Cerebral microbleeds are predictive of mortality in the elderly

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Purpose

Cerebral microbleeds represent focal hemosiderin deposits (1) which result from minimal blood leakage from damaged small vessels and can be detected on T2*-weighted MRI, which is highly sensitive for iron-containing compounds (2). In terms of etiology, cerebral microbleeds can be divided into microbleeds probably associated with cerebral amyloid angiopathy (CAA) which are located in the cerebral lobes (3) and microbleeds associated with hypertension and atherosclerosis which are located in the thalamus, basal ganglia, brain stem and cerebellum (4). Microbleeds are not only common in patients with ischemic stroke (5), intracerebral hemorrhage (ICH) (6) and Alzheimer disease (7) but also in healthy aging (8). Recently Hennemann et al. have shown that microbleeds are the strongest predictor of all-cause mortality within a group of MRI biomarkers of vascular damage and atrophy in a memory clinic population (9). To our knowledge it is not known whether microbleeds or distributive patterns of microbleeds are also predictive of mortality in the general population. Therefore, we investigated the prognostic value of microbleeds in terms of all-cause mortality and cardiovascular mortality in a population suffering from vascular disease or at high risk for developing this condition.

Methods

Patients were included from the nested MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) who were recruited from the general population. Inclusion and exclusion criteria have been described in detail elsewhere (10). A susceptibility-weighted scan for microbleed score was available for 435 women and men aged between 70 and 82 years. All imaging was performed on an MR system operating at a field strength of 1.5 T (Philips Medical Systems, Best, The Netherlands). Dual fast spin echo [repetition time (TR) = 3,000 ms; echo time (TE) = 27/120 ms; slice thickness = 3 mm; 48 slices; no interslice gap; field of view (FOV) = 220 x 220 mm; matrix = 256 x 204], FLAIR (TR = 8,000 ms; TE = 100 ms; slice thickness = 3 mm; 48 slices; no interslice gap; FOV = 220 x 176 mm; matrix = 256 x 153) and susceptibility-weighted images (multislice gradient echo sequence; TR = 2593 ms; TE = 48 ms; slice thickness = 6 mm; 22 slices; interslice gap = 0.6 mm; whole brain coverage; FOV = 220 x 198 mm; matrix = 256 x 176) were obtained from all subjects.. All MRI scans were read in consensus by 2 experienced raters, who were blinded to the clinical history. Microbleeds were defined as focal areas of signal loss on T2-weighted images that increased in size on the T2-weighted gradient echo planar images ('blooming effect') (Figure 1) (11). In this way, microbleeds were differentiated from areas of signal loss based on vascular flow void. Areas of symmetric hypointensity in the basal ganglia likely to represent calcification or nonhemorrhagic iron deposits were disregarded. The location, number, and size of microbleeds were recorded (12). In a first analysis, we dichotomized subjects into a group having at most 1 microbleed and into a group having two or more microbleeds. Subsequently, we applied the so-called Boston criteria for cerebral amyloid angiopathy (CAA) in all subjects. The Boston criteria are designed to estimate the likelihood of the presence of CAA during life by means of location and number of intracerbral hemorrhages (13, 14). Mean follow-up time of all-cause mortality was 6.4 (± 1.8) years. Mean follow-up time of cardiovascular mortality was 5.7 (± 1.5) years.

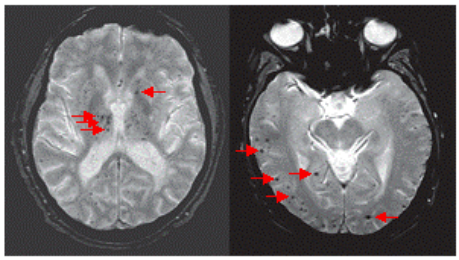

Figure 1

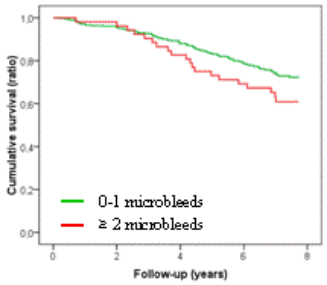

Figure 2

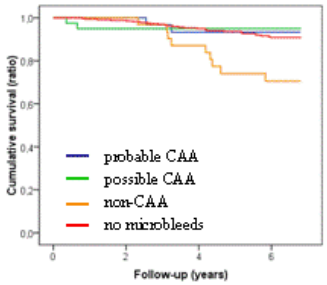

Figure 3

Results

Figure 2 shows Kaplan Meier survival curves for microbleeds for all-cause mortality. Cox proportional hazard models show that subjects with two or more microbleeds had a statistical significant increased risk of death compared to persons with no or 1 microbleed (HR 1.75, 95% CI 1.07-2.87, p = 0.027). In terms of cardiovascular mortality Kaplan Meier survival curves show the same trend although reaching no statistical significance (HR 2.12, 95% CI 0.95-4.72, p = 0.07). Figure 3 shows Kaplan Meier survival curves for microbleeds for cardiovascular mortality during follow-up period II with microbleeds scored according to the Boston criteria. Cox proportional hazard models show that non-CAA had a strong predictive effect. Persons diagnosed with non-CAA had a more than 4 fold risk of death compared to persons with at most 1 microbleed (HR 4.21, 95% CI 1.85-9.58, p = 0.001). In terms of all-cause mortality Cox proportional hazard models show that probable CAA and non-CAA had a predictive effect although reaching no statistical significance (HR 1.65, 95% CI 0.89-3.08, p = 0.11 and HR 1.73, 95% CI 0.92-3.23, p = 0.09 respectively).

Conclusions

In this population-based study we found that the presence of two or more microbleeds implicates an increased risk of overall death. Furthermore, only "non-CAA" type microbleeds were associated with increased risk of cardiovascular death, which is in line with the assumption that these microbleeds are associated with hypertension and atherosclerosis. Therefore, CAA type small vessel disease cannot be considered as risk factor for (cardiovascular) mortality.

References

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