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LETTER TO THE EDITORS

Aceruloplasminemia: neurodegeneration with brain iron accumulation (NBIA) associated with parkinsonism

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Dear editor,

Inborn errors of metabolism (IEM) leading to metal-storage disorders are important causes of parkinsonism. We read with great interest the paper by Garcia-Cazorla and Duarte (2014), who reviewed IEMs causing parkinsonism and proposed diagnostic algorithms depending on the age at onset of this neurological symptom. The authors suggested that IEM should be included in the differential diagnosis of parkinsonism at any age, while metal-storage disorders should be particularly considered if parkinsonism manifests in adolescents or adults. Special consideration was given to the group of neurodegeneration with brain iron accumulation (NBIA). Currently, nine phenotypes of NBIA and their associated gene mutations have been distinguished. Most NBIA diseases are associated with parkinsonism. Garcia-Cazorla and Duarte however failed to include aceruloplasminemia in their list of IEM which cause NBIA with features of parkinsonism.

Aceruloplasminemia (OMIM #604290) is caused by mutations of the ceruloplasmin (CP) gene and is associated with iron accumulation in visceral organs and in the central nervous system. Clinically, aceruloplasminemia has been characterized by a triad of diabetes mellitus, retinal degeneration and neurological symptoms. Clinical manifestations in 45 Japanese patients showed a neurological phenotype consisting of cerebellar ataxia, dysarthria, involuntary movements, parkinsonism and cognitive impairment, manifesting around the fifth decade of life and usually preceded by visceral manifestations (Miyajima et al 2003). Although cerebellar ataxia with dysarthria was the most common neurological manifestation of aceruloplasminemia (McNeill et al 2008; Miyajima et al 2003), signs of parkinsonism developed in 41 % of the neurologically symptomatic patients (Miyajima et al 2003). Parkinsonism related to aceruloplasminemia was rarely treated by dopaminergic agents; administration of Levodopa was without benefit in two reported cases (Kohno et al 2000). It has been proposed that iron chelation before the onset of neurodegeneration might slow the neurodegenerative process in aceruloplasminemia (McNeill et al 2008).

Main characteristics of aceruloplasminemia, regarding the age of onset, clinical signs, imaging features, biological markers and response to dopaminergic agents, are summarized in Table 1. Among NBIA diseases that cause parkinsonism, neurological manifestations of aceruloplasminemia show similarities to neuroferritinopathy (Garcia-Cazorla and Duarte 2014). However, neuroferritinopathy can be distinguished from aceruloplasminemia by the absence of additional clinical signs, while aceruloplasminemia is associated with systemic signs as diabetes mellitus and anemia. Furthermore, serum ferritin levels are low in neuroferritinopathy and aceruloplasminemia is characterized by hyperferritinemia (Table 1).

In conclusion, aceruloplasminemia is associated with parkinsonism and should be included in the NBIA etiology of parkinsonism. Additionally, aceruloplasminemia merits consideration in the diagnostic approach of parkinsonism manifesting in adulthood, especially if a combination with diabetes mellitus, anemia or retinal degeneration is present.

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Table 1 Main characteristics of aceruloplasminemia causing parkinsonism

	Onset age of parkinsonism signs	Distinctive features	Associated clinical signs	Neuroimaging	Biological marker	Treatment response to dopaminergic agents
Aceruloplasminemia (CP/AR)	Adulthood, around 50 years of age	Cerebellar ataxia, dysarthria, dyskinesia, parkinsonism, cognitive decline	*Diabetes mellitus, anemia, retinal degeneration*	T2 hypointensity in globus pallidus, putamen, thalamus, and dentate nucleus, minimal iron accumulation in cerebral and cerebellar cortices	*Undetectable serum ceruloplasmin, low serum copper and iron, high serum ferritin*	Unresponsiveness to Levodopa

AR autosomal recessive

Conflict of interest None.

References

Garcia-Cazorla A, Duarte ST (2014) Parkinsonism and inborn errors of metabolism. J Inherit Metab Dis 37:627–642

Kohno S, Miyajima H, Takahashi Y, Inoue Y (2000) Aceruloplasminemia with a novel mutation associated with parkinsonism. Neurogenetics 2:237–238

McNeill A, Pandolfo M, Kuhn J, Shang H, Miyajima H (2008) The neurological presentation of ceruloplasmin gene mutations. Eur Neurol 60:200–205

Miyajima H, Takahashi Y, Kono S (2003) Aceruloplasminemia, an inherited disorder of iron metabolism. Biometals 16:205–213