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Poster Abstract: Diagnostic

Broad Spectrum of c.2015 G>A Mutation in the GAA Gene Manifesting as a Mild Infantile Variant of Pompe Disease in Jordanian Patients

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BACKGROUND

A wide spectrum of Pompe disease exists ranging from the infantile form to a milder juvenile or adult form. The clinical heterogeneity primarily relates to the occurrence of different mutations that lead to a different rate of lysosomal glycogen accumulation and non-genetic factors that are thought to modulate the disease phenotypes. To date, almost 300 distinct GAA mutations have been identified.

MATERIALS AND METHODS

We describe two unrelated families from Jordan presenting with the infantile variant form of Pompe disease sharing the same homozygous mutation c.2015 G>A in exon 14. This mutation has been previously described in juvenile onset cases, although in vitro functional studies have found virtually no residual enzyme activity.

RESULTS

The first family consists of two female siblings (5.5 years and 3.5 years of age) born to first-degree cousins of Muslim descent. The elder girl presented between 3 and 6 months of age with marked hypotonia, hypertrophic cardiomyopathy, proximal muscle weakness, motor delay, and no DTRs. Genetic analysis revealed the c.2015 G>A (p.Arg672Gln) mutation, with cross-reactive immunological material (CRIM)-positive status. She was started on enzyme replacement therapy (ERT) at 24 months of age. She walked independently at 27 months. Neutralizing antibody assay was negative. Currently, she has nasal speech, muscle weakness, and mild cardiomyopathy. Hearing examination is normal (25 dB). Her younger sister, presented at 3 months of age with hypotonia, motor delay, and hepatomegaly. Genetic analysis revealed the same mutation. She started ERT at 6 months and her neurological examination is currently normal.

In the second family, a 5-year-old boy presented with hypertrophic cardiomyopathy, hypotonia, and an enlarged tongue. His parents are first-degree cousins. One sibling died before the age of 1 month due to heart failure; the mother had a history of three abortions. The same mutation was found with a CRIM-positive status. The boy started ERT at 14 months of age, and follow-up echocardiography revealed improved ventricular and septal thickness. He started to walk independently at 18 months of age. Neutralizing antibody assay was negative. He currently has nasal speech, an articulation disorder, and otherwise no muscle weakness. Cardiac examination is normal. Hearing examination is mildly decreased at 30 dB.

CONCLUSIONS

Our cases confirm the phenotypic variability among patients, even among those carrying the same genotype. Two patients, for whom ERT was commenced later, suffer from nasal speech and a severe articulation disorder in spite of improved cardiac and motor function.

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