Clinical Observations

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

Amal Al Teneiji MD, Komudi Siriwardena MD, Kristen George NP, Seema Mital MD, Saadet Mercimek-Mahmutoglu MD, PhD

Division of Clinical and Metabolic Genetics, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Canada

Department of Medical Genetics, University of Alberta, Edmonton, Canada

Division of Cardiology, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Canada

Genetics and Genome Biology Research Program, Research Institute, The Hospital for Sick Children, Toronto, Canada

**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

**Pediatr Neurol 2016; 62: 58-61**

Crown Copyright © 2016 Published by Elsevier Inc. All rights reserved.

**Introduction**

The dilated cardiomyopathy with ataxia (DCMA) syndrome was first described by Davey et al. 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.

Since its first description in 2006, there have been 20 patients described in the literature. 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
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 non-compaction 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.
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. In our patient, we also found elevated 3-methylglutaconic acid in 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 to DCMA syndrome.

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. 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.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Muscle n moles/min/mg Mitochondrial Protein</th>
<th>Fibroblasts n moles/min/mg Mitochondrial Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient</td>
<td>Control</td>
</tr>
<tr>
<td>NADH-Q1-reductase (complex I)</td>
<td>40.98</td>
<td>95.1 ± 11.3</td>
</tr>
<tr>
<td>NADH-cytochrome c reductase (complex I + III)</td>
<td>42.74</td>
<td>94.5 ± 9.5</td>
</tr>
<tr>
<td>Succinate cytochrome c reductase (complex III + III)</td>
<td>145.82</td>
<td>102 ± 6.9</td>
</tr>
<tr>
<td>Cytochrome oxidase (complex IV)</td>
<td>155.88</td>
<td>119 ± 11.3</td>
</tr>
<tr>
<td>Citrate synthase</td>
<td>540.36</td>
<td></td>
</tr>
<tr>
<td>Pyruvate dehydrogenase</td>
<td>NP</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NP = Not performed.
Reduced respiratory chain enzyme activities in complexes I, II, and IV in muscle biopsy specimen were previously reported in one individual with DCMA syndrome. 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.

The authors thank the parents for allowing to present their child’s results. They thank Mrs. Cordeiro for her excellent clinical support.

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