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Chapter 7

Descriptive analysis of the Boston criteria applied to a Dutch-type cerebral amyloid angiopathy population

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Abstract

Validation of the Boston criteria for the in vivo diagnosis of cerebral amyloid angiopathy (CAA) is challenging, because non-invasive diagnostic tests do not exist. Hereditary cerebral hemorrhage with amyloidosis- Dutch type (HCHWA-D) is an accepted monogenetic model of CAA and diagnosis can be made with certainty based on DNA analysis. The aim of this study was to analyze and refine the existing Boston criteria in HCHWA-D patients. We performed T2*-weighted MRI in 27 HCHWA-D patients to assess the presence and location of microbleeds (MBs), intracranial hemorrhages (ICHs), and superficial siderosis (SS). Using the Boston criteria, subjects were categorized as having: no hemorrhages, possible CAA, probable CAA, and hemorrhagic lesions not qualifying for CAA. The sensitivity of the Boston criteria was calculated separately using ICHs only and using ICHs and MBs. The sensitivity of the Boston criteria for probable CAA increased from 48% to 63% when MBs were included. For symptomatic subjects only, the sensitivity was 100%. No hemorrhages were identified in the deep white matter, basal ganglia, thalamus, or brainstem. SS, observed in six patients, did not increase the sensitivity of the Boston criteria in our study group. Our data show that using T2*-weighted MRI and including MBs increase the sensitivity of the Boston criteria. The exclusion of hemorrhages in the deep white matter, basal ganglia, thalamus, and brainstem does not lower the sensitivity of the Boston criteria.

Introduction

Cerebral amyloid angiopathy (CAA) is a common cerebrovascular pathology of the elderly and is caused by the deposition of amyloid-β in the media and adventitia of small- to medium-sized cerebral arteries. Brain autopsy studies demonstrated that CAA pathology occurs with a prevalence ranging from 2% at the age of 50 years old to 74% in subjects above 90 years old [1-7]. Moreover, 92% to 98.5% of Alzheimer's disease (AD) patients also suffer from CAA [1,7]. A distinct type of CAA with a genetic basis is called hereditary cerebral hemorrhage with amyloidosis- Dutch type (HCHWA-D). This autosomal dominant disease is caused by a single base mutation at codon 693 of the amyloid precursor protein gene on chromosome 21, and occurs in a limited number of families in the Dutch villages of Katwijk and Scheveningen [8]. The mutation leads to extensive amyloid-β deposition in meningocortical arterioles. The chemical composition and underlying pathology of these amyloid deposits is similar to that in sporadic CAA [9,10].

Clinically, both sporadic CAA and HCHWA-D are characterized by recurrent strokes and cognitive impairment [11]. The most common radiological manifestations of both sporadic CAA and HCHWA-D are microbleeds (MBs) and lobar intracerebral hemorrhage (ICH), caused by amyloid-β deposition leading to fragility and rupture of the vessel wall. Additionally, superficial siderosis (SS) has been described [12,13]. Apart from these hemorrhagic manifestations, CAA and HCHWA-D are characterized by white matter hyperintensities [14-16], and in a subset of patients CAA-related vascular inflammation has been reported [17].

A major problem with sporadic CAA is the absence of reliable, non invasive diagnostic tests. Currently, the only certain diagnosis is based on histological examination of brain tissue, and consequently in most cases the diagnosis is made only at post-mortem. The so-called 'Boston criteria' represented an effort to estimate the likelihood of the presence of CAA during life, with categories of *probable* and *possible* CAA based on the pattern of hemorrhagic lesions on neuroimaging studies (see appendix) [18,19]. According to these criteria, lobar, cortical, and corticosubcortical hemorrhages are suggestive for the presence of CAA. The presence of a single hemorrhage in these areas gives rise to the diagnosis *possible* CAA, whereas the presence of multiple hemorrhages in these areas is a requirement for *probable* CAA. Hemorrhages in the basal ganglia, thalamus, or brainstem, brain regions typically spared by CAA, are exclusions to the diagnosis of probable CAA.

The Boston criteria have been validated in only one study [20]. In that study, subjects were included who were older than 55 years, who had a primary lobar ICH, and in whom brain specimen and radiographic information was available. The study had several limitations. First, since only patients with symptomatic lobar ICH and pathologic brain specimens were included, it is uncertain whether the results can be extrapolated to other patient categories. Second, the radiographic documentation in the included patients was based on different radiological modalities (CT, T2-weighted MRI, T2*-weighted MRI), with different sensitivities for hemorrhagic lesions.

The aim of the present study was to analyze and refine the imaging components of the Boston criteria based on T2*-weighted MRI in a group of symptomatic and asymptomatic HCHWA-D patients. This analysis takes advantage of the ability of noninvasive genetic testing to diagnose HCHWA-D, allowing the results to be extended to patients without available neuropathologic specimens.

Materials and Methods

Participants

Subjects were identified and selected via the outpatient clinic of the Department of Neurology of the Leiden University Medical Center based on DNA analysis for confirmation of the codon 693 mutation in the amyloid-β precursor protein (AβPP) gene. Twenty-seven DNA-proven HCHWA-D mutation carriers were included in the present study. These subjects had a mean age of 49.4 years (range 34 to 63 years). Fourteen of them were female (mean age 49.5 y, range 34 to 63) and 13 male (mean age of 49.4 y, range 37 to 60). Both symptomatic (n=15) and asymptomatic (n=12) mutation carriers were included. Subjects were considered symptomatic when they had clinically experienced one or multiple strokes. The patients did not experience new symptoms in the period directly preceding the MRI examination. The ethics committee of our institution approved the study, and written informed consent was obtained from all subjects.

MRI

Image acquisition

MRI was performed on a 1.5T MR whole body system (Philips Medical Systems, Best, the Netherlands). All images were obtained in the axial plane parallel to the inferior border of the genu and splenium of the corpus callosum. In all subjects dual spin-echo (TR/TE1/ TE2 2500-3000/23-27/120 ms, flip angle 90°, slice thickness 3 mm, 48 slices, no interslice gap, field of view 220 x 220 mm, matrix size 256 x 204) and T2*-weighted gradient echo (TR/ TE: 2593- 3070/ 45-48 ms, flip angle 60°, slice thickness 6 mm with a 0.6-mm interslice gap, field of view 220 x 220 mm, 188/256 matrix size) sequences were performed.

Image Analysis

For the detection of hemorrhagic lesions, T2* and T2-weighted sequences were evaluated. Hemorrhagic lesions that were included were MBs, ICHs, and SS. MBs were defined as focal, nodular areas of signal loss in brain parenchyma on T2*-weighted gradient-echo images that are invisible or smaller on T2-weighted spin echo images ("blooming effect"). MBs are not associated with parenchymal defects and therefore do not show high signal within the area of signal void on spin-echo images. It is possible that in the area of signal loss on T2* images a few voxels do show some signal, due to ringing artifacts (consequence of spread signal function), but this is not found on the corresponding spin-echo images. MBs were differentiated from other causes of signal voids on T2* as follows; a) vascular flow voids: do not show blooming effect on susceptibility images, tubular appearance; b) cavernomas: area of high signal within the signal void on spin-echo images, in larger cavernomas this is typically popcorn shaped; c) calcifications in the globus pallidus: bilateral hypointensities in the globus pallidus; d) iron or calcification deposition in the basal ganglia: bilateral diffuse or focal areas of reduced signal intensity in the basal ganglia. Acute or subacute ICHs were not observed in our patients. Only remote, resorbed ICHs were observed and they were defined as parenchymal defects with evidence of hemosiderin in their wall.

The presence, location and number of MBs and ICHs were assessed for each of the following locations: cortical/corticosubcortical area, deep white matter (all other white matter), basal ganglia, thalamus, brainstem, and cerebellum [21]. Cortical and corticosubcortical lesions were defined as lesions occurring in or abutting the cortical gray matter respectively. Deep white matter lesions were

defined as lesions occurring in the white matter not abutting the gray matter. Furthermore the presence of SS was assessed, which is defined as linear residues of blood in the superficial layers of the cerebral cortex and in the subarachnoid space [12]. Figure 1 shows examples of how these different lesions appear on T2*-weighted images in our subjects.

Based on the number and location of hemorrhages (excluding SS) all subjects were subdivided into the following categories: no hemorrhages, possible CAA, probable CAA, and hemorrhagic lesions not qualifying for CAA.

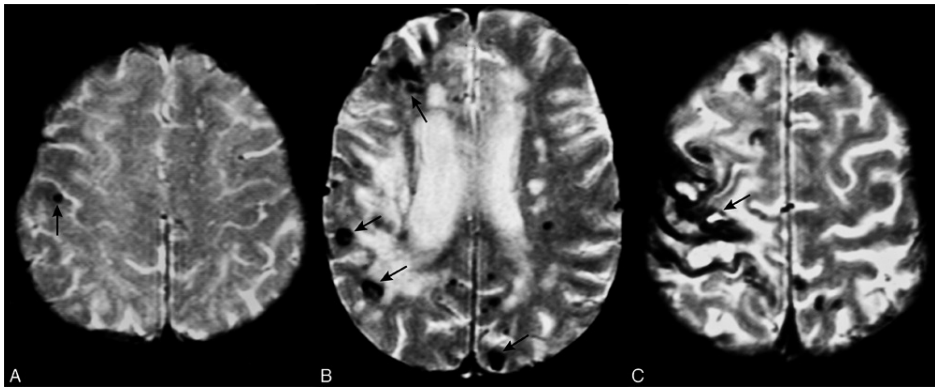

Figure 1: T2*-weighted images of HCHWA-D mutation carriers. Image 1A shows an MB in the cortical/corticosubcortical brain region (arrow), image 1B shows several ICHs in the cortical/corticosubcortical brain region (arrows), and image 1C shows SS (arrow).

Statistics

An independent-samples t-test was used to assess whether the group with and without hemorrhagic lesions differed in age. The sensitivity for the different subject categories was calculated by dividing the number of subjects correctly diagnosed with CAA according to the Boston criteria by this same number plus the number of subjects with the mutation not diagnosed with CAA according to the Boston criteria. In this cross-sectional study design, statistical analyses were performed with the Statistical Package of Social Sciences (SPSS), version 14.0.2.

Results

Of the 27 HCHWA-D mutation carriers eighteen subjects (66.7%) demonstrated MBs on MRI, in 16 (59.3%) of whom also ICHs were detected. All patients with ICHs had MBs. Nine of the HCHWA-D mutation carriers did not show hemorrhagic lesions. Patients without any hemorrhagic lesion were younger (M = 41.56, SE = 2.72) than patients with hemorrhagic lesions (M = 53.67, SE = 1.12). This difference was significant $t(25) = -4.91$, $p<.05$. Table 1 shows the prevalence and median of MBs and ICHs in the HCHWA-D patients with MBs/ICHs. Figure 2A shows the distribution of all 1074 detected MBs in the brain, showing involvement of all cerebral lobes. No MBs were detected in the deep white matter, basal ganglia, thalamus or brainstem. Figure 2B shows the distribution of all 129 detected ICHs, also showing involvement of all cerebral lobes. Again, the deep white matter, basal ganglia, thalamus and brainstem remained unaffected. This is also shown in table 2 which displays the number of HCHWA-D patients with hemorrhagic lesions and SS in six different brain regions.

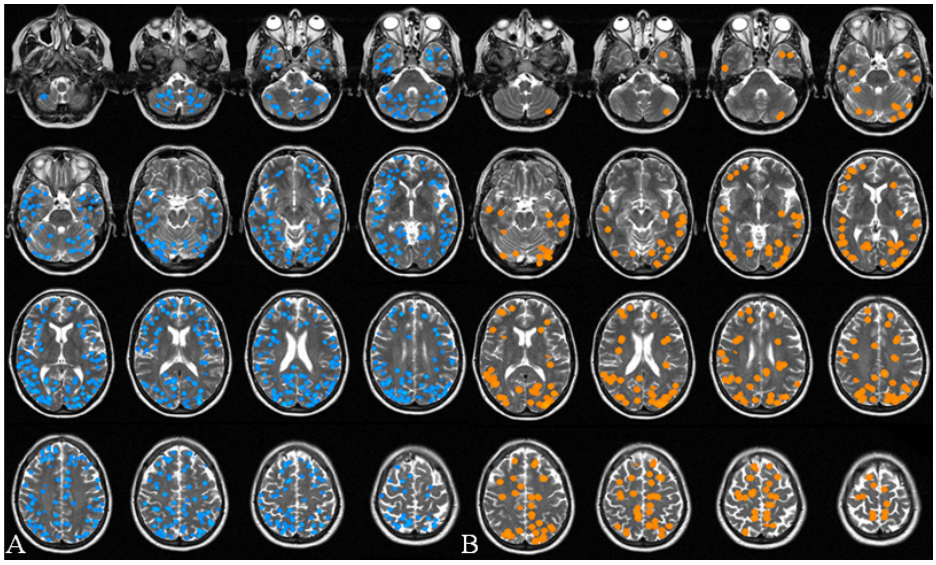

Figure 2: Image 2A shows the location of all 1074 MBs in the 18 HCHWA-D mutation carriers with MBs projected in one brain. Image 2B shows the location of all 129 ICHs in the 16 HCHWA-D mutation carriers with ICHs projected in one brain.

Table 1: MB and ICH characteristics of the HCHWA-D group with MBs/ICHs.

	MB	ICH
Mean age (range)	53.4 (46-63)	54.1 (47-63)
Male/female	10/8	9/7
Prevalence	66.7% (18/27)	59.3% (16/27)
Prevalence temporal lobe	55.6% (15/27)	37.0% (10/27)
Prevalence parietal lobe	63.0% (17/27)	44.4% (12/27)
Prevalence frontal lobe	63.0% (17/27)	40.7% (11/27)
Prevalence occipital lobe	51.9% (14/27)	55.6% (15/27)
Prevalence cerebellum	51.9% (14/27)	18.6% (5/27)
Prevalence basal ganglia	0% (0/27)	0% (0/27)
Prevalence thalamus	0% (0/27)	0% (0/27)
Prevalence brain stem	0% (0/27)	0% (0/27)
Total nr.	1074	129
Median total (25^{th} - 75^{th} percentile)	30 (11-101)	8 (4-12)
Median temporal lobe (25^{th} - 75^{th} percentile)	7 (1-18)	1 (0-2)
Median parietal lobe (25^{th} - 75^{th} percentile)	6.5 (2-24)	2.5 (0-4)
Median frontal lobe (25^{th} - 75^{th} percentile)	5 (2-21)	2 (0-4)
Median occipital lobe (25^{th} - 75^{th} percentile)	4.5 (1-16)	1 (1-2)
Median cerebellum (25^{th} - 75^{th} percentile)	5 (1-11)	0 (0-2)
Median basal ganglia	0	0
Median thalamus	0	0
Median brain stem	0	0

Table 2: Number of patients with hemorrhagic lesions and superficial siderosis in the different brain regions.

	ICHs	MBs	SS
Cortical/corticosubcortical	16	18	6
White matter	0	0	NA
Basal ganglia	0	0	NA
Thalamus	0	0	NA
Brain stem	0	0	NA
Cerebellum	5	14	0

Based on the criteria for possible and probable CAA (including MBs and ICHs), all HCHWA-D subjects with at least one MB or ICH, fulfilled the Boston criteria. Table 3 shows the sensitivity of the Boston criteria when excluding and including MBs. In the entire HCHWA-D group, the number of subjects that qualified for CAA (both possible and probable CAA) when MBs are not taken into account was lower (59% of which 11% possible and 48% probable CAA) than when MBs were included (67% of which 4% possible CAA and 63% probable CAA). For the 15 symptomatic subjects, the sensitivity of the Boston criteria was 93% (6% possible CAA and 87% probable CAA) with MBs not taken into account and 100% (0% possible CAA and 100% probable CAA) with MBs included.

Table 3: Sensitivity of the Boston criteria excluding and including MBs.

Sensitivity	Possible + probable CAA (only probable CAA) without inclusion of MBs	Possible + probable CAA (only probable CAA) with inclusion of MBs
Whole HCHWA-D population, n = 27	59% (48%)	67% (63%)
HCHWA-D patients with hemorrhagic lesions, n = 18	89% (72%)	100% (94%)
Symptomatic HCHWA-D patients, n = 15	93% (87%)	100% (100%)

In six of the 16 patients with ICHs also SS was found (table 2). SS was found in 22.2% of all HCHWA-D subjects and in 37.5% of the HCHWA-D subjects with ICHs. In the group of patients studied, SS was only found in patients with both ICHs and MBs, and always in the direct vicinity of a superficial ICH or MB.

Discussion

The main findings in our study are: 1) using T2*-weighted MRI, the Boston criteria have a high sensitivity for detection of lesions caused by CAA, 2) the sensitivity of the Boston criteria increases when MBs are included, and 3) there is no loss in sensitivity conferred by excluding subjects with hemorrhages in the deep white matter, basal ganglia, thalamus, or brainstem. SS is relatively

common in our population but did not influence the sensitivity of the Boston criteria in the studied subjects.

In our entire group of HCHWA-D patients, T2*-weighted MRI allowed detection of hemorrhagic lesions in the majority (67%), which all fulfilled the Boston criteria. The sensitivity in patients with MBs and in symptomatic patients was 100%. MBs were the most prevalent and consistent hemorrhagic manifestation of CAA and were present in all patients with hemorrhagic lesions. In most patients with hemorrhagic lesions (89%), ICHs were found in addition to MBs. Based on the higher prevalence of MBs, and the fact that ICHs did not occur without MBs, the data suggest that the sensitivity of the Boston criteria is increased using T2*-weighted MRI for MB detection relative to CT scanning and clinical history alone.

In the previous validation study of Knudsen et al., all 13 of the patients diagnosed with probable CAA (100%) and 16 of the 26 diagnosed with possible CAA (62%) based on the Boston criteria were neuropathologically confirmed to have CAA [20]. Inherent to performing validation studies of clinical diagnostic criteria in sporadic CAA patients is the difficulty to obtain final proof of the presence of the disease, since obtaining a sample of brain tissue, which is a requisite for making the final diagnosis, is not part of the clinical routine in patients presenting with hemorrhagic strokes. A major advantage of our study design was the possibility of assessing the presence of the disease based on DNA testing and our access to HCHWA-D families, in whom the presence of the disease was guaranteed.

Another limitation of the study by Knudsen et al. was the heterogeneity of imaging studies that were used for categorizing patients according to the Boston criteria. CT alone was used in 17 patients, MRI without T2*-weighted MRI sequences in 7 patients, and MRI with T2*-weighted sequences in 15 patients [20]. Given the difference in sensitivity of these techniques for hemorrhagic lesions in the brain, they would be expected to influence the sensitivity of the Boston criteria, particularly with regard to detection of MBs.

The Boston criteria were developed and validated based on a population of patients who presented with clinically symptomatic ICH [19,20]. However, it has been demonstrated in population-based studies that especially MBs often occur in asymptomatic individuals too [22]. Currently it is unknown whether the Boston criteria have any diagnostic value in asymptomatic individuals with hemorrhagic lesions. It is, for instance, conceivable that the pattern of hemorrhages that is observed in symptomatic patients differs from the pattern

in asymptomatic patients. Our study does not permit answering this question, since in only three asymptomatic patients hemorrhagic lesions were observed.

The current analysis helps to operationalize the definition of hemorrhagic lesions that qualify for evidence of CAA. According to the original Boston criteria, observation of hemorrhagic lesions with a cortical, corticosubcortical, and lobar distribution is required to meet the Boston criteria for possible or probable CAA (appendix). In the present study, we defined cortical/corticosubcortical lesions as lesions occurring in the cortex or abutting it and all observed ICHs and MBs were found to fulfill these location criteria (fig. 1A, 1B and fig. 2). This observation supports inclusion of such lesions as bona fide radiological markers for the purpose of diagnosing probable CAA. Conversely, the absence of any ICHs or MBs in basal ganglia, thalamus, brainstem and deep white matter not close to the corticosubcortical junction argues that these regions are generally spared in CAA, even in patients with large numbers of MBs. The stipulation in the Boston criteria that hemorrhages be restricted to cortical or corticosubcortical regions (with cerebellar hemorrhages allowed, but excluding patients with any MBs in basal ganglia, thalamus, or brainstem) therefore appears to be reasonable and to result in relatively little loss of diagnostic sensitivity. The reason that CAA pathology and CAA-related hemorrhages tend to spare the basal ganglia, thalamus, and brainstem has not been fully elucidated, but may reflect the interstitial fluid drainage pathways by which ß-amyloid is postulated to gain access to the perivascular space where CAA originates [23].

Linn et al. described SS in three sporadic CAA patients and suggested that SS should be interpreted as evidence for CAA [12]. However, whether SS is another hemorrhagic manifestation that is suggestive for the diagnosis CAA has not been evaluated systematically. SS has also been observed in other conditions, such as CNS tumors, head trauma, arteriovenous malformations, and intracranial aneurysms [24]. Our study showed that SS is common in a hereditary form of CAA, although including SS as a hemorrhagic lesion qualifying for CAA did not change the sensitivity of the Boston criteria in our patients. Furthermore, we observed that SS was in all cases adjacent to a superficial ICH or MB, suggesting that it resulted from spontaneous evacuation of parenchymal blood collections to the subarachnoid space.

We note several limitations of this study. The used population was limited to 27 subjects. The reason for this small population is the limited size of the HCHWA-D population as a whole. HCHWA-D is found only in a limited

number of families (four) originating from the villages of Katwijk (136 patients) and Scheveningen (14 patients) [8]. Furthermore, our results were obtained in patients with HCHWA-D, a particularly severe form of CAA. Although HCHWA-D appears similar to sporadic CAA in most respects other than its earlier age of onset [25], the generalizability of these findings to sporadic CAA remains to be established. We also note that since all subjects in this study had CAA, the results pertain only to the sensitivity of the Boston criteria, not their specificity. Finally, we note that recently developed T2*-weighted MRI methods such as use of thin slices and post-processing techniques appear to increase the sensitivity of MRI for MB detection [26,27]. Further studies will be required to validate the sensitivity and specificity of the Boston criteria using these emerging MRI methods.

Conclusion

Our data show that using T2*-weighted MRI in patients with proven CAA, the Boston criteria have a high sensitivity for the interpretation of a hemorrhagic lesion as a manifestation of CAA. The sensitivity of the criteria is increased by inclusion of corticosubcortical MBs and is not reduced by excluding hemorrhagic lesions in the deep white matter, basal ganglia, thalamus, or brainstem.

Appendix: Boston Criteria for cerebral amyloid angiopathy [18,19].

1. Definite CAA
   Full postmortem examination demonstrating:
   - Lobar, cortical, or corticosubcortical hemorrhage
   - Severe CAA with vasculopathy
   - Absence of other diagnostic lesion

2. Probable CAA with supporting pathology
   Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:
   - Lobar, cortical, or corticosubcortical hemorrhage
   - Some degree of CAA in specimen
   - Absence of other diagnostic lesion

3. Probable CAA
   Clinical data and MRI or CT demonstrating:
   - Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
   - Age ≥ 55 years
   - Absence of other cause of hemorrhage

4. Possible CAA
   Clinical data and MRI or CT demonstrating:
   - Single lobar, cortical, or corticosubcortical hemorrhage
   - Age ≥ 55 years
   - Absence of other cause of hemorrhage

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