

Aceruloplasminemia: Unique Clinical and MRI Findings in a Patient with a Novel Frameshift Mutation

Fabiana Colucci, MD,^{1,2*} Silvia Barca, MD,^{3†} Roberto Cilia, MD,^{1,*} Valentino De Franco, MD,⁴ Antonio E. Elia, MD,¹ Nico Golfè Andreasi, MD,¹ Luigi Romito, MD,¹ Roberta Telesse, MD,¹ Arianna Braccia, MD,¹ Valentina Leta, MD,¹ Marina Grisoli, MD,⁵ Celeste Panteghini, MS,⁶ Barbara Garavaglia, PhD,⁶ Grazia Devigili, PhD,^{1*} and Roberto Eleopra, MD^{1*}

Aceruloplasminemia (ACP; OMIM #604290) is a rare disorder caused by biallelic mutations of the *ceruloplasmin* (CP) gene, resulting in the absence of serum CP.¹ CP inactivation leads to iron metabolism abnormalities with subsequent cellular iron accumulation. ACP may present with systemic symptoms (eg, anemia, liver disease, diabetes mellitus, and retinopathy) several years before the onset of progressive movement disorders and dementia.² Although genetic testing and biochemical analysis are mandatory to confirm the diagnosis, brain MRI is considered useful for distinguishing neurodegeneration with brain iron accumulation (NBIA) subtypes.³ Here, we report an ACP patient with cystic basal ganglia cavitations on MRI, a feature considered typical of neuroferritinopathy.^{3,4}

Case Report

A 61-year-old Caucasian female, born to nonconsanguineous parents, presented with a 25-year history of gait impairment. Symptoms began at the age of 36 with lower limb pain and weakness followed by trunk and limb involuntary movements. In her 50s, she became dependent due to progressive motor disability and cognitive impairment. Non-motor symptoms included constipation, urinary urgency and incontinence, and mood deflection. Neurological examination revealed: saccadic pursuit and slow vertical saccades; cerebellar-dystonic dysarthria; tetraparesis with brisk osteotendinous reflexes; dysmetria at finger-nose maneuver; global akinesia associated with irregular choreic movements involving her

face, trunk, upper and lower limbs (Video 1, Segment A). Her gait was possible only with bilateral aid, wide-based and associated with dystonia of the trunk and lower limbs (Video 1, Segment B). Cognitive evaluation showed deficit of attention, visual constructive abilities, and long-term memory (MoCA 21.1/30); right arm apraxia; depression.

Headache and iron deficiency anemia (refractory to iron supplementation) were reported since childhood.

Her mother and her maternal uncle presented similar clinical findings (iron-deficiency anemia, progressive gait impairment and cognitive decline) since their 30s (Fig. 1, panel A).

Biological analysis in serum proved low iron (40 µg/dl; normal values (n.v.) 40–145) and copper levels (3 µg/dl; n.v. 65–165), absence of ceruloplasmin (2 mg/dl; n.v. 20–60). Ferritin levels were increased in serum (730 ng/mL; n.v. 10–150) and CSF (137 mg/mL; n.v. <17 mg/mL). Albeit liver function was normal, abdomen ultrasonography showed steatosis. Laboratory tests and ophthalmologic evaluation excluded diabetes mellitus and retinal involvement.

Cardiovascular autonomic function testing showed baroreflex failure: delayed orthostatic hypotension at head up tilt test and impaired adrenergic sympathetic function at the Valsalva maneuver, with relatively preserved muscle sympathetic function. Plasma epinephrine levels were reduced both supine and after 3-minute standing, whereas norepinephrine levels were normal in both conditions. 123I-MIBG SPECT showed reduced density of postganglionic sympathetic myocardial nerve terminals. Dopamine transporter SPECT imaging was normal.

¹Fondazione IRCCS Istituto Neurologico Carlo Besta, Department of Clinical Neurosciences, Parkinson and Movement Disorders Unit, Milan, Italy; ²Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy; ³Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; ⁴Department of Medical, Surgical and Neurological Sciences, University of Siena, Siena, Italy; ⁵Fondazione IRCCS Istituto Neurologico Carlo Besta, Department of Neurosurgery, Functional Neurosurgery Unit, Milano, Milano, Italy; ⁶Fondazione IRCCS Istituto Neurologico Carlo Besta, Unit of Medical Genetics and Neurogenetics, Milan, Italy

*Correspondence to: Dr. Roberto Cilia, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via G. Celoria, 11, 20133 Milan, Italy; E-mail: roberto.cilia@istituto-besta.it

Keywords: aceruloplasminemia, MRI, iron accumulation, NBIA, basal ganglia cavitation.

[†]Equal contribution as first authors.

^{*}Equal contribution as senior authors.

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Received 10 November 2023; revised 10 January 2024; accepted 19 January 2024.

Published online 23 February 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.14000



Video 1. Segment A: Video shows saccadic slowness, especially in vertical gaze. Cerebellar-dystonic dysarthria is audible during speech, and dystonic facial movements are observed during the examination. Upper limbs do not show weakness, but random and irregular choreic movements are present especially on left arm. Upper limbs ataxia (left>right) is also observed and during sitting position ataxia involves trunk. While sitting, the lower limbs show involuntary choreic movements, which are less prominent than those of the upper limbs and mainly involved the right leg. Mild global akinesia is observed during finger and toe tapping, mainly on the left side. Left>right cerebellar dysmetria is also observed. Video Segment B: Video shows a wide-base gait associated with dystonic features involving the trunk and lower limbs. Walking is possible only with aid. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14000>

T_2^* and susceptibility-weighted brain MR showed hypointensity of bilateral striata (caudate nuclei and putamina), thalami, red nuclei, dentate nuclei, coupled with hyperintensity (cavitation) of anterior putamina (Fig. 1, Panel B–F). T_1 -weighted images showed cortical and cerebellar atrophy. CT scan excluded basal ganglia calcification (Fig. 1, Panel F,G).

Prior to brain MRI, genetic testing for Huntington's disease, Huntington-like forms (prion protein gene, JHP3, SCA17, ACDY5), C9orf72, SCA2, SCA3, and α -tocopherol-transfer-protein gene were negative. Subsequent next-generation sequencing panel for NBIA genes revealed a homozygous variant in exon 4 of CP gene (c.650 T > C with p.Phe217Ser). This variant is not present in the ExAc database and it is predicted to be pathogenic by in silico analysis.

Iron chelating therapy (deferroxamine) did not change clinical and MRI abnormalities. Tetrabenazine 25 mg t.i.d. partially improved choreic movements.

Discussion

Fewer than 60 ACP cases have been reported so far. The natural course of ACP is variable and the phenotypic spectrum may include ataxia, involuntary movements (facial and neck dystonia, tremor, and chorea), parkinsonism, depression, and cognitive impairment.^{2,5} Genotype–phenotype correlation is still unclear.⁵

This patient showed unique clinical and MRI features. Clinically, our case had young-onset chorea-dystonia combined with

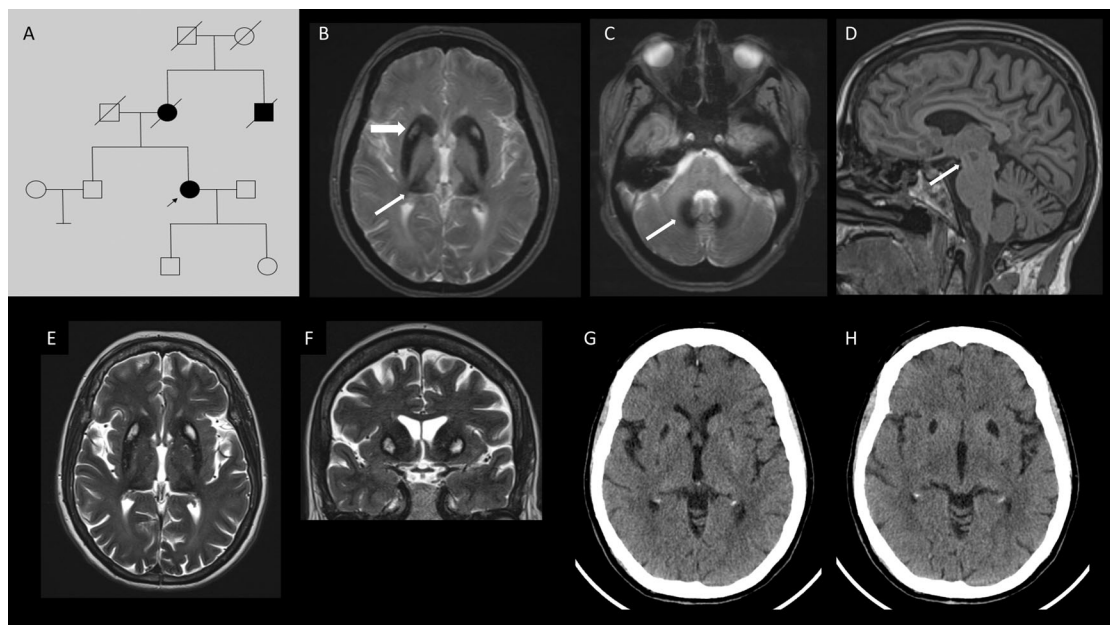


Figure 1. Panels A: patient pedigree. Panel B–F: MRI Gradient-echo and SWI, shows basal ganglia iron accumulation with putamina cavitations. Panels G–H: CT scan excludes basal ganglia calcifications and shows putaminal cavitation.

parkinsonism and ataxia, complicated by anemia refractory to iron treatment and elevated ferritin in serum and CSF. A novel clinical finding worth underlining is cardiovascular autonomic dysfunction with abnormal response of plasma epinephrine and norepinephrine. Although iron accumulation may be toxic to sympathetic neurons and cause adrenergic cardiovascular impairment,^{6,7} the relationship between iron overload and dysautonomia in ACP needs further investigation.

We recommend investigating orthostatic hypotension in ACP as a potential cause of falls.

Concerning MRI, ACP typically shows a unique pattern: a simultaneous iron deposition in all basal ganglia, thalami, dentate nuclei, and cortex.^{8,9} MRI findings had been claimed to differentiate ACP from neuroferritinopathy, the latter typically showing hyperintensities of the globus pallidus and putamen, due to cystic degeneration (cavitations).^{8,10} This case represents the first description of striatal cavitations in ACP, suggesting that cystic degeneration are not specific and develop as a function of time in different NBIA subtypes. Longitudinal MRI studies may shed light on the pathophysiology of cavitations due to iron accumulation in basal ganglia.

Iron chelation therapy is usually beneficial for ACP, as early treatment leads to decreased iron accumulation and subsequent disability.¹¹ Unfortunately, deferoxamine was unsuccessful due to delayed diagnosis.

Acknowledgment

We thank Dr. Luigi Santilio, MD, for his help in video recording. Open access funding provided by BIBLIOSAN.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

F.C.: 1A, 1B, 1C, 3A

S.B.: 1A, 1B, 1C, 3A

R.C.: 1A, 1B, 1C, 3A, 3B

V.D.F.: 1C, 3A

A.E.E.: 1B, 1C, 3B

N.G.A.: 1B, 1C, 3B

L.R.: 1B, 1C

R.T.: 1B, 1C

A.B.: 1B, 1C

V.L.: 1B, 1C, 3B

M.G.: 1B, 3B

C.P.: 1C

B.G.: 1C

G.D.: 1A, 1B, 1C, 3B

RE: 1A, 1B, 1C, 3B

Disclosures

Ethical compliance statement: The authors confirm that the approval of an institutional review board was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The manuscript submitted for publication has been performed in accordance with ethical standards stated in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the patient for the publication of this case report and for the publication of all iconographic and video materials.

Funding Sources and Conflicts of Interest: The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the previous 12 months: All authors have nothing to disclose. ■

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