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Case report and review

Idiopathic siderosis of the CNS: report and review

Isabela da Costa Rodrigues[1], Mohamad Ali Hussein[2], Pedro Cougo Samueli[2], Matheus Kahakura Franco Pedro[2], Pedro André Kowacs[2], Emanuel Cassou[2]

[1]Assis Gurgacz Foundation University Center (FAG) - Cascavel, Parana, Brazil
[2]Neurology Institute Hospital of Curitiba (INC) - Curitiba, Parana, Brazil

Isabela da Costa Rodrigues
isacostarod.2001@gmail.com

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Marcelo Moraes Valença

Superficial siderosis (SS) of the central nervous system (CNS) is a potentially disabling disorder characterized by the deposition of ferrous iron and hemosiderin, products of hemolysis, in the leptomeninges and superficial layers of the cerebral and cerebellar cortexes, as well as the brainstem and spinal cord. Persisting in the subarachnoid space, accumulation leads to demyelination, axonal loss and subsequent atrophy and neurodegeneration mediated by free radicals. In most cases, a potentially causative spinal or cranial dural abnormality is identified. The classification of SS is based on anatomical distribution, etiology and clinical manifestations, resulting in distinct subtypes: Classical infratentorial (i) SS (type 1), secondary SSi (type 2) and cortical SS (c). The classical clinic manifests with sensorineural hypoacusis, cerebellar ataxia and occasionally myelopathic and radicular signs. Although it is not a classic symptom of SS, infrequently some patients develop chronic intracranial hypertension, which is believed to be associated with obstruction of the interventricular foramen and/or malabsorption of cerebrospinal fluid (CSF). When present, the headache is usually a consequence of intracranial hypotension and its intensity varies according to the type of dural defect and the rate of bleeding or CSF leakage through a fistula. Diagnosis is established by means of magnetic resonance imaging (MRI) of the entire neuroaxis combined with clinical assessment. As alternatives aimed at preventing the progression of the disease and preserving the patient's functional integrity, in addition to controlling the deficits generated by siderosis, surgical closure of the dura mater and chelation are the main therapeutic alternatives.

Keywords:
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Infratentorial siderosis

SSi always affects the infratentorial structures and is divided into two types: "classic" SSi or type 1, characterized by symmetrical and widespread involvement of the medulla and posterior fossa, which may also affect the supratentorial region (1,2). This form shows no signs of spontaneous or potential traumatic bleeding, suggesting that the hemorrhage is secondary to silent events (4). The second type, secondary SSi or type 2, has deposition more restricted to the infratentorial portion (2). It is often associated with neurological events attributable to major bleeding, such as intracranial hemorrhages and fistulas, systemic arterial hypertension, aneurysm rupture, arteriovenous malformation (AVM), trauma, among others (1,2,4).

Etiology

SIH is classically associated with chronic low-volume, slow-flow bleeding, which can occur intermittently or persistently in the subarachnoid space (1,4,6). The main cause of this hemorrhage, which characterizes classic SSi, are pathologies that cause ruptures in the dura mater, allowing extravasation and accumulation of cerebrospinal fluid (CSF) over time, often occurring years before diagnosis (1,2).

Among the causes of ruptures are spinal pathologies such as disc disease and spiculated osteophytes, trauma, brachial plexus avulsions and cranio-spinal surgeries (1-4,6). Connective tissue abnormalities such as Marfan's syndrome, neurofibromatosis and ankylosing spondylitis can cause meningeal alterations, such as ectasias, without necessarily causing a dural rupture (2). In addition, arteriovenous malformations (AVMs), vascular abnormalities such as engorgement and friability, tumors, hemorrhages from post-surgical cavities and spontaneous cerebrospinal fluid hypotension are also considered etiologies (1,2,6).

Pathophysiology

Once erythrocyte hemoglobin leaks into the CSF, the microglia are stimulated to release hemoxygenase-1, which is responsible for breaking down the heme group into biliverdin and free iron, the latter of which is neurotoxic (2,6). Simultaneously, Bergmann's glia synthesize apoferritin, which binds to neurotoxic iron to form ferritin. Ferritin, in turn, is converted into hemosiderin, which supposedly plays a neuroprotective role against ferrous iron (2,6).

However, excessive ferritin synthesis and subsequent hemosiderin, associated with compound stasis in the subarachnoid space, trigger processes of demyelination, axonal loss and subsequent atrophy, mediated by free radicals(6).

It is notable that hemosiderin has an affinity for the cerebellum, possibly due to its rich Bergmann microglia and the CSF flow pattern in the organ, which facilitates more extensive contact with hemorrhagic CSF (2,6). In addition, hemosiderin tends to accumulate in transition zones between oligodendrocytes and Schwann cells in pure glial cranial nerves, such as the olfactory, optic, trochlear, abducent and vestibulocochlear nerves, as well as in spinal nerves (1).

Clinic

The typical symptoms of classic SSi usually manifest between the fourth and sixth decades of life and include bilateral sensorineural hearing loss, potentially asymmetrical, of cochlear and retro-cochlear origin, cerebellar manifestations and, occasionally, myelopathic signs and symptoms (1-6).

The origin of the hearing deterioration is probably due to the exposure of the long glial segment of the eighth pair to hemorrhagic CSF, manifesting early in relation to the other symptoms and progressing slowly, and routinely accompanied by tinnitus and high-pitched tones (2,6). A diagnostic challenge is to distinguish SSi from presbycusis due to epidemiological, clinical and audiometric similarities (1,2,6). Vestibular involvement, which is still little analyzed, is described as a mixed cerebellar and peripheral deficit (2).

Due to SSi's affinity with the cerebellum, especially the cerebellar vermis, gait ataxia with inability to sit or walk unaided is very common, as well as intention tremor, nystagmus and slurred speech (1,2). Individuals with few or no symptoms may have involvement restricted to the superior cerebellar vermis, indicating an early stage of the disease (2).

Myelopathic signs can be related to the corticospinal tract, such as spasticity and decreased dexterity, pyramidal signs and compressive polyradiculopathies, as well as spinal cord compression by the collection (Kharytaniuk et al., 2022; Kumar, 2021). Lower motor neuron manifestations are rare, possibly attributed to arachnoiditis resulting from the contact of hemorrhagic CSF with the organ. It also includes sphincter dysfunction, sensory symptoms and radicular pain(1,2,6).

Visual impairment is rare due to the shorter and more protected path of the optic nerve in the subarachnoid space, compared to other cranial nerves(1,2). The headache associated with intracranial hypotension depends on the type of dural defect and the rate of bleeding or cerebrospinal fluid outflow through a fistula. When manifested, it is usually sudden and the statement

of the day it all started is an important semiological landmark (1,2,5,7).

In secondary SSi, hypoacusis and cerebellar deficits are rarely present or even absent. On the other hand, focal symptoms are very present, varying according to the site of involvement (1). Among them, the most common is paralysis of the cranial nerves, especially the abducens, with its fixation inside Dorello's canal when it enters the clivus (1). Severe and persistent low back pain, suggestive of arachnoiditis when included in the siderosis picture, focal epileptic seizures, dysphagia and cognitive impairment manifesting as executive dysfunctions, although greatly underestimated, may also be present (2,6). The majority of cases that develop chronic intracranial hypertension are related to secondary SS (4).

Diagnosis

The definitive diagnosis of SS is made through MRI of the entire neuroaxis, preferably with iron-sensitive paramagnetic sequences, together with an assessment of the clinical syndrome (2,4,6). The aim of the diagnosis is to rule out other pathologies that have the same symptoms as the patient, to distinguish between different types of SS and to identify possible sources of bleeding (2).

MRI should be contrasted and with some sensitive paramagnetic sequence - Gradient-Recall Echo (GRE) in T2 and susceptibility-weighted imaging (SWI) - especially with the highest field strength (1,2,6). These techniques have proven to be more sensitive and specific than T2-weighting, the method used in the first MRI investigation of SS, for identifying hemosiderin deposits (2,6).

The main radiological criterion for analysis is the presence of symmetrical hemosiderin deposition, manifested by loss of signal and inhomogeneity in the local magnetic field (1,2). This is reflected in dark borders on the surface of the affected structures, always including the superior cerebellar vermis, and may extend to the cerebellar hemispheres, peduncles or both, and at least one other infratentorial structure (1). Cerebellar atrophy is common, mainly affecting its anterior portion (6).

When a dural defect is suspected, often characterized by the extradural collection not coinciding with the level of the rupture identified on the MRI, it is advisable to add an additional technique to the analysis that allows for a more precise identification of the pathology (4,6). The options of choice are spine computed myelography (spine CT) and digital subtraction myelography (DSM), which are dynamic techniques with highly accurate temporal images that enable the onset of extradural extravasation to be identified and increase the accuracy of the affected site, especially in more subtle segments (8). These techniques, if used properly, are able to identify the etiology in up to 94% of patients who are candidates for diagnosis, but the findings can go unnoticed because the deposition follows the contours of the structures (4,6).

Since macrovascular lesions are unlikely to cause the low-volume bleeding classic of SS, angiographic techniques such as CT angiography, MRA angiography and digital subtraction angiography are generally not very revealing (2,6).

CSF analysis is performed to identify the presence of active or recent bleeding, indicated by the red blood cell count (RBC) and ferritin (2). The main findings are the xanthochromic appearance and the RCC is usually high and disproportionate to the white blood cell count, maintaining a ratio of more than 500:1, and indicating very recent bleeding (2,5). On the other hand, the ferritin count tends to remain high for several months after the initial bleeding (2).

Treatment

The main therapeutic objectives in the management of both infratentorial and cortical siderosis are the prevention of disease progression and the functional decline of the patient, although there is still no robust evidence proving the efficacy of any disease-modifying treatment (2,6). The approach consists of identifying and, when possible, treating the underlying etiology of the hemorrhage, as well as reducing iron concentration and its clinical implications (2). Among the therapeutic options for siderosis are surgical correction and the administration of iron chelators, with limited data on the combined use of these modalities (1,2,6).

The indication for surgical closure of the dura mater is meticulous and considers inherent characteristics of the patient, such as comorbidities and suitability for the procedure, as well as technical viability, including the presence of active subarachnoid hemorrhage and the etiology of the disease (2,6). Furthermore, clinical progression and recognition of potential signs impacting quality of life are included, along with the risk-benefit relationship for the patient (2,6). The surgical procedure can correct xanthochromia and the presence of ferritin in the cerebrospinal fluid (CSF), and auxiliary intraoperative techniques, such as spinal endoscopy with CT myelography and ultrasound, aid in the identification and correction of tiny dural defects (2,6).

The iron chelator deferiprone crosses the blood-brain barrier and is used as a pharmacological alternative in the management of Siderosis, administered at a dose of 30 mg/kg/day, in 2 to 3 divided doses (2,6). Among the possible complications of pharmacological therapy,

agranulocytosis and neutropenic sepsis are the most alarming (2,6). Neutropenic sepsis can occur, on average, over two years of treatment (6). A study involving 19 patients with central nervous system siderosis undergoing chelation indicated that fatigue is the most commonly observed adverse effect (2,6). Additionally, other findings such as iron deficiency anemia, zinc deficiency, and arthralgia were reported in approximately 6% of the studied participants (2).

Although observational studies have shown radiological improvement with its use, imaging criteria for hemosiderin deposition are not considered valid biomarkers, and there is a lack of comprehensive studies on all symptoms associated with Siderosis (2).

Furthermore, a multidisciplinary approach is crucial for maintaining and optimizing the functional capacity and controlling the symptoms of patients with Siderosis, including teams from neurotherapy, speech therapy, occupational therapy, and psychology, which are essential for managing complex neurological conditions and improving patients' quality of life (2).

Cortical siderosis

Also known as subarachnoid or sulcal hemosiderosis, Cortical Siderosis (CS) is a distinct type of siderosis, differing from Siderosis in both clinical and neuroradiological presentation (1,2). Characterized by the restricted deposition of hemolytic products on the convexities of the supratentorial structures in an asymmetric manner, the condition is divided into focal CS, when it affects up to three sulci, and disseminated CS, when at least four or more sulci are involved (1,2,4,6). CS is a risk factor for intracranial hemorrhages (6).

Cerebral amyloid angiopathy (CAA) involves the deposition of beta-amyloid peptide in the leptomeninges and small to medium-caliber cortical vessels (1,2,4). This etiology is the most commonly associated one with CS, especially in the elderly (1,2,4,6). This accumulation can lead to vascular rupture and subarachnoid bleeding, followed by the deposition of hemosiderin in the previously described areas (2). Additionally, inflammation and ischemia of the affected vessels are further consequences (4).

Other less frequent causes of bleeding associated with Cortical Siderosis (CS) include subarachnoid hemorrhage (SAH), arteriovenous malformations (AVM), reversible cerebral vasoconstriction syndrome, vasculitis, high-grade proximal arterial stenosis, thrombosis of cerebral veins and/or sinuses, trauma, hemorrhagic transformation of an infarct, and coagulopathies, which are generally distinguishable by their clinical or radiological characteristics (1,2,4).

Unlike Siderosis, CS is not associated with hearing loss, ataxia, or myelopathy (2). Its most common clinical manifestations are transient focal neurological episodes, "amyloid crises," and progressive neurological impairment in the disseminated form (1,2,4,6). The main focal involvement is seizures (1,4).

Radiographically, CS presents as a "tram line" bilaterally along the cerebral sulci, resembling a typical bilinear trail (1,2).

Case Report

MADP, a 52-year-old male, married, a professor and geologist, and a Catholic from Curitiba-PR, sought medical attention due to progressive occipital headache. The headache started in 2014, intensified in 2022, and moderately interfered with daily activities. The pain is described as mild to moderate in intensity, tight, occurring consistently between 11:30 AM and 12:30 PM, characterized by prolonged periods of relief, radiating to the right shoulder, and accompanied by tinnitus while lying down. The pain improved when lying down, after caffeine intake, and with any form of physical activity. There was slight worsening immediately after getting up and severe aggravation when sitting and flexing the neck. The patient also reported symptoms of instability and imbalance, which were not evident during the physical examination. He denied the need for analgesics or anti-inflammatories, episodes of hypertension, nausea, photophobia, phonophobia, visual aura symptoms, ocular pain, and trigeminal-autonomic signs.

He has a history of depressive disorder associated with burnout in 2019 and glaucoma, treated with Triplenex. He is currently taking Finasteride 1 mg and Minoxidil for hair treatment and has previously undergone umbilical herniorrhaphy and hair transplantation. He reported previous hospitalizations due to diplopia between 2006 and 2007 and for a car accident without traumatic brain injury in 2011. He stated rare social alcohol use and engages in regular physical activity. He denied allergies and smoking. His family history includes his father's death from intestinal neoplasm and his maternal grandfather's death from a cerebrovascular accident (CVA).

On physical examination, he appeared in good general condition, lucid, oriented in time and space, non-jaundiced, acyanotic, afebrile, with stable vital signs, and reporting mild pain upon palpation of right occipital and posterior cervical trigger points. He also exhibited slight intention tremor on the right. No other abnormalities were noted in the physical exam.

Subsequently, an MRI of the brain was requested, including multiplanar T1, T2, FLAIR, and diffusion sequences, along with a post-gadolinium series. The MRI revealed extensive SSi, predominantly in the upper portion of the cerebellum,

suggesting a sequela of meningeal hemorrhage. Areas of mild siderosis were also identified in the left anterior transverse temporal gyrus, bilaterally in the parieto-occipital transitions, and in the bilateral frontobasal convexity, predominantly on the right. Additionally, faint T2/FLAIR hyperintensities in the white matter of the cerebral hemispheres were observed, nonspecific, potentially related to gliosis due to microangiopathy.

Throughout the investigation, the patient continued to experience the same complaints, with no improvement following initial treatment with venlafaxine, which was later replaced with nortriptyline, yielding no clinical benefit. Initially diagnosed with tension-type headache, further investigation was initiated to determine the possible etiology of the hemosiderosis.

Subsequently, a brain MRI was requested with multiplanar sequences weighted in T1, T2, FLAIR, and diffusion, including a post-gadolinium series, which showed extensive Siderosis, predominantly in the superior portion of the cerebellum, and suggested sequelae of meningeal hemorrhage. Light siderosis areas were also identified in the left anterior transverse temporal gyrus, bilaterally at the parieto-occipital transitions, and bilaterally in the frontobasal convexity, with a predominance on the right side. Additionally, faint hyperintense foci in T2/FLAIR in the white matter of the cerebral hemispheres were observed, which are nonspecific and may be related to gliosis due to microangiopathy.

Throughout the investigation, the patient continued to have the same complaints, showing no improvement after the initial use of venlafaxine, which was later replaced by nortriptyline, without clinical benefit. Initially diagnosed with tension-type headache, an investigation was initiated to determine the possible etiology of the hemosiderosis.

After performing venous intracranial angio-MRI using the 3D-FAST gradient echo post-gadolinium technique, MRI of the brain evaluating cerebrospinal fluid flow to exclude obstructive etiologies, cervical, thoracic, and lumbosacral spine MRIs to investigate associated hemorrhagic lesions, and angiography to detect dural fistula, the patient was admitted for myelography with digital subtraction to identify epidural cerebrospinal fluid leakage. The procedure was conducted in two phases: first, positioned in right lateral decubitus and then in left lateral decubitus, where no extravasations were observed that could suggest findings compatible with spontaneous cerebrospinal fluid hypotension. Furthermore, the CSF appeared clear, limpid, and with normal opening pressure. Besides the brain MRI, only the cervical, thoracic, and lumbosacral spine MRIs showed changes, which included multisegmental degenerative spondylodiscopathies in the C4-C5 and C5-C6 segments, with mild neuroforaminal stenosis in the right C4-C5 and bilateral C5-C6, marginal osteophytes of the vertebral bodies, more pronounced in C5-C6 and T8-T9, and degenerative changes suggestive of Modic type 1 (Figures 1-3).

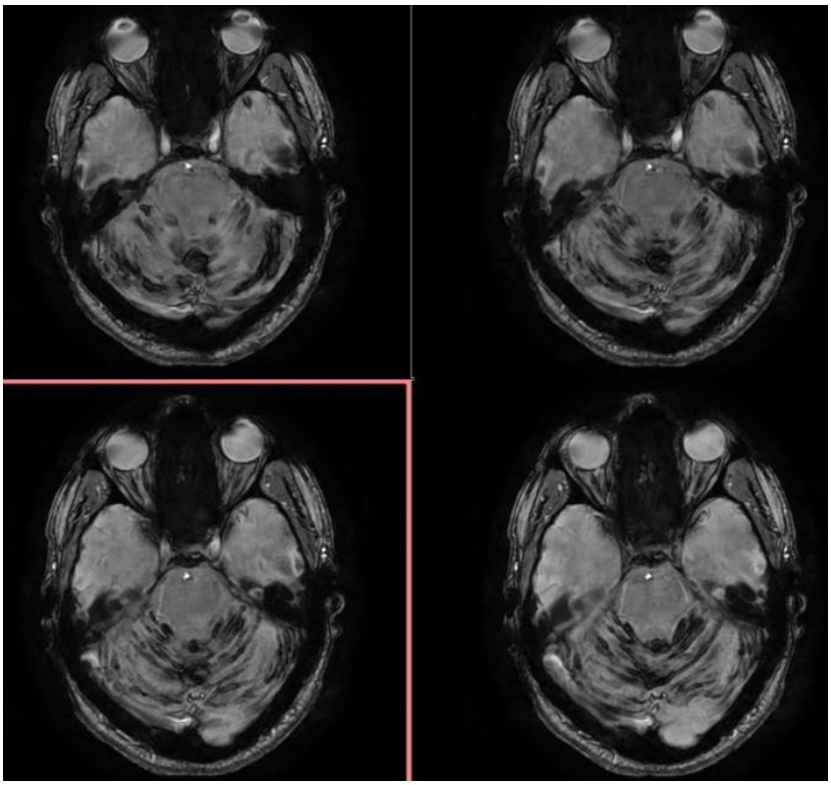

Figure 1. Brain MRI with CSF flow study showing hyposignal compatible with SSi in the cerebellum, left anterior transverse temporal gyrus, bilateral parietociptal transitions and bilateral frontobasal convexity. 2024. Available at: personal archive author MKFP.

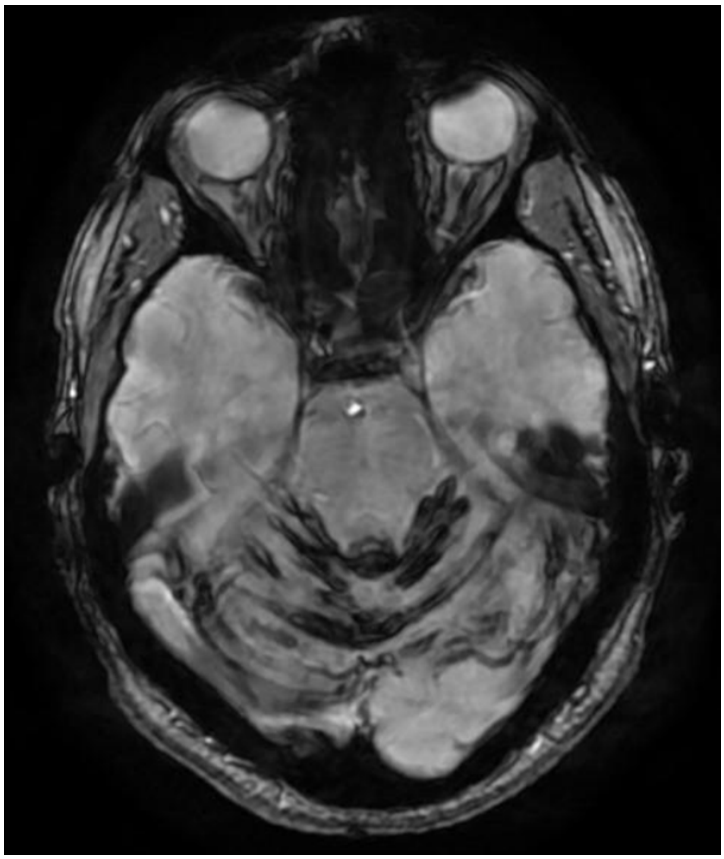

Figure 2. Brain MRI with CSF Flow Study showing hyposignal compatible with SSi in the cerebellum, left anterior transverse temporal gyrus, bilateral parietociptal transitions and bilateral frontobasal convexity. 2024. Available at: author MKFP's personal archive.

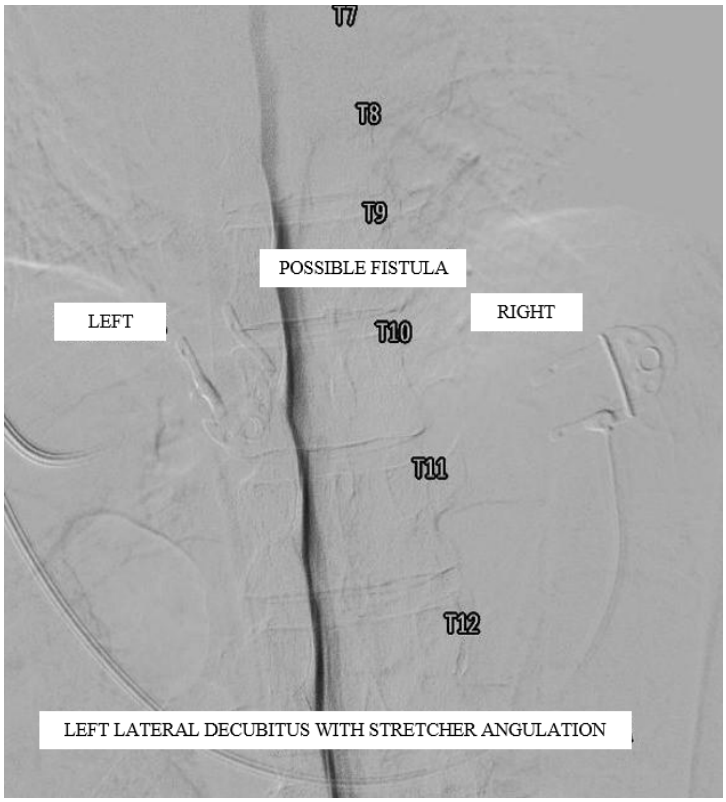

Figure 3. Myelography in Left Lateral Decubitus Position with Stretcher Angulation. 2024. Available at: author MKFP's personal archive.

Discussion and Conclusion

In the reported case, the patient was initially diagnosed with tension-type headache. During the investigation, there was a suspicion of spontaneous cerebrospinal fluid hypotension (HLE) due to a potential venous cerebrospinal fluid fistula (FVL) identified in the myelography, which later turned out to be an artifact. Ultimately, after all imaging studies failed to reveal a finding compatible with the origin of the bleeding and subsequent deposition, the case was categorized as idiopathic infratentorial siderosis, with mild supratentorial findings.

With the increasing availability of the necessary radiological techniques for diagnosing siderosis, when properly utilized, it is possible to identify its etiology in up to 94% of classic cases, leaving only 6% classified as idiopathic—substantially lower than the 35% of cases previously described in the literature as "idiopathic" (4,6,9).

HLE is a treatable syndrome of secondary headache resulting from the extravasation and reduction of circulating cerebrospinal fluid in the spinal canal (8,10,11). It is defined by spontaneous headache temporally associated with visible epidural extravasation on imaging and/or cerebrospinal fluid hypotension (8,10–12). Its incidence is estimated at about 5 cases per 100,000 people per year, affecting all age groups, with higher prevalence around 40 years and in females (7,8,10,12). Cerebrospinal fluid extravasation is classified into four main types, including ventral dural defects, spinal nerve root diverticula, FVL, and etiologies that remain unknown (7,8,10,11,13). Orthostatic headache—which worsens upon standing and alleviates when lying down—is the most common symptom, potentially mimicking patterns of chronic daily headache due to its orthostatic nature that may gradually decrease over time, resulting in non-orthostatic complaints, primarily manifesting in the occipital region (7,8,10–13). Despite up to 18% of cases presenting without alterations, MRI is the most sensitive test for detecting HLE, and analyzing the entire neuroaxis with this technique is essential for diagnosis (8,10–12). Brain MRI allows for the observation of typical HLE findings, while total spine MRI helps analyze the segment where there is extravasation and determine its extent, with the need for additional techniques such as digital subtraction myelography, depending on the need to analyze adjacent veins (8,10–12). Treatment is stratified, with initial management including rest, hydration, and pain control with medications, while percutaneous interventions such as blood patches (BP) are used to seal fistulas, and surgical corrections are reserved for cases refractory to less invasive treatments (8,10–13).

Described for the first time in 2014 and more common in middle-aged women, the venoliquoric fistula (FVL) is defined as an anomalous communication between the spinal subarachnoid space and an epidural paravertebral vein or adjacent venous network near the spinal nerve root, resembling a diverticulum (7,8,10,11,13). This alteration leads to a dysregulation in cerebrospinal fluid (CSF) drainage, causing rapid circulation and outflow, which results in consequent spontaneous cerebrospinal fluid hypotension (HLE) (8,11,13). The flow is unidirectional due to the favorable pressure gradient of CSF relative to the venous system, with drainage occurring paravertebrally (45%), centrally toward the epidural plexus (32%), or laterally along the neural foramen (23%) (8,10,13). Although most cases are considered spontaneous, there are reports of iatrogenic fistulas following lumbar puncture or myelography (11,13).

The patient described had occipital pressure headaches without a classic orthostatic pattern, although they worsened during daily activities. This complaint was associated with tinnitus, present in 30 to 50% of HLE cases, as well as instability and imbalance, seen in up to 10% of cases (8,10,12). Additionally, the pain positively responded to caffeine consumption, although no conservative management has scientifically proven efficacy in handling the condition (8).

From a radiological standpoint, the patient fit both the diagnosis of idiopathic siderosis (SSi), due to extensive deposition in the upper part of the cerebellum, and cortical siderosis (SSc), evidenced by the presence of hemossiderin in the aforementioned regions and the suggestion of cerebral amyloid angiopathy (CAA), the main etiology of SSc. Furthermore, the patient had degenerative spondylodiscopathy in the previously mentioned segments. Although not definitively diagnosed, ankylosing spondylitis can induce meningeal changes that may eventually result in hemosiderosis (2).

After the myelography, it was observed that the CSF was clear and had normal opening pressure, suggesting the absence of bleeding in the subarachnoid space. This finding raises hypotheses about the subsequent clinical evolution and possible diagnostic and etiological interpretations of the bleeding.

The first question is whether the apparent absence of bleeding may indicate that it has resolved spontaneously, a hypothesis that prompts reflection on the temporal dynamics of bleeding and the body's ability to resolve potential complications without specific interventions.

Another consideration is the possibility that the patient may have presented an etiology that justified the bleeding, which could have resolved spontaneously prior to the myelography. In this context, the hypothesis of a possible vascular malformation could still be considered a viable alternative.

Moreover, the discussion extends to the possibility that the apparent absence of bleeding may indicate a decrease in disease activity. In this context, it is relevant to consider

whether the possible resolution of the bleeding is correlated with some degree of remission of the disease or if other factors are contributing to the improvement of symptoms. Finally, it is concluded that superficial siderosis of the central nervous system is a rare pathology that demands more research for a deeper understanding of its pathophysiology, therapeutic management, and prognoses. Additionally, due to the increased availability of imaging studies and the growing knowledge about the syndrome, although still underdiagnosed, spontaneous cerebrospinal fluid hypotension has emerged as a condition increasingly suspected in the presence of orthostatic headache.

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Isabela da Costa Rodrigues
https://orcid.org/0009-0001-2203-9710
Mohamad Ali Hussein:
https://orcid.org/0009-0006-3208-2241
Emanuel Cassou
https://orcid.org/0000-0003-3822-8003
Pedro Cougo Samueli
https://orcid.org/0000-0002-5934-9392
Matheus Kahakura Franco Pedro
https://orcid.org/0000-0003-1166-9722
Pedro André Kowacs
https://orcid.org/0000-0001-7770-7475

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