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Clinical Observations

Progressive Cerebellar Atrophy and a Novel Homozygous Pathogenic *DNAJC19* Variant as a Cause of Dilated Cardiomyopathy Ataxia Syndrome

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ABSTRACT

BACKGROUND: The dilated cardiomyopathy with ataxia syndrome is a rare autosomal recessive multisystem disorder caused by mutations in *DNAJC19*. We present a new patient with a novel pathogenic variant in *DNAJC19* with novel neuroimaging finding of progressive cerebellar atrophy. **PATIENT DESCRIPTION AND RESULTS:** We describe a new patient with dilated cardiomyopathy with ataxia syndrome presenting with global developmental delay, hypotonia, ataxia, and dilated cardiomyopathy. During follow-up, her cardiac phenotype improved but she exhibited progressive cerebellar atrophy and developed bilateral increased T2 signal intensities in the thalami, parietal lobes, and pons on magnetic resonance imaging. Dilated cardiomyopathy and 3-methylglutaconic aciduria in her urine organic acid analysis also improved. **CONCLUSIONS:** This child with dilated cardiomyopathy with ataxia syndrome developed progressive cerebellar atrophy, a novel feature of this syndrome. In individuals with global developmental delay, hypotonia, ataxia, the dilated cardiomyopathy with ataxia syndrome should be considered even in the differential diagnosis in the absence of cardiomyopathy or 3-methylglutaconic aciduria.

Keywords: ataxia, dilated cardiomyopathy, *DNAJC19* gene, cerebellar atrophy, 3-methylglutaconic acid

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Introduction

The dilated cardiomyopathy with ataxia (DCMA) syndrome was first described by Davey et al.[1] among the Canadian Hutterite population. It is a rare autosomal recessive multisystem disorder. It is caused by mutations in *DNAJC19*, located on chromosome 3q26, encoding DNAJC19 protein. This protein is a component of mitochondrial protein import machinery in the inner mitochondrial membrane. It has been shown that DNAJC19 protein interacts with mitochondrial prohibitins complexes and affect the functional integrity of mitochondria by disturbing phospholipid homeostasis causing mitochondrial cristae alterations.[2]

Since its first description in 2006, there have been 20 patients described in the literature.[1,3] The main clinical features are global developmental delay and failure to thrive. Ataxia has been documented in two third of patients and dilated cardiomyopathy (DCMP) in 80% of the patients. Some patients had cryptorchidism and hypospadias. Elevated liver enzymes and anemia are common. Elevated 3-Methylglutaconic acid in the urine organic acid analysis is suggestive of DCMA syndrome. The diagnosis is confirmed by the identification of a *DNAJC19* mutation. Eighteen patients from the Canadian Hutterite population had a

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homozygous splice site mutation (IVS3-1G>C), and two siblings had a homozygous one base pair deletion (c.300delA p.Ala100fsX11).

We describe a new patient with DCMA syndrome with global developmental delay, hypotonia, ataxia, transient noncompaction DCMP and transient 3-methylglutaconic aciduria. We include a comprehensive literature review of all patients with genetically confirmed DCMA syndrome.

Patient and Results

This 13-year-old girl was born at 35 weeks gestation by spontaneous vaginal delivery to consanguineous parents. Her birth weight was at the tenth percentile. Apgar scores were 9 and 9 at one and five minutes, respectively. She was admitted to the neonatal intensive care unit for nine days because of failure to thrive.

Concerns about developmental delay were first raised at age four months. She developed an unsteady wide-based gait and intention tremor at age three years. Her ataxic gait worsened, causing recurrent falls at age five years. She developed truncal ataxia at the same time. Short episodes of fatigue, dysarthria, and encephalopathy have occurred during intercurrent illnesses since the age of five years.

She underwent cardiac evaluation at age seven months due to a heart murmur. Electrocardiography revealed a short PR interval, T wave inversion, and mildly prolonged QTc (490 ms). Echocardiography showed moderate left ventricular dilatation and mild mitral regurgitation. Repeat echocardiography at age seven years revealed noncompaction left ventricular dilatation, mitral valve prolapse, and mild-to-moderate mitral regurgitation. Her ejection fraction was 40%. Echocardiography at ages ten and 11 years revealed normal left ventricular size and function.

Developmentally, she sat unsupported at age nine months, crawled at age 12 months, and pulled up to stand at age 13 months. She transferred objects between her hands at age seven months and had a pincer grasp at age 14 months. She started babbling at age nine months. She had five words at age 21 months. She started supported walking at age five years. Currently, she can walk with a walker. She speaks in two-word sentences

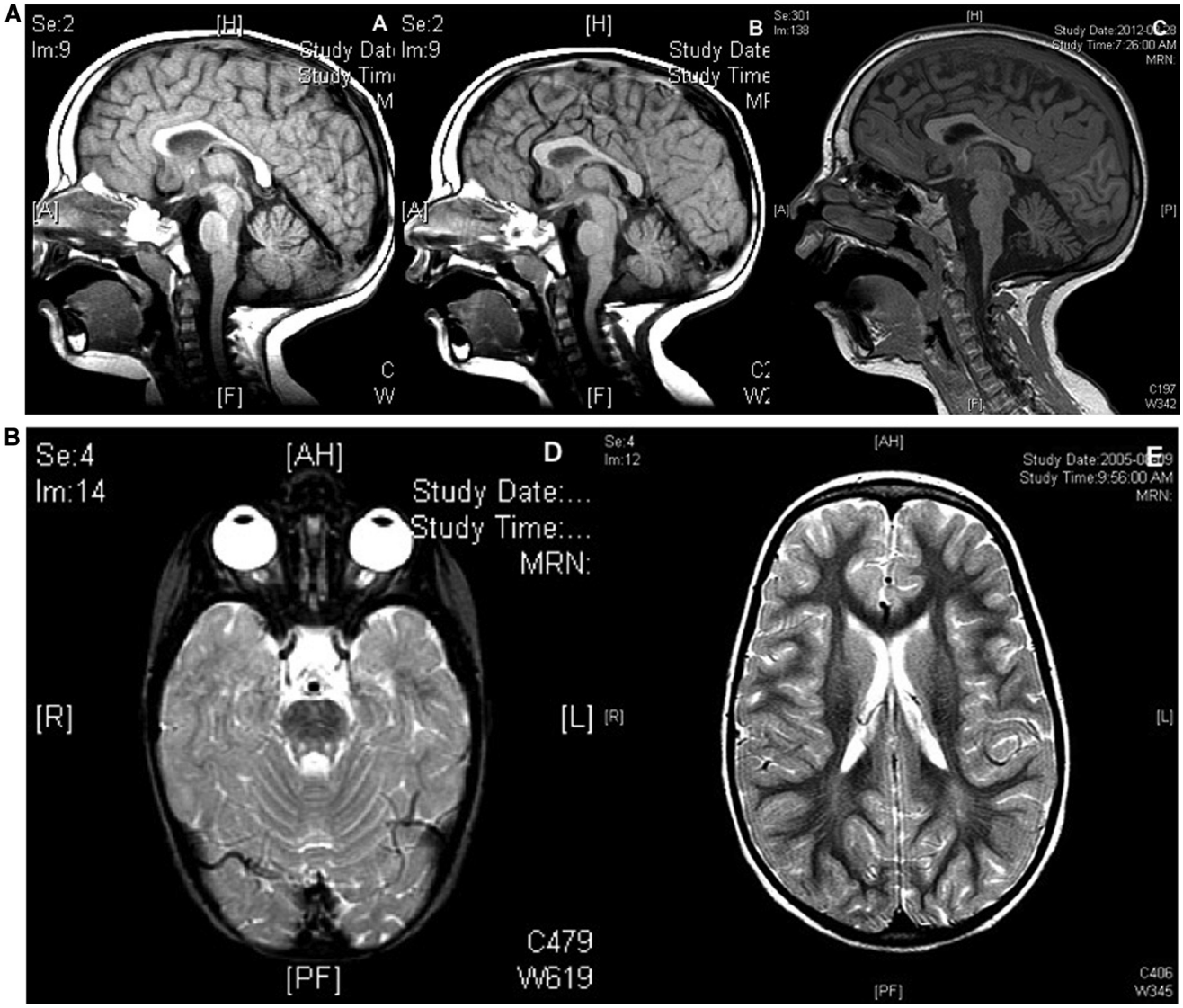

FIGURE.
Progressive cerebellar atrophy on the T1-weighted sagittal images. A: normal cerebellum at age two years; B: mild cerebellar atrophy at age four years; C: severe cerebellar atrophy at age 11 years; D and E: increased signal intensity in the subcortical and deep white matter of the parietal lobes and pons bilaterally on the axial T2-weighted images at age four years.