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CASE REPORT

Aceruloplasminemia with Neurodegenerative Condition: A Case Report

CK Li, CY Lau, KH Chin, CY Chu

Department of Radiology, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China

CASE PRESENTATION

A 68-year-old Chinese woman presented to the Accident and Emergency Department of our institution in March 2023 with confusion, gait instability, and a history of falls. She had experienced a rapid decline in mobility and motivation, rendering her homebound since December 2022. Her medical history revealed repetitive behaviour spanning over a decade, alongside co-morbidities such as diabetes mellitus and mild anaemia since 2007. Neither the patient nor her relatives reported seizures or loss of consciousness. Physical examination showed no focal neurological deficits. Dementia evaluation by the Montreal Cognitive Assessment test yielded a score of 2 out of 30, indicating a high clinical suspicion.

Non-contrast computed tomography (CT) of the brain was unremarkable with known chronic ventriculomegaly as the only notable finding. Subsequent contrast-enhanced magnetic resonance imaging (MRI) showed extensive symmetrical blooming artefacts in various deep grey matter areas on the susceptibility-weighted imaging (SWI) sequence, including the bilateral caudate nuclei, lentiform nuclei, thalami, red nuclei, substantia nigra, and bilateral dentate nuclei of the cerebellum. Diffuse gyriform-like blooming artefacts were observed outlining the surfaces of the cerebrum and cerebellum (Figure 1). These MRI findings suggested significant mineral deposition, raising suspicion of aceruloplasminemia and other differential diagnoses such as other neurodegeneration with brain iron accumulation. In view of the suspected iron accumulation, contrast-enhanced CT of the abdomen and the pelvis, as well as MRI of the liver and the heart, were performed. The CT scan revealed diffuse hyperattenuation of the liver parenchyma, while MRI showed evidence of iron overload in both the liver parenchyma and myocardium (Table 1).

Biochemically, the patient exhibited a markedly low ceruloplasmin level of under 0.02 g/L (normal range = 0.22-0.58), an elevated ferritin level of 3270 pmol/L (normal range = 25-689), and a low iron saturation of 13.1% (Table 2). She also had a history of chronic mild anaemia for at least a decade, with haemoglobin levels

Correspondence: *Dr CK Li, Department of Radiology, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China*
Email: lck340@ha.org.hk

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Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics Approval: The study was approved by the Central Institutional Review Board of Hospital Authority, Hong Kong (Ref No.: IRB-2024-245). The patient was treated in accordance with the tenets of the Declaration of Helsinki. Informed verbal consent was obtained from the patient's first-degree relative for the publication of this case report, including the accompanying images.

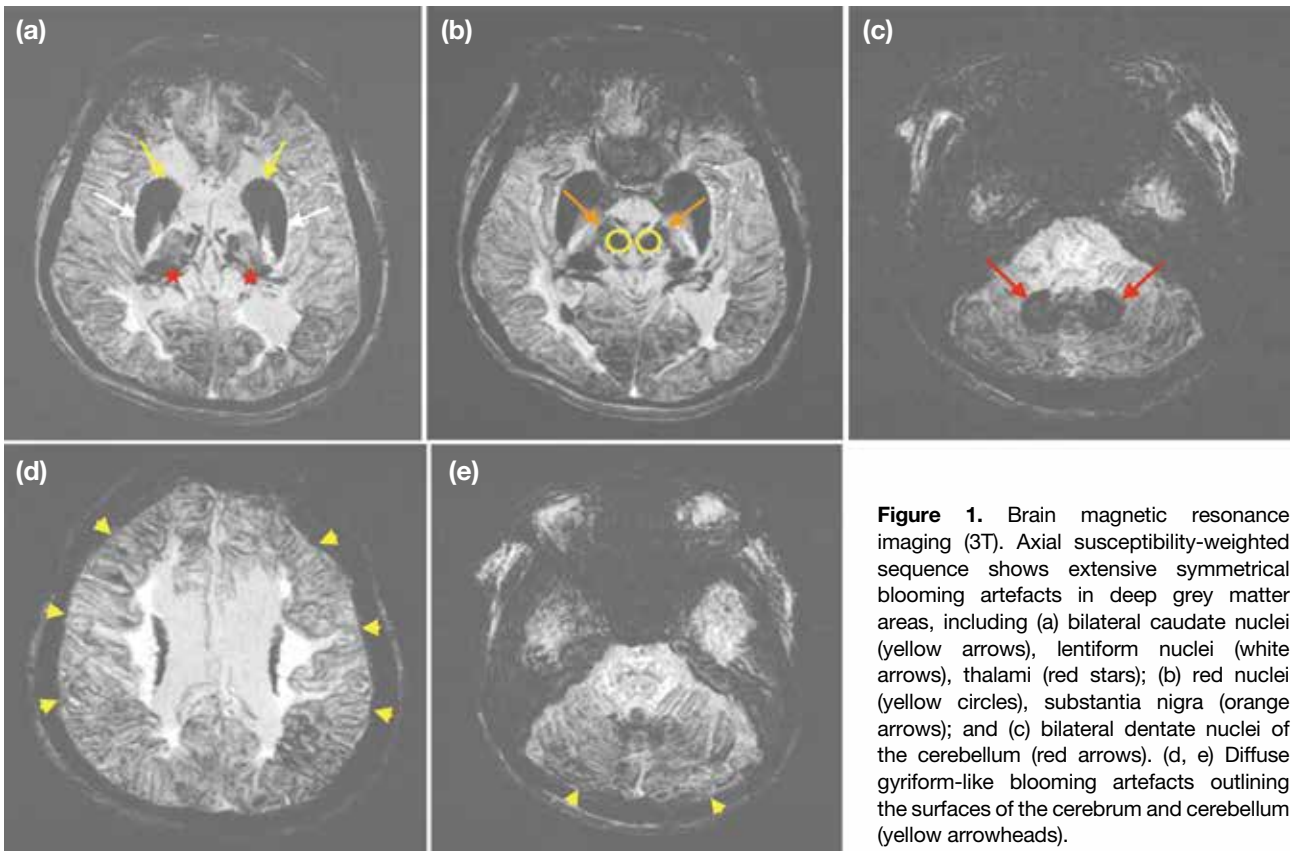

Figure 1. Brain magnetic resonance imaging (3T). Axial susceptibility-weighted sequence shows extensive symmetrical blooming artefacts in deep grey matter areas, including (a) bilateral caudate nuclei (yellow arrows), lentiform nuclei (white arrows), thalami (red stars); (b) red nuclei (yellow circles), substantia nigra (orange arrows); and (c) bilateral dentate nuclei of the cerebellum (red arrows). (d, e) Diffuse gyriform-like blooming artefacts outlining the surfaces of the cerebrum and cerebellum (yellow arrowheads).

Table 1. Calculated T2-star value of liver parenchyma and myocardium.

	Calculated T2-star value, ms	Reference levels of iron load, ms
Liver parenchyma	1.7	None: >6.3 Mild: 2.7-6.3 Moderate: 1.4-2.7 Severe: <1.4
Myocardium at cardiac septum	17.9	None: >20 Mild: 14-20 Moderate: 10-14 Severe: <10

Table 2. Laboratory findings in our case.

	Results	Normal range
Haematology		
Haemoglobin, g/dL	8.9 (Low)	11.5-15.4
Mean corpuscular volume, fL	94.2	80.0-96.0
White blood cell, × 10^9/L	5.29	3.7-9.3
Platelet, × 10^9/L	208	160-420
Iron studies		
Serum iron, μmol/L	3.4 (Low)	5.9-31.1
Transferrin saturation, %	13.1 (Low)	20-50
Serum ferritin, pmol/L	3270 (High)	25-689
Biochemical		
Serum ceruloplasmin, g/L	<0.02 g/L (Low)	0.22-0.58

ranging from 10.4 g/dL in April 2013 to 8.9 g/dL in March 2023. Genetic testing subsequently identified a pathogenic variant of the ceruloplasmin gene, confirming the diagnosis of aceruloplasminemia.

The patient and her relative were counselled about the definitive diagnosis, and the features of the disease were explained. No specific treatment was prescribed for aceruloplasminemia due to chronic neurological symptoms and impaired cognitive function. The patient continued to receive holistic care in a residential elderly care home, with monitoring for her diabetes. Genetic testing was also offered to her first-degree relatives.

DISCUSSION

Aceruloplasminemia is a rare autosomal recessive disorder characterised by the absence or dysfunction of ceruloplasmin with consequent iron accumulation in various tissues and organs, leading to a spectrum of neurological and systemic manifestations.[1] Our case illustrates the importance of recognising the clinical and radiological features of aceruloplasminemia to facilitate accurate diagnosis and management.

Aceruloplasminemia was first documented in 1987 by Miyajima et al[2] in a 52-year-old woman with blepharospasm, retinal degeneration, and diabetes mellitus. The estimated prevalence is approximately 1 in 2,000,000 population among Japanese individuals born from non-consanguineous marriages.[3] Nonetheless, this estimation is region-specific and may not be applicable to other populations.[4] Clinical manifestations leading to diagnosis by neurologists include cerebellar signs such as dysarthria, trunk and limb ataxia, and involuntary movements including dystonia, chorea, and tremors. Symptoms may vary widely among individuals and may overlap with other neurological or metabolic disorders.[5]

To understand the pathophysiology of aceruloplasminemia, two distinct isoforms of ceruloplasmin are produced via alternative splicing in exons 19 and 20, resulting in a soluble form in plasma and a glycosylphosphatidylinositol-anchored membrane form.[6] The ferroxidase activity of the membrane-bound ceruloplasmin plays a vital role for incorporating ferric cation Fe^{3+} into plasma transferrin, facilitating its delivery to other cells via transferrin receptor 1. In the absence of ceruloplasmin, iron initially accumulates in astrocytes, triggering neuronal iron starvation. Consequently, neurons resort to alternative iron sources such as non–transferrin-bound iron, exacerbating toxicity (Figure 2).[1,7]

The hallmark radiological feature of aceruloplasminemia manifests as symmetric blooming artefacts on SWI, attributable to iron accumulation in the brain. Typically, this involves regions such as the basal ganglia and thalamus, cerebral cortex and dentate nuclei of the cerebellum.[8] Aceruloplasminemia stands out as the sole recognised disorder featuring both cerebral and systemic manifestations of iron accumulation.[9] As in our patient, cardiac and hepatic iron overload may also occur. Hepatic iron overload often presents with hyperattenuation of the liver parenchyma on CT scans and is quantitatively assessed via MRI dedicated to evaluating iron overload in the liver. Nonetheless, liver iron accumulation seldom leads to clinical manifestations such as cirrhosis or liver failure.[10] Iron deposition in other organs, including the heart, pancreas, and other endocrine glands, has been documented and can be evaluated by MRI.[7]

The neurological manifestations of aceruloplasminemia are heterogeneous and often progressive. In our patient, initial symptoms such as confusion, gait instability, and falls were consistent with those commonly reported in the literature. Documented neurological features included behavioural changes or psychiatric manifestations, cognitive impairment, extrapyramidal signs, cerebellar signs, and involuntary movements.[5] Another classic clinical manifestation is diabetes mellitus, typically presenting in the fourth to sixth decades of life in individuals without classic risk factors or need for insulin treatment.[11] The mechanism underlying the development of diabetes mellitus in aceruloplasminemia remains poorly understood, although iron accumulation is noted predominantly in exocrine rather than endocrine pancreatic cells.[12] Some studies suggest that the clinical triad of aceruloplasminemia may

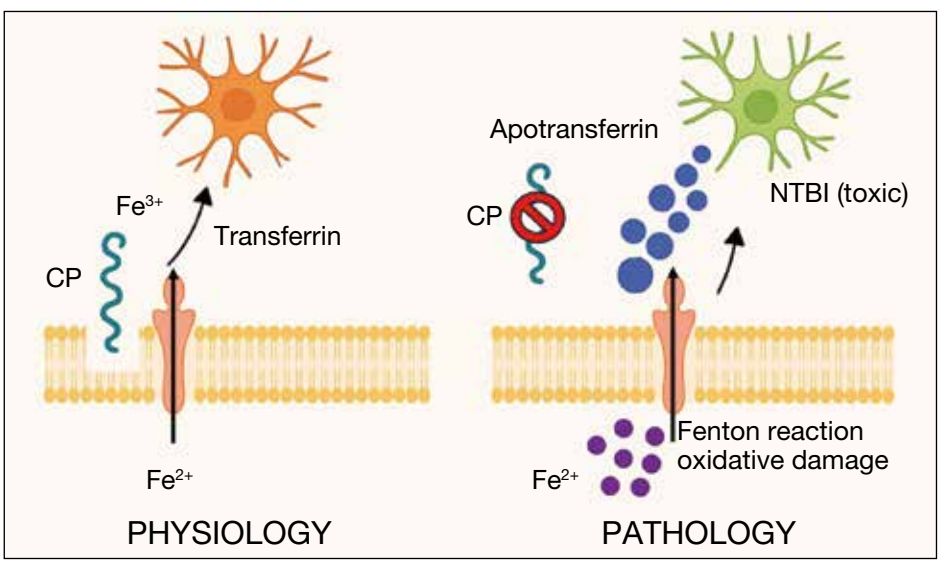

Figure 2. The ferroxidase activity of the membrane-bound ceruloplasmin (CP) plays a vital role in incorporating ferric cation Fe^{3+} into plasma transferrin, facilitating its delivery to other cells. In the absence of CP, iron accumulates in astrocytes, triggering neuronal iron starvation. Consequently, neurons resort to alternative iron sources, such as non–transferrin-bound iron, exacerbating toxicity.[1,7] Apotransferrin is the iron-free form of transferrin, indicating failure of iron incorporation. The accumulation of ferric cation Fe^{2+} also leads to fenton reaction with generation of highly reactive hydroxyl radicals, causing oxidative damage.
Abbreviations: CP = ceruloplasmin; NTBI = non–transferrin-bound iron.

comprise neurodegeneration, diabetes mellitus, and retinal degeneration.[13,14] Nonetheless retinopathy is less frequently observed in non-Japanese case series, and its direct association with aceruloplasminemia remains uncertain.[13,14]

Biochemically, the first detectable parameters of aceruloplasminemia, as indicated by all major case series including our own, encompass mild microcytic anaemia, low transferrin saturation, and hyperserotonaemia. This biochemical triad holds crucial diagnostic significance long before other clinical manifestations emerge. Serum ceruloplasmin is typically undetectable or markedly reduced and serves as an important diagnostic parameter. Although mild microcytic anaemia often emerges as the earliest biochemical sign of aceruloplasminemia,[5,10] it rarely leads to diagnosis at the early pre-symptomatic stage. By integrating biochemical studies with radiological and clinical manifestations, the exclusion of other differential neurodegenerative diseases becomes more manageable. As in our case, genetic testing provides definitive evidence to confirm the diagnosis of aceruloplasminemia and enables genetic counselling and family screening for at-risk individuals.

Treatment of aceruloplasminemia primarily involves iron-chelating agents; however, their effectiveness in reducing brain iron and alleviating neurological symptoms remains uncertain. Currently, there is no convincing evidence supporting the clinical benefits of iron removal therapy. Phlebotomy, another treatment option, is also considered suboptimal. Alternative strategies focus on preventing oxidative tissue damage, such as administering vitamin E or zinc sulphate.[10] Timely diagnosis and treatment are paramount to prevent irreversible neurological complications.[7]

CONCLUSION

Aceruloplasminemia is difficult to diagnose and requires a high level of awareness of its clinical features, biochemical parameters, and radiological findings. The biochemical triad of mild anaemia, low transferrin saturation, and hyperserotonaemia serves as a key diagnostic indicator when no alternative explanation is evident. The condition should be considered in patients who present with mild microcytic anaemia, early-onset diabetes mellitus, and unexplained liver iron overload. In later stages, adult-onset neurological dysfunction, such as behavioural changes, psychiatric disturbances, as well as cerebellar and extrapyramidal signs, become apparent. Corresponding MRI findings often reveal symmetrical hypointensity in the basal ganglia and thalamus, cerebral cortex and dentate nuclei of cerebellum in T2 and T2-star sequences, along with a pronounced blooming artifact in SWI. Prompt diagnosis is crucial to prevent irreversible neurological complications.

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