Superficial siderosis associated with aceruloplasminemia. Case report

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Key words: Aceruloplasminemia, Superficial siderosis, Blood-cerebrospinal fluid (CSF) barrier, CSF-brain barrier, Ceruloplasmin, Macrophage

Abstract

A 63-year-old woman with a past history of right subdural hematoma (SDH) at the age of 61 years was referred to our hospital under a suspicion of aceruloplasminemia (ACP). A neurological examination revealed very mild cognitive impairment and cerebellar ataxia. Blood chemistry data showed deficient ceruloplasmin (Cp), decreased copper, and increased ferritin. A nonsense mutation (c.2630G>A, p.Trp877Ter) was detected in the Cp gene. Brain magnetic resonance imaging (MRI) showed marked hypointensity at the surface of the cerebrum, cerebellum, and brainstem bilaterally, in addition to the bilateral basal ganglia, thalamus, and dentate nucleus, suggesting the coexistence of ACP and superficial siderosis (SS). The characteristics of SS in ACP have not been examined neuroradiologically or neuropathologically in great detail, while SDH and its curative surgery are known to cause SS. The distribution of the hypointensity areas on MRI was expanded bilaterally to the subtentorial areas of this patient, which was much more widespread than observed in typical SS after SDH. We speculate that the underlying ACP may expand the SS induced by SDH. Cp would accelerate iron export from the brain via the blood-cerebrospinal fluid (CSF) barrier, or CSF-brain barrier when excessive iron is loaded into the subarachnoid space.

(195 words)

Introduction

In superficial siderosis (SS), hemosiderin deposition is seen in various parts of the central nervous system especially in the cerebellum, basal frontal lobe, temporal cortex, brainstem, spinal cord, nerve roots, and cranial nerves I and VIII [1]. Hemosiderin is found in the subpial and subependymal regions and leptomeninges, where it is observed as coarse deposits in macrophages and astrocytes [2]. SS usually presents with hearing loss, ataxia, and pyramidal tract signs. Magnetic resonance imaging (MRI) scans, particularly T2*-weighted imaging (T2*WI) is very useful for the diagnosis of SS [3].

Conversely, aceruloplasminemia (ACP) is an autosomal recessive disorder of iron metabolism caused by mutations in the ceruloplasmin gene (*CP*) [4]. Ceruloplasmin (Cp) promotes iron export from iron-storage cells through its ferroxidase activity. Cp facilitates iron binding to transferrin via the ferroxidation of ferrous iron (Fe^{2+}) into ferric iron (Fe^{3+}), as a result, Cp helps to transport iron to iron-utilizing cells. In ACP, massive iron accumulation occurs in several tissues and organs including the liver, brain, and pancreas [4]. In the brain, Cp is expressed mainly in astrocytes, ependymal cells, and pia mater cells [5, 6]. At the cellular level, iron mainly accumulates in astrocytes in the basal ganglia, thalamus, and dentate nucleus in the cerebellum [7-9].

Correspondingly, these regions shows hypointensity on T2*WI [10]. To a lesser

degree, iron accumulates in the cerebral cortex; however, it is rarely detected on the surface of the cerebral or cerebellar cortex. Clinically, ACP usually shows retinal degeneration, diabetes mellitus, and central nervous system manifestations [4]. Thus, both disorders share excessive brain iron accumulation and neurological symptoms, but the site of iron accumulation is quite different.

In the present case report, we describe a patient with SS after a chronic subdural hematoma (SDH) in the background of ACP. The SS seen in this patient was much more wide-spread than that associated with SDH in previous reports. We speculate that Cp deficiency might enhance the pathological process of SS following SDH.

Case report

The patient was a 63-year-old woman who had been treated for mild dementia for the previous 3 years. Her family members noted her forgetfulness, but she was fully independent in her daily life. She was previously diagnosed with impaired glucose tolerance, but had never taken anti-diabetes drugs. At age 61 years, she suffered from a right SDH after a fall and underwent surgery. At age 63 years, areas of hypointensity in the bilateral basal ganglia and thalamus on brain MRI were noticed incidentally when she was hospitalized because of urinary tract infection. Liver MRI also showed areas of

hypointensity, suggesting abnormal iron accumulation. She was referred to our hospital under a suspicion of ACP. Careful taking of her history revealed that she had noticed slight unsteadiness while walking in recent years. Her parents were first cousins.

On admission, a neurological examination revealed very mild cognitive impairment (MMSE score: 26/30), mild bilateral terminal tremor in the finger-nose test, and mild bilateral decomposition in the heel-knee test. Her walking was almost normal, but she sometimes stepped out on tandem gait. She had no compliant of hearing, but mild bilateral sensory deafness was detected on audiometry. She had no retinal degeneration on ophthalmological examination.

Brain MRI showed areas of marked hypointensity on the surface of the cerebrum, to lesser extent, of the cerebellum, and brainstem bilaterally, in addition to the bilateral basal ganglia and thalamus (Figure 1). On the surface of cerebrum, the area of hypointensity was found not only at the top of the gyral surface, but also around the gyrus. The hypointensity of the brain surface was symmetrical, and not different between regions near and far from the site of the SDH (Figure 1). Her serum iron level was 21 μg/dL; ferritin 448 ng/mL; copper 3 μg/dL; Cp 2.1 mg/dL; glucose 176 mg/dL; HbA1c (NGSP) 6.9%; hemoglobin 10.0 g/dL; mean corpuscular volume 84.4 fL. The cerebrospinal fluid (CSF) was watery clear and not xanthochromic, and the cell count

was 3 cells/μL; total protein 90 mg/dl; glucose 77 mg/dL; immunoglobulin G 6.3 mg/dl (IgG index 0.6); and iron 8 μg/dL (normal: 6.10 ± 1.83 μg/dL, [11]). A nonsense mutation (c.2630G>A, p.Trp877Ter) was detected in *CP* (Figure 2), confirming the diagnosis of ACP. Iron chelation therapy was not initiated because her diabetes mellitus was very mild, her neurological complaints were not significant, and her serum ferritin level was constantly below 500 ng/mL.

Her younger sister had diabetes mellitus and underwent insulin therapy, but she was neurologically normal. Her HbA1c level was 7.0 %; Cp 13.4 mg/dL; ferritin 13 ng/mL, iron 150 μg/dL; and copper 51 μg/dL. Her daughter had no particular symptoms and her HbA1c level was 5.4 %; Cp 12.2 mg/dL; ferritin 13 ng/mL; iron 201 μg/dL; and copper 46 μg/dL.

Discussion

Herein, we report a patient with the coincidental occurrence of SS and ACP. Subjective symptoms derived from both disorders were not significant, and they had not been noticed until MRI was taken by chance in her hospitalization with urinary tract infection. Both are well-known disorders of iron accumulation in the brain, but, to our best knowledge, no previous report has described the coincidence of

neuroradiologically-evident SS and ACP.

SS occurs as a result of continuous or intermittent bleeding into the subarachnoid space. Red blood cell hemoglobin is degraded to release heme, which is further catabolized to iron. Glial cells, such as Bergmann glia and microglia, which have heme-oxygenase-1 activity, are involved in the conversion of heme to ferritin [1, 2]. Finally hemosiderin is made from dense ferritin, and is deposited in subpial, subependymal and leptomeningeal regions. Several diseases including brain tumors, head or back trauma, and arteriovenous malformations, and neurosurgical procedures are reported as the underlying etiologies of SS [3]. Through the introduction of MRI sequences sensitive to susceptibility change such as T2*WI and SWI, asymptomatic SS is often found [3].

The present patient had undergone surgery due to SDH. SDH and its curative surgery are very likely to cause the development of SS [12]. Hemosiderin deposition occurs only at the top of the gyral surface in SS after SDH (SS-SDH); conversely, deposition involves the surrounding gyrus of the cerebral hemisphere in SS after subarachnoid hemorrhage (SS-SAH) [13]. Furthermore, hemosiderin deposition is restricted to supratentorial areas in SS-SDH, while it is expanded to subtentorial areas in SS-SAH [13]. In our case, however, it is noticeable that the distribution and degree of SS on MRI

was more widespread than in the previously reported cases with SS-SDH [13]. Careful observation of MR images showed that hypointensity was more conspicuous in the supratentorial areas than in the subtentorial areas, suggesting the idea that SDH was a trigger event for the development of SS in our case. The point that was characteristic of this case was that the underlying ACP might amplify SS much more.

Several neuropathological studies on ACP have shown that iron accumulation is mainly found in astrocytes around the blood vessels in the brain parenchyma [7-9]; however, little attention has been paid to iron accumulation around leptomeningeal or periventricular regions in ACP. The present case prompted us to examine this neuroradiologically and neuropathologically. As shown in Figure 3, slight SS was detected on T2*WI in an ACP patient we reported previously [9]. This patient had a longer duration (approximately 18 years) of neurological symptoms and more extensive brain pathology affecting the cerebral cortex than the ACP patients reported hitherto [9]. Compared with a typical SS case [14], there was very much less quantity of iron deposition on the brain surface in the ACP patient (Figure 3). However, this autopsy case clearly shows that ACP can be an etiology of pathologically-proven SS, and indicates simultaneously that widespread SS observed in the present case cannot be explained solely by ACP. Taken together, it is reasonable to suppose that Cp deficiency

might disturb iron export from the brain via the blood-CSF or brain-CSF barrier, and expand SS triggered by SDH in our case.

Red blood cells derived from a hemorrhage are the source of excess iron in the CSF. Excess iron in the CSF, if present, is normally transported into the blood stream via the blood-CSF barrier and into the brain parenchyma via the CSF-brain barrier by mechanisms that have not defined precisely [15]. In some pathological conditions developing SS, macrophages may be loaded with excessive amounts of iron. Cp is required for the efficient release of iron from macrophages [16]. Thus, in case of Cp deficiency, iron cannot be released effectively by macrophages, and iron accumulation in macrophages at the subpial or subependymal regions may occur more easily. In addition, released iron from macrophages (maybe ferrous iron) cannot be oxidized to ferric iron due to Cp deficiency. As a result, iron is not transported and then accumulates in astrocytes at the subpial regions more markedly in case of SS-SDH with ACP than in case of SS-SDH alone. It has passed only two years since the onset of SDH, therefore, further careful follow-up of MRI scan is needed on this patient.

In conclusion, the present case indicates that Cp has an important role in iron export from the brain via the blood-CSF or CSF-brain barrier, when excessive iron is loaded into the subarachnoid space, although the precise functions of Cp at the blood-CSF or

CSF-brain barrier needs to be clarified further.

Acknowledgements

The authors are deeply grateful to Mrs. Mika Asakawa (Division of Neuropathology, Department of Brain Disease Research, Shinshu University School of Medicine) for her technical assistance of iron staining.

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Figures Legends

Fig.1. Brain MRI. (a) A T2-weighted axial image showing hypointensity in the bilateral basal ganglia and thalamus, which is typical for ACP. (b) A T2*-weighted axial image showing more clearly recognizable hypointensity than the T2-weighted image (T2WI). (c) A susceptibility-weighted axial image (SWI) clearly showing hypointensity at the surface of the entire cerebral cortex, in addition to the bilateral basal ganglia and thalamus.T2WI (d-f) and SWI (g-i) at the cerebellum (d, g), pons (e, h), and frontal lobe (f, i). Hypointensity rims without laterality are evident at the cerebellar folia, pons, and the surface of the frontal cortex.

Fig.2. Nucleotide sequence analysis of *CP*. A nonsense mutation (p.Trp877Ter; c.2630G>A) is indicated by the arrow.

Fig. 3. MRI in an ACP patient (56-year-old man) carrying c.3019-1G>A mutation in *CP* [9] (a, d). A T2*-weighted axial images show hypointensity at the surface in some parts of the cerebral cortex (arrows, a), but not in the cerebellar cortex (d). Berlin blue staining of the cerebrum (b, c) and cerebellum (e, f). Patchy accumulation is observed in the subpial regions of the cerebral cortex (b), mainly in astrocytes (arrowheads, insert in

b) and macrophages (arrows, insert in b), but not of the cerebellar cortex (e) in an ACP patient described above. Iron accumulation is obvious in Bergmann glial cells (arrowheads, e) and the cerebellar white matter (CWM, e). In contrast, iron accumulation at the surface and in the parenchyma of the cerebral cortex is much more prominent in a SS patient (49-year-old man) (c). In the cerebellum, iron accumulation is seen at the surface, as well as in Bergman glial cells and CWM (f). GL: granular layer; ML: molecular layer. Bars = 200 μm (b, c, e, and f).

Fig. 1

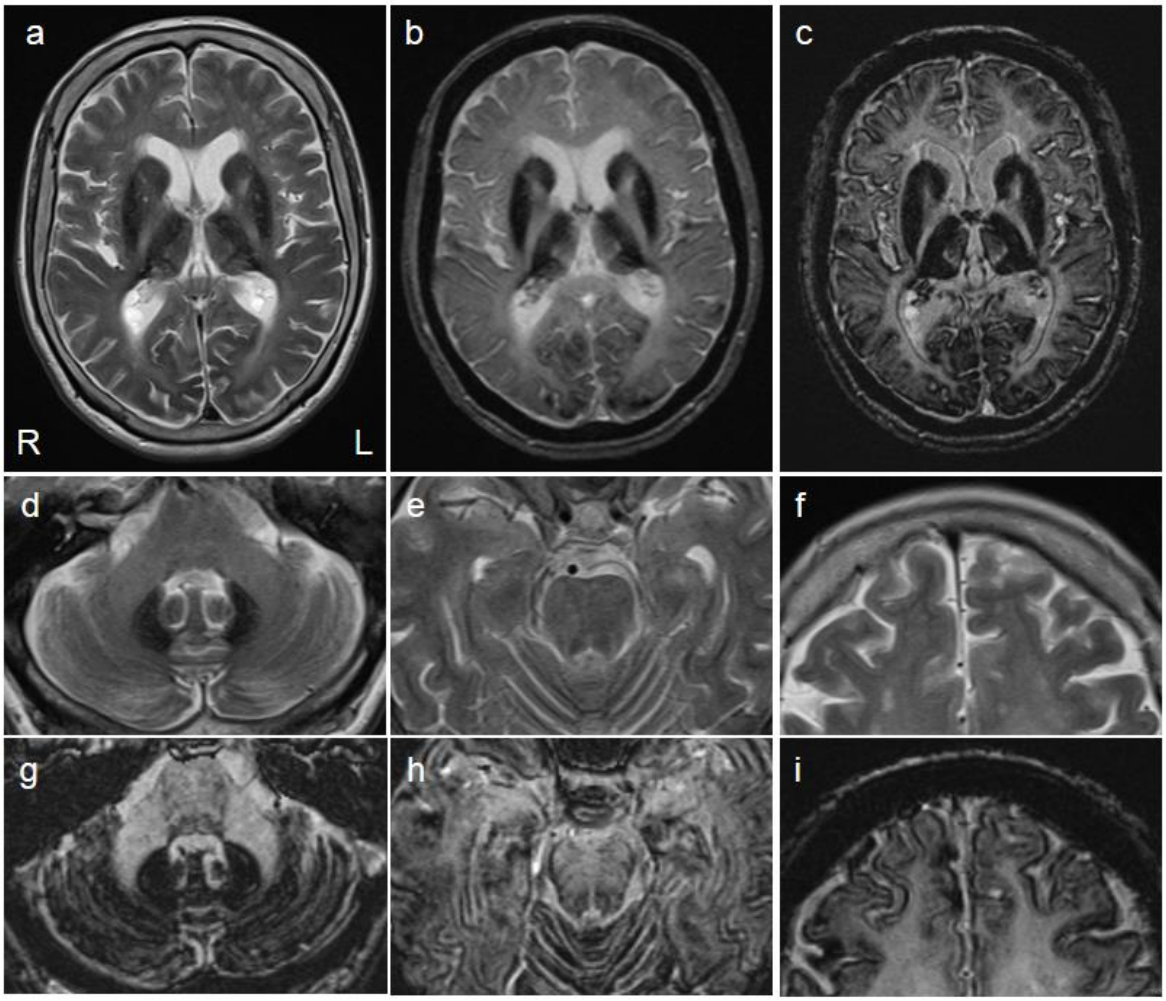

Fig. 2

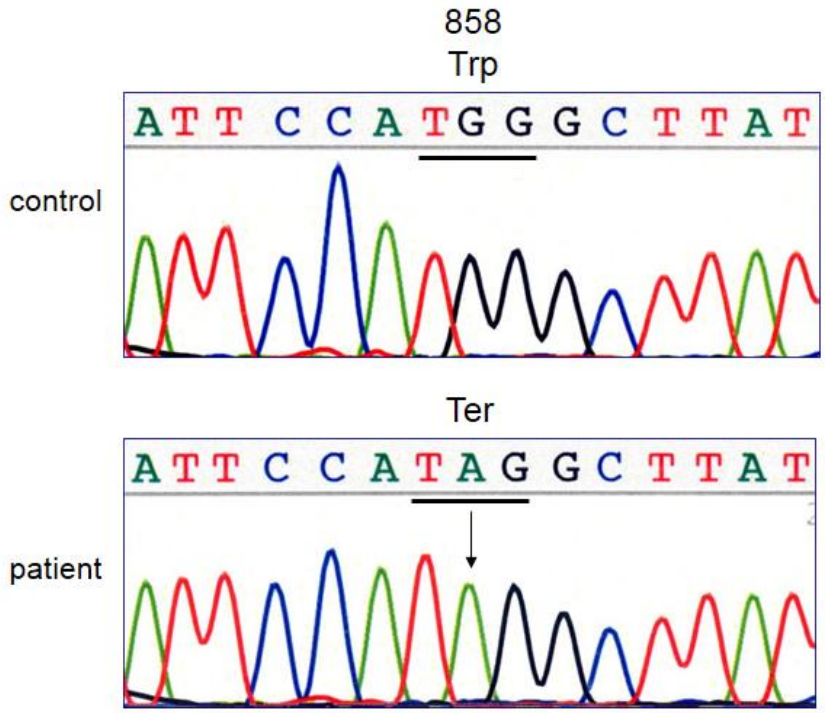
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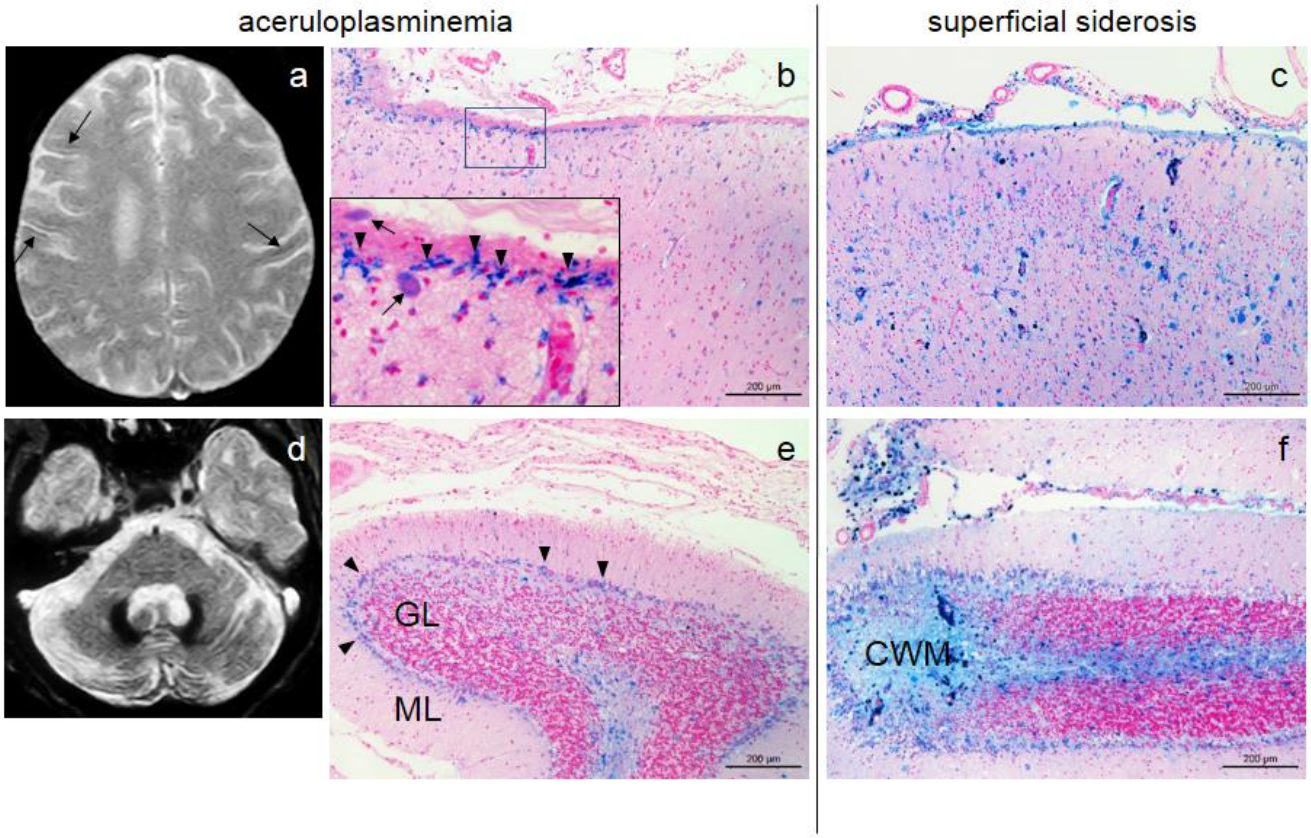
Fig. 3


aceruloplasminemia
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