Journal of the Neurological Sciences 322 (2012) 56–58

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Clinical aspects of microbleeds in Alzheimer's disease

Wiesje M. van der Flier *

Alzheimer Center, Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands
Department of Epidemiology & Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 29 January 2012
Received in revised form 29 June 2012
Accepted 5 July 2012
Available online 24 July 2012

Keywords:
Microbleeds
Alzheimer's disease
Mild cognitive impairment
Cognition
Microhemorrhage

ABSTRACT

Microbleeds are small lesions, appearing as black dots on T2*-weighted magnetic resonance imaging. They occur frequently in Alzheimer's disease (AD), but the clinical relevance of these radiological observations remains unclear. In this paper an overview is given on currently available evidence on the clinical relevance of microbleeds in AD. The evidence linking microbleeds to severity of cognitive impairment in AD is not unambiguous. From the existing literature, it seems reasonable to conclude that multiple microbleeds negatively impact cognitive performance, but there is less consensus on the importance of location of microbleeds in this respect. Regarding progression of disease, there is hardly any evidence that microbleeds affect disease course in terms of progression to AD in patients with MCI or with respect to rate of cognitive decline in AD patients. This may imply that microbleeds simply do not affect disease course, but an alternative explanation for the negative findings would be that these studies are hampered by selective drop-out, as individuals with many microbleeds have an increased risk of (stroke-related) mortality.

1. Introduction

Microbleeds are small lesions, appearing as black dots on T2*-weighted magnetic resonance imaging. Microbleeds, which have long been considered to be innocent observations on MRI, have now been shown to occur more frequently in patients with Alzheimer's disease (AD) than in the general population, with an estimated prevalence of 23% [1–5]. An example of microbleeds in a patient with AD is shown in Fig. 1. Together with white matter hyperintensities and lacunes, microbleeds can be considered a third expression of small vessel disease on MRI. Many questions still surround the observation of microbleeds: for example, it is unclear what their underlying pathological substrate is. Furthermore, the clinical implications of microbleeds are insufficiently known.

Based on mainly epidemiological evidence, the hypothesis has been coined that the etiology of microbleeds differs according to their location. Microbleeds with a deep location supposedly result from underlying hypertensive vasculopathy, while microbleeds in a lobar location are thought to reflect underlying cerebral amyloid angiopathy (CAA). This makes microbleeds especially relevant in the context of AD, in which diseases both amyloid pathology (including amyloid deposition in parenchyma [plaques] and in vessels [CAA]) and ischemic vascular pathology play a role. It is not known how these two types of pathology interact, but the fact that microbleeds appear to be related to both types of pathology makes them highly relevant [5].

2. Microbleeds reflect amyloid burden

In a proof of principle study, we retrospectively selected AD patients with many microbleeds (arbitrarily defined as >8, corresponding to the top 5%) and matched these for age and gender on a one-to-two basis with AD patients without any microbleeds [6]. There were no differences between groups in the degree of (medial temporal) atrophy. Patients with many microbleeds however, had more severe white matter hyperintensities, confirming the association with small vessel disease. Moreover, they had lower (i.e. more abnormal) levels of amyloid-beta 1–42 in their cerebrospinal fluid (CSF), providing evidence for a link with amyloid burden. We recently confirmed the latter finding in a completely independent sample of patients with ≥1 microbleed which we compared with an age and gender matched group of patients without any microbleeds [7]. Patients with microbleeds had lower (i.e. more abnormal) levels of CSF amyloid-beta 1–42, but contrary to our expectation, there was no relation with CSF amyloid-beta 1–40. This may have several potential explanations. First, microbleeds in AD may represent an earlier stage or milder form of CAA compared to sporadic CAA patients presenting with full blown hemorrhages. Alternatively, AD patients may have a different subtype of CAA, arising from a different pathomechanism. The finding of lowered amyloid-beta 1–42 was largely attributable to patients with lobar microbleeds, providing circumstantial evidence that lobar microbleeds in AD are related to CAA. Additional evidence for a spatial relationship between microbleeds and amyloid-beta comes from an elegant study using Positron Emission

* Alzheimer Center PK-1 Z 44, VU University Medical Center, de Boelelaan 1118, 1081 HZ Amsterdam, The Netherlands. Tel.: +31 20 4440816; fax: +31 20 4440715.
E-mail address: wm.vdflier@vumc.nl.

0022-510X
doi:10.1016/j.jns.2012.07.009

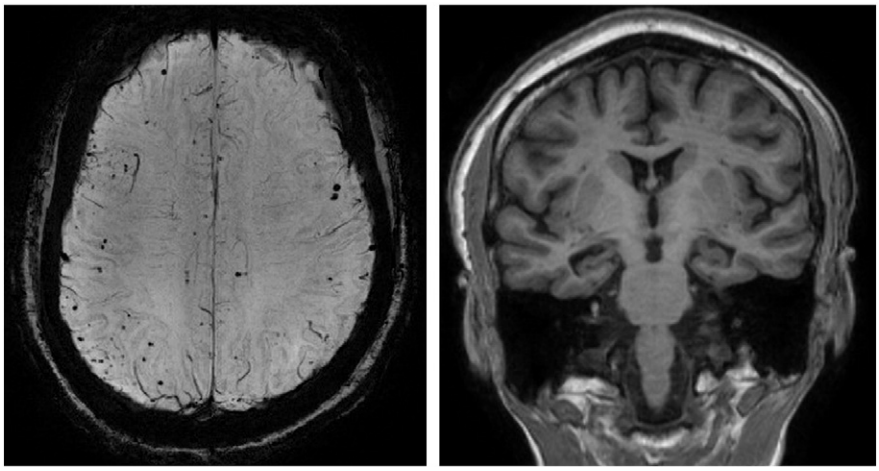

Fig. 1. A 56-year old female patient with Alzheimer's disease. On the Mini-Mental State Examination, she has a score of 16. On MRI, axial susceptibility-weighted imaging (left panel) shows multiple lobar microbleeds. On the coronal T1-weighted image (right panel), atrophy of the medial temporal lobe can be appreciated.

Tomography (PET) with Pittsburgh-compound-B (PIB), which showed a local increase in PIB retention at the site of microbleeds [8]. Regions of interest in concentric circles around the microbleed showed a gradual decline in PIB retention with increasing distance from the microbleed location.

3. ARIA

The studies above underline the relevance of microbleeds in the context of AD. Interest in microbleeds has further boosted because of the observation of microbleeds and vasogenic edema as side effects of immunization therapy [9,10]. This has led to the recent introduction of the term Amyloid Related Imaging Abnormalities (ARIA) [11]. ARIA encompass both vasogenic edema related observations (ARIA-E) supposedly reflecting an increase in extracellular fluid, and hemosiderin-related observations (ARIA-H). The latter include both microbleeds and superficial siderosis. The article attempts to provide recommendations for the detection and monitoring of ARIA in AD clinical trials, but at the same time acknowledges that many aspects regarding the etiology of these radiological observations, and especially regarding their clinical relevance remain unclear. In the remainder of this paper, I will give an overview of currently available evidence on the clinical relevance of microbleeds in AD. First, I will focus on cross-sectional studies studying the relationship between microbleeds and severity of cognitive impairment. Subsequently, I will discuss the relationship between microbleeds and rate of decline.

4. Cognitive impairment

Most studies in AD have shown hardly any relationship between the presence of microbleeds and cognition [1,2,4,12]. The relatively small sample sizes and the low number of microbleeds (most patients with microbleeds have only one microbleed) may account for these negative findings. Alternatively, the disease process may have advanced too far, masking the subtle effect of microbleeds on cognition. To account for the problem of low number of microbleeds, we took a proof of principle approach, comparing AD patients with many microbleeds to age and gender matched AD patients without any microbleeds [6]. We found that patients with many microbleeds performed five points worse on their Mini-Mental State Examination at first examination. This effect remained significant after adjustment for age, gender, medial temporal lobe atrophy and white matter hyperintensities, and shows that number of microbleeds may be a highly relevant factor to take into account.

Epidemiological studies of large cohorts of non-demented individuals may reveal the subtle impact of microbleeds on cognition that may become obscured later in the disease process. In the Rotterdam study, a respectable number of 3979 elderly from the general population (60 ± 9 years; 54% female, MMSE 28 ± 2, ≥1 microbleed: 15%) were included [13]. The researchers found an association between a higher number of microbleeds and lower MMSE-score and worse performance on tests for information processing speed and motor speed. These associations were mostly attributable to individuals with many microbleeds (≥5), preferably with a lobar location. In a non-demented cohort of 500 patients with small vessel disease (RUN DMC cohort; 66 ± 9 years; 43% female, MMSE 28 ± 2, ≥1 microbleed: 10%) associations between both presence and number of microbleeds and measures of global cognition, memory, speed and attention were found [14]. The relationship between microbleeds and cognitive performance was mainly driven by frontal and temporal (lobar) microbleeds. Additionally, deep microbleeds were related to worse global cognitive function, psychomotor speed and attention. Finally, the PROSPER study investigated 439 nondemented individuals with vascular risk factors (78 ± 3 years; 40% female, MMSE 28, ≥1 microbleed: 24%) and found no effect of microbleeds on cognitive performance [15]. In a direct comparison between patients with infratentorial microbleeds and patients without infratentorial microbleeds (including patients with microbleeds in another location) however, they found that the former group performed worse on memory tests.

5. Rate of decline

Subsequently, one may question whether the presence of microbleeds negatively impacts the course of the disease. Progression of disease can be defined in a number of ways. A first and important question is whether the presence of microbleeds predicts progression to AD among patients with mild cognitive impairment (MCI). We followed 152 patients with MCI presenting at our memory clinic for an average of 2 ± 1 years [16]. At follow-up, 80 patients (53%) had remained stable, 56 (37%) had developed AD, and 16 (10%) had developed another type of dementia (e.g. vascular dementia, frontotemporal dementia, dementia with Lewy bodies). On baseline MRI, atrophies of the medial temporal lobe and white matter hyperintensities were graded using a simple visual rating scale and microbleeds were counted. We found that atrophy of the medial temporal lobe predicted progression to AD, while white matter hyperintensities and presence of microbleeds predicted progression to another type of dementia, but not to AD.

A second way to look at progression of disease, is by looking at rate of cognitive decline. We followed 221 patients with AD (68 ± 9 years; 49% female, baseline MMSE 22 ± 4, ≥1 microbleed: 18%) for an average duration of follow-up of 3 ± 1 years [17]. Cognitive performance was repeatedly measured using MMSE. Linear mixed models showed that

on average, patients lost 2 MMSE points per year. There was no relation between presence or number of microbleeds and baseline MMSE or change in MMSE over time. Results did not change when we took location of microbleeds into account. It is still possible that subtle effects of microbleeds on rate of decline in specific cognitive domains would have been found when other neuropsychological tests had been used. Nonetheless, the abovementioned study shows that presence and number of microbleeds are not a major determinant of disease course.

A third way to look at disease progression is by taking mortality as outcome measure. We followed 1138 patients from our memory clinic (including 357 patients with AD) for an average period of 3 ± 2 years [18]. Information on mortality was obtained from the general practicioner and/or the patient file. Baseline MRI was assessed using simple visual rating scales for atrophy of the medial temporal lobe, global cortical atrophy, white matter hyperintensities and microbleeds (categorized as 0/1–2/≥3). We found that the presence of multiple microbleeds was the strongest predictor of mortality with an almost two and a half times increased risk of mortality, after adjustment for other MRI-measures and vascular risk factors. In this study, information on cause of death was not available. An attempt to take into account the cause of death was made in a study based on the PROPSER cohort [19]. The cohort of 435 nondemented individuals with vascular risk factors was followed for 7 ± 2 years. Information on cause of death was obtained from the Central Bureau of Statistics of the Netherlands. In this study, multiple (>1) microbleeds modestly though non-significantly, predicted overall mortality, but they strongly predicted stroke-related mortality (hazard ratio 6). Furthermore, this increased risk of stroke-related mortality was largely attributable to microbleeds with a strictly lobar distribution.

6. Conclusion and discussion

Microbleeds are a radiological construct, reflecting deposits of hemosiderin. They can presumably result from two neuropathological routes; [1] hypertensive vasculopathy and [2] cerebral amyloid angiopathy. Microbleeds are of particular interest in the context of AD for a number of reasons. First, their prevalence is higher in patients with AD than in the general population. Second, resulting from two neuropathological routes, they may form a bridge between amyloid initiated brain changes and ischemic cerebrovascular pathology. Associations with expressions of small vessel disease on the one hand and with amyloid-beta on the other hand provide evidence for this double association. Finally, interest in microbleeds has boosted due to their occurrence as side effect of anti-amyloid immunization therapy [11]. At the same time, relatively little is known about their clinical relevance.

The evidence linking microbleeds to severity of cognitive impairment is not unambiguous. From the existing literature, we can conclude that multiple microbleeds negatively impact cognitive performance. There is no consensus on the importance of location of microbleeds in this respect, however. The conflicting findings may be partly explained by the specific characteristics of the cohorts under study. In the context of (preclinical) AD, lobar microbleeds may impact cognitive performance most, while in the context of cerebrovascular disease, microbleeds with a deep or infratentorial location may have a stronger impact on cognitive performance.

Regarding progression of disease, it seems that microbleeds do not affect the course of AD in terms of progression to AD in patients with MCI or with respect to rate of cognitive decline. A potential explanation for this finding is that microbleeds have only a subtle effect on cognition and disease course, which is diluted once the disease has progressed too far. An alternative explanation would be that selective drop-out accounts for the negative findings in longitudinal studies. This would be the case when patients with multiple microbleeds are at risk of such fast disease progression that they are less likely to return to the memory clinic for follow-up evaluation. Circumstantial evidence for this line of reasoning stems from studies showing that individuals with many microbleeds have an increased risk of (stroke-related) mortality [18,19]. In the context of clinical trials, this means that one or a few microbleeds seem to be unharmful, but patients with many microbleeds should not be exposed to unnecessary risks [11]. At this point, there is insufficient evidence to make recommendations about the specific number of microbleeds that might be harmful. Moreover, it is not known yet if microbleeds developing as a result of immunization trials (i.e. ARIA-H) have the same neuropathological substrate and risk profile as spontaneously developing microbleeds. This implies that we do not know yet if results of studies on risks associated with microbleeds can be generalized to ARIA-H. Furthermore, data regarding the question whether baseline microbleeds actually increase the risk of incident hemorrhage and vasogenic edema (ARIA-E) are dearly needed.

Conflict of interest

None.

References

[1] Cordonnier C, van der Flier WM, Sluimer JD, Leys D, Barkhof F, Scheltens P. Prevalence and severity of microbleeds in a memory clinic setting. Neurology May 9 2006;66(9):1356–60.
[2] Nakata-Kudo Y, Mizuno T, Yamada K, Shiga K, Yoshikawa K, Mori S, et al. Microbleeds in Alzheimer disease are more related to cerebral amyloid angiopathy than cerebrovascular disease. Dement Geriatr Cogn Disord 2006;22(1):8–14.
[3] Hanyu H, Tanaka Y, Shimizu S, Takasaki M, Abe K. Cerebral microbleeds in Alzheimer's disease. J Neurol Dec 2003;250(12):1496–7.
[4] Pettersen JA, Sathiyamoorthy G, Gao FQ, Szilagyi G, Nadkarni NK, St George-Hyslop P, et al. Microbleed topography, leukoaraiosis, and cognition in probable Alzheimer disease from the Sunnybrook dementia study. Arch Neurol Jun 2008;65(6):790–5.
[5] Cordonnier C, van der Flier WM. Brain microbleeds and Alzheimer's disease: innocent observation or key player? Brain Feb 2011;134(Pt 2):335–44.
[6] Goos JD, Kester MI, Barkhof F, Klein M, Blankenstein MA, Scheltens P, et al. Patients with Alzheimer disease with multiple microbleeds: relation with cerebrospinal fluid biomarkers and cognition. Stroke Nov 2009;40(11):3455–60.
[7] Goos JD, Teunissen CE, Veerhuis R, Verwey NA, Barkhof F, Blankenstein MA, et al. Microbleeds relate to altered amyloid-beta metabolism in Alzheimer's disease. Neurobiol Aging 2012;33(5):1011.e1–9.
[8] Dierksen GA, Skehan ME, Khan MA, Jeng J, Nandigam RN, Becker JA, et al. Spatial relation between microbleeds and amyloid deposits in amyloid angiopathy. Ann Neurol Oct 2010;68(4):545–8.
[9] Black RS, Sperling RA, Safirstein B, Motter RN, Pallay A, Nichols A, et al. A single ascending dose study of bapineuzumab in patients with Alzheimer disease. Alzheimer Dis Assoc Disord Apr 2010;24(2):198–203.
[10] Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, et al. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology Dec 15 2009;73(24):2061–70.
[11] Sperling RA, Jack Jr CR, Black SE, Frosch MP, Greenberg SM, Hyman BT, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement Jul 2011;7(4):367–85.
[12] Werring DJ, Gregoire SM, Cipolotti L. Cerebral microbleeds and vascular cognitive impairment. J Neurol Sci Dec 15 2010;299(1–2):131–5.
[13] Poels MM, Ikram MA, van der Lugt A, Hofman A, Niessen WJ, Krestin GP, et al. Cerebral microbleeds are associated with worse cognitive function: the Rotterdam scan study. Neurology 2012;78(5):326–33.
[14] van Norden AG, van den Berg HA, de Laat KF, Gons RA, van Dijk EJ, de Leeuw FE. Frontal and temporal microbleeds are related to cognitive function: the Radboud University Nijmegen diffusion tensor and magnetic resonance cohort (RUN DMC) study. Stroke Dec 2011;42(12):3382–6.
[15] van Es AC, van der Grond J, de Craen AJ, Westendorp RG, Bollen EL, Blauw GJ, et al. Cerebral microbleeds and cognitive functioning in the PROSPER study. Neurology Oct 11 2011;77(15):1446–52.
[16] Staekenborg SS, Koedam EL, Henneman WJ, Stokman P, Barkhof F, Scheltens P, et al. Progression of mild cognitive impairment to dementia: contribution of cerebrovascular disease compared with medial temporal lobe atrophy. Stroke Apr 2009;40(4):1269–74.
[17] van der Vlies AE, Goos JD, Barkhof F, Scheltens P, van der Flier WM. Microbleeds do not affect rate of cognitive decline in Alzheimer's disease. Neurology 2012;79(8):763–9.
[18] Henneman WJ, Sluimer JD, Cordonnier C, Baak MM, Scheltens P, Barkhof F, et al. MRI biomarkers of vascular damage and atrophy predicting mortality in a memory clinic population. Stroke Feb 2009;40(2):492–8.
[19] Altmann-Schneider I, Trompet S, de Craen AJ, van Es AC, Jukema JW, Stott DJ, et al. Cerebral microbleeds are predictive of mortality in the elderly. Stroke Mar 2011;42(3):638–44.