Neuropsychological and neuroimaging characteristics of classical superficial siderosis

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Abstract

Objective: To define the neuropsychological and neuroimaging characteristics of classical infratentorial superficial siderosis (iSS), a rare but disabling disorder defined by hemosiderin deposition affecting the superficial layers of the cerebellum, brainstem and spinal cord, usually associated with a slowly progressive neurological syndrome of deafness, ataxia and myelopathy.

Methods: We present the detailed neuropsychological and neuroimaging findings in 16 patients with iSS (mean age 57 years; 6 female).

Results: Cognitive impairment was present in 8/16 (50%) of patients: executive dysfunction was the most prevalent (44%), followed by impairment of visual recognition memory (27%); other cognitive domains were largely spared. Disease symptom duration was significantly correlated with the number of cognitive domains impaired (r=0.59, p=0.011). Mood disorders were also common (anxiety 62%, depression 38%, both 69%) but not associated with disease symptom duration. MRI findings revealed siderosis was not only in infratentorial brain regions, but also in characteristic widespread symmetrical supratentorial brain regions, independent of disease duration and degree of cognitive impairment. The presence of small vessel disease markers was very low and did not account for the cognitive impairment observed.

Conclusion: Neuropsychological disturbances are common in iSS and need to be routinely investigated. The lack of association between the anatomical extent of hemosiderin and cognitive impairment or disease duration suggests that hemosiderin itself is not directly neurotoxic. Additional biomarkers of iSS disease severity and progression are needed for future research and clinical trials.

Keywords: Siderosis; Neuropsychology; Cognition; Executive functions

Introduction

Classical, or infratentorial, superficial siderosis (iSS) of the central nervous system (CNS) is characterised by hemosiderin deposition in the subpial tissue layers (to a depth of about 1-2 mm) of the brain, cranial nerves, and spinal cord. This condition, previously considered rare, is now increasingly detected on susceptibility-weighted imaging (SWI) and other blood-sensitive sequences as a low signal intensity (dark) rim around CNS structures. Although it is defined by involvement of infratentorial brain regions such as the brainstem and cerebellum [1], supratentorial involvement has also been described [2]. Classical iSS is hypothesised to result from a chronic, slow, low volume continuous or intermittent leak of red blood cells into the subarachnoid space (see Fig. 1) [1-3]. Haem - produced from haemoglobin - is broken down by haem oxygenase into toxic ferrous iron and bilirubin. Ferrous iron binds to ferritin (produced by Bergmann glial cells in CNS tissues) to produce the stable compound haemosiderin (which is visualised by MRI sequences sensitive to magnetic susceptibility). The continuous slow leakage and catabolism of haemoglobin in brain parenchyma eventually overwhelms local iron storage mechanisms and provides a mechanism for continuous generation of iron-mediated free radical injury to neurons.

Insert Figure 1 here.

Classical iSS typically presents with a slowly progressive neurological syndrome comprising deafness, ataxia and myelopathy [2]. Surprisingly, since the first clinical-pathological description of iSS more than a century ago [4], the cognitive and affective sequelae of iSS have not been systematically studied in detail. In a review of 87 reported cases of iSS, Fearnley and colleagues [2] found that “dementia” was reported in 24% of cases, mostly categorised as ‘severe’ or ‘probably severe’ but with no detailed description of the patterns of cognitive

impairment. The largest neuropsychological study in iSS to date is a convenience sample of six patients [5], which identified impaired visual recall memory and executive dysfunction but no evidence of dementia; two of the six patients showed minimal cognitive impairment despite long symptom duration (both 12 years). Furthermore, this study did not systematically use modern paramagnetic-sensitive MRI sequences (e.g. susceptibility-weighted or T2*-weighted gradient echo) to detect siderosis, nor consider contributions from cerebral small vessel disease or neurodegeneration (including Alzheimer's disease), the commonest causes of acquired cognitive impairment in adults.

Subsequently, there have been only three single case studies all describing severe and widespread impairments [6-8] but without the use of standardised diagnostic criteria or control for other possible causes of cognitive impairment, with high risks of availability and publication bias. We are not aware of any previous systematic studies of mood impairments in classical iSS.

Here we report the comprehensive neuropsychological assessment and detailed neuroimaging findings in 16 consecutively assessed patients with a diagnosis of iSS, defined by objective radiological criteria [1]. Our aims were: (1) to document the frequency of neuropsychological (cognitive and mood) impairment in this population; and (2) to investigate relationships between neuropsychological impairment, iSS neuroimaging markers and symptomatic disease duration, while controlling for the other common potential causes of cognitive impairment (cerebral small vessel disease and neurodegeneration).

Methods

Participants

We searched a prospectively collected database of individuals with iSS who attended a specialist clinic at the National Hospital for Neurology and Neurosurgery (NHNN), Queen Square, London (a tertiary neurology centre) between February 2016 and August 2019. All patients with iSS are discussed at a monthly iSS multidisciplinary team meeting (including neurology, neuroradiology, neurosurgery, neuro-otology, neuropsychology and haematology input) according to a standardized investigation and management pathway [1]. Patients are routinely asked about any cognitive or mood concerns and referred for neuropsychological evaluation based on either patient-reported symptoms, clinical assessment, or both. For this study, the inclusion criteria were: 1) available comprehensive neuropsychological assessment; 2) no obvious spontaneous or traumatic intracranial haemorrhage on MRI, and 3) iSS defined by standard radiological criteria on MRI: bilateral (symmetrical) well-defined curvilinear homogeneous low signal on T2-weighted or blood-sensitive sequences (T2*-weighted gradient echo or SWI) over the superficial surface of at least 2 of the following regions: (1) brainstem (midbrain, pons, medulla); (2) cerebellum; and (3) spinal cord or craniocervical junction [1]. A consultant vascular neurologist (D.J.W.) and neuroradiologist (P.C.) reviewed all available imaging. The distribution of siderosis in infratentorial and supratentorial regions was recorded using a standardised rating form by D.J.W. In addition, all structural markers of cerebral small vessel disease were rated by a trained observer blinded to the neuropsychological data, in accordance with consensus criteria [9], including the presence of microbleeds [10], white matter hyperintensities [11], lacunes [9] as well as global and medial temporal atrophy [12] which are associated with both vascular and neurodegenerative conditions. The demographic

and clinical information collected included: age; sex; presence of "classical" iSS clinical features (i.e. hearing loss, ataxia, myelopathy); symptom duration (years); and presumed cause of iSS.

Neuropsychological assessment

The neuropsychological battery assessed seven different cognitive domains including general intellectual functioning, verbal and non-verbal memory, naming, perception, information processing speed, and executive functioning (see Table 1 for a list of tests administered). Patients received a tailored collection of tests which was considered appropriate by the clinical neuropsychologist, so not all patients received the exact same set of tests. In particular, tests were tailored to circumvent hearing impairment (e.g. providing written instructions, minimizing aural tasks). All patients were assessed in all relevant cognitive domains. Performance on tests was scored according to published standardized normative data. For intellectual functioning, a decline of ≥ 15 points between estimated premorbid functioning based on the National Adult Reading Test (NART) [13] and either the Verbal or Performance IQ on the Wechsler Adult Intelligence Scale- third edition (WAIS-III) [14] was considered impaired. For all other tests, raw scores were converted to percentiles scores. Scoring at or below the fifth percentile was categorized as impairment. Mood was assessed using the Hospital Anxiety and Depression Scale (HADS) [15] or the Depression, Anxiety and Stress Scale (DASS) [16].

Insert Table 1 here

Statistical analysis

Statistical analyses were performed using SPSS (Version 13.0). A partial correlation with one-tailed significance was used to examine the relationship between symptom duration and the

number of cognitive domains impaired, controlling for age. Fisher's exact test was used to investigate whether the likelihood of cognitive impairment was influenced by the presence or absence of small vessel disease markers.

Results

We included 16 patients (6 females), aged between 23 and 73 (mean age: 57 years). Table 2 summarizes their demographic characteristics and clinical symptoms. The prevalence of typical iSS impairments was as follows: deafness 15/16 (94%); ataxia 15/16 (94%); and myelopathy 9/16 (56%). Nine patients (56%) had all three of the typical clinical features of iSS, 5 (31%) had two features and 2 (13%) had one feature.

Insert Table 2 here.

Table 3 summarizes the anatomical distribution of hemosiderin in the included patients. All patients had characteristically symmetrical hemosiderin staining in infratentorial brain regions involving brainstem, cerebellum, craniocervical junction and midbrain regions (see Figure 2a-c for examples of infratentorial findings). For 15 patients (14 of whom who had paramagnetic-sensitive sequences available), there was also evidence of extensive bilateral supratentorial siderosis. The areas involved were typically medial temporal, medial frontal (interhemispheric fissure), insular, perisylvian and medial occipital regions (see Figure 2d-f for examples of supratentorial findings).

Insert Table 3 here.

Insert Figure 2 here.

Table 4 summarizes the prevalence of MRI markers of cerebral small vessel disease in our cohort. Two patients (12%) had cerebral microbleeds, and 2 (12%) had a single lacune; and none had significant white matter hyperintensities (Fazekas score >1). Two patients (13%) had evidence of global atrophy, while 6 patients (38%) had mild medial temporal atrophy.

Insert Table 4 here.

Table 5 details individual patients' performance on the neuropsychological assessment. The percentages describe the proportion of patients who were impaired out of those who were administered that test (see [30] for a similar approach). All patients had intact verbal IQ while 5/15 patients (33%) had significantly reduced performance IQ (PIQ). The most commonly impaired cognitive domain was executive function: 7/16 (44%) were impaired with 2 patients impaired on 2 executive tasks and 5 patients impaired on 1 task. Of the different tests, impairment in verbal response inhibition, set-switching and cognitive estimation was most common (33% each). Four patients (27%) had visual recognition memory impairment, while 2 patients (13%) had verbal recognition memory impairment while. Only 1 patient had recall memory impairment, with none of the other patients showing signs of impairment either in the immediate or delayed condition. Two patients (13%) failed a test of processing speed, but both patients scored in the average range on an alternative test purported to measure the same domain. Naming and visuo-perceptual functions were preserved in all patients.

Eight patients (50%) were impaired in at least 1 cognitive domain, with 4 patients (Patients 1, 3, 5, 14) impaired in 2 domains, 1 patient (patient 16) was impaired in 3 domains and 2 patients (patients 11 and 15) were impaired in 4 domains. Longer symptom duration (in years) was significantly correlated with the number of impaired domains ($r=0.59$, $p=0.011$). Indeed, patients 13-16 had the longest duration of symptoms and all had impairment in at least 1 domain. However, it should be noted that patient 1 had impairment in 2 domains even though they only had reported non-cognitive symptoms for one year. There was no significant relationship between the presence or absence of cognitive impairment and any one or combination of the small vessel disease markers ($p>0.1$).

Of the 13 (81%) patients who had their mood formally assessed, 9 patients (69%) reported mood problems. Anxiety symptoms were more commonly reported than depression symptoms (62% vs 38%). All patients with cognitive impairment reported significant mood problems. However, 3 patients without cognitive impairment also reported mood problems. There were no significant associations between mood problems and disease duration or the extent of siderosis.

Insert Table 5 here.

Discussion

In this detailed neuroimaging and neuropsychological study of 16 patients with classical infratentorial superficial siderosis our main findings were: (1) cognitive impairment was present in 50% of the patients, most often affecting executive functions; (2) the number of cognitive domains impaired was correlated with disease symptom duration; (3) mood disturbance was extremely common, present in 69% of the patients assessed; and (4) in 15/16 (94%) patients (and in all with blood-sensitive MRI), in addition to infratentorial involvement, there was strikingly uniform and distinctive pattern of symmetrical siderosis involving medial frontal, medial temporal, insular and perisylvian regions, regardless of disease duration or cognitive function.

An immediate practical clinical implication of our results is that neuropsychological assessment should be considered as part of the management pathway for people with of iSS. The finding that cognitive impairment was common, together with previous reports, suggests that this is a typical clinical feature of classical iSS, along with the classical triad of deafness, ataxia and myelopathy. Half of the patients included had impairment in at least one cognitive domain, and more than a third had impairment in two or more domains. Comprehensive neuropsychological assessment revealed that executive functions were the most commonly affected, consistent with a previous small study that found executive impairment in all six patients studied [5]. Executive deficits likely arise from neuronal damage disrupting cortico-cerebellar loops [31] as well as disruption of cortico-subcortical pathways mediating executive functions [32]. Given that the patients included had both extensive infratentorial and supratentorial siderosis, our data does not allow us to distinguish the possible separate contributions of these two pathways on cognitive impairment.

In addition to executive impairments, a significant reduction in performance IQ (PIQ) was found in 33% of our sample. However, only one of the five patients scored in the "impaired" range (patient 15). Thus, although the deficit in general intellect is frequent, the effect appears to be mostly subtle. Four patients (27%) were impaired on visual memory, all in recognition but not recall, suggesting that poor performance might be driven by a secondary process such as poor familiarity judgement rather than a visual memory impairment per se [33]. Indeed, all four of our patients with visual recognition impairment also had executive impairment, which might also account for the seemingly contradictory visual recall deficits found by van Harskamp and colleagues [5].

Our cognitive findings do not suggest that iSS is frequently associated with dementia. Although single case studies have all presented patients who have progressive and severe multi-domain cognitive impairment [6-8], these are likely to be at high risk of ascertainment and availability bias. In contrast, our larger study showed a more selective pattern of cognitive impairment, with preserved recall memory, naming, visuo-perception and processing speed. Our findings are more consistent with the large case review of Fearnley and colleagues[2] who found that dementia was reported in only 24% of cases.

With our larger sample and comprehensive assessment, we were able for the first time to examine associations between the frequency and severity of cognitive impairment and the duration of iSS-related symptoms and neuroimaging findings. After controlling for age, longer symptom duration was significantly correlated with the number of cognitive domains impaired, consistent with the notion of continued exposure of CNS tissue to free toxic iron species. However, patients 1 and 3 (with iSS symptoms for 1 and 3 years respectively) showed

impairment in 2 cognitive domains, while patients 10 and 12 (with iSS symptoms for 7 years) showed no impairment. The reason for these discrepancies remains unclear, but are consistent with some previously reported cases [5-6].

Patients had strikingly uniform and symmetric radiological superficial siderosis involving not only infratentorial regions, but also supratentorial brain regions, irrespective of symptom duration. Supratentorial siderosis typically involved the medial frontal, medial temporal, insular and perisylvian regions. The generalised and symmetrical involvement is consistent with the most widely accepted hypothesis that classical superficial siderosis is due to continuous or intermittent low volume bleeding into the subarachnoid space, allowing cerebrospinal fluid (CSF) to carry haem and neurotoxic haem derivative products (including free iron) to exposed CNS surfaces, where sequestration by ferritin (produced by Bergmann glial cells) generates subpial haemosiderin that is visible on paramagnetic-sensitive MRI sequences. The strikingly uniform and characteristic involvement of supratentorial regions might be due to CSF flow or turbulence patterns since CSF flows upward from the basal cisterns providing a constant source of CSF containing blood products. Recent MRI studies of CSF motion show evidence of turbulent CSF flow around the brainstem and sylvian fissures [34].

The lack of association between the extent of hemosiderin deposition and cognitive status provides further support for the hypothesis that hemosiderin itself is not neurotoxic and does not directly cause cognitive impairment (i.e. more widespread siderosis is not related to a greater likelihood of cognitive impairment). Small vessel disease and neurodegenerative markers were rare in our sample, and not related to cognitive impairment, which – by contrast with previous studies - allows us to be confident that the cognitive impairment identified is not

confounded by other vascular or neurodegenerative mechanisms. More sophisticated quantitative MRI studies measuring regional atrophy of the cortical ribbon [35], might be more sensitive to neuronal loss in iSS that could underlie cognitive impairment

More than two-thirds of our patients (69%) reported significant mood problems on a formal self-report measure. Anxiety symptoms were more common than depressive symptoms, but they often occurred together. Although all patients with cognitive impairment had mood problems, some without cognitive impairment also experienced mood symptoms. Although social and behavioural changes in iSS have previously been reported [5-8], mood problems have not been systematically studied. It is unsurprising that patients with iSS should suffer from psychogenic mood problems given the rare, disabling and progressive nature of their condition. However, mood difficulties in iSS could also have a neurological cause from disruption of pre-frontal-limbic, frontal-subcortical and cerebellar-limbic circuits [36-37].

We acknowledge limitations to our study. A large proportion of our sample had hearing impairment which restricted the breadth of neuropsychological tests that could have been administered, potentially decreasing the likelihood of finding cognitive deficits in certain domains, for example in verbal memory where many tests require aural presentation. However, we used a flexible assessment battery and written instructions where appropriate to ensure we assessed all domains across patients, irrespective of their neurological symptoms. In addition, assessment was conducted by a clinical neuropsychologist to ensure possible confounding variables were accounted for clinically. Since not all patients with iSS underwent detailed neuropsychological testing, our cohort might be prone to ascertainment bias and not be fully generalisable to all patients with iSS. Assessment was guided by clinical assessment and self-reported symptoms, so the true prevalence of cognitive and mood impairment in iSS might be

lower than reported. Alternatively, we may not have identified patients with subtle cognitive or mood difficulties. Nevertheless, our data suggests that routine multidisciplinary assessment of people with iSS should include a formal neuropsychological assessment. We also acknowledge that our cross-sectional data were unable to address directly the question of whether there is a causal link between siderosis and cognitive impairment.

Our study of the largest cohort to date reveals that cognitive impairment is common in iSS and is related to disease symptom duration. The extensive and distinct distribution of hemosiderin appears not to be related to iSS symptom duration or the severity of cognitive impairment, although the areas affected by siderosis are consistent with the pattern of cognitive impairment observed. The mechanisms underlying cognitive impairment in iSS remain uncertain but appear unrelated to the anatomical extent of siderosis. Future longitudinal studies with repeated neuroimaging and neuropsychological testing, combined with other biomarkers of disease activity and severity (for example, CSF markers of active bleeding) could help to better clarify the relationship between clinical progression and cognitive involvement. In the meantime, providing psychological interventions for the cognitive and affective consequences of iSS may help alleviate some of the long-term burden of this rare but debilitating disease for patients and their carers.

Declarations

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Conflicts of interest/Competing interests: The authors declare no competing interests

Availability of data and material: Anonymized data supporting the findings of this study will be made available to appropriately qualified investigators on request.

Ethics approval: This study included anonymised data collected as part of standard care, in accordance with a Service Evaluation Agreement approved by the local Research Ethics Committee (National Hospital for Neurology and Neurosurgery).

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Table 1. List of neuropsychological tests used to assess cognitive domains.

Premorbid Intellectual functioning	
	National Adult Reading Test (NART) [13]
General intellectual functioning	
	Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III) [14]
Memory	
	Recognition Memory Tests (RMT), Words and Faces [17]
	Adult Memory and Information Processing Battery (AMIPB), Story and Figure recall [18]
Naming	
	Graded Naming Test [19]
	Oldfield Naming Test [20]
Visuo-perception	
	Visual Object and Space Perception Battery (VOSP) [21]
Executive functions	
	Stroop Colour Word Test [22]
	Hayling Sentence Completion Test [23]
	Modified Card Sorting Test [24]
	Cognitive Estimation Test [25]
	Phonemic fluency [26]
Speed of Processing	
	Symbol Digit Modalities Test (SDMT) [27]
	Trail-Making Test Part A [28]
	'A' Cancellation [29]
Mood	
	Hospital Anxiety and Depression Scale (HADS) [15]
	Depression Anxiety and Stress Scale (DASS) [16]

Table 2. Summary of patient demographic characteristics and clinical findings

Patient	Sex	Age	Symptom Duration (years)	Suspected aetiology of iSS	Hearing loss	Ataxia	Myelopathy
1	M	49	1	CNS tumour/cyst associated with likely dural defect	Yes	Yes	Yes
2	M	71	3	Ankylosing spondylitis with likely dural defect	Yes	Yes	Yes
3	F	23	3	Previous neurosurgery associated with dural defect	Yes	No	No
4	M	49	4	Road traffic accident associated with dural defect	Yes	Yes	Yes
5	M	58	4	Marfan's syndrome associated with dural ectasia and likely dural defect	Yes	Yes	Yes
6	F	67	4	Previous neurosurgery associated with dural defect	No	Yes	No
7	F	65	5	Spinal trauma associated with dural defect	Yes	Yes	No
8	M	44	5	Spinal trauma associated with dural defect	Yes	Yes	Yes
9	M	67	5	Previous trauma with spinal dural defect	Yes	Yes	Yes
10	M	40	7	CNS tumour/cyst associated with dural defect	Yes	Yes	Yes
11	M	54	7	CNS tumour/cyst associated with dural defect	Yes	Yes	Yes
12	F	73	7	Previous neurosurgery associated with dural defect	Yes	Yes	No
13	F	73	9	Spinal trauma with dural defect	Yes	Yes	No
14	F	66	11	Unknown, but spinal imaging was not performed	Yes	Yes	No
15	M	50	15	Previous neurosurgery associated with dural defect	Yes	Yes	Yes
16	M	62	17	Road traffic accident associated with dural defect	Yes	Yes	No

Table 3. Summary of the anatomical distribution of superficial siderosis (+ indicates presence).

Patient	Distribution		Bilateral Involvement	Infratentorial				Supratentorial				
	Infratentorial	Supratentorial		Brainstem	Cerebellum	CCJ	Midbrain	Medial temporal	Medial frontal	Insular	Perisylvian	Occipital
1	+	+	+	+	+	+	+		+	+	+	
2	+	+	+	+	+	+	+		+	+		+
3	+	+	+	+	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+		+		R only
5	+	+	+	+	+	+	+	+	+	+	+	
6	+	+	+		+	+	+				+	
7	+	+	+		+		+	+	+			+
8*	+			+	+							
9	+	+	+	+	+	+	+	+	+	+	+	R only
10	+	+	+	+	+	+	+		+	+	+	
11	+	+	+	+	+	+	+		+	+	+	+
12*	+	+	+	+	+	+	+	+			+	
13	+	+	+	+	+	+	+	+	+	+	+	+
14	+	+	+	+	+	+	+	+	+	+		
15	+	+	+	+	+	+	+	+	+	+	+	+
16	+	+	+	+	+	+	+		+	+		

***siderosis rated on T2-weighted MRI only*

Table 4. Summary of the prevalence of cerebral small vessel disease markers

Pt	Symptom Duration (years)	Cerebral Microbleeds (n)		White Matter Hyperintensities (Fazekas score)		Lacunes (n)		Atrophy	
		Deep	Lobar	pvWMH	dWMH	Deep	Lobar	Global	Medial Temporal
1	1	-	-	1	1	-	-	-	1
2	3	-	-	-	1	1	-	2	1
3	3	-	-	-	-	-	-	-	1
4	4	-	-	-	1	-	-	-	-
5	4	2	6	-	1	-	-	-	-
6	4	-	-	-	-	-	-	-	-
7	5	-	-	1	1	-	-	-	1
8	5	-	-	-	-	-	-	-	-
9	5	-	-	1	1	1	-	1	1
10	7	-	-	-	1	-	-	-	-
11	7	-	-	-	1	-	-	-	1
12	7	-	-	-	-	-	-	-	-
13	9	-	-	-	-	-	-	-	-
14	11	-	-	-	-	-	-	-	-
15	15	-	5	-	1	-	-	-	-
16	17	-	-	-	-	-	-	-	-

MARS: Microbleed Anatomical Rating Scale [10] for identifying the number of deep and lobar microbleeds; Fazekas scale score greater than 1 (0=none; 1=mild; 2=moderate; 3=severe) for the presence of peri-vascular (pv) and deep (d) white matter hyperintensities (WMH) [11]; Number of lacunes were identified according to standardized criteria [9]; Global and medial temporal atrophy was rated using the Pasquier scale (0=None; 1=mild; 2=Moderate; 3=severe) and Scheltens visual scale (0=None; 1=mild; 2=Moderate; 3=severe; 4=very severe) respectively [12].

Table 5. Neuropsychological test results (raw score (percentile); significant impairment is indicated in bold within boxes).

	n (%) impaired	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13	Pt 14	Pt 15	Pt 16
Symptom Duration		1	3	3	4	4	4	5	5	5	7	7	7	9	11	15	17
Premorbid functioning																	
NART		118	101	97	86	80	92	-	122	124	-	106	113	124		102	108
General intelligence	**5/15 (33)**																
WAIS-VIQ		115	93	98	88	88	88	96	128	125		93	-	125	-	91	
WAIS-PIQ		**90**	97	95	110	83	104	95	117	117	125	**90**	110	**97**	-	**69**	**95**
Verbal Memory	**3/15 (20)**																
RMT-W		48 (75-90)	24 (50)	25 (>50)	46 (50-75)	46 (75)	22 (10-25)	44 (50-75)	50 (90)	45 (50-75)	-	**32 (<5)**	23 (25)	48 (75-90)	**11 (<5)**	48 (75-90)	44 (50-75)
AMIPB Story Immediate		-	43 (75-90)	**13 (<5)**	-	42 (50-75)	36 (50-75)	-	25 (25)	35 (50-75)	-	-	-	45 (>90)	22 (10-25)	35 (25-50)	
AMIPB Story Delayed		-	40 (75-90)	**6 (<5)**	-	37 (50-75)	33 (50-75)	-	28 (25-50)	27 (50)	-	-	-	47 (>90)	14 (10-25)	28 (25-50)	
Visual Memory	**4/16 (25)**																
RMT-F		44 (50)	21 (25)	**17 (<5)**	42 (25-50)	**31 (<5)**	21 (25)	44 (50-75)	-	47 (95)	40 (10-25)	42 (25-50)	21 (25)	38 (10-25)	23(50)	**32 (<5)**	**35 (5)**
RMT-Topographical		-	-	-	-	-		-	29 (95)	-	-	-	-	-		-	
AMIPB Figure Immediate		-	76 (25-50)	54 (5-10)	-	57 (25-50)	52 (50-75)	-	72 (50-90)	76 (95)	76 (90)	71 (75-90)	63 (>90)	53 (50-75)		53 (25-50)	63 (75-90)
AMIPB Figure Delayed		-	53 (50)	46 (5-10)	-	68 (50-75)	39 (25-50)	-	74 (75-90)	76 (95)	76 (>90)	74 (90)	63 (>90)	53 (50-75)		46 (25-50)	59 (75-90)
Naming	**0/16 (0)**																
GNT		27 (90-95)	24 (75-90)	17 (25-50)	20 (50)	19 (25-50)	20 (50)	24 (75-95)	28 (99)	29 (>99)		19 (25-50)	21 (50-75)	23 (75)		21 (50-75)	19 (25-50)
ONT		-	-	-	-	-		-	-	-	25/30			-	24/30	-	
Visuo-perceptual functions	**0/16 (0)**																
VOSP-OD		-	-	-	19 (>5)	17 (>5)		-	20 (>5)	18 (>5)	17 (>5)		-	-	-	18 (>5)	18 (>5)
VOSP-IL		-	19 (>5)	-	-	-	20 (>5)	20 (>5)	-	-	-	20 (>5)		-	18 (>5)	-	-
VOSP-SIL		22 (25-50)	-	25 (>5)	-	-		-	-	-	-		23 (>50)	-	-	-	-
VOSP-PD		-	-	-	-	-		-	-	-	-			-	20 (>5)	-	-
VOSP-CA		-	-	-	-	10(>5)		-	-	-	10 (>5)	10 (>5)	9 (>5)	-	-	10 (>5)	10 (>5)
AMIPB Figure Copy		-	-	-	-	-	-	-	-	-	-	-	-	80 (>5)	-	-	-
Executive functions	**7/16(44)**																
Stroop		**75 (2-3)**	-	**70 (2-3)**	93 (15)	-	91 (36)	61 (10-12)	112 (>90)	-	-	86 (24-30)	61 (10-12)	72 (16)	**(<5)**	**56 (2-4)**	78 (20-24)
Hayling SS		6	6 (50)	**3 (5)**	-	6 (50)		-	-	6 (50)	-		-	-		5 (25)	
MCST		-	5/6	-	6/6	6/6		-	-	-	6/6	**4/6**	-	-		-	**4/6**
CETA		-	-	1 (85)	-	-		-	-	-	1 (90)		-	-		**11 (1-5)**	
Fluency S		16 (52)	18 (77-79)	**6 (2)**	12 (30-32)	**4 (1)**	11 (23)	17 (50-75)	20 (82)	21 (75-77)	-	10 (18)	14 (50)	12 (19)	9 (10-25)	17 (61-63)	35 (34)
Speed of processing	**2/16 (13)**																
SDMT		42 (28-29)	-	59 (69)	44 (37)	38 (34)		34 (25-50)	49 (42)	56 (95)	49 (39-42)	**30 (2)**	32 (32)	37 (50)		**26 (1)**	42 (50)
Trail Time A		-	-	-	-	43 (25-50)		36 (25-50)	-	-	32 (25-50)	45 (25-50)	41 (25-50)	34 (50-75)	47 (25-50)	57 (25)	44 (25-50)
Cancelling A		-	42 (5-10)	-	-	-	34 (80)	-	-	-	-			-		-	
Mood	**9/13 (69)**																
HADS - Anxiety		**11 (mod)**	-	-	**12 (mod)**	-	4 (normal)	**16 (sev)**	-	**12 (mod)**	7 (normal)			-	-	-	
HADS - Depression		9 (mild)	-	-	**12 (mod)**	-	8 (mild)	**14 (mod)**	-	5 (normal)	9 (mild)			-	-	-	
DASS - Depression		-	-	4 (normal)	-	**42 (sev)**		-	-	-	-	**20 (mod)**	2 (normal)	6 (normal)	-	**18 (mod)**	2 (normal)
DASS - Anxiety		-	-	**24 (sev)**	-	**26 (sev)**		-	-	-	-	18 (mild)	0 (normal)	0 (normal)	-	**12 (mod)**	**10 (mod)**
DASS – Stress		-	-	**20 (mod)**	-	**32 (sev)**		-	-	-	-	**28 (sev)**	2 (normal)	2 (normal)	-	14 (mild)	8 (normal)

NART= National Adult Reading Test; WAIS= Wechsler Adult Intelligence Test; VIQ= Verbal Intelligence Quotient; PIQ=Performance Intelligence Quotient; RMT= Recognition Memory Test: W – Words, -F: Faces; AMIPB= Adult Memory and Information Processing Battery; GNT= Graded Naming Test; ONT= Oldfield Naming Test; VOSP= Visual Object and Space Perception: OD-Object Decision, IL- Incomplete Letters, SIL-Silhouette, PD-Position Discrimination, CA- Cube Analysis; SS= Scaled Score; MCST= Modified Card Sorting Test; CET A= Cognitive Estimation Test Form A; SDMT= Symbol Digit Modalities Test; HADS=Hospital Anxiety and Depression Scale; DASS=Depression Anxiety and Stress Scale.; Mod-moderate; Sev-severe.

Figure legends

Fig 1. Pathophysiology of classical superficial siderosis.

Fig 2. Axial susceptibility-weighted MR image showing hemosiderin deposition (dark rim) in infratentorial (A-C) and supratentorial (D-F) brain regions: (A) midbrain at the level of the cerebral peduncles (arrowheads) and superior cerebellar vermis (arrow); (B) pons (arrowheads) and cerebellar folia (arrow); (C) craniocervical junction (arrow) and inferior cerebellum; (D) medial frontal lobes (arrowheads), and perisylvian and insular regions (arrows); (E) medial temporal lobe (arrows); (F) medial occipital lobe (arrows).

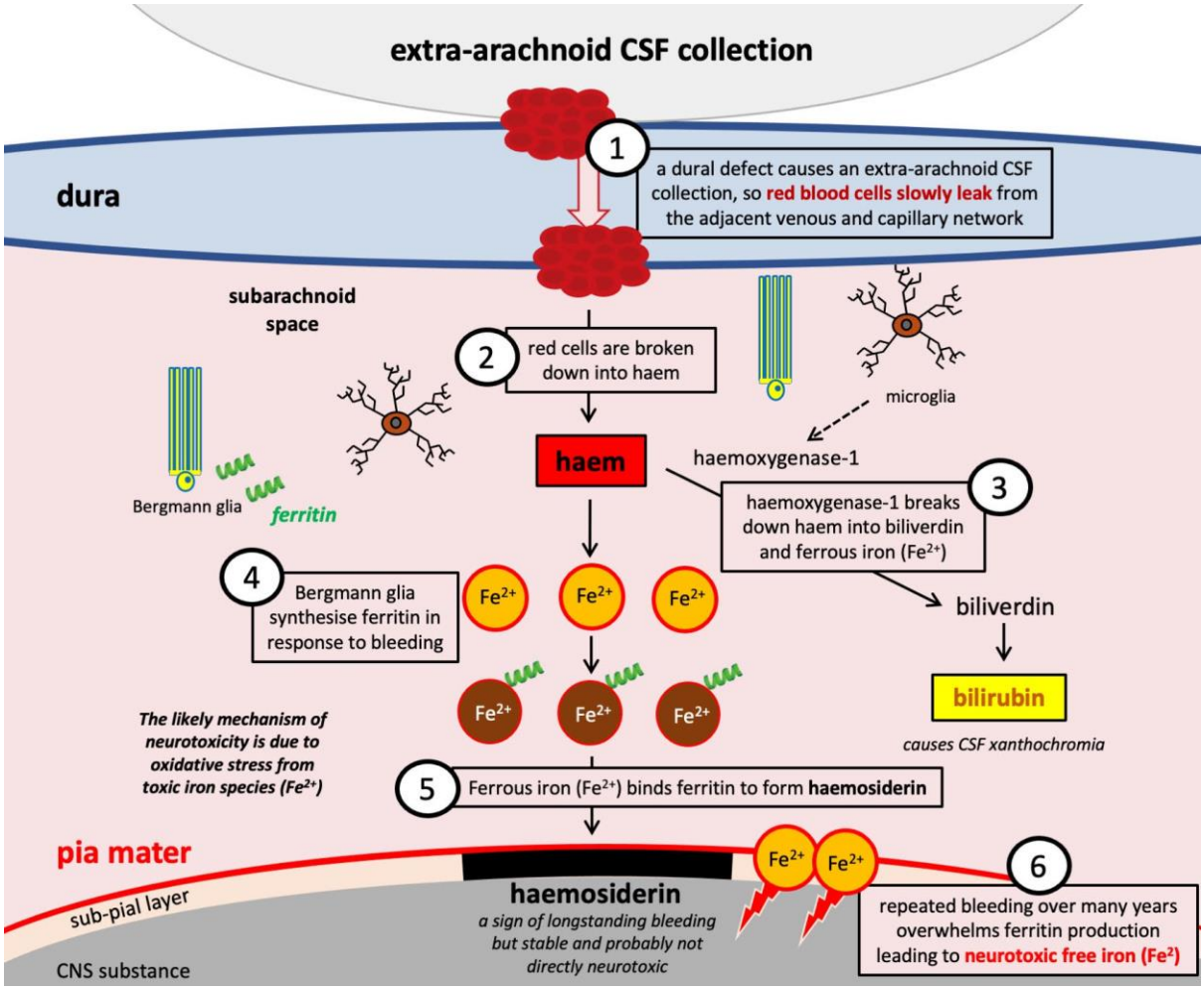
extra-arachnoid CSF collection
dura
1
a dural defect causes an extra-arachnoid CSF collection, so red blood cells slowly leak from the adjacent venous and capillary network
subarachnoid space
2
red cells are broken down into haem
microglia
haem
haemoxygenase-1
3
haemoxygenase-1 breaks down haem into biliverdin and ferrous iron (Fe2+)
Bergmann glia
ferritin
4
Bergmann glia synthesise ferritin in response to bleeding
Fe2+
biliverdin
bilirubin
causes CSF xanthochromia
The likely mechanism of neurotoxicity is due to oxidative stress from toxic iron species (Fe2+)
5
Ferrous iron (Fe2+) binds ferritin to form haemosiderin
pia mater
sub-pial layer
CNS substance
haemosiderin
a sign of longstanding bleeding but stable and probably not directly neurotoxic
6
repeated bleeding over many years overwhelms ferritin production leading to neurotoxic free iron (Fe2)

FIGURE 1.

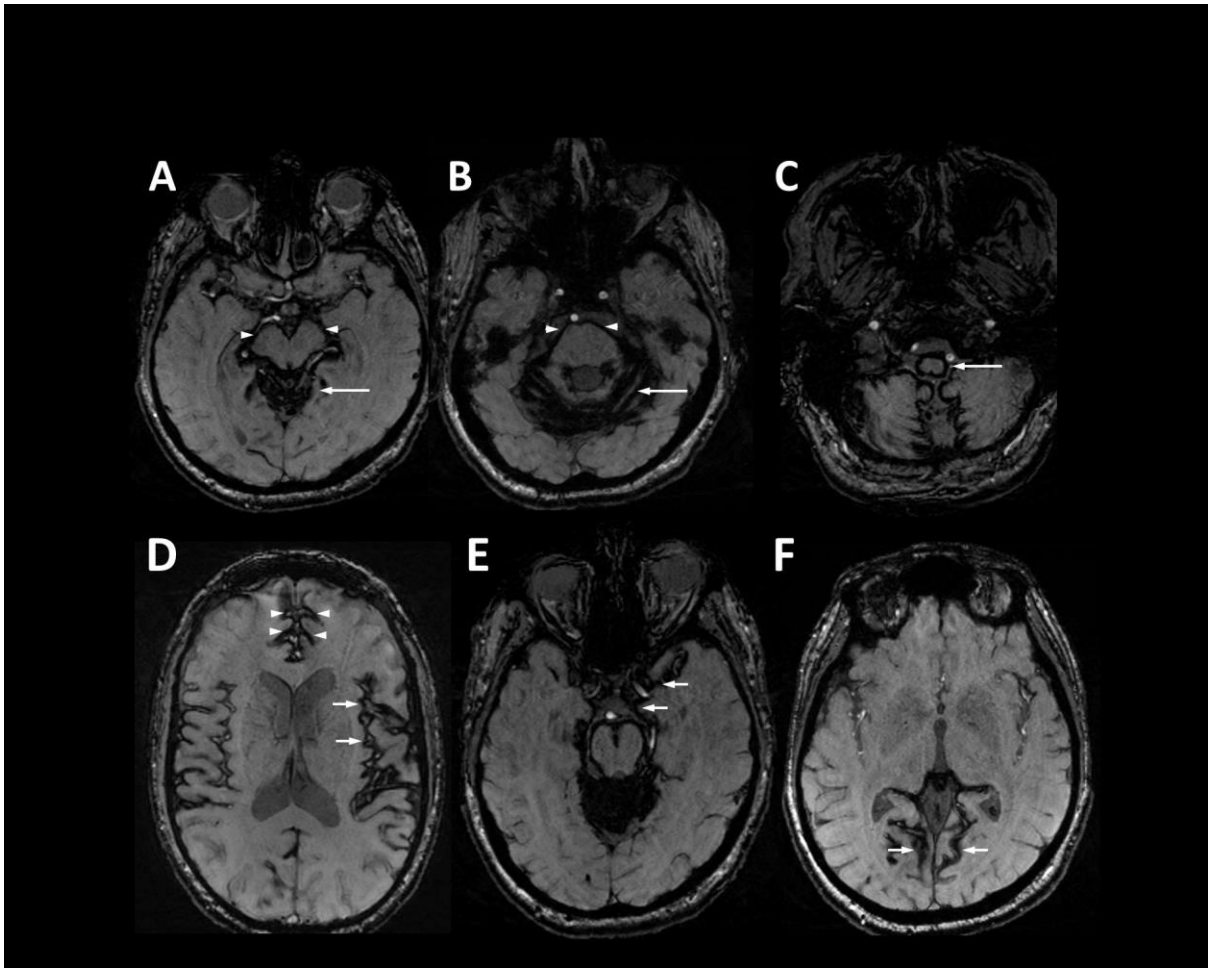

FIGURE 2.