Benign SLC39A14 Course of Dystonia-Parkinsonism Secondary to Inherited Manganese Accumulation

Montaser Namnah, MD,[1] Max Bauer, MD,[1] Hagar Mor-Shaked, PhD,[2] Susan B. Bressman, MD,[3] Deborah Raymond, MS,[3] Laurie J. Ozelius, PhD,[4] and David Arkadir, MD, PhD[1],*

Dystonia-parkinsonism, associated with inherited errors in manganese metabolism, is caused by biallelic pathogenic variants in the *SLC30A10*[1] or *SLC39A14*[2] genes. This rare and potentially treatable disease was almost exclusively reported in children[2–4]. Chelation therapy is administered for this condition based on few reports indicating clinical improvement in young patients with a progressive disease.[2] To demonstrate the possible benign course of some patients with this condition and the difficulty in recommending chelation therapy in elderly diagnosed patients with clinically stable disease, we present here a patient with manganese brain accumulation attributed to a *SLC39A14* homozygous mutation diagnosed in late adulthood.

A 65-year-old woman was evaluated in our clinic for long-term dysarthria and general dystonia. The patient is from a consanguineous family of Ashkenazi origin, with no other family members affected. She reported a change in her handwriting at the age of 18 years as her first noticeable symptom and impaired gait and balance, frequent falls, and unintelligible speech gradually developing in the subsequent year. This deterioration was followed by 4 decades of clinical stability and even certain improvement of her speech following the administration of a low dose of lamotrigine.

Neurological examination revealed impaired ocular convergence, deep nasolabial folds, comprehensible dysarthria, and moderate bradykinesia that was more pronounced on the right side of the body, dystonia of her right limbs, and spastic gait with dystonic features. Brain magnetic resonance imaging revealed a prominent T1 hyperintense, diffuse, and nonenhancing signal involving the basal ganglia and subcortical white matter (Fig. 1) compatible with manganese accumulation.

Whole-exome sequencing revealed a homozygous missense variant, g.8:22273712G>A (GRCh37) c.1066G>A (p.G356S), almost exclusively found in Ashkenazi Jews (gnomAD v3 frequency 1:3316, 1/42004 in Africans), situated in a highly evolutionarily conserved position (GERP = 5.9899) in the *SLC39A14* gene. This variant is predicted to damage the translated protein by SIFT, Mutation Taster, and PolyPhen. An increased manganese blood level was also demonstrated (60.4 µg/L, normal range 4.2–16.5 µg/L).

Chelation therapy by either intravenous EDTA or oral para-aminosalicylic acid[5] was recommended to the patient. The patient chose to avoid these therapies because of her long-standing clinical stability. The lack of clear evidence in the medical literature regarding the efficacy of these treatments in elderly patients with stable disease also played a role in her decision. A daily oral iron supplement was commenced instead. A clinical follow-up lasting 2 years and repeated brain magnetic resonance imaging scan performed 2 years after diagnosis did not demonstrate any clinical progression or a change in T1 signal or brain volume.

The natural history of dystonia-parkinsonism secondary to pathogenic variants of *SLC39A14* is unknown. Although the clinical benefit of chelation therapy was anecdotally reported,[2] the long-term need of this therapy was not established. Intravenous EDTA therapy is considered safe but requires repetitive, monthly infusions. Data regarding its safety in chronic conditions are also limited. We show that in some clinically stable cases, withholding chelating therapy is a reasonable course of action. This case report raises the need for further research to establish the natural history of patients with a genetic error in manganese metabolism and the appropriate conditions for administering chelation therapy.

[1]Department of Neurology, Hadassah Medical Center and the Hebrew University, Jerusalem, Israel; [2]Department of Genetics and Metabolic Diseases, Hadassah Medical Center and the Hebrew University, Jerusalem, Israel; [3]Department of Neurology, Mount Sinai Beth Israel, New York, New York, USA; [4]Department of Neurology, Massachusetts General Hospital, Charlestown, Massachusetts, USA

*Correspondence to: Dr. David Arkadir; Hadassah Medical Center, Department of Neurology, POB 12000, Jerusalem 91120, Israel
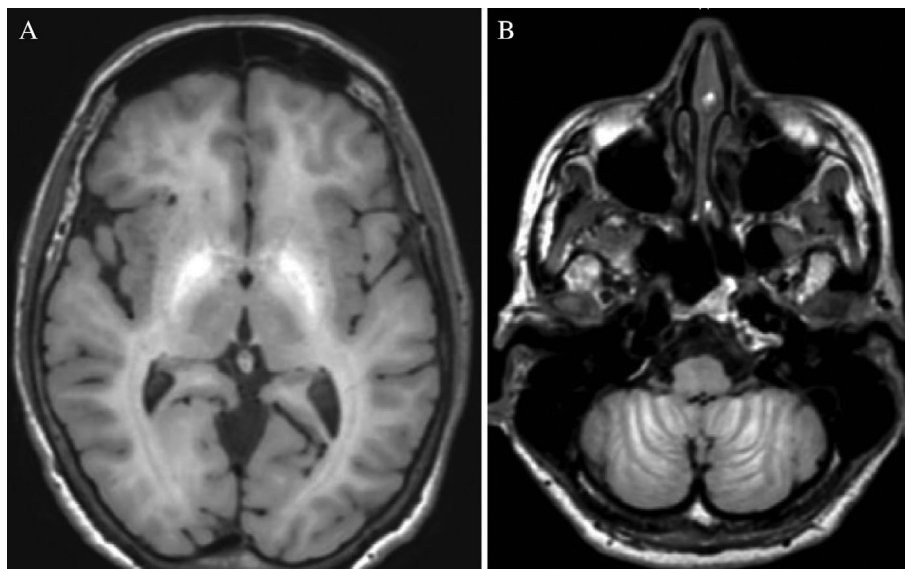E-mail: arkadir@hadassah.org.il

FIG. 1. Brain magnetic resonance imaging demonstrates hyperintense T1 signal of the pallidum (**A**) as well as in the cerebellar folds (**B**). To a lesser degree, hyperintense T1 signals were also observed in the subcortical white matter, anterior midbrain, and vermis. Fluid attenuated inversion recovery and susceptibility weighted images were normal.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

M.N.: 1B, 1C, 2A
M.B.: 1B, 1C, 2A
H.M.S.: 1C, 2A, 2B
S.B.B.: 1C, 2B
D.R.: 1C, 2B
L.J.O.: 1C, 2B
D.A.: 1A, 1C, 2A, 2B

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