Infratentorial Superficial Siderosis: Classification, Diagnostic Criteria, and Rational Investigation Pathway

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Central nervous system infratentorial superficial siderosis (iSS) is increasingly detected by blood-sensitive magnetic resonance imaging (MRI) sequences. Despite this, there are no standardized diagnostic criteria, and the clinical–radiological spectrum, causes, and optimum investigation strategy are not established. We reviewed clinical and radiological details of patients with iSS assessed at a specialist neurological center during 2004–2016 using predefined standardized radiological criteria. All imaging findings were rated blinded to clinical details. We identified 65 patients with iSS, whom we classified into 2 groups: type 1 (classical) and type 2 (secondary) iSS. Type 1 (classical) iSS included 48 patients without any potentially causal radiologically confirmed single spontaneous or traumatic intracranial hemorrhage, of whom 39 (83%) had hearing loss, ataxia, or myelopathy; type 2 (secondary) iSS included 17 patients with a potentially causal radiologically confirmed spontaneous or traumatic intracranial hemorrhage, of whom none had hearing loss, ataxia, or myelopathy. Of the patients with type 1 (classical) iSS, 40 (83%) had a potentially causal cranial or spinal dural abnormality, 5 (11%) had an alternative cause, and 3 (6%) had no cause identified. Intra-arterial digital subtraction angiography did not identify any underlying causal lesions for type 1 iSS. Type 1 (classical) iSS, defined using simple radiological criteria, is associated with a characteristic neurological syndrome. Rational investigation, including spinal MRI, nearly always reveals a potential cause, most often a dural abnormality. Catheter angiography appears to be unhelpful, suggesting that classical iSS is not associated with macrovascular arterial pathology. Recognition of type 1 (classical) iSS should allow timely diagnosis and early consideration of treatment.

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Superficial siderosis of the central nervous system (CNS) is considered to be a rare condition resulting from hemosiderin deposition in the subpial layers of the brain, cranial nerves, and spinal cord.[1] It was first described in 1908[2] and is hypothesized to result from an insidious, low-volume, but protracted or repetitive "leak" of red blood cells into the subarachnoid space.[3] In response to the resultant neurotoxic heme, Bergmann glia and microglia release hemoxygenase-1 and ferritin. Hemoxygenase-1 breaks down heme into free iron and biliverdin, whereas ferritin binds free iron to produce hemosiderin, a likely cause of radiologically detected superficial siderosis. Continuous subarachnoid leakage is hypothesized to eventually overwhelm ferritin synthesis, leading to the neuronal accumulation of neurotoxic iron and light chain ferritin (Fig 1), often with a very long latency (sometimes decades) between the presumed origin of the leak and the development of the clinical and radiological syndrome. The posterior fossa is most affected by siderotic deposition due to the abundance and close proximity of microglia and Bergmann glia in the cerebellum[4] and vestibulocochlear nerve.[5] The cerebellar convexities and superior cerebellar vermis are particularly affected, often with associated atrophy, probably because
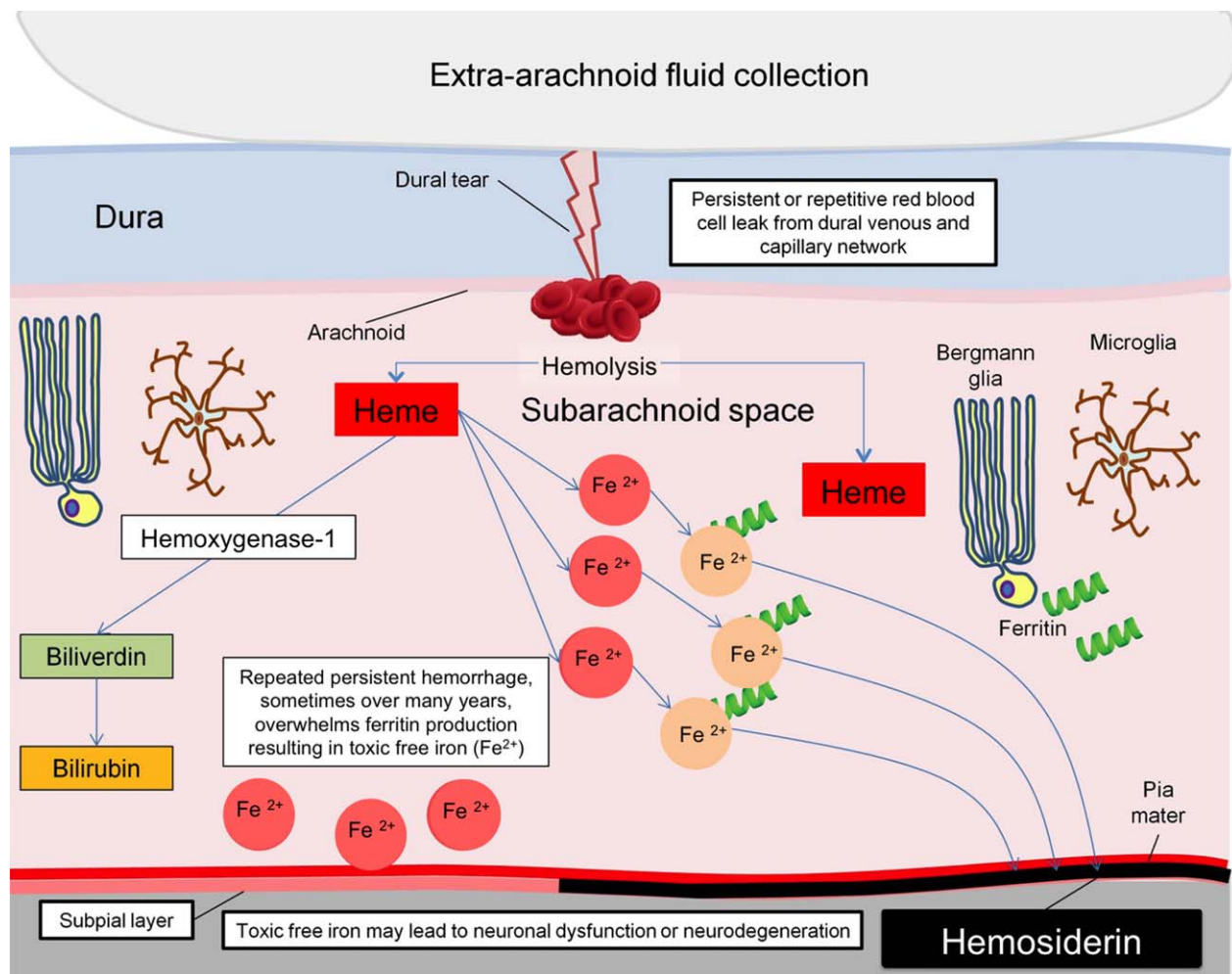
FIGURE 1: Pathophysiology of type 1 classical infratentorial siderosis. [Color figure can be viewed at wileyonlinelibrary.com]

of the pattern of cerebrospinal fluid (CSF) flow; the cerebellar convexities and flocculus are irrigated earliest[6] and are continuously exposed to hemorrhagic cerebrospinal fluid.[7] The olfactory and vestibulocochlear cranial nerves are also especially vulnerable: the olfactory nerve is a CNS structure, whereas the eighth cranial nerve, in contrast to other "true" cranial nerves, has a glia limitans that is nearly 10mm from the medulla.[8,9]

Until the advent of magnetic resonance imaging (MRI), superficial siderosis of the CNS could only be inferred in life from clinical findings and CSF studies, with diagnostic confirmation only possible postmortem.[10] With the increasing use of MRI, including blood-sensitive sequences, "superficial siderosis" is now a common radiological diagnosis. Two anatomical patterns of superficial siderosis are increasingly recognized: (1) cortical superficial siderosis (cSS) restricted to the supratentorial cerebral convexities, which (in older individuals) is often associated with cerebral amyloid angiopathy[11,12] and transient focal neurological episodes[13]; and (2) infratentorial superficial siderosis (iSS), with or without supratentorial involvement, which typically presents with slowly progressive hearing loss, ataxia, and myelopathy.[1,9] A wide range of suggested causes of iSS[9] include subarachnoid hemorrhage from intracranial aneurysms, arteriovenous malformations, tumors, cerebral amyloid angiopathy, and spinal epidural CSF collections.[14–19] Investigations used include MRI of the brain and spine; intra-arterial digital subtraction angiography of the brain or spine, computed tomographic (CT) myelography,[20] and surgical exploration.[17] Although diagnostic criteria and investigation pathways for cSS have recently been suggested,[21] we are not aware of such criteria or pathways for iSS. There thus remains uncertainty regarding how to define, classify, or investigate iSS.

We therefore reviewed all cases of superficial siderosis assessed at our specialist neurological center, aiming to (1) describe the clinical and radiological spectrum and causes of iSS, using predefined standardized radiological criteria for iSS; and (2) develop a rational investigation algorithm.
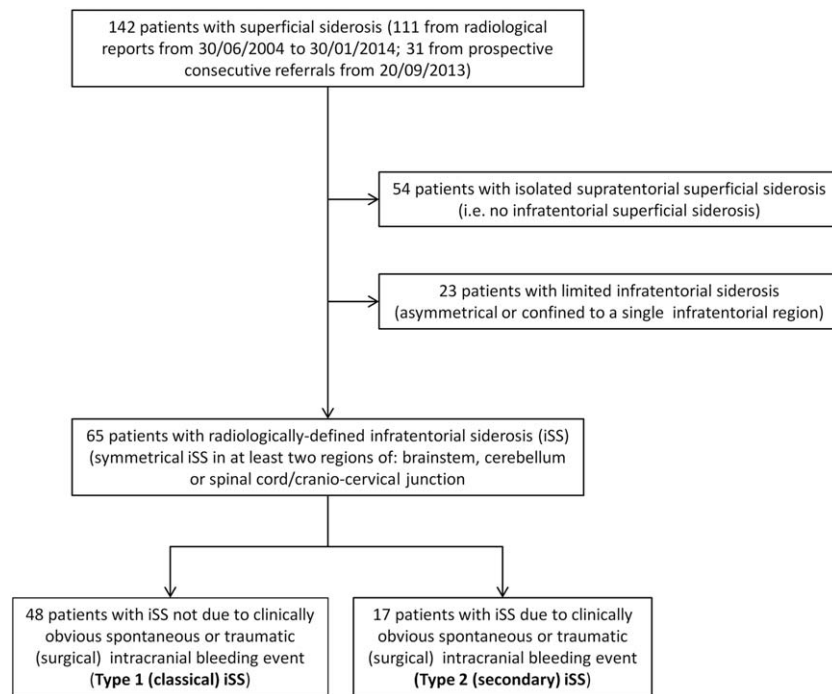
FIGURE 2: Flow chart of patients in study.

Patients and Methods

We prospectively included all patients with suspected iSS referred for assessment to the National Hospital for Neurology and Neurosurgery, Queen Square, London (a tertiary neurology center), from September 20, 2013, as well as those identified by a retrospective keyword search of radiological reports for the term "superficial siderosis" between June 30, 2004 and January 30, 2014. Two consultant neuroradiologists (F.C. and P.C.), and a consultant vascular neurologist (D.J.W.) reviewed all available imaging, blinded to all patient details. iSS was defined according to prespecified standardized radiological criteria based upon many years of author experience of reviewing imaging of patients with the typical syndrome of superficial siderosis of the CNS and internal author consensus, consisting of bilateral (symmetrical) well-defined curvilinear homogeneous low signal on T2 or blood-sensitive sequences (T2* gradient echo or susceptibility-weighted imaging [SWI]) over the superficial surface of at least 2 of the following regions: (1) brainstem (including midbrain, pons, medulla), (2) cerebellum (including the cerebellar folia, vermis, and cerebellar peduncles), and (3) spinal cord or craniocervical junction. The additional presence of supratentorial siderosis was not an exclusion criterion. In each patient, the presumed epicenter and distribution (both infratentorially and supratentorially) of siderosis was noted, and the severity of siderotic deposition was visually graded as mild (a slender rim on SWI but visible on T2), moderate, or severe (an obvious thick rim seen on T2). Associated intracerebral hemorrhage was classified as lobar or deep (including the basal ganglia, brainstem, or cerebellum) depending on the presumed epicenter of the hemorrhage.

All authors reviewed the clinical features (from all available medical records and with additional personal clinical evaluation by D.J.W., D.W., M.O.M., or S.F.F.). We recorded the presence of the typical clinical features of "classical" iSS for each patient (we prespecified these as hearing loss, ataxia, or myelopathy, but also noted other neurological abnormalities, eg, anosmia or sphincter dysfunction). We documented radiological features and all other investigations (eg, CSF analysis). We determined the presumed cause of iSS by consensus among all authors, based upon all available clinical and radiological information.

The project involved only routinely collected clinical data, and was approved as a clinical service evaluation by the Clinical Governance department of the National Hospital for Neurology and Neurosurgery, University College Hospitals NHS Foundation Trust, and was judged not to require formal ethical committee approval.

Results

Identification of Patients

We identified 65 patients with iSS: 31 from a prospective consecutive registry of referrals to our service, and 34 from a retrospective radiological search (Fig 2; Table 2). The radiology keyword search initially yielded 111 unique patients with definite superficial siderosis, of whom 77 were excluded (54 with only supratentorial siderosis [causes shown in Table], and 23 with restricted infratentorial siderosis not fulfilling our predefined radiological criteria), providing a final total of 34 patients with iSS. None of the patients identified from this search with either isolated supratentorial siderosis (n = 54) or restricted infratentorial siderosis (n = 23) had any of the predefined "classical" clinical features of superficial siderosis of the CNS (hearing loss, ataxia, or myelopathy).

TABLE. Causes of Superficial Siderosis in All Patients Identified from Our Prospective Consecutive Registry and Retrospective Radiological Search

Presumed Cause of Superficial Siderosis	Isolated Supratentorial Superficial Siderosis, n = 54	Restricted Infratentorial Superficial Siderosis Not Fulfilling Diagnostic Criteria, n = 23[a]	Type 1/ Classical Infratentorial Superficial Siderosis, n = 48	Type 2/ Secondary Infratentorial Superficial Siderosis, n = 17
Intracerebral hemorrhage ± convexity SAH	28 (52%)	6 (26%)	0	9 (53%)
Traumatic contusions	16 (30%)	3 (13%)	0	0
Aneurysmal SAH	5 (9%)	3 (13%)	1 (2%) atypical aneurysm with slow rather than acute SAH	6 (35%)
Ruptured AVM	2 (4%)	1 (4%)	0	0
Cerebral venous sinus thrombosis	1 (2%)	1 (4%)	0	0
Nonaneurysmal/perimesencephalic SAH	0	1 (4%)	0	0
Surgical trauma directly causing hemorrhage and related siderosis	2 (4%)	4 (17%)	0	1 (6%)
Subdural hemorrhage	0	1 (4%)	0	1 (6%)
Dural abnormality[b]	0	0	40 (83%)	0
Tumor	0	0	4 (9%)	0
Spinocerebellar ataxia with associated brain iron accumulation	0	1 (4%)	0	0
Hemorrhagic transformation of an infarct	0	1 (4%)	0	0
Cause identified	54 (100%)	22 (96%)	45 (94%)	17 (100%)
No cause identified	0	1 (4%)	3 (6%); none had adequate spinal imaging	0

[a]These patients had infratentorial superficial siderosis that was not present bilaterally (symmetrically) in at least 2 of the following regions: (1) brainstem (including midbrain, pons, medulla), (2) cerebellum (including the cerebellar folia, vermis, cerebellar peduncles), and (3) spinal cord or craniocervical junction.
[b]Dural abnormalities included the following: pseudomeningocele, extra-arachnoid cerebrospinal fluid collection, dural ectasia, et cetera. Some of these dural abnormalities were related to previous surgery or trauma, often many years earlier (see Supplementary Table for details).
AVM = arteriovenous malformation; SAH = subarachnoid hemorrhage.

Clinical and Radiological Features of iSS

The median age of the 65 patients with iSS defined according to our standardized criteria was 56 years (range = 44–65 years); 47 (72%) were male. We identified 2 distinct groups, classified by their presumed mechanism, which we term type 1 (classical) iSS and type 2 (secondary) iSS. Type 1 (classical) iSS occurs where there is no obvious spontaneous or traumatic intracranial hemorrhage that could account for the observed pattern of siderosis. Type 2 (secondary) iSS
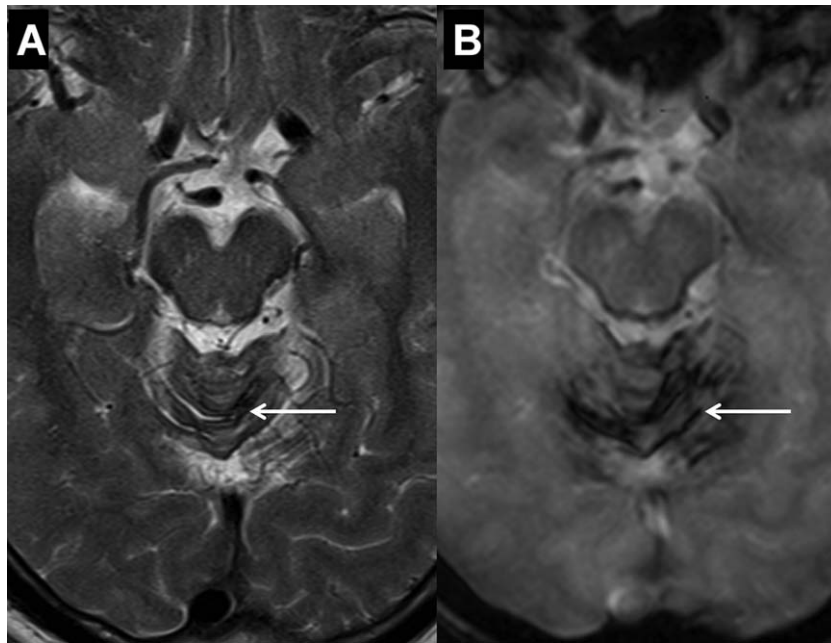
FIGURE 3: Type 1 (classical) infratentorial superficial siderosis shown on T2-weighted axial magnetic resonance image (A) and corresponding T2*-weighted gradient recalled echo (GRE) magnetic resonance image (B) showing the typical pattern of hemosiderin centered on the cerebellar vermis (*arrows*). Note the "blooming" effect on the T2*-weighted GRE image (B) compared to the T2-weighted image (A).

occurs where there is an obvious single spontaneous or traumatic intracranial hemorrhage that, based on its spatial distribution and timing, was thought to be the likely cause of the observed pattern of siderosis.

TYPE 1 (CLASSICAL) ISS. Forty-eight patients had type 1 (classical) iSS. Forty (83%) of these patients had at least 1 of the 3 typical clinical features of "classical" superficial siderosis of the CNS (hearing loss in 31 of 40 [78%], ataxia in 31 of 40 [78%], and myelopathy in 20 of 40 [50%]). The other neurological features of type 1 (classical) iSS included: bladder/bowel problems in 12 of 40 (30%) and swallowing problems in 3 of 40 (8%). In the 17 patients in whom we had sufficient historical data to calculate the latency between the presumed casual event and onset of first symptoms, the median was 19 years (interquartile range = 15–27 years; range = 4–50 years). All but 1 of patients with type 1 (classical) iSS had symmetrical hemosiderin staining centered on the posterior fossa, with involvement of cerebellar folia, with a predilection for the superior vermis (Fig 3); a few also had less extensive supratentorial superficial siderosis and/or superficial siderosis of the cervical or thoracic spine (Supplementary Table).

TYPE 2 (SECONDARY) ISS. In 17 patients, we identified a single episode of acute, spontaneous, or traumatic (surgical) intracranial hemorrhage (spontaneous intracerebral hemorrhage [n = 8], aneurysmal subarachnoid hemorrhage [n = 6], intraventricular hemorrhage [n = 1],

surgical trauma associated with removal of a pineal tumor [n = 1], and bilateral subdural hemorrhages [n = 1]; see Supplementary Table). In all cases, the intracranial hemorrhage was temporally and/or spatially associated with the radiological pattern of superficial siderosis, and judged by consensus to be a sufficient cause of the pattern of siderosis observed. In all of these patients, the siderosis surrounding the site of intracranial bleeding was far more extensive than the iSS (which, in most cases, consisted of a slender rim of hemosiderin, often centered on the fourth ventricle outlet [Fig 4, Supplementary Table]). None of the patients with type 2 (secondary) iSS had a slowly progressive clinical syndrome, and none had any of the clinical features of "classical" superficial siderosis of the CNS. The mean time from the intracranial hemorrhage event to diagnosis on MRI for type 2 iSS was 25 months (range = 11 days to 13 years).

Investigation Findings in Type 1 (Classical) iSS

CRANIAL MRI. Forty-eight of 48 (100%) of the type 1 (classical) iSS patients underwent brain MRI. Of these, 45 patients (94%) had paramagnetic sequences using either T2* or SWI. Although the "blooming artifact" with either T2* or SWI makes hemosiderin deposition far more visible (see Fig 3), in our cohort there were no cases where siderosis was only visible on T2*/SWI and not T2-weighted MRI. Relevant
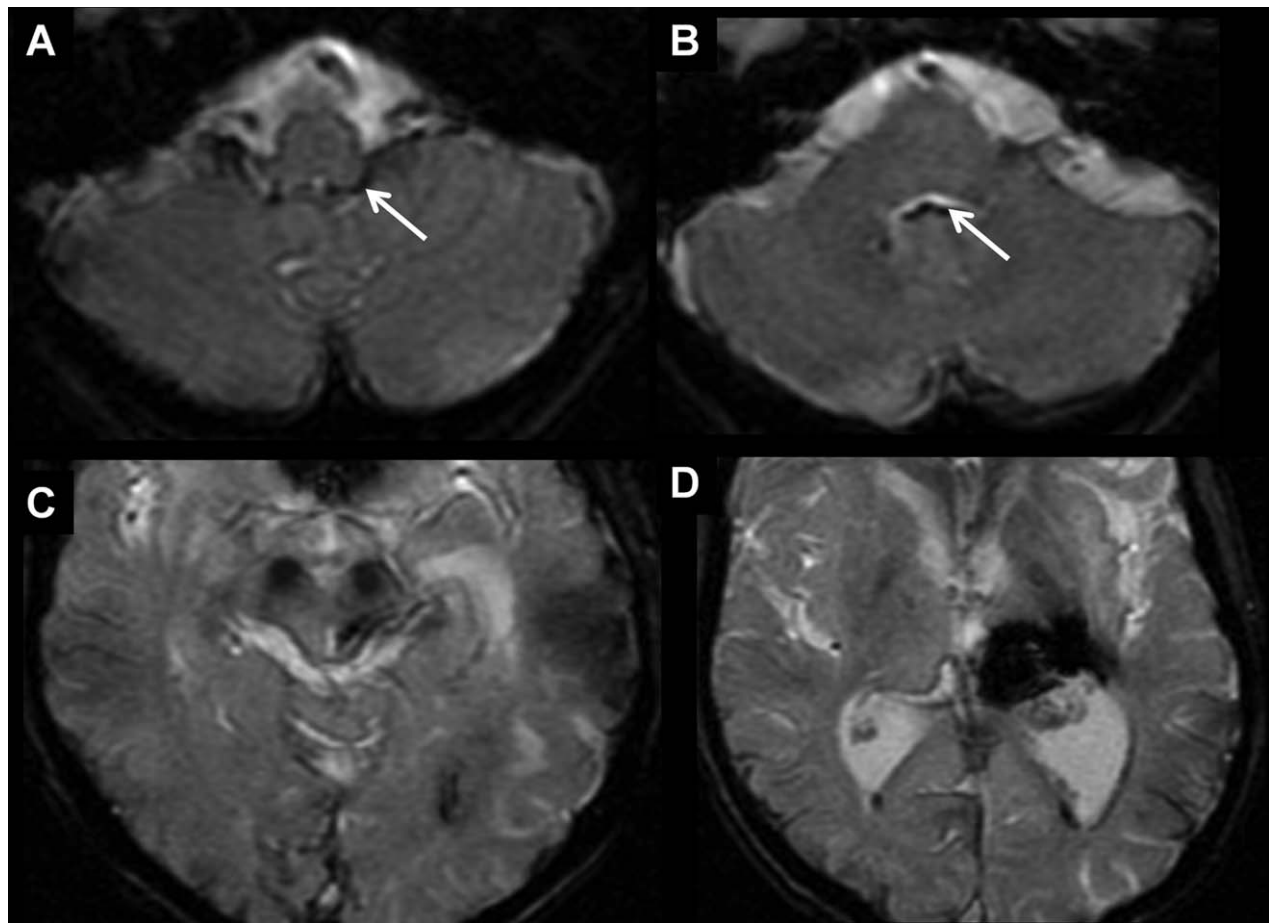
FIGURE 4: Type 2 (secondary) infratentorial superficial siderosis, caused by a deep basal ganglia intracerebral hemorrhage, shown on axial T2*-weighted gradient recalled echo magnetic resonance images. Note that the infratentorial superficial siderosis consists of only a slender rim of hemosiderin, centered around the fourth ventricle outlet and extending toward the craniocervical junction *(arrows)*.

presumed causal abnormalities were found on cranial MRI in 13 of 48 (27%) patients. A suboccipital meningocele was identified on cranial MRI in 12 patients (Fig 5I, J); 1 patient had a large posterior fossa arachnoid cyst.

SPINAL MRI. Forty of 48 (83%) classical iSS patients underwent spinal imaging, 27 of whom had high-resolution MRI of the spine using either SPACE (single-slab 3-dimensional T2-weighted turbo spin echo sequence with high sampling efficiency) or CISS (constructive interference in steady state) sequences. Potentially causal abnormalities were noted in 25 of 48 (52%) patients. An extra-arachnoid collection associated with a dural defect was identified in 21 patients (see Fig 5A–F; 9 ventral spinal defects, 7 posterior spinal defects, 4 nerve root pseudomeningoceles, and 1 anterior intracranial dural defect). Four patients had dural ectasia without an obvious frank dural defect (see Fig 5G, H).

INTRA-ARTERIAL DIGITAL SUBTRACTION ANGIOGRAPHY. Eleven of 48 (23%) type 1 (classical) iSS patients underwent intra-arterial digital subtraction angiography (IADSA): 6 cerebral only, 2 spinal only, and 3 both cerebral and spinal. IADSA did not identify any potential cause for siderosis in any of the patients.

CT MYELOGRAPHY. Five of 48 patients underwent CT myelography, which identified potentially causal extra-arachnoid dural abnormalities in all patients; 2 patients had ventral thoracic extra-arachnoid collections, 2 had postsurgical posterior pseudomeningoceles, and 1 had a nerve root avulsion and pseudomeningocele. In the 2 ventral CSF collections, the precise site of the dural defect was not identified on conventional CT myelography; in 1 patient, the precise site of dural defect was subsequently identified by direct injection of contrast into the CSF collection (Fig 6).

CSF ANALYSIS. CSF was available in 17 of 48 (35%) type 1 (classical) iSS patients (see Supplementary Table);
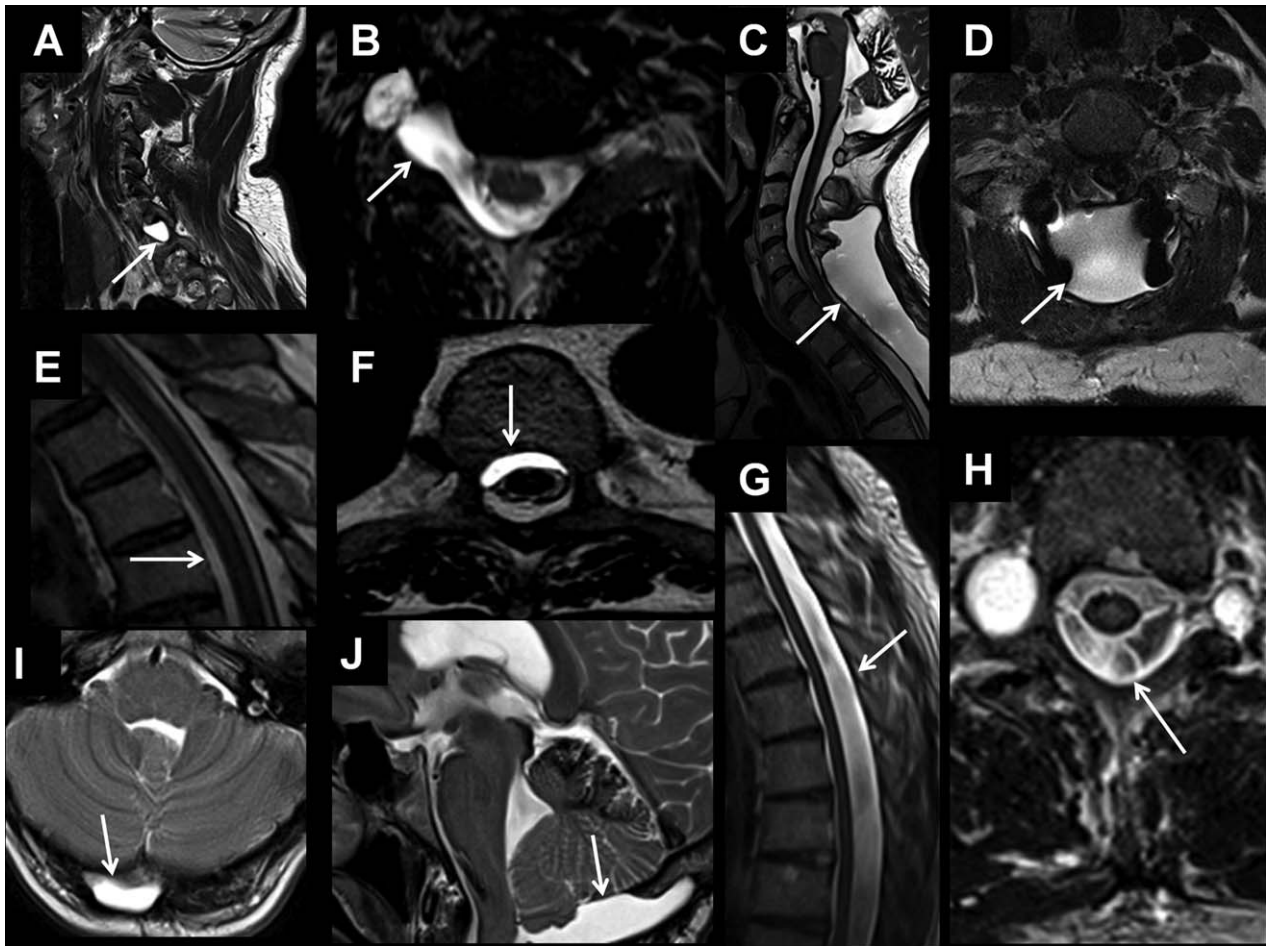
FIGURE 5: Imaging examples of dural defects associated with infratentorial superficial siderosis. (A, B) A nerve root pseudomeningocele *(arrows)* on sagittal T2-weighted spinal magnetic resonance imaging (MRI; A) and axial T2-weighted spinal MRI (B). (C, D) A large posterior spinal cerebrospinal fluid (CSF) collection *(arrows)* on sagittal T2-weighted spinal MRI (C) and axial T2-weighted spinal MRI (D). (E, F) An anterior spinal CSF collection *(arrows)*—in this patient probably related to previous trauma—on sagittal T2-weighted spinal MRI (E) and axial T2-weighted spinal MRI (F). (G, H) Dural ectasia in a patient with Marfan syndrome *(arrows)* on sagittal T2-weighted spinal MRI (G) and axial T2-weighted spinal MRI (H). (I, J) A suboccipital pseudomeningocele on axial T2-weighted MRI (I) and sagittal T2-weighted MRI with associated siderosis over the superior folia of the cerebellar vermis.

red blood cells were present in all cases tested, but ferritin, oxyhemoglobin, and bilirubin were only measured in a few selected cases. Where tested, ferritin was always raised; bilirubin was raised in 60% of patients tested, and oxyhemoglobin in 66% of patients tested. Because of the retrospective nature of this study, detailed data on CSF cell counts, opening pressure, et cetera were not available due to limited clinical documentation.

Presumed Causes of Type 1 (Classical) iSS

A dural abnormality was the commonest finding, found in 40 of 48 (83%) patients with type 1 (classical) iSS; 8 were associated with previous spinal trauma, 21 with previous neurosurgery, 3 with both neurosurgery and spinal trauma, 1 with neurofibromatosis, 1 with Marfan syndrome, 2 with ankylosing spondylitis, and 4 of the dural abnormalities had no obvious underlying cause.

Of the 8 patients with no evidence of any definite dural abnormality, 5 had another potential cause of iSS identified: 2 pineal tumors (where the siderosis preceded any surgery); 1 spinal tumor (not operated upon); 1 partially thrombosed giant aneurysm with an enhancing wall, treated conservatively; and 1 slowly growing thalamostriatal tumor, treated conservatively. Only 3 patients with classical iSS had no possible causative lesion on imaging, but none of these had adequate imaging of the spine.

Presumed Causes of Type 2 (Secondary) iSS

Type 2 (secondary) iSS is attributable to a clear single spontaneous or traumatic intracranial bleeding event (eg, subarachnoid hemorrhage, intracerebral hemorrhage, or surgery), where a significant volume of blood rapidly accumulates and "spills over" to be deposited in the
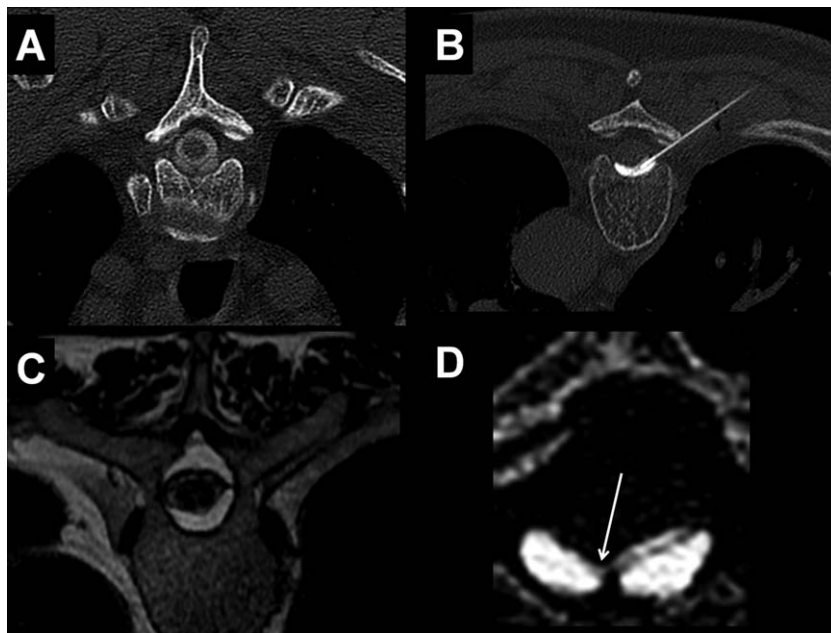
FIGURE 6: Computed tomographic (CT) myelography in the investigation of infratentorial superficial siderosis. (A) CT myelography showing ventral extra-arachnoid spinal collection in the upper thoracic region. (B) Transforaminal injection into the ventral extra-arachnoid collection. (C) Magnetic resonance image showing ventral extra-arachnoid spinal collection (note that differentiation of extra-arachnoid cerebrospinal fluid collection from epidural fat can be difficult). (D) Direct injection of dense contrast into the ventral upper thoracic collection fills the cavity in a gravity-dependent fashion (*arrow* shows the point at which the contrast first enters the subarachnoid space at T2/3, revealing the precise level of the dural defect).

subpial layers of supratentorial and infratentorial structures. By contrast with type 1 (classical) iSS, none of the patients with type 2 (secondary) iSS had any of the typical clinical features of classical superficial siderosis, or a progressive neurological deterioration. Furthermore, in type 2 (secondary) iSS, the siderosis was mainly supratentorial, whereas the infratentorial component was generally a slender hemosiderin rim, often centered around the fourth ventricle outlet. It seems very unlikely that a high-pressure arterial leak (eg, from an aneurysm or arteriovenous malformation) of the type underlying type 2 (secondary) iSS could cause a continuous or highly repetitive low-volume hemorrhage, which may explain the lack of association of secondary iSS with the slowly progressive clinical syndrome that is typical of type 1 (classical) iSS.

Results in the Context of Previous Findings
To the best of our knowledge, the largest previous single series of patients with superficial siderosis included 30 participants.[14] We are not aware of previous studies using a similar classification scheme for iSS.[9] The high incidence of dural abnormalities we found in type 1 (classical) iSS is consistent with a previous case series[14] as well as a number of case reports.[16,17,22,23] Furthermore, case reports show bleeding and venous abnormalities occur at the site of a dural tears.[15,16,22,24–28] However, our findings differ from some previous reports on the causes of

type 1 (classical) iSS; although arteriovenous malformations have been reported to cause 9% of cases of superficial siderosis of the CNS,[9] we found none, and only 1 very atypical aneurysm, visible on plain MRI, with a contrast-enhancing wall. There were no other cranial or spinal macrovascular lesions in our type 1 (classical) iSS cohort. Whereas cerebral amyloid angiopathy (CAA) has been suggested to account for 3% of cases of superficial siderosis of the CNS,[9] we did not find any cases of CAA as a cause of type 1 (classical) iSS; moreover, patients with CAA-related secondary iSS did not have any of the "classical" iSS clinical features of hearing loss, ataxia, or myelopathy. We identified some rarer causes of type 1 (classical) iSS. Neurofibromatosis was the presumed cause of type 1 (classical) iSS in 2 patients, in keeping with previous single case reports.[29,30] Neurofibromatosis, ankylosing spondylosis, Marfan syndrome, and arachnoid cysts might all cause iSS by injury or distortion of the dura, leading to a weak point and a source of slow blood leakage through communication with the subarachnoid space.

Our clinical observations, including a long and slowly progressive history with a characteristic clinical syndrome as well as a symmetrical and stereotyped pattern of iSS, are consistent with the hypothesis that type 1 (classical) iSS results from continuous or repetitive low-volume subarachnoid hemorrhage, which is disseminated
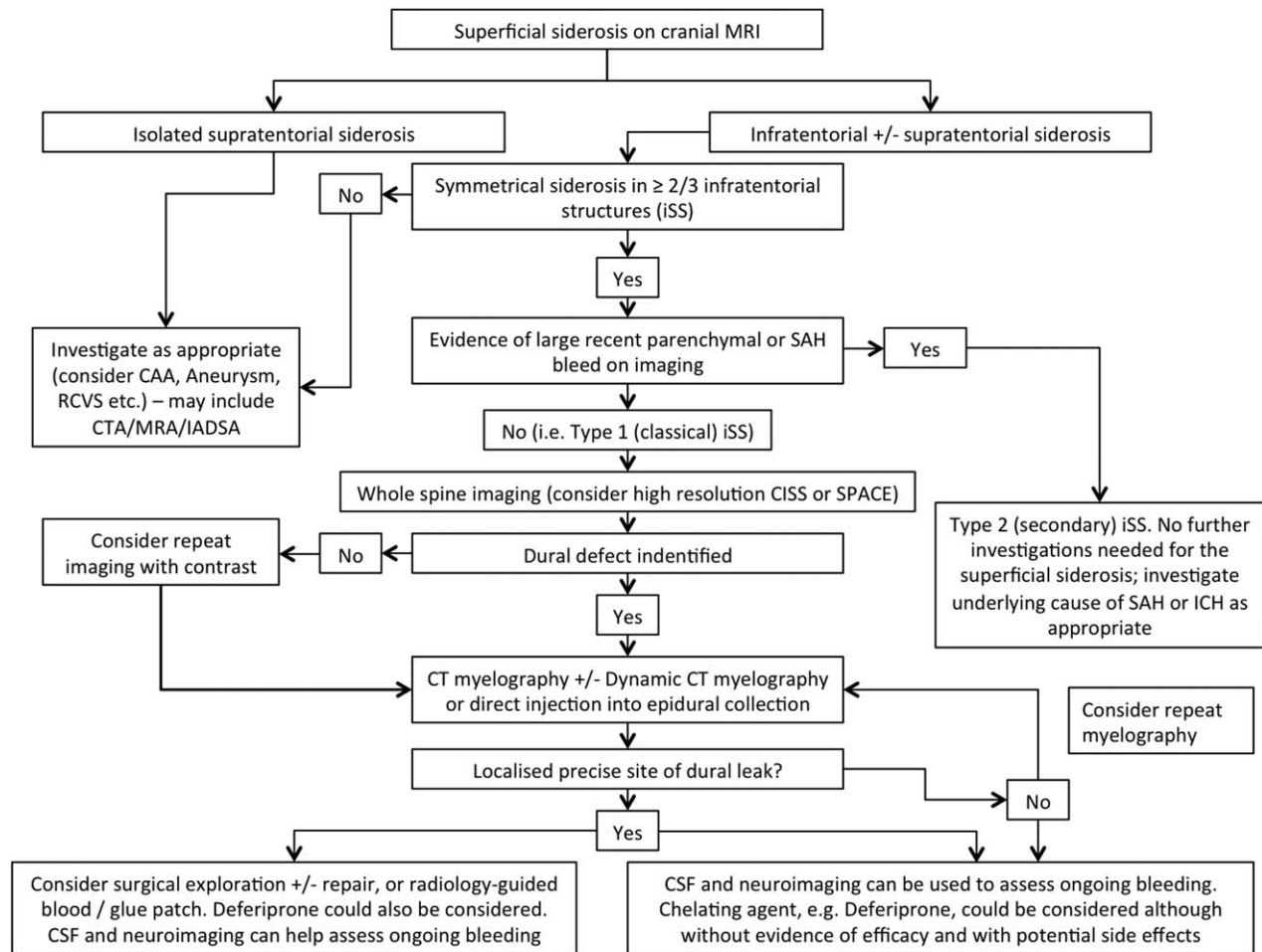
Superficial siderosis on cranial MRI

Isolated supratentorial siderosis

Infratentorial +/- supratentorial siderosis

Symmetrical siderosis in ≥ 2/3 infratentorial structures (iSS) → No

Yes

Evidence of large recent parenchymal or SAH bleed on imaging → Yes

No (i.e. Type 1 (classical) iSS)

Investigate as appropriate (consider CAA, Aneurysm, RCVS etc.) – may include CTA/MRA/IADSA

Whole spine imaging (consider high resolution CISS or SPACE)

Dural defect indentified → No → Consider repeat imaging with contrast

Yes

Type 2 (secondary) iSS. No further investigations needed for the superficial siderosis; investigate underlying cause of SAH or ICH as appropriate

CT myelography +/- Dynamic CT myelography or direct injection into epidural collection

Localised precise site of dural leak? → No → Consider repeat myelography

Yes

Consider surgical exploration +/- repair, or radiology-guided blood / glue patch. Deferiprone could also be considered. CSF and neuroimaging can help assess ongoing bleeding

CSF and neuroimaging can be used to assess ongoing bleeding. Chelating agent, e.g. Deferiprone, could be considered although without evidence of efficacy and with potential side effects

FIGURE 7: Proposed investigation and treatment algorithm in patients with superficial siderosis detected on neuroimaging. CAA = cerebral amyloid angiopathy; CISS = constructive interference in steady state; CSF = cerebrospinal fluid; CT = computed tomographic; CTA = computed tomographic angiography; IADSA = intra-arterial digital subtraction angiography; ICH = intracerebral hemorrhage; iSS = infratentorial superficial siderosis; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; RCVS = reversible cerebral vasoconstriction syndrome; SAH = subarachnoid hemorrhage; SPACE = single-slab 3-dimensional T2-weighted turbo spin echo sequence with high sampling efficiency.

and hemolyzed in the CSF. This suggests the bleeding source is slow, under low pressure, probably of microvascular or venous origin, and most likely to arise in the spine or posterior fossa at the site of a dural defect. The lack of any macrovascular abnormalities on craniospinal IADSA in type 1 (classical) iSS argues against a macroscopic arterial bleeding point. In our series, neurosurgery, often many years prior to the development of clinical or radiological features of iSS, was a common association with type 1 (classical) iSS.

Strengths and Limitations

Our study has some important strengths. Using overlapping methods of case ascertainment, we identified both consecutively referred and retrospectively identified patients over a long period, providing, to the best of our knowledge, the largest single reported case series of patients with iSS. We used predefined standardized radiological diagnostic criteria, with review (blinded to clinical details) by 2 certified consultant vascular neuroradiologists and a consultant vascular neurologist with a specialist interest in superficial siderosis.

Our study also has some limitations. We included referrals to a hospital specialist center, which might cause selection bias. Our prespecified radiological criteria are based upon consensus derived from previous publications and our extensive combined multidisciplinary team clinical experience, rather than a formal consensus group, and have not been validated in other populations. Clinical information from standard healthcare records may have been incomplete. We do not have long-term follow-up data to exclude the possibility that those with type 2 iSS might subsequently develop symptoms of type 1 (classical) iSS. However, we think that this is unlikely. First,

none of the patients with type 2 (secondary) iSS presented with or subsequently developed any symptoms suggesting type 1 (classical) iSS (hearing loss, ataxia, or myelopathy); and second, the radiological features, underlying causes, and clinical presentations suggest that type 1 (classical) and type 2 (secondary) iSS are distinct entities. Finally, over the time period of the study, secular trends in investigation (eg, the wider use of high-resolution spinal imaging and CT myelography) may have affected our detection of potential underlying causes, although the high rate of finding an underlying diagnosis suggests that this was not a major problem.

Clinical Implications

Our study, including a large case series of 65 patients with iSS, confirms a broad clinical and radiological spectrum with numerous different causes. We build on previous observations on superficial siderosis by developing a classification, which we hope will be of value to clinicians faced with the clinical and radiological syndrome of iSS. Using simple predefined standardized radiological criteria, we describe 2 distinct groups of iSS based on presumed etiology, which have different clinical and radiological profiles: type 1 (classical) iSS occurs in the absence of any obvious single intracranial bleeding event and is associated with a slowly progressive neurological deterioration, usually including combinations of deafness, ataxia, and myelopathy. Type 2 (secondary) iSS is clearly attributable to a single spontaneous or post-traumatic intracranial bleeding event and is not associated with slowly progressive neurological deterioration. With a combination of targeted cranial and spinal imaging methods, we found a likely underlying cause of iSS in 94% of patients with type 1 (classical) iSS. IADSA (catheter angiography) of the brain and/or spine did not contribute to detecting a cause for iSS in any patients in our cohort.

Based on our observations, we also propose a rational diagnostic algorithm to follow when superficial siderosis is detected on imaging (Fig 7). Using this approach, we identified a cause for type 1 (classical) superficial siderosis in 45 of 48 patients (94%). The very small proportion without an underlying diagnosis in our series (3 patients, 6%) is much lower than the 35% of unexplained or "idiopathic" cases suggested in the literature.[9] Furthermore, these 3 patients did not have adequate spinal MRI available, so a cause might have been identified if our recommended algorithm was followed. The high diagnostic yield (and frequent finding of dural abnormalities) in our study is likely due to our systematic use of cranial and spinal imaging.

Although there is no treatment proven to alter the natural history of classical iSS, there is preliminary evidence for the safety and tolerability of deferiprone, an iron-chelating drug, which crosses the blood–brain barrier.[31–33] Although iron chelation has unproven efficacy in iSS, it has been associated with possible clinical or radiological improvement[31–36] and decreased ferritin in the CSF.[37] However, agranulocytosis is a potentially serious side effect of deferiprone.[35] Thus, whether iron chelation might lead to clear clinical benefit in iSS remains unproven; randomized controlled trials are needed to test this hypothesis, but will be challenging due to the rarity and slow progression of iSS. An observational trial of deferiprone in superficial siderosis (ClinicalTrials.gov identifier: NCT01284127), with a planned follow-up period of 2 years, has completed recruitment but is not yet published. Iron chelation therapy has also been investigated in other neurological disorders including neurodegeneration with brain iron accumulation; although it can decrease cerebral iron content assessed by MRI, there is currently no compelling evidence that iron removal has beneficial effects in any neurological disorder.[38]

Observational reports suggest that defining and treating causal structural anomalies (eg, surgical repair or blood patches to seal dural defects[17] might be of benefit, but large-scale controlled studies are lacking. Nevertheless, we suggest that it is important to recognize the typical clinical and radiological pattern of type 1 (classical) iSS to ensure rational investigation, timely diagnosis, and early consideration of treatment (ideally in the context of randomized controlled trials); our proposed diagnostic criteria and investigation pathway should help to facilitate this goal.

Author Contributions

D.W., P.C., and D.J.W. were involved with study concept and design, data acquisition and analysis, and drafting the manuscript and figures. F.C., S.F.F., P.R., and M.O.M. were involved with data acquisition and analysis, and drafting the manuscript. D.W. and F.C. contributed equally to the article. P.C. and D.J.W. contributed equally to the article.

Potential Conflicts of Interest

Nothing to report.

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