LETTER TO THE EDITOR

To The Editor

Seizures in Hereditary Aceruloplasminemia

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Hereditary aceruloplasminemia (HA) is a rare autosomal recessive disorder caused by mutations of the *CP* gene encoding for ceruloplasmin (Cp), a key enzyme in iron metabolism. Together with neuroferritinopathy (or hereditary ferritinopathy, HF), HA is classified among the adult-onset neurodegeneration with brain iron accumulation syndromes (NBIAs) caused by primary defects in iron metabolism. Almost 70 *CP* mutations are described so far, leading to a well-characterized clinical picture caused by the massive total body iron overload: adult-onset refractory anemia, diabetes, retinopathy followed by variable neuropsychiatric presentations. In HA, motor functions deteriorate together with cognition and behavior, with various degrees of severity.[1] Symptoms are thought to be caused by the massive iron overload within the basal ganglia, thalamus, and dentate nucleus. Although the additional presence of cortical iron overload has been revealed by neuroimaging and pathological studies,[2] seizures and other clinical signs of cortical involvement, other than late-stage dementia, have not been described. Herein, we reviewed clinical and neuroimaging findings of the follow-up of two previously reported cases of HA,[3-5] pointing out clinical clues on the role of cortical and subcortical iron overload in determining seizures, a clinical feature never described in HA thus far.

The first is the case of a woman diagnosed with HA at the age of 56, carrying a homozygous deletion of *CP* exon 12 (Figure 1A). Her early neurological complaints were irritability and disinhibition, slightly worsened over a few years, later accompanied by gait ataxia and mild chorea. A detailed description of this case is published elsewhere.[4] We have followed the patient for 4 years since the diagnosis. She showed a stable clinical picture until the 3rd year, when she presented with stereotyped episodes of impaired awareness preceded by right side paresthesia and expressive aphasia. She underwent an EEG showing left posterior interictal spike-wave discharges (Figure 1B). A diagnosis of epilepsy with focal impaired awareness seizures was made and she was successfully treated with levetiracetam 2000 mg/day. In one further year, severe ataxia and generalized dystonia led to an at-home bedridden condition, eventually causing death at the age of 60 due to the refractory diabetes and severe dementia with Anton-like features (i.e. cortical blindness). During the late stage of the disease, the patient's condition was complicated by encephalopathy, and focal seizures reported almost once a month.

The second patient is another woman, carrier of a homozygous deletion of two nucleotides (1257–1258 TT del) in exon 7 of the *CP* gene. Her neurological disorder started in 1991 with stereotyped episodes of impaired awareness followed by post-ictal aphasia, when the patient was 35. At that time, her MRI already depicted iron deposition, misdiagnosed as hereditary hemochromatosis due to splanchnic involvement, as already described.[3] She was diagnosed with left temporal lobe epilepsy based on clinical semiology and standard EEG showing epileptiform discharges (spikes and sharp waves) over left temporal regions and was treated successfully with carbamazepine 600 mg daily. She also received periodic cycles of iv deferoxamine in 1992, 1996, and 1999 and oral deferiprone since 2004. The patient has been seizure free from 1993 (when she had a single relapse after an attempt to discontinue carbamazepine) to 1998, when focal seizures characterized by speech arrest were confirmed with a 24-hour EEG showing left temporal epileptiform activity, both during wakefulness and N1–N2 sleep. The patient has been seizure free since 1998 and was able to withdraw carbamazepine in 2006. Other neurological signs included mild generalized dystonia/parkinsonism, stable until today. The detailed clinical presentation and treatment outcome have been reported elsewhere.[3-5] Last brain MRI was comparable to previous ones (Figure 1C).

EEG epileptiform abnormalities are not described in the classical phenotype of adult onset NBIAs, that is, HA and HF. Nevertheless, cortical iron deposition is a disease hallmark of both. For instance, Grisoli and colleagues provided the first MRI evidences of iron deposition within the superficial layers of the cerebral and cerebellar cortices in a case of HA, corroborating previous neuropathological findings.[2] HF is caused by *FTL* gene mutations, leading to deposition of iron-rich ferritin bodies in the striatum, cerebellum, and especially the cortex, the latter contributing to the "cortical pencil lining," an MRI diagnostic clue.[6]

NBIAs like PLAN (PLA2G6-Associated Neurodegeneration, *PLA2G6* gene) and BPAN (Beta-propeller protein-associated neurodegeneration, *WDR45* gene) can cause seizures in childhood, with the latter being associated with epileptic encephalopathies such as Lennox-Gastaut syndrome.[7,8] Other known NBIAs such as PKAN (pantothenate kinase-associated neurodegeneration, *PANK2* gene), MPAN (mitochondrial-membrane protein-associated neurodegeneration, *C19orf12* gene), FAHN (fatty acid hydroxylase-associated neurodegeneration, FA2H gene), Kufor-Rakeb disease (*ATP13A2* gene), and Woodhouse-Sakati syndrome (*DCAF17* gene) seldom manifest with seizures and only during late disease stages, while epilepsy is not described in CoPAN or COASY-protein associated neurodegeneration (Table 1).[9] However, they are all very rare diseases and reported phenotypes are expanding. In contrast with HA and HF, the aforementioned syndromes do not directly involve metal metabolism and central nervous system (CNS) iron deposition is an epiphenomenon of other pathophysiological mechanisms. Another non-NBIA condition caused by metal deposition is Wilson's disease, an autosomal recessive disease caused by *ATP7B* mutations, in which CNS copper deposition leads to seizures in 10% of cases (both focal and generalized), especially if white matter degeneration is present.[9]

Cortical iron pathology has been already associated with seizures independently from the cause of metal deposition. For instance, iron-induced epilepsy is a well-known model of post-traumatic epilepsy in rats, thus mimicking the iron release occurring by blood cell rupture after a traumatic/vascular lesion. Both HA and HF lead to cortical iron accumulation; however, given that the cortical iron pathology may drive an epileptic pathogenesis, why have only HA patients been documented with seizures so far?

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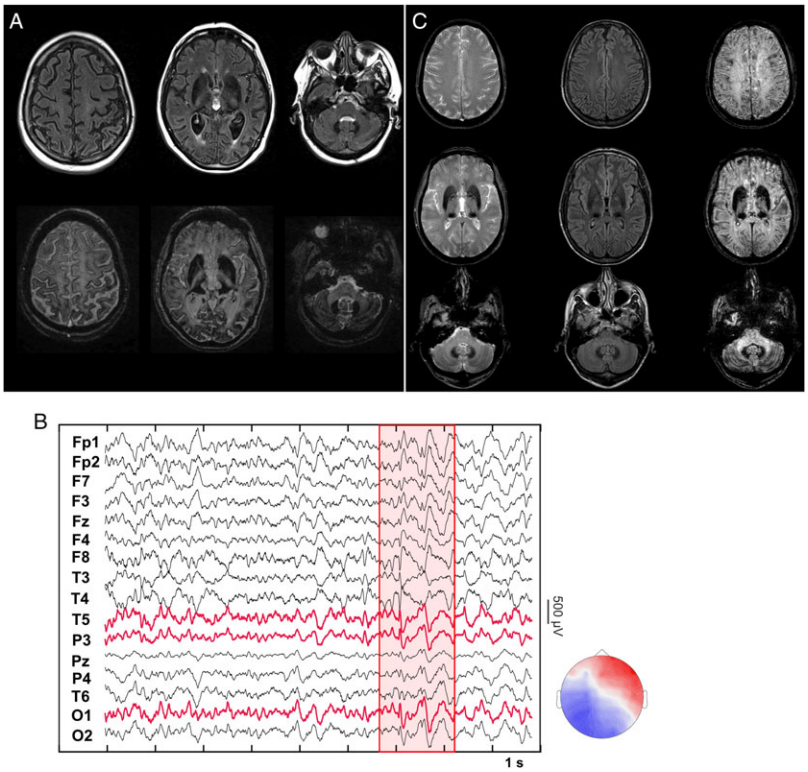

Figure 1. *(A) Brain MRI of Patient 1, 3 years after the case, was reported by Melgari et al. in 2015. FLAIR and SWI sequences are depicted in the upper and lower panel: iron is massively deposited in the cortex, within the basal ganglia, especially in the dorsomedial thalamus, and in the dentate and cerebellar cortices. (B) EEG recording of Patient 1 (high-pass filter: 1 Hz; low-pass filter: 70 Hz; average reference). On the right lower panel: topographic 2D voltage-map at the negative peak of the left temporo-parieto-occipital (T5, O1 > P3) epileptiform discharges. (C) Brain MRI of Patient 2 at last imaging follow-up (2012): gradient echo (left), FLAIR (middle) and especially BOLD (right) show iron deposition similar to Patient 1.*

Table 1: Age at onset and seizure presentation in NBIAs

Syndrome	Gene	Inheritance	Age at onset	Seizures
PKAN	PANK2	AR	Childhood	Later disease course
BPAN	WDR45	XL	Childhood	Various types
Woodhouse-Sakati syndrome	DCAF17	AR	Childhood	Later disease course
CoPAN	COASY	AR	Childhood	Not described
FAHN	FA2H	AR	Childhood	Later disease course
Kufor-Rakeb syndrome	ATP13A2	AR	Childhood	Later disease course
MPAN	C19orf12	AR, AD	Childhood to early adulthood	Later disease course
PLAN	PLA2G6	AR	Childhood to early adulthood	Various types
HF	FTL	AD	Adulthood	Not described
HA	Ceruloplasmin gene	AR	Adulthood	Various types

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

First, although in both conditions ferritin is oversaturated and the presence of highly reactive ferrous iron is toxic for glia and neurons, HA neurons suffer from a paradoxical iron starvation due to the impairment of astrocyte iron efflux, which neuronal metabolism is strictly dependent on.[4] Interestingly, iron deficiency has been associated with seizures in other condition such as febrile seizures and human ferritin L-chain deficiency. Second, the thalamus, which is severely and specifically involved in HA but not HF, could contribute to seizure pathophysiology and propagation.[10]

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In our cases, we observed left hemispheric focal seizures manifesting at different stages. The clinical course of Patient 1 changed radically after the onset of seizures, whereas in Patient 2 seizures were an early feature showing a prompt and sustained response to carbamazepine. The reasons for these differences are unknown at the moment, but the use of chelation therapies may have had a key role in Patient 2's epilepsy management.

In conclusion, the present report should raise awareness of the presence of seizures in patients with HA. The latter is a very rare disorder and further studies are necessary to estimate the real prevalence of seizures. While awaiting further studies, our experience expanded the phenotype of HA – including this syndrome in the differential diagnosis of NBIAs with seizures – and emphasizes that the presence of seizure in the context of an adult-onset form of NBIA should raise a suspicion of HA rather than HF.

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Statement of Authorship

MM, FB, LR, and AF: clinical data collection and drafting of the manuscript; VDL, GA, MR, and AF: drafting the article and revising it critically for important intellectual content, final approval of the version to be submitted.

Ethics Approval and Consent to Participate

The authors declare that ethics approval was not required for this case report, which is conducted in accordance with the declaration of Helsinki.

Massimo Marano
Unit of Neurology, Neurophysiology and Neurobiology, Department of Medicine, Campus Bio-Medico of Rome University, Rome, Italy

Francesco Bove
U.O.C. Neurologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

Lorenzo Ricci
Unit of Neurology, Neurophysiology and Neurobiology, Department of Medicine, Campus Bio-Medico of Rome University, Rome, Italy

Mohammad Rohani
Department of Neurology, Hazrat Rasool Hospital, Iran University of Medical Sciences, Tehran, Iran

Vincenzo Di Lazzaro
Unit of Neurology, Neurophysiology and Neurobiology, Department of Medicine, Campus Bio-Medico of Rome University, Rome, Italy

Giovanni Assenza
Unit of Neurology, Neurophysiology and Neurobiology, Department of Medicine, Campus Bio-Medico of Rome University, Rome, Italy

Alfonso Fasano
Department of Neurology, Hazrat Rasool Hospital, Iran University of Medical Sciences, Tehran, Iran

Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Centre, Toronto Western Hospital, UHN, Toronto, Ontario, Canada

Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Krembil Brain Institute, Toronto, Ontario, Canada

Center for Advancing Neurotechnological Innovation to Application (CRANIA), Toronto, Ontario, Canada

Correspondence to: Massimo Marano, MD, Neurology, Neurophysiology and Neurobiology Unit, Department of Medicine, University Campus Bio-Medico of Rome, Viale Alvaro del Portillo, 200, 00128 Rome, Italy. Email: m.marano@unicampus.it, masmarano@gmail.com

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