Risk of Thrombolysis-Related Hemorrhage Associated With Microbleed Presence

To the Editor:

We appreciate the article by Fiehler and colleagues regarding thrombolysis-associated bleeding risk in stroke patients. This is the largest prospective study to date that investigated the relation between presence of cerebral microbleeds on MRI and the risk of secondary thrombolysis-associated intracranial hemorrhage (ICH) in ischemic stroke patients. However, we respectfully disagree with the authors that on the basis of these data one can conclude that the risk of hemorrhage associated with microbleed presence is negligible.

First, the prevalence of microbleeds in their study is 15%. This is much lower than expected based on previous studies that reported microbleed prevalence in ischemic stroke patients up to 68%, and even lower than the microbleed prevalence in a general population of the same age range which we found to be over 20%. Also, the reported microbleed prevalence differed largely across the participating study centers, ranging from 0 to 37%, possibly through differences in the MRI sequences used. This suggests that microbleed presence was underrated in at least some of the centers. If a substantial proportion of individuals in the study by Fiehler et al were misclassified as having no microbleeds, whereas they actually had, this will have attenuated the estimated risks associated with microbleed presence.

Second, we disagree that multivariate analysis of the relation between microbleed presence and ICH risk was unnecessary because, we cite, “the presence of microbleeds was not a risk factor for symptomatic ICH”. Quite the contrary, the crude analysis between exposure (microbleed prevalence) and outcome (ICH) may well have been confounded by factors that are associated to both exposure and outcome: for example, age or hypertension. Adjustment for these potential confounders in multivariate analyses could potentially have altered the results.

Thirdly, the authors did not take microbleed location into account. There is increasing evidence that lobar microbleeds are a hallmark of cerebral amyloid angiopathy (CAA), whereas deep microbleeds may be related to hypertension. Animal models have revealed an increased risk of hemorrhage associated with thrombolysis in CAA mice. A pooled analysis showed that 7 of 10 patients with thrombolysis-related ICH had CAA at autopsy. It may thus be that thrombolysis-related hemorrhage risk differs according to microbleed location, and is especially pronounced for lobar microbleeds.

Finally, the authors put disproportionate emphasis on the probability values, ignoring their actual risk estimate of 2.76 (odds ratio) for thrombolysis-associated hemorrhage risk in persons with microbleeds. The lack of significance of this finding is likely explained by a lack of power of this study. Based on the study prevalence of microbleeds of 15% and risk of ICH of 3%, a study to assess an odds ratio of 2.76 or higher for increased risk of ICH in patients with microbleeds would require a total sample of at least 1008 patients (power 80%, significance level 0.05).

Because the actual odds ratio of 2.76 may be an underestimate due to any of the factors described above (potential misclassification of microbleeds, confounding by factors not adjusted for in the analysis, and not accounting for the fact that microbleed etiology and potentially prognosis differs according to location), the data presented by Fiehler et al are compatible with a substantial increased risk of hemorrhage associated with thrombolysis therapy in patients with microbleeds.

Disclosures

None.

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