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CASE REPORT



Optic Neuropathy Revealing Severe Superficial Siderosis in the Setting of Long-standing Low-grade Intracranial Neoplasm

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ABSTRACT

Two cases of optic neuropathy due to superficial siderosis (SS) are reported in two patients, aged 29 and 38 years, operated for intracranial neoplasms, the first one with a desmoplastic infantile ganglioglioma excised in 1991, and the other one with a pilocytic astrocytoma, operated on in 1997, 1998 and 2016. Both patients presented with progressive loss of visual acuity, as a result of bilateral optic nerve atrophy, as well as unsteadiness, ataxic gait and hearing loss. Magnetic resonance imaging (MRI) of the brain and spine, including gradient echo (GRE) T2-weighted acquisitions, revealed thin optic nerves and strong hypointensity with susceptibility artefacts corresponding to haemosiderin deposits within the meningeal layers of the spine, the infra- and supratentorial spaces of the brain and the peri-optic sheaths in both patients. The cerebrospinal fluid (CSF) was macroscopically haemorrhagic in one patient, who underwent a dynamic myelography, which failed to reveal any trans-dural CSF leakage. Neuro-ophthalmological symptoms due to SS, such as visual acuity loss, have been scarcely reported. MRI using GRE T2-weighted sequences highlighting the presence of haemosiderin deposits plays a key role in the diagnosis of this condition. Treatment should aim at preventing haemosiderin deposition by treating the cause of the subarachnoid bleeding.

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Introduction

Initially described in 1908 by Hamill, superficial siderosis (SS) is characterised by haemosiderin deposits within the subpial layers of the brain, spinal cord, and cranial nerves resulting from massive or repeated subarachnoid haemorrhage.¹ In SS cases, irreversible neurological and cranial nerve dysfunction may occur, which are predominantly sensorineural deafness, cerebellar ataxia, and pyramidal signs.¹ An increasing number of SS cases have been reported since the availability of the magnetic resonance imaging (MRI) technique in clinical settings. The technique highlights haemosiderin deposits as strongly hypointense foci, mainly on gradient-echo (GRE) and susceptibility-weighted imaging (SWI) acquisitions.

Few cases of SS with neuro-ophthalmological symptoms have been reported up to now. Oculomotor nerve dysfunction has been documented, mainly trochlear nerve palsies with diplopia.² Optic

neuropathies due to SS have rarely been described.^{3,4} We present two cases of visual acuity loss in patients with long-standing histories of brain tumours leading to the diagnosis of SS during MRI work-up.

Case description

The research protocol followed the tenets of the Declaration of Helsinki and was approved by the University of Louvain's Human Biomedical Ethics Board under the Belgian registration number 2020/006.

Patient 1

A 29-year-old man presented with a painless onset of bilateral visual acuity loss, after 6 months of worsening ataxia and walking impairment.

The patient had a past medical history of a right fronto-parietal desmoplastic infantile ganglioglioma, located on the upper aspect of the vermis, which was diagnosed shortly after birth and treated by incomplete surgical excision in another institution at the age of 6 months. The tumour gradually regrew without the need for a second surgical excision. By the age of 10, seizures, cognitive and memory dysfunction, and a mild left hemiparesis appeared, and the patient came to our institution. The tumoural residue had neither changed in size nor in morphology at the time. Contrast-enhanced MRI at the age of 20 showed a right temporal postoperative cavity communicating with the adjacent lateral ventricle, a chronic subdural cerebrospinal fluid (CSF) collection, hydrocephalus, and a slight growth of the tumoural residue, without any anterior visual pathway involvement. Eye examination at the age of 27 in another hospital showed optic atrophy and intraretinal fluid, but the patient did not have any complaints regarding his vision. At age 29, he developed loss of vision, unsteadiness and walking impairment precluding work, which worsened over the course of 6 months. The patient also complained of headaches that were present for a few days. Neurological examination revealed an ataxic gait, along with bilaterally impaired coordination, which was predominantly left-sided with abnormal finger-to-nose testing. At this time, he also had moderate retrocochlear deafness in both ears, with a vocal audiometry

more affected than the tonal audiometry. Neuro-ophthalmological examination showed a best-corrected visual acuity of 20/200 with the right eye and hand movement perception with the left eye. The Hirschberg corneal reflex test revealed an exotropia of 15°, but complete motility. Furthermore, he could not recognise any of Hardy-Rand-Rittler colour plates. Funduscopy demonstrated a swollen and pale optic disc with papillary haemorrhages in the right eye, and a pale optic disc in the left eye (Figure 1). Confrontational and kinetic visual fields showed a complete left homonymous hemianopia. Visual evoked potentials failed to record any significant occipital activity to flash and pattern-reversal stimulations, regardless of whether the right or left eye was stimulated.

A comprehensive cerebral and spinal MRI work-up, which included GRE T2-weighted (T2*) and SWI acquisitions, showed intracranial post-treatment changes with hydrocephalus and thin optic nerves within enlarged optic nerve sheaths. Furthermore, extensive SS of the spinal cord, posterior fossa and peri-optic sheaths was revealed, with a thick rim of haemosiderin deposits around the optic nerves and chiasm (Figure 2). Serial review of images performed for tumoural follow-up over the last 10 years demonstrated progressive increase in the size of the ventricles, which had remained asymptomatic until the recent functional decompensation. A pathophysiological mechanism combining impairment of CSF resorption and circulation due to the meningeal hemosiderosis was hypothesised. At lumbar puncture, which was not traumatic, the CSF

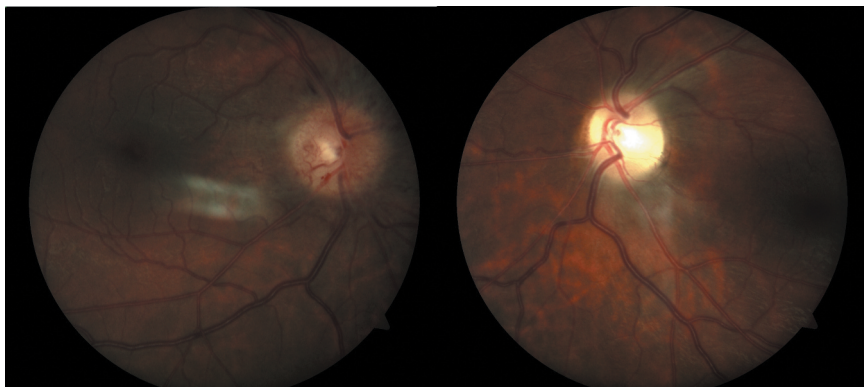


Figure 1. Fundus photograph of patient 1 at the age of 29 showing a swollen and pale optic disc with papillary haemorrhages in the right eye and a pale optic disc in the left eye.

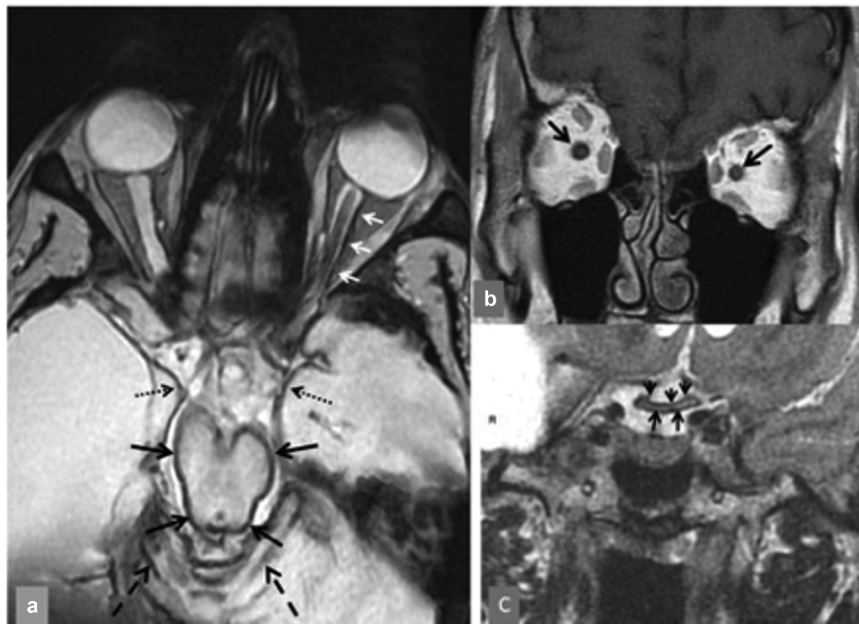


Figure 2. Magnetic resonance work-up of patient #1 (a) Transverse susceptibility-weighted imaging view showing black lining corresponding to hemosiderin deposits within the peri-optic meningeal sheaths of both optic nerves (white arrows), the pial layer of the mesio-temporal borders (dotted black arrows), the mesencephalon (black arrows), and the cerebellar foliation (discontinuous black arrows). (b) Coronal T1-weighted view showing thick, strongly hypointense rim of hemosiderin (arrows) around both optic nerves. (c) Coronal T2-weighted view showing hypointense rim of hemosiderin around the optic chiasm (arrows).

was macroscopically and microscopically haemorrhagic, with a count of 24×10^3 red cells/ μL . The CSF protein (295 mg/dL), lactic acid (5 mmol/L) and the number of white cells (60/ μL) were all increased. The increased number of white cells probably included cells associated with the red cells in the context of the subarachnoid haemorrhage and macrophages with hemosiderin granules. A dynamic myelography failed to show any transdural leakage responsible for chronic subarachnoid bleeding. Although the high CSF flow at lumbar puncture suggested an abnormally elevated opening pressure, the opening pressure was not formally measured and removal of 30 mL of CSF did not lead to any improvement in the walking test. However, a subsequent ventriculo-peritoneal shunt (VPS) resulted in improved gait leading to walking recovery and a decrease in headaches. Unfortunately, the visual acuity failed to improve after shunting. Funduscopy, 1-month post VPS, revealed pale optic nerves with a resolution of optic disc oedema. Optical coherence tomography (OCT) demonstrated severe bilateral thinning of the retinal nerve fibre layer. Walking recovery, improvement in headaches and resolution of optic disc oedema following VPS, together with the high CSF flow at lumbar puncture,

suggested that these symptoms and signs occurred in the context of long-term intracranial hypertension.

Patient 2

The second patient was a 38-year-old male patient with a ten-year history of progressive decrease of visual acuity. Like the previous patient, he had a medical history of low-grade intracranial neoplasm. At the age of 15 he presented with worsening headaches, vomiting, blurred vision, gait imbalance, and left-arm paresis. He was transferred from an Algerian hospital to the Leuven University Hospital. In Leuven, a pilocytic astrocytoma in the right hypothalamus was diagnosed and he underwent surgery followed by adjuvant radio- and chemotherapy. After the first excision, he developed epilepsy and a left spastic hemiparesis. A second excision was then performed at the age of 16. He developed progressive hearing loss at the age of 33 associated with progressive bilateral loss of vision and worsening gait. A hearing work-up showed a moderate right and a mild left sensorineural deafness, with similarly affected tonal and vocal audiometries. A last excision was performed at the age of 34.

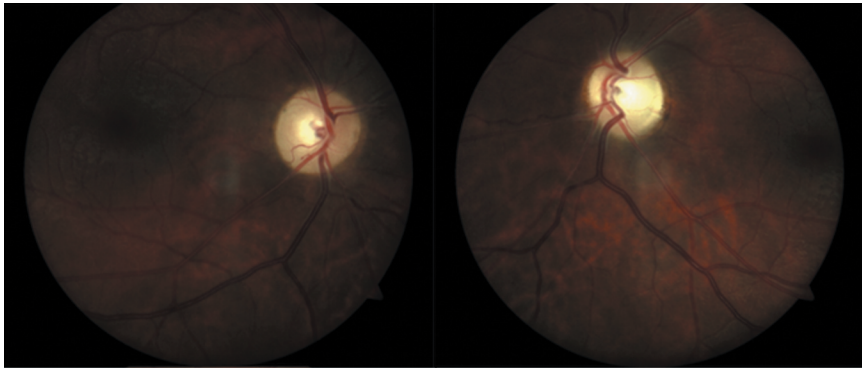


Figure 3. Fundus photograph of patient 2 at the age of 37 showing bilateral optic atrophy.

At the initial neuro-ophthalmological work-up in our institution at the age of 33, he had a best-corrected visual acuity of count fingers with the right eye and 20/32 with the left eye. He could not recognise any of the Hardy-Rand-Rittler colour plates with either eye and had a right relative afferent pupillary defect. Kinetic visual fields were reduced to a small island in the inferior temporal quadrant of the right eye, and to the nasal hemifield of the left eye. He had an exotropia of 40 prismatic dioptres, without any oculomotor restriction. The intraocular pressures were normal and the eye examination was unremarkable apart from the presence of pale optic discs in each eye (Figure 3). OCT revealed diffuse retinal nerve fibre layer and ganglion cell layer thinning in both eyes. At the age of 37 his visual acuity was reduced to hand movement perception with the right eye and 20/200 with the left eye. At his last consultation in our clinic at the age of 38, his vision was still at hand movement perception with the right eye and 20/200 with the left eye.

At the age of 33, MRI work-up of the brain and spine led to the diagnosis of SS, based on extensive haemosiderin deposits within meningeal layers, with haemosiderin impregnation of the optic nerves and chiasm. These deposits were associated with strong hypointensity of the optic nerves and chiasma on GRE T2- and even GRE-T1-weighted images (Figure 4).

Discussion

In patient 1, although the parents had described that he had had sudden onset of visual acuity loss,

it could be hypothesised that the visual loss may have been slowly progressive, as suggested by the optic atrophy at the age of 27, and he was therefore asymptomatic until the recent sudden visual decompensation. The repeated MRI, lumbar puncture and biological work-up rendered alternative causes, such as compressive, infiltrative or inflammatory aetiologies unlikely. The hypothesis of an optic neuropathy caused by a chronic ischaemia due to severe and long-term intracranial hypertension in the context of SS was considered. In patient 2, the radiological findings, associated with the slowly progressive visual acuity loss and bilateral optic atrophy, suggested that SS was the most plausible aetiology of the visual and hearing loss. An extensive neurological work-up allowed the exclusion of inflammatory, infiltrative and chronic ischaemic causes.

As for blindness onset, visual acuity loss is expected to worsen progressively in these cases, as was observed in patient 2, as a result of gradually increasing haemosiderin deposition over time on the chiasm and optic nerves. The underlying mechanism reported in a patient with a similar clinical picture was slow demyelination of the optic nerve fibres, highlighted by an anato-pathological study of the optic nerves.³ A more acute presentation, as described in patient 1, may also occur in cases of synergistically co-existing pathological conditions, such as intracranial hypertension, which is present in about one-third of SS cases.⁵

In a comprehensive review of 270 cases of SS,⁶ the most common aetiologies were central nervous system (CNS) tumours (21%), head and/or back trauma (13%), and arteriovenous malformations/

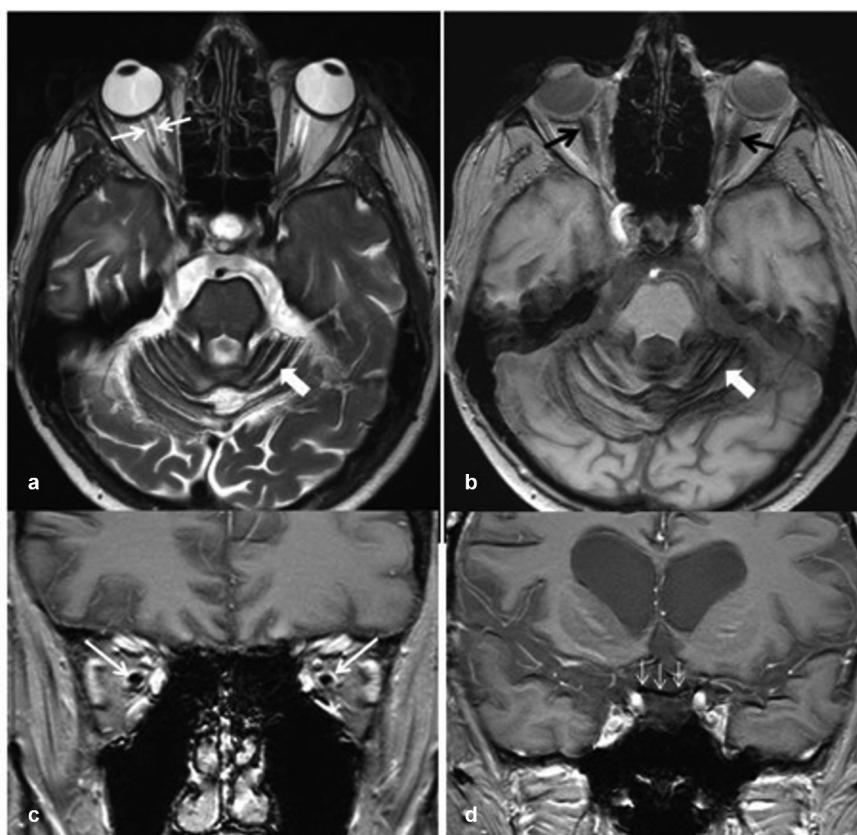


Figure 4. Magnetic resonance work-up of patient #2 (a) Axial transverse T2-weighted view revealing strongly hypointense haemosiderin deposits within the pial layer covering the cerebellar foliation (thick arrow) and apparently unremarkable peri-optic sheaths (between thin arrows) with bright cerebrospinal fluid surrounding the optic nerves. (b) Axial transverse gradient echo T1-weighted view in a similar slice location as (a) confirming siderosis of the cerebellar foliation (thick white arrow) and displaying strong hypointensity within both peri-optic sheaths (black arrows) corresponding to susceptibility artefacts due to haemosiderin deposits. (c) Contrast-enhanced gradient echo T1-weighted coronal view with fat suppression showing enhanced peri-optic sheaths (arrows) surrounding abnormally hypointense optic nerves because of haemosiderinic pial impregnation. (d) Contrast-enhanced gradient echo T1-weighted coronal view with fat suppression showing atrophy and deep hypointensity of the chiasm (arrows) which is 'blackened' by haemosiderin-related susceptibility artefacts.

aneurysms (9%). Other causes of SS include complications of neurosurgical interventions, brachial plexus injury, amyloid angiopathy and chronic subdural haematomas. The cause remained unidentified in 35% of the cases in this series, instead of the 50% reported in previous reviews. Technical refinements in computed tomography dynamic myelography and magnetic resonance myelography, with intrathecal injection of gadolinium chelates, should lead to increased demonstration of CSF leakage through occult dural breaches.⁷ SS affects males more than females with a 2:1 ratio, and while the average age of onset ranges from 50 to 70 years, it can be observed over the entire lifespan.⁶

The pathophysiological process through which a chronic subarachnoid haemorrhage leads to haemosiderin deposits has been experimentally investigated

by Koeppen et al.⁸ They repeatedly injected red blood cells (RBC) into the cisterna magna of rabbits over a period of 3–6 months. After physiological haemoglobin breakdown and the action of haem oxygenase, molecular iron is released from haem. As iron acts as a catalyst in the formation of neurotoxic reactive oxygen species, protective mechanisms of iron sequestration within ferritin are activated to prevent local excess of iron. After a period of 6 months of repeated RBC injections, granules of haemosiderin made of ferritin and other materials appear in the molecular layer of the cerebellum and the superficial piriform cortex, in the arachnoidal membrane, and in the cytoplasm of normal microglia.

The vestibulo-cochlear nerves, the cerebellar cortex and the brainstem are especially vulnerable to haemosiderin incrustation in SS, with symptoms

of sensorineural hearing loss, gait ataxia, dysmetria and myelopathy. This susceptibility probably derives from their specific ability to synthesise ferritin in response to haem, which is later stored in the form of haemosiderin. This ability is likely due to Bergmann glia in the cerebellum and to microglia in CNS tissues, and only exists in CNS tissues.^{9,10} This may explain the susceptibility of the vestibulo-cochlear nerve, in which the transition from CNS to peripheral nervous system occurs near the internal auditory meatus rather than near the brainstem as is the case for cranial nerves III, IV, V, VI, VII, IX, X and XII. In Koeppen et al.'s experiments, cranial nerves incrustated with haemosiderin included the vestibulo-cochlear nerves, as well as the olfactory tracts, the optic nerves and chiasm, which fully consist of CNS tissue. The facial nerves, adjacent to the vestibulo-cochlear nerves, were devoid of the iron stain.⁹

Close exposure to iron in the CSF is required to develop SS. The terminal expansions of Bergmann glia in the cerebellum take up iron from the CSF in the cerebellar subarachnoid space, while Bergmann glia in the depth of the interfolia spaces do not develop prominent ferritin immunoreactivity.⁹ The importance of haemosiderin incrustation is also linked to the flow pattern of CSF in the CNS. The cerebellum and brain stem receive the earliest irrigation¹¹ and therefore undergo continuously renewed exposure to haemorrhagic CSF.^{3,11} In contrast, parts of the cerebellum enclosed in a tight bony chamber that limits CSF flow were unaffected when Koeppen et al. experimentally induced SS in rabbits.⁹ The more limited CSF flow around the optic nerves compared with the vestibulo-cochlear nerves might explain why the optic nerves are generally spared.

There have been seven cases of optic neuropathy due to SS reported in the literature. First, a 70-year-old patient presented with bilateral decreased visual acuity, gait instability, ataxia and dysarthria. Brain MRI showed hypointensity of the surface of the brainstem, superior vermis, cerebellar hemisphere and spinal cord.⁴ A second 69-year-old patient complained of deteriorating visual acuity several years after she became paraplegic and suffered from hearing loss. A brain MRI revealed a T2 hypointense signal of the intraorbital optic nerves, optic chiasm and optic tracts, associated with

haemosiderin deposits.³ A third 53-year-old patient suffered from balance problems, tinnitus, profound deafness and visual acuity loss, with a similar T2 hypointensity of the optic nerves.³ A fourth 8-year-old patient presented with ataxia, nystagmus, deafness and visual acuity loss. Histological analysis of this patient's brain highlighted a brown colouration of the cerebellar hemisphere and optic chiasm, as a result of haemosiderin deposition. A post-mortem examination showed macrophages filled with iron in the pial region of the optic chiasm.³ The three last patients suffered from cerebellar tumours that were treated surgically.¹² Besides bilateral optic neuropathies, they presented with bilateral sensorineural hearing loss, gait ataxia, upper and lower limb ataxia, and mild cognitive impairment. MRI with T2-weighted and T2* sequences showed hypointensity on the surface of the cerebellar vermis and hemispheres in all three of the patients and on the optic chiasm in two of them.

Once visual symptoms have appeared, no currently available treatment can reverse tissue damage due to haemosiderin deposits. Various chelating agents, targeting either iron (e.g., desferrioxamine), or iron and copper (e.g., trientine), have been used in observational reports with little clinical improvement.¹³ Furthermore, no significant results have been reported to date in a larger number of patients. As SS is a progressive disease that can irreversibly lead to dementia and death, the goal of its treatment should be to prevent haemosiderin deposition by curatively treating the cause of the chronic subarachnoid bleeding.^{1,6} Therefore, haemosiderin-sensitive sequences including GRE T2- and even T1-weighted ones (T1* and T2*) and/or the so-called 'SWI using the blood oxygen level dependent' (SWI-BOLD) should be requested for an early identification of haemosiderin deposit in the anterior visual pathway.

In conclusion, our cases depicted two presentations of the uncommon condition of SS affecting the anterior visual pathway, one with a subacute onset, and the other one with a slowly progressive onset. These two different presentations suggest that different mechanisms, possibly ischaemia due to long-standing intracranial hypertension and demyelination, underlie the visual loss in SS.

Radiological findings also suggested two different mechanisms, as the first case resulted in a deposit of haemosiderin around the optic nerves and chiasm, while the second one was associated with haemosiderin impregnation of the optic nerves and chiasma. In both cases, occult subarachnoid bleeding was due to low-grade intracranial neoplasms.

Disclosure statement

No potential conflict of interest was reported by the authors.

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