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# Microbleeds in vascular dementia: Clinical aspects

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ABSTRACT

Microbleeds are small dot-like lesions which can be appreciated on gradient echo, T2*-weighted magnetic resonance images as hypointensities. They are considered as an expression of small vessel disease on MRI, next to lacunes and white matter hyperintensities (WMH). Microbleeds are relatively common in vascular dementia, with reported prevalences between 35% and 85%. In the context of vascular dementia, microbleeds are mainly thought to result from hypertensive vasculopathy, but the frequent co-occurrence of lobar microbleeds suggests that neurodegenerative pathology and/or cerebral amyloid angiopathy is also of importance. The presence of multiple microbleeds in vascular dementia or in patients with vascular cognitive impairment is related to worse performance on cognitive tests, mainly in psychomotor speed and executive functioning. They may have some predictive value in terms of predicting development of (vascular) dementia, mortality and disability. Data on the occurrence of stroke and post-stroke dementia in patients with microbleeds are to date not available. New definitions and diagnostic criteria for vascular dementia and vascular cognitive impairment are needed and should take into account microbleeds.



## 1. Introduction

Microbleeds are small dot-like lesions which can be appreciated on gradient echo (GRE), T2*-weighted or susceptibility-weighted imaging (SWI) magnetic resonance images as hypointensities. Microbleeds are considered as an expression of small vessel disease on MRI, next to lacunes and white matter hyperintensities (WMH). As such, and potentially being related to large bleedings (intracerebral hemorrhage), microbleeds may have an important role in vascular dementia (VaD). In this article, we will review available evidence on the clinical aspects of microbleeds in VaD.

### 1.1. Vascular dementia

Vascular dementia (VaD) is the second most common type of dementia worldwide. At present, the 1993 criteria of the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et al'Enseignement en Neurosciences (NINDS-AIREN) are most often used to diagnose VaD (Roman et al., 1993). These criteria require the presence of dementia, defined as cognitive decline with interference in activities of daily living, and evidence of cerebrovascular disease, including proof on brain imaging. Radiological evidence for VaD includes both large vessel infarcts and small vessel disease (lacunes and white matter hyperintensities). Microbleeds are not mentioned in these criteria, as the first paper mentioning them was only published in 1996 (Offenbacher et al., 1996). The research criteria for subcortical ischemic vascular dementia (SIVD) were published in 2000 to more clearly define the important subset of patients with VaD due to small vessel disease (Erkinjuntti et al., 2000). The diagnosis of SIVD is based on the presence of severe WMH or moderate WMH in combination with more than 5 lacunes. Again, microbleeds are not mentioned. Far more common than pure VaD are patients in whom vascular pathology contributes to cognitive impairment and dementia, often captured under the umbrella term *vascular cognitive impairment* (VCI) (Gorelick et al., 2011; O'Brien et al., 2003).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a purely genetic form of VaD. It is an arteriopathy caused by mutations of the *Notch3* gene (Tournier-Lasserve et al., 1993). The main clinical manifestations of the disease include migraine with aura, mood disturbances, recurrent ischemic strokes and progressive cognitive decline eventually leading to dementia (Dichgans et al., 1998).

### 1.2. Microbleeds

Available data suggest that two main mechanisms can lead to microbleeds. Typically, deep and infratentorial microbleeds are presumed to result from hypertensive vasculopathy, while cortico-subcortical (also called lobar) microbleeds seem to be closely related to cerebral amyloid angiopathy (CAA) (Cordonnier and van der Flier, 2011). Especially deep microbleeds are more frequent in hypertensive people, both in general

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(odds ratio [OR] 3.9; 95% CI 2.4 to 6.4) and in cerebrovascular populations (OR 2.3; 95% CI 1.7 to 3.0) (Cordonnier et al., 2007). Moreover, they are associated with markers of ischemic small-vessel disease (lacunes and WMH).

## 2. Prevalence

Prevalence of microbleeds differs strongly by patient population and varies from roughly 5% in the general population to 35% in ischemic and 60% in hemorrhagic stroke (Cordonnier et al., 2007). There are hardly any studies on the prevalence of microbleeds in VaD. Moreover, comparison of the few studies available is difficult due to the heterogeneity in definitions of VaD. Table 1 provides an overview of studies reporting prevalence of microbleeds in VaD or VCI-like populations. To capture the heterogeneity of the study samples, population definitions are provided. Based on these diverse populations, it does not seem appropriate to calculate an overall prevalence. But taken together, these studies suggest that microbleeds are a common finding in VaD with estimates varying from 33% to 85%, which are found both in deep and lobar locations (example: Fig. 1). This may mirror the heterogeneity of VaD. One would expect the deep microbleeds to be related to hypertensive vasculopathy in VaD. Lobar microbleeds on the other hand are considered to result from underlying cerebral amyloid angiopathy, which may be an isolated vascular disease process, or may occur in the context of concomitant Alzheimer's pathology (mixed disease is common, especially at old age). A recent observation of decreased concentrations of amyloid-beta 1–40 in cerebrospinal fluid in VaD patients corroborates the notion of a role for amyloidosis VaD (Goos et al., 2012).

Although most studies available have scanned their patients at 1 or 1.5 T with conventional GRE T2* imaging, there is rapid development in scanning techniques. With the upcoming availability of susceptibility-weighted MRI-techniques and ultra-high field strength (i.e. 7 T) prevalences will further increase (Biessels et al., 2010; de Bresser et al., submitted for publication; Theysohn et al., 2011).

### 2.1. CADASIL

In CADASIL, the overall prevalence of microbleeds is around 36% (Dichgans et al., 2002; Lesnik Oberstein et al., 2001; Viswanathan et al., 2006). Interestingly, the prevalence progressively increases with age: in patients in the 5th decade, microbleeds may be observed in 19% of patients, while after the 6th decade nearly all patients have microbleeds (van den Boom et al., 2003). Microbleeds are scattered throughout the brain with a slight predominance in the basal ganglia and thalamus (Viswanathan et al., 2006). However, CADASIL patients also exhibit microbleeds in lobar regions (Dichgans et al., 2002).

## 3. Clinical aspects

Microbleeds have long been considered to be silent lesions. But studies investigating relations with clinical aspects are only few. There are a number of clinical aspects one might think about in relation to microbleeds, including cognitive dysfunction, prediction of dementia, risk of bleeding, and prediction of functional and/or vital outcome.

### 3.1. Cognitive dysfunction

Studies focusing on relationships between microbleeds and cognitive dysfunction are hampered by a number of methodological issues. First, patients with microbleeds often have only one or a few microbleeds, which by themselves may not exert a strong influence. Second, microbleeds hardly occur in isolation. Especially in VaD, there are often multiple expressions of (small) vessel disease, and their effects may be difficult to disentangle. Third, it is still not known whether microbleeds reflect focal underlying pathology or whether they reflect more widespread disease. This has implications for the type of associations one expects to find. Finally, associations depend on the specific characteristics of the population under study. In the context of VaD this means that results are hard to compare, as definitions of VaD differ widely among studies.

One of the first studies to show the relation between microbleeds and cognitive dysfunction was published in 2004 (Werring et al., 2004). From patients referred to a neurovascular unit with suspected ischemic stroke or transient ischemic attack, 25 patients with microbleeds and a control group of 30 patients without any microbleeds, but otherwise similar in vascular risk factors were selected. Patients with microbleeds (mostly in the basal ganglia, but also in lobar and infratentorial regions) more often showed problems in executive functioning than patients without any microbleeds. Furthermore, baseline microbleeds were associated with executive dysfunction after more than 5 years of follow-up, although the longitudinal study was hampered by a large proportion of drop-outs (Gregoire et al., 2012). Two other studies evaluated patients with subcortical vascular dementia (Nardone et al., 2011; Won et al., 2007). Microbleeds were most commonly located in the cortex, and were independently related to dysfunction in multiple cognitive domains, including memory, attention and executive functioning.

In CADASIL, cross-sectional studies showed no relationship between microbleeds and cognitive impairment (Liem et al., 2007; Viswanathan et al., 2007). Incident microbleeds occurring over a period of 7 years however, were shown to be related to cognitive decline, most prominently executive dysfunction (Liem et al., 2009).

There are a number of studies assessing the relationships between presence and number of microbleeds and cognitive function in nondemented populations. In the RUN-DMC study including 500 nondemented individuals with any degree of small vessel disease, presence and number of microbleeds were found to be independently related to global cognitive performance, psychomotor speed and attention (van Norden et al., 2011). These associations were mainly driven by lobar microbleeds in temporal and frontal areas and by strictly deep microbleeds. The PROSPER study included patients at increased risk of vascular disease (van Es et al., 2011). Microbleeds were seemingly not related to cognitive performance, but in an analysis comparing participants with infratentorial microbleeds to all others, the former group performed slightly on memory.

**Table 1**
Prevalence of microbleeds in vascular dementia.

| Study | Prevalence | N | VaD criteria | Field strength | Sequence |
|---|---|---|---|---|---|
| Cordonnier et al. (2006) | 65% (47–79) | 31 | NINDS-AIREN (Roman et al., 1993) | 1.0 T | T2* |
| Won et al. (2007) | 85% (76–91) | 86 | SIVD (Erkinjuntti et al., 2000) | – | T2* |
| Goos et al. (2012) | 82% (52–95) | 11 | NINDS-AIREN (Roman et al., 1993) | 3.0 T | EPI |
| Qiu et al. (2010) | 33% (22–47) | 51 | ADDTC (Chui et al., 1992) | 1.5 T | T2* |
| Hanyu et al. (2003) | 77% (59–88) | 30 | Binswanger (Bennett et al., 1990) | 1.0 T | T2* |
| Viswanathan et al. (2006) | 52% (28–43) | 147 | Notch 3Mutation | 1.5 T | T2* |
| Dichgans et al. (2002) | 69% (44–86) | 16 | Notch 3Mutation | 1.5 T | T2* |
| Lesnik Oberstein et al. (2001) | 25% (14–40) | 40 | Notch 3Mutation | 1.5 T | T2* |

Point estimates and 95% confidence intervals for prevalence are provided. The table demonstrates the paucity in data on vascular dementia, and illustrates how interpretation of the available literature is hampered by the large variability in definitions of vascular dementia and in radiological parameters.