Alzheimer's & Dementia 11 (2015) 1480-1488

Featured Article

Diagnostic value of lobar microbleeds in individuals without intracerebral hemorrhage

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Abstract

Introduction: The Boston criteria are the basis for a noninvasive diagnosis of cerebral amyloid angiopathy (CAA) in the setting of lobar intracerebral hemorrhage (ICH). We assessed the accuracy of these criteria in individuals with lobar microbleeds (MBs) without ICH.

Methods: We identified individuals aged >55 years having brain magnetic resonance imaging (MRI) and pathological assessment of CAA in a single academic hospital and a community-based population (Framingham Heart Study [FHS]). We determined the positive predictive value (PPV) of the Boston criteria for CAA in both cohorts, using lobar MBs as the only hemorrhagic lesion to fulfill the criteria.

Results: We included 102 individuals: 55 from the hospital-based cohort and 47 from FHS (mean age at MRI 74.7 ± 8.5 and 83.4 ± 10.9 years; CAA prevalence 60% and 46.8%; cases with any lobar MB 49% and 21.3%; and cases with ≥2 strictly lobar MBs 29.1% and 8.5%, respectively). PPV of "probable CAA" (≥2 strictly lobar MBs) was 87.5% (95% confidence interval [CI], 60.4–97.8) and 25% (95% CI, 13.2–78) in hospital and general populations, respectively.

Discussion: Strictly lobar MBs strongly predict CAA in non-ICH individuals when found in a hospital context. However, their diagnostic accuracy in the general population appears limited.

Keywords: Cerebral amyloid angiopathy; Microbleed; Intracerebral hemorrhage; Boston criteria; Sensitivity; Specificity; Predictive value; Likelihood ratio

1. Introduction

Cerebral amyloid angiopathy (CAA) is caused by the accumulation of β-amyloid protein in the walls of cortical and leptomeningeal arteries [1–3]. It represents a common

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http://dx.doi.org/10.1016/j.jalz.2015.04.009
1552-5260/

etiology of lobar intracerebral hemorrhage (ICH) in the elderly [4,5]. Lobar microbleeds (MBs) are a hallmark of the disease when seen in patients with lobar ICH [6]. Although frequently associated with Alzheimer's disease (AD), CAA also independently contributes to cognitive impairment [7]. Indeed, lobar MBs are often identified in patients followed in memory clinics [8–10], where they may potentially serve as markers of CAA. However, lobar MBs are also found in the absence of any of the known above-described clinical features of the disease. Up to 19% of community-based healthy elderly subjects exhibit lobar MBs and they are strictly lobar in 58.4% of these cases [11]. Understanding the true diagnostic value of lobar MBs, both as clinical and incidental findings, could help improve our ability to detect CAA in its early stages, before dementia or devastating ICH.

The Boston criteria are a set of clinical radiological criteria that were developed as a means of diagnosing CAA in a noninvasive way [12]. According to these criteria, the detection of multiple ($\geq$2) strictly lobar hemorrhages (large or small, symptomatic or asymptomatic) without known underlying cause in individuals aged >55 years is highly specific of the disease [4]. However, validation studies of these criteria have been mostly based on patients admitted because of lobar ICH [4,13,14], precluding the study of the diagnostic value of lobar MBs without symptomatic ICH. At a community level, the Rotterdam and Framingham studies have shown that healthy elderly individuals with strictly lobar MBs have an increased frequency of the *APOE*-ε4 allele (compared with patients with MBs not strictly confined to lobar regions) [11,15], which is in agreement with increased *APOE*-ε4 frequencies seen in patients with "probable CAA" [16]. Also, strictly lobar MBs do not correlate with classic vascular risk factors [11,15], which further reinforces their possible association with CAA. However, pathological data supporting the suspected link between lobar MBs and CAA in individuals without lobar ICH are currently lacking.

Using pathological assessment of CAA as a gold standard, we aimed to determine the positive predictive value (PPV) and negative predictive value (NPV) of the Boston criteria for CAA applied to MB-only subjects, in two highly different settings: a hospital-based cohort and a population-based cohort from the Framingham Heart Study (FHS).

2. Methods

2.1. Study cohorts

2.1.1. Hospital-based cohort

We searched across data sets of the Massachusetts General Hospital (MGH) for patients aged >55 years having both brain magnetic resonance imaging (MRI) and either brain biopsy or brain autopsy. Data search covered patients seen at the hospital during the period 1997–2012. On >3200 cases initially retrieved, we applied a multistep exclusion algorithm (Fig. 1). We excluded all individuals with lobar ICH at, or before, baseline MRI as lobar ICH has been shown to be strongly associated with CAA [4] and could confound the interpretation of the results.

2.1.2. Population-based cohort

This second cohort of individuals came from the FHS. Original [17] and offspring cohort [18] participants were invited to undergo MRI brain imaging beginning in March 1999. T2*-weighted MRI protocols were added in December 2000. Details on MRI protocol and subject enrollment have been described elsewhere [15]. In 1997, the FHS began a postmortem brain tissue donation program in collaboration with the Boston University Alzheimer's Disease Center's Neuropathology Core. Details of the enrollment process are available elsewhere [19]. As of June 2009, 16% of surviving original cohort participants (n = 35) and 11% of surviving offspring cohort participants (n = 398) were enrolled as potential brain donors. After 12 years since the program began, a total of 1804 original and offspring cohort participants had died, 10% of whom (n = 186) were registered brain donors. Of the latter, 139 brains (74%) were received and detailed neuropathology reports were available for all cases. Fifty-eight percent of the brains analyzed were deemed pathologically normal. The present study sample was obtained from the original and offspring cohort participants with available brain MRI and neuropathological data, including explicit CAA assessment. All these individuals were aged >55 years.

2.2. Standard protocol approvals, registrations, and patient consents

The local Institutional Review Boards at Massachusetts General Hospital and Boston University Medical Center approved the study protocol. Informed consent was obtained from all subjects in the FHS.

2.3. Imaging

MGH and FHS protocols were similar regarding the acquisition parameters of T2*-gradient echo sequences (GRE). Some MGH cases had susceptibility-weighted image (SWI) studies, which are recognized as more sensitive for hemosiderin detection than GRE [20]. Table 1 shows the MRI protocols used in each institution.

Detection of MBs was performed on either GRE or SWI sequences as previously described [20,21]. Briefly, MBs were defined as focal round or ovoid areas of marked signal loss, different from vascular flow voids, calcifications, cavernous malformations, and basal ganglia mineralization.

MBs were rated and labeled by a stroke neurologist (M.E.G.) for the MGH cohort and a trained neurologist (J.-R.R.) for the FHS cohort, both blind to the subjects' demographics, clinical characteristics, and neuropathological findings. MB rating was assisted by image processing