over 60% living in low- and middle-income countries. As the proportion of older people in the population is increasing in nearly every country, this number is expected to rise to 78 million in 2030 and 139 million in 2050. In Spain, although there are no official statistics available concerning dementia cases, some estimates place the number between 500,000 and 600,000, with a forecast of close to one million by the year 2050, according to the Instituto Nacional de Estadística (INE).

Figure 2. Survey on Disability, Personal Autonomy and Dependency Situations, Autonomous Community, Dementia of Alzheimer's Type, both Sexes[4].



The term Mild Cognitive Impairment (MCI) generally refers to a prodromal state of relatively intact functioning with some signs of neuropsychological impairment[5]. In postmortem studies, autopsy samples of dead individuals with MCI showed significant AD brain pathology, suggesting progression of the disease from MCI to AD[6–8]. It has been argued that MCI is more of an incipient form of AD than preclinical AD[9]. This suggests that AD is a life-course condition[10] with an insidious onset that may occur decades before any clinical symptoms appear[11–13].

The term Major Neurocognitive Disorder (MND) - previously called dementia - is a syndrome that progresses with significant deterioration of cognitive domains as compared to previous levels of cognitive performance in any evaluation process or subprocess, i.e., attention, executive functions, language, memory, and/or spatiotemporal perception, and may also be associated with changes in emotional behavior and difficulties at the functional level[3]. The deficits must represent a decline from previous level of function and be severe enough to interfere with daily function and independence.

MND comes in a variety of forms. AD is the most common form and may account for 60-70% of cases. Other major forms include VaD, dementia with Lewy bodies (abnormal aggregates of protein that develop inside nerve cells), and a group of diseases that contribute to frontotemporal dementia (degeneration of the frontal lobe of the brain).

MND may also become prevalent after a stroke or in the context of certain infections such as HIV, alcohol abuse, repeated physical injuries to the brain (such as chronic traumatic encephalopathy) or coexist.

In the light of the aging population and growing awareness of AD and other late-life MND, clinicians need to be equipped to identify cognitive impairment and ask about functional decline to avoid missing AD cases and related MND. Clinicians must be able to recognize and manage the early cognitive manifestations of AD and other MND.

1.1.1. Alzheimer's/Vascular Spectrum Dementia Heterogeneity

It is widely believed that AD and VaD are distinct types of dementia. A growing body of evidence, however, indicates that many patients diagnosed with either AD or VaD have biological substrates that are associated with both dementias, suggesting considerable clinical and pathological heterogeneity.

In terms of neuropathology underlying insidious onset AD/VaD spectrum dementia, there is now a growing body of research demonstrating considerable heterogeneity[14,15]. Several epidemiological and community-based studies show that many, if not the majority, of dementia patients present with mixed neuropathology[16–20]. For example, Boyle and colleagues[21] examined over 1.000 participants. Eight types of neuropathology (i.e., macroscopic infarct, Lewy bodies, hippocampal sclerosis, TDP-43, cerebral amyloid angiopathy, atherosclerosis, and arteriosclerosis) including neuropathology traditionally associated with AD (i.e., neuritic plaques/neurofibrillary tangles) were quantified.

Approximately 67.5% of dementia cases could be attributed to a combination of all eight neuropathologic indices. Research in subsequent years revealed that mixed AD/VaD dementia syndromes are much more common than either "pure" AD or VaD dementia syndromes[22]. In sum, neuropathological heterogeneity is likely present for most AD/VaD patients.

The hypothesis that the pathological changes associated with these two disorders are additive, or directly interrelated to each other, is a matter of lively debate[23,24]. Identifying *how much* or *what proportion* of a patient's clinical or phenotypic presentation correlates with *what* type of underlying neuropathology requires an inclusive algorithm that defines meaningful neuropsychological phenotypes and biological indicators of dementia via imaging and fluid biomarkers. It is important to note that this type of algorithm for diagnosing AD/VaD spectrum dementia differs greatly from current dementia diagnostic schemes, which rely on a positive finding on an imaging study or a single fluid biomarker to determine the diagnosis[25]. We agree that models associating phenotypic features - which are largely defined through neuropsychological tests - in conjunction with quantification of biological substrates, would be a more heuristically meaningful method for AD/VaD classification.

On the other hand, several studies point to the association between vascular disease and dementia. First, defects in perfusion caused by impaired heart function and cerebral arterial disease could be associated with dementia, such as AD[26,27] .

Second, research has linked midlife hypertension[28,29], hypercholesterolemia[30,31], diabetes mellitus[31,32], obesity[33], smoking[34], and physical inactivity[34] with AD/VaD dementia. Third, epidemiological research, including data from the Framingham Heart Study (FHS)[35] and the Rotterdam Study[36], suggests that vascular risk factors can impair neuropsychological performance, as well as develop clinical syndromes like MCI and dementia, such as AD. Fourth, it is possible to identify and possibly treat all vascular risk factors previously listed. The management of medical illnesses associated with cardiovascular risk, including diet and other modifiable lifestyle factors, such as cardiovascular fitness[37], can delay or prevent dementia[38].

1.1.2. Risk Factors for Cognitive Decline and Dementia

The Framingham Heart Study (FHS), globally known as the Framingham study, established in 1948[39], has been the longest ongoing prospective cohort study with cardiovascular diseases and stroke as primary outcomes. The FHS challenged the notion of a single-cause disease model by adopting a presumptive multicausal approach. Its initial purpose was to study cardiovascular diseases and stroke but was extended in recent decades to include other chronic diseases, such as neurodegenerative disorders. The link between cardiovascular and nervous system disorders has become evident over the last several decades.

1.1.2.1. Hypertension

Hypertension impairs functional hyperemia, i.e., the ability of the brain to coordinate brain activity and blood flow[31,33]. It is caused by structural changes in blood vessels and inadequate autoregulation. Aβ accumulation increases hypertension and weakens functional hyperemia in animal models[30,31]. There is growing evidence that vascular risk factors, such as hypertension, might contribute to cognitive decline. Early and recent FHS studies suggest that elevated blood pressure and/or the presence of hypertension may negatively affect cognition, particularly executive function, language, and memory.

1.1.2.2. Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (DM) is a chronic disease affecting about 422 million people worldwide, and about 20% of individuals aged 65 years and above suffer from it[40]. It is a major vascular risk factor and contributes to the development of AD. Raising plasma insulin levels through intravenous infusion in human AD patients increased cerebrospinal fluid (CSF) levels of Aβ1-42. DM patients have also been shown to have alterations in the vascular system and increased permeability of the blood-brain barrier (BBB)[30,41]. Increased insulin resistance, impaired insulin signaling, reduced insulin transport across the BBB, and increased levels of receptors for advanced glycation end-products (RAGE and AGEs) are the mechanistic factors linked to diabetes and dementia[32].

The link between diabetes and cognition was first posited by Miles and Root more than 85 years ago when they observed impaired memory and psychomotor performance in diabetes patients[42]. In line with their findings, several FHS researchers found a complex relationship between diabetes, high blood pressure, and cognitive performance.[43] There is an association between a longer duration of noninsulin-dependent diabetes mellitus (NIDDM) and worse performance on verbal memory and verbal concept formation tests.

1.1.2.3. Hyperlipidemia

Studies have demonstrated that hyperlipidemia contributes to VaD, small vessel disease, and AD[33,44]. In a meta-analysis, midlife total cholesterol levels were associated with an increased risk of all dementias[30,31]. Dyslipidemia has been linked to the insulin-resistant syndrome, as insulin is a primary regulator of lipid metabolism. Furthermore, lipids and lipoproteins play a crucial role in the production and clearance of Aβ.

1.1.2.4. Smoking and Serum Cholesterol

The risk of cardiovascular disease is well known to be influenced by smoking and serum cholesterol[45–49]. Although a large body of research has demonstrated a significant correlation between cardiovascular health and brain health, the relationship between these variables and cognition remains ambiguous. The effects of smoking on cognitive function have been documented by some researchers[48].

It has been suggested that smoking status can accelerate the progression of vascular brain injury, global and hippocampal atrophy, and a decline in executive function[50], as demonstrated by smokers' slower performances on alternating attention measured by the Trail B test[51]. However, other studies have not found any correlation[52].

Regarding low serum total cholesterol levels, which may be caused by poor nutrition and chronic illness, have been linked with lower cognitive performance as it relates to abstract reasoning, attention, verbal fluency, and executive functioning[53] . In contrast, higher total cholesterol levels in midlife have been linked to an increased risk of cognitive impairment in late life[49]. In sum, these studies suggest that both low and high levels of total cholesterol may adversely affect cognition, so maintaining normal cholesterol levels is beneficial to preserving brain health.

1.1.3. Neuropsychological Contributions to MCI/MND Diagnosis

As noted, MCI is an intermediate stage between normal aging and, with many patients, the development of MND such as AD. Patients with MCI demonstrate cognitive impairment in the presence of generally intact functional abilities[54]. MCI research has grown rapidly over the last several decades as researchers have sought to better understand and characterize the disease. This growth has been driven in part by the need to accurately identify individuals with an increased risk of MND, prior to the onset of frank dementia. The number of cases has increased year over year as well as the enormous burden on society due to high healthcare costs and caregiving requirements. It is becoming increasingly clear to researchers and healthcare professionals that the best way to avoid a public health crisis involving MND is to treat putative neurodegenerative illnesses well before dementia and irreversible neuronal loss develop[55].

1.1.3.1. Contributions to the Diagnosis of MCI/MND due to AD

Following the introduction of the term MCI in the 1980s[56], extensive research has been conducted to improve diagnostic sensitivity and specificity. As a result, AD risk identification has been improved. However, Petersen's criteria for the conventional diagnosis of MCI[57] were not proposed until the dawn of the 21st century. Although these improvements, from a neuropsychological perspective, this early definition was based solely on memory deficits as well as complaints related to instrumental activities of daily living (IADLs). Petersen's initial criteria for MCI included: a) a memory complaint, preferably corroborated by an informant; b) impaired memory function for one's age and education; c) preserved general cognitive function; d) intact activities of daily living; and d) not dementia. The generally exclusive focus on "memory" as the predominant neuropsychological impairment in MCI was (and remains) consistent with research showing that patients with MCI often perform poorly on memory measures that healthy older adults, while still maintaining intact performance in other cognitive domains[58]. Then, critiques pointed to the overly narrow definition of impairment.

For that reason, the authors expanded the definition of cognitive impairment to include both memory and nonmemory domains. These criteria form the basis of the four commonly used conventional MCI subtypes[59]: a) single-domain amnestic MCI, b) single-domain nonamnestic MCI, c) multidomain amnestic MCI, and d) multidomain nonamnestic MCI.

Even though these criteria have improved, they tended to focus primarily on the presence or absence of memory impairment, anchoring MCI subtypes in terms of "amnestic" or "nonamnestic" deficits.

Another challenge was determining the cut-score(s) to indicate cognitive impairment. Initially, a score of 1.5 standard deviations below age- and education-matched control subjects was considered abnormal for amnestic MCI[58]. Upon further consideration, Petersen suggested that this criterion may need to be adjusted for certain factors such as low educational attainment[59].

Finally, questions remain regarding the paradigm and specific test used to assess amnestic impairment. For example, the performance of both delayed recall and recognition tests is often omitted in many settings, despite considerable empirical evidence that clinical amnesia should be diagnosed using both tests[60]. Despite these methodological issues, conventional diagnostic criteria[59] continue to be the method of choice in research including clinical trials targeting MCI and other large-scale studies.

Despite improvements over the past decade, MCI is still evaluated most often by subjective rating scales, brief cognitive screens, and/or single impaired test scores rather than objective empirical methods[61]. For the purpose of more accurately diagnosing MCI subtypes, a neuropsychological-based diagnostic criteria referred to as *comprehensive criteria* have been developed. Jak, Bondi, et al[62]. introduced the term comprehensive diagnostic criteria for MCI by comparing the psychometric performances of five different MCI diagnostic strategies on a comprehensive neuropsychological protocol. Based on five different strategies (i.e., historical, typical, comprehensive, liberal, and conservative), 90 nondemented and neurologically normal older adults were classified as having either normal aging or MCI.

To assess the stability of the diagnosis, a subset of 73 patients was evaluated 17 months later. Each of the five diagnostic strategies differed in the cutoff used to determine objective cognitive impairment and in the number of neuropsychological tests within a cognitive domain necessary for an MCI diagnosis.

Table 1. MCI Diagnosis Schemes

Criteria	Origin	Impairment Cutoff (SD below age-appropriate norms)	Number of Tests required to be impaired for MCI diagnosis
Historical	Original Petersen (2001)	>1.5 SD	1 (WMS-R LM subtest only)
Conventional	Petersen and Morris (2005)	>1.5 SD	1 (within any cognitive domain)
Comprehensive	Jak et. al (2009)	>1 SD	2 (within any cognitive domain)
Liberal	Jak et. al (2009)	>1 SD	1 (within any cognitive domain)
Conservative	Jak et. al (2009)	>1.5 SD	2 (within any cognitive domain)

MCI diagnostic schemes as compared in Jak et al.[63]. MCI, mild cognitive impairment; WMS-R LM, Wechsler Memory Scale-Revised – Logical Memory.

To overcome the common pitfalls of many MCI diagnostic paradigms, comprehensive diagnostic criteria were developed. First, to improve the balance between reliability and sensitivity of the criteria to detect mild impairment, a lower cutoff of 1 SD below normative data (compared to 1.5 SD) was adopted[64,65]. Second, it was considered that isolated impaired scores often have limited interpretive value.

A study conducted by Heaton and colleagues[65] found that most neurologically normal adults obtained at least one “abnormal” test score on the expanded Halstead-Reitan neuropsychological test battery with the prevalence of false-positive impaired scores being even greater among older adults.

According to Palmer and colleagues[66], considerable numbers of healthy adults earned one impaired score in two different cognitive domains, but only a small fraction (approximately 5% or less) earned two or more impaired scores within the same domain. As a result, two or more test within a domain must be impaired for a domain to be considered impaired under the comprehensive MCI criteria. Jak, Bondi, et al.[62] further discussed the relative advantages and disadvantages of each diagnostic approach, to provide insight into the most appropriate MCI diagnostic approach. It has been noted that the comprehensive criteria offered a better balance between sensitivity and specificity for detecting mild impairment than conventional criteria[59]. Comprehensive criteria exhibited superior diagnostic stability over time compared to other schemes. In other words, schemes that merely required impaired performances on one test within a domain tended to result in relatively high percentages of individuals changing subtypes over time (18%-33%).

In conclusion, the comprehensive criteria maintained a satisfactory level of diagnostic stability while offering the best balance between sensitivity and specificity.

1.1.3.2. Neuropsychological Contributions to the Diagnosis of VCI/VaD

Vascular cognitive impairment (VCI) is a clinical syndrome in which there is a decline in neurocognitive functions induced by cerebrovascular disease. This decline can vary in severity, ranging from MCI to MND[67].

The term VCI was introduced based on three considerations: 1) It is evident that there are diverse neuroradiological and clinical presentations of disorders where vascular disease is believed to be either the cause or a contributor factor to a decline in neurocognitive functions; 2) According to Hachinski and colleagues, cerebrovascular and cardiovascular risk factors are often identifiable[68]. By identifying and treating cerebrovascular and cardiovascular risk factors, this illness may be significantly reduced; 3) In their study, Hachinski and colleagues point out that dementias with insidious onset tend to be viewed through an AD lens[69]. As a result of this "*Alzheimerization of dementia*", memory impairment becomes the most prevalent and salient neurocognitive characteristic. This point of view has been challenged. It has been noted that impairment on memory test does not necessarily correspond to clinical amnesia[70]. For example, there are patients who present with low scores on both delayed free recall and recognition tests and other patients who score higher on recognition compared to delay free recall. In some cases, these differences were not appreciated.

VCI is caused by a variety of etiological factors that are diverse. In clinical practice, etiological perspectives frequently differentiate between cognitive changes associated with cortical territory infarctions and those associated with subcortical infarctions. There are several factors that can cause cortical territory vascular incidents, including arterial thrombosis in the carotid artery, vertebral artery, of the middle cerebral artery, of the anterior cerebral artery, and of the posterior cerebral artery. As for the subcortical causes, they may include strategic strokes (in the thalamus or basal ganglia)[71] as well as small vessel disease, lacunes, and leukoaraiosis. Furthermore, cerebral hypoperfusion has been identified as a pathophysiological process that may contribute to degeneration and cognitive decline in VaD[72].

VCI has different diagnostic criteria, with several groups putting forward competing criteria[73,74]. They share similar characteristics but differ in terms of the emphasis placed on information derived from the patient's history, a physical examination, diagnostic testing, the neurocognitive profile, and a neuroimaging[15,75]. An essential question concerning VCI is the cause-and-effect relationship between vascular disease and neurocognitive impairment.

Clinical classification criteria for VCI were published as part of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[3]. Furthermore, the International Society of Vascular Behavioral and Cognitive Disorders (VAS-COG)[15] and the American Heart Association (AHA)[75] have both suggested criteria for classifying neurocognitive impairment with vascular contributions.

In general, these criteria require objective evidence of deterioration in neurocognitive function, either following a cardiovascular event or associated with cerebrovascular disease. Depending on the severity of symptoms, these criteria also allow for classifications of vascular MCI or VaD. Depending on the availability of supporting evidence, all of these criteria can be used to subclassify VCI as possible or probable. It allows for the diagnosis of VCI even without neuroimaging or when there is evidence of another neurocognitive disorder present. The Vascular Impairment of Cognition Classification Consensus Study (VICCCS)[73] surveyed an international sample of clinicians and research to achieve a conceptual consensus for VCI, along with VCI subtypes such as multi-infarct dementia, mixed dementia, and postroke dementia and have suggested areas of research that could further support the construct and subtyping of VCI. These suggestions include determining if subtypes of mild VCI are empirically supported and improving our understanding of the relative contribution of co-occurring pathology in cases of mixed dementia comorbid with psychiatric disorders or other neurodegenerative conditions.

1.1.4. Neuropsychological Perspective of Daily Living

Everyday activities, such as grooming and meal preparation, are cognitively complex tasks that involve the coordination of multiple cognitive, perceptual, and motor operations. It is therefore not surprising that older adult's ability to perform daily tasks smoothly and efficiently is diminished over time as their cognition changes. Several studies have shown mild difficulties in performing everyday tasks in people with MCI; in dementia, impairments in everyday activities are a diagnostic criterion associated with several negative outcomes. Everyday difficulties have been linked to decreased quality of life, frustration, depression[76–78], and institutionalization[79] as well as caregiver burden[80] and costs of care[81,82].

Often, neuropsychologists are consulted to assess patients' independence and suggests ways to improve their daily lives. Thus, understanding the link between cognitive constructs precisely measured in neuropsychological evaluations and everyday functioning is crucial.
As mentioned before, deficiencies in everyday action associated with loss of autonomy are essential AD criteria[54,83]. During mild to moderate stages of AD, it is common to lose competence performing everyday tasks like cooking and managing finances, while during severe stages, it is common to lose competence performing basic functions like feeding and bathing[84]. It was reported that patients with white matter ischemia and cortical infarcts showed greater cognitive impairment and impaired everyday activities compared to those with only white matter ischemia, even though they did not differ on more basic everyday tasks[85]. Cognitive impairment has been shown to be a strong predictor of functional ability, even though other factors such as behavioral disturbances[86] and apathy may play a role as well[87].

When cognition is impaired, functional activities are also impaired to a greater extent. Some studies examining the relation between neuropsychiatric disturbances and functional impairment have theorized that psychiatric symptoms arise from neurobiological correlates shared by the cognitive processes relevant to functional abilities (e.g., executive functioning)[88].

Fewer details are known about how MCI affects every day functioning[83,89]. In order to be diagnosed with MCI, everyday action difficulties must not cause a loss of independence in functional activities[54,83]. Despite this, recent research suggests that everyday action difficulties are commonly observed in the MCI stage[90–93]. According to Farias et al.[93], participants with MCI had everyday memory ratings about one standard deviation worse than normal controls, and the rest of domains were about half a standard deviation worse.

Problems with functional activities in healthy older adults start out as subtle deficits and progress over time[94]. Moreover, it has been found that slight functional changes may predict conversion from normal aging to MCI[93,95].

Several studies have examined the role of cognitive processes in everyday functioning and found significant associations with measures of episodic memory and executive function. A number of studies have found that episodic memory impairment is the most significant disrupting everyday functioning, especially in cases of early dementia and MCI[93,96,97].
However, an in-depth study of participants with VaD found that executive functioning, rather than memory or other cognitive traits, correlated with informant-based measures of everyday functioning[98].

Further studies have demonstrated that executive functioning is strongly correlated with future functional decline. Using a sample of participants who were cognitively normal or diagnosed with MCI, AD, VaD, or mixed dementia, Cahn-Weiner et al.[99] examined the correlation between executive functioning, episodic memory, and neuroimaging factors compared to baseline and follow-up everyday functioning. At baseline, both executive functioning and episodic memory were associated with level of everyday function, over time, only executive functioning predicted rate of decline. When both cognitive and neuroimaging variables were included in the model, memory and hippocampal volume were associated with baseline everyday functioning, but once again, only executive functioning independently predicted rate of decline in everyday functioning.

When it comes to survivors of ICH, the level of injury to the brain and the specific circuits disrupted determine the severity of the impairment and the level of therapy needed. When a stroke occurs, the brain has the innate ability to rearrange its connections within months or years to maximize function. Stroke patients may have complex needs depending on their stage of illness, the cause and severity of their stroke, and other factors, such as the presence of other chronic illnesses[100]. Globally, 60% of stroke patients develop permanent disabilities and experience limitation in mobility, vision, speech[101] and cognitive impairment[102]. Cognitive impairment is a common consequence of stroke and has direct implications for post-stroke functioning and quality of life, including the ability to maintain a job, live independently, sustain interpersonal relationships, and drive a vehicle.

The prevalence of post-stroke cognitive impairment (PSCI) ranges from mild to severe and affects up to 60% of stroke survivors within the first year after the stroke[103–105106]. It is estimated that up to 20% of people with mild PSCI recover fully, with the highest recovery rates observed immediately following a stroke[107]. However, improvement in cognitive impairment without return to pre-stroke levels is more frequent than complete recovery[108,109]. Even those with transient cognitive impairment have a greater chance of developing future dementia after stroke[110].

1.1.5. Psychiatric Symptoms and Cognitive Impairment: Understanding the Importance of Co-Morbid Symptoms

The presence of psychiatric symptoms (PsyS) is a common feature of all types of dementia, regardless of the underlying cause and stage of the disease[111].

This group of non-cognitive symptoms and behaviors[112] is observed in high rates across the spectrum from MCI to dementia. Untreated PsyS are one of the most challenging and costly aspects of dementia, leading to accelerated disease progression, worsened daily functioning, decreased quality of life, and increased placement in residential care[113].

Psychiatric symptoms are increasingly recognized as an early indicator of cognitive decline and an intrinsic feature of prodromal stages of dementia (e.g., MCI)[114]. According to Geda and colleagues[115], cognitively healthy older adults (aged >70) with psychiatric symptoms, specifically agitation, apathy, anxiety, irritability, and depression, are at a higher risk of developing MCI than cognitively healthy individuals without PsyS. This late-life transitional state is commonly referred to as 'mild behavioral impairment' (MBI), in which the presence of PsyS in the absence of cognitive symptoms is associated with an increased risk of incident MCI and dementia[116].

An estimated 31%-50% of individuals with MCI[117–119] and 61%-97% of individuals with dementia[120,121] have psychiatric symptoms. They are associated with an increased likelihood of progression from mild to severe dementia in patients with MCI[122–128]. Besides, psychiatric symptoms are associated with an increased risk of progression from mild to severe dementia in patients with AD[129].

Intracerebral hemorrhage (ICH) is associated with poor long-term outcomes, especially mortality, disability, and cognitive decline[130–132]. In this population, PsyS screening has rarely been explored, although ICH survivors are potentially at high risk. A small subgroup of stroke patients with ICH had higher rates of behavioral disturbances[133]. This might be due to the higher prevalence of dementia and cerebral amyloid angiopathy (CAA) among patients with ICH[134,135].

The American Heart Association/American Stroke Association (AHA/ASA) 2018 guidelines recommend routinely screening stroke patients for depression[136]. Despite the class of this recommendation is strong, a significant amount knowledge gaps persist regarding how and when to screen survivors for depression, which may be related to the complexities of the course of depressive symptoms after stroke[137–139].

A number of factors play a role after stroke, including neurovascular, biochemical, psychological, and social factors[137,140,141]. As a result of stroke's pathophysiological changes, mood regulation may be disrupted by reduced cerebral perfusion, inflammation, dysfunctions of the hypothalamic-pituitary-adrenal system, and changes in neuroplasticity and neurotransmission during the acute stage. In the post-acute stage, the residual disabilities of stroke-related cognitive and functional deficits can have a negative impact on an individual's quality of life and employment trajectory[142].

Furthermore, stroke can trigger psychological reactions such as catastrophizing, emotion distress, and a lack of self-efficacy. As a result of the overlap between depression symptomatology and stroke sequalae, diagnosis and screening are made more challenging[138,139,143] .

Consequently, the identification of psychiatric symptoms may influence ICH survivor's treatment planning and preventative strategies to reduce cognitive and functional impairment. As final consideration, PsyS screening may assist in identifying patients who are at higher risk for long-term cognitive decline after ICH.

1.2. Cerebral Amyloid Angiopathy: from Vessel Alterations to Cortical Damage

1.2.1. Conceptual and Clinical Delimitations

Cerebral small vessel disease (cSVD) is a collection of medical conditions affecting the small vessels of the brain that tend to be age-related or associated with vascular risk factors[144,145]. It refers to a series of neurological disorders caused by alterations in small cerebral vessels (ranging in diameter from about 5μm to 2 mm). CSVD is characterized by two main types of microangiopathies, sporadic hypertension-related microangiopathies (Figure 3) and CAA (Figure 4), both of which can cause ischemic or hemorrhagic damage, including clinically overt strokes[146–148].

Figure 3. Spectrum of Imaging Changes with Hypertensive Arteriopathy[149]

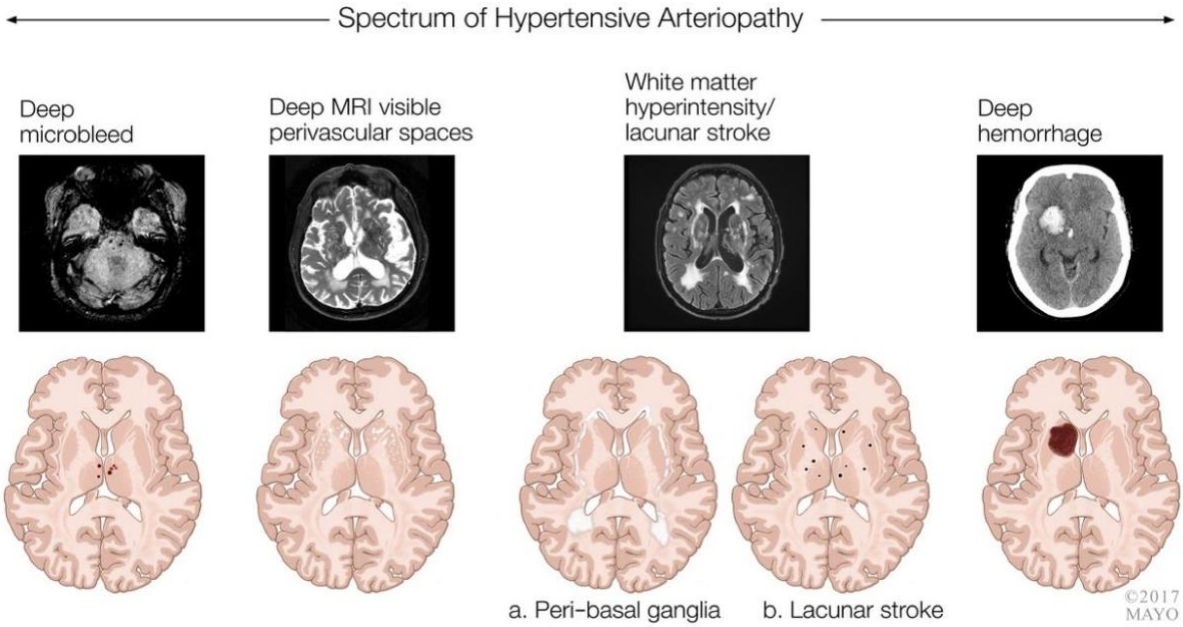
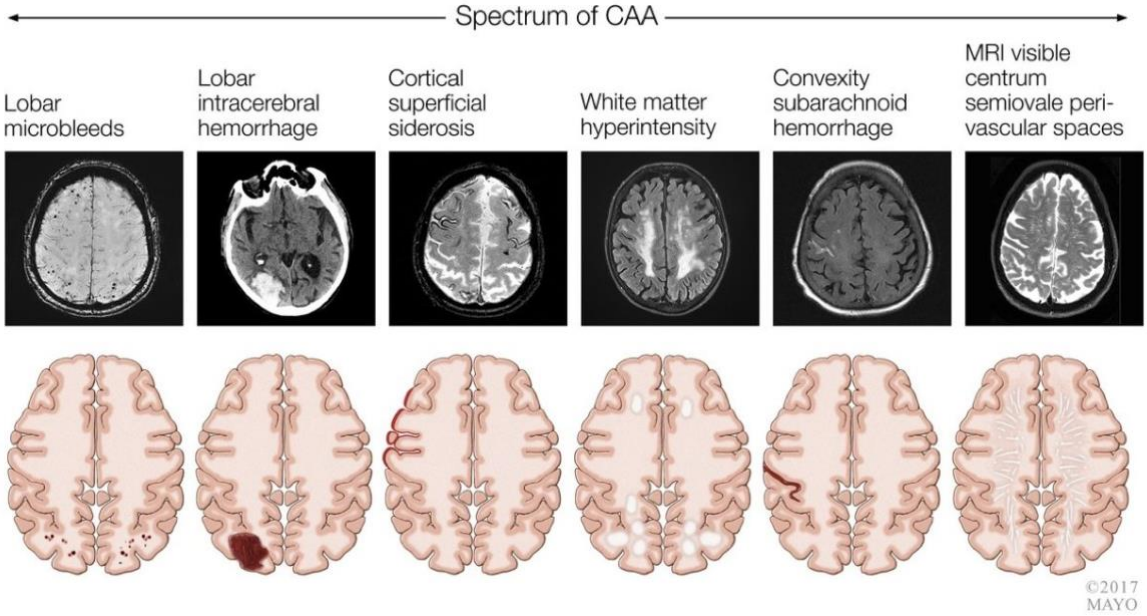


Figure 4. Spectrum of Imaging Changes Associated with CAA[149]



Specifically, the term CAA refers to a group of biochemically and genetically diverse disorders of the central nervous system (CNS). On pathological examination, all these medical conditions are associated with amyloid fibrils deposited primarily in the walls of small to medium-sized blood vessels. The capillaries within the parenchyma and leptomeninges of the CNS have also been found to contain amyloid deposits in some instances[150–152].

Primary CAA occurs in three different epidemiological forms: the sporadic form, which is common in our territory, and two types of hereditary transmission: the type that is prevalent in those of Icelandic descent (HCHWA-I), and the type that is prevalent in those of Dutch descent (HCHWA-D). CAA mostly occurs in the sporadic form in the elderly, while rare familial forms occur in younger patients and generally lead to more severe clinical manifestations[153].

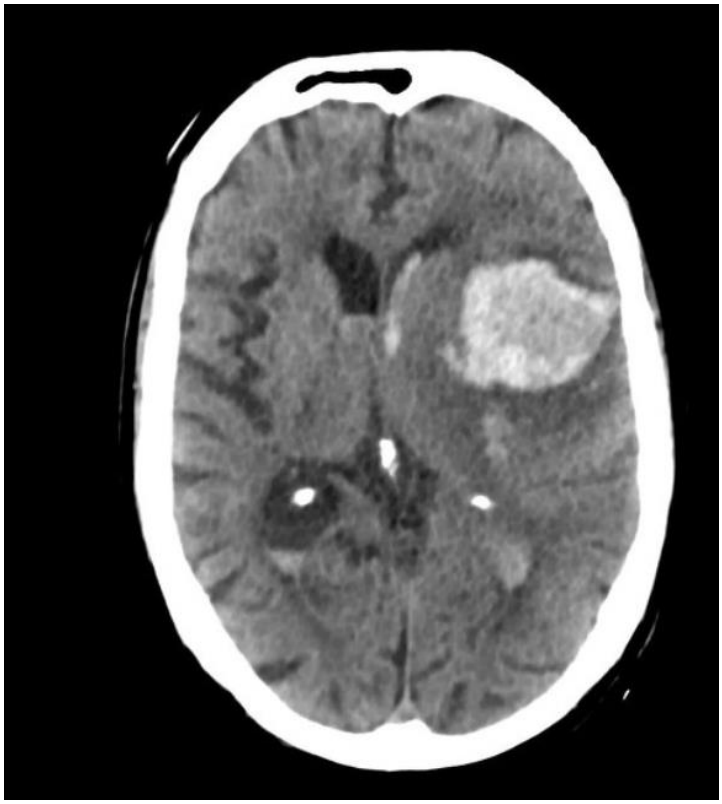
Sporadic CAA occurs when amyloid b-protein (Aβ) accumulates in the media and adventitia of parenchymal and leptomeningeal vessels. This microangiopathy can be associated with other neurologic conditions such as AD and it appears to increase with age[150,154].

There are four main clinical presentations of CAA, which may occur in isolation or in combination: (1) progressive cognitive impairment, (2) transient neurological spells (so-called amyloid spells) or transient focal neurological symptoms (TFNs), and (3) sudden focal neurological deficits related to ICH. Finally, (4) a CAA-associated angiitis which has been termed CAA-related inflammation (CAA-RI) is an important, although rare, clinical presentation of CAA[152]. In the elderly, spontaneous ICH is the most dramatic and immediately life-threatening sign of CAA.

Typically, these hemorrhages are lobar in nature, and re-bleeding is common if the patient survives[155]. The term “lobar” refers to a location in the cortex and subcortical white matter of a hemispheric lobe of the brain[156] (image 1); in contrast to deep locations, such as the putamen, thalamus, or pons, which show signs of hypertensive hemorrhage[157]. The lobar location of the hemorrhages correlates with the distribution of the vascular amyloid deposits, which favor cortical vessels and largely spare white matter, deep gray matter, and the brainstem[158]. The involvement of blood vessels in the cerebellum and leptomeninges can also cause the clinical presentation of cerebellar hemorrhage or subarachnoid hemorrhage (SAH)[159].

CAA has also been shown in recent years to produce ischemic subcortical tissue damage, which is likely due to vascular dysfunction. The consequence of such ischemic damage is that CAA contributes independently to age-related cognitive decline in patients with no symptomatic ICH[160]. In addition, CAA may present with transient neurological symptoms, an inflammatory leukoencephalopathy, incidental microbleeds or hemosiderosis on MRI and as a contributor of ICH.

Image 1. Lobar Hemorrhage in CAA[161]

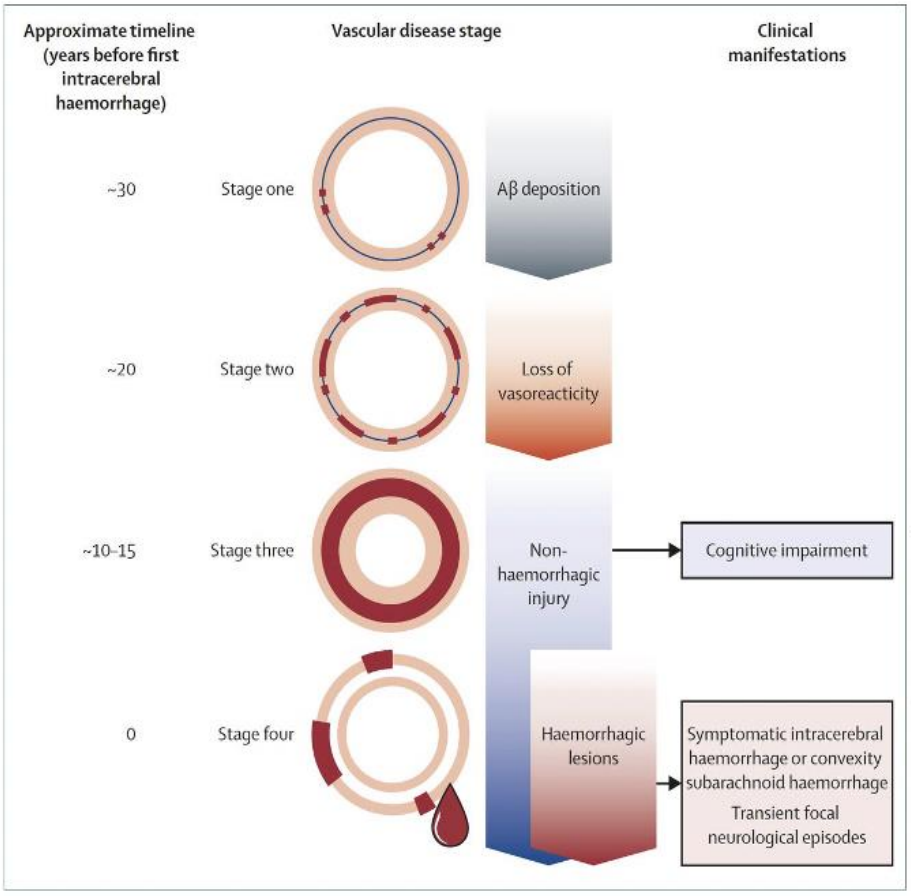


Acute superficial large left frontal lobar hemorrhage involving the cortex, subcortical white matter and periventricular white matter is seen on a computed tomography scan in a patient with cerebral amyloid angiopathy.

Using biomarker data from carriers of the Dutch-type CAA mutation, a broad timeline of the progression of the disease can be created (Figure 5). The vascular histopathology of Dutch-type (also referred to as hereditary cerebral hemorrhage with amyloidosis of the Dutch type) CAA closely resembles that of sporadic CAA, whereas cardinal features of AD pathology, such as dense-core plaques and neurofibrillary tangles, are scarce[162], making it an essentially pure form of CAA. According to these studies, amyloid deposition occurs 20-30 years before the first ICH (based on reduced CSF Aβ), followed by measurable changes in vascular physiology approximately 20 years before the first ICH, and then non-hemorrhagic MRI injury appears approximately 10 years before the first ICH.

Development of disease-modifying approaches and trials designs require a detailed understanding of early amyloid deposition in the cerebrovascular system and its relationship to subsequent non-hemorrhagic and hemorrhagic brain injuries. Research supports the existence of four broad stages for the progression of CAA (Figure 5): 1) cerebrovascular amyloid deposition; 2) alteration of cerebrovascular physiology; 3) non-hemorrhagic brain injury, and 4) hemorrhagic brain lesions.

Figure 5. Schematic of CAA Progression[163]



Stage one: cerebrovascular amyloid deposition

The earliest mechanistic step detected in carriers of the Dutch-type CAA mutation appears to be vascular amyloid deposition. There is no evidence for substantial Aβ overproduction in sporadic or Dutch-type hereditary CAA, suggesting that Aβ deposition might instead reflect increased aggregation or impaired clearance[164]. However, the exact triggers for initial deposition of vascular amyloid are not yet identified, although characteristics of the Aβ peptide, age, and other factors, such as ApoE genotype, appear to play an important role[165].

Vascular amyloid deposition in the brain can be inferred by reductions in the concentration of Aβ species in CSF[166], which have been shown to correlate inversely with neuritic plaques. Patients with sporadic CAA have consistently been found to have abnormally low concentrations of Aβ42 and Aβ40 in CSF[167].

CSF samples from individuals with Dutch-type CAA mutations show decreases in both Aβ species as early as their mid-20s, approximately 30 years before the average of symptomatic ICH. CSF and plasma levels of both the aggregation-prone Aβ42 peptide and the less aggregation-prone Aβ40 are reduced in Dutch-type CAA, whereas sporadic AD is characterized by reduced Aβ42 without a major reduction in Aβ40.[168,169]

Stage two: alterations in vascular physiology

Impaired cerebrovascular reactivity, measured by transcranial Doppler or blood-oxygen-level dependent functional MRI (BOLD fMRI) response to visual stimulation, most notably reduced BOLD fMRI response amplitude and delayed to peak response, has been identified as a robust feature of sporadic CAA[170]. The finding of impaired vascular reactivity in presymptomatic carriers of the Dutch-type CAA mutation indicate that impaired vascular reactivity is an early manifestation of CAA and can occur in the absence of any MRI-detectable structural brain injury.

Stage three: non-hemorrhagic injury

Advanced CAA is distinguished from hemorrhagic brain lesions by focal tissue damage and microstructural changes. Among the non-hemorrhagic MRI findings linked with sporadic CAA are lobar lacunes, microinfarcts, white matter hyperintensities and visible perivascular spaces in the centrum semiovale (CSO-PVS).

Based on white matter MRI findings in people with Dutch-type CAA, non-hemorrhagic brain injury appears to begin approximately 10-15 years before the mean age of symptomatic ICH[171]. The onset of these non-hemorrhagic changes occurs substantially later than the onset of abnormalities in CSF Aβ or BOLD fMRI-based vascular reactivity. It is unclear if the observed white matter changes in carriers of the Dutch-type CAA mutation affect cognition, because cognitive impairment has not been detected before the first ICH, although only 12 presymptomatic carriers have been tested at a mean age of 34 years[171].

A high count of CSO-PVS is another non-hemorrhagic MRI marker associated with sporadic and hereditary CAA[172,173]. As a result of the relative specificity of the CSO-PVS count for advanced CAA (defined as >20 visible lesions on one axial MRI slice), it has been incorporated into de Boston diagnostic criteria as one of the imaging features of probable CAA.

Because of the relative specificity for advanced cerebral amyloid angiopathy of a high CSO-PVS count (defined as >20 visible lesions on a single axial MRI slice of one hemisphere[174]), this marker has been incorporated as one of the imaging features of probable CAA in the most recent version of the Boston diagnostic criteria[175]. A higher CSO-PVS count was found in symptomatic but not presymptomatic carriers with Dutch type CAA[171], suggesting visible enlargement occurs relatively late in the disease's course. An analysis of histopathology of brain vessels from sporadic CAA patients revealed most enlarged CSO-PVS surrounding penetrating arterioles in the white matter accompanied by extensive Aβ deposition[176].

Stage four: hemorrhagic lesions

ICH is the most widely recognized clinical manifestation of sporadic and hereditary CAA, appearing as macrobleed typically larger than 1 cm in diameter located in the lobar and superficial cerebellar cortex[177]. Another hemorrhagic manifestation of sporadic and hereditary CAA has been identified using T2-weighted MRI techniques: cerebral microbleeds (CMBs), cortical superficial siderosis (cSS), and convexity subarachnoid hemorrhage (cSAH). A microbleed is characterized by a round hemorrhagic lesion[178] located in the lobar and superficial cerebellar brain regions[175,179]. Cortical superficial siderosis appears as chronic blood products in the cerebral and cerebellar sulci[180,181], possibly caused by a previous subarachnoid hemorrhage over cortical and cerebellar convexities.

The interrelationship between ICH, CMBs, cSS and cSAH is complex because individual patients with CAA can appear predisposed to one of these hemorrhagic subtypes over others[177]. According to evidence from Dutch-type CAA patients, all hemorrhagic lesions appear roughly concurrently during a distinct hemorrhagic phase of the disease following vascular amyloid deposition, altered vascular physiology, and non-hemorrhagic brain injury. In carriers of the Dutch-type CAA mutation, CMBs and cSS are first detected at approximately the same age as first ICH (mean age 54 years)[171,182] and at least a decade after the earliest evidence of non-hemorrhagic imaging changes in white matter.

1.2.2. Epidemiology

Age plays a significant role in the incidence of CAA. Because a definite diagnosis of CAA requires a neuropathological examination, the prevalence of CAA among the general population may be underestimated. On autopsy, CAA can be identified by the presence of amyloid beta-peptide in some cerebral blood vessels. According to an analysis of 784 autopsy samples, the prevalence of CAA varied from 2.3% in patients between the ages of 65 and 74 to 8.0% in those between 75 and 84, and 12.1% in those over the age of 85. One autopsy study examined 1079 patients whose mean death age was 89.7 years and found that 36% of patients had moderate-to-severe CAA[183]. Individuals less than 60 years of age are less likely to develop CAA-related symptoms[184,185].

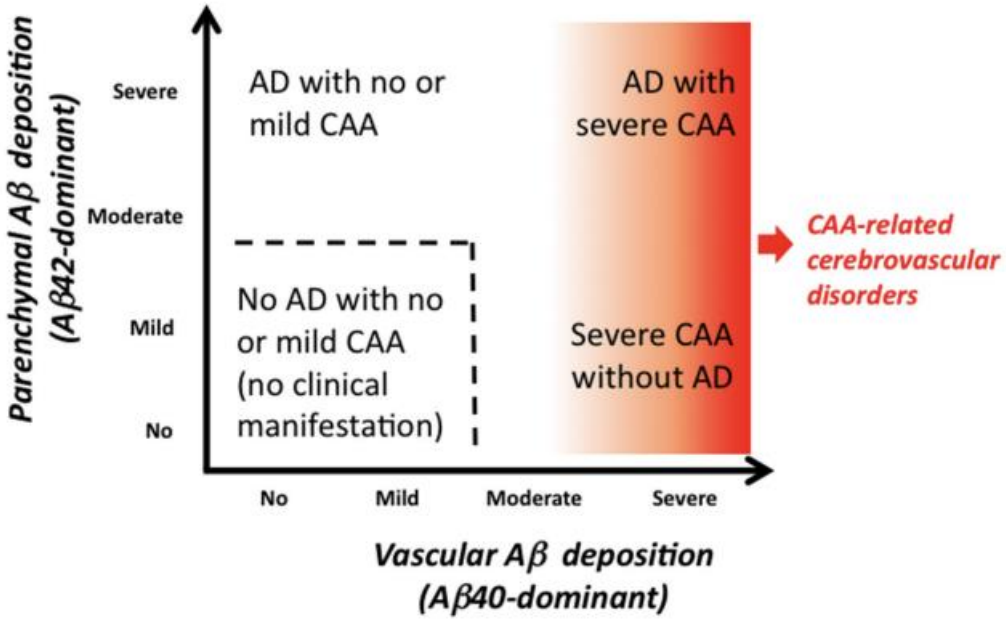
CAA is more prevalent in older patients with dementia than in healthy older adults. According to a systematic review of population-based studies, approximately 60% of patients with dementia had CAA pathology as compared to less than 40% of patients without dementia[186]. It was found that more than 80% of patients with AD had pathologic evidence of CAA[187].

Despite the close molecular relationship between the two entities, CAA remains clinically distinct from AD, but has the potential to link cerebrovascular and neurodegenerative pathways in the ageing brain[188].

1.2.3. The Neuropathology of CAA

As explained previously, CAA is characterized by a deposition of amyloid beta-peptide (Aß) within the cerebral vasculature. The 40-amino-acid-long Aß (Aß 1-40) is more soluble than the longer Aß 1-42 and the two molecules differ in the distribution in brain and vessel walls. Aß 1-40 tends to be the major form in the amyloid in artery walls in CAA, whereas Aß 1-42 is more prominent in the plaques in brain tissue[189,190]. There is no evidence of an increase in Aß production in sporadic CAA, suggesting that an imbalance between Aß production and clearance is responsible of forming amyloid deposits. The severity of each of vascular and parenchymal amyloid deposition varies. The wide spectrum of cerebral Aß amyloidosis is shown in Figure 6, including "AD with severe CAA", "severe CAA without AD", "AD with no or mild CAA", and "no AD with no or mild CAA".

Figure 6. The Spectrum of Cerebral Aß Amyloidosis[191]



In addition to aging, there are other factors that initiate and promote the deposition of amyloid beta-peptides in CAA. Genetic factors can cause CAA in an autosomal dominant manner and can increase the risk for sporadic CAA[192,193].

The process of vascular rupture and bleeding in CAA appears to be a multistep process which involves the deposition of amyloid beta-peptide in the vascular wall and resulting changes to the vascular walls such as concentric splitting. It has been debated whether CAA is associated with hypertension. The recurrence rate of CAA-related hemorrhage appears to be enhanced when blood pressure is elevated, even if many patients are normotensive[194,195].

Topographically, sporadic CAA frequently affects posterior cortical regions. Occipital lobes are the most severely affected, followed by frontal, temporal, and parietal lobes. The cerebellum is also susceptible to the disease, however the white matter, the brain stem, the thalamus, and the basal ganglia are usually spared.

The distribution of CAA pathology can be described as patchy where affected and spared regions might be adjacent. Consequently, a cerebral biopsy may miss CAA pathology and result in a false negative[152,153].

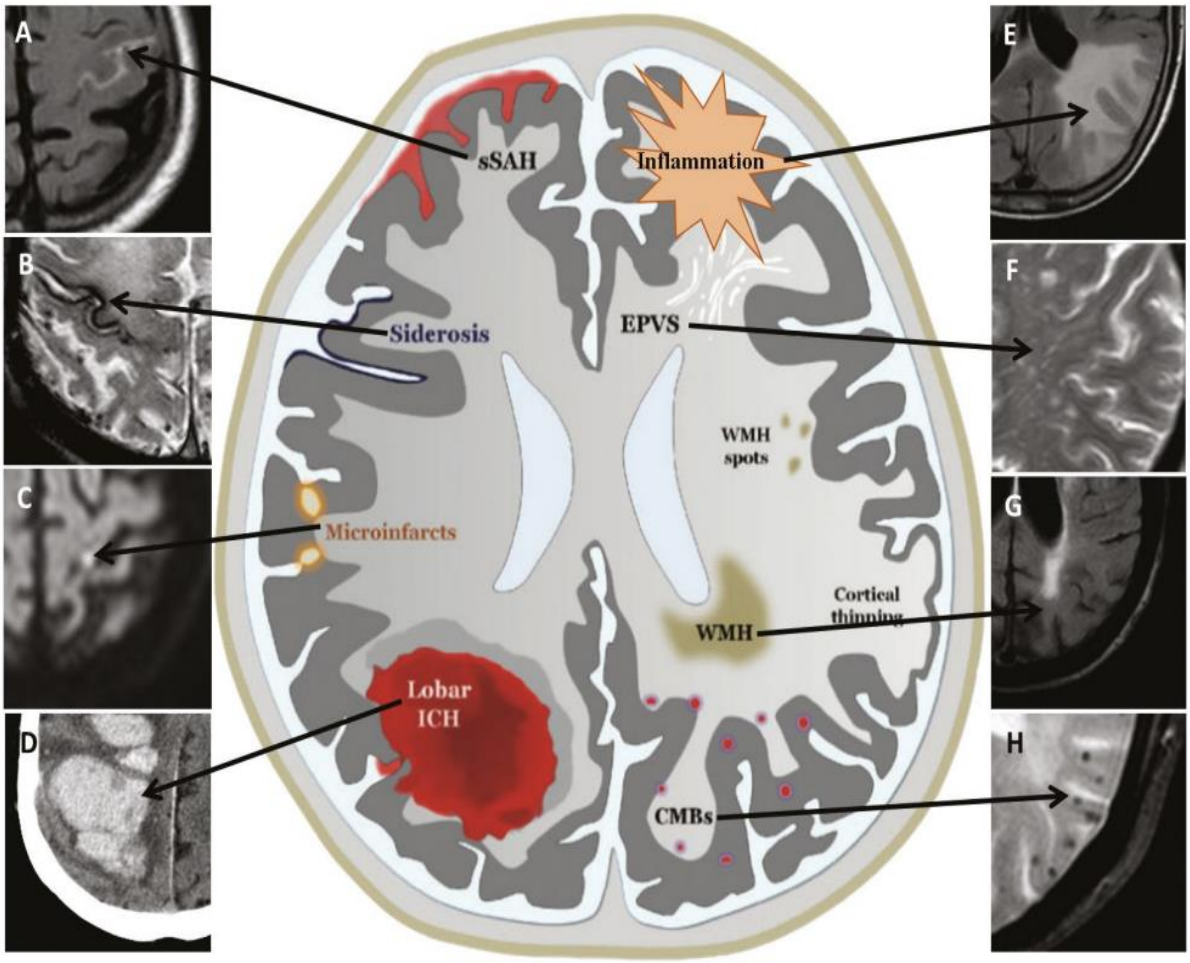
1.2.4. The Clinical Spectrum of CAA: Evidence for Different Disease Phenotypes

A thorough understanding of the biological changes that lead to CAA is vital to predicting its onset, strategizing appropriate interventions, tracking the progression of the disease, assessing treatment effects, and, ultimately, developing a cure. As previously mentioned, normal aging-that is, aging in the absence of major neurodegenerative conditions, is associated with macrostructural changes. How to disambiguate these two constructs has emerged as a challenge in neuroimaging literature. CAA manifests itself in a variety of ways. It can be completely asymptomatic, especially since nearly 50% of people over the age of 80 show signs of amyloid deposition as part of natural aging processes. Even so, amyloid deposits in cerebral blood vessels are associated with several clinical conditions. Amyloid deposits can weaken the blood vessel walls, leading to ruptures resulting in cortical microbleeds (cMBs) and spontaneous ICHs, transient focal neurological episodes (TFNEs), disturbances of consciousness, inflammation associated with CAA, cognitive impairment, dementia, and death[196].

CAA is becoming increasingly evident to be a complex and heterogeneous entity that can follow various pathways. It is associated with several clinical syndromes and neuroimaging features because of both hemorrhagic and non-hemorrhagic SVD (Image 2).

The relative frequency of the different clinical and neuroimaging presentations of CAA is difficult to estimate because it relies heavily on diagnosing the underlying CAA accurately in different settings and using the appropriate MRI sequences.

Image 2. Schematic Representation of the Neuroimaging Spectrum of Hemorrhagic (left) and Non-Hemorrhagic (right) Manifestations of Sporadic CAA. Modified from[152].



A. Convexal subarachnoid atraumatic hemorrhage in a FLAIR sequence; B. Cortical superficial siderosis in T2* gradient echo sequence; C. Microinfarcts in diffusion weighted imaging; D. Lobar intracerebral hemorrhage in a computerized tomography scan; E. Inflammatory reaction in FLAIR sequence; F. Dilated perivascular spaces in T2-weighted sequence; G. White matter hyperintensities in FLAIR sequence; H. Cortico-subcortical microbleeds in susceptibility weighted imaging.

1.2.4.1. CAA Hemorrhagic Manifestations

1.2.4.1.1 CAA-related ICH (ICH-CAA)

The most common clinical manifestation of CAA and the basis for the Boston criteria for CAA (Table 2) diagnosis is spontaneous lobar ICH[156]. The term lobar refers to the site of the hemorrhage in the cortex and subcortical white matter (Image 2D), as opposed to the basal ganglia, brainstem, and cerebellum characteristics of the hypertensive hemorrhages (Image 2D).

After hypertension, CAA is the second most common cause of spontaneous ICH in the elderly[197,198]. The etiology of ICH can be classified according to several systems. A recently introduced classification scheme, the H-ATOMIC system (Hypertension, CAA, tumor, oral anticoagulants, and vascular Malformations), confirmed that CAA was the second most common cause of spontaneous ICH in population studies. It was the suspected cause in 31% of the studied cases: probable in 20%, possible in 10.5%, and definite in 0.5%[199].

This lobar location of CAA-related ICH can be explained by vascular amyloid deposits, which largely affect cortical vessels and spare white matter, deep gray matter, and the brainstem. ICH caused by CAA typically extend into the subarachnoid space and less frequently rupture into the ventricles due to their superficial location. Furthermore, CAA-related ICH are more likely to occur in posterior brain regions. The explanation for the posterior brain clustering of CAA-related ICH is unclear, but it may be related to yet unknown characteristics of posterior circulation vessels that influence Aß peptide elimination, or a greater vulnerability of these brain regions to minor trauma[200,201].

There is a wide range of clinical presentation for CAA-related ICH, depending on the size and location of the lesion. The overall mortality rate of CAA-related ICH is 10-30%[202,203].
However, CAA is associated with substantially higher risk of lobar ICH recurrence in patients who survive the initial bleed. Amyloid imaging has shown that high Aß deposition indicates areas at risk for ICH in the future[204].

History and number of previous lobar ICH, increasing number of lobar microbleeds[155,205], anticoagulant or antiplatelet use[205], hypodense lesions on CT scan and the presence of the ε2 or ε4 APOE alleles are associated with an increased risk of recurrence. It is not well established whether age, sex, and arterial hypertension predict recurrence[206,207].

1.2.4.1.2. Cerebral Microbleeds (cMBs)

Small (generally 2-5 mm in diameter, but sometimes up to 10 mm) areas of signal void with associated blooming seen on T2-weighted on susceptibility-weighted MRI.

Over the past few years, cMBs has been gaining attention as SVD prognostic markers, especially regarding hemorrhagic risk. However, they still need to be investigated further in order to determine how they affect neurocognition. In the Rotterdam Study, the presence of lobar microbleeds were associated with a decline in executive functions, information processing, and memory function, whereas microbleeds in other brain regions were associated with a decline in information processing and motor speed[208]. Another study found that microbleeds were associated with the rate of cognitive decline in 221 AD patients who had baseline MRI scans and repeated neuropsychological tests at least 1 year apart[209].

No association was found between the presence of microbleeds and baseline cognitive performance, even after adjustment for atrophy, white matter hyperintensities (WMHs), lacunes, or vascular risk factors, after stratifying by microbleed location, apolipoprotein E ε4 (APOE 4) carriers, or age at onset.

1.2.4.1.3. Cortical Superficial Siderosis (cSS)

cSS represents chronic accumulations of blood breakdown residues (hemosiderin) in the subarachnoid space in a curvilinear pattern. It has been suggested that cSS is the third cardinal hemorrhagic neuroimaging signature of CAA, along with ICH and microbleeds.

The current hypothesis is that cSS (Image 2B) appears to be caused by repeated episodes of blood leakage originating from fragile leptomeningeal or very superficial subpial cortical layers, such as acute convexal subarachnoid hemorrhage (cSAH) (Image 2A)[210]. Degradation of those blood products leads to blood residues being deposited in superficial cortical layers, resulting in chronic cSS.

Pathological mechanisms underlying the association between cSS and AD are not clear. The close relation between cSS and CAA might support the amyloid pathology. In the Rotterdam Scan Study, all individuals who presented with cSS had cMBs in lobar locations[211].

Patients with disseminated cSS were more likely to have cognitive impairment, while patients with focal cSS were more likely to have transient focal neurological episodes[212]. Among patients with spontaneous ICH, disseminated cSS was a significant risk factor for dementia and recurrent symptoms[134,213]. A recent longitudinal study of patients with probable CAA found no association between disseminated cSS and dementia incidence (OR=1.268,95% CI 0.702-2.292; *p*=0.431)[214].

1.2.4.1.4. Transient Focal Neurologic Episodes (TFNE)

TFNE, also called "amyloid spells", are the second most common clinical presentation of sporadic CAA after CAA-related ICH.[215] They consist of brief, transitory, stereotypic episodes of paresthesia, weakness, or numbness, that usually resolve within 30 minutes, with an onset ranging from seconds to minutes.[215]. There is no consensus on the underlying mechanisms, but they may be related to cortical spreading depression that occurs in migraine auras or epileptic seizures[216,217].

The presence of TFNE can serve as a clinical marker for hemorrhagic CAA and is the best clinical marker for cSS[218]. There is an anatomical correlation between TFNE symptoms and lobar microbleeds or cSAH/cSS locations[219].

It is important to consider CAA-related TFNEs as a warning sign of future symptomatic CAA-related ICH[220], which has implications for antiplatelet or anticoagulant treatment decisions, highlighting the clinical importance of their diagnosis when they are misdiagnosed with transient ischemic attacks[221]
.

1.2.4.1.5. Iatrogenic Cerebral Amyloid Angiopathy (iCAA)

There have been increasing reports of iatrogenic CAA (iCAA), attributed to the transmission of Aβ seeds, in the 6 years since the first pathological description was reported in humans[222] and subsequently confirmed experimentally[223]. This newly described form of CAA is associated with early disease onset (typically in the third to fifth decade), and often presents with ICH, but also seizures of cognitive impairment.

Recently, new insights were revealed about young patients who developed CAA years after undergoing (neuro)surgical procedures as children. It was hypothesized that cadaveric material used during these procedures caused this suspected iCAA. A cadaveric dural graft (cadaveric dura) or embolization material[224–228], cadaveric human growth hormone[222,229,230], or surgical instruments[230–232] were proposed as transmission routes.

Although assumed to be rare, it is important that clinicals remain vigilant for potential cases, particularly as the optimal management, prognosis, true incidence, and public implications remain unknown.

1.2.4.2. CAA and Cerebral Ischemia

1.2.4.2.1 White Matter Hyperintensities (WMHs) of Presumed Vascular Origin

Signal abnormality in the white matter appearing as hyperintensities on T2-weighted images such as fluid-attenuated inversion recovery, without cavitation (signal different from cerebrospinal fluid). The size may be variable from punctate to confluent hyperintensities.

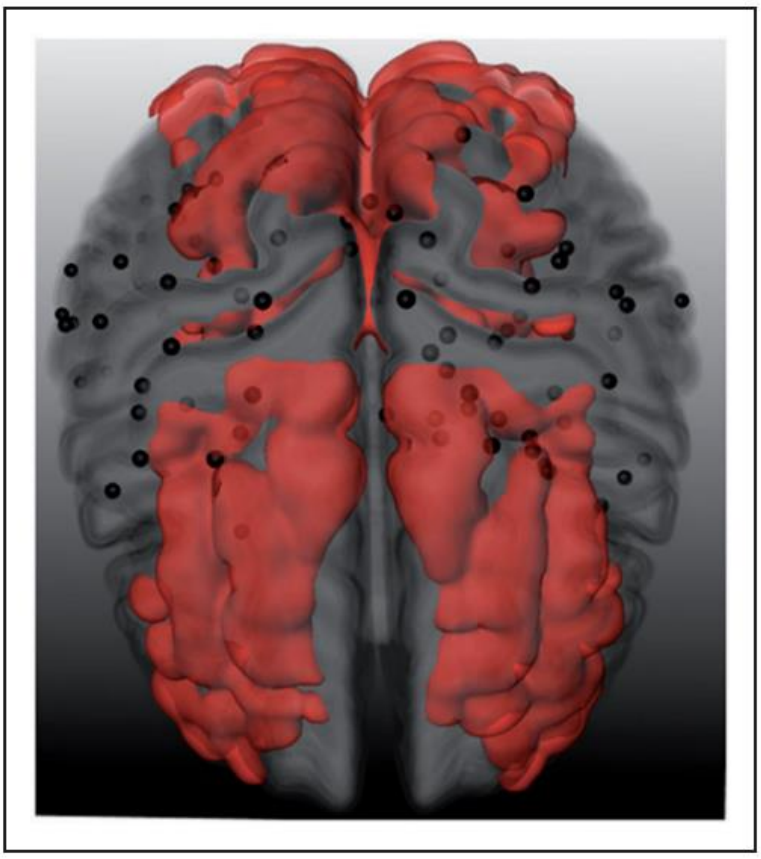
The association between WMH and cognitive impairment in the elderly is well established[233]. WMHs are associated with subsequent neurocognitive decline due to disruption of the fronto-subcortical pathways underlying complex networks that regulate cognitive control and information processing[234].

As a result, WMHs are generally associated with a neurocognitive profile typified by frontal lobe or frontal systems dysfunction with impairments mainly in processing speed, attention, and executive functions[235].

1.2.4.2.2. Cerebral Cortical Microinfarcts (CMIs)

Cerebral cortical microinfarcts are defined as areas of ischemic-related tissue loss. CMIs have been traditionally visualized through neuropathological examination[236]. Due to their small size, research on the association between CMIs and cognition during life has been hampered by the difficulty of detecting CMIs using conventional MRI. Recently, it has been demonstrated that cortical CMIs can be visualized in vivo using 7 tesla (7T) MRI[237]. The incidence of CMIs is higher in CAA patients than in CAA-free subjects[238], and it is also higher following acute CAA-related ICH than after other spontaneous bleeds[239]. CAA-related ischemic infarcts are more often located in the cerebral cortex.

Figure 7. 3D Representation of Cerebral Cortical Microinfarcts with Watershed Overlay. Superior view of a 3D representation of cerebral cortical microinfarcts (black dots) in the cohort projected on an MNI-standard brain. The red overlay signifies the cortical watershed regions[240].



CMIs have suggested to be a major component of the causal pathway between SVD and cognitive dysfunction [241]. CMIs commonly occur in patients with stroke and dementia and their contribution to VCI is increasingly recognized[236]. Recently, cortical CMIs detected on 3T MRI have been associated with dementia and poorer performance on visuoconstruction and language in a memory clinic population.[242]

1.2.4.2.3. Enlarged Perivascular Spaces (EPVS)

Enlarged Perivascular Spaces refers to fluid-filled spaces that follow the typical course of a vessel as it goes through gray or white matter. The spaces have signal intensity similar to cerebrospinal fluid on all sequences. Because they follow the course of penetrating vessels, they appear linear when imaged parallel to the course of the vessel, and round or ovoid, with a diameter generally smaller that 3mm, when imaged perpendicular to the course of the vessel. EPVS, also referred to as Virchow-Robin spaces, is considered one of morphological features of SVD[243]. The clinical significance of EPVS is still somewhat controversial. Whereas cross-sectional[14,244–248] and longitudinal [249,250] studies provide some preliminary evidence for an association between EPVS and cognitive impairment or dementia, additional studies examining the longitudinal predictive power of EPVS in different locations on incident cognitive decline are needed to clarify the clinical significance.

1.2.4.3. CAA-Related Cognitive Decline

Cognitive impairment in the context of CAA was reported over the past three decades[215,251,252]. CAA is an important contributor to cognitive impairment, although it is hard to dissect its specific contribution in the elderly due to the overlap with other age-related brain pathologies.

CAA is frequently seen in memory clinics in patients with cognitive impairment or dementia with underlying AD pathology[253]. No neuropsychological correlate exists for mild CAA, suggesting that mild CAA represents the physiologic clearance of beta-amyloid rather than a pathological condition. Cognitive impairment is associated with advanced CAA, which may reflect comorbid AD, VD, or both. Despite the high comorbidity rate, the contribution of CAA to cognitive impairment is partly independent of the parenchymal AD pathology[254,255]. Moderate to severe CAA (presented in one-third of the population) correlates most profoundly with perceptual speed, episodic memory, semantic memory, attention, and executive function, and global cognitive impairments are among the most reported symptoms, considering CAA as a risk factor for the development of dementia in previous studies[256].

Additionally, CAA is also diagnosed in stroke units after lobar ICH[135]. Although the association between ICH and cognitive decline is generally recognized, less is known about its extents and nature. To date, most studies investigating cognitive profiles in this population had just used screening instruments such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MOCA)[134,257]. Research in the past few years has examined impairments in specific domains related to ICH, but studies have centered mainly on executive functions, information processing speed, and verbal memory[256,258,259]. A large amount of information remains largely unknown about the prevalence of impairments in non-verbal memory, visuoperceptual function, and language following an ischemic stroke, yet these domains are frequently impaired early after an ischemic stroke and have significant predictive value[260]. Along these same lines, one group showed that cognitive deficits following ICH are common across domains, and that those with CAA appear to have a different cognitive profile[261].

1.2.5. The Diagnostic Process

Diagnosis of CAA is important because it has a higher recurrence risk of recurrent intracerebral hemorrhage than arteriolosclerosis-associated intracerebral hemorrhage (7.4 per year in a pooled analysis of cohort studies) and might require specific prevention strategies or, in the future, disease-modifying treatment targeting vascular B-amyloid[262]. As noted, the gold standard for diagnosing definite CAA requires postmortem autopsy confirmation by histopathology, but living patients have limited access to tissue samples[135]. Clinical and radiological criteria are used to diagnose possible or probable CAA in life.

The modified Boston criteria (or the Boston criteria 1.5) for CAA-related hemorrhage were clinico-pathologically validated in 2010 to attribute an ICH *in vivo* to CAA based on age, an appropriate clinical history, MRI findings and pathological data[135]. They consist of combined clinical, imaging, and pathological parameters, and are based upon the original Boston criteria which were proposed in 1995[263]. The radiological findings of the modified Boston criteria include single or multiple lobar hemorrhages restricted to lobar, cortical, or cortico-subcortical regions. Sensitivity is improved by including cerebral lobar microbleeds as a CAA-related feature in the criteria. It is considered that both cerebral lobar microbleeds and lobar ICH represent independents vascular rupture events which are assumed to offer equal evidence for the presence of CAA. These criteria have since been superseded by the Boston criteria 2.0[175].

1.2.5.1. Diagnosis Based on Imaging

Conventional computed tomography (CT) and magnetic resonance imaging (MRI) methods reveal anatomical alterations and remain the most reliable tool in identifying CAA according to modified Boston criteria[135]. CAA results in hemorrhagic and ischemic manifestations on MRI, which include perivascular spaces, cortical microinfarcts, cortical superficial siderosis (cSS), and white matter hyperintensity.

1.2.5.1.1. MRI

MRI-based techniques with blood-sensitive sequences are used in clinical practice to detect most CAA patients. It can detect hemorrhagic small vessel disease biomarkers, including cerebral microbleeds (cMBs) and cortical superficial siderosis (cSS), making it the best in-vivo diagnostic tool for CAA. According to modified Boston criteria, patients older than 55 years who develop multiple strictly lobar, cortical, or cortico-subcortical hemorrhage, including ICH and cMBs, or single lobar hemorrhage plus focal or disseminated cortical superficial hemosiderosis (cSS), could be diagnosed with probable CAA after excluding other possible causes of hemorrhagic events (Table 2).

In the radiologic/pathologic validation studies, the MRI-based criteria were shown to be extremely accurate in CAA diagnosis with excellent sensitivity (95%, 95% CI 83-99%) and good specificity (81%, 95% CI 62-93% in a hospital-based cohort with ICH).

Boston criteria have been used to define diagnostic certainty of CAA in patients presenting with acute intracerebral hemorrhage based on specific hemorrhagic findings. Despite this, the criteria did not address non-hemorrhagic CAA presentations. As of version 2.0, Boston criteria now include hemorrhagic and non-hemorrhagic presentations for sporadic CAA, as well as imaging features such as cortical microbleeds and white matter lesions.

The Boston criteria version 2.0 performed a better diagnostic accuracy for probable CAA than previous modified Boston criteria (85 versus 80 percent) in a retrospective multicenter review of 341 patients with clinical features consistent with CAA and both magnetic resonance imaging and brain tissue were available for analysis. However, both were highly specific (95 percent). Based on these results, these updated criteria are useful for identifying patients with CAA.

Table 2. Evolution of the Boston Criteria for Cerebral Amyloid Angiopathy

Boston criteria **2001**[263]	**Modified Boston criteria** **Versión 1.5, 2010**[264]	**Boston criteria for sporadic CAA** **Version 2.0, 2022**[265]
Definite CAA		
Full postmortem examination demonstrating: - Lobar, cortical or cortico-subcortical hemorrhage - Severe CAA with vasculopathy - Absence of another diagnostic lesions	**Full postmortem examination demonstrating:** - Lobar, cortical or cortico-subcortical hemorrhage - Severe CAA with vasculopathy - Absence of another diagnostic lesion	**Full postmortem examination demonstrating:** - Spontaneous ICH, TFNE, cSAH, cognitive impairment - Severe CAA with vasculopathy - Absence of another diagnostic lesion
Probable CAA with supporting pathology		
Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy): - Lobar, cortical or cortico-subcortical hemorrhage - Some degree of CAA in specimen - Absence of another diagnostic lesion	**Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy):** - Lobar, cortical or cortico-subcortical hemorrhage - Some degree of CAA in specimen - Absence of another diagnostic lesion	**Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy):** - Presentation with spontaneous ICH, TFNE, cSAH, or cognitive impairment - Some degree of CAA in specimen - Absence of another diagnostic lesion

Table 2. Evolution of the Boston Criteria for Cerebral Amyloid Angiopathy *(continuation)*

Boston criteria **2001**[263]	**Modified Boston criteria** **Versión 1.5, 2010**[264]	**Boston criteria for sporadic CAA** **Version 2.0, 2022**[265]
Probable CAA		
Clinical data and MRI demonstrating: - Age ≥55 years - Multiple hemorrhages restricted to lobar, cortical, or cortico-subcortical regions (cerebellar hemorrhage allowed) - Absence of another cause of hemorrhage◊	**Clinical data and MRI demonstrating:** - Age ≥55 years - **Plus, either:** ○ Multiple hemorrhages restricted to lobar, cortical, or cortico-subcortical regions (cerebellar hemorrhage allowed) **or** ○ Single lobar, cortical or cortico-subcortical hemorrhage and focal§ or disseminated¥ superficial siderosis - Absence of another cause of hemorrhage or superficial siderosis	**Clinical data and MRI demonstrating:** - Age ≥50 years - **Plus, either:** ○ Presentation with spontaneous ICH, TFNE, or cognitive impairment ○ Two or more lobar hemorrhagic lesion on T2*-weighted imaging (e.g. ICH, cMB, cSS, cSAH)¶ ○ Absence of another cause of hemorrhage$^{\Delta}$ **or** ○ One lobar hemorrhagic lesion on T2*-weighted imaging (e.g., ICH, cMB, cSS, cSAH)◊ ○ One white matter feature (e.g., >20 perivascular spaces in centrum semiovale or WMH in a multispot pattern) ○ Absence of any deep hemorrhagic lesions on T2*-weighted imaging ((e.g., ICH, cMB)¶ - Absence of other cause of hemorrhagic lesions$^{\Delta}$

Table 2. Evolution of the Boston Criteria for Cerebral Amyloid Angiopathy *(continuation II)*

Boston criteria **2001**[263]	**Modified Boston criteria** **Versión 1.5, 2010**[264]	**Boston criteria for sporadic CAA** **Version 2.0, 2022**[265]
Possible		

Clinical data and MRI demonstrating:
 	
- Age ≥55 years
- Single lobar, cortical, or cortico-subcortical hemorrhage
- Absence of other cause of hemorrhage◊
	Clinical data and MRI demonstrating:
	
	- Age ≥55 years
	- **Plus, either:**
	  ○ Single lobar, cortical or cortico-subcortical hemorrhage
	  or
	  ○ Focal§ or disseminated¥ superficial siderosis
	- Absence of other cause of hemorrhage or superficial siderosis
		Clinical data and MRI demonstrating:
		
		- Age ≥50 years
		- **Plus, either:**
		  ○ Presentation with spontaneous ICH, TFNE, cSAH, or cognitive impairment
		  ○ One lobar hemorrhagic lesion on T2*-weighted imaging (e.g. ICH, cMB, cSS, cSAH)¶
		  ○ Absence of other cause of hemorrhageΔ
		  or
		  ○ One white matter feature (e.g., >20 perivascular spaces in centrum semiovale or WMH in a multispot pattern)
		  ○ Absence of any deep hemorrhagic lesions on T2*-weighted imaging (e.g., ICH, cMB)¶
		Absence of another cause of hemorrhagic lesionsΔ

¶ Hemorrhagic lesion in the cerebellum is not counted as either lobar or deep hemorrhagic lesion.

Δ Other causes of hemorrhagic lesion: antecedent head trauma, hemorrhagic transformation of an ischemic stroke, arteriovenous malformation, hemorrhagic tumor, and vasculitis. Other causes of cortical superficial siderosis and acute convexity subarachnoid hemorrhage should also be excluded.

◊ Other causes of intracerebral hemorrhage: excessive warfarin (INR >3.0); antecedent head trauma or ischemic stroke; central nervous system tumor, vascular malformation, or vasculitis; and blood dyscrasia or coagulopathy. (INR> 3.0 or other nonspecific laboratory abnormalities permitted for diagnosis of possible CAA.)

§ Siderosis restricted to 3 or fewer sulci.

¥ Siderosis affecting at least 4 sulci.

1.3. Study Justification

The question of the origin of cognitive disorders after ICH is a complex topic linked to the presence of hemorrhage itself, but also to the pathophysiological mechanisms that evolve silently and are present well before a stroke happens. Furthermore, most ICH studies are focused on the differences between lobar and non-lobar hemorrhages, but these dichotomous distinctions would certainly obscure the impact of individual causes of disease.

Even though cognitive impairment has been observed clinically in CAA, little is known about the frequency, severity, and comprehensive neuropsychological profile of patients clinically diagnosed with CAA after a lobar ICH. Such knowledge can inform prevention and intervention efforts, as well as predictions regarding course, correlates, and outcomes. For all these reasons, greater sophisticated neuropsychological assessment is needed to operationally define cognitive impairment.

Our proposal is to implement a new approach in the management of ICH-CAA patients. In this population, detecting cognitive, behavioral, and emotional changes at an early stage is crucial to reducing the risk of dementia. Considering all the reasons outlined above, it would be prudent to suggest stricter follow-up, diagnosis, and treatment strategies in this population.

Therefore, this research has high implications for clinical care because it will enable accurate diagnosis, personalized management, and prognosis of the disease, allowing for individual risk assessment, early decision-making, and appropriate treatment, both to avoid potentially harmful medication, like the use of anticoagulants.

HYPOTHESES AND OBJECTIVES

Hypotheses

CAA refers to a group of genetically and biochemically distinct disorders of the central nervous system (CNS) whose main manifestation is the well-reported spontaneous ICH. However, due to the devastating prognosis associated with ICH-CAA, there is little information about the neuropsychological outcomes in this cohort.

This doctoral thesis is based on the following hypotheses: (1) A proportion of patients with ICH-CAA may present with cognitive alterations (defined as an in impairment of <1 SD relative to the reference group in 2 cognitive domains, according to the comprehensive criteria of Jack et al. 2009)[62] after ICH, similar to that of small vessel disease vascular cognitive impairment. (2) In these patients, individuals with a greater burden of small vessel diseases are more likely to experience worse cognitive impairment.

Overarching Objective

This study aims to gather information from patients with lobar or cortical intracerebral hemorrhages associated to possible or probable CAA about their clinical, radiological and neuropsychological characteristics. In this thesis, the following objectives are specifically addressed:

Specific Objectives

- To analyze the cognitive profile of patients who survived ICH caused by CAA.
- To assess the presence of affective symptoms in this population.
- To perform an assessment of functional capacity ≥180 days after ICH.
- To describe markers of vascular pathology and neurodegeneration through 1.5T and 3T MRI.
- To determine the degree to which CAA and neurodegenerative imaging markers mediate the association of CAA with cognitive dysfunction.

METHODS

3.1. Overview of the Study Design

It is a descriptive, ambispective, cross-sectional, analytical-observational, multidisciplinary, single-center study that assesses the relationship between cognitive profile and imaging biomarkers in subjects ≥ 55 years of age inclusive (no upper limit was imposed), who experienced a first primary symptomatic parenchymal ICH associated with probable or possible CAA from 2016 to 2021.
Participants were drawn from an ongoing longitudinal cohort study of ICH admitted to our center's Neurology Department. The study was conducted in an outpatient setting.

The study consisted of 2 phases:

- Screening period: carried out during the patient's admission to our center in which subject eligibility was assessed based on CT or MRI scans performed as per clinical practice. All patients met the criteria for probable or possible CAA. This visit included signing the Informed Consent Form (ICF) and collection of the study participant's medical history and concomitant medications. Furthermore, the Informant Questionnaire on Cognitive Decline (IQCODE) shortened Spanish version[266] and Blessed Dementia Rating Scale (BDRS[267]) was performed to rule out a possible cognitive impairment prior to the event. Patients were eligible for the study if they met all the inclusion criteria and none of the exclusion criteria. Evidence of any brain disease, other than potential ICH related to CAA, was assessed during screening by mean of cerebral MRI. Once eligibility was confirmed with these tests, study participants had the option to undergo a neuropsychological assessment.

- Neuropsychological assessment period: following screening and baseline evaluations, subjects who met all the inclusion criteria and none of the study exclusion criteria had an appointment to perform an extensive neuropsychological assessment at least six months (≥ 180 days) later.

- End of study definition: the end of the study is defined when the last patient was completed all the neuropsychological assessment visits. Once the last participant was completed the neuropsychological study, the data was analyzed.

3.2. Study Design Rationale

3.2.1. Participants

Study participants were drawn from an ongoing longitudinal cohort study of ICH in our center from March 2016 to December 2021. Participants were eligible to be included in the study only if all the following criteria applied:

3.2.2.1. Inclusion Criteria

Age and Sex

1. Participant had to be a man or woman ≥ 55 years of age inclusive, at the time of signing the ICF.

Type of Participant and Disease Characteristics

2. Participants who had a primary acute lobar (cortex or subcortical white matter) ICH that fulfilled the criteria for probable or possible sporadic CAA according to the pathologically validated modified Boston criteria.
3. Participants with available brain MRI sequences of adequate quality including T2-weighted, T2*-weighted gradient-recalled echo (T2*-GRE), or susceptibility weighted imaging (SWI) and fluid-attenuated inversion recovery (FLAIR) sequences, which also documented that there was no other disease clinically relevant that may affect the cognitive state of the subject.
4. Subjects were healthy for their age group or medically stable with or without medication based on a physical exam, medical history, and vital signs.
5. Estimated premorbid intelligence quotient (IQ) equal to or greater than 85.
6. A functional status that allowed participants to come to the center to undergo neuropsychological assessment according to the protocol designed (mRS ≤ 3).
7. Adequate visual and auditory acuity to perform neuropsychological testing (eyeglasses and hearing aids permitted), based on Investigator judgment.
8. No pre-existing cognitive decline having a score of ≤ 57 on short version of the Informant Questionnaire on Cognitive Decline (IQCODE) shortened Spanish version and a score of <3.5 on the Blessed Dementia Rating Scale (BDRS).

9. Participant had an identified informant who had and will maintain sufficient contact with the participant to be able to provide accurate information on the participant's cognitive, functional, and emotional states, as well as personal care information. The informant had to be able to provide informed consent for their own participation, to read, write, and to participate in assessments that require written or oral input from them.

Inform Consent

10. Ability of the participant to understand the purpose of the study and provide signed and date informed consent and authorization to use confidential health information in accordance with national and local participant privacy regulations.

3.2.2.2. Exclusion Criteria

Participants were excluded from the study if any of the following criteria applied:

Medical Conditions:

1. Any neurological condition that contributed to cognitive impairment above and beyond that caused by the participant's ICH (e.g., folic acid/vitamin B12 deficiency).
2. MRI scanning was contraindicated for the participant, for example, cardiac pacemakers, defibrillators, ferromagnetic metal implants (for example, skull and cardiac devices approved for use in MRI scanners), or inability to tolerate brain MRI.
3. Any psychiatric diagnosis or symptoms (e.g., hallucinations, major depression, or delusions) that could interfere with study procedures.
4. A history of alcohol and/or drug abuse within 2 years of screening.
5. Other significant pathological findings on brain MRI at screening including, but not limited to, evidence of hemorrhagic transformation of an ischemic stroke; evidence of vasogenic edema; evidence of cerebral contusion; encephalomalacia, aneurysms, vascular malformations, or infective lesions; space occupying lesions; or brain tumors.
6. Untreated thyroid disease.
7. History of severe infectious disease affecting the brain (i.e., neurosyphilis, meningitis, encephalitis).

8. History of positive human immunodeficiency virus antibody test.

9. History of cranial radiation therapy.

Prior and Concomitant Therapy

10. Participant receiving any anticoagulant treatment.

3.2.2. Study Assessments and Procedures

All screening evaluations had to be completed and reviewed to confirm that potential study participants met all eligibility criteria. The investigator maintained a screening log to record details of all study participants screened and to confirmed eligibility or records reasons for screening failure, as applicable.

3.2.2.1. Clinical Outcomes

Detailed clinical data of patients were obtained from prospective databases and medical records using standardized data collection forms. Specifically, the following parameters were extracted at the time of enrollment: (1) demographics (sex, age of onset, years, and level of education), (2) vascular risk factors (arterial hypertension, diabetes mellitus, hyperlipidemia, smoking, and alcohol habits) and (3) medical history (previous stroke -ischemic or hemorrhagic- or transient ischemic attack (TIA), atrial fibrillation and pre-ICH dementia using the IQCODE/TIN[266] and BDRS[267]. As well, we measured the functional status throughout the evaluation of (4) stroke severity with the National Institutes of Health Stroke Scale (NIHSS[268]), both at admission and discharge, (5) level of consciousness with the Glasgow Coma Scale (GCS[269]) and (6) the level of dependency with the modified Rankin Scale (mRs)[270,271] at discharge and, finally, ≥ 3 months follow up.

On the other hand, regarding the medication, we collected those taken by the patient at the onset of symptoms which could be related to the ICH*:* oral anticoagulation or platelet inhibitors, number and type of antihypertensive drugs and those drugs intended to reduce abnormally high levels of cholesterol in the blood (statins).

3.2.2.2. Cognitive and Affective Outcomes Measures

3.2.2.2.1. Cognitive Assessment

The cognitive assessment comprised a protocol of 16 tests assessed the overall cognitive status and cognitive functions such as attention, executive function (EF), processing speed (PS), language, memory, visuoperceptive, visuospatial, and visuoconstructive functions. Tasks were grouped into broad cognitive functions, and these were used to construct cognitive indices:

1. Premorbid IQ: It was estimated using the Word Accentuation Test (WAT)[272]. It has been used to predict premorbid intelligence and cognitive performance in Spanish-speaking populations. It requires participants to read a list of words without the accent marks that indicate the stressed syllable.

2. Overall cognitive status: It was assessed through the administration of the Mini Examen Cognoscitivo (MEC)[273]. It is a 14-item neuropsychological test that is used to assess cognitive status in adults and can be used for cognitive impairment and to estimate severity of cognitive impairment. It assesses orientation (temporal and spatial), audioverbal memory, attention, language (ability to name, ability to follow verbal and written commands, ability to write a sentence and ability to sentence repetition), mental arithmetic, mental abstraction, and visuo-constructive graphomotor function through copying a drawing. The test takes approximately 10 to 15 minutes to complete. The score ranges from 0 to 35 adjusted for age and educational level. Scores <23 indicate cognitive impairment in patients over 65 years of age. In younger patients (<65 years old), a <27 score in indicative of impairment.

3. Attention, Executive Function (EF) and Processing Speed (PS): These were primarily assessed using Digits subtest (WAIS-III)[274], Spatial Location subtest (WMS-III)[275], Trail Making Test (Part A and B)[276], Words and Colors Stroop Test[277], Tower of London (ToL)[278], and Symbol Digits Modalities Test (SDMT)[279]-oral version.

4. Language: It was conducted using the Controlled Words Association Test (COWAT)[280] which has two parts: Letter Fluency (PMR) and category fluency (animals) and the Boston Naming Test-shortened version[281].

5. Verbal and visual memory: Subprocesses of encoding, storage and consolidation, recall/retrieve, and recognition was assessed using Test de Aprendizaje Verbal España-Complutense (TAVEC)[282] for verbal memory and Rey-Osterrieth Figure Complex Test (ROFCT)[283] for visual memory.

6. Visuospatial function: It was assessed using Judgement of Line Orientation (JLO)[284] and two subtests of the Visual Object and Space Perception Battery (VOSP)[285].

7. Visuoperceptive function: Hooper Visual Organization Test (HVOT)[286] and two subtests of the VOSP[285] (object decision and progressive silhouettes).

8. Visuoconstructive function: Based on ROCFT copy.

Neuropsychological test scores were converted to t-scores, adjusting for age, sex, and education, according to the normative data in the test manuals. For the purpose of the study, we categorized tests into 11 domains and global cognition:

- Attention: average of the Digits forward, Spatial Span forward and TAVEC A1;
- Executive function:
    - Working memory: average of the Digit backward, Spatial Span backward, TMT-B;
    - Planification: average of ToL correct and ToL total move;
    - Inhibition: average of Stroop interference; access to semantic memory stores: COWAT-PMR;
- Processing speed: average from the SDMT, ROCFT copy time, ToL Execution Time, ToL Solving Time and TMT A;
- Language: average of COWAT-animals and Boston Naming Test-shorted version;
- Memory: average of TAVEC RL-CP, TAVEC RCL-CP, TAVEC RL-LP, TAVEC RCL-LP, TAVEC recognition, ROFCT immediate, ROFCT delay and ROFCT recognition;
- Visuoperception: average of Hooper Visual Organization Test -HVOT-, Visual Object and Space Perception Battery – VOSP- object decision and VOSP progressive silhouettes,
- Visuospatial: average of Judgement of Line Orientation -JLO-, VOSP position discrimination and VOSP number location; and
- Visuoconstruction: ROFCT copy.

For the purpose of this study, cognitive impairment was defined as an impairment of <1 SD relative to the reference group in 2 cognitive domains, according to the comprehensive criteria of Jack et al. 2009)[62] after ICH.

Composite measures were derived by converting the raw scores of individual tests to *t* scores, using the mean and standard deviation from the normative data, and averaging the *t* scores.

3.2.2.2.2. Functional Status

All patients were interviewed with structured scales:

- Barthel index (Bi): It is an assessment tool that allows to evaluate the autonomy of people to perform the Basic Activities of Daily Living (BADL's)[287]. The data are obtained through observation and through an interview with the user and the family or main caregiver. It evaluates the functional situation of the elderly person in a range that oscillates between 0 and 100 points; values closer to 0 would indicate that the elderly person has a high degree of dependence and, on the contrary, if the score obtained is close to 100, it would indicate that the elderly person has slight dependence or is independent.

- Lawton & Brody index (LBi): The Lawton Instrumental Activities of Daily Living scale (IADL) is an appropriate instrument to assess independent living skills[288]. These skills are considered more complex than the basic activities of daily living as measured by the Bi. The instrument is most useful for identifying how a person is functioning at the present time, and to identify improvement or deterioration over time. There are eight domains of function measured with the Lawton IADL scale. Women are scored on all 8 areas of function; historically, for men, the areas of food preparation, housekeeping, laundering are excluded. Patients are scored according to their highest level of functioning in that category. A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women, and 0 through 5 for men.

- Modified Rankin Scale (mRs): It is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It runs from 0-6, running from perfect health without symptoms to death[289].

3.2.2.2.3. Psychiatric Symptoms: Evaluation of the Affective Disorders

All patients were interviewed with structured questionnaires:

- Anxiety: In order to measure via self-report, the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious the State-Trait Anxiety Inventory (STAI)[290] was used. There are 2 subscales within this measure. First, the State Anxiety Scale (S-Anxiety) evaluates the current state of anxiety, asking respondents to describe their current feelings, using items that measure subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system. The Trait Anxiety Scale (T-Anxiety) evaluates relatively stable aspects of "anxiety proneness," including general states of calmness, confidence, and security. The STAI has 40 items, 20 of which are allocated to each of the S-Anxiety and T-Anxiety subscales.

- Depression: In order to evaluate, on the one hand, degree of affectation (State) and frequency of occurrence (Trait), the Inventory for state-trait depression was used (IDER)[291]. The test items are constructed to evaluate both depression (Dysthymia) and its absence (Euthymia) on a very brief inventory (20 items).

3.2.3. Biomarker Acquisition

3.2.3.1. Determination of Imaging Markers: Image Acquisition Protocol

Neuroimaging markers of SVD were defined according to the criteria for reporting Vascular changes on neuroimaging (STandards for ReportIng Vascular changes on nEuroimaging, STRIVE)[68].

Imaging biomarker assessments (MRI) were performed during screening to assess the baseline status for these biomarkers.

3.2.3.1.1. Magnetic Resonance Imaging

MRI was performed when the patient was hospitalized according to local standard clinical protocols. The MRI served as evidence to document the suitability of the participant's inclusion in the study, evidencing that no other disease than ICH or any other abnormality could cause cognitive impairment.

All subjects underwent a 1.5T or 3T MRI scan sequence.

- In 1.5T MRI, sequences for all subjects included a T1-weighted sagittal 3D-IR GrEcho (slice thickness, 1.2 mm; TR/TE/TI, 8,35/3.1/450; imaging matrix 256x256), a coronal fluid-attenuated inversion recovery (FLAIR) 2D scan (slice thickness, 5.5 mm; TR/TE/TI, 8000/144/2000; imaging matrix 288x224), an axial FSE-T2-weighted scan (slice thickness, 5 mm; TR/TE , 6740/104; imaging matrix 320x256), an axial DWI scan (b-value= 1000), and either a high resolution 3D Susceptibility- weighted imaging (SWI) scan (slice thickness, 2.4 mm; TR/TE/FA 103/49/15, imaging matrix 288x192), or an axial T2∗- weighted gradient-echo (GRE) scan (slice thickness, 5 mm; TR/TE/FA , 600/20/20 ms; imaging matrix 256x224), using an 8-channel head coil.
- In 3T MRI, sequences for all subjects included a T1-weighted sagittal 3D-IR GrEcho (slice thickness, 1.2 mm; TR/TE/TI, 7.1/3.1/400; imaging matrix 288x288), a coronal fluid-attenuated inversion recovery (FLAIR) 2D scan (slice thickness, 5 mm; TR/TE/TI, 10000/152/2250; imaging matrix 352x256), an axial FSE-T2-weighted scan (slice thickness, 1.4 mm; TR/TE, 8080/105; imaging matrix 320x256), an axial DWI scan (b-value= 1000), and either a 3D Susceptibility-weighted imaging (SWI) scan (slice thickness, 2.4 mm; TR/TE/FA 42/26/15, imaging matrix 320x256), or an axial T2∗- weighted gradient-echo (GRE) scan (slice thickness, 5 mm; TR/TE/FA, 420/17/20 ms; imaging matrix 288x288), using an 8-channel head coil.

We used a group of validated MRI visual rating scales to assess imaging markers:

- Cortical microbleeds (CMBs): were defined as a black or hypointense round signal loss with a diameter 5 mm on SWI or gradient-echo images in areas of the signal void with associated blooming seen on T2*-weighted MRI or other sequences that are sensitive to susceptibility effects. The number of CMBs was counted using the Microbleed Anatomical Rating Scale (MARS)[292] to guide the identification and to describe the location of CMBs. CMBs that resulted from cavernomatosis and diffuse axonal injuries were excluded.

- Cortical Superficial Siderosis (cSS): There is some evidence that superficial hemorrhage in the cortical sulcus may also represent a source of bleeding related to CAA. Cortical superficial siderosis was identified on blood-sensitive sequences and classified as either focal (involving ≤ 3 sulci) or disseminated (involving ≥ 4 sulci).

- White matter hyperintensity (WMH): signal abnormality of variable size in the white matter that showed the following characteristics: hyperintensity on T2-weighted images such as fluid-attenuated inversion recovery, without cavitation (signal different from CSF). Lesions in the subcortical grey matter or brainstem are not included in this category unless explicitly stated. If deep grey matter and brainstem hyperintensities are also included, the collective term should be hyperintensities. The location and grade of WMH were defined according to the Fazekas scale[293] classification as “periventricular” and “deep white matter” and were scored from being absent (0) to a large extension or confluent formation (3) at each location.

- Enlarged Perivascular Spaces (EPVS) or enlarged Virchow–Robin spaces were defined as fluid-filled spaces that follow the typical course of a vessel as it goes through grey or white matter. The spaces have signal intensity similar to CSF on all sequences. Because they follow the course of penetrating vessels, they appear linear when imaged parallel to the course of the vessel, and round or ovoid, with a diameter generally smaller than 3 mm, when imaged perpendicular to the course of the vessel. They were assessed on the contralateral side of the ICH at the basal ganglia and centrum semiovale.

  We retained the frequency and range of EPVS as following the EPVS rating scale[294]: the absolute numbers for the basal ganglia and centrum semiovale EPVS (CSO-EPVS) were graded as absent (0), mild (1) for 1 to 10, moderate (2) for 11 to 40, frequent (3) for 21 to 40 and severe (4) for over 41, using an overall score for both hemispheres by assessing and scoring each hemisphere separately and then using the hemisphere with the higher score where hemispheres were asymmetric. Midbrain PVS were rated nonvisible (0) or visible (1).

- CAA total score: It was calculated with a 6-point scale[295]. This scale awards 1 point for CSO-EPVS rating of frequent-to-severe grades (i.e., presence of >20 CSO-EPVS) and WMH that is either Fazekas grade 3 if periventricular, or Fazekas grade ≥2 if deep[296]. Additional points are awarded for the presence of lobar microbleeds (1 point if 2–4 were present; 2 points if there were ≥5) and cSS (1 point if focal; 2 points if disseminated).

- Brain atrophy: A lower brain volume that was not related to a specific macroscopic focal injury such as trauma or infarction. Thus, infarction was not included in this measure unless explicitly states.

  We used the hemisphere that was not affected by ICH.

Brain atrophy can be general or focal (affecting only particular lobes or specific brain regions—e.g., the hippocampus), symmetrical or asymmetrical, or tissue selective (affecting a certain tissue class—e.g., white matter). We used the following scales:

- Global Cortical Atrophy (GCA) scale[297]. The scale was described in 1997 by Florence Pasquier, a French neurologist, as a tool to quantify atrophy in patients after stroke. Global atrophy was rated as: 0: No cortical atrophy; 1: Mild atrophy (opening of sulci)**;** 2: Moderate atrophy (volume loss of gyri); 3: Severe atrophy "knife blade atrophy". The scores were dichotomized into normal (0-1 points) or abnormal (2-3 points) as a score of 1 point could represent normal aging[298].

- Medial Temporal Lobe Atrophy (MTA) score: The MTA score, also known as Scheltens' scale[299], is useful in distinguishing patients with mild cognitive impairment and AD from those without impairment. It is helpful in the assessment of patients with possible dementia. Medial Temporal Lobe Atrophy was rated as: 0: No atrophy; 1: Widening of choroid fissure; 2: As +1 widening of temporal horn of lateral ventricle; 3: As +2 lowered height of hippocampal formation; 4: As +3 further volume loss of hippocampus. The scores were dichotomized into normal (0-1 if age <75, 0-2 if age ≥ 75) and abnormal (2–4 if age < 75, 3–4 if age ≥ 75) as a certain amount of MTA occurs in normal aging[300,301].

A panel composed of the study neurologist and at least two other physicians with expertise in cerebrovascular pathology reviewed the subject's information and assigned clinical diagnosis. In vivo diagnosis was made with the modified Boston criteria which incorporate imaging and clinical items. According to modified Boston criteria, patients older than 55 years who develop multiple strictly lobar, cortical, or cortico-subcortical hemorrhage, including ICH and cerebral microbleeds (cMBs), or single lobar hemorrhage plus focal or disseminated cortical superficial hemosiderosis (cSS), could be diagnosed with probable CAA after excluding other possible causes of hemorrhagic events (Table 2). The MRI-based criteria have been shown very accurate in CAA diagnosis in the radiologic/pathologic validation studies.

3.3. Ethical Considerations

This study has been approved by the Ethics Committee of the Instituto de Investigación Sanitaria La Fe (IIS La Fe) and the Spanish Agency for Medicines and Health Products (AEMPS), with registration number 2018/0532 for all phases, as well as the linkage to patient registers and death certificates.

Informed and written consent was obtained from all participants of the study. The examination process was conducted in a friendly, comfortable environment. If participants expressed anguish or discomfort during the interview, the interview ended regardless of whether they consented. In addition, participants were asked whether they wanted to be informed of any diseases detected during the examination; if so, they were referred to their referring neurologist. MRI images and neuropsychological assessment results were also provided to the participants as feedback on the research conducted. The right to withdraw consent was guaranteed throughout the research process.

The data from the participants had been obtained ensuring compliance with all the obligations derived from Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (GDPR) and Spanish data protection Law (Organic Law 3/2018, of 5 December, on the Protection of Personal Data and the guarantee of digital rights). Technical and organizational security measures applied in the information systems involved in the study. Including paper-based files, are those stipulated In Royal Decree 311/2022 of 3 May, which regulates the National Security Scheme. Thus, a pseudonymization process has been included in order to enhance security. Personal data involved in the study will be duly retained for 5 years after the conclusions has been published.

All researches declares that the procedures established according to the ethical principles of the responsible human experimentation committee and the Declaration of Helsinki have been followed. Good Clinical Practice (GCP) has also been followed.

3.4. The Overall Statistical Analysis Plan

We assessed normality of distribution for all quantitative measures using Shapiro-Wilk W test. Normally distributed continuous variables are presented by the mean and standard deviation (SD), while the non-normally distributed continuous variables were presented by median and interquartile range (IQR). The categorial variables are shown in percentages. Baseline variables on demographical and clinical data were compared by Student's t-test or Wilcoxon-W-test for continuous variables and Chi-square test were used for categorical variables.

To determine whether patients were representative of the whole ICH survivor's cohort, we compared their main baseline characteristics using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. We performed the same analyses for patients who were not fit enough to undergo neuropsychological assessment.

Comparisons on demographic and clinical characteristics between the included and excluded group were performed using the independent t tests (two tailed) for continuous variables and chi square test for categorical variables as appropriate (Table 3).
We compared the patients who had undergone CT scans and MRI from both groups regarding baseline characteristics. Student's t-test, chi-square tests and Mann-Whitney U-tests were applied where appropriate.

In further analyses (Table 9), we performed multiple regression models to explore associations with neuroimaging markers suggestive of CAA (the presence of strictly lobar microbleeds, cSS, EPVS and WMH) as well a composite CAA score and neurodegeneration markers composite scores (MTA, GCA) ant t-score in each cognitive domain, adjusting for age, education, and sex. In these analyses, each neuroimaging marker was considered individually (i.e., each adjusted model included only 1 neuroimaging marker at a time).

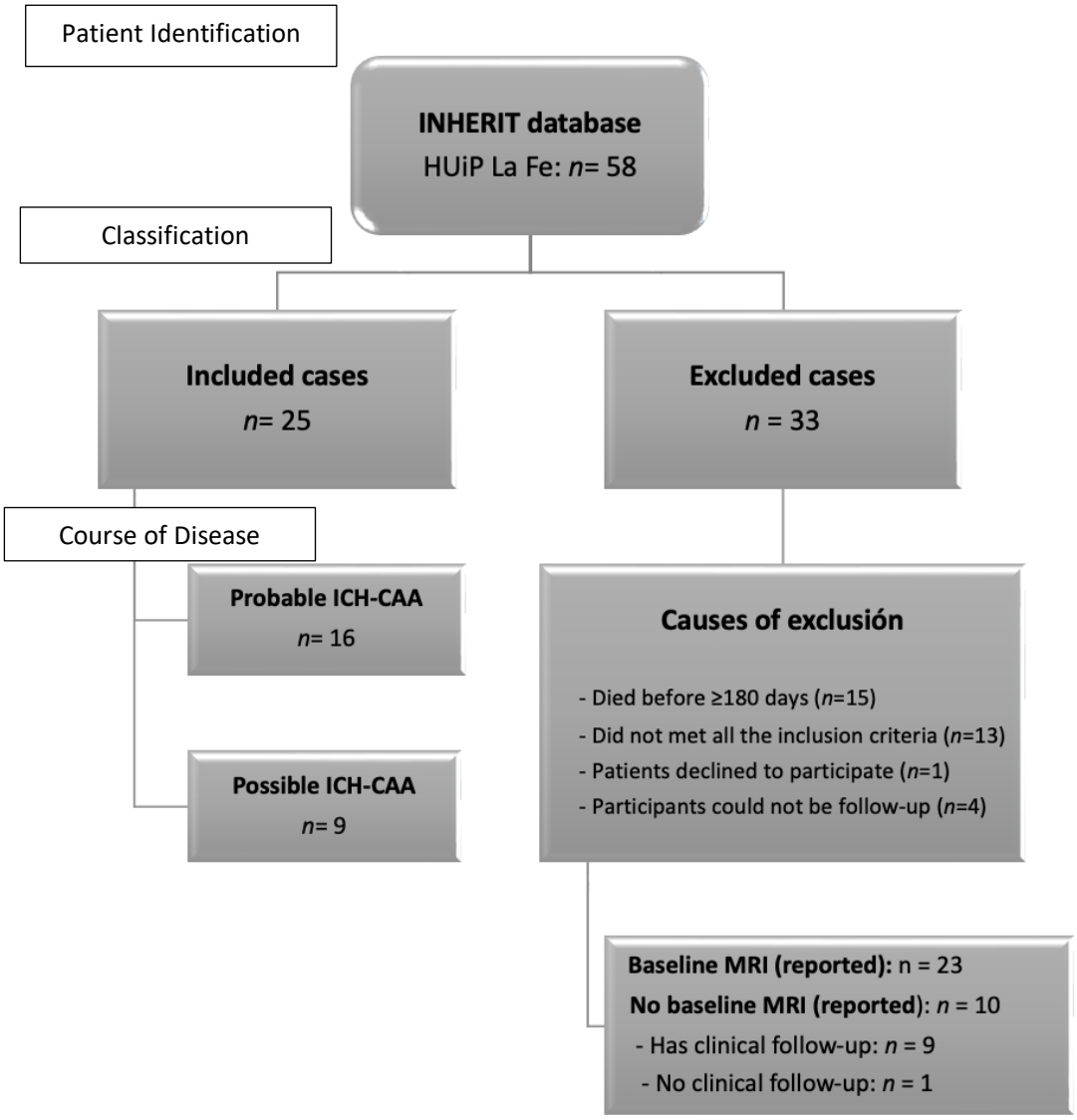
Analyses were carried out using Jamovi version 2.4.11 workstation. All statistical tests were done at the two-tailed α level of 0.05.

FINDINGS

4.1. Sociodemographic and Epidemiological Characteristics

After the application of pre-specified inclusion and exclusion criteria a total of 58 ICH-CAA patients were selected from the INHERIT database between May 2016 and December 2021. Among the 33 excluded patients, 15 died, 13 did not met all the inclusion criteria, 1 declined to participate and 4 were not able to follow-up. Enrolled information is shown in Figure 8.

Figure 8. Enrollment Flow Chart and Study Inclusion and Exclusion Criteria



Baseline Characteristics

A summary of demographic and clinical features for patients is displayed in Table 3 and a summary of the main imaging characteristics for patients at inclusion are shown in Table 4. Tables in appendices provide in-depth details on clinical and neuroimaging features.

We analyzed all consecutive ICH-CAA patients admitted in our Unit. Of the 58 enrolled patients, the median age was 74.3 (SD 8.04), being significantly older those in the excluded group (p=0.006) and 30 (51.7%) were male.

Overall, both groups presented similar medical history findings, with hypertension (63.8%) and dyslipidemia (59.3%) being the most frequent vascular risk factors, followed by diabetes (25.9%) and previous stroke (17.2%). Both, median (minimum-maximum) National Institutes of Health Stroke Scale and Glasgow Coma Scale scores at admission were different (3 [0–15] and 15 [11–15] respectively for the included group); 8 [0–36] and 14 [5–15] respectively for the excluded group, p=0.006 each).

An analysis of the CT ICH-CAA characteristics showed that the most prevalent hematoma location was parietal (40.4%) and frontal (34.9%), more frequent located in the left hemisphere (n= 29 vs. n=20, respectively). The ICH volume was larger in the excluded group than in the included group (35.2 cm^3 vs. 12.8 cm^3 respectively; p= 0.003). Also, IVE (2.1% vs 20.8%, p=0.009) and FLPs (27.1% vs 6.3%, p=0.015) were more common in the excluded group.

MRI analysis of hemorrhagic features showed a total of 47.9% of the patients showed cMBs, with a median of 12 microbleeds. We found differences between both groups in terms of cSS presence, being more prevalent in the excluded group (29.8% vs. 17%, p=0.003) and located in the frontal lobe (19.6% vs. 8.7%; p=0.048).

In term of ischemic MRI markers, Pasquier's scale indicated that 51.9% our patients had moderate-to-severe global cortical atrophy, being more prevalent in the excluded group (14.8% vs. 37.1%; p= 0.006). Patients of our cohort had mild to moderate burden of WMH (41.7% vs 39.6%), with a posterior prevalence just over half of the patients (52.1%).

Finally, for the long-term follow-up, with a median observation period of 15.6 (6-39), months, 12 (21.8%) had no symptoms, 12 (21.8%) had no significant disability, and 15 (27.3%) died.

Table 3. Comparison Between Groups of Demographic and Clinical Profiles at Inclusion

	Overall *n*= 58	**Included *n* = 25**	**Excluded *n* = 33**	***p* value**
Demographics				
Age at onset, mean (SD), y.	74.3 (8.04)	71.0 (6.48)	76.8 (8.31)	**0.006**
Male gender, n (%)	30 (51.7)	16 (27.6)	14 (24.1)	0.107
Clinical characteristics, n (%)				
Hypertension	37 (63.8)	18 (31)	19 (32.8)	0.266
Diabetes	15 (25.9)	9 (15.35)	6 (10.3)	0.131
Dyslipidemia	35 (59.3)	16 (27.6)	19 (32.8)	0.630
Atrial Fibrillation	5 (8.6)	3 (5.2)	2 (3.4)	0.438
Previous stroke	10 (17.2)	4 (6.9)	6 (10.3)	0.838
Smoker	7 (12.1)	4 (6.9)	3 (5.2)	0.117
Alcohol consumption	2 (3.4)	1 (1.7)	1 (1.7)	0.862
Antiplatelet use	13 (22.8)	5 (8.8)	8 (14.0)	0.666
Severity of stroke, median (min-max)				
NIHSS on admission, median (min-max)	4 (0-36)	3 (0-15)	8 (0-36)	**0.006**
GCS on admission, median (min-max)	15 (5-15)	15 (11-15)	14 (5-15)	**0.006**
Post ICH level of dependency, n (%)				
4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	4 (7.3)	0 (0)	4 (7.3)	**<0.001**
5: Severe disability; bedridden, incontinent and requires nursing care and attention	2 (3.6)	0 (0)	2 (3.6)	**<0.001**
6: Dead	15 (27.3)	0 (0)	15 (27.3)	**<0.001**

Table 4. Summary of the Comparison Between Groups of the Main Imaging Features at Inclusion

	Overall ***n*= 58**	**Included** ***n* = 25**	**Excluded** ***n* = 33**	***p*** **value**
Imaging characteristics				
ICH volume (cm^3), median (min-max)	19.1 (1.32-139)	12.8 (1.40-54.7)	35.2 (1.32-139)	**0.003**
Left side ICH, n (%)	29 (54.7)	13 (24.5)	16 (30.2)	0.821
Hematoma Location				
Frontal lobe, n (%)	25 (34.9)	8 (14.0)	17 (29.8)	0.116
Parietal lobe, n (%)	23 (40.4)	11 (19.3)	12 (21.1)	0.629
IVE, n (%)	11 (22.9)	1 (2.1)	10 (20.8)	**0.009**
FLPs, n (%)	16 (33.3)	3 (6.3)	13 (27.1)	**0.015**
Patients with strictly cMBs, n (%)	23 (47.9)	11 (22.9)	12 (25.0)	0.583
Total number of cMBs, media (SD)	12.1 (24.8)	09.36 (18.6)	15.4 (30.9)	0.416
Patients with strictly cSS, n (%)	22 (46.8)	8 (17.0)	14 (29.8)	**0.033**
cSS Frontal Lobe Location, n (%)	13 (28.3)	4 (8.7)	9 (19.6)	**0.048**
WMH (Fazekas), median (min-max)	2 (0-3)	2 (0-3)	2 (1-3)	0.315
CAA score, median (min-max)	3 (0-5)	3 (0-5)	3 (0-5)	0.676
MTA, median (min-max)	1 (0-4)	1 (0-3)	1 (0-4)	0.835
GCA				
0-1, n (%)	26 (48.1)	17 (31.5)	9 (16.7)	**0.006**
2-3, n (%)	28 (51.9)	8 (14.8)	20 (37.1)	**0.006**

Abbreviations: NIHSS: National Institute Stroke Scale; GCS: Glasgow Coma Scale; IVE: Intraventricular Extension; FLPs: Finger Like Projections; cMBs: cortical microbleeds; cSS: cortical superficial siderosis; EPVS: Enlarged Perivascular Spaces; CAA score: Cerebral Amyloid Angiopathy total core; MTA: Medial Temporal Lobe; GCA: Global Cortical atrophy

4.2. The Neuropsychological Aspects after ICH due to CAA

In total, only 25 of the 58 patients were able to undergo neuropsychological evaluations, as mentioned above. Patients were not actively working during the assessment, as de majority were retired (88%). There is a low level of study among almost half of the sample (44%), with an average of 8.16 years of schooling.

Table 5. Social Characteristics of the Neuropsychologically Assessed Patients

	Included n = 25
Civil Status, n (%)	
Married	18 (72)
Single	2 (8)
Widow	5 (20)
Employment Status, n (%)	
Retired	22 (88)
Disabled	3 (12)
Years of education, mean (SD)	8.16 (4.61)
Level of education, n (%)	
Less than primary	11 (44)
Primary	8 (32)
High school	1 (4)
Undergraduate	2 (8)
Graduate/Ph.D.	3 (12)

As shown in table 5, patients presented an adequate level of global cognition (27; 17-35) and with cognitive functioning within the expected range for their premorbid characteristics (IQCODE=51.08; BDRS = 3.08).

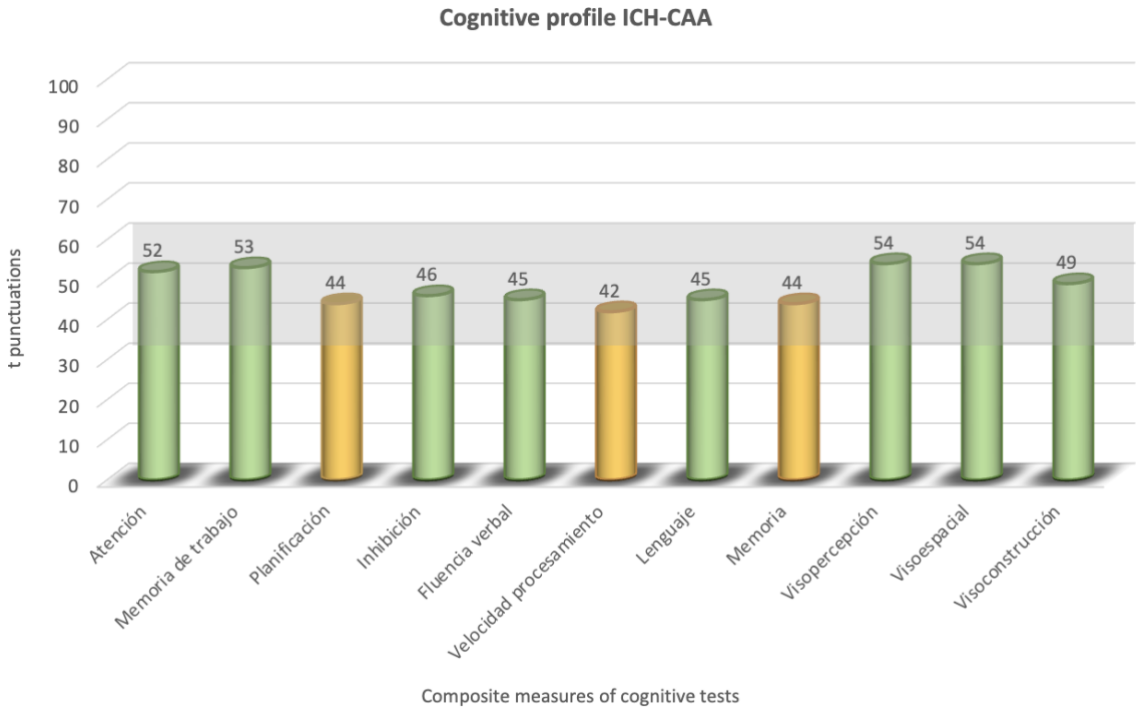
Regarding cognitive assessment, tests were expressed as a t-score based on published age, education-, and sex-adjusted normative data supplied by each test and by NEURONORMA, then grouped into domains of attention, executive functions, processing speed, language, memory, visuospatial, visuopercetive, and visuoconstructive function.

At a mean delay of 15.6 months after the index event (10.00 SD; IQR:6-39) the cognitive assessment showed that none of the process and subprocess assessed were impaired. However, the processes in which they have the lowest performance are processing speed with a mean (±standard deviation) *t* score of 42 (± 1.47), followed by memory (44 ± 1.61) and planning (44 ± 1.97). Results are summarized in Figure 5.

Table 6. Composite Measures of Cognitive Tests Scores, expressed as *t* Scores Relative to Published Norms

							95% Confidence Interval	
	N	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**	**Lower**	**Upper**
Time between Index Event and NPS assessment, (m.)	25	15.6	10.00	11	6	39	9.77	18.0
IQCODE	25	51.8	2.63	51	45	56	50.7	52.9
BDRS	25	3.08	2.00	2.98	0.00	9.50	1.85	4.31
Premorbid IQ	25	95.040	8.218	93	85	114	91.818	98.262
Global Cognition	25	27.444	4.830	28	17.000	35.000	25.622	29.266
Attention	25	52.827	8.466	55.000	36.333	73.333	49.508	56.145
Working memory	19	53.386	7.046	53.333	38.333	64.667	50.218	56.554
Planning	24	44.375	9.672	44.750	30.000	64.000	40.505	48.245
Inhibition	24	46.125	7.980	46.000	28.000	66.000	42.932	49.318
Verbal Fluency	25	45.387	9.445	46.000	30.000	61.333	41.684	49.089
Processing Speed	22	42.400	6.917	44.000	28.400	53.200	39.509	45.291
Language	24	45.1888	11.129	47.500	16.500	59.000	40.735	49.640
Memory	24	44.917	7.887	45.000	25.857	60.714	41.761	48.072
Visuoperception	25	54.600	5.754	53.333	46.333	66.333	52.344	56.856
Visuospatial	25	54.373	9.475	56.333	34.000	70.000	50.659	58.088
Visuoconstruction	24	49.833	11.052	49.000	34.000	77.000	45.412	54.255

Figure 9. Cognitive Profile of ICH-CAA Patients



Based on t-scores, the gray band represents the range of normality, where 50 is the mean and 10 is the standard deviation.

The Barthel test showed that our cohort were able to carry out basic daily activities with low dependency levels (Bi=98.60), although both men (LBi=4) and women (LBi=7.56) face some difficulties in instrumental activities as shown in Table 7.

Table 7. Ability to Perform Daily Living Activities

							95% Confidence Interval	
	N	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**	**Lower**	**Upper**
Bi	25	98.60	3.69	100	85	100	97.16	100.04
LBi								
Male	16	4.00	1.265	4.00	0	5	__	__
Female	9	7.56	0.882	8	6	8	__	__

Abbreviations: Bi: Barthel Index; LBi: Lawton & Brody Index

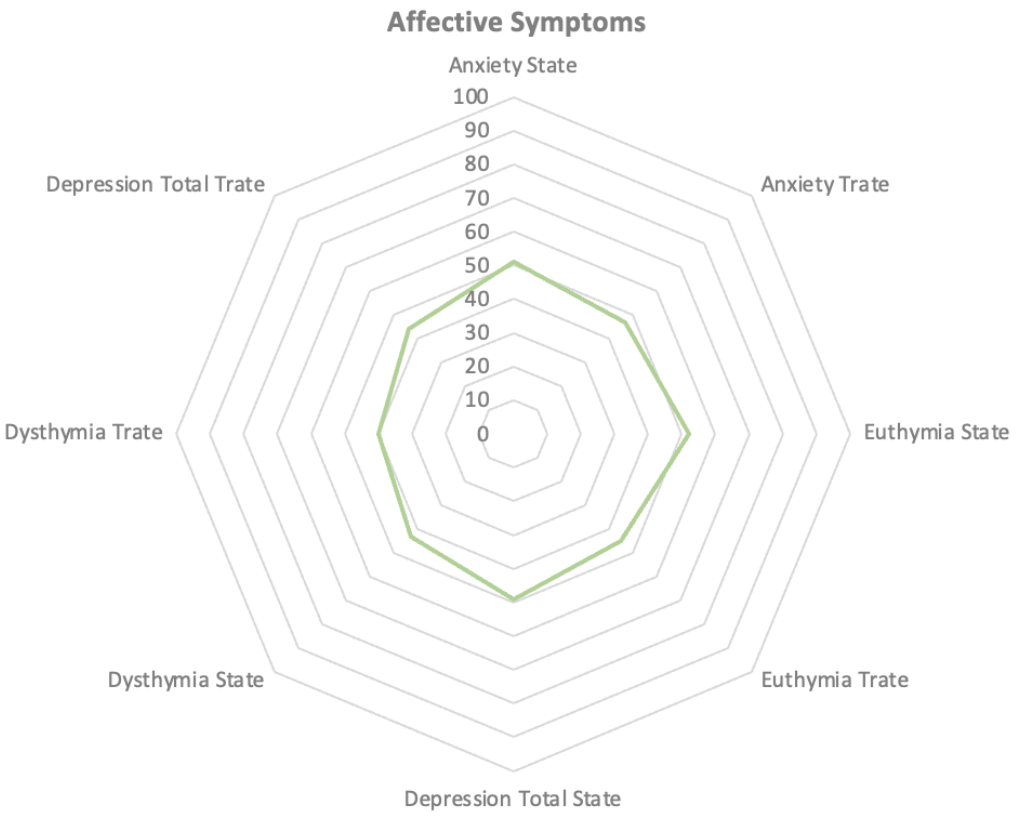
Median STAI-State, STAI-Trait, Euthymia-State, Euthymia-Trait, Depression Total State and Depression Total Trait are presented in Table 8.

In our cohort, none of the patients had symptoms of depression. Patients presented adequate scores on the state scale (Depression total state: t=49, SD=11,24; Dysthymia State: t=43, SD=13.56 and Euthymia State: t=52, SD=11.29) and on the trait scale (Depression total trait: t=44, SD=9.96; Dysthymia Trait: t= 40, SD=10.22; Euthymia Trait: t= 45, SD 11.61).
On the other hand, we observed similar results for anxiety, with appropriate severity (Anxiety State: t=51, SD=11.79) and frequency (Anxiety Trait: t=45, SD=8.27). No antidepressant and anxiolytic medication were used in this cohort.

Table 8. Summary of the Punctuations in Anxiety and Depression

							95% Confidence Interval	
	N	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**	**Lower**	**Upper**
Anxiety								
State	25	51	11.79	53	29	83	46.54	55.78
Trait	25	47	8.27	47	32	60	43.88	50.36
Depression								
Euthymia State	25	52	11.29	53	29	67	47.77	56.63
Dysthymia State	25	43	13.56	41	28	63	38.61	49.23
Depression Total State	25	49	11.24	51	29	67	44.91	53.73
Euthymia Trait	25	45	11.61	46	28	67	41.33	50.43
Dysthymia Trait	25	40	10.22	43	28	56	36.59	44.61
Depression Total Trait	25	44	9.96	47	29	63	40.97	48.79

Figure 10. Summary of Affective Punctuations



4.3. A Connection between Brain Vascular and Structural Alterations common in ICH-CAA and Cognition

The association between neuroimaging markers and performance on cognitive tests was examined in linear regression models as showed in Table 9.

After adjustment for age, education, sex, and the presence of symptomatic ICH, correlational analysis revealed a significant association between MTA and most of the processes assessed (Attention: *p*=0.002, adjusted R^2= 31; Planning: *p*= 0.006, adjusted R^2= 26; Verbal fluency: *p*=0.001, adjusted R^2= 35); Language: *p*=0.001, adjusted R^2= 36; Memory: *p*=0.003, adjusted R^2= 29; Visuospatial: *p*=0.005, adjusted R^2= 26; Visuoconstruction: *p*=0.006, adjusted R^2= 26). Besides, a significant correlation was found between CAA total score and GCA with Memory (*p*=0.018, adjusted R^2= 19; p=0.021, adjusted R^2= 15) and Visuoperception (*p*=0.0326, adjusted R^2= 15; *p*=0.022, adjusted R^2= 17).

Table 9. Influence of Brain Vascular and Structural Alterations and Cognition

	t	*p*	Adjusted R2 (%)	RMSE
Attention				
ICH volume	1.40	0.175	4	7.09
CAA score	-1.23	0.230	20	8.03
MTA	-3.41	**0.002**	31	6.76
GCA	-1.56	0.132	6	7.89
Working memory				
ICH volume	0.27	0.789	7	6.41
CAA score	0.06	0.949	6	6.86
MTA	-1.52	0.147	7	6.44
GCA	-0.31	0.758	5	6.84
Planning				
ICH volume	0.879	0.391	1	9.075
CAA score	0.29	0.774	4	9.45
MTA	-3.01	**0.006**	26	7.97
GCA	-1.00	0.328	0	9.26
Inhibition				
ICH volume	-0.408	0.688	4	8.48
CAA score	-1.04	0.307	0	7.63
MTA	-0.36	0.721	4	7.79
GCA	-0.50	0.625	3	7.77

Table 9. Influence of Brain Vascular and Structural Alterations and Cognition (*continuation*)

	t	*p*	Adjusted R2 (%)	RMSE
Verbal Fluency				
ICH volume	0.529	0.603	3	9.73
CAA score	-1.66	0.109	7	8.74
MTA	-3.71	**0.001**	35	7.32
GCA	-0.72	0.476	2	9.15
Processing Speed				
ICH volume	0.894	0.385	1	5.95
CAA score	0.29	0.771	5	6.74
MTA	-1.56	0.134	0.06	6.38
GCA	0.26	0.797	5	6.75
Language				
ICH volume	0.476	0.640	4	10.67
CAA score	-1.23	0.232	2	10.54
MTA	-3.74	**0.001**	36	8.52
GCA	-1.44	0.163	4	10.42
Memory				
ICH volume	1.17	0.267	1	7.34
CAA score	-2.55	**0.018**	19	6.78
MTA	-3.24	**0.003**	29	6.36
GCA	-2.69	**0.013**	21	6.70
Visuoperception				
ICH volume	-0.52	0.608	3	4.58
CAA score	2.27	**0.032**	15	5.09
MTA	1.06	0.300	10	5.51
GCA	2.45	**0.022**	17	5.02
Visuospatial				
ICH volume	0.49	0.630	3	9.44
CAA score	-1.74	0.094	8	8.73
MTA	-3.10	**0.005**	26	7.79
GCA	-0.86	0.396	10	9.14
Visuoconstruction				
ICH volume	0.47	0.644	4	9.97
CAA score	0.32	0.752	4	10.79
MTA	-3.02	**0.006**	26	9.10
GCA	0.29	0.772	4	10.80

Abbreviations: CAA score: Cerebral Amyloid Angiopathy score; MTA: Medial Temporal Atrophy; GCA: Global Cortical Atrophy

DISCUSSION

5.1. General discussion

In this doctoral thesis, we investigated the neuropsychological profile in an ICH-CAA in a Spanish single-center. We have also analyzed the imaging characteristics of this cohort by using CT and 1.5T MRI and 3T MRI. Furthermore, we have identified neuroimaging markers that could predict cognitive impairment in the future.

To understand the prognosis of this heterogeneous entity, neuroimaging and neuropsychological markers must be thoroughly examined. As a result of using this integrative approach, we would be able to better characterize and diagnose these clinical manifestations in order to improve the prognosis for these patients as well as their diagnosis and treatment or intervention.

The aim of this thesis was to take advantage of several neuropsychological and neuroimaging biomarkers to study CAA from a translation perspective. This study moves beyond a screening cognitive assessment of ICH related to CAA and provides a broader framework for neuropsychological characterization in this patient population.

INHERIT Population Clinical Features

The sample has been exhaustively selected with the intention of analyzing a homogeneous cohort. Because of the restrictive inclusion and exclusion criteria, our sample represents a small portion of the clinical spectrum of CAA. This decision was taken in order to characterize neuropsychologically patients with *de novo* symptoms and determine the presence of cognitive impairment. This decision was supported by previous studies where the impact of pre-existing cognitive deficits on post-ICH CI was generally acknowledged. To address this, several studies also excluded individuals with pre-ICH or dementia[106,302–307]. In our study, 11 of the 13 patients initially excluded for not meeting the inclusion criteria were excluded due to this reason.

Among the INHERIT cohort, 51.7% are men with a mean age of 74.3 (SD 8.04), having hypertension (63.8%) and dyslipidemia (59.3%) as the main cardiovascular risk factors. NIHSS and GCS at the time of the index event were 4 and 15, respectively, and median ICH volume was 19.1 (1.32-139) cm^3. As mentioned before, the clinical presentation of ICH-CAA patients was highly homogeneous, consisting of parietal lobar hemorrhage in 40.04% of the cases, followed by frontal location (34.9%), temporal (21.1%) and occipital (17.5%). No further lobar ICH was detected during the 15-months follow-up.

In our study, there is no significant difference in the prevalence of hypertension between the included and excluded patients, being the most frequent vascular risk factor (n= 37; 63.8%), followed by hyperlipidemia (n= 35; 59.3%), diabetes (n=15: 25.9%) and previous stroke (n= 10; 17.2%).

In the past, CAA development was not associated with cerebrovascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, or atherosclerosis severity of the cerebral arteries[308]. As a result, the correlation between CAA and cerebral arteriosclerosis and arteriolar sclerosis has gained attention. A recent postmortem pathological investigation of elderly subjects showed a correlation between SVD severity and CAA severity[309]. As mentioned before, the prevalence of CAA in the elderly increases with age. According to autopsy reports, CAA prevalence over 70 years of age was 43%, with nearly half of all cases being moderate to severe[310]. The prevalence of hypertension also increases with the age. The prevalence of hypertension at age 50 is about 30%, and it increase to about 60% and 50% at age 70[311]. With the increase in CAA and hypertension prevalence in older adults, it is possible they coexist at a higher rate in older age. Actually, Smith et al. reported that 25% of the patients with ICH had both CAA and hypertensive microangiopathy[312]. According to one study, the widespread of CMBs may be caused by the coexistence of CAA and hypertension. Consequently, fibrinoid necrosis or microaneurysm formation can occur in patients with CAA, causing the vessel walls to rupture, resulting in lobar hemorrhage. We cannot exclude the possibility of ICH-CAA in the diagnosis of patients with lobar hemorrhage and hypertension[263], and it is difficult to strictly distinguish ICH-CAA from hypertensive ICH solely based on clinical and radiological findings.

CT characteristics

Traditionally, it has been said that CAA-related lobar hemorrhages preferentially arise in posterior lobar brain regions. Analysis of the spatial distribution of 321 intracerebral hemorrhages in 59 patients with CAA revealed that hemorrhages were significantly more likely to occur in the temporal and occipital than the frontal and parietal lobes[200]. However, according to our cohort, 23 (40.4%) of patients presented with parietal hematomas, followed by 25 (34.9%) with frontal hematomas. In the same direction, we found several studies that described the locations in 262 patients[313–319]. The most frequent ICH locations were the frontal (83 [24%]) and parietal (83 [24%]) lobes. 72 (21%) ICHs were occipital, 58 (17%) were located in the temporal lobes and 7 (2%) were cerebellar. The remaining 43 ICHs involved multiple supratentorial lobes, with the parieto-occipital (15 [4%]) and fronto-parietal (14 [4%]) regions being the most frequently involved.

CAA-related lobar hemorrhages often extend beyond the brain tissue into the subarachnoid and subdural spaces and, less frequently, may rupture into ventricles[320,321]. Extension of the hemorrhage into de subarachnoid spaces and the presence of elongated “finger-like” projections appear to be characteristics features of ICH-CAA that may assist in diagnosis[322].

In our cohort, the pooled proportion of participants with irregular border was (64.6%), followed by FLPs (33.3%) and SAE in (39.6%) of the cases. Despite being poorly understood, irregular borders may be caused by either impaired endothelial or subendothelial function in CAA-affected vessels and/or impaired vasoconstriction, which negatively affect haemostasis[313,323].

In conclusion, in our radio-pathological analysis we had showed that irregular border and SAE are the most common imaging features of ICH-CAA. There is, however, a need for rigorous diagnostic test accuracy studies that examine the diagnostic value of these features and other imaging features. In the future, CT-based diagnostic criteria will be most widely applicable to ICH-CAA, especially in cases where patients cannot tolerate MRIs and PETs, and in countries with limited access to advanced imaging.

Ischemic and Hemorrhagic MRI Biomarkers

The identification of sensitive biological and neuroimaging markers has become an essential component of CAA research**.**

We identified three retrospective, hospital-based cross-sectional studies, one of CAA-associated ICH which fulfilled the Boston criteria for CAA (we assumed CAA-associated ICH was either lobar or cerebellar [*n* = 27] vs. non-CAA ICH [n = 22])[135,264], one of CAA-associated lobar ICH (*n* = 54) vs. CAA without ICH (*n* = 51)[253] and a cross sectional study which used MRI on a subset of 17 adults with corticosubcortical (i.e. lobar) ICH which fulfilled the Boston criteria for CAA vs. non-CAA ICH (*n* = 7)[324].

The pooled proportion of focal or disseminated superficial siderosis in CAA-associated ICH was 52% (95% CI 39–65%, I 2 = 35%, 3 studies; S3 Fig). The imaging features of ICH reported in one study were lobar brain microbleeds (n = 36 [67%]), severe centrum semiovale enlarged perivascular spaces (n = 29 [55%]), severe white matter hyperintensities (n = 13 [24%]) and severe basal ganglia enlarged perivascular spaces (n = 11 [21%]).[32]

In our study, we had found similar results that those described above, which 22 (46.8 (%) of the patients showing focal or disseminated superficial siderosis and the presence of lobar microbleeds was present in 47.9% of the patients. However, we found that only 5 (10.4) presented with severe centrum semiovale and basal ganglia enlarged perivascular spaces. In terms of white matter hyperintensities, only 8 (16.7) of our studied patients had a severe stage.

Atrophy

Loss of cortical grey matter is a maker of many neurodegenerative diseases, such as AD, and is a key mediator of associated cognitive impairment. Medial temporal lobe atrophy represents loss of volume in the hippocampal area. MTA is sensitive for AD but not specific; it can be found in other dementias as well[325]. In prospective studies in non-demented subjects, MTA has been shown to predict future dementia in general and AD in particular[326,327]. Global cortical atrophy represents the mean volume loss of the cerebral cortex as a whole. In this context, the GCA rating scale is used to give an overall estimate of atrophy without regional bias.

CAA has been associated with thinning of the cerebral cortex in regions remote from focal ICH damage[328]. The researchers compared neurologically asymptomatic healthy controls with 63 patients with age-related CAA using high resolution T1-weigted MRI. Multiple brain regions showed cortical thinned. The same pattern was observed in 26 patients with hereditary CAA caused by an amyloid precursor protein mutation[328]. According to another study, smaller brain volumes in CAA patients were associated with slower cognitive processing speed and worse executive functions[256].

There are several possible explanations for cortical atrophy in AD: confounding from concomitant parenchymal AD pathology; cortical effect of CAA-related structural lesions; or CAA-related vascular dysfunction. In our study, the first possibility was mitigated by excluding patients with cognitive impairment prior to the index event so that the confounding of AD could be minimized. Our results further showed more prevalent moderate cortical atrophy in the frontal and parietal regions, affecting up to 50% and 43.8% of the patients, respectively. These areas differ from those reported to be particularly susceptible to vascular amyloid load by pathology and in-vivo amyloid imaging[329–331].

Additionally, 51.9% of participants had a moderate-to-severe GCA, resulting in substantial qualitative differences in cortical thinning patterns between excluded and included participants (p= 0.006).

5.2. Neuropsychological Features of ICH-CAA: A Comprehensive Perspective

To better understand the whole neuropsychological features of ICH related to CAA, we first studied a cohort who survived ≥180 days after the index event without prior cognitive impairment. By analyzing the results of the neuropsychological assessment in this cohort, the four main conclusions of this study were: 1) patients demonstrate adequate cognitive performance in all processes and sub-processes assessed compared to normative test of similar age, sex, and educational level, 2) even though this adequate cognitive performance, some difficulties (ranged between t=40 to t=45) are observed in tasks involving planning, speed of information processing, and episodic memory; 3) patients are functionally capable in both basic daily activities and instrumental activities after more than 1 year follow-up, although they start having some difficulties when it comes to performing more demanding activities. Finally, 4) patients do not display symptoms of affective disturbance.

Cognitive function

According to previously reported studies, CAA subjects with a history of ICH showed significantly poorer cognitive performances in all cognitive domains compared with healthy controls. Affected cognitive functions included processing speed, executive functioning, episodic memory, and semantic fluency and attention.

In a study conducted by Case et al., cognitive profiles of CAA, AD, MCI, and survivors of ischemic stroke were compared[258]. This study found that patients with clinically diagnosed CAA met criteria for MCI and performed significantly worse on neuropsychological tests of executive functioning, perceptual speed and episodic memory compared with test norms. Compared to AD patients, CAA participants had similarly low executive functioning score. However, their memory was relatively preserved.

Moreover, it has been observed that non-demented CAA perform poorly in processing speed and executive functioning due to reduced efficiency of the brain structural network[332]. In addition, an observational cohort study conducted by Moulin et al. evaluated cognition after a first ICH (n=218) in patients with no preexisting dementia and found that 63 (14%) developed new-onset dementia during a median follow-up of 6 years, leading to an incidence of 28% 4 years after ICH[130]. Furthermore, patients with lobar ICH experience a two-fold higher incidence of new-onset dementia at 1 year (23%) than those with non-lobar ICH (9%). One group showed that in this patient's lower global network efficiency is related to worse performance on test of processing speed and executive functioning[332].

Our study provides detailed description of the neuropsychological features of ICH-CAA patients in a medium-term period (median 15 months after the index event). Our main new findings are that, in terms of cognition, patients without previous dementia perform adequately on a wide range of cognitive tests compared with subjects with similar age and educational level, though there is a tendency to exhibit greater difficulty in tasks that evaluate processing speed, memory and planning which is in line with the previous studies mentioned[130,258,332].

In the aftermath of a stroke, there are usually several phases. As proposed by the Stroke Roundtable Consortium, the *hyperacute* phase begins within the first 24 hours, the *acute* phase begins within the first 7 days, the *early sub-acute* phase begins within the first 3 months, the *late sub-acute* phase begins within the first 4 months, and the *chronic* phase begins after 6 months[333]. The rationale behind this differentiation is that recovery-related processes post-stroke are time-dependent. In addition, the greatest improvement occurs within the first few weeks following stroke, reaching a relative plateau after 3 months, when recovery becomes less significant, especially when it comes to motor symptoms[334,335]. In most cases, spontaneous recovery has reached its limit after 6 months, leading to more or less stable deficits, i.e., chronic deficits. Training or other interventions, however, can improve some stroke-induced deficits in the chronic phase, especially for cognitive domains such as language[336].

Among this population of ICH-CAA patients, impairment rates post-ICH were reported to range from 37% after 6 months follow up[337] to 88% after 3 months follow-up[307]. However, most of these studies performed its neuropsychological assessments along the sub-acute phase[307] or in some cases they do not even perform a neuropsychological evaluation or screening[338]. Furthermore, the criteria that are used to define cognitive impairment can influence the prevalence ratios of cognitive impairment in addition to the time elapsed between the index event and the neuropsychological evaluation. Compared with other similar studies, we used very restrictive criteria that may explain the difference in prevalence of post-stroke cognitive impairment in our study.

We considered that in order to better understand the neuropsychological characteristics of these patients, evaluations should be carried out during the chronic phase, as our study shows, always examining cognition, functioning, and emotional characteristics. When it comes to diagnosing MCI or dementia, it is worthwhile to note that the median time of diagnosis of new-onset dementia is 3 years, and a substantial 25% of them are diagnosed 6 years after the ICH: this finding underlines the importance of follow-up of ICH survivors over time.

In summary, according to most studies, ICH has been associated with cognitive alterations in executive function, attention, processing speed and episodic memory. However, it is possible to experience such a cognitive pattern due to other neurological conditions, including AD or VCI resulting from an ischemic stroke. Variations in the results observed so far may be explained by methodological biases such as delay of cognitive assessment after ICH, methods of cognitive assessment and controlling for preexisting dementia, or by differences in sample sizes between studies such as ours.

Functional status

On the other hand, ICH is a devastating subtype of stroke, with mortality rates up to 50% within 1 month[339,340]. In early clinical studies, mortality and its reduction have been the primary focus, but more recent efforts have begun to address disability among survivors. The number of longitudinal studies evaluating all aspects of disability in this population is scant.

An important consideration when evaluating neurologic recovery is to consider disability from the perspective of the International Classification of Functioning, Disability and Health of the World Health Organization[341]. There are three hierarchical levels of disability in this taxonomy: a) impairment of a part of function of the body; b) limitation of activity performance (previously known as a disability or functional limitation), and c) limitation of social participation (previously known as a handicap). As a result of these definitions, we can better understand the impact of ICH on personal independence, and treatment approaches can be tailored to specific levels of dysfunction. Of note, in our study we had capture activity limitation-the inability to perform an activity interpedently, through the modified Rankin Scale (mRS)[289], the Barthel Index (Bi)[287] and the Lawton & Brody Index (LBi)[288].

Research has shown that 50 to 64% of ICH survivors are independent in their activities of daily living (ADLs) within 6 to 32 months after the index event[340,342]. Despite some studies showing similar limitations to ischemia and hemorrhagic strokes[343–345]others report superior recovery of activity in ICH[346–348].

In our observational study, we report medium-term functional outcome of ICH-CAA in a Spanish single-center. A total of 36.7% of patients survives at 15 months and a large proportion of ICH-CAA survivors can live functionally independent lives; three-quarters were functionally independent, with mRS 0-2, LBi 4 (0-5) form men and 7.65 (6-8) for women and a Bi of 98.60 (07.16-100.04).

To our knowledge, this is the first published cohort of patients with ICH-CAA considering all neuropsychological aspects at medium-term outcomes, not just cognitive ones. Considering aspects of disability, the first study published, released by Kaiser et al., examined the percentage, risk factors, and comorbidities of ICH-CAA patients[349]. Then, Ruiwen Che et al. included 367 ICH-CAA Chinese patients treated with surgery. However, it included patients younger than 55 years were included, as well as more patients with deep ICH (135/367 patients 36.7%) who did not meet the Boston criteria[350]. Finally, Yakushiji et al. included 141 ICH-CAA patients, as well as more patients with previous stroke and with anticoagulant medication (27/141 patients 19.1%)[351].

As compared with orient countries, our study shows higher favorable outcomes, survival probability, and lower mortality. The studies differed greatly in terms of their inclusion criteria, scoring systems, and definitions of favorable outcomes. Secondly, our patients appear to have milder symptoms that these patients. Meanwhile, geographical differences in CAA prevalence, severity, and outcome may be related to genetics or environmental exposures[351].

Psychiatric Symptoms

A wide range of psychiatric symptoms (PsyS), regardless of the underlying cause, are prominent features of neurodegenerative diseases and cognitive decline[111,352,353]. It appears that PsyS may also be predictors of cognitive impairment in cognitively normal elderly people as well as the transition from MCI to dementia[354,355].

A high percentage of ICH survivors may develop PsyS, but PsyS screening in this group is rarely investigated. To the best of our knowledge, the study we conducted is the first to investigate the presence of PsyS in a national clinical cohort of ICH-CAA patients. According to a recent study on stroke patients of all types, there were higher rates of behavioral disturbances among those with ICH[356]. The overrepresentation of psychiatric disturbances in patients with ICH might be related to the higher prevalence of dementia and CAA in this population[134,264].

PsyS were more severe in patients with post-ICH dementia and in those showing CAA MRI profile. In Alzheimer-type and VCI NPS are highly prevalent suggesting a contribution of cortical beta-amyloid load[111,357,358].

For the purpose of identifying possible PsyS at an early stage, we conducted an affective symptoms screening. The identification of PsyS could impact care planning and prevention strategies to reduce the burden of cognitive and functional decline in ICH survivors. Finally, PsyS screening might improve the early identification of patients at higher risk for long-term cognitive decline after ICH. We found that affective disturbances are not observed on patients without post-ICH dementia. The results presented in our study differ from those proposed by various studies focusing on anxiety and depression after stroke that have been reported that the most frequent PS are affective disturbances also in the absence of cognitive impairment[359,360].

These differences might be related to a lack of power, to the appropriate cognitive and functional status of our sample, since the most serious cases could not be included, or to a lower specificity of markers such as WMH, cSS, cerebral atrophy for underlying CAA. However, we cannot exclude a potential inaccuracy of brief screening tools in assessing affective symptoms. The recent systematic review focused on patients with SVD[361] highlighted that more studies are needed, and ICH cohorts should also include a large number of patients.

5.3. CAA and the Risk of Cognitive Decline and Dementia

Our main new finding is that MRI neuroimaging markers of CAA could be associated with future ICH cognitive impairment. This suggests that cognitive impairment in CAA is not only because of brain injury caused directly by ICH but also independently related to the underlying small vessel disruption associated with CAA.

Our study of ICH-CAA survivors did not find frank cognitive alterations, probably due to the small sample size and the fact that we only studied outpatients with mild CAA. However, thanks to the application of a rigorously selected and administered neuropsychological battery, we can reveal interesting results: 1) Memory seems to be the cognitive domain most susceptible to the influence of various brain changes; 2) MTA continues to be the best predictor of memory impairment followed by GCA and CAA score; 3) MTA correlates significantly not only with memory but also with other processes, such as attention, planning, verbal fluency, language, visuospatial and visuoconstruction function; 4) CAA related neuroimaging markers, rather than ICH volume and location, could be predictors of long-term dementia incidence.

An increasing body of research suggests that CAA's pathophysiology is much more complex than originally believed, resulting in a multitude of brain injuries. There is now evidence that CAA can cause significant brain atrophy in areas not directly affected by ICH, and to increase the risk of progressive cognitive decline even without new hemorrhagic strokes[161,362]. In other words, CAA is characterized by features associated with neurodegenerative diseases, such as brain atrophy and progressive decline. Even though CAA is usually associated with some degree of AD pathology, the profile of cortical thinning and cognitive impairment does not completely overlap with AD, suggesting CAA-specific neurodegenerative pathways. Furthermore, ischemic brain injury caused by CAA is one of the key mechanisms responsible for brain injury, cortical disconnection, and cognitive impairment.

When discussing structural MRI in the context of CAA and its antecedent conditions, most authors focus on the vascular aspects of the disease, with particular regard to WMHs and cMBs. However, structural MRI scans can also be used to identify and quantify neurodegenerative aspects of the disease, like cortical atrophy, which have emerged as important elements in our understanding of CAA[328]

The relation between vascular (ischemic brain injury) and degenerative lesions (hippocampal atrophy) and subsequent neurocognitive decline is based on the interactive hypothesis that suggests that the co-occurrence of vascular and degenerative lesions can induce a synergistic effect that might potentiate and accelerate cognitive decline. The interactive hypothesis is supported in several systematic reviews and meta-analysis[363–366].

To make my case that CAA should be considered both a cerebrovascular and a neurodegenerative disease, I will focus on associations between CAA and cardinal imaging features of both neurological syndromes.

In our study, several MRI findings have been incorporated in an MRI-based composite 'score' which aim to capture the overall burden of CAA-SVD in the brain: the CAA score. Total CAA-SVD summary score using the principal MRI markers of CAA (lobar CMBs, WMH according to Fazekas[293], CSO-PVS, and cSS) as previously validated[295]. This yielded an ordinal score of total SVD burden (ranging from 0 to 5). A number of other measures have been considered in this study, including scores related to brain atrophy in specific areas, such as the hippocampus (MTA), as well as measurements related to global cortical atrophy (GCA).

Pathological or degenerative changes in the medial temporal lobe are thought to mediate the earliest cognitive symptoms of AD. Thinning of the medial temporal lobe cortex is the best predictor of poorer episodic memory performance in AD. By analyzing the results of the neuroimaging markers in our cohort, this thesis has provided evidence upon the existence of preclinical markers of possible later cognitive impairment. Our findings add to growing evidence that degenerative markers - like hippocampal atrophy- had strong associations with several cognitive domains - such attention, planning, verbal fluency, language, memory, visuospatial and visuoconstruction functions- and not only with episodic memory, suggesting that atrophy in the hippocampus might be an especially important pathological process impairing cognition in CAA patients. The observation suggests that this *AD cortical thickness signature* might be a biomarker for individual differences and not for AD per se.

However, when it comes to the hematoma's volume, our results suggests that CAA related neuroimaging markers, rather than ICH volume and location were predictors on long-term dementia incidence, in line with two recent studies. These studies together support the important role of CAA-related SVD in ICH survivors[134,304].

The identification of sensitive biological and neuroimaging marker for CAA has become an essential component of CAA research. Concurrently, this research had shown that there was a strong correlation between structural imaging markers of CAA (cerebral microbleeds, centrum semiovale perivascular spaces (CSO-PVS) and white matter hyperintensities (WMHs)) and the possibility to later progression to cognitive impairment and dementia, predicting potential changes in cognitive processes such as verbal fluency, memory, visuoperception and visuospatial functions. Longitudinal studies are essential in this aim.

Identifying the biological changes that induce CAA is key to predicting the disease's onset, strategizing appropriate interventions, monitoring disease progression, assessing drug efficacy and or other treatments, and ultimately, developing a cure. MRI has become a powerful noninvasive tool for assessing brain structure and function *in vivo* due to improvements in acquisition and analysis tools. As a result of works such as the one we have conducted, it is possible to identify through MRI patients who have the brain changes above mentioned, and then follow them up more extensively in light of the risk of cognitive impairment and, eventually, dementia.

5.4. Strong Points and Limitations

The main strength of this study is our detailed neuropsychological battery which includes almost the totally of cortical and subcortical processes and subprocess, screening of affective symptoms and functional features, that has not been used before on such a very well-defined cohort. Additionally, comprehensive data were collected by almost the same data collection group of trained health-care professionals as objectively as possible following standard procedures. The pathological data were obtained by personnel blinded to clinical data, and experts adjudicating presence of cognitive impairment and dementia were not aware of the pathological findings. Hence, our detailed neuroimaging description of the structural markers of cerebral SVD in the context of ICH-CAA, in a richly phenotype prospective cohort of patients.

Traditionally, neuropsychological assessment has been used primarily to assess outcome in dementia research and clinical practice. This needs to change. According to Edmonds et al.[367], neuropsychological assessment can and should be used as an independent variable to classify patients for treatment. The neuropsychological research addressed in this doctoral thesis herein clearly how one can leverage theoretical constructs to define clinical syndromes. Further studies are needed to better understand how the neuropathology of AD/VaD spectrum disorders is associated with specific panels of neuropsychological symptoms. By adopting this kind of paradigm, one explicitly jettisons the notion of syndromic or pathological “purity”. This type of synthesis maximizes and uses all available data to manage and treat what has become one of the world’s leading public health concerns.

However, the present doctoral thesis is not exempt from several limitations that require our findings to be examined in future complementary studies. Firstly, the patients in this cohort were all non-demented patients recruited from a Stroke Unit because of previous ICH, therefore these patients may not be representative of all CAA patients, and the results from this study may not be generalizable to all CAA populations. Secondly, the totality of the sample was only clinically diagnosed as probable or possible CAA without histopathological confirmation. However, previous clinicopathological studies have reported high specificity of Boston Criteria for CAA diagnosis. Thirdly, the CAA patients in our cohort have a low education which again, this may not be representative of the entire CAA population. However, our choice of transform all raw punctuations to standardized scores attempts to reduce this bias by allowing us to detect more subtle dysfunction in the cognitive profile of these patients.

Meanwhile, broader neuropsychiatric symptom screening questionnaires should be included so we can detect potential symptoms early, since, for example, a recent study found that apathy, but not depression, predicted dementia development in patients with cerebral SVD[368].
Finally, we acknowledge that our study size is small, and so our results should be interpreted cautiously, particularly the adjusted analyses.

5.5. Implications for Clinical Practice: Improving Healthcare Team Outcomes

Multidisciplinary teams including neurologists, radiologists, neurosurgeons, stroke-trained nurses, pathologists, physical therapists, and neuropsychologists could be more effective in managing patients with CAA. Stroke symptoms are the most common reason for patients to present to the emergency department. ICH-CAA is treated similarly to other spontaneous ICH, possibly requiring neurosurgery intervention. An accurate measurement of blood pressure and intracranial pressure by the staff is essential. In order to regain mobility and function, rehabilitation is necessary in cases where there is a residual physical impairment. In order to evaluate recurrence and cognitive and functional status, long-term follow-up is essential. In depth analysis of this issue, clinicians should be aware that there is a risk of cognitive impairment in patients with CAA. Patients without dementia frequently have MCI. Concerns about cognitive function should be raised with patients with CAA, including patients who have survived lobar ICH and patients with TFNEs. Considering the results of this study, it seems appropriate to monitor every 6-12 months those patients who have a greater burden of SVD and hippocampal atrophy in order to detect possible cognitive changes early enough so that neuropsychological, pharmacological, and social interventions can be applied effectively.

5.6. Open Questions and Directions to be Taken

Neuroimaging has substantially advanced our understanding of the neural mechanism engaged in the recovery of function after a stroke and brain induced improvements. Despite all these advances, we are still far away from a personalized approach that considers the individual network pathology in order to precisely identify its cognitive deficits and its preserve domains, the functional and emotional impact they have and how all of these factors interact with patient's familiar structure.

Research on CAA and neurodegeneration should focus on identifying predictors of cognitive decline, discovering pathomechanisms of atrophy and cognitive decline, developing new diagnostic and monitoring methods, examining whether cognitive enhancing drugs for AD also improve cognition in CAA, and identifying new treatment strategies through multicenter studies with larger populations.

Further larger studies investigating patients in specific cognitive subgroups are needed (no cognitive complaints, subjective cognitive complaints, and MCI). Additionally, comparison between patients with CAA and other small vessel diseases on neuropsychological performance may help further define the clinical profile of CAA.

Cognitive impairment before ICH is common and is associated with imaging findings consistent with an important contribution from CAA. This suggests that a future strategy aiming to reduce the impact of poststroke dementia in ICH will need to extend beyond stroke prevention and include strategies that address the small vessel impact of CAA. Further work on the natural history of when and how CAA may influence, and individual's cognitive profile is a priority for future research.

Emerging assessment techniques such as measuring carotid intima-media thickness and arterial pulse wave velocity (PWV) in select population might become tools that can help identify those at risk for developing VCI. The analysis of blood biomarkers also holds promise in furthering our understanding of prodromal dementia states.

Hence, future research is needed to further explore the role of APoE genotypes and other genetic biomarkers across different subtypes of MCI. These studies may provide insight into the genetic basis of some of the clinical heterogeneity associated with MCI and furthermore help identify risk factors for different clinical outcomes.

The way dementia presents in various parts of the world is likely quite diverse. For all these reasons, greater sophistication is needed to operationally define MCI/VCI/VaD. Combining statistical modeling procedures using the previously discussed assessment techniques, along with the longitudinal assessment of participants drawn from both the community and memory clinics, may ultimately lead to appropriate diagnostic criteria. The development of these criteria has the potential of preventing and alleviating suffering throughout the world.

Finally, it has become increasingly recognized that cortical thickness, the distance between the external layer of cortex and the junction between gray and white matter in the cortical ribbon, is a valuable tool for capturing neuronal integrity that complements or is more relevant than volumetric measures. Evaluation of cortical thickness may provide more specific data about changes related to disease and how they influence clinical outcomes.

CONCLUSIONS

The overarching aim of this thesis was to advance the current scientific evidence of comprehensive neuropsychological profile in ICH-CAA and highlight the effects of CAA markers on cognition, brain structure, and risk of cognitive decline and dementia. This study suggests a complex synergistic relationship between ischemic and hemorrhagic brain markers, brain atrophy and cognition. Therefore, because of this thesis, we have been able to demonstrate that:

1. In terms of cognition, patients without previous dementia, and with minor volume hemorrhage, perform adequately on a wide range of cognitive test, though there is a tendency to exhibit greater difficulty in tasks that evaluate processing speed, memory, and planning at 15-months follow-up.

2. Patients are functionally capable in both basic daily activities and instrumental activities at 15-months follow-up.

3. Affective disturbances are not observed on patients without post-ICH dementia at 15-months-follow-up.

4. Medial hippocampal atrophy is the brain structural marker that may influence and contribute to the final clinical picture of this neurodegenerative processing affecting almost at most of the cognitive domains assessed (attention, planning, verbal fluency, language, visuospatial and visuoconstruction functions), not only episodic memory as previously thought.

5. Global cortical atrophy and hemorrhagic and ischemic brain markers has a significant correlation with memory and visuoperception.

6. In our cohort, CAA related neuroimaging markers, rather than ICH volume and location, could be predictors of long-term dementia incidence.

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APPENDICES

8.1. In-depth Clinical and Neuroimaging Features of ICH-CAA

Table 3. Comparison Between Groups of Demographic and Clinical Profiles at Inclusion *(continuation)*

	Overall ***n*= 58**	**Included** ***n* = 25**	**Excluded** ***n* = 33**	***p* value**
Previous treatment, n (%)				
Antiplatelet	13 (22.8)	5 (8.8)	8 (14.0)	0.666
Anticoagulant	7 (12.3)	0 (0)	7 (12.3)	**0.001**
IECA-ARA II	27 (48.2)	14 (25)	13 (23.2)	0.304
Calcium Antagonist	11 (19.6)	8 (14.3)	3 (5.4)	**0.039**
Beta-Blockers	9 (16.1)	4 (7.1)	5 (8.9)	1.000
Statin	24 (42.9)	9 (16.1)	15 (26.8)	0.361
High-dose statin	7 (12.7)	3 (5.5)	4 (7.3)	0.895
Functional status, median (min-max)				
Pre-existing level of dependency (mRs <3)	0 (0-1)	0 (0-1)	0 (0-1)	0.187
Clinical presentation, n (%)				
Lobar Hemorrhage	49 (84.5)	21 (36.2)	28 (48.3)	0.940
SAH	9 (15.5)	4 (6.9)	5 (8.6)	0.940
Modified Boston Criteria, n (%)				
Probable	30 (51.7)	15 (25.9)	15 (25.9)	0.280
Possible	28 (48.3)	10 (17.2)	18 (31.0)	0.280

Abbreviations: GCS: Glasgow Coma Scale; NIHSS: National Institute of Health stroke scale; SAH: Subarachnoid Hemorrhage

Table 10. Grade of Dependency after ICH-CAA measured by of mRs of the Study Cohort

	Overall ***n*= 58**	**Included** ***n* = 25**	**Excluded** ***n* = 33**	***p* value**
Post ICH level of dependency, n (%)				
0: No symptoms	12 (21.8)	10 (18.2)	2 (3.6)	**<0.001**
1: No significant disability, despite symptom; able to perform all usual duties and activities	12 (21.8)	9 (16.4)	3 (5.5)	**<0.001**
2: Slight disability: unable to perform all previous activities but able to look after own affairs without assistance	7 (12.7)	4 (7.3)	3 (5.5)	**<0.001**
3: Moderate disability: requires some help, but able to walk without assistance	3 (5.5)	2 (3.6)	1 (1.8)	**<0.001**
4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	4 (7.3)	0 (0)	4 (7.3)	**<0.001**
5: Severe disability; bedridden, incontinent and requires nursing care and attention	2 (3.6)	0 (0)	2 (3.6)	**<0.001**
6: Dead	15 (27.3)	0 (0)	15 (27.3)	**<0.001**

Table 11. CT- based CAA Biomarkers in the Study Cohort

	Overall ***n*= 58**	**Included** ***n*= 25**	**Excluded** ***n*= 33**	***p* value**
Hematoma Location, n (%)				
Frontal lobe	25 (34.9)	8 (14.0)	17 (29.8)	0.116
Temporal lobe	12 (21.1)	6 (10.5)	6 (10.5)	0.641
Parietal lobe	23 (40.4)	11 (19.3)	12 (21.1)	0.629
Occipital lobe	10 (17.5)	4 (7.0)	6 (10.5)	0.798
Others	1 (1.8)	1 (1.8)	0 (0)	0.273
Hematoma Lateralization, n (%)				
Left	29 (54.7)	13 (24.5)	16 (30.2)	0.821
Right	20 (37.7)	8 (15.1)	12 (22.6)	0.778
Bilateral	4 (7.5)	2 (3.8)	2 (3.8)	0.787
Hemorrhage volume (cm3), median (min-max)	19.1 (1.32-139)	12.8 (1.40-54.7)	35.2 (1.32-139)	**0.003**
CT characteristics of ICH-CAA, n (%)				
SAE	19 (39.6)	5 (10.4)	14 (29.2)	0.053
IVE	11 (22.9)	1 (2.1)	10 (20.8)	**0.009**
Multiple simultaneous	7 (14.6)	2 (4.2)	5 (10.4)	0.395
Irregular ICH border	31 (64.6)	11 (22.9)	20 (41.7)	0.126
FLPs	16 (33.3)	3 (6.3)	13 (27.1)	**0.015**

Abbreviations: SAE: Subarachnoid Extension; IVE: Intraventricular Extension; FLPs: Finger Like Projections

Table 12. Hemorrhagic MRI Markers in the Study Cohort

	Overall ***n*= 58**	**Included** ***n*= 25**	**Excluded** ***n*= 33**	***p* value**
cMBs, n (%)	23 (47.9)	11 (22.9)	12 (25.0)	0.583
Nº of lobar CMBs, media (SD)	12.1 (24.8)	09.36 (18.6)	15.4 (30.9)	0.416
Microbleeds Location, n (%)				
Cortical	21 (45.7)	10 (21.7)	11 (23.9)	0.413
Cortico-subcortical	13 (28.3)	6 (13.0)	7 (15.2)	0.497
Basal Ganglia	6 (13.0)	5 (10.9)	1 (2.2)	0.135
Brainstem	3 (6.5)	3 (6.5)	0 (0.0)	0.110
Cerebellum	11 (23.9)	5 (10.9)	6 (13.0)	0.511
cSS, n (%)	22 (46.8)	8 (17.0)	14 (29.8)	**0.033**
Focal (≤3 sulci)	9 (20)	3 (6.7)	6 (13.3)	0.140
Disseminated (≥ 4 sulci)	13 (29.5)	5 (11.4)	8 (18.2)	0.119
cSS Location, n (%)				
Frontal lobe	13 (28.3)	4 (8.7)	9 (19.6)	**0.048**
Temporal lobe	6 (13.0)	3 (6.5)	3 (6.5)	0.835
Parietal lobe	12 (26.1)	5 (10.9)	7 (15.2)	0.317
Occipital lobe	7 (15.2)	3 (6.5)	4 (8.7)	0.524
Cerebellar lobe	2 (4.3)	2 (4.3)	0 (0.0)	0.190

Abbreviations: cMBS: Cortical Microbleeds; cSS: Cortical Superficial siderosis

Table 13. Ischemic MRI Markers in the Study Cohort

	Overall ***n*= 58**	**Included** ***n*= 25**	**Excluded** ***n*= 33**	***p* value**
WMH (Fazekas), n (%)				
0	1 (2.1)	1 (2.1)	0 (0.0)	0.343
1	20 (41.7)	11 (22.9)	9 (18.8)	0.739
2	19 (39.6)	10 (20.8)	9 (18.8)	0.952
3	8 (16.7)	3 (6.3)	5 (10.4)	0.376
Posterior Leukoaraiosis Prevalence, n (%)	25 (52.1)	12 (25.0)	13 (27.1)	0.565
EPVS Midbrain, n (%)	23 (47.9)	14 (29.2)	9 (18.8)	0.252
EPVS BG, n (%)				
1-10 (mild)	26 (54.2)	13 (27.1)	13 (27.1)	0.760
11-20 (moderate)	17 (35.4)	9 (18.8)	8 (16.7)	0.932
21-40 (frequent)	5 (10.4)	3 (6.3)	2 (4.2)	0.715
EPVS CSO, n (%)				
1-10 (mild)	13 (27.1)	7 (14.6)	6 (12.5)	0.893
11-20 (moderate)	18 (37.5)	9 (18.8)	9 (18.8)	0.834
21-40 (frequent)	12 (25.0)	6 (12.5)	6 (12.5)	0.880
>40 (severe)	5 (10.4)	3 (6.3)	2 (4.2)	0.726
CAA score, n (%)				
0	4 (8.7)	1 (2.2)	3 (6.5)	0.231
1	11 (23.9)	10 (21.7)	1 (2.2)	**0.006**
2	4 (8.7)	1 (2.2)	3 (6.5)	0.231
3	13 (28.3)	4 (8.7)	9 (19.6)	**0.048**
4	6 (13.0)	5 (10.9)	1 (2.2)	0.135
5	8 (17.4)	4 (8.7)	4 (8.7)	0.801

Abbreviations: WMH: White Matter Hyperintensities; EPVS: Enlarged Perivascular Spaces; BG: Basal Ganglia; CSO: Centrum Semiovale

Table 14. Bivariate Analysis to Demonstrate the Differences Between the Groups According to SMD Quantification by the Fazekas in Each Location, Scheltens (hippocampal atrophy), and Pasquier Scale (global cortical atrophy)

	Overall ***n*= 58**	**Included** ***n*= 25**	**Excluded** ***n*= 33**	***p* value**
Frontal, n (%)				
0	2 (4.2)	1 (2.1)	1 (2.1)	0.953
1	19 (39.6)	11 (22.9)	8 (16.7)	0.524
2	24 (50.0)	11 (22.9)	12 (25.0)	0.581
3	3 (6.3)	1 (2.1)	2 (4.2)	0.512
Temporal, n (%)				
0	9 (18.8)	4 (8.3)	5 (10.4)	0.625
1	21 (43.8)	14 (29.2)	7 (14.6)	0.080
2	12 (29.2)	5 (10.4)	9 (18.8)	0.153
3	4 (8.3)	2 (4.2)	2 (4.2)	0.948
Parietal, n (%)				
0	3 (6.3)	1 (2.1)	2 (4.2)	0.522
1	23 (47.9)	12 (25.0)	10 (20.8)	0.765
2	21 (43.8)	12 (25.5)	9 (19.1)	0.638
3	1 (2.1)	0 (0.0)	1 (2.1)	0.306
Occipital, n (%)				
0	22 (45.8)	11 (22.9)	11 (22.9)	0.802
1	24 (50.0)	13 (27.1)	11 (22.9)	0.784
2	2 (4.2)	1 (2.1)	1 (2.1)	0.976
MTA, n (%)				
0	8 (17.0)	3 (6.4)	5 (10.6)	0.414
1	22 (46.8)	14 (29.8)	8 (17.0)	0.112
2	14 (29.8)	5 (10.6)	9 (19.1)	0.179
3	2 (4.3)	2 (4.3)	0 (0)	0.171
4	1 (2.1)	0 (0)	1 (2.1)	0.328
GCA, n (%)				
0-1	26 (48.1)	17 (31.5)	9 (16.7)	**0.006**
2-3	28 (51.9)	8 (14.8)	20 (37.1)	**0.006**

Abbreviations: MTA: Medial Temporal Atrophy; GCA: Global Cortical Atrophy

8.2. Extended Spanish Summary/ Resumen extendido en castellano

8.2.1. Introducción

Dado que el envejecimiento de la población es cada vez mayor, se está produciendo un fuerte aumento de la incidencia de múltiples enfermedades, como las cardiovasculares, el cáncer y los trastornos neurodegenerativos, incluidas las demencias como la enfermedad de Alzheimer (EA).

Hay que tener en cuenta que la demencia no es una enfermedad, sino un conjunto de síntomas provocados por muchas circunstancias clínicas y/o causas subyacentes. En general, implica dificultades en el razonamiento, la memoria y la atención, que afectan a la capacidad de los pacientes para ser independientes.

La demencia es un trastorno adquirido que se caracteriza por una alteración de la cognición que implica uno o más procesos cognitivos (atención, funciones ejecutivas, velocidad de procesamiento, lenguaje, memoria, etc.). Por otra parte, el deterioro cognitivo leve (DCL) es un estado intermedio entre la cognición normal y la demencia en la cual existen alteraciones cognitivas objetivas, pero no existe una disminución del nivel general de funcionamiento. Si bien pueden producirse cambios específicos en la cognición en el envejecimiento normal, el DCL también puede ser un precursor de la demencia. La demencia puede tener más de una casusa, especialmente a medida que la enfermedad avanza sobre todo en personas mayores.

Una de las causas más comunes de deterioro cognitivo es la angiopatía amiloide cerebral (AAC), la cual es una enfermedad de pequeño vaso caracterizada por el acúmulo de la proteína beta-amiloide dentro de los vasos sanguíneos de tamaño pequeño del cerebro y en las leptomeninges. En la población mayor, la hemorragia intracerebral (HIC) espontánea es el signo más dramático y potencialmente mortal de la AAC y se ha evidenciado que la AAC es un factor de riesgo para el desarrollo de demencia. Aunque se ha observado clínicamente deterioro cognitivo en pacientes con AAC, poco se sabe sobre la frecuencia, la gravedad y el perfil cognitivo de los pacientes diagnosticados con esta condición después de debutar con una HIC lobar. Este conocimiento puede servir de base para la prevención y la intervención, así como para el pronóstico sobre el curso de la enfermedad. En la Tabla 1 se presentan los criterios radiológicos para el diagnóstico de la AAC, conocidos como los criterios modificados de Boston.

Tabla 1. Criterios de Boston Modificados para la Hemorragia Intracerebral asociada a Angiopatía Amiloide.

	Criterios de Boston Modificados
AAC Definitiva	Examen postmortem completo demostrando: - Hemorragia lobar[a], cortical o córtico-subcortical - AAC grave con vasculopatía - Ausencia de otra lesión diagnóstica
AAC probable con estudio patológico	Con patología clínica y biopsia que muestre: - Hemorragia cerebral lobar[a], cortical o córtico-subcortical - Algún grado de AAC en la biopsia - Ausencia de otra lesión diagnóstica
AAC probable	Cínica y RM o TC que muestre: - Edad ≥ 55 años - Hemorragias cerebrales lobares[a], corticales o córtico-subcorticales, múltiples (se permite hemorragia cerebelosa), o única más HSSc o HSAc - Ausencia de otras causas de hemorragia[b]
AAC posible	Cínica y RM o TC que muestre: - Edad ≥ 55 años - Hemorragia cerebral lobar[a], cortical o córtico-subcortical, única, o HSSc o HSAc - Ausencia de otras causas de hemorragia[b]

AAC: angiopatía amiloide cerebral; RM: resonancia magnética cerebral; TC: Tomografía Computarizada cerebral; HSSc: hemosiderosis superficial de la convexidad cerebral; HSAc: hemorragia subaracnoidea de la convexidad cerebral; [a]hemorragia cerebral lobar incluye macro y microhemorragia; [b]diagnóstico diferencial de hemorragia cerebral lobar: antecedente de traumatismo cráneo-encefálico, infarto con transformación hemorrágica; malformación vascular; tumor con hemorragia; terapia con warfarina e INR mayor de 3; vasculitis; trombosis venosa.

La AAC se observa con frecuencia en las Unidades de Trastornos Cognitivos en pacientes con deterioro cognitivo o demencia con patología subyacente de enfermedad de Alzheimer (EA). El deterioro cognitivo en el contexto de la AAC fue descrito por primera vez hace tres décadas. No existe un correlato neuropsicológico para la AAC leve, lo que sugiere que la AAC leve representa la eliminación fisiológica de beta-amiloide más que una condición patológica. El deterioro cognitivo se asocia a la AAC avanzada, que puede reflejar EA comórbida, demencia vascular (DV) o ambas. A pesar de la elevada tasa de comorbilidad, la contribución de la AAC al deterioro cognitivo es, en parte, independiente de la patología parenquimatosa de la EA. La AAC moderada a grave (presente en un tercio de la población) está altamente correlacionada con alteraciones en atención y funciones ejecutivas, velocidad de procesamiento de la información, memoria semántica y episódica y el deterioro cognitive global, considerándose la AAC como un factor de riesgo para el desarrollo de demencia en estudios previos. Además, la AAC también se diagnostica en Unidades de Ictus tras una hemorragia intracerebral lobar (HIC). Sin embargo, poco se sabe sobre la frecuencia, gravedad y características neuropsicológicas de los pacientes diagnosticados clínicamente de AAC tras una HIC lobar. La cuestión del origen de los trastornos cognitivos después de una HIC es un tema complejo relacionado con la presencia de la hemorragia en sí, pero también con los mecanismos fisiopatológicos silentes que están presentes mucho antes de que se manifieste el ictus. Además, la mayoría de los estudios de HIC se centran en las diferencias entre hemorragias lobares y no lobares, pero este enfoque dicotómico ensombrece el impacto de las causas individuales de la enfermedad.

Nuestra propuesta es implementar un nuevo enfoque en el manejo de los pacientes con HIC-AAC. En esta población, detectar cambios cognitivos, conductuales y emocionales en una etapa temprana es crucial para reducir el riesgo de progresión a demencia. Considerando todas las razones expuestas anteriormente, sería prudente sugerir estrategias de seguimiento, diagnóstico y tratamiento más estrictas en esta población.

Por lo tanto, este estudio tiene grandes implicaciones para la asistencia clínica, ya que permitirá un diagnóstico preciso, una atención personalizada y un pronóstico de la enfermedad, lo que permitirá una evaluación individual del riesgo, una toma de decisiones temprana y un tratamiento adecuado, evitando, entre otros, la prescripción de medicación potencialmente perjudicial, como puede ser la toma de anticoagulantes.

8.2.2. Hipótesis y Objetivos

8.2.2.1. Hipótesis

(1) Una proporción de pacientes con HIC-AAC puede presentar alteraciones cognitivas (definidas como un deterioro de < 1 DT en relación con el grupo de referencia en 2 procesos cognitivos, según los criterios integrales de Jack y otros) después de una HIC, similar al deterioro cognitivo vascular de la enfermedad de pequeño vaso; (2) Aquellos pacientes con una mayor carga de enfermedad de pequeño vaso tienen más probabilidades de experimentar un peor rendimiento cognitivo.

8.2.2.2. Objetivo general

Este estudio tiene como objetivo recopilar información de pacientes con HIC lobares o corticales asociadas a AAC probable o posible sobre sus características clínicas, radiológicas y neuropsicológicas.

En esta tesis se abordan específicamente los siguientes objetivos:

- Analizar el perfil cognitivo de los pacientes que sobrevivieron a la HIC asociada a la AAC.
- Evaluar la presencia de síntomas afectivos en esta población.
- Evaluación de la capacidad funcional ≥ 180 días después del evento índice.
- Describir marcadores de patología vascular y neurodegeneración mediante resonancia magnética de 1.5T y 3T.
- Determinar el grado en que la AAC y los marcadores de imagen sugestivos de neurodegeneración median la asociación de la AAC con la función cognitiva.

8.2.3. Material y Métodos

8.2.3.1. Diseño

Estudio descriptivo, ambispectivo, transversal, analítico-observacional, multidisciplinar, de un solo centro, que evalúa la función cognitiva, emocional y funcional, así como su relación con los biomarcadores en imagen en pacientes ≥ 55 años (sin límite superior), que experimentaron una primera con HIC lobar y/o cortical sintomática asociada a AAC probable o posible según los criterios modificados de Boston.

8.2.3.2. Sujetos de estudio

Los pacientes se reclutaron consecutivamente en la Unidad de Neurovascular del Hospital Universitari i Politècnic La Fe entre marzo de 2016 y diciembre de 2021. El estudio se llevó a cabo en un entorno ambulatorio.

Para el análisis estadístico se incluyeron a los pacientes que cumplían los siguientes criterios de inclusión: (1) edad mínima de 55 años, (2), diagnóstico de HIC lobar o cortical, diagnosticada mediante TC sin contraste en los 7 días siguientes al presunto inicio de los síntomas, acompañada del patrón de (3) microsangrados cerebrales lobares y siderosis superficial, y (4) HIC asociada a AAC probable o posible, (5) ausencia de demencia basada en una evaluación clínica del estado funcional diario para reducir los efectos de confusión de la EA concomitante realizada en el momento de la inclusión con la versión abreviada del TIN (Test del Informador) y BDRS (Blessed Dementia Rating Scale). Por último, (6) los participantes deben saber leer y escribir y tener una agudeza visual y auditiva adecuada, sin afasia ni déficit campimétrico.

Se excluyeron a los pacientes que cumplían los siguientes criterios; (1) no hablar español con fluidez, (2) tener <55 años, (3) antecedentes de fibrilación auricular con tratamiento anticoagulante, (4) presencia de deterioro cognitivo previo al evento índice, (5) antecedentes de otros trastornos estructurales o psicosis, (6) abuso de sustancias, o (7) presencia de contraindicaciones para la RM.

8.2.3.3. Procedimientos

Evaluación clínica

Los detalles intrahospitalarios, incluidas las características clínicas, de neuroimagen y el diagnóstico se obtuvieron a través de la revisión de la historia clínica y se incluyeron en nuestro cuaderno de recogida de datos electrónico (CRDe). Cada paciente fue sometido a una evaluación clínica estructurada, que incluía una historia clínica y un examen neurológico. Para la historia clínica, se registraron la hipertensión, la diabetes mellitus, la hiperlipidemia, el ictus previo, el tabaquismo actual, el consumo de alcohol, los antiagregantes plaquetarios y anticoagulantes y el tratamiento antihipertensivo. El estado clínico incluía la escala de coma de Glasgow (Glasgow Coma Scale, GCS), en la que una puntuación más baja indicaba un peor estado de conciencia, y la escala de ictus del Instituto Nacional de Salud (National Instituted of Health Stroke Scale, NIHSS), de 0 a 42, en la que las puntuaciones más altas indicaban déficits neurológicos más graves. También se recogieron variables demográficas como la edad, el sexo y los años de educación de todos los pacientes.

Análisis de marcadores en imagen -TC y RM-

Todos los pacientes con HIC se sometieron a una TC cerebral al ingreso en Urgencias y una RM en algún momento de la hospitalización.

Los marcadores de imagen asociados a AAC se calificaron de acuerdo con los criterios de consenso de STandards for ReportIng Vascular changes on nEuroimaging (STRIVE). Los microsangrados corticales se evaluaron utilizando secuencias sensibles a la sangre (imágenes ponderadas en T2* o de susceptibilidad) y la escala validada de calificación anatómica de microsangrados (MARS).
Los espacios perivasculares (EPVs) en el centro semioval (CSO) (EPVs-CSO) y los ganglios basales (EPVs-GGBB) se definieron y calificaron en secuencias T2 y FLAIR utilizando una escala de calificación visual validada de 4 puntos en un único corte predefinido (primer corte por encima de la comisura anterior para los ganglios basales, y el primer corte por encima del nivel de los ventrículos laterales para el centro semioval. Se valoró preferentemente el hemisferio contralateral al hematoma. Las hiperintensidades en sustancia blanca (HSB), también denominadas leucoaraiosis, se calificaron en secuencias T2 y FLAIR utilizando la escala de Fazekas. La siderosis superficial cortical (SSC) se identificó en secuencias sensibles a la sangre y se clasificó como focal (involucrando ≤3 surcos), o diseminada (involucrando ≥4 surcos), de acuerdo con la terminología descrita anteriormente.

La atrofia temporal medial (ATM) se calificó en imágenes coronales T1 o FLAIR utilizando la escala visual de Scheltens. La atrofia cortical global (ACG) se calificó mediante la escala Pasquier en imágenes axiales en T1 o FLAIR. Tanto para ATM como para ACG, se tomó como referencia el hemisferio contralateral a la HIC.

Evaluación neuropsicológica

Evaluación cognitiva

La evaluación cognitiva se basó en una batería estandarizada compuesta por pruebas seleccionadas para evaluar una amplia gama de procesos cognitivos que suelen verse afectados tras una HIC. Se utilizaron dieciséis pruebas neuropsicológicas para formar medidas compuestas de 11 procesos cognitivos independientes y una medida del estado cognitivo global: atención (media de Dígitos Directos, Spatial Span directos y TAVEC A1), función ejecutiva (memoria de trabajo: media Dígitos inversos, Spatial Span inversos y TMT-B; planificación: media de nº de ensayos correctos en Torre de Londres y nº de movimientos totales en Torre de Londres; inhibición: interferencia Stroop; acceso a almacenes de memoria semántica: COWAT-PMR,); velocidad de procesamiento (media del SDMT, FCR tiempo de copia, tiempo de ejecución en Torre de Londres, tiempo de resolución en Torre de Londres y TMT-A), lenguaje (COWAT-animales y Boston Naming Test-versión abreviada), memoria (media del TAVEC RL-CP, TAVEC RCL-CP, TAVEC RL-LP, TAVEC RCL-LP, TAVEC reconocimiento, FCR inmediata, FCR diferida, FCR reconocimiento), visuopercepción (Hooper Visual Organization Test -HVOT-, Visual Object and Space Perception Battery -VOSP- decisión de objetos y VOSP siluetas progresivas), visuoespacial (Judgement of Line Orientation -JLO-, VOSP discriminación de posición y VOSP localización de números) y visuoconstrucción (FCR copia). La cognición global se midió con el Mini Examen Cognoscitivo de Lobo.

Evaluación emocional

El cribado de los síntomas afectivos se realizó con cuestionarios estructurados como el Inventario de Ansiedad Estado-Rasgo (STAI) para identificar a los pacientes con ansiedad, y con el Inventario de Depresión Estado-Rasgo (IDER), cuyo objetivo principal es identificar el grado de afectación (Estado) y la frecuencia de aparición (Rasgo) del componente afectivo de la depresión.

Evaluación funcional

Para evaluar la capacidad funcional de los pacientes, se administraron la escala de Rankin modificada (mRs) y tanto el Índice de Barthel (iB) como el Índice de Lawton & Brody (iLB).

8.2.3.4. Análisis estadístico

El análisis estadístico se realizó utilizando el software libre Jamovi versión 2.4.11. En todos los análisis se consideraron significativos lo valores de $p < 0.05$. Todos los intervalos de confianza se calcularon al 95%.

Se evaluó la normalidad de la distribución de todas las medidas cuantitativas mediante la prueba W de Shapiro-Wilk. Las variables continuas de distribución normal se presentan mediante la media y la desviación típica (DT), mientras que las variables continuas de distribución no normal se presentaron mediante la mediana y el rango intercuartílico (RIQ). Las variables categóricas se presentan en porcentajes. Las variables basales sobre datos demográficos y clínicos se compararon mediante la prueba de la *t* de Student o la prueba de Wilcoxon-W para las variables continuas, y se utilizó la prueba de chi-cuadrado para las variables categóricas.

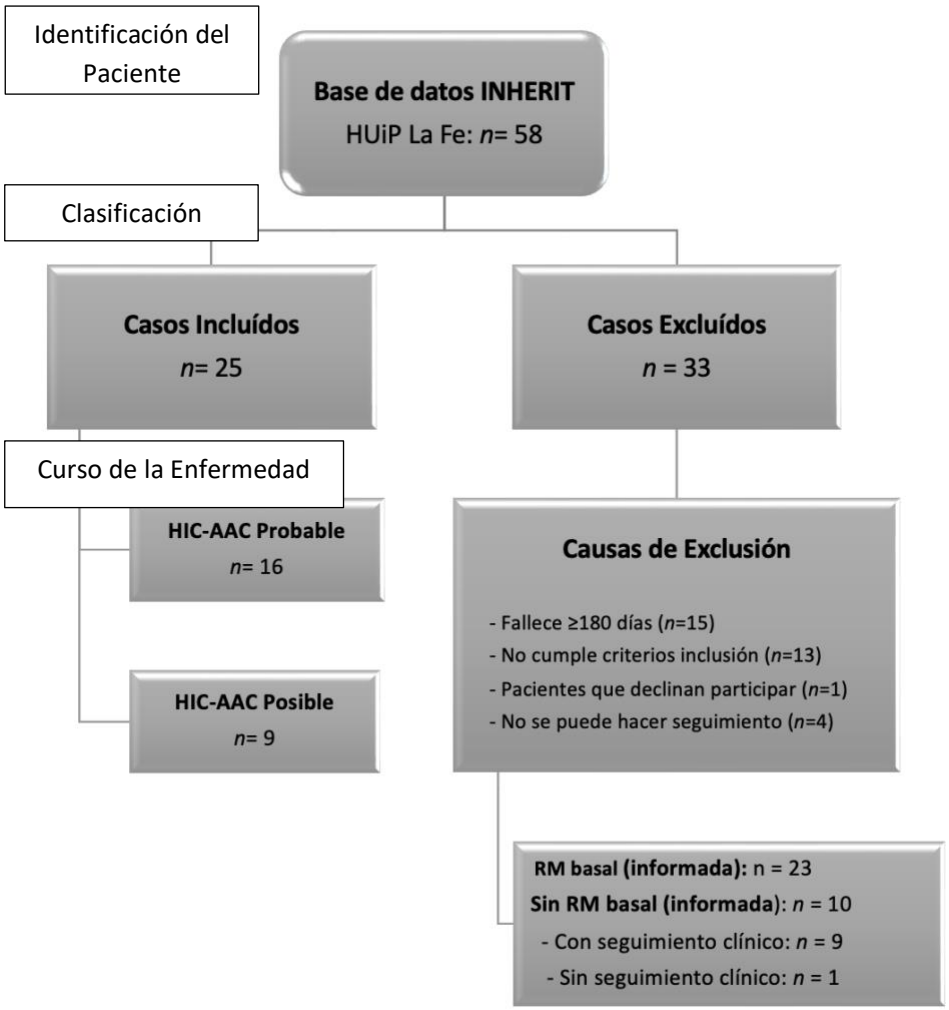
Para determinar si los pacientes eran representativos de toda la cohorte de supervivientes de HIC, se compararon sus principales características basales mediante la prueba $\chi 2$ para las variables categóricas y la prueba U de Mann-Whitney para las variables continuas. Realizamos los mismos análisis para los pacientes que no cumplían los criterios para someterse a una evaluación neuropsicológica.

8.2.4. Resultados

8.2.4.1. Características Sociodemográficas y Epidemiológicas

Tras la aplicación de criterios de inclusión y exclusión preespecificados, se seleccionaron un total de 58 pacientes con HIC-AAC de la base de datos INHERIT entre mayo de 2016 y diciembre de 2021. Entre los 33 pacientes excluidos, 15 fallecieron, 13 no cumplían todos los criterios de inclusión, 1 declinó participar y 4 no pudieron ser objeto de seguimiento. La información sobre los pacientes incluidos se muestra en la Figura 1.

Figura 1. Diagrama de Inclusión y Criterios de Inclusión y Exclusión del Estudio



Características basales

En la tabla 1 se muestra un resumen de las características demográficas y clínicas de los pacientes. De los 58 pacientes incluidos, la media de edad fue de 74,3 años (DT 8,04), siendo significativamente mayores los del grupo excluido (*p*=0. 006) y 30 (51,7%) eran hombres.

En general, ambos grupos presentaban factores de riesgo cardiovascular similares, siendo la hipertensión (63,8%) y la hiperlipidemia (59,3%) los más frecuentes, seguidos de la diabetes (25,9%) y el ictus previo (17,2%). Tanto la mediana (mínimo-máximo) de las puntuaciones de la National Institutes of Health Stroke Scale (NIHSS) como la de la Escala de Coma de Glasgow (GCS)al ingreso fueron diferentes (3 [0-15] y 15 [11-15] respectivamente para los pacientes incluidos en el estudio; *p*=0.006).

Un análisis de las características de la HIC-AAC en TC mostró que la localización más prevalente del hematoma fue parietal (40,4%) y frontal (34,9%), siendo más frecuentemente localizado en el hemisferio izquierdo (*n*= 29 vs. *n*=20, respectivamente). El volumen de HIC fue mayor en el grupo excluido que en el incluido (35,2 cm3 *vs*. 12,8 cm3 respectivamente; *p*= 0.003). Además, la extensión intraventricular (2,1% *vs.* 20,8%, p=0,009) y las proyecciones digitiformes (27,1% *vs*. 6,3%, *p*=0.015) fueron más frecuentes en el grupo excluido.

El análisis por RM de las características hemorrágicas mostró que un total de 47,9% de los pacientes presentaban microsangrados corticales, con una media de 12 microsangrados. Encontramos diferencias entre ambos grupos en cuanto a la presencia de siderosis superficial cortical, siendo más prevalentes en el grupo de pacientes excluidos (29,8% vs. 17%, *p*=0.003) y localizados en el lóbulo frontal (19,6% vs. 8,7%; *p*=0.048).

En cuanto a los marcadores isquémicos de la RM, la escala de Pasquier indicó que el 51,9% de nuestros pacientes presentaban atrofia cortical global de moderada a grave, siendo más prevalente en el grupo de pacientes excluidos (14,8% vs. 37,1%; *p*= 0.006).

Por último, en el seguimiento a largo plazo de 15.6 meses (6-39), 12 (21,8%) pacientes no presentaron síntomas de dependencia, 12 (21,8%) ninguna discapacidad significativa y 15 (27,3%) fallecieron.

Tabla 1. Comparación entre Grupos de Perfiles Demográficos y Clínicos en el Momento de la Inclusión

	Total ***n*= 58**	**Incluídos** ***n* = 25**	**Excluídos** ***n* = 33**	***p* valor**
Datos demográficos				
Edad de inicio, media (DT), años	74.3 (8.04)	71.0 (6.48)	76.8 (8.31)	**0.006**
Sexo masculino, n (%)	30 (51.7)	16 (27.6)	14 (24.1)	0.107
Características clínicas, n (%)				
Hipertensión	37 (63.8)	18 (31)	19 (32.8)	0.266
Diabetes	15 (25.9)	9 (15.35)	6 (10.3)	0.131
Dislipemia	35 (59.3)	16 (27.6)	19 (32.8)	0.630
Fibrilación auricular	5 (8.6)	3 (5.2)	2 (3.4)	0.438
Ictus previo	10 (17.2)	4 (6.9)	6 (10.3)	0.838
Fumador	7 (12.1)	4 (6.9)	3 (5.2)	0.117
Consumo alcohol	2 (3.4)	1 (1.7)	1 (1.7)	0.862
Tratamiento antiplaquetario	13 (22.8)	5 (8.8)	8 (14.0)	0.666
Gravedad del ictus, mediana (min-max)				
NIHSS al ingreso	4 (0-36)	3 (0-15)	8 (0-36)	**0.006**
GCS al ingreso	15 (5-15)	15 (11-15)	14 (5-15)	**0.006**
Nivel de dependencia post HIC, n (%)				
4: Discapacidad moderadamente grave; incapaz de caminar sin ayuda e incapaz de atender sus propias necesidades corporales sin ayuda	4 (7.3)	0 (0)	4 (7.3)	<0.001
5: Discapacidad grave; encamado, incontinente y requiere cuidados y atención de enfermería	2 (3.6)	0 (0)	2 (3.6)	<0.001
6: Exitus	15 (27.3)	0 (0)	15 (27.3)	<0.001

Tabla 1. Comparación entre Grupos de Perfiles Demográficos y Clínicos en el Momento de la Inclusión *(continuación)*

	Total ***n*= 58**	**Incluídos** ***n* = 25**	**Excluídos** ***n* = 33**	***p* valor**
Características neuroimagen				
Volumen HIC (cm^3), mediana (min-max)	19.1 (1.32-139)	12.8 (1.40-54.7)	35.2 (1.32-139)	**0.003**
Hemisferio izquierdo, n (%)	29 (54.7)	13 (24.5)	16 (30.2)	0.821
Localización del hematoma, n (%)				
Lóbulo frontal	25 (34.9)	8 (14.0)	17 (29.8)	0.116
Lóbulo parietal	23 (40.4)	11 (19.3)	12 (21.1)	0.629
Extensión intraventricular	11 (22.9)	1 (2.1)	10 (20.8)	**0.009**
Proyecciones digitiformes	16 (33.3)	3 (6.3)	13 (27.1)	**0.015**
Pacientes con microsangrados corticales, n (%)	23 (47.9)	11 (22.9)	12 (25.0)	0.583
Número total de microsangrados corticales, media (DT)	12.1 (24.8)	09.36 (18.6)	15.4 (30.9)	0.416
Pacientes con siderosis superficial cortical, n (%)	22 (46.8)	8 (17.0)	14 (29.8)	**0.033**
Pacientes con siderosis superficial cortical en lóbulo frontal, n (%)	13 (28.3)	4 (8.7)	9 (19.6)	**0.048**
Hiperintensidades en sustancia blanca (Fazekas), mediana (min-max)	2 (0-3)	2 (0-3)	2 (1-3)	0.315
Escala CAA, mediana (min-max)	3 (0-5)	3 (0-5)	3 (0-5)	0.676
Atrofia Temporal Medial, mediana (min-max)	1 (0-4)	1 (0-3)	1 (0-4)	0.835
Atrofia Global Cortical, n (%)				
0-1	26 (48.1)	17 (31.5)	9 (16.7)	**0.006**
2-3	28 (51.9)	8 (14.8)	20 (37.1)	**0.006**

8.2.4.2. Aspectos Neuropsicológicos tras una HIC debida a AAC

Los pacientes no trabajaban activamente durante la evaluación, ya que la mayoría estaban jubilados (88%). El nivel de estudios es bajo en casi la mitad de la muestra (44%), con una media de 8.16 años de escolaridad.

Tabla 2. Características sociales de los pacientes evaluados neuropsicológicamente

	Incluídos n = 25
Estado civil, n (%)	
Casado	18 (72)
Soltero	2 (8)
Viudo	5 (20)
Situación laboral, n (%)	
Jubilado	22 (88)
Discapacitado	3 (12)
Años de escolarización, media (DT)	8.16 (4.61)
Nivel educativo, n (%)	
Leer y escribir hasta primaria incompleta	11 (44)
Primaria complete, Bach inf, FPI, Comercio	8 (32)
Bach superior, BUP, FP II, COU, PREU	1 (4)
Carrera grado medio	2 (8)
Carrera grado superior, Doctorado	3 (12)

Como se muestra en la tabla 3, los pacientes presentaban un nivel adecuado de cognición global (27; 17-35) y con un funcionamiento cognitivo dentro del rango esperado para sus características premórbidas (IQCODE=51.08; BDRS = 3.08).

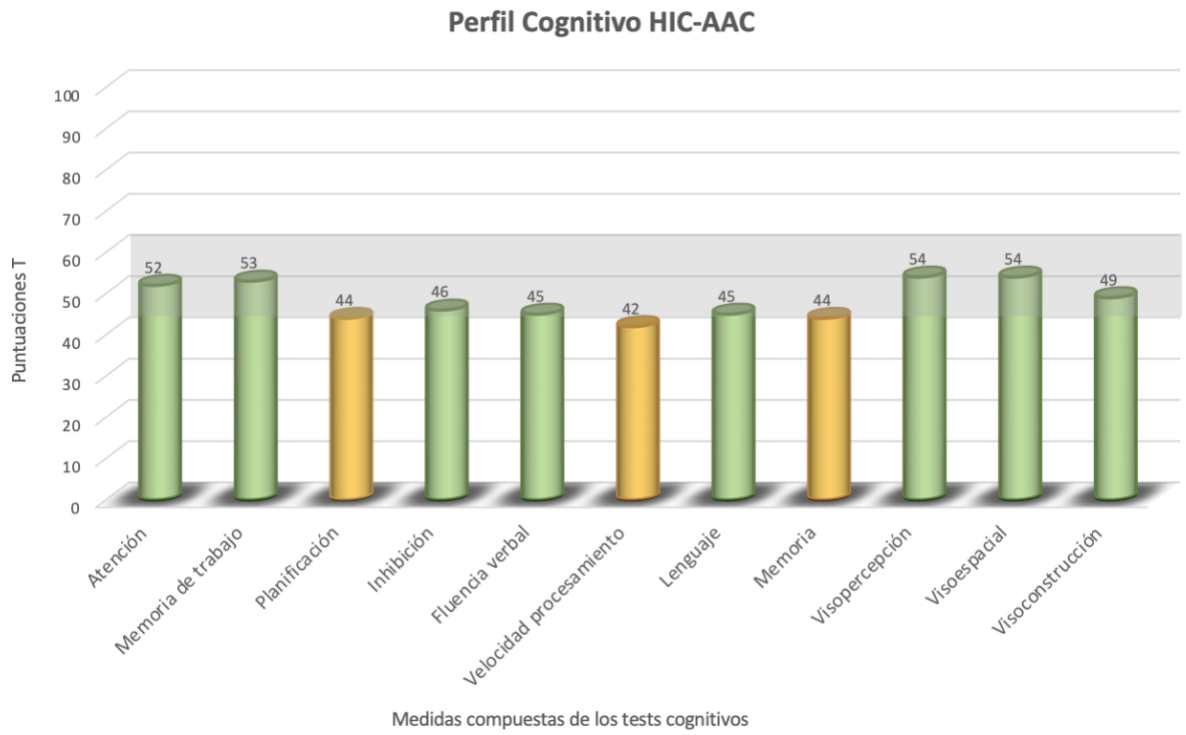
En cuanto a la evaluación cognitiva, las pruebas se expresaron como una puntuación t basada en los datos normativos publicados ajustados por edad, educación y sexo suministrados por cada prueba y por los baremos NEURONORMA. Posteriormente, se agruparon en procesos de atención, funciones ejecutivas, velocidad de procesamiento, lenguaje, memoria, función visoespacial, visoperceptiva y visoconstructiva.

Tras 15,6 meses del evento índice (10,00 DE; IQR:6-39), la evaluación cognitiva mostró que ninguno de los procesos y subprocesos evaluados presentaba alteraciones. Sin embargo, los procesos en los que presentan un menor rendimiento eran la velocidad de procesamiento, con una puntuación t media (±desviación estándar) de 42 (± 1,47), seguida de la memoria (44 ± 1,61) y la planificación (44 ± 1,97). Los resultados se resumen en la Figura 2.

Tabla 3. Medidas compuestas de las puntuaciones de las pruebas cognitivas, expresadas como puntuaciones t relativas a los baremos publicados

							95% Intervalo de Confianza	
	N	**Media**	**DT**	**Mediana**	**Mínimo**	**Máximo**	**Inferior**	**Superior**
Tiempo entre el evento índice y la evaluación neuropsicológica, (m.)	25	15.6	10.00	11	6	39	9.77	18.0
IQCODE	25	51.8	2.63	51	45	56	50.7	52.9
BDRS	25	3.08	2.00	2.98	0.00	9.50	1.85	4.31
CI premórbido	25	95.040	8.218	93	85	114	91.818	98.262
Cognición global	25	27.444	4.830	28	17.000	35.000	25.622	29.266
Atención	25	52.827	8.466	55.000	36.333	73.333	49.508	56.145
Memoria de trabajo	19	53.386	7.046	53.333	38.333	64.667	50.218	56.554
Planificación	24	44.375	9.672	44.750	30.000	64.000	40.505	48.245
Inhibición	24	46.125	7.980	46.000	28.000	66.000	42.932	49.318
Fluencia verbal	25	45.387	9.445	46.000	30.000	61.333	41.684	49.089
Velocidad de procesamiento	22	42.400	6.917	44.000	28.400	53.200	39.509	45.291
Lenguaje	24	45.1888	11.129	47.500	16.500	59.000	40.735	49.640
Memoria	24	44.917	7.887	45.000	25.857	60.714	41.761	48.072
Visopercepción	25	54.600	5.754	53.333	46.333	66.333	52.344	56.856
Visoespacial	25	54.373	9.475	56.333	34.000	70.000	50.659	58.088
Visoconstrucción	24	49.833	11.052	49.000	34.000	77.000	45.412	54.255

Figura 1. Perfil cognitivo de los pacientes con HIC-AAC



Basándonos en las puntuaciones t, la banda gris representa el rango de normalidad, donde 50 es la media y 10 la desviación típica.

El índice de Barthel mostró que nuestra cohorte era capaz de realizar las actividades básicas de la vida diaria con bajos niveles de dependencia (iB=98,60), aunque tanto los hombres (iLB=4) como las mujeres (iLB=7) se enfrentan a algunas dificultades en las actividades instrumentales como se muestra en la Tabla 4.

Tabla 4. Capacidad para realizar las actividades de la vida diaria

							95% Intervalo de Confianza	
	N	**Media**	**DT**	**Mediana**	**Mínimo**	**Máximo**	**Inferior**	**Superior**
iB	25	98.60	3.69	100	85	100	97.16	100.04
iLB								
Hombre	16	4.00	1.265	4.00	0	5	__	__
Mujer	9	7.56	0.882	8	6	8	__	__

iB: Índice Barthel; iLB: Índice Lawton & Brody

Las medianas de STAI-Estado, STAI-Rasgo, Eutimia-Estado, Eutimia-Rasgo, Depresión Total-Estado y Depresión Total-Rasgo se presentan en la Tabla 5.

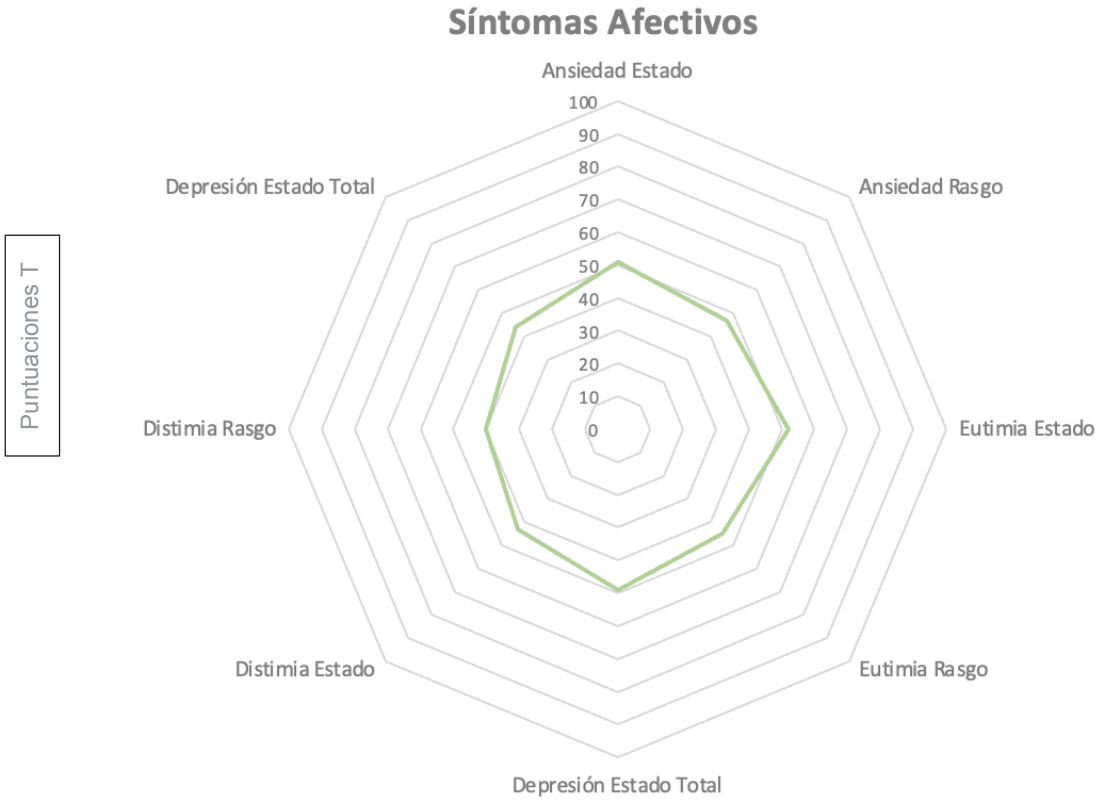
En nuestra cohorte, ninguno de los pacientes presentaba síntomas de depresión. Los pacientes presentaron puntuaciones adecuadas en la escala de estado (Depresión estado-total: t=49, DT=11,24; Distimia-estado: t=43, DT=13,56 y Eutimia-estado: t=52, DT=11,29) y en la escala de rasgo (Depresión rasgo-total: t=44, DT=9,96; Distimia-rasgo: t=40, DT=10,22; Eutimia-rasgo: t=45, DT=11,61).

Por otro lado, observamos resultados similares para la ansiedad, con una gravedad (Estado de Ansiedad: t=51, DT=11,79) y frecuencia (Rasgo de Ansiedad: t=45, DT=8,27) adecuadas. En esta cohorte no se utilizó medicación antidepresiva ni ansiolítica.

Tabla 5. Resumen de las puntuaciones de ansiedad y depresión

							95% Intervalo de Confianza	
	N	**Media**	**DT**	**Mediana**	**Mínimo**	**Máximo**	**Inferior**	**Superior**
Ansiedad								
Estado	25	51	11.79	53	29	83	46.54	55.78
Rasgo	25	47	8.27	47	32	60	43.88	50.36
Depresión								
Eutimia Estado	25	52	11.29	53	29	67	47.77	56.63
Distimia Estado	25	43	13.56	41	28	63	38.61	49.23
Depresión Estado Total	25	49	11.24	51	29	67	44.91	53.73
Eutimia Rasgo	25	45	11.61	46	28	67	41.33	50.43
Distimia Rasgo	25	40	10.22	43	28	56	36.59	44.61
Depresión Rasgo Total	25	44	9.96	47	29	63	40.97	48.79

Figura 2. Resumen de las puntuaciones afectivas



8.2.4.3. Conexión entre las Alteraciones Vasculares y Estructurales Cerebrales comunes en la HIC-AAC y la Cognición

La asociación entre los marcadores de neuroimagen y el rendimiento en las pruebas cognitivas se examinó en modelos de regresión lineal como se muestra en la Tabla 6.

Tras ajustar por edad, educación, sexo y presencia de HIC sintomática, el análisis correlacional reveló una asociación significativa entre la atrofia temporal medial (ATM) y la mayoría de los procesos evaluados (Atención: p=0.002, R^2 ajustado= 31; Planificación: p= 0.006, R^2 ajustado= 26; Fluidez verbal: p=0.001, R^2 ajustado= 35); Lenguaje: p=0.001, R^2 ajustado= 36; Memoria: p=0.003, R^2 ajustado= 29; Visuoespacial: p=0.005, R^2 ajustado= 26; Función visoconstructiva: p=0.006, R^2 ajustado= 26). Además, se encontró una correlación significativa entre la puntuación total del AAC y la atrofia cortical global (ACG) con Memoria (p=0.018, R^2 ajustado= 19; p=0.021, R^2 ajustado= 15) y Función visoperceptiva (p=0.0326, R^2 ajustado= 15; p=0.022, R^2 ajustado= 17).

Tabla 6. Influencia de las Alteraciones Vasculares y Estructurales Cerebrales y la Cognición

	t	***p***	**Adjusted R^2 (%)**	**RMSE**
Atención				
Volumen HIC	1.40	0.175	4	7.09
Puntuación AAC	-1.23	0.230	20	8.03
ATM	-3.41	**0.002**	31	6.76
AGC	-1.56	0.132	6	7.89
Memoria de trabajo				
Volumen HIC	0.27	0.789	7	6.41
Puntuación AAC	0.06	0.949	6	6.86
ATM	-1.52	0.147	7	6.44
AGC	-0.31	0.758	5	6.84
Planificación				
Volumen HIC	0.879	0.391	1	9.075
Puntuación AAC	0.29	0.774	4	9.45
ATM	-3.01	**0.006**	26	7.97
AGC	-1.00	0.328	0	9.26
Inhibición				
Volumen HIC	-0.408	0.688	4	8.48
Puntuación AAC	-1.04	0.307	0	7.63
ATM	-0.36	0.721	4	7.79
AGC	-0.50	0.625	3	7.77

Tabla 6. Influencia de las alteraciones vasculares y estructurales cerebrales y la cognición *(continuación)*

	t	*p*	Adjusted R^2 (%)	RMSE
Fluencia Verbal				
Volumen HIC	0.529	0.603	3	9.73
Puntuación AAC	-1.66	0.109	7	8.74
ATM	-3.71	**0.001**	35	7.32
AGC	-0.72	0.476	2	9.15
Velocidad de Procesamiento				
Volumen HIC	0.894	0.385	1	5.95
Puntuación AAC	0.29	0.771	5	6.74
ATM	-1.56	0.134	0.06	6.38
AGC	0.26	0.797	5	6.75
Lenguaje				
Volumen HIC	0.476	0.640	4	10.67
Puntuación AAC	-1.23	0.232	2	10.54
ATM	-3.74	**0.001**	36	8.52
AGC	-1.44	0.163	4	10.42
Memoria				
Volumen HIC	1.17	0.267	1	7.34
Puntuación AAC	-2.55	**0.018**	19	6.78
ATM	-3.24	**0.003**	29	6.36
AGC	-2.69	**0.013**	21	6.70
Func. Visoperceptiva				
Volumen HIC	-0.52	0.608	3	4.58
Puntuación AAC	2.27	**0.032**	15	5.09
ATM	1.06	0.300	10	5.51
AGC	2.45	**0.022**	17	5.02
Func. Visoespacial				
Volumen HIC	0.49	0.630	3	9.44
Puntuación AAC	-1.74	0.094	8	8.73
ATM	-3.10	**0.005**	26	7.79
AGC	-0.86	0.396	10	9.14
Func. Visoconstructiva				
Volumen HIC	0.47	0.644	4	9.97
Puntuación AAC	0.32	0.752	4	10.79
ATM	-3.02	**0.006**	26	9.10
AGC	0.29	0.772	4	10.80

8.2.5. Discusión

En nuestra cohorte, el 51.7% eran hombres con una media de edad de 74.3 (DT 8.04) años, teniendo como principales factores de riesgo cardiovascular la hipertensión (63.8%) y la dislipemia (59.3%). La NIHSS y el GCS en el momento del evento índice fueron de 4 y 15, respectivamente, y el volumen medio de la HIC fue de 19.1 (1.32-139) cm^3. La presentación clínica de los pacientes con HIC-AAC fue muy homogénea, consistiendo en hemorragia lobar parietal en el 40.04% de los casos, seguida de localización frontal (34.9%), temporal (21.1%) y occipital (17.5%). No se detectó ninguna otra HIC lobar durante los 15 meses de seguimiento.

Nuestro estudio proporciona una descripción detallada de las características neuropsicológicas de los pacientes con HIC-AAC en un seguimiento a los 15 meses de media del evento índice. Nuestros principales hallazgos son que, en términos de cognición, los pacientes sin demencia previa rindieron adecuadamente en una amplia gama de pruebas cognitivas en comparación con sujetos de edad y nivel educativo similares. Sin embargo, los procesos en los que presentan un rendimiento más bajo son la velocidad de procesamiento, con una puntuación t de 42 ± 1,47 (media ± desviación estándar), seguida de la memoria (44 ± 1,61) y la planificación (44 ± 1,97). Estos resultados coinciden con los de estudios anteriores; sin embargo, es posible experimentar un patrón cognitivo de este tipo debido a otras enfermedades neurológicas, incluida la EA o el DCL derivado de un ictus isquémico.

Entre esta población de pacientes con HIC-AAC, se notificaron tasas de deterioro tras la HIC que oscilaban entre el 88% tras un seguimiento de 3 meses y el 37% tras un seguimiento de 6 meses.

Las variaciones en los resultados observados hasta ahora pueden explicarse por sesgos metodológicos como la diferencia de tiempo entre el evento índice y la evaluación cognitiva tras la HIC, los métodos de evaluación cognitiva y la evaluación de la demencia preexistente, o por diferencias en el tamaño de las muestras entre estudios como el nuestro. La mayoría de estos estudios realizaron sus evaluaciones neuropsicológicas a lo largo de la fase subaguda o en algunos casos ni siquiera realizan una evaluación neuropsicológica o cribado. Además, los criterios que se utilizan para definir el deterioro cognitivo pueden influir en las ratios de prevalencia del deterioro cognitivo, además del tiempo transcurrido entre el evento índice y la evaluación neuropsicológica. En comparación con otros estudios similares, nuestro estudio utilizó criterios muy restrictivos que pueden explicar la diferencia en la prevalencia del deterioro cognitivo tras el ictus en nuestro estudio.

En cuanto al estado emocional, ninguno de los pacientes de nuestra cohorte presentaba síntomas de depresión. Tanto en la escala de estado (estado total de depresión: t=49, DT=11,24; estado de distimia: t=43, DT=13,56 y estado de eutimia: t=52, DT=11,29) como en la de rasgo (rasgo total de depresión: t=44, DT=9,96; rasgo de distimia: t=40, DT=10,22; rasgo de eutimia: t=45, DT=11,61), los pacientes puntuaron adecuadamente. Los resultados de este análisis indican que ninguno de los pacientes de nuestra cohorte presentaba síntomas de depresión. Se observaron resultados similares con la ansiedad, con un nivel adecuado de gravedad (Estado de Ansiedad: t=51, DT=11,79) y frecuencia (Rasgo de Ansiedad: t=45, DT=8,27). En esta población no se prescribieron antidepresivos ni ansiolíticos.

Finalmente, entre los 24 supervivientes a largo plazo, 18 (75%) eran independientes (mRs 0-2) y 4 (17%) eran dependientes (mRs=3) presentando una buena capacidad tanto para realizar las actividades básicas de la vida diaria (iB = 98.60) así como las actividades instrumentales de la vida diaria (iLB = 6.56).

Consideramos que, para comprender mejor las características neuropsicológicas de estos pacientes, las evaluaciones deben realizarse durante la fase crónica, como muestra nuestro estudio, y examinando siempre la cognición, la funcionalidad y las características emocionales. En cuanto al diagnóstico de DCL o demencia, cabe destacar que la media del tiempo de diagnóstico de demencia de nueva aparición es de 3 años, y un considerable 25% de ellas se diagnostican 6 años después de la HIC: este hallazgo subraya la importancia del seguimiento de los supervivientes de HIC a lo largo del tiempo.

En cuanto a los biomarcadores en imagen, nuestro principal hallazgo es que los marcadores de neuroimagen por RM de la AAC podrían estar asociados con un futuro deterioro cognitivo por HIC. Esto sugiere que el deterioro cognitivo en la AAC no se debe únicamente a la lesión cerebral causada directamente por la HIC, sino que también está relacionado de forma independiente con la alteración subyacente de pequeño vaso asociada a la AAC.

Nuestro estudio con supervivientes de HIC-AAC no encontró alteraciones cognitivas francas, probablemente debido al pequeño tamaño de la muestra y al hecho de que sólo estudiamos pacientes ambulatorios con AAC leve. Sin embargo, gracias a la aplicación de una batería neuropsicológica rigurosamente seleccionada y administrada, podemos revelar resultados interesantes: 1) La memoria parece ser el proceso cognitivo más susceptible a la influencia de diversos cambios cerebrales; 2) La ATM sigue siendo el mejor predictor del deterioro de la memoria, seguido de la puntuación de la ACG y la AAC total; 3) La ATM se correlaciona significativamente no sólo con la memoria, sino también con otros procesos, como la atención, la planificación, la fluidez verbal, el lenguaje y la función visoespacial y visoconstructiva; 4) Los marcadores de neuroimagen relacionados con la AAC, más que el volumen y la localización de la HIC, podrían ser predictores de la incidencia de demencia a largo plazo.

Cada vez son más las investigaciones que sugieren que la fisiopatología de la AAC es mucho más compleja de lo que se creía en un principio y que da lugar a multitud de lesiones cerebrales. Ahora hay pruebas de que la AAC puede causar atrofia cerebral significativa en zonas no afectadas directamente por la HIC, y aumentar el riesgo de deterioro cognitivo progresivo incluso sin recurrencia de hemorragias. En otras palabras, la AAC se caracteriza por rasgos asociados a las enfermedades neurodegenerativas, como la atrofia cerebral y el deterioro cognitivo progresivo. Aunque la AAC suele asociarse con cierto grado de patología de EA, el perfil de atrofia cortical y deterioro cognitivo no se solapa completamente con la EA, lo que sugiere vías neurodegenerativas específicas de la AAC. Además, la lesión cerebral isquémica causada por la AAC es uno de los mecanismos clave responsables de la lesión cerebral, la desconexión cortical y el deterioro cognitivo.

Cuando se habla de la RM estructural en el contexto de la AAC y sus antecedentes, la mayoría de los autores se centran en los aspectos vasculares de la enfermedad, con especial atención a las hiperintensidades en sustancia blanca y los microsangrados. Sin embargo, las pruebas de RM estructural también pueden utilizarse para identificar y cuantificar aspectos neurodegenerativos de la enfermedad, como la atrofia cortical, que han surgido como elementos importantes en nuestra comprensión de la AAC.

La relación entre lesiones vasculares (lesión cerebral isquémica) y degenerativas (atrofia del hipocampo) y el posterior deterioro neurocognitivo se basa en la hipótesis interactiva que sugiere que la coocurrencia de lesiones vasculares y degenerativas puede inducir un efecto sinérgico que podría potenciar y acelerar el deterioro cognitivo. Esta hipótesis interactiva está respaldada por varias revisiones sistemáticas y metaanálisis.

Para argumentar que la AAC debe considerarse tanto una enfermedad cerebrovascular como neurodegenerativa, me centraré en las asociaciones entre la AAC y las características cardinales de imagen de ambos síndromes neurológicos.

En nuestro estudio, se han incorporado varios hallazgos de RM en una "puntuación" compuesta basada en RM que pretende captar la carga global de AAC-EPV (enfermedad de pequeño vaso) en el cerebro: la puntuación total de AAC. La puntuación total AAC-EPV se calculó utilizando los principales marcadores RM de AAC (microsangrados cortical, leukoaraiosis/hiperintensidades de sustancia blanca según la escala Fazekas, espacios dilatados en centro semioval y siderosis superficial cortical). De este modo se obtuvo una puntuación ordinal de la carga total de EPV (de 0 a 5). En este estudio se han tenido en cuenta otras medidas, incluidas puntuaciones relacionadas con la atrofia cerebral en áreas específicas, como el hipocampo (ATM), así como medidas relacionadas con la atrofia cortical global (ACG).

Se cree que los cambios patológicos o degenerativos en el lóbulo temporal medial intervienen en los primeros síntomas cognitivos de la EA. La atrofia de la corteza del lóbulo temporal medial es el mejor predictor de un peor rendimiento de la memoria episódica en la EA. Mediante el análisis de los resultados de los marcadores de neuroimagen en nuestra cohorte, esta tesis ha aportado pruebas sobre la existencia de marcadores preclínicos de un posible deterioro cognitivo posterior.

Nuestros hallazgos se suman a la creciente evidencia de que los marcadores degenerativos -como la atrofia del hipocampo- tiene fuertes asociaciones con varios procesos cognitivos -como la atención, la planificación, la fluidez verbal, el lenguaje, la memoria, las funciones visoespaciales y de visoconstructivas- y no sólo con la memoria episódica, lo que sugiere que la atrofia del hipocampo podría ser un proceso patológico especialmente importante que deteriora la cognición en pacientes con EA. La observación sugiere que esta atrofia cortical típica de la EA podría ser un biomarcador de diferencias individuales y no de la EA *per se.*

Sin embargo, en lo que respecta al volumen del hematoma, nuestros resultados sugieren que los marcadores de neuroimagen asociados a la AAC, más que el volumen y la localización de la HIC, serían predictores de la incidencia de demencia a largo plazo, en consonancia con dos estudios recientes. Estos estudios apoyan conjuntamente el importante papel de la enfermedad de pequeño vaso asociada con la AAC en los supervivientes de una HIC.

La identificación de marcadores biológicos y de neuroimagen sensibles en la AAC se ha convertido en un componente esencial de la investigación de la AAC. Al mismo tiempo, esta investigación ha demostrado que existe una fuerte correlación entre los marcadores estructurales de imagen de la AAC (microhemorragias cerebrales, espacios perivasculares en el centro semioval e hiperintensidades de la sustancia blanca) y la posibilidad de una progresión posterior hacia el deterioro cognitivo y la demencia, prediciendo cambios potenciales en procesos cognitivos como la fluidez verbal, la memoria y las funciones visoperceptivas y visoespaciales o visoconstructivas. Los estudios longitudinales son esenciales para este objetivo.

Identificar los cambios biológicos que inducen la AAC es clave para predecir el inicio de la enfermedad, diseñar las intervenciones adecuadas, controlar su progresión, evaluar la eficacia de los fármacos u otros tratamientos y, en última instancia, desarrollar una cura. La RM se ha convertido en una potente herramienta no invasiva para evaluar la estructura y función cerebral *in vivo* gracias a las mejoras en las herramientas de adquisición y análisis. Gracias a trabajos como el que hemos llevado a cabo, es posible identificar mediante RM a los pacientes que presentan las alteraciones cerebrales antes mencionadas y hacerles un seguimiento más exhaustivo ante el riesgo de deterioro cognitivo y, a la larga, demencia.

Conclusiones

El objetivo general de esta tesis fue avanzar en la evidencia científica actual del perfil neuropsicológico integral en la HIC-AAC y destacar los efectos de los marcadores de la AAC en la cognición, la estructura cerebral y el riesgo de deterioro cognitivo y demencia. Este estudio sugiere una compleja relación sinérgica entre los marcadores cerebrales isquémicos y hemorrágicos, la atrofia cerebral y la cognición. Por lo tanto, gracias a esta tesis, hemos podido demostrar que:

1. En cuanto a la cognición, los pacientes sin demencia previa, y con hemorragias de menor volumen, rinden adecuadamente en una amplia gama de pruebas cognitivas, aunque hay una tendencia a mostrar mayor dificultad en tareas que evalúan la velocidad de procesamiento, la memoria y la planificación a los 15 meses de seguimiento.

2. Los pacientes son funcionalmente capaces tanto en las actividades básicas de la vida diaria como en las actividades instrumentales a los 15 meses de seguimiento.

3. No se observan alteraciones afectivas en los pacientes sin demencia post-HIC a los 15 meses de seguimiento.

4. La atrofia del hipocampo es el marcador estructural cerebral que puede influir y contribuir al cuadro clínico final de este proceso neurodegenerativo afectando a casi la mayoría de los procesos cognitivos evaluados (atención, planificación, fluidez verbal, lenguaje, funciones visuoespaciales y visoconstrucción), no sólo a la memoria episódica como se pensaba anteriormente.

5. La atrofia cortical global y los marcadores cerebrales hemorrágicos e isquémicos tienen una correlación significativa con la memoria y las funciones visoperceptivas.

6. En nuestra cohorte, los marcadores de neuroimagen relacionados con la AAC, más que el volumen y la localización de la HIC, podrían ser predictores de la incidencia de demencia a largo plazo.

Esto sugiere que una estrategia futura dirigida a reducir el impacto de la demencia postinfarto en la HIC necesitará extenderse más allá de la prevención del infarto e incluir estrategias que aborden el impacto de la AAC. Es prioritario seguir investigando sobre la historia natural de cuándo y cómo puede influir la AAC en el perfil cognitivo de un individuo.

Consideramos que la investigación sobre la AAC y la neurodegeneración debe centrarse en la identificación de factores cognitivos, descubrir los mecanismos patológicos de la atrofia y el deterioro cognitivo, nuevos métodos de diagnóstico y seguimiento, evaluar si los fármacos que mejoran la cognición en la EA pueden ser eficaces en el tratamiento de la AAC e identificar nuevas estrategias terapéuticas mediante estudios multicéntricos con muestras más amplias.