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Short communication

Superficial siderosis associated with aceruloplasminemia. Case report

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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.Trp858Ter) 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.

1. 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 show 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.

2. 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

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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 (Fig. 1). On the surface of the 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 (Fig. 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; and 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.Trp858Ter) was detected in *CP* (Fig. 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.

3. 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

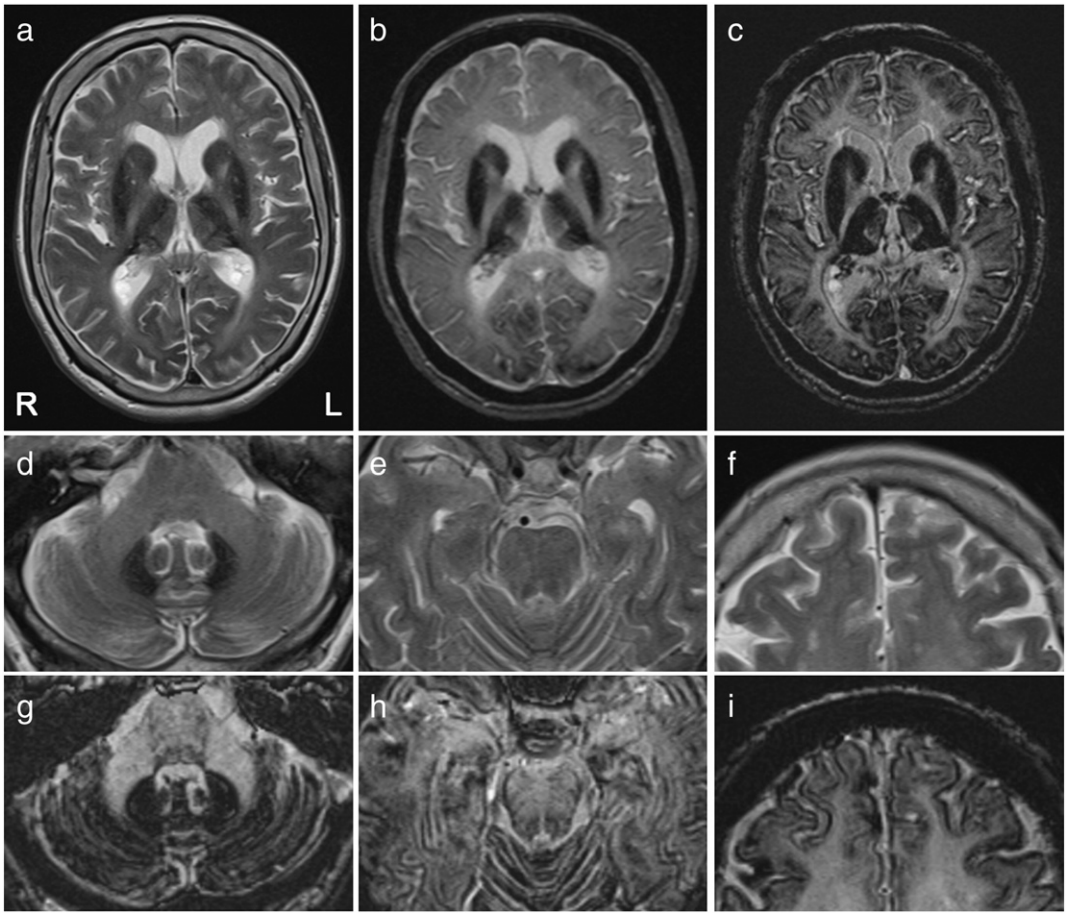

Fig. 1. Brain MRI. (a) A T2-weighted axial image showing hypointensity in the bilateral basal ganglia and thalamus, which is typical for ACP. (b) A T2*-weighted axial image showing more clearly recognizable hypointensity than the T2-weighted image (T2WI). (c) A susceptibility-weighted axial image (SWI) 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.