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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

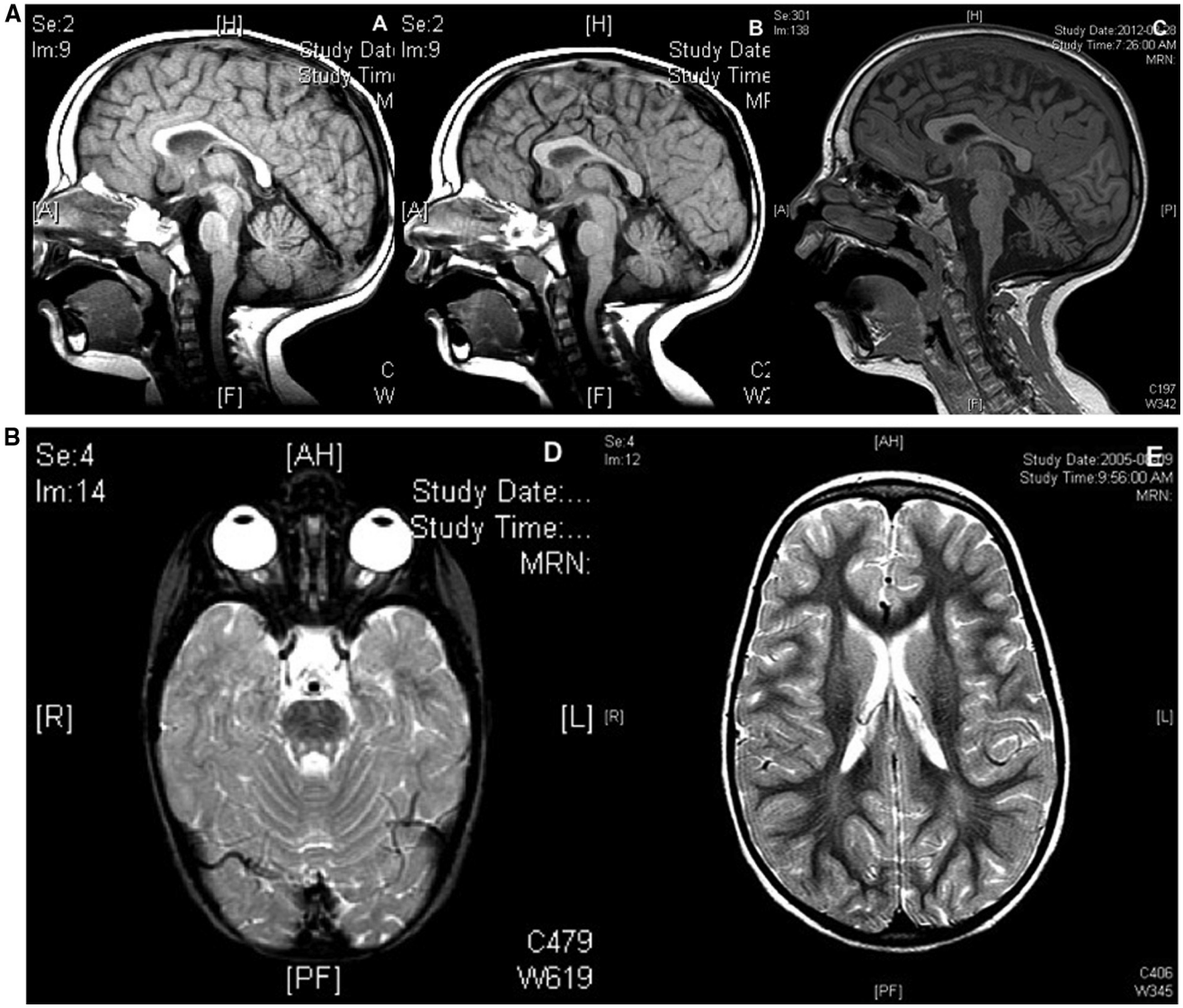

FIGURE.
Progressive cerebellar atrophy on the T1-weighted sagittal images. A: normal cerebellum at age two years; B: mild cerebellar atrophy at age four years; C: severe cerebellar atrophy at age 11 years; D and E: increased signal intensity in the subcortical and deep white matter of the parietal lobes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

TABLE.
Mitochondrial Respiratory Chain Enzyme Activity in Skeletal Muscle and Cultured Skin Fibroblasts

Specimen	Muscle		Fibroblasts	
	n moles/min/mg Mitochondrial Protein		*n* moles/min/mg Mitochondrial Protein	
Results	Patient	Control	Patient	Control
NADH-Q1-reductase (complex I)	40.98	95.1 ± 11.3	NP	NP
NADH-cytochrome c reductase (complex I + III)	42.74	94.6 ± 9.5	24.9 ± 5.7	30.5 ± 2.5
Succinate cytochrome c reductase (complex III + III)	145.82	102 ± 6.9	6.88 ± 0.22	8.10 ± 1.82
Cytochrome oxidase (complex IV)	155.88	119 ± 11.3	5.93 ± 1.05	8.36 ± 1.52
Citrate synthase	540.36		45.9 ± 15.1	38.6 ± 3.6
Pyruvate dehydrogenase	NP	NP	1.53 ± 0.03	1.34 ± 1.09

Abbreviation: NP = Not performed

and uses about 200 words. She requires assistance to carry out activities of daily living.

Her examination revealed head circumference at the forty-eighth percentile and height and weight below the third percentiles. Neurological examination at age 21 months revealed central and peripheral hypotonia with elicitable deep tendon reflexes. At 13 years of age, her neurological examination showed a generalized decrease in muscle bulk, decreased axial tone, increased peripheral tone, symmetrical brisk deep tendon reflexes, ankle clonus, intention tremor, and dysmetria.

Cranial magnetic resonance imaging (MRI) was normal at age two years. Repeat MRI at age four years showed prominence of cerebellar sulci and slightly increased signal intensity within the subcortical and deep white matter of the parietal lobes and pons bilaterally. At age ten years, cranial MRI showed diffuse cerebellar atrophy with no additional white matter changes (Figure). Magnetic resonance spectroscopy was normal.

Her investigations revealed moderately elevated lactate (5.1-6.4 mmol/L, reference range, 0-2.4 mmol/L), mildly elevated alanine aminotransferase (111 U/L; reference range, 0-40 U/L), and aspartate aminotransferase levels (108 U/L; reference range, 0-45 U/L). Initial urine organic acid analysis revealed moderately increased 3-methylglutaconic acid and 2-ketoglutarate and marginally elevated 3-methylglutaric acid. This result was no longer seen in subsequent urine organic acid analysis at age 5 years. Muscle and cultured skin fibroblast respiratory chain enzyme activity measurements revealed low complex I and I + III activities suggestive of mitochondrial dysfunction (Table). Muscle histopathology, histochemistry, and electron microscopy investigations were normal.

More than 20 single gene tests, targeted next-generation sequencing gene panels for mitochondrial disorders and ataxia, and microarray were normal. Comprehensive next-generation sequencing-based cellular energetics panel including 650 genes revealed a homozygous five base pair splice site deletion in the *DNAJC19* (c.280+1_280+5delGTAAG). This variant is predicted to disrupt the splice donor site at this location and reported as a likely pathogenic variant. Both parents were heterozygous for the same pathogenic variant.

Literature review

The PubMed database was searched using *DNAJC19* gene and DCMA syndrome key words. In addition, references of all published articles regarding DCMA syndrome were reviewed for case reports. Four reports with 20 patients have been identified.[1-4] Sixty percent of the patients died between age four months and age eight years, who had DCMA. Fifty-five percent of the patients had ataxia. DCMP has been reported in 70% of the patients. The onset of DCMP was between one and 12 months of age. The homozygous pathogenic splice site variant (IVS3-1G>C) was reported in 90% of the patients.

Discussion

We describe a new patient with DCMA syndrome who presented in the early infantile period with global developmental delay, hypotonia, ataxia, and DCMP. Despite severe and early-onset clinical features and multiorgan involvement suggestive of mitochondrial encephalopathy, her genetic diagnosis was only confirmed at age 12 years by next-generation energetic panel genetic testing. She exhibited progressive cerebellar atrophy and bilateral increased T2 signal intensities in the thalami, parietal lobes, and pons. Our patient is the first patient with DCMA syndrome to develop progressive cerebellar atrophy and white matter changes on cranial MRI. Progressive gait and truncal ataxia can be explained by progressive cerebellar atrophy in our patient. DCMA syndrome should be included in the differential diagnosis of progressive cerebellar atrophy and ataxia with or without DCMP.

DCMP is one of the cardinal features of the DCMA syndrome described as severe and early onset.[1-4] It is accompanied by prolonged QT syndrome in approximately a third of the patients.[4] It can present either as pure DCMP or accompanied with noncompaction. According to reports in the literature, 15% of the patients with DCMA syndrome greater than 15 years of age do not have DCMP, but all have either prolonged QT or nonspecific ST/T wave changes on electrocardiogram.[3,4] In three patients, DCMP resolved or improved during follow-up. In our patient, a noncompaction DCMP and prolonged QT were detected at age seven months, which has resolved after ten years of age. Our report and previous reports suggest that in older patients with global developmental delay, hypotonia, ataxia, the DCMA syndrome should be considered in the absence of DCMP.

Most patients with DCMA syndrome reported in the literature had a five to ten times elevated 3-methylglutaconic and 3-methylglutaric acids in urine organic acid analysis.[1] In two affected siblings, one with more severe clinical presentation had elevation of 3-methylglutaconic and 3-methylglutaric acids, whereas the other sibling with milder phenotype had normal urine organic acid analysis.[3] In our patient, we also found elevated 3-methylglutaconic acid in urine organic acid analysis until five years of age. However, repeated urine organic analyses after this age were all normal. The absence of 3-methylglutaconic and/or 3-methylglutaric acids in urine organic acid analysis is not exclusive of DCMA syndrome.

Reduced respiratory chain enzyme activities in complexes I, II, and IV in muscle biopsy specimen were previously reported in one individual with DCMA syndrome.[3] We also found reduced respiratory chain enzyme activity in all complexes in our patient, supporting mitochondrial respiratory chain dysfunction. Interestingly, all patients reported so far with DCMA syndrome had pathogenic splice site or nonsense variants.

In conclusion, we describe a new patient with DCMA syndrome who developed progressive cerebellar atrophy on cranial MRI. The DCMP and excretion of 3-methylglutaconic acid in urine organic acid analysis improved with age despite neurological progression. Therefore the absence of all features does not exclude DCMA syndrome, and this condition should be considered in individuals with global developmental delay, ataxia, and progressive cerebellar atrophy.

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Author contributions: Dr. Al Teneiji drafted the manuscript, reviewed the literature, and approved final version of the manuscript. Dr. Siriwardena diagnosed the patient, drafted clinical information details, and approved the final version of the manuscript. Mrs. George and Dr. Mital drafted the cardiac part of the manuscript and approved final version of the manuscript. Dr. Mercimek-Mahmutoglu is a senior clinician and provided supervision and mentorship for Dr. Al Teneiji in data analysis and completing the manuscript.

Ethical approval: The parents consented for case report.

References

1. Davey KM, Parboosingh JS, McLeod DR, et al. Mutation of DNAJC19, a human homologue of yeast inner mitochondrial membrane co-chaperones, causes DCMA syndrome, a novel autosomal recessive Barth syndrome-like condition. *J Med Genet*. 2006;43:385-393.
2. Richter-Dennerlein R, Korwitz A, Haag M, et al. DNAJC19, a mitochondrial cochaperone associated with cardiomyopathy, forms a complex with prohibitions to regulate cardiolipin remodeling. *Cell Metab*. 2014;20:158-171.
3. Ojala T, Polinati P, Manninen T, et al. New mutation of mitochondrial DNAJC19 causing dilated and noncompaction cardiomyopathy, anemia, ataxia, and male genital anomalies. *Pediatr Res*. 2012;72:432-437.
4. Sparkes R, Patton D, Bernier F. Cardiac features of a novel autosomal recessive dilated cardiomyopathic syndrome due to defective importation of mitochondrial protein. *Cardiol Young*. 2007;17:215-217.