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Review

Associations and implications of cerebral microbleeds

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ABSTRACT

Cerebral microbleeds (CMB) are small haemosiderin deposits, detected with varying sensitivity by specific MRI sequences. CMB prevalence increases most clearly and reliably with age, but CMB are also associated with various acquired and heritable cerebral vasculopathies (most commonly arteriolosclerosis and amyloid angiopathy). CMB often coincide with the other radiological features of small vessel disease, cortical microinfarction, lacunar infarction and periventricular white matter hyperintensity. CMB distribution may suggest an underlying cause; in particular, lobar-restricted or corticosubcortical CMB suggest amyloid angiopathy. In both ischaemic stroke and intracerebral haemorrhage, CMB appear to be a marker of underlying vasculopathy severity, and therefore a predictor of recurrence. Although CMB are also associated with several broad clinical neurological impairments (cognitive impairment, depression and gait instability), it is debatable whether CMB themselves are causative. The clinical implications of CMB detection remain unclear. Thrombolysis for ischaemic stroke is not contraindicated. It is uncertain whether more conservative antithrombotic strategies are warranted if CMB are detected in patients with symptomatic vascular disease or atrial fibrillation. Studies (observational and randomized) of various treatment strategies in patients with CMB and these concomitant conditions are required to resolve these treatment dilemmas.

1. Introduction

Several MRI sequences are sensitive to small haemosiderin deposits in the brain, variously named in the literature as cerebral (or brain) microbleeds (CMB) (or microhaemorrhages). Incidental detection of CMB has increased dramatically with routine use of these MRI sequences in neurological disease. This has led to an exponential increase in literature exploring their significance.

This review does not comprehensively review all aspects of microbleed detection and association, which can be found elsewhere.[1–3] Rather, it focuses on the clinical associations of CMB and their therapeutic implications.

2. Methods

An unrestricted PubMed search for articles published before July 2012 was performed using the strategy "microbleed* OR microhemorrhage* OR microhaemorrhage*". Articles were selected for relevance, and further articles added from the articles' reference lists or the author's own files. Only articles in English were reviewed.

3. Technical aspects of cerebral microbleed detection

When microbleeds are visible on MRI, the physical haemosiderin deposit is not anatomically depicted. Rather, the radiological artifact ("susceptibility artifact") caused by haemosiderin is seen.

Haemosiderin is an iron-rich breakdown product of haemoglobin. Normally brain iron is exported by ferritin, but intracerebral haemorrhage (ICH) overwhelms this transport system. Brain macrophages respond by incorporating iron into haemosiderin, a poorly defined, inert compound containing at least 25% iron by weight. Haemosiderin is not easily exported - microbleeds, once present, rarely disappear.[4]

Haemosiderin is superparamagnetic; it produces a large local magnetic field in the same direction as the external magnetic field applied by the scanner. This produces regional field inhomogeneity resulting in more rapid dephasing of nearby proton spins and thus significantly shortened T2-weighted and T2* relaxation times. This manifests as signal hypointensity. Spin-echo T2-weighted sequences (used routinely in brain MRI) largely correct for field inhomogeneity by a 180° radiofrequency pulse, but gradient echo (GE) sequences do not. Thus, the hypointensity produced by haemosiderin is much more pronounced on GE T2* weighted sequences. Susceptibility weighting imaging (SWI) is a modified GE sequence specifically tailored to detect haemosiderin.

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CMB are sometimes visible on fluid-attenuated inversion recovery (FLAIR) and spin echo T2 sequences. They are more readily visualized by the B0 diffusion weighted imaging (DWI) sequence. This is acquired using an echoplanar technique making it similar to a GE T2* sequence.[5] CMB are most readily viewed by GE T2* and, in particular SWI sequences (Fig. 1). Compared with GE, SWI roughly doubles detection rates.[6] Other factors that appear to improve microbleed detection are flip angle, increasing echo time,[7] increasing field strength[8] and three-dimensional post-processing techniques.[9]

Microbleed identification is time-consuming, and interobserver agreement is moderate at best.[8,10] Small signal inhomogeneities may be 'called' or not. Semi-automated approaches[11–13] and rating scales[14] have been proposed as a solution. Various microbleed mimics compromise detection: calcification, basal ganglionic iron deposition, cavernomas, bone artifact and (most prominently) end-on veins (Fig. 2). Deoxyhaemoglobin is also paramagnetic, and therefore appears hypointense on these sequences. Particular caution is needed in the basal ganglia, where iron and calcium deposition may mimic microbleeding.[15] Consensus agreement[3] states that a signal hypointensity should only be classified as a microbleed when it meets all of the following criteria: (i) black ovoid or round small hypointensity on T2*-weighted MRI, demonstrating a blooming effect; (ii) no signal hyperintensity on T1-weighted or T2-weighted sequences (to exclude cavernomas); (iii) at least half of the lesion is surrounded by brain parenchyma (to help exclude focally dilated blood vessels); (iv) the lesion is distinct from other potential mimics (calcium deposits, bone, or vessel flow voids); and (v) clinical history excludes traumatic diffuse axonal injury. CT scans of the area help distinguish haemosiderin from calcium, and scrolling up and down the images ensures any abnormality is not due to bone artifact or flow voids. Minimum intensity projection (MIP) images assist in this latter task.[16]

As the spatial extent of blooming artifact varies with the MRI parameters used,[17] apparent microbleed "sizes" are not directly comparable between scanners or studies. It is therefore not yet clear what the optimum size cut-off for a microbleed should be; however, this dilemma may be more theoretical than practical, as the brain haemosiderin deposits segregate into two distinct sizes (using a 1.5 Tesla standard GE sequence, mean microbleed size was around 3 mm, and macrobleed size 38 mm).[18] Therefore the various size cut-offs used in prevalence studies (5-10 mm)[2] probably do not compromise interstudy comparisons to any significant extent. With routine use of SWI and higher magnet strength, 10 mm seems like a reasonable upper limit.

4. Radiopathological correlation and pathophysiology

To our knowledge, no large-scale radiopathological studies of CMB have been published, only single reports and small case series,[15,19–21] totaling less than 50 patients. The most common

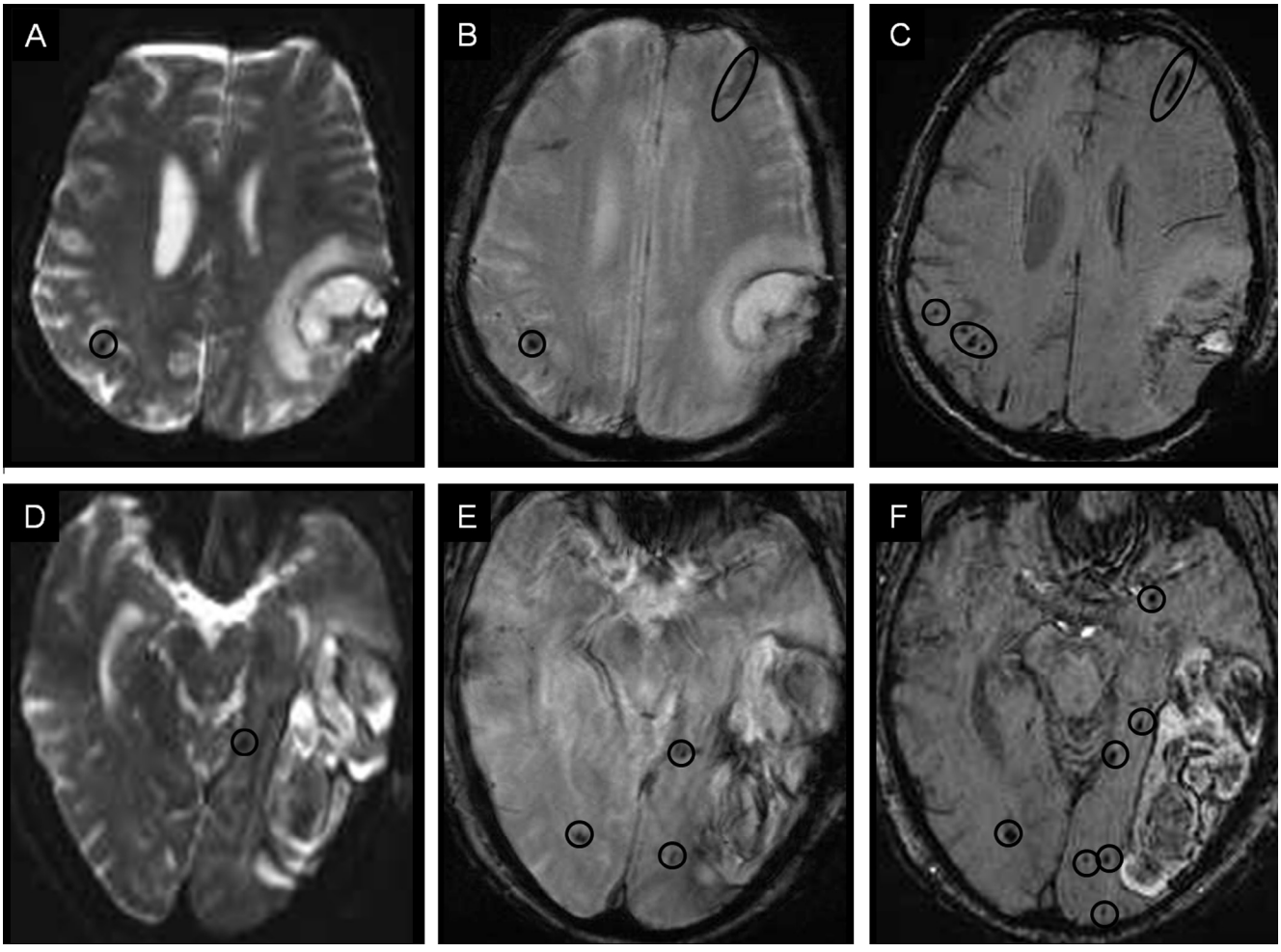

Fig. 1. (A, D) Axial B0 diffusion weighted MRI of patient with a left lobar haemorrhage and numerous microbleeds. Two microbleeds are seen (circled). (B, E) Gradient echo axial T2* MRI through the same levels as (A) and (D) demonstrates two additional microbleeds and an area of superficial siderosis (circled). (C, F) Axial susceptibility weighted MRI demonstrates seven additional microbleeds and all microbleeds seen with other sequences (circled).