Advancing diagnostic criteria for sporadic cerebral amyloid angiopathy: study protocol for a multicenter MRI-pathology validation of Boston criteria v2.0

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Abstract

Rationale: The Boston Criteria are used worldwide for the *in vivo* diagnosis of cerebral amyloid angiopathy (CAA) and the basis for clinical decision-making and research in the field. Given substantial advances in CAA's clinical aspects and MRI biomarkers, we designed a multicenter study within the International CAA Association aimed at updating the Boston Criteria and improving and validating their diagnostic accuracy.

Aim: We aim to derive and validate an updated "version 2.0" of the Boston Criteria across the spectrum of CAA-related presentations and MRI biomarkers.

Sample size estimates: Participating centers with suitable available data (see Methods) were identified from existing collaborations and an open invitation to the International CAA Association emailing list. Our study sample will include: 1) a derivation cohort – MGH, Boston cases from inception to 2012 (~178 patients); (2) temporal external validation cohort - MGH, Boston cases from 2012-2018 (~120 patients); and (3) geographical external validation cohort – non-Boston cases (~85 patients).

Methods and design: Multicenter collaborative study. We will collect and analyze data from patients age ≥50 with any potential sporadic CAA-related clinical presentations (spontaneous intracerebral hemorrhage, transient focal neurological episodes and cognitive impairment), available brain MRI ("index test"), and histopathologic assessment for CAA ("reference standard" for diagnosis). Trained raters will assess MRI for all hemorrhagic and non-hemorrhagic small vessel disease markers according to validated criteria and a prespecified protocol, masked to clinical and histopathologic features. Brain tissue samples will be rated for CAA, defined as Vonsattel grade ≥2 for whole brain autopsies and ≥1 for cortical biopsies or hematoma evacuation. Based on our estimated available sample size, we will undertake pre-specified cohort splitting as above. We will: (a) pre-specify variables and statistical cut-offs; (b) examine univariable and multivariable associations; and (c) then assess classification measures (sensitivity, specificity etc.) for each MRI biomarker individually, in relation to the CAA diagnosis reference standard on neuropathology in a derivation cohort. The MRI biomarkers strongly associated with CAA diagnosis will be selected for inclusion in provisional (probable and possible CAA) Boston criteria v2.0 and validated using appropriate metrics and models.

Study outcomes: Boston criteria v2.0 for clinical CAA diagnosis.

Discussion: This work aims to update and improve the diagnostic test accuracy of the Boston criteria for CAA, to better meet the needs of clinicians and investigators and help accelerate progress towards better treatment of CAA.

Introduction and rationale

Sporadic cerebral amyloid angiopathy (CAA) is a common age-related cerebral small vessel disease, caused by the progressive deposition of amyloid-β in the walls of small-to-medium sized arteries, arterioles and capillaries in the cerebral cortex and overlying leptomeninges.[1-3] CAA is the main cause of lobar intracerebral hemorrhage (ICH) and a key contributor to cognitive impairment in elderly patients, two major challenges in cerebrovascular disease.[4] Similar to most neurodegenerative disorders, the gold standard for CAA diagnosis is histopathological analysis from brain autopsy or biopsy samples.[2, 5] However, CAA is strongly associated with key hemorrhagic MRI biomarkers of small vessel disease, including lobar ICH, strictly lobar cerebral microbleeds (CMBs) and cortical superficial siderosis (cSS).[4, 6]

Non-invasive diagnosis of CAA in patients presenting with lobar ICH or other clinical syndromes is important for guiding prognosis and treatment decisions in clinical practice, as well as for including patients in research studies and clinical trials.[7-9] Combining clinical and imaging data within the original and modified Boston criteria has proved a useful framework for non-invasive *in vivo* diagnosis of CAA (Table 1 demonstrates the modified Boston criteria).[5, 10-13] The Boston Criteria for CAA diagnosis, first introduced in 1996, have indeed become the basis for clinical decision-making as well as a rapidly growing body of literature investigating the disease's clinical manifestations, phenotypic spectrum, progression, and potential for disease-modifying therapies.[13] MRI-histopathological studies to date,[5, 11, 14, 15] with relatively small sample sizes (n<100), have provided validated evidence for the Boston Criteria "probable" CAA diagnostic category that has been most commonly used (Table 1).[13] Probable CAA requires evidence of multiple strictly lobar hemorrhages (micro- or macro-) without another cause in patients ≥55 years old. Among three hospital-based studies of patients presenting primarily with spontaneous ICH who underwent T2*-weighted MRI, probable CAA by original Boston Criteria showed sensitivities ranging from 57.9% to 76.9% and specificities of 87.5% to 100%.[5, 11, 14] By contrast, the sensitivity has been reported to be much lower in hospital populations without ICH (Sensitivity: 42.4%; 95%CI: 25.9%-60.6% and Specificity: 90.9%; 95%CI: 69.3%-98.45).[15] Modifying the Boston Criteria by incorporation of cSS presence (Yes/No) in one head-to-head comparison[11] appeared to improve sensitivity without lowering specificity and these modified criteria are now widely used for non invasive CAA diagnosis.

The spectrum of hemorrhagic and non-hemorrhagic clinical and MRI biomarkers of CAA and small vessel disease have expanded in recent years, offering a new opportunity to refine existing diagnostic criteria across the full spectrum of CAA presentations.[2, 3] Moreover, it is increasingly recognised that it might not be necessary to exclude patients with a single or few deep CMBs from having a CAA diagnosis.[16] As a next step towards updating and improving the diagnosis of CAA, we are undertaking a multicenter effort to validate and update the Boston criteria within the International CAA Association.[13] This project will analyze all available clinical and neuroimaging data from individuals age ≥50 with any of the potential CAA-related clinical presentations, brain MRI, and histopathologic diagnosis from autopsy or biopsy. The goal is to produce and validate a "version 2.0" of the Boston Criteria that will better meet the needs of clinicians and investigators and help maintain the rapid pace of progress towards better treatment of CAA.

Aims

This project aims to systematically obtain histopathological, neuroimaging, clinical and other available data from eligible patients with histopathologically-confirmed CAA and patients with histopathological absence of advanced CAA as a control group (see definitions below). We will include patients presenting with either spontaneous ICH or other clinical syndromes potentially associated with CAA, including transient focal neurological episodes or cognitive impairment/dementia. Patients with other clinical presentations and diagnoses, in whom CAA was picked up incidentally (e.g. brain tumours, Parkinson's disease) will not be considered for this project. Our specific objective is to analyse the diagnostic performance of different MRI biomarkers of CAA[17] (see details below) and provide clinically useful estimates of specificity and sensitivity. Based on the performance of the CAA imaging biomarkers in the derivation criteria, the existing Boston diagnostic criteria for CAA will be refined and validated across the spectrum of potential clinical presentations of the disease using independent internal and external datasets.

Methods and design

The protocol for this study was developed by investigators from the coordinating center (MGH, Boston, USA) and UCL (DJW) in August 2016. An initial draft of the protocol was presented and discussed among investigators in September 2016 at the 5th International CAA Conference. Comments and feedback were incorporated and the protocol was finalised in

January 2017. The study will be performed in line with Standards for Reporting of Diagnostic Accuracy (STARD) guidelines.[18]

Design

Table 2 and Figure 1 summarise the main steps of the study.

Patient population and eligibility criteria

Patients will be identified through systematic searches of hospital/research neuropathology databases supplemented by clinical, radiology and research databases (depending on the local setting in each participating center) for patients with all of the following features: (a) brain tissue (obtained by biopsy, hematoma evacuation, or autopsy) evaluated for CAA; (b) potential CAA-related clinical presentation (including symptomatic ICH, transient focal neurological episodes, cognitive impairment and dementia- not restricted by a particular neuropsychological phenotype, but likely to be diagnosed clinically as vascular or Alzheimer's disease-related) to stroke service clinics, memory clinics, or relevant research clinics; (c) availability of minimum defined clinical and demographic details (age, hypertension, previous history of ICH etc.); and (d) available adequate MRI data with known acquisition date in relation to the presenting clinical syndrome (for the hospital-based sample, but not cases coming from population-based studies – see note on substudies) (Table 2). At least T2-weighted, FLAIR and T2*-weighted based axial sequences (including simple T2*-gradient recalled-echo and/or modern susceptibility weighted imaging) are required for this project. Although MRI sequence parameters and field strength are not pre-specified, all imaging needs to pass a central quality check (to ensure acceptable quality to assess all of the MRI biomarkers we are investigating) for all of the following essential sequences: T2-weighted, T2*-weighted and FLAIR. The study will include population-based cohorts or brain banks with relevant (in vivo and ex vivo) data in separate analyses and projects to better capture the full spectrum of manifestations of CAA by including community-dwelling individuals in a follow-up sub-study.

Pathological analysis

Routine hematoxylin-eosin staining should be available for morphological assessment and the presence or absence of vascular amyloid-β deposition and confirmed by immunohistochemistry where possible. Samples not containing any assessable vessels (an ideal sample should have >10 vessels) will be excluded from the analysis. CAA presence and severity will be assessed in all available vessels (including solid tissue fragments and isolated vessels); we will also determine, wherever possible, whether vessels are leptomeningeal or

parenchymal, and score these separately for CAA grade. CAA severity will be graded, masked to the brain MRI findings, using the modified Vonsattel grading system (Table 3).[19, 20] Pathological analysis will be performed either locally at the source hospital by an experienced neuropathologist or on tissue slides provided for central review in Boston if local expertise is not available.

Selected centers with autopsy cases can additionally use a recently validated consensus protocol for CAA assessment in post-mortem brain tissue.[21] This protocol allows scoring parenchymal and meningeal CAA individually on a 0-3 scale, capillary CAA as present/absent and vasculopathy on a 0-2 scale in designated Brodmann areas from the frontal, temporal, parietal and occipital lobes.[21] The use of this protocol is optional.

Definition of cases

Patients presenting to hospital stroke or neurological services or to memory clinics with potential CAA-related clinical syndromes (symptomatic spontaneous ICH due to no apparent cause other than small vessel disease after adequate investigation, transient neurological symptoms, or cognitive decline) and with histopathologically-proven sporadic CAA demonstrated by brain biopsy, hematoma evacuation samples or autopsy (see section Pathological analysis). Brain samples will be graded for CAA severity using modified Vonsattel grading system.[19, 20] (Table 3). For the purposes of classifying individuals as positive for histopathologically-confirmed CAA, samples obtained via full brain autopsy will be required to demonstrate at least Vonsattel grade 2 (i.e. replacement of the whole vessel wall by amyloid-β), as mild Vonsattel grade 1 CAA can occur as an incidentally finding.[18] Samples obtained by brain biopsy or hematoma evacuation will be considered cases if Vonsattel grade ≥1 is detected (i.e. any amyloid in the vessel wall); the rationale for the lower threshold is that detecting any amyloid in the vessel wall is likely to be clinically significant when such a limited amount of brain tissue is examined. This classification approach has been applied to previous MRI-pathological validation studies in CAA.[11, 22, 23]

Definition of controls

Patients presenting to hospital stroke or neurological services or to memory clinics with the potential CAA-related clinical syndromes noted and with adequate histopathological sample from brain biopsy, hematoma evacuation samples or autopsy demonstrating absence of

advanced CAA as described above (Vonsattel ≤1 in autopsy, Vonsattel=0 in brain biopsy or hematoma evacuation).

List of clinical data to be collected

See Excel database in the Supplementary material for the full and minimum acceptable dataset needed for the project.

MRI assessment and analysis

Key MRI biomarkers of CAA and small vessel disease were derived from a systematic review of the relevant literature.[4] These included characteristic hemorrhagic MRI biomarkers of CAA[6] (cerebral microbleeds-CMBs, ICH, cortical superficial siderosis-cSS), as well as non-hemorrhagic markers[6] (white matter hyperintensities-WMH, posterior predominant WMH, WMH spots and MRI-visible perivascular spaces in the centrum semiovale-CSO-EPVS[14, 24, 25]). All MRI markers will be rated by a trained observer blinded to clinical and pathological information, according to STandards for ReportIng Vascular changes on nEuroimaging (STRIVE)[26] where applicable and validated scales and guidelines. Additional trained raters will assess a random sample of the MRI scans (n=100) to generate inter-rater agreement measures.

CMBs presence and number will be evaluated on axial T2*-weighted images using current consensus criteria[27] and categorized according to a simplified version of the previously validated Microbleeds Anatomic Rating Scale (MARS).[28] For purposes of statistical analyses, the number of lobar CMBs as a continuous variable as well as categories using cut-points (0, 1, 2–4, ≥5 or 5-10 and ≥10).[9] Non-lobar (i.e. deep CMBs) will also be categorized accordingly. ICH will be defined and categorized as lobar or non-lobar according to the The Cerebral Hemorrhage Anatomical RaTing inStrument (CHARTS) definitions.[29]

cSS will be defined as per recent consensus recommendations[30] (curvilinear hypointensities following the cortical surface, distinct from the vessels, and assessed on axial blood-sensitive sequences according to a validated scale: absent, focal (restricted to ≤3 sulci) or disseminated (affecting 4 or more sulci).[11, 31] cSS will also be rated for multifocality (i.e. taking into account cSS presence at spatially separate foci in each hemisphere) using another developed and validated protocol as: (a) 0 – none; (b) 1 -1 sulcus or up to 3 immediately adjacent sulci with cSS; or (c) 2 - 2 or more non-adjacent sulci or more than 3 adjacent sulci with cSS. Based on the total score: 0–no cSS, 1 –unifocal cSS, while ≥2 multifocal cSS.[32]

Periventricular and deep WMH will be classified using the 0-3 Fazekas scale on axially oriented FLAIR images.[33] In patients with ICH, the unaffected hemisphere will be scored. In patients with bilateral ICH or significant edema, an estimation will be made, using the non-involved white matter areas. The antero-posterior ratio of WMH lesions' distribution will be computed using a validated approach on FLAIR,[34] using multiplanar reformatting as necessary to provide axial orientation. In this method, WMH in the frontal lobe are evaluated around the frontal horn of the lateral ventricle and WMH in the occipital lobe are evaluated around the occipital horn of the lateral ventricle. For the frontal and occipital lobes, visual scales are separately used to rate WMH surrounding the ventricles (≤5 mm from ventricle), within juxtacortical white matter (≤5 mm from the cortex) and within the deep white matter (defined as the region between juxtacortical and ventricular areas). Periventricular WMH are graded as 0 (absent), 1 (caps or pencil-thin periventricular lining), 2 (smooth halo or thick lining), and in deep or in juxtacortical white matter as 0 (absent), 1 (punctate or nodular foci), 2 (confluent areas). The overall severity is then calculated separately for the frontal and occipital lobes by adding the scores for these three areas (range 0–6), and then the frontal-occipital (FO) gradient calculated as the WMH score in the frontal lobe minus that in the occipital lobe, ranging −6 to 6 (>0 implies frontal dominance and <0 implies occipital dominance). As previously shown, using this method, a lower score reflects more posteriorly distributed WMH lesions.[34]

Multiple subcortical spots WMH refers to a pattern which appears in the subcortical white matter and corresponds to more than 10 small spots (circular or ovoid) of WMH on FLAIR images.[35]

MRI-visible PVS will be rated on axial T2-weighted MR images, in the basal ganglia (BG) and CSO, using a validated 4-point visual rating scale (0=no PVS, 1=<10 PVS, 2=11-20 PVS, 3=21-40 PVS and 4=>40 PVS).[14, 36-39, 14] The numbers refer to PVS on one side of the brain: after reviewing all relevant slices for the anatomical area being assessed, the count for the slice and side with the highest number of PVS is recorded. The assessment of PVS may be influenced by the presence of confluent WMH; in such cases estimation is made for the PVS rating category, using the non-involved white matter region, and cortical gray matter according to the rating scale used. In cases of large lobar or deep ICH, PVS are assessed in the contralateral hemisphere, an estimation of the closest category ipsilateral to the lesion is made, and the highest severity is recorded. We pre-specified a dichotomised classification of

PVS degree as high (score >2) or low (score ≤2). This definition is in line with the PVS burden used in previous studies and found to relate with different vascular risk factors and imaging markers of small vessel disease,[38, 39] in particular the association between CSO-EPVS and CAA.[14, 39, 40]

Participating centers and sample size estimates

Potential participating centers are identified from existing collaborations with suitable data available and an invitation through the International CAA Association. It is estimated that the total sample size will be around 380 patients.

Data transfer

Clinical and imaging data will be sent in anonymized format to MGH, Boston, MA, USA for central imaging rating and statistical analysis. Ethical approval for obtaining, recording and sending these data will be obtained by the local research teams. The study will include only routinely collected clinical data. Basic clinical and demographic details will be provided using an Excel database for each patient included in the study. MRI scans will be sent to the coordinating center on anonymized CDs or using a secure electronic transfer pathway.

Design of Boston Criteria v2.0 and statistical considerations

The Boston Criteria v2.0 will be designed using a pre-specified model and structural principles for the criteria categories to reduce overfitting. Statistical analysis will be performed with reference to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD)[41] guidelines for prediction model studies, and on literature for validating clinical prediction models.[42-45]

The statistical approach (see details in the second part of this section) will be partly informed by the general theoretical framework of the current Boston Criteria diagnostic categories (i.e. probable and possible CAA as core categories), which takes into account advantages and limitations of their use for over 20 years in clinical practise and research.[13] In this context, the most widely used diagnostic category for both clinical practice and research is *probable CAA*, which provided the highest specificity currently achievable without obtaining brain tissue.[13] As first formulated ("original Boston Criteria", *now defined as Boston criteria version 1.0*), probable CAA entailed neuroimaging demonstration of multiple (i.e. two or more) hemorrhages restricted to lobar brain regions,[46, 47] defined as cerebral cortex, the corticosubcortical (grey-white) junction, and subcortical white matter. Presence of only one

lobar hemorrhagic lesion was denoted *possible CAA*, with lower corresponding diagnostic certainty. A modification to count blood products in cortical sulci (cSS) as one additional hemorrhagic lesion ("modified Boston Criteria", *now considered Boston criteria version 1.5*), was proposed and validated in 2010.[11] The requirement for multiple strictly lobar hemorrhages is based on the lobar predilection of CAA pathology and recurrent ICHs,[48] an anatomic distribution that contrasts to the predominantly deep hemispheric and brainstem locations (or mixed lobar and deep) typically favored by ICHs due to hypertensive arteriopathy.[49] Since CAA typically spares these deep territories, the presence of any hemorrhagic lesions in basal ganglia, thalamus, or pons precludes the probable CAA diagnosis.

Given these considerations, we have hypothesized that MRI markers might fall into two frameworks: (a) cardinal MRI markers, which carry important and specific diagnostic weight, likely include the strong hemorrhagic signatures of CAA (but other candidate MRI markers will be explored), and are useful in defining the probable CAA category; and (b) supporting MRI markers, which might be less specific for CAA but enhance diagnostic sensitivity by highlighting additional individuals not meeting the hemorrhagic criteria for CAA, thus generating a more useful "possible CAA" diagnosis category. The combination of cardinal and supporting MRI markers that retain and further improve the accuracy of the probable and possible CAA diagnoses will be validated in the Boston criteria v2.0. Diagnostic performance analysis in this setting, will govern how cardinal and supporting MRI markers will be applied within the Boston criteria v2.0. Our goal is to achieve the optimal sensitivity and specificity for the probable CAA category, while using the supporting MRI markers to increase sensitivity without overly compromising specificity for possible CAA, which by definition will not have additional cardinal CAA hemorrhagic features beyond a single lobar ICH or single strictly lobar CMB. Using the category terminology applied to other brain disorders such as Alzheimer's disease,[50, 51] *definite* CAA based on full autopsy, and an additional category of *probable CAA with supporting pathology* based on clinical scenarios of having limited brain tissue from biopsy or hematoma evacuation will also be retained in the Boston criteria v2.0 (Table 1).

Based on the available sample size, we have undertaken pre-specified cohort splitting: (1) a derivation cohort – MGH, Boston cases from inception to 2012 (~178 patients); (2) temporal external validation cohort - MGH, Boston cases from 2012-2018 (~120 patients); and (3) geographical external validation cohort – non-Boston cases (~85 patients). In

summary, our overall approach will be to: (a) pre-specify variables and statistical cut-offs; (b) examine univariable and multivariable associations quantified as odds ratios (ORs); (c) then assess classification measures (sensitivity, specificity etc.) for each MRI biomarker individually, in relation to the CAA diagnosis reference standard on neuropathology in a derivation cohort; (d) select the MRI biomarkers strongly associated with CAA diagnosis for inclusion in provisional rule in Boston criteria v2.0; and (e) validate the criteria using appropriate metrics and models.

Within the derivation cohort, we will assess classification measures (sensitivity, specificity) and univariable logistic regression (ORs with 95%CI) for each MRI biomarker individually, in relation to CAA diagnosis reference standard on neuropathology. Sensitivity, specificity, positive predictive value (PPV) (Disease+|Test+) and negative predictive value (NPV) (Disease-|Test-), will be calculated for each potential MRI marker. For continuous or ordinal variables, these will be derived from receiver operating characteristic (ROC) analyses. Predictors of pathologically-proven CAA (the reference standard, as defined above) from univariable analyses will then be entered into a multivariable logistic regression analysis followed by backward elimination of non-significant predictors ($p<0.05$). We will also apply classification and regression tree analyses (CART) which may provide better predictions in the setting of non-linearity and interactions between variables.

The final form of the criteria to be tested in the validation phase will depend on the number of significant variables, their explanatory power, their relationship to each other, and the feasibility of collection in routine research and clinical practice. Our primary objective is to create a set of criteria for probable CAA that firstly have high specificity (ideally ≥90%), while secondly maximizing sensitivity to the extent possible given the constraint of the required high specificity. In another set of analyses, we will draft criteria for possible CAA that weigh sensitivity and specificity equally. As part of the final Boston Criteria v.2.0 we will also provide specific guidelines and classification rules for each MRI marker included as a component, according to current consensus guidelines. Depending on the results of our analyses, the criteria may be operationalized as a multi-component risk score, a simple threshold based on one or two variables, or a decision tree, in secondary exploratory models. Secondary analyses will be stratified by the pathological reference standard source (autopsy versus biopsy or hematoma evacuation)[52], according to time between MRI and tissue sampling,

and across predominant clinical presentation (ICH versus non-ICH also including presentations with transient focal neurological episodes and cognitive decline separately).[22]

The provisional criteria from the derivation cohort will then be tested in the external validation cohorts. We will test the diagnostic prediction model performance and assess discrimination using c-statistic and ROC curves in each validation cohort. We will test the discrimination of version 2.0 vs. 1.5 and 1.0 by comparing c statistics.

Further alternative model-building approaches, e.g. involving machine learning of this dataset will be considered for follow-up projects.

Secondary analyses and focussed hypotheses to be further explored

The current project and protocol focus on the main effort to update and validate the Boston criteria for CAA diagnosis. As it's becoming evident, in many steps of the project we are accepting certain assumptions that are potentially testable in more focussed projects and are of clinical relevance. Hence, we plan to undertake the following specific secondary analyses using the current cohort in follow-up publications (detailed protocols will be developed separately):

(a) We will investigate the diagnostic yield and potential classification schemes for cases with mixed lobar/deep CMB/ICH, using number of lobar and non-lobar CMBs in univariable and multivariable analysis, testing different cut-offs, lobar-to-deep CMB ratios and the presence or absence of other markers of small vessel disease (e.g. basal ganglia vs. centrum semiovale EPVS, deep vs. cortical cerebellar CMBs etc.), to potentially develop criteria for this smaller but still important patient subset in a future pooled analysis. Within this secondary analysis, we will also test differential classification schemes for CMBs which are located in the deep periventricular white matter. According to the MARS rating tool,[28] these are classified as deep CMBs (i.e. non-lobar), but in current practise often hemorrhagic lesions are considered deep only when involving the basal ganglia, thalamus, internal capsule and brainstem.[13]

(b) In addition to clinical populations and hospital settings, we will also explore the diagnostic yield in non-clinical settings by applying the criteria to individuals from population-based studies in sub-analyses (the detailed protocol for these will be developed separately).

(c) We will explore ways to stratify the diagnostic yield of CAA diagnostic criteria according to different cut-offs of the our neuropathologic reference standard (e.g. compare Vonsattel≥2 to Vonsattel=1).

Discussion

The Boston Criteria have become the basis for clinical decision-making and research in CAA, substantially influencing and moving the field forward.[13] Validation studies for the current Boston Criteria to date have some limitations, mainly reliance on hospital-based cohorts, small sample sizes, testing of a limited selection of CAA MRI biomarkers and CAA-related clinical presentations, and lack of internal and external validation.[13] These concerns notwithstanding, data suggest that current diagnostic criteria for probable CAA have 1) reasonably high specificity for pathologic CAA across different settings, and 2) high sensitivity among patients presenting with symptomatic hemorrhages and possibly lower sensitivity for non-ICH presentations.[13, 22] Application of the current criteria has identified a subset of patients with distinct genetics, risk factors, and prognosis, suggesting that they have served the field well.

As a next step towards updating and improving the diagnosis of CAA, and building on the established Boston criteria, a multicenter effort to update and extensively validate the Boston Criteria is being undertaken by the International CAA Association. This project will analyze all available clinical and neuroimaging data from individuals age ≥50 with any of the potential CAA-related clinical presentations, MRI imaging, and histopathologic diagnoses. The goal is to produce and validate a "version 2.0" of the Boston Criteria that will meet the needs of clinicians and investigators and help maintain the rapid pace of progress towards better treatment of CAA.[13] Our hypothesis is that a new version of the diagnostic criteria incorporating markers discovered since 2011 will exhibit higher sensitivity and specificity than criteria 1.0 or 1.5.

From a clinical standpoint, the Boston criteria 2.0 will provide a optimized and simplified combination of relatively specific cardinal markers and less specific supporting markers for diagnosing CAA in routine clinical care. From a research standpoint, the Boston criteria can help in exploring which CAA markers have sufficiently high sensitivity and specificity to be used for the selection of patients in CAA trials and observational or mechanistic studies, across the clinical-imaging spectrum of the disease. Limitations of the current effort are mainly those inherent to a retrospective observational study that relies on clinical MRI markers and

availability of neuropathologic tissue. First, there is potential selection bias due to the requirement for MRIs done as part of clinical care. In addition, the availability of neuropathological samples tends to bias the sample towards more severe underlying CAA leading either to death (and hence autopsy), rapidly-progressing clinical symptoms (leading to brain biopsy), or large ICH (leading to hematoma evacuation). There is hence the risk for partial verification bias since not all potentially suspected CAA patients with MRI undergo the reference standard. Given the retrospective design of the study and the use of clinical MRI scans, blood-sensitive sequences parameters will vary (e.g. T2*-GRE vs. SWI), potentially impacting the accuracy, despite our analytic approach in adjusting for this. Other methodological aspects that might introduce bias include the delay between MRI and neuropathological sampling. To increase the sample size of the study, we haven't established a maximum delay between MRI and histopathology. Autopsy in particular may be performed years after the MRI, artificially reducing the sensitivity of the MR biomarkers and hence the criteria. Indeed, the ideal diagnostic study compares the index test against a reference standard acquired at the same or similar time. Delayed tissue sampling can conversely lead to a false positive reference standard due to interval development of CAA; hence we are planning to include time to tissue sampling in a sensitivity analysis. Similarly, the temporal validation cohort (i.e. post-2012) could pose a challenge due to the evolution of MRI methods over time. However, deriving criteria using a cohort before 2012 and utilizing temporal validation, also has advantages, since the criteria validation will be performed on the most up-to-date patient sample and thus have the closest resemblance to current practice. Lastly, the age cut-off of 50 years is somewhat arbitrary (as were the age thresholds of previous versions of the Boston criteria), but is representative of the age range where the question of CAA is most commonly encountered in clinical practice.

Summary and conclusions

This project described here is taking place at a time of great progress towards understanding and treating CAA - and incidentally, around the 20th anniversary of the original publication of the Boston criteria for CAA. Taking advantage of the momentum in the field, the project will help galvanize the collaborative culture of the CAA community, encouraging international research initiatives and will lead to a multi-authored research publication of the main findings. This work is a next step towards updating and improving CAA diagnosis, that will meet the needs of clinicians and investigators.[13]

Tables

Table 1. The Original (*Version 1.0*) and Modified Boston Criteria for Cerebral Amyloid Angiopathy (*Version 1.5*). Modifications appear in *Italics*.

	Original Boston Criteria (*Version 1.0*)	**Modified Boston Criteria (*Version 1.5*)**
1. Definite CAA	Full post-mortem examination demonstrating: • Lobar, cortical, or cortical-subcortical hemorrhage • Severe CAA with vasculopathy • Absence of other diagnostic lesion	No modification compared to Version 1.0
2. Probable CAA with supporting pathology	Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating: • Lobar, cortical, or cortical-subcortical hemorrhage (including ICH and/or CMB) • Some degree of CAA in specimen • Absence of other diagnostic lesion	No modification compared to Version 1.0
3. Probable CAA	Clinical data and MRI or CT demonstrating: • Multiple hemorrhages (ICH, CMB) restricted to lobar, cortical, or cortical-subcortical regions (cerebellar hemorrhage allowed), • Age ≥55 years • Absence of other cause of hemorrhage*	Clinical data and MRI or CT demonstrating: • Multiple hemorrhages (ICH, CMB) restricted to lobar, cortical, or cortical-subcortical regions (cerebellar hemorrhage allowed), *OR* • *Single lobar, cortical, or cortical-subcortical hemorrhage and cSS (focal or disseminated)* • Age ≥55 years • Absence of other cause of hemorrhage* or cSS
4. Possible CAA	Clinical data and MRI or CT demonstrating: • Single lobar, cortical, or cortical-subcortical ICH, CMB; • Age ≥55 years • Absence of other cause of hemorrhage*	Clinical data and MRI or CT demonstrating: • Single lobar, cortical, or cortical-subcortical ICH, CMB; *OR* • *Presence of cSS (focal or disseminated)* • Age ≥55 years • Absence of other cause of hemorrhage* or cSS

***Other causes of hemorrhage (differential diagnosis of lobar hemorrhages):** antecedent non-minor head trauma, hemorrhagic transformation of an ischemic stroke, arteriovenous malformation, hemorrhagic tumour, warfarin therapy with international normalisation ratio > 3, vasculitis

Table 2. Summary of the main steps required for the project.

Project stage	Definitions	Notes/Inclusion-Exclusion criteria
A. **Pathology databases searches or** **Research studies' databases**	Cases with histopathological evaluation for CAA (from brain biopsy, hematoma evacuation or autopsy)	-Age ≥50y at the time of presentation -Amount of pathology to reliably rate CAA (ideally >10 vessels in the sample) -Presented to stroke, neurology services or memory clinics with symptomatic ICH (any location), ischemic stroke, transient focal neurological symptoms or cognitive decline (due to clinical diagnosis of AD, MCI, VaD per local definitions or no clear cause) -Clinical presentation will be defined based on all available clinical and MRI data (see flowchart) -Exclude: non-minor head trauma, brain tumors, vascular malformations, coagulopathies causing the syndrome at presentation, hereditary CAA
B. **MRI availability**	-T2 and T2*-weighted or SWI sequences at the time of presentation (≤3 months) (T1, FLAIR, DWI also of interest)	-Exclude: cases without MRI -Exclude: cases without T2*-weighted or SWI MRI sequences -CAA-ri cases are eligible for inclusion if an MRI scan from a clinically quiescent period of the disease (before or after an acute episode) is available
C. **Data collection from eligible cases** (exclude cases if minimum datasets are not available)	Pathology data -CAA severity assessment -Other pathologies in the aging brain – to be decided (e.g. arteriolosclerosis, AD etc.) -Ask centers if a neuropathologist will participate	<u>Depending on center's capacity:</u> -Obtain copy of the pathology report -Re-rate CAA pathology if necessary, in order to generate Vonsattel score -Send representative photos from each case -Send histopathological slides Optional *Rate centrally a sub-set from each center for validation ** **Consensus post-mortem CAA rating scale: sub-projects in selected centers
	Demographic-clinical data	Minimum defined clinical and demographic details (age, hypertension, antithrombotic drug use, previous history of ICH) -Clinical presentation variables will include MMSE, MoCA, CDR etc. -Simple pre-specified variables (Excel database to be provided) – link data collection with other CAA association-driven projects +Optional database with more detailed variables (vascular risk factors, APOE, CSF, PiB-PET)
	MRI data -At the time of presentation	-Indications for the scans should be provided -Scans will be analysed centrally -All images to be sent to Boston in CDs or secure electronic transfer systems
D. Data to coordination center in MGH, Boston, USA		

CAA-ri: CAA-related inflammation, MMSE: Mini–Mental State Examination, MoCA: Montreal Cognitive Assessment, CDR: Clinical Dementia Rating Scale, CSF: Cerebrospinal Fluid; PiB-PET: Pittsburgh Compound B Positron Emission Tomography

Table 3. Vonsattel grading for CAA severity on neuropathology samples. This method scores the most advanced degree of CAA present within the specimen. Leptomeningeal and parenchymal vessels should be scored separately.

CAA severity	**Description**
Grade 0	Absence of amyloid-β staining in vessels
Grade 1	Presence of some patchy amyloid-β staining in an otherwise normal-appearing vessel
Grade 2	Complete replacement of the media by amyloid - wall is thickened
Grade 3	The vessel shows total replacement of the media with amyloid-β and cracking of the vessel wall that creates a "vessel-within-vessel" affecting at least 50% of the circumference of the vessel
Grade 4	Presence of an amyloid-laden vessel with scarring and fibrinoid necrosis, recognized as homogeneous discrete foci or segments of the vascular wall that contain smudgy eosinophilic material obscuring the cytoarchitecture.

Table 4. Summary of MRI markers of small vessel disease and CAA to be evaluated in the project, including their definition, ratings scales and important points/modifications in their assessment specifically for clinical use within the Boston criteria v.2.0.

MRI marker	Definition	Rating scale	Classification categories	Notes on specific classification rules
ICH				
CMBs				
cSS				
PVS				
WMH				
Posterior predominant WMH	Occipital predominance and posterior-to-frontal ratio			
WMH multispot pattern				

Figures

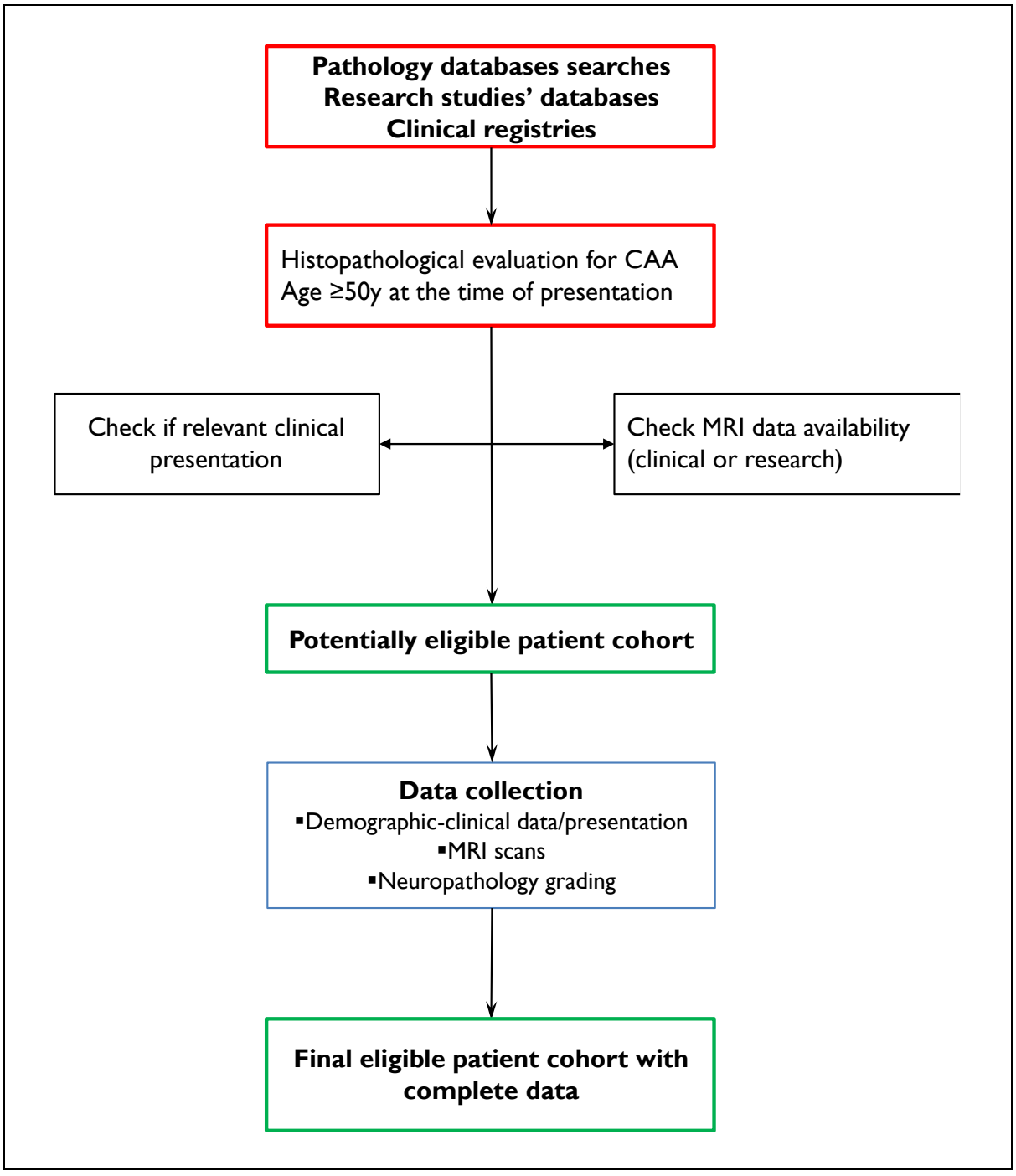

Figure 1. Practical flow chart of the project's main steps.

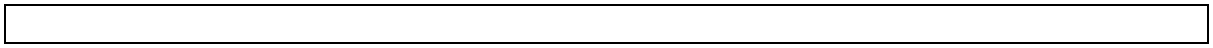

Figure 2. Path examples of CAA severity by Vonsattel rating system.

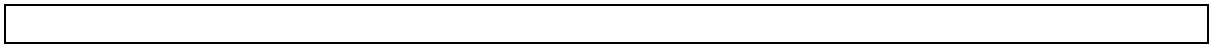

Figure 3. MRI biomarkers representative examples.

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