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REVIEW ARTICLE

Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions

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Cortical superficial siderosis describes a distinct pattern of blood-breakdown product deposition limited to cortical sulci over the convexities of the cerebral hemispheres, sparing the brainstem, cerebellum and spinal cord. Although cortical superficial siderosis has many possible causes, it is emerging as a key feature of cerebral amyloid angiopathy, a common and important age-related cerebral small vessel disorder leading to intracerebral haemorrhage and dementia. In cerebral amyloid angiopathy cohorts, cortical superficial siderosis is associated with characteristic clinical symptoms, including transient focal neurological episodes; preliminary data also suggest an association with a high risk of future intracerebral haemorrhage, with potential implications for antithrombotic treatment decisions. Thus, cortical superficial siderosis is of relevance to neurologists working in neurovascular, memory and epilepsy clinics, and neurovascular emergency services, emphasizing the need for appropriate blood-sensitive magnetic resonance sequences to be routinely acquired in these clinical settings. In this review we focus on recent developments in neuroimaging and detection, aetiology, prevalence, pathophysiology and clinical significance of cortical superficial siderosis, with a particular emphasis on cerebral amyloid angiopathy. We also highlight important areas for future investigation and propose standards for evaluating cortical superficial siderosis in research studies.

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Abbreviations: CAA = cerebral amyloid angiopathy; cSAH = convexity subarachnoid haemorrhage; cSS = cortical superficial siderosis; GRE = gradient recalled echo; ICH = intracerebral haemorrhage; SWI = susceptibility-weighted imaging

Introduction

Siderosis—derived from the Greek word *sideros* meaning iron—refers to the deposition of iron-containing compounds in body tissues. Superficial siderosis of the CNS describes linear deposits of the blood-breakdown product haemosiderin within the subarachnoid space, the leptomeninges and the superficial layers of the cerebral or cerebellar cortices, or the spinal cord. For many years superficial siderosis could only be clearly identified at post-mortem, but with the recent advent of iron-sensitive MRI techniques, such as T_2*-gradient recalled echo (T_2*-GRE) or other susceptibility-weighted sequences, it can now be diagnosed *in vivo* as a characteristic low signal intensity (dark) rim around the outer surfaces of the brain or spinal cord. There are two types of siderosis, which differ with regard to underlying pathologies and clinical presentation. 'Classical' superficial siderosis of the CNS, first described in 1908 (Hamill, 1908), primarily affects the infratentorial regions and spinal cord, and typically presents with slowly progressive sensorineural hearing impairment, cerebellar ataxia and corticospinal tract signs. Although this form of superficial siderosis is assumed to be caused by chronic intermittent or continuous minor bleeding into the subarachnoid space, only in ~50% of cases is a definite bleeding source identified (e.g. tumours of the CNS, history of head trauma, or history of head or spinal surgery) (Fearnley *et al.*, 1995).

Within the past decade, a second type of brain siderosis restricted to the supratentorial compartment and the convexities of the cerebral hemispheres, has been identified and referred to as 'cortical' superficial siderosis (cSS) (Linn *et al.*, 2008). cSS has a different range of potential causes and clinical presentation to classical siderosis, but in older individuals is emerging as a key feature of cerebral amyloid angiopathy (CAA), a common and important age-related cerebral small vessel disorder (Linn *et al.*, 2010; Viswanathan and Greenberg, 2011; Charidimou *et al.*, 2012*a*). cSS is associated with characteristic clinical symptoms, including transient focal neurological episodes (Greenberg *et al.*, 1993), and might be a marker of future intracerebral haemorrhage (ICH) risk in CAA patients (Charidimou *et al.*, 2013*c*; Linn *et al.*, 2013). Thus, cSS has relevance to neurologists working in neurovascular, memory and epilepsy clinics, and neurovascular emergency services. Given the rapidly increasing interest and clinical relevance of cSS, in this focused review we discuss current knowledge on neuroimaging and detection, differential diagnosis, prevalence, pathophysiology and clinical significance of cSS with an emphasis on CAA, and highlight areas for future investigation.

Search strategy and selection criteria

References for this Review were identified by searches on PubMed between 1990 and February 2015, and references from relevant articles. The search terms 'amyloid angiopathy', 'congophilic angiopathy', 'CAA', 'cortical superficial siderosis', 'cSS', 'acute cSAH', 'fSAH' and 'convexity/convexal or focal subarachnoid h(a)emorrhage' were used as keywords and MeSH headings. References were also identified from the bibliography of identified articles and the authors' own files. Only papers published in English were considered. The final list of references was generated on the basis of relevance to the topics covered in this Review and discussed in the relevant sections.

Neuroimaging of cortical superficial siderosis

The MRI appearance of cSS results from paramagnetic blood breakdown residues (including haemosiderin, a stable end-product of blood breakdown), which cause local magnetic field inhomogeneity resulting in signal loss on T_2*-GRE and susceptibility-weighted imaging (SWI) sequences (Atlas *et al.*, 1988; Greenberg *et al.*, 1996; Haacke *et al.*, 2004) in a curvilinear pattern following the gyral cortical surface. The detection of cSS, like cerebral microbleeds and other paramagnetic lesions, depends on sequence type and parameters including spatial resolution, echo time, slice thickness, and field strength.

T_2*-GRE is a 2D sequence with a typical slice thickness in the order of 4 or 5 mm; the image contrast is dependent on the decay of transverse magnetization (T_2* relaxation), due to a combination of spin-spin relaxation and magnetic field inhomogeneity. For cSS, no formal comparisons of rate of detection for varying T_2*-GRE sequence parameters have been performed. Nevertheless, for other haemosiderin deposits such as microbleeds increased spatial resolution (e.g. thinner slices thickness or 3D acquisition), increased echo time (leading to more dephasing) of T_2*-GRE sequences, and increased magnetic field strength lead to increased visualization of the areas of signal loss (Vernooij *et al.*, 2008; Gregoire *et al.*, 2010).

The SWI sequence uses a 3D acquisition, with a typical slice thickness of 1–2 mm and high in-plane resolution, which generates both 'phase' and 'magnitude images'. SWI exploits additional information from filtered phase images, which reflect local susceptibility changes between neighbouring tissues. The multiplication of 'magnitude images' with filtered phase images yields 'susceptibility-weighted' images which accentuate the visibility of paramagnetic substances such as haemosiderin (Haacke *et al.*, 2009). In addition the SWI images can be displayed as minimum intensity projections (mIP), which produces thicker section (e.g. 10-mm thick) images to further increase the conspicuity of blood products and of cerebral veins. The generation of SWI images is illustrated in Fig. 1C–E. Generally susceptibility effects are more pronounced on studies acquired at 3 T compared to those acquired at 1.5 T (Stehling *et al.*, 2008), which benefits the detection of cerebral microbleeds and cSS, but is also associated with the comparatively small drawback of increased susceptibility artefacts near the skull base.

There have been a few studies comparing T_2*-GRE and SWI for detection of cerebral microbleeds in patients with memory impairment (Goos *et al.*, 2011), dementia (Shams *et al.*, 2015) and CAA (Nandigam *et al.*, 2009; Cheng *et al.*, 2013). All of these showed SWI to have superior sensitivity to T_2* GRE, with almost double the prevalence of microbleeds in one study (Goos, 2011). A formal systematic comparison between T_2* and SWI for detection of cSS has not yet been published but our current clinical experience also suggests that SWI may well be superior (Fig. 1). The ability to produce minimum intensity projection images with SWI has the advantage that cortical veins, which can be a mimic of cSS, are more readily visualized. cSS is typically not detected on T_1-weighted (unless there has been a subacute bleed); occasionally, T_2-weighted MRI might show some evidence of cSS.

Relationship between acute convexity subarachnoid haemorrhage and cortical superficial siderosis on neuroimaging

In most instances, cSS is hypothesized to result from previous acute convexity subarachnoid haemorrhage (cSAH)

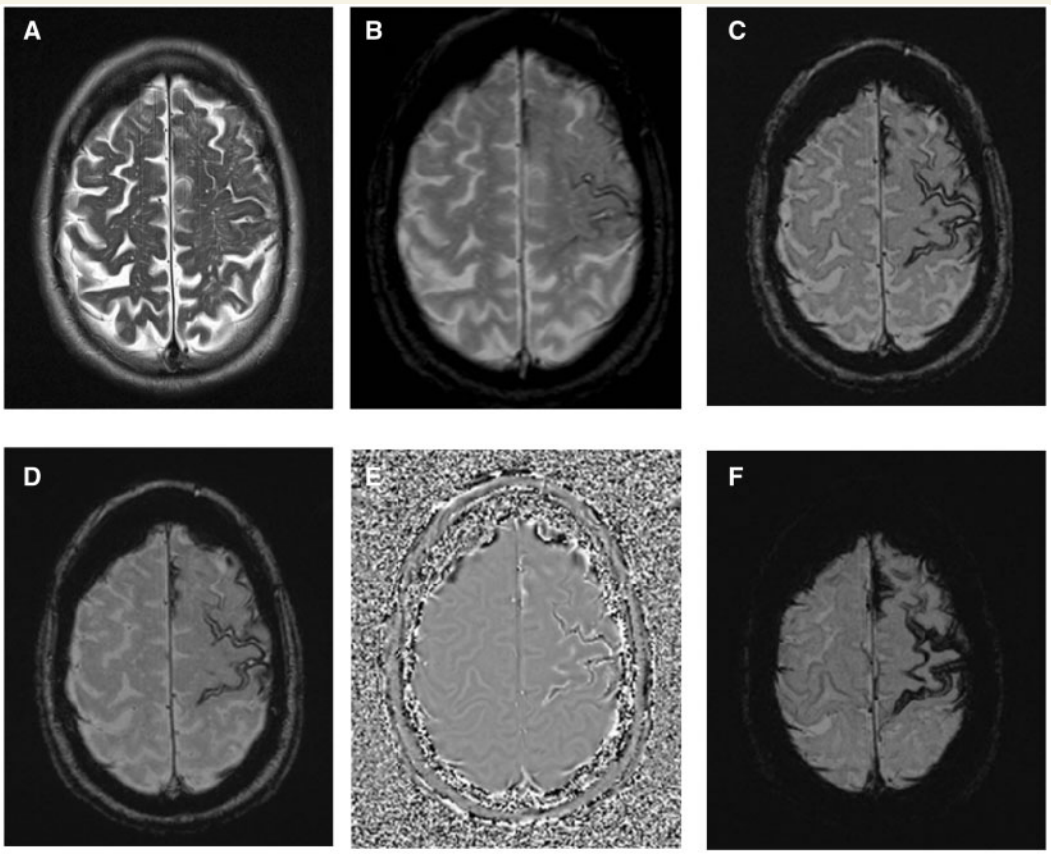

Figure 1 Detection of cSS on different MRI sequences. Axial slices through superior cerebral convexity in a patient with probable CAA. The T_2-weighted image (**A**) shows no cSS, while the T_2*-GRE (**B**) shows cSS as curvilinear low signal intensity areas on the surface of the left frontal gyri. SWI imaging (**C–F**): susceptibility-weighted image (**C**) is produced by the magnitude image (**D**) multiplied with a filtered phase image (**E**), which demonstrates more widespread and more conspicuous cSS than the T_2*-weighted GRE (**B**). The conspicuity of the cSS and of cortical veins is further enhanced in the minimum intensity projection image (**F**).

(Linn *et al.*, 2008, 2010), which may be visualized in the acute phase as high density within the subarachnoid space on CT, or high signal on proton-density or fluid attenuated inversion recovery (FLAIR) MRI. As the acute blood products are further degraded over time (weeks to months), blood residues (typically haemosiderin stored in macrophages; Oehmichen and Raff, 1980) are deposited in the superficial cortical layers. This process results in a bilinear 'track-like' appearance with cSS on either side of a cerebral sulcus in subacute and chronic stages (Fig. 2) (Linn *et al.*, 2008, 2010). Consequently, appropriate imaging can show different time points of the same pathophysiological processes, providing information about the timing, as well as pattern, of bleeding events. At present there are few studies on the neuropathology of cSS but it is most likely that depending on its age or stage of evolution, cSS reflects haemosiderin deposition within macrophages in the leptomeninges or superficial cerebral cortex (Koeppen and Barron, 1971; Feldman *et al.*, 2008; Koeppen *et al.*, 2008).

Terminology and operational criteria for cortical superficial siderosis detection

Many different terms have been used to describe similar lesions including 'subarachnoid haemosiderosis', 'superficial cortical haemosiderosis', 'sulcal siderosis', 'superficial cortical siderosis', 'convexity SAH', convexal SAH', 'cortical SAH', and 'focal subarachnoid bleeding'. In line with the recent STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) initiative (Wardlaw *et al.*, 2013), we suggest that the standardized term 'cortical superficial siderosis (cSS)' is used to describe neuroimaging evidence of chronic blood products in either the superficial (subpial) layers of the cerebral cortex, within the subarachnoid space (sometimes called 'sulcal siderosis'), or both. For acute blood products in the subarachnoid space of cortical sulci, we recommend the term 'acute convexity subarachnoid haemorrhage (acute cSAH)'. We also advocate description of the extent of cSS, e.g. focal cSS (restricted to

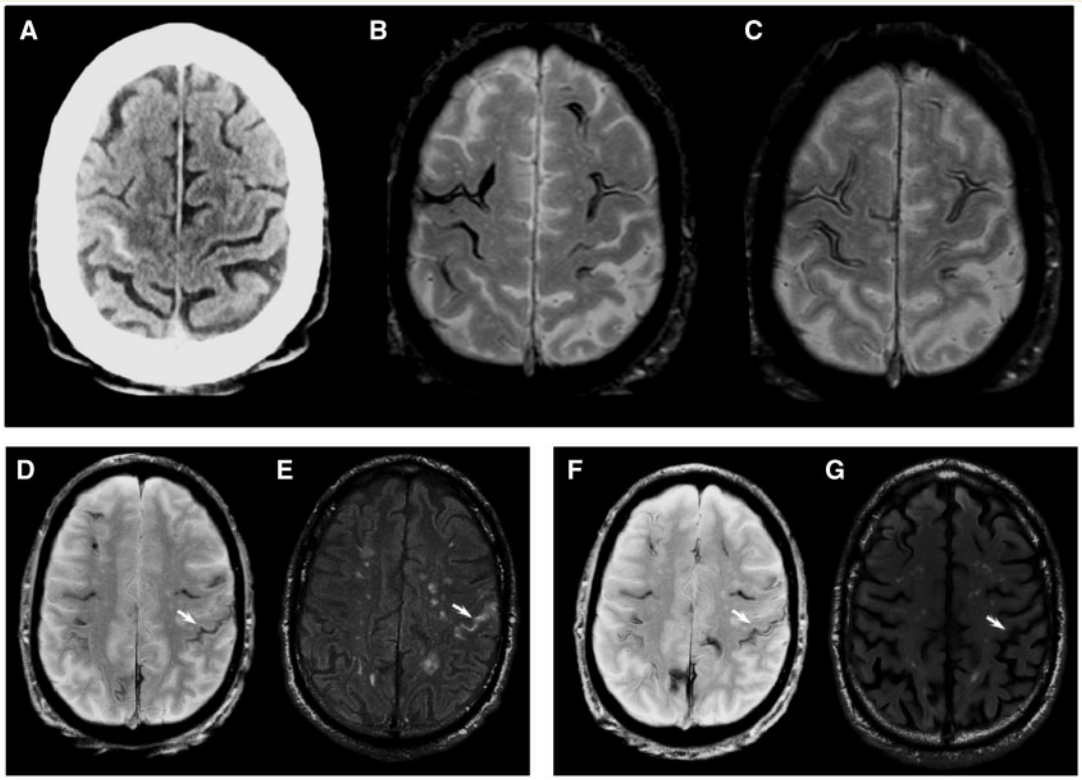

Figure 2 Evolution of acute cSAH into cSS over time in two separate patients with CAA. Axial unenhanced CT (**A**) and axial T2*-GRE magnetic resonance images (**B** and **C**) in a patient with probable CAA illustrate the evolution of acute cSAH into cSS. Acute cSAH corresponds to hyperdensity in sulci on CT (**A**). The MRI shown in **B** was performed 1 day after the CT (**A**). In the chronic stage, cSS forms a characteristic bilinear 'track-like' appearance on the 6 month follow-up axial T_2*-weighted magnetic resonance image (**C**). This pattern is caused by the signal intensity of the normal-appearing subarachnoid space in the middle, bordered bilaterally by the linear haemosiderin deposits in the superficial layers of the adjacent cortex. Panels **D–G** show images from a separate patient with an acute cSAH in the left central sulcus [linear hypointense signal within the subarachnoid space on the axial T_2*-GRE image (**D**, arrow) and hyperintense signal on FLAIR MRI image; **E**, arrow]. At 6-months follow-up (**F** and **G**), cSS again presents with a bilinear appearance on T_2*-GRE (**F**) while no sulcal hyperintensity is visible on FLAIR-MRI (**G**, arrow). Note pre-existing multifocal areas of chronic cSS in the baseline examination, representing probable residues of prior acute cSAHs.

three or fewer sulci) and disseminated cSS (affecting at least four sulci) in line with the modified Boston criteria (Linn *et al.*, 2010) and with potential prognostic relevance (Charidimou *et al.*, 2013*c*). We recommend that radiological reports should differentiate clearly between cSS and 'classical' (infratentorial) superficial siderosis of the CNS, which affects predominantly the infratentorial compartment (posterior fossa, brain stem and spinal cord) and basal cisterns, though may also extend supratentorially (Kumar *et al.*, 2006) (Fig. 3A) due to the differences in causes, clinical features and prognosis.

'Mimics' of cortical superficial siderosis

Suggested criteria for cSS identification and differentiation between true cSS and its 'mimics' are shown in Box 1. Most cSS 'mimics' contain deoxygenated blood or blood degradation products (e.g. cortical veins, thrombosed vessels, or haemorrhagic transformation of ischaemic lesions), but similar appearances may occasionally be unrelated to blood or its products (e.g. mineralization). Due to paramagnetic deoxy-haemoglobin in venous blood, cerebral veins appear markedly hypointense on susceptibility-sensitive sequences (Reichenbach *et al.*, 1997) but, unlike cSS, do not consistently run parallel to convexity sulci and superficial cortical layers, and can be followed into a draining vessel, especially using SWI minimum intensity projection images (Haacke *et al.*, 2011). Cortical vein thrombosis typically causes a pronounced 'blooming effect' on susceptibility-sensitive sequences, yielding a tubular aspect on slices parallel to the thrombosed vein, and a round to oval cross section on slices perpendicular to it (Fig. 3B) (Linn *et al.*, 2010*a*, *b*).

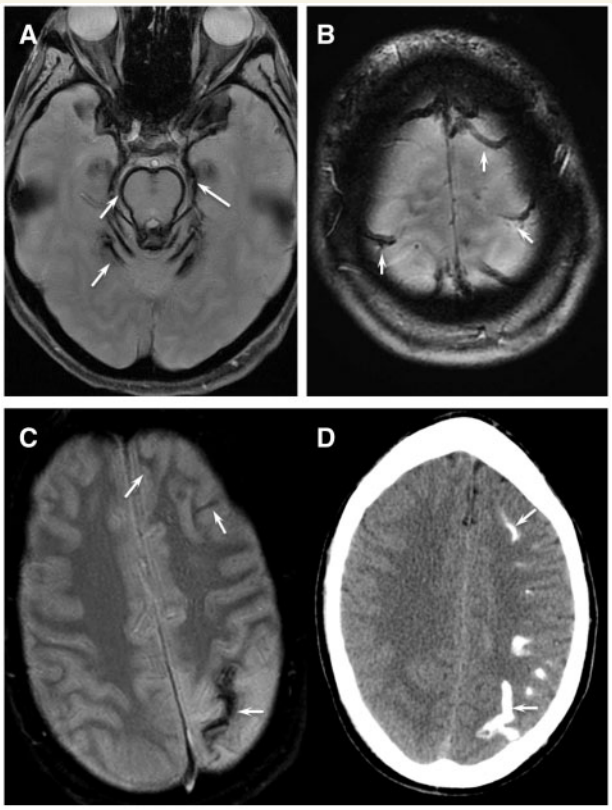

Figure 3 Differential diagnosis and mimics of cSS and acute cSAH. (**A**) A 42-year-old patient with infratentorial superficial siderosis of the CNS (arrows) caused by clinically silent persistent small bleeds into the subarachnoid space following cranial surgery. (**B**) A 34-year-old patient with thrombosis of the cortical veins and the superior sagittal sinus (white arrows). (**C** and **D**) A 30-year-old patient with Sturge-Weber-syndrome. On T_2*-GRE sequence (**C**) the cortical calcifications appear as linear hypointense signals (arrows), similar to superficial siderosis. Unenhanced CT (**D**) allows the correct diagnosis of cortical calcifications (arrows) based on their marked high density.

Haemorrhagic transformation of cortical infarcts can have a linear or serpiginous appearance, usually associated with more extensive parenchymal damage deep to the cortex, with acutely restricted diffusion and gliosis on FLAIR and T_2-weighted images in the chronic stage. Cortical laminar necrosis from hypoxic-ischaemic injury has a characteristic band-like appearance (hyperintense on T_1-weighted images and hypointense on SWI and T_2*-weighted sequences). Sometimes very superficial clusters of multiple cerebral microbleeds can be mistaken for cSS, but these may be distinguished by their irregular, rather than smooth and curvilinear, appearance. Previous chronic lobar ICH can also cause cSS, but in this case, haemosiderin in the sulci is usually contiguous with parenchymal damage, visible on T_2-weighted and FLAIR MRI; review of the clinical history and previous images can also be helpful.

Hypointensity due to mineralization (e.g. calcium) may be linear and cortical (e.g. as in Sturge-Weber syndrome), mimicking cSS, but can be easily distinguished on unenhanced CT (Fig. 3C and D); phase and magnitude information from SWI can also distinguish diamagnetic mineralization from paramagnetic haemosiderin (Mittal *et al.*, 2009; Wu *et al.*, 2009).

Causes of cortical superficial siderosis and acute convexity subarachnoid haemorrhage

In patients presenting with an acute cSAH or with cSS, recent or prior head trauma should first be excluded. Non-traumatic causes should then be considered. CAA is consistently the most likely aetiology of acute cSAH and cSS in older patients (e.g. over 60 years of age), whereas reversible cerebral vasoconstriction syndrome is most likely in younger patients (Kumar *et al.*, 2010; Linn *et al.*, 2010; Khurram *et al.*, 2014), though the number of studies is small, and the prevalence of these and other causes remains uncertain. Reversible cerebral vasoconstriction syndrome is a clinical-radiological syndrome (Ducros, 2012) defined as: (i) acute severe ('thunderclap') headache at onset with or

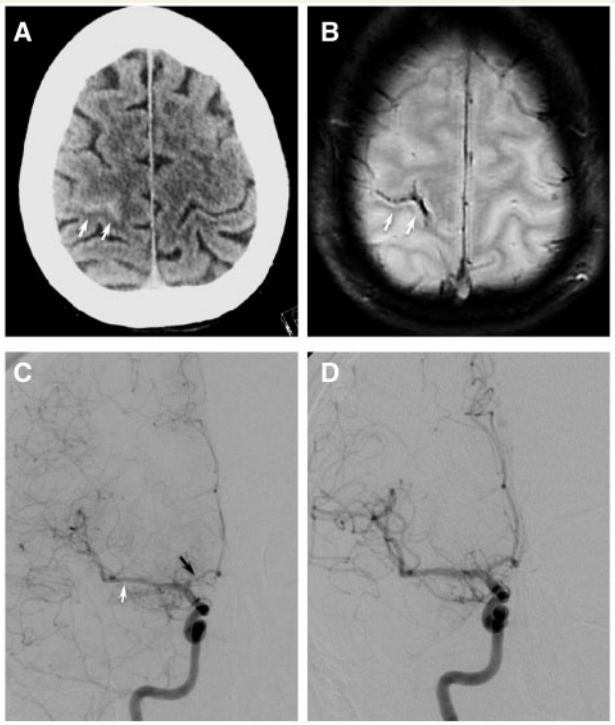

Figure 4 Reversible cerebral vasoconstriction syndrome. Unenhanced CT (**A**) and T_2*-GRE (**B**) show an acute cSAH in the right central sulcus in a 38-year-old patient who presented with thunderclap headache. Digital subtraction angiography after catheterization of the right internal cerebral artery (**C**) depicts severe narrowing of the right middle and anterior cerebral arteries (arrows). Follow-up digital subtraction angiography after intra-arterial infusion of nimodipine shows a normalization of the vessel diameters in response to nimodipine (**D**) supporting vasospasm as the mechanism.

without focal neurological symptoms; (ii) angiographically documented multifocal cerebral vasoconstriction; and (iii) reversibility of vasoconstriction within 3 months (Fig. 4). Known triggers include vasoactive (including sympathomimetic) substances, pregnancy or recent childbirth, but in more than one-third of patients no predisposing cause can be identified (Ducros *et al.*, 2007, 2010). Long-term prognosis is often favourable and determined largely by the occurrence of stroke, although $<5\%$ of the patients develop life-threatening stroke and case-fatality is $<1\%$ (Ducros, 2012). By contrast, aneurysmal rupture typically causes larger SAHs involving the basal cisterns and the interhemispheric fissure, and only rarely causes acute cSAH from a ruptured small peripheral aneurysm (Cuvinciuc *et al.*, 2010).

Less common causes of non-traumatic acute cSAH and cSS include primary angiitis of the CNS, infective endocarditis (Goulenok *et al.*, 2013), hyperperfusion syndrome after revascularization (carotid stenting or carotid endarterectomy), dural arteriovenous fistulae, and cortical venous thrombosis (Cuvinciuc *et al.*, 2010; Panda *et al.*, 2010; Beitzke *et al.*, 2011; Field and Kleinig, 2011; Mas *et al.*, 2013; Geraldes *et al.*, 2014). The diagnosis of primary angiitis of the CNS is very challenging, but clinical history, CSF analysis, irregularities of the distal branches of the cerebral arteries on digital subtraction angiography and cerebral biopsy may be helpful (Hajj-Ali *et al.*, 2011). Cortical venous thrombosis may cause acute cSAH, but the frequency remains uncertain (Panda *et al.*, 2010; Field and Kleinig, 2011). Some studies report high-grade carotid stenosis as a cause of acute cSAH due to altered haemodynamics in dilated pial collateral vessels (Geraldes *et al.*, 2014), but it is possible that the association is coincidental and that the acute cSAH might have an alternative cause (e.g. CAA).

Prevalence and associations of cortical superficial siderosis in healthy elderly populations

In 2009, the population-based Rotterdam Study of 1062 non-demented subjects $\geqslant 60$ years, reported cSS in seven individuals (0.7% prevalence; Vernooij *et al.*, 2009), compared to a much higher prevalence of lobar microbleeds (nearly 14%; Vernooij *et al.*, 2008). Interestingly, all of these subjects with cSS also had lobar cerebral microbleeds, with at least one microbleed close to the area of cSS (Fig. 5). For the present review, the Rotterdam Study group updated this prevalence estimate for all 3401 study individuals aged $\geqslant 60$ years (mean age 71.7, range: 60–98 years; 44.6% male) and found 15 cases (0.4%) of cSS. All subjects had concurrent microbleeds, the large majority (80%) lobar in location. Among 1425 individuals aged >60 years who had two brain scans ~ 3 years apart (mean age 66.5, range: 60–96.8 years; 47.2% male), two developed new cSS (incidence 0.14%) (Fig. 5), one of whom also developed new lobar microbleeds. Of those who had cSS at baseline, four of seven showed progression at 3 years follow-up (Fig. 5). All of these subjects also had multiple lobar microbleeds at baseline, ranging in number from 7 to 130. These data, though originating from a single Caucasian population, suggest a link between lobar cerebral microbleeds and the prevalence, incidence and progression of cSS in non-demented populations, and support the hypothesis that in community-dwelling subjects, CAA is the prevailing underlying pathology of cSS.

Clinical significance and mechanisms of cortical superficial siderosis in cerebral amyloid angiopathy

The two most common sporadic forms of cerebral small vessel disease are: (i) an arteriolar process often related to ageing and other common vascular risk factors (e.g. hypertension and diabetes), characterized pathologically by lipohyalinosis, arteriolosclerosis or fibrinoid necrosis, and

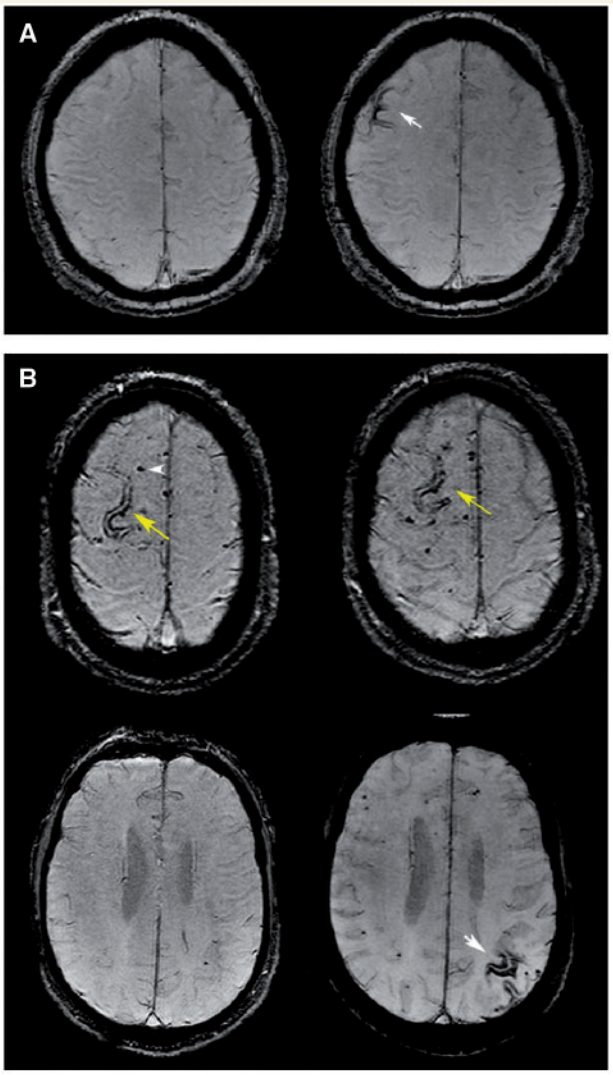

Figure 5 Incident and progression of cSS in healthy elderly individuals. (**A**) Baseline (*left*) and 3-year follow up (*right*) T_2*-GRE scans of the same participant, showing incident cSS (arrow) on the follow up scan. (**B**) Baseline (*left*) and 3-year follow-up (*right*) T_2*-GRE images of community dwelling subject showing right frontal lobe cSS on baseline not changing at follow up (yellow arrows) as well as new left parietal cSS at follow-up (white arrow). Note the presence of multiple microbleeds in close vicinity to the area cSS (**B**, white arrowhead).

typically affecting the small perforating end-arteries of the deep grey nuclei and deep white matter (often termed 'hypertensive arteriopathy'); and (ii) sporadic CAA (Greenberg, 2006; Pantoni, 2010). CAA is characterized by progressive amyloid-β accumulation within cortical and leptomeningeal vessel walls (Charidimou *et al.*, 2012*a*), causing both haemorrhagic and ischaemic brain injury (Smith *et al.*, 2008; Gregoire *et al.*, 2011; Charidimou *et al.*, 2012*a*; Peca *et al.*, 2013). CAA is associated with spontaneous symptomatic lobar ICH in older individuals, which have a high risk of recurrence (Charidimou *et al.*, 2012*a*), and is an important contributor to cognitive impairment (Keage *et al.*, 2009; Arvanitakis *et al.*, 2011). CAA is also associated with characteristic MRI biomarkers including multiple lobar microbleeds (Greenberg *et al.*, 2009), white matter hyperintensities (leukoaraiosis) and more recently, cSS (Linn *et al.*, 2008, 2010), cerebral microinfarcts (Gregoire *et al.*, 2011; Smith *et al.*, 2012) and multiple enlarged perivascular spaces in the cerebral white matter (Martinez-Ramirez *et al.*, 2013; Charidimou *et al.*, 2014). cSS is hypothesized to be more characteristic of CAA than hypertensive arteriopathy because CAA preferentially affects the superficial cortical and leptomeningeal vessels.

Cortical superficial siderosis as a neuroimaging biomarker of cerebral amyloid angiopathy

One study found cSS in 60.5% of patients with histopathologically-proven CAA ($n = 38$; mean age 70 ± 6.4 years) but in none of the controls with histopathologically-proven non-CAA-related ICH ($n = 22$; mean age 54 ± 18 years) (Linn *et al.*, 2010). Of note, the majority of patients with histopathologically-proven CAA in this study had a symptomatic ICH, thus likely representing a selected subset with pathologically advanced disease. A subsequent imaging study further investigated the strength of this association and found cSS in 40% of probable CAA patients, but $<5\%$ of patients with a 'strictly deep' pattern of ICH (Charidimou *et al.*, 2013*b*); cSS was also detected in 15% of patients with a single lobar ICH or mixed (lobar and deep) haemorrhages but in most of these cases lobar cerebral microbleeds were also presence of suggesting some degree of CAA pathology (Charidimou *et al.*, 2013*b*). In another longitudinal cohort of probable CAA cases ($n = 84$), the prevalence of cSS was also high (48%) (Shoamanesh *et al.*, 2014). cSS has also been detected in Dutch-type amyloid angiopathy, a hereditary form of CAA, always in the direct vicinity of a lobar ICH or microbleed(s) (van Rooden *et al.*, 2009). Some of these studies are limited to retrospective convenience samples. There are no data on the prevalence of cSS in other types of hereditary cerebral small vessel disease (e.g. CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Based on these observations, cSS has been suggested as a marker of rupture of CAA-laden cortical or leptomeningeal vessels, offering equal evidence to cerebral microbleeds or ICH for CAA presence. One study included cSS in modified Boston criteria for CAA diagnosis (Supplementary Table 1), and showed a potential improvement in sensitivity (Linn *et al.*, 2010), but further validation studies are needed to determine whether disseminated cSS increases the specificity for CAA. Currently, clinical-imaging diagnostic criteria for

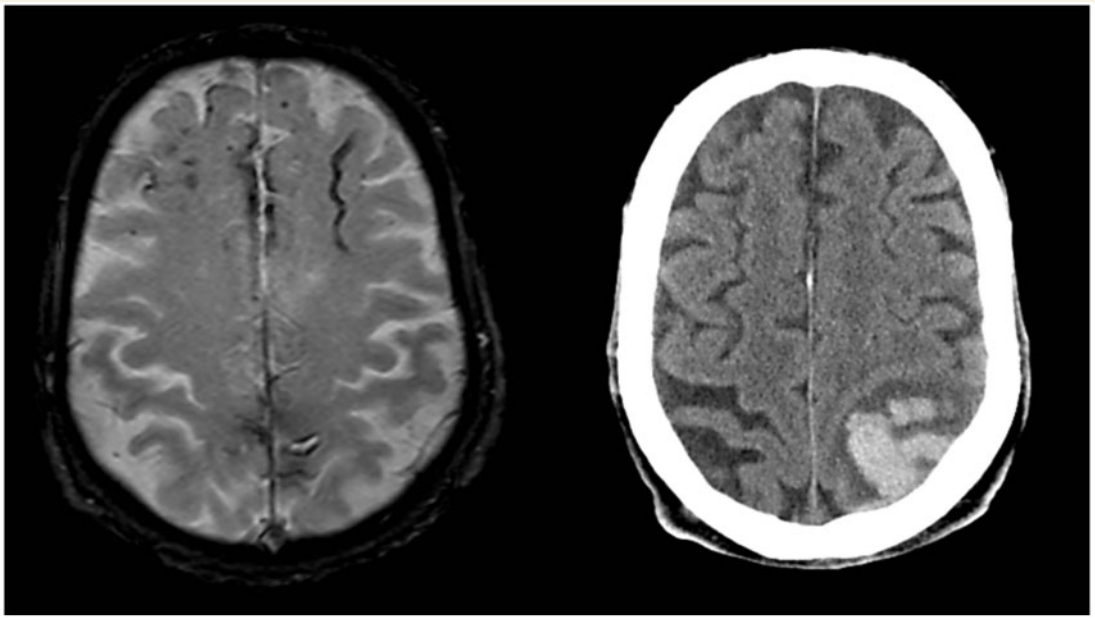

Figure 6 cSS and subsequent ICH. Axial T_2*-GRE MRI (*left*) showing disseminated cSS, with a subsequent spontaneous symptomatic left parietal ICH shown on an unenhanced CT (*right*) at follow-up 4 months later.

CAA can only indicate a high probability of the presence of disease in the absence of histopathological material.

Cortical superficial siderosis and future ICH risk in cerebral amyloid angiopathy

Case reports and small case series (Katoh *et al.*, 2007; Kawahara *et al.*, 2010; Kumar *et al.*, 2010; Profice *et al.*, 2011) suggest that cSS in the context of symptomatic CAA may be a marker of vulnerability to bleeding (Fig. 6). A retrospective cohort on 51 CAA patients with cSS observed new intracranial haemorrhages in 24 patients (47.1%), new ICHs in 18 patients (35.3 %), and new acute cSAHs in six patients (11.7%), during a median follow-up time period of 35.3 months (Linn *et al.*, 2013). A European multicentre study of patients with probable or possible CAA ($n = 118$), including those without cSS at baseline (Charidimou *et al.*, 2013*c*), found that over a median follow-up time of 24 months, 23 of 118 patients experienced symptomatic lobar ICH; cSS was a predictor of ICH risk. The ICH risk at 4 years was 25% (95% CI: 7.6–28.3%) for patients without siderosis, 28.9% (95% CI: 7.7–76.7%) for patients with focal siderosis and 74% (95% CI: 44.1–95.7) for patients with disseminated cSS (log-rank test: $P = 0.0031$). These results remained consistent after adjusting for age, the presence of multiple ($\geqslant 2$) lobar cerebral microbleeds (a haemorrhagic marker of CAA previously shown to influence the risk of ICH; Greenberg *et al.*, 2004), and previous symptomatic ICH prior to the index qualifying inclusion event.

Transient focal neurological episodes related to cortical superficial siderosis and acute convexity subarachnoid haemorrhage

Transient focal neurological episodes have long been known as a feature of CAA, often termed 'amyloid spells' (Greenberg *et al.*, 1993; Charidimou *et al.*, 2012*b*). CAA patients with transient focal neurological episodes are more likely to have cSS than those without (50% versus 19% in one study; Charidimou *et al.*, 2012*c*), which, given the association between cSS and ICH risk, has implications for future ICH risk in patients presenting with transient focal neurological episodes if they are misdiagnosed with transient ischaemic attack and exposed to antithrombotic therapy (Charidimou *et al.*, 2012*b*). Transient focal neurological episodes in CAA were found in 14% of patients with CAA in a recent study (Charidimou *et al.*, 2012*c*); they are typically recurrent, stereotyped, transient (typically lasting minutes to hours) episodes of paraesthesias, numbness or weakness of smoothly spreading onset over seconds to minutes, usually resolving over a similar period (Smith *et al.*, 1985; Greenberg *et al.*, 1993; Roch *et al.*, 2005; Brunot *et al.*, 2010; Finelli, 2010; Raposo *et al.*, 2011). CAA-related transient focal neurological episodes can resemble transient ischaemic attacks, migraine auras or seizures, although may not be quite typical of any of them

(Greenberg *et al.*, 1993; Charidimou *et al.*, 2012*c*). The typically spreading nature of symptom onset, their short duration, and stereotyped character suggest focal seizure activity (Baumann *et al.*, 2006; Hammen *et al.*, 2007; Cianchetti *et al.*, 2009), cortical spreading depression (Dreier *et al.*, 2000; Dreier, 2011) or local vasospasm (Dreier *et al.*, 2000; Feldman *et al.*, 2008), due to fresh blood or blood-breakdown products accumulating in superficial cortical layers of eloquent areas (such as the central sulcus).

Importantly, CAA-related transient focal neurological episodes were associated with an early risk of symptomatic lobar ICH [24.5% (95% CI: 15.8–36.9%) at 8 weeks in one recent multicentre study; Charidimou *et al.*, 2012*c*]; cSS might underpin this increased clinical risk, at least in some patients (Charidimou *et al.*, 2013*c*). It is currently difficult to estimate how often in clinical practice transient neurological symptoms are due to CAA and cSS or cSAH rather than typical transient ischaemic attacks. As few centres routinely acquire blood-sensitive MRI sequences, CAA-related transient focal neurological episodes are likely to be under-recognized.

We therefore suggest that MRI, including not only DWI but also blood-sensitive sequences, is essential in the investigation of older patients with unexplained transient focal neurological episodes, especially if they are atypical for transient ischaemic attack (i.e., recurrent and stereotyped or without known risk factors) (Charidimou *et al.*, 2013*a*). The identification of cSS or acute cSAH as potential mechanisms of transient focal neurological episodes may lead to a diagnosis of previously unsuspected CAA, which should mandate aggressive treatment of known risk factors for recurrent ICH (including hypertension and avoiding antithrombotic exposure). Case series suggest that anticonvulsant or migraine preventive medications may be helpful for symptomatic treatment of transient focal neurological episodes (Finelli, 2010; Paterson *et al.*, 2013), though attacks may also cease spontaneously (Charidimou *et al.*, 2012*c*).

Possible pathophysiological mechanisms of cortical superficial siderosis in cerebral amyloid angiopathy

There are several mechanisms by which CAA might cause cSS: (i) a 'primary' mechanism, unrelated to large parenchymal ICH, due to (repeated) episodes of acute cSAH from brittle and fragile leptomeningeal or superficial cortical CAA-affected vessels; (ii) a 'secondary' mechanism due to leakage or expansion of a lobar ICH (or superficial lobar microbleeds) into the subarachnoid space; or (iii) haemorrhagic transformation of small cortical infarcts.

Acute cSAH precedes cSS in patients with CAA *in vivo* (Linn *et al.*, 2010), a mechanism supported by subpial cortical haemosiderin deposition following experimental models of subarachnoid bleeding (Koeppen *et al.*, 1993). Moreover, recent clinical studies noted cSS mostly distant from ICH (often in the opposite hemisphere), and even in the absence of any ICH (Linn *et al.*, 2010; Charidimou *et al.*, 2013*b*). In one study, 20% of CAA patients with cSS also had evidence of acute cSAH, also consistent with recurrent bleeding into the subarachnoid space (Charidimou *et al.*, 2013*b*).

Lobar ICH causing 'secondary' cSS is supported by associations between previous lobar ICH and cSS in CAA cohorts (Charidimou *et al.*, 2013*b*), as well as CT and direct post-mortem evidence of rupturing from the superficial surface of lobar ICH into the subarachnoid space, or into the ventricles (Itoh *et al.*, 1993; Itoh and Yamada, 1997; Zhan *et al.*, 2004; Maas *et al.*, 2013). A neuropathological series of six autopsy cases of CAA also suggests a link between cSAH and ICH: multiple leptomeningeal arteries can rupture to cause connected haematomas in both the subarachnoid space and the brain parenchyma (Takeda *et al.*, 2003, 2012). These observations might help explain the association between cSS and future ICH risk (Charidimou *et al.*, 2013*c*); cSS (particularly disseminated) may reflect numerous and widespread leptomeningeal blood vessels damaged by advanced CAA, providing multiple potential initiation sites for future ICH (Takeda *et al.*, 2003, 2012).

How cerebral microbleeds relate to cSS remains uncertain. Cerebral microbleeds were almost invariably associated with cSS in the Rotterdam scan study, suggesting a common underlying mechanism (see 'Prevalence and associations of cSS in healthy elderly populations' section). By contrast, a recent study in CAA reported that cSS was not associated with lobar microbleed burden (Charidimou *et al.*, 2013*b*), raising the possibility that cSS and cerebral microbleeds may result from different mechanisms. In support of this idea, a recent observational cohort of patients with symptomatic and likely advanced CAA found that cSS occurred in patients with lower microbleed counts and with the *APOE* e2 allele (Shoamanesh *et al.*, 2014). The hypothesis that cSS and cerebral microbleeds might have partially distinct vasculopathic mechanisms, at least in CAA, requires validation in larger external cohorts.

A 7 T post-mortem MRI study including elderly subjects with various neurodegenerative and cerebrovascular pathologies, suggested that cSS could result from haemorrhagic transformation of cortical microinfarcts (De Reuck *et al.*, 2013) although microinfarcts could also appear close to cSS (Join-Lambert *et al.*, 2013) due to focally active severe microangiopathy.

Prevalence and clinical significance of cortical superficial siderosis in a memory clinic setting including individuals with Alzheimer's disease

Two recent imaging studies evaluated cSS in a memory clinic setting (Wollenweber *et al.*, 2014; Zonneveld *et al.*, 2014). Patients with mild cognitive impairment (MCI) or

dementia had prevalence rates of cSS between 2.1% (in MCI) and 7.1% (any dementia according to ICD-10) (Wollenweber *et al.*, 2014; Zonneveld *et al.*, 2014). Patients fulfilling the criteria for Alzheimer's disease showed a prevalence of 4.8%. cSS was associated with lower MMSE score, *APOE* e4 genotype, higher number of cerebral microbleeds, and white matter hyperintensities burden. The majority of cSS-affected patients did not have a history of ICH. Moreover, not all patients with cSS had cerebral microbleeds [~6% of cases with cSS had no cerebral microbleeds in one study (Zonneveld *et al.*, 2014); 54% in another study (Wollenweber *et al.*, 2014)], so cSS might be the only diagnostic clue to CAA in these patients. In another recent study from a memory clinic population, cSS was also associated with markers of CAA, including higher cortical PET-based Pittsburgh compound B (PiB) retention and *APOE* e2 presence (Na *et al.*, 2015). The available data thus support the hypothesis that cSS might be a manifestation of advanced CAA in memory clinic cohorts, but the exact relationships between cSS, CAA and Alzheimer's disease require further study.

Cortical superficial siderosis and relevance for treatments

Antithrombotic drugs

Currently, there are no evidence-based data outside observational studies to guide antithrombotic treatment decision in patients with CAA and cSS. However, the risk of ICH recurrence in patients with a history of previous CAA-related ICH who are not on antithrombotic therapies is high: ~10% per year (Biffi *et al.*, 2010), which is further increased with antithrombotic drugs (Biffi *et al.*, 2010) or the presence of cSS (Charidimou *et al.*, 2013*c*). In patients with cSS and other neuroimaging or clinical manifestations indicative of CAA (e.g. multiple lobar microbleeds and lobar ICH), we suggest that the risks and benefits of administering antithrombotic drugs (including antiplatelets) should be carefully balanced, especially when a strong indication for antithrombotic treatment that might outweigh the risk of ICH exists (for example unstable ischaemic heart disease or non-valvular atrial fibrillation). A well-designed randomized controlled trial might ultimately resolve these important clinical questions, but will be challenging to perform. Future studies should explore if cSS is a clinically important feature for haemorrhagic risk assessment in older patients without symptoms, in the context of anticoagulants, including recently approved newer direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban) (Connolly *et al.*, 2009; Granger *et al.*, 2011; Patel *et al.*, 2011; Giugliano *et al.*, 2013). Careful control of blood pressure in CAA-associated cSS is reasonable in this situation, as it is likely to provide protection against CAA-related cerebral haemorrhage (Arima *et al.*, 2010).

Cortical superficial siderosis in clinical trials: immunization therapy in Alzheimer's disease and cerebral amyloid angiopathy

cSS could have implications for disease-modifying immunotherapy treatments in Alzheimer's disease for which there are concerns regarding inflammatory and haemorrhagic complications attributed to rapid amyloid-β shifts from brain parenchyma to the perivascular spaces of small vessels (Salloway *et al.*, 2009; Sperling *et al.*, 2011, 2012; Ostrowitzki *et al.*, 2012). These complications have been collectively referred to as amyloid-related imaging abnormalities (ARIA). Subtypes of ARIA include MRI signal abnormalities suggestive of vasogenic oedema and sulcal effusions (ARIA-E) and cerebral microbleeds and haemosiderin deposits in the form of cSS (ARIA-H) (Sperling *et al.*, 2011). In a consensus paper from the US Alzheimer's Association, cerebral microbleeds (>4) have been considered a possible caution for such treatments (Sperling *et al.*, 2011), but the role of cSS should also be explored as a risk factor for ARIA. With increasing knowledge of CAA pathophysiology, disease-modification by modulating amyloid-β production or elimination may be a realistic option in future; cSS should be investigated as a potential marker for ICH or ARIA risk in future immunotherapy trials in CAA.

Conclusion, critical appraisal of current evidence, and future directions

Accumulating evidence suggests that cSS is a central component of haemorrhagic small vessel associated pathology in various populations, including healthy elderly cohorts, memory clinics and in CAA. cSS is of particular interest in expanding the clinical-imaging spectrum of CAA (Greenberg *et al.*, 1993; Maia *et al.*, 2007; Charidimou, 2015, Mehndiratta and Mendel, 2015), with the potential to identify new mechanisms and subtypes of the disease. cSS and acute cSAH may have clinical relevance for: future haemorrhage risk and the effect of antithrombotic drugs; relationship to other manifestations of small-vessel disease; and for cognitive impairment and neurological dysfunction (including transient focal neurological episodes).

It is, however, important to highlight the methodological limitations and potential biases of currently available studies. First, the strength of the association between cSS and CAA and the clinical significance may differ depending on the cohort under study. The different study populations include: (i) symptomatic and likely advanced CAA mainly presenting with lobar ICH and fulfilling the Boston criteria; (ii) memory clinic cohorts where the severity and clinical impact of CAA needs to be further defined; and (iii) healthy elderly individuals, in whom CAA may be asymptomatic but suspected on the basis of associated imaging and

Box 1 Recommended criteria for identification of cortical superficial siderosis and acute convexity subarachnoid haemorrhage (acute cSAH) in the context of CAA

- Well-defined, homogeneous hypointense curvilinear signal intensity (black) on T_2*-GRE or SWI MRI in the superficial layers of the cerebral cortex, within the subarachnoid space, or both
- Blooming effect on T_2*-GRE and SWI compared to T_1- or T_2-weighted sequences
- If there is corresponding signal hyperintensity in the subarachnoid space on proton density-weighted or FLAIR sequences (or hyperdense on CT if available) we recommend the term 'acute cSAH'
- Axial T_1-weighted or FLAIR images should be used for anatomical confirmation of the gyral location of the signal hypointensities identified on T_2*-GRE or SWI sequences
- Absence of infratentorial (brainstem, cerebellum, spinal cord) siderosis
- Ensure exclusion of potential haemorrhagic and non-haemorrhagic mimics (e.g. vessels flow voids, thrombosed vessels, petechial haemorrhagic transformation of infarcts, calcium deposits)
- Consider all potential non-CAA secondary aetiologies of cSS and acute cSAH

Box 2 Advised standards for evaluating cortical superficial siderosis (cSS) in research studies of small vessel disease and cerebral amyloid angiopathy

- cSS and acute cSAH should be clearly defined according to the criteria in Box 1
- cSS should be categorized as focal or disseminated (e.g. in line with the modified Boston criteria)
- In each patient the location (cerebral lobes etc.) of cSS and number of cerebral sulci affected should be recorded
- cSS and acute cSAH should be evaluated separately as they convey information on the chronicity of bleeding events
- cSS or acute cSAH clearly connected with any lobar intracerebral haemorrhage should be rated separately as they may not provide clear evidence of individual bleeding events distinct from the ICH
- Other relevant vascular neuroimaging lesions both remote from and in close proximity (e.g. up to 1 cm) to cSS (e.g. cerebral microbleeds, acute small DWI lesions, perivascular spaces) should be evaluated using established standards [e.g. those described in the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) initiative]

genetic findings. The Boston diagnostic criteria have high specificity and relatively good sensitivity in ICH populations (Knudsen *et al.*, 2001), but have not been validated in community samples. Even in ICH populations, the specificity of the 'probable' category may not be 100%, so that some individuals without CAA may have been misclassified. Robust large-scale unselected prospective data on cSS in all populations of interest remain scarce; studies to date have been mainly performed by a small number of research groups including potentially biased convenience samples. For example, the evidence for an independent link between cSS and future ICH risk comes from one multicentre hospital-based cohort. Defining the true clinical relevance of cSS requires replication of currently available data in larger systematic unbiased prospective studies in relevant hospital and community populations; key areas for future research are shown in Supplementary Table 2. The ongoing SuSPect-CAA trial (Superficial Siderosis in Patients with suspected Cerebral Amyloid Angiopathy; clinical trials identifier: NCT01856699) is a multicentre study, which aims to prospectively evaluate acute cSAHs and cSS as independent predictors for future stroke and mortality in patients with possible or probable CAA, as well as to better define their clinical presentation and outcome. Data from the SuSPect-CAA study may help further define the role of cSS as a neuroimaging biomarker in future CAA treatment trials (Greenberg *et al.*, 2014). Further promising areas of research include correlations of cSS with non-invasive amyloid-β molecular imaging with PET agents such as PiB to determine its relationship to amyloid deposition (Gurol *et al.*, 2012, 2013; Baron *et al.*, 2014), assessment of associations with *APOE* genotype (Rannikmae *et al.*, 2014; Charidimou *et al.*, 2015; Mehndiratta and Mendel, 2015), and systematic radiological-pathological correlation studies. We suggest in the meantime that clear standards for cSS definition, detection and evaluation will help facilitate cross-study comparisons and pooling of data in future collaborative research efforts (Boxes 1 and 2).

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Supplementary material

Supplementary material is available at *Brain* online.

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