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 >90 years old.1-7 Moreover, 92% to 98.5% of patients with Alzheimer disease also have 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 meningo cortical 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, noninvasive 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 postmortem. The so-called “Boston criteria” represented an effort to estimate the likelihood of the pres-
ence of CAA during life with categories of probable and possible CAA based on the pattern of hemorrhagic lesions on neuroimaging studies (see Appendix). 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. In that study, subjects were included who were >55 years, who had a primary lobar ICH, and in whom brain specimen and radiographic information was available. The study had several limitations. First, because only patients with symptomatic lobar ICH and pathological brain specimen 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 patients with HCHWA-D. 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.

Methods

Participants

Subjects were identified and selected through 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 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 years; range, 34 to 63 years) and 13 male (mean age, 49.4 years; range, 37 to 60 years). 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.

Magnetic Resonance Imaging

Image Acquisition

MRI was performed on a 1.5-T 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 to 3000/23 to 27/120 ms, flip angle 90°, slice thickness 3 mm, 48 slices, no interslice gap, field of view 220×220 mm, matrix size 256×204) and T2*-weighted gradient echo (TR/TE: 2593 to 3070/45 to 48 ms, flip angle 60°, slice thickness 6 mm with a 0.6-mm interslice gap, field of view 220×220 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: (1) vascular flow voids: do not show blooming effect on susceptibility images, tubular appearance; (2) cavernomas: area of high signal within the signal void on spin-echo images, in larger cavernomas this is typically popcorn-shaped; (3) calcifications in the globus pallidus: bilateral hypointensities in the globus pallidus; and (4) 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, resolved 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. 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. 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.

Statistics

An independent-samples t test was used to assess whether the group with and without hemorrhagic lesions differed in age. The sensitivity

Figure 1. T2*-weighted images of HCHWA-D mutation carriers. A, An MB in the cortical/corticosubcortical brain region (arrow); B, several ICHs in the cortical/corticosubcortical brain region (arrows); C, SS (arrow).
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, 18 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 (mean, 41.56 years; SE, 2.72) than patients with hemorrhagic lesions (mean, 53.67 years; SE, 1.12). This difference was significant (t[25] = 4.91, P < 0.05). Table 1 shows the prevalence and median of MBs and ICHs in the patients with HCHWA-D with hemorrhagic lesions.

Table 1. MB and ICH Characteristics of the HCHWA-D Group With MBs/ICHs

<table>
<thead>
<tr>
<th></th>
<th>MB</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>53.4 (46–63)</td>
<td>54.1 (47–63)</td>
</tr>
<tr>
<td>Male/female</td>
<td>10/8</td>
<td>9/7</td>
</tr>
<tr>
<td>Prevalence</td>
<td>66.7% (18/27)</td>
<td>59.3% (16/27)</td>
</tr>
<tr>
<td>Prevalence in temporal lobe</td>
<td>55.6% (15/27)</td>
<td>37.0% (10/27)</td>
</tr>
<tr>
<td>Prevalence in parietal lobe</td>
<td>63.0% (17/27)</td>
<td>44.4% (12/27)</td>
</tr>
<tr>
<td>Prevalence in frontal lobe</td>
<td>63.0% (17/27)</td>
<td>40.7% (11/27)</td>
</tr>
<tr>
<td>Prevalence in occipital lobe</td>
<td>51.9% (14/27)</td>
<td>55.6% (15/27)</td>
</tr>
<tr>
<td>Prevalence in cerebellum</td>
<td>51.9% (14/27)</td>
<td>18.6% (5/27)</td>
</tr>
<tr>
<td>Prevalence in basal ganglia</td>
<td>0% (0/27)</td>
<td>0% (0/27)</td>
</tr>
<tr>
<td>Prevalence in thalamus</td>
<td>0% (0/27)</td>
<td>0% (0/27)</td>
</tr>
<tr>
<td>Prevalence in brainstem</td>
<td>0% (0/27)</td>
<td>0% (0/27)</td>
</tr>
<tr>
<td>Total no.</td>
<td>1074</td>
<td>129</td>
</tr>
<tr>
<td>Median total (25th–75th percentile)</td>
<td>30 (11–101)</td>
<td>8 (4–12)</td>
</tr>
<tr>
<td>Median temporal lobe (25th–75th percentile)</td>
<td>7 (1–18)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>Median parietal lobe (25th–75th percentile)</td>
<td>6.5 (2–24)</td>
<td>2.5 (0–4)</td>
</tr>
<tr>
<td>Median frontal lobe (25th–75th percentile)</td>
<td>5 (2–21)</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>Median occipital lobe (25th–75th percentile)</td>
<td>4.5 (1–16)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>Median cerebellum (25th–75th percentile)</td>
<td>5 (1–11)</td>
<td>0 (0–2)</td>
</tr>
<tr>
<td>Median basal ganglia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median thalamus</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median brainstem</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. No. of Patients With Hemorrhagic Lesions and SS in the Different Brain Regions

<table>
<thead>
<tr>
<th></th>
<th>ICHs</th>
<th>MBs</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical/corticosubcortical</td>
<td>16</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>White matter</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Brainstem</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>5</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

NA indicates not applicable.

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

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

In 6 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 patients with HCHWA-D, 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. Inherent to performing validation studies of clinical diagnostic criteria in patients with sporadic CAA is the difficulty to obtain final proof of the presence of the disease, because 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. 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. However, it has been demonstrated in population-based studies that especially MBs often occur in asymptomatic individuals too. 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, because in only 3 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 (Figures 1A–B and 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 are 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 β-amyloid is postulated to gain access to the perivascular space where CAA originates.
Linn et al described SS in 3 patients with sporadic CAA and suggested that SS should be interpreted as evidence for CAA. 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 central nervous system tumors, head trauma, arteriovenous malformations, and intracranial aneurysms. Our study showed that SS is common in a hereditary manifestation that is suggestive for the diagnosis CAA has not been evaluated systematically. SS has also been observed in other conditions such as central nervous system 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 (4) originating from the villages of Katwijk (136 patients) and Scheveningen (14 patients). 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 because 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 postprocessing techniques appear to increase the sensitivity of MRI for MB detection. 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 CAA

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

**Probable CAA With Supporting Pathology**
- Clinical data and pathological tissue (evacuated hematoma or cortical biopsy) demonstrating:
  - Lobar, cortical, or corticosubcortical hemorrhage
  - Some degree of CAA in specimen
  - Absence of other diagnostic lesion

**Probable CAA**
- Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
- Age ≥ 55 years
- Absence of other cause of hemorrhage

**Possible CAA**
- Single lobar, cortical, or corticosubcortical hemorrhage
- Age ≥ 55 years
- Absence of other cause of hemorrhage

Disclosures
None.

References


Descriptive Analysis of the Boston Criteria Applied to a Dutch-Type Cerebral Amyloid Angiopathy Population
Sanneke van Rooden, Jeroen van der Grond, Rivka van den Boom, Joost Haan, Jennifer Linn, Steven M. Greenberg and Mark A. van Buchem

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