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An ultra-rare cause of severe hypotonia mimicking Pompe disease in an infant: *RRM2B* related mitochondrial DNA depletion syndrome with a novel mutation

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Abstract

Ribonucleotide-diphosphate reductase subunit M2B(RRM2B)-related mitochondrial disease is one of the ultra-rare mitochondrial depletion syndromes. A-2-months of age girl who had severe hypotonia with absent reflexes, failure to thrive, and developmental delay was hospitalized under our care. The initial diagnosis was Pompe disease with absent reflexes and increased creatine kinase level. Enzyme analysis for Pompe disease was normal and next-generation sequence panel analysis of 450 genes related to metabolic disorders revealed a novel mutation in the *RRM2B gene*. The patient died at the age of 2.5 months. Up to date, there have been reports of 31 patients with infantile forms of RRM2B. This patient presented with little features to suggest a mitochondrial disorder. In conclusion, *RRM2B* mutations should be included in the differential diagnosis of the Pompe disease in infants with severe hypotonia. This case report also expands the mutation spectrum of rare infantile form of the *RRM2B* mutations.

Keywords: Pompe disease; mimicking; hypotonia; elevated creatine kinase; RRM2B mutations; absent reflexes; lactic acidosis

INTRODUCTION

Ribonucleotide-diphosphate reductase subunit M2 B (RRM2B) related mitochondrial disease is a very rare cause of mitochondrial DNA depletion syndrome characterized by a reduction of mitochondrial DNA (mtDNA) content.[1]

The disease can be transmitted both in an autosomal recessive or dominant manner. The autosomal recessive form is mostly seen in the early infantile period manifesting as severe multisystem involvement. Lactic acidosis, failure to thrive, hearing loss, peripheral neuropathy, psychomotor delay, and epilepsy are the common signs of the disease and mortality is high due to multiorgan involvement during infancy. Progression of the disease is rapid leading to death in the first years of life.[2,3]

We report here a girl with a novel RRM2B gene mutation presenting with severe hypotonia and absent reflexes. She was initially thought to have Pompe disease.

CASE REPORT

A two-month-old girl was hospitalized due to severe hypotonia. There were no gastrointestinal complaints including diarrhea, constipation or vomiting except feeding difficulties. The birth history was normal. The parents did not notice any tachypnea, or respiratory insufficiency although she had feeding difficulties and severe hypotonia, and there was no hospitalisation for respiratory infection up to the time of admission to our hospital. The antenatal history did not reveal any abnormalities including decreased fetal movement.

The weight was 10 percentile, the height was 25 percentile and the head circumference was 25 percentile according to her age. Physical examination revealed severe hypotonia with absent deep tendon reflexes without fasiculations. Deafness was revealed with 2 repetitive auditory tests. There was no history of neurological disorders in her family but there was consanguinity

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between parents (first degree cousin marriages). Laboratory evaluations showed mild elevations in alanine aminotransferase 56 U/L (N:0-45U/L), moderate elevations in aspartate aminotransferase 126U/L (N:0-45U/L), and creatine kinase (CK) 624U/L (N:0-145U/L). Electrocardiography revealed no hypertrophy. For severe hypotonia with absent reflexes and increased CK levels, Pompe enzyme analysis was performed. The result showed normal activity which did not support the diagnosis of Pompe disease. Electroencephalography and magnetic resonance imaging of the cranium showed no abnormality. Electromyography (EMG) revealed positive sharp wave denervation potentials in the right biceps brachii and right tibialis anterior. Although myopathic changes in both upper and lower extremities were prominent, nerve conduction studies showed no abnormality. Semiconductor next-generation DNA sequencing (NGS) of a custom panel of 450 metabolic disease-related genes revealed a homozygote change in *the RRM2B* gene. During the clinical course of the hospitalization, the patient deteriorated with lactic acidosis (pH:7.21, lactate:5.4 mM (N<2 mmol/L), followed by bradycardia with hypertension, suggestive of increased intracranial pressure. The patient died due to brain edema. The urine organic acid analysis taken at the time of decompensation showed increased lactic acid, pyruvic acid, fumaric acid, sebacic acid excretions. The urinary amino acid assay showed generalized aminoaciduria suggestive of tubulopathy with 70% tubular phosphate reabsorption.

Genetic analysis

DNA was extracted from peripheral leukocytes of the patient by IprepTM PureLink® gDNA Blood Kit (Invitrogen, Carlsbad, CA) according to the manufacturer's protocol. Semiconductor NGS of a custom panel of 450 metabolic disease-related genes was performed.[4] The data was analyzed and interpreted by the Ingenuity Variant Analysis (IGV)[5] (Figure 1 shows the IGV imaging of the patient). The results revealed the novel change c.425T>C; p.Ile 142Thr in exon 4 in a very highly conserved region of *RRM2B* gene (Figure 2 shows the conserved domain of the gene) which was interpreted as "likely pathogenic" according to The American College of Medical Genetics and Genomics (Polyphen score:1.00).[6]

DISCUSSION

Autosomal recessive *RRM2B* mutations are one of the most severe and rare forms of the mitochondrial encephalomyopathies associated with the disruption of mt DNA maintenance. Affected children carrying autosomal recessive *RRM2B* mutations present at an earlier age with muscle, liver, brain, or kidney involvement. Thirty-one patients carrying *RRM2B* mutations in 22 reports were described up to now. Patients were hospitalized mostly due to respiratory insufficiency resulting from muscle weakness. Severe muscle weakness with areflexia is a typical feature of either motor neuronopathy or polyneuropathy.[7] In the Pompe disease, infants usually present with severe hypotonia with areflexia, macroglossia, and failure to thrive and EMG findings reveal positive sharp wave denervation potentials.[8] In our patient, we could not find supportive evidence of peripheral neuropathy in EMG, but there was areflexia.

Peripheral neuropathy is a common finding in mitochondrial disorders especially in mitochondrial neurogastrointestinal encephalopathy, polymerase gamma mutations, and adult forms of *RRM2B* mutations. In the literature, only 2/31 cases

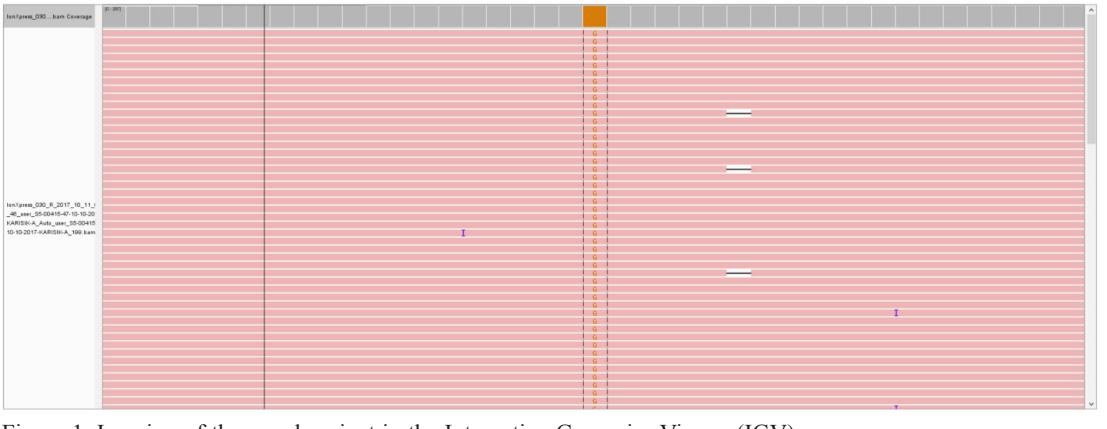

Figure 1. Imaging of the novel variant in the Integrative Genomics Viewer (IGV)

Figure 2. Conservation of RRM2B gene p.Ile 142Thr in exon 4 variant along with flanking amino acids in orthologs domain among species

with peripheral neuropathy and 9/31 cases with areflexia were observed.[9] In our patient, we could not find evidence to support the presence of peripheral neuropathy in EMG, although there was areflexia. Deafness which was present in our patient was found to be related to cochlear pathologies in two other patients by Iwanicka-Pronickaa *et al*.[9]

Up to now 17 patients reported in the literature had Fanconi-Type proximal tubulopathy. In this patient, urine amino acid excretion and tubular phosphate reabsorption were high indicating proximal tubulopathy that began prominently in the later stages of the disease. Keshavan suggested that earlier presentation of the proximal tubulopathy might be associated with the severe infantile form of the disease.[10] In our patient, tubulopathy became prominent very late and rapidly progressed before death.

It has been said that the severity of the disease phenotype was associated with the mt DNA content of the affected tissues. There is no exact genotype-phenotype correlation but it was clear that the autosomal recessive form of the disease has poor clinical outcomes among all RRMB2 patients due to low residual enzyme activity. In our patient, the novel mutation led to a very early and severe multisystem involvement and death.

NGS technology has facilitated the investigation of many genes responsible for the same phenotype and even the whole genome. In this patient, a custom panel of 450 genes responsible for inborn errors including the ones for the mitochondrial disease was used as an initial diagnostic approach. This facilitated the investigation of a group of genes leading to mt DNA depletion in a very short time without a need for muscle biopsy. This method might be an alternative to the determination of the DNA copy number as an initial test.

This is the youngest patient described presenting very early during infancy, with rapid progression in a *RRM2B*-related mitochondrial depletion syndrome. In the presence of severe hypotonia with increased CK and depressed tendon reflexes, *RRM2B* mutations should be thought of in the differential diagnosis of Pompe disease.

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DISCLOSURE

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