Sir, We read with interest the letter from Ryan et al. in response to our article. The authors add interesting information concerning brain microbleeds in Alzheimer’s disease, as they determined the prevalence of brain microbleeds in a set of familial Alzheimer’s disease cases. In a sample of 12 (11 Presenilin 1, one amyloid precursor protein mutations), they observed brain microbleeds in three patients, i.e. a prevalence of 25% (95% confidence interval 9–53%). Despite large confidence intervals, this prevalence is in line with studies on prevalence of brain microbleeds in sporadic Alzheimer’s disease (Cordonnier and van der Flier, 2011).

The authors conclude that even in genetically confirmed Alzheimer’s disease, brain microbleeds are not an inevitable feature. We feel that their data in fact illustrate a more important point: even in a set of ‘pure’ and young patients with Alzheimer’s disease, where cerebrovascular disease is unlikely to play a role, the prevalence estimate of brain microbleeds is 25%. This supports the hypothesis that brain microbleeds are not just an age-related epiphenomenon, but are implicated in the aetiology of Alzheimer’s disease.

Two of the patients had lobar brain microbleeds, the third patient had an infratentorial microbleed. In samples of sporadic Alzheimer’s disease, a considerable proportion of brain microbleeds are in deep location. This could be explained by the hypothesis that especially lobar brain microbleeds are related to amyloid deposition in the vessel wall (cerebral amyloid angiopathy) not necessarily accompanied by other expressions of small vessel disease such as white matter hyperintensities. In older patients with Alzheimer’s disease, brain microbleeds with a deep location may also occur, likely related to hypertensive vasculopathy and more often accompanied by other expressions of small vessel disease. Brain microbleeds seem to be a common downstream product of these two pathological processes that together may cause Alzheimer’s disease.

The results of Ryan et al. show that monogenetic forms of Alzheimer’s disease represent a good model for Alzheimer’s disease in general. The question remains whether brain microbleeds are a reflection of very severe cerebral amyloid angiopathy, a process that is observed in the majority of patients, or that patients with brain microbleeds represent a specific subgroup with a different pathological process. Studies linking the observation of brain microbleeds directly to their underlying neuropathology are needed to answer this question. In light of the development of brain microbleeds and vasogenic oedema in patients undergoing vaccination therapy, these questions become increasingly relevant.

Reference
