

The Changing Face of Infantile Pompe Disease: A Report of Five Patients from the UAE

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Abstract *Objective:* We aim to present our experience with infantile Pompe disease with focus on the impact of availability of treatment on awareness, diagnosis, and management of such patients.

Method: Case – review study of patients diagnosed with infantile Pompe disease and literature search.

Results: We identified five cases of infantile Pompe disease. The first was diagnosed by muscle biopsy; all others were diagnosed by enzyme assay on peripheral blood lymphocytes or dried blood spot. There was no determination of the CRIM status on these patients. Two have died at a much later age than the reported median age of death for untreated cases. One died very early at 2 months of age with severe cardiomyopathy and had received only one dose of enzyme replacement therapy (ERT). The remaining two surviving patients are siblings: the younger was diagnosed by prenatal ultrasound screening and started on ERT at 24 h of age; she is the youngest treated patient in our case series.

Conclusion: The natural history of infantile Pompe disease is changing, so are the challenges of managing these infants in the post- ERT era. Currently, increased awareness and early access to therapy provide the best outcomes and incur the least shift of burden from mortality to morbidity.

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Introduction

Pompe disease (Glycogen Storage Disease II; OMIM# 232300) is an autosomal recessive lysosomal storage disorder caused by deficiency of acid α -glucosidase. The cardinal features of severe cardiomyopathy and muscle weakness represent the phenotype of infantile Pompe disease, with prediction of death at a median age of 7.7 and 6 months in Dutch and non-Dutch patients, respectively (Van den Hout et al. 2003). Kishnani et al. reported on the impact of rhGAA on prolonging the survival of infants with Pompe disease (Kishnani et al. 2009), while Kanter et al. have demonstrated the substantial burden of disease both on the individual and the society in adults with Pompe disease (Kanter et al. 2011). There are emerging challenges with the prolonged survival of patients with infantile Pompe disease, with a potential shift of burden of illness from high mortality to high morbidity, given the current limitations in response to enzyme replacement therapy (ERT), particularly when started late. On the other hand, the clear efficacy of early treatment has shifted the focus of diagnostic window to the presymptomatic period, i.e., neonatal screening. According to the results of the Taiwan screening program, e.g., the newborn screening allowed initiation of treatment at an age of less than 1 month compared with the age of 3 to 6 months in infants in the control group (Chien et al. 2008).

We aim to review our case series of infantile Pompe disease in context of the evolving new natural history of this fascinating and challenging disease.

Methods

A case review study of all cases of infantile Pompe disease diagnosed and treated with enzyme replacement therapy

(ERT) with alglucosidase alfa, recombinant human GAA (rhGAA, Myozyme), at the dose of 20 mg/kg every 2 weeks between 2006 and 2011. Charts of all patients were reviewed and the following information collected: clinical presentation, diagnostic confirmation method, clinical course, complications, and outcomes.

Case Reports

Case 1: This UAE male infant of consanguineous marriage referred to our pediatric neurology service at 4 months of age for delayed development. He was found to have hypotonia, weakness, and hypertrophic cardiomyopathy. Diagnosis was confirmed by muscle biopsy. Weakness had progressed to $-1/5$ before ERT was started. Viral-induced respiratory failure occurred after his first infusion at 8 months of age; he became ventilator dependent. Despite significant cardiac response to ERT, muscle strength improvement was minimal. He continued on a biweekly ERT infusion and remained cognizant of his parents until he died at 5 years of age.

Case 2: This Bangladeshi male infant was referred to our pediatric neurology service at 9 months of age for motor delay. We found him to have hypotonia, hypertrophic cardiomyopathy, and motor delay. Infantile Pompe disease was confirmed by peripheral blood lymphocyte enzyme assay. ERT started at 11 months of age. He required no respiratory support. He had significant reduction in cardiac hypertrophy, improvement in muscle power, and acquisition of new motor skill. He had feeding problems that required G-tube placement. He continued on biweekly ERT and had occasional acute respiratory illness requiring hospitalization. He never required invasive ventilator support. His parents were excited at 18 months of age because he outlived his previous sibling who died of weakness of unknown cause (probably a missed case of infantile Pompe disease). He unexpectedly died in sleep at 2 years of age.

Case 3: This Palestinian female infant of consanguineous marriage presented at 2 months of age with massive hypertrophic cardiomyopathy and severe cardiac failure. She also had profound hypotonia and mild hepatomegaly. Pediatric neurology consult was requested to rule out Infantile Pompe disease. Diagnosis was confirmed by dried blood spot enzyme assay (α -glucosidase at pH 3.8 was 0.23 nmol/spot*21 h, reference range 1.5–10 nmol/spot*21 h). She received one dose of ERT, but died from cardiac failure before receiving her second dose.

Case 4: This UAE male of consanguineous marriage was referred by a pediatric cardiologist for neurological assessment of possible infantile Pompe disease at 4 months of age after diagnosing for hypertrophic cardiomyopathy.

He had significant hypotonia, mild hepatomegaly, and CPK elevation. ERT was started after confirming his diagnoses by dried blood test enzyme assay. He was evaluated in another center abroad on parental choice, and genetic testing confirmed his homozygous mutation as well as carrier state of both his parents (exact mutation not available in our records). His cardiomyopathy improved and his left ventricular mass index normalized with ERT, but he continued to have some gross motor delay, and he suffered most significantly from dysphagia; requiring G-J tube placement. He had repeated respiratory infections requiring frequent admissions to the intensive care unit for mechanical ventilation; eventually he required nocturnal BiPAP. He continues on biweekly ERT.

Case 5: This UAE female is the sibling of case 4. Her diagnosis was suspected by prenatal obstetrical ultrasound demonstrating cardiac hypertrophy. She was started on ERT at 24 h of age based on clinical suspicion (hypertrophic cardiomyopathy) and family history (an affected sibling and confirmed carrier status in both parents). Dried blood spot testing confirmed her diagnosis within 3 days of sending her specimen (α -glucosidase at pH 3.8 was 0.90 nmol/spot*21 h, reference range 1.5–10 nmol/spot*21 h). Genetic testing in a lab abroad later confirmed homozygous mutation (exact mutation not available in our records). Hypertrophic cardiomyopathy resolved completely by 3 months of age. At 21 months of age she is bearing weight and taking steps with support, but having mild pooling of saliva. Speech however is not well developed. She continues on biweekly ERT.

Discussion

Our case series demonstrates several important points in the evolving picture of infantile Pompe disease. First, given the rates of consanguinity in the UAE, reported in one study to be as high as 40% to 54.2% in two sampled cities in the UAE (Al-Gazali et al. 1997), one would expect that cases are underdiagnosed; increased awareness becomes critical in early recognition and referral of such cases. This is indeed the case in our patient series, where the trends of referral have changed from more vague complaints of delayed development, as in cases 1 and 2, to a more focused referral to exclude infantile Pompe disease per se as in cases 3 and 4. This in our review represents increased awareness of what is now a treatable orphan disease.

Second, all of our patients, except case 3 which was in severe decompensated cardiac failure and did not survive beyond her first dose of ERT, had hypertrophic cardiomyopathy that responded to ERT including complete resolution in cases 4 and 5. However, the skeletal muscle response to ERT was less robust except for case 5 which

was started on ERT for the sole indication of mild hypertrophic cardiomyopathy prior to development of weakness and hypotonia. These observations may in part explain the contribution of ERT to a shift of disease burden from mortality to morbidity; infants who would have died of progressive cardiac involvement are now living longer only to manifest a more protracted course of muscle weakness and risk of respiratory complications, i.e., unless started on ERT before development of clinically noticeable motor weakness. The attenuated skeletal muscle response to ERT has been attributed to many factors such as the degree of pre-ERT muscle damage, humoral immunity, and paucity of mannose 6 phosphate receptors (M-6-P), the latter was the focus of Koeberl et al.'s recent publication in which they demonstrated the positive role of increasing M-6-P expression in mice, using the β 2-agonist therapy with clenbuterol, on enhancing the efficacy of ERT in Pompe disease (Koeberl et al. 2011). Until such strategies are clinically proven, the best chance for these patients remains in initiating ERT before onset of weakness. The third observation is the early recognition of infantile Pompe cases through targeted prenatal ultrasound in high-risk families, defined as parents with previously affected children or a known carrier state such as the situation in case 5. This approach was previously reported in another city in the UAE, and resulted in early successful therapy with ERT (Hamdan et al. 2008), and later expanded to a full fetal echocardiography screening program as demonstrated by the same group (Hamdan et al. 2010). The advantages of prenatal ultrasonography approach is that it picks up affected patients in whom the indication for ERT is unequivocal; it bypasses the dilemma of what to do with neonates with biochemical diagnosis of Pompe with no symptoms. The other advantage is that the practice of prenatal ultrasonography is already in place, it only requires increased awareness for early postnatal evaluation of newborns in which hypertrophic cardiomyopathy has been identified.

The fourth observation in our patient cohort is the high prevalence (80%) of feeding problems compared to a reported 44–55% in non-Dutch and Dutch groups (Van den Hout et al. 2003). Cases 1, 2, and 4 all had swallow studies confirming significant dysphagia and aspiration risk requiring placement of gastrostomy tubes in all three patients. Despite that, they continued to have difficulty handling their secretions. Feeding problems are a significant morbidity in infantile Pompe, and early intervention is essential in these cases. Case 5 demonstrates that this symptom too is potentially preventable with early ERT.

The fifth alarming observation is represented in the sudden unexpected death of case 2. Unfortunately, autopsies are not routinely performed in UAE, and hence we were not able to confirm the cause of death in this infant who was

responding very well to ERT having normalized cardiac function and acquiring new motor skills. Interestingly, Dr. Pompe's first report of the disease was that of a 7-month-old girl with sudden death from "idiopathic myocardial hypertrophy" (Pompe 1932). Metzl et al reported a case of sudden death in an infant with severe hypertrophic cardiomyopathy due to Pompe disease (Metzl et al. 1999); the mechanism attributed to the effect of glycogen on the conduction system of the heart. Whether ERT contributes to the risk of conduction system abnormalities during the phase in which the glycogen overload is mobilized by the effect of ERT is a theoretical but important question. The involvement of the cardiac conduction system may be supported by the association of the general anesthesia with increased risk of cardiac arrhythmias in infantile Pompe disease (Wang et al. 2007). Our case died unexpectedly at home, raising concerns of other contributing factors to mortality in infantile Pompe disease despite successful ERT.

Finally, our 2 sibships (cases 4 and 5) demonstrate the clear impact of early ERT, especially with the known fact of phenotype concordance among infantile Pompe sibships (Smith et al. 2007). They also demonstrate the effectiveness of targeted neonatal screening as outlined earlier, and show how the face of infantile Pompe disease is changing even within an individual family.

Conclusion

The diagnosis of infantile Pompe disease is no longer just a matter of academic curiosity and family counseling. It has become an important commitment of the medical community caring for children with orphan diseases. Increasing awareness of the manifestations of the disease and targeted screening in high-risk families are readily available approaches that unequivocally contribute to better outcomes. The concern over shift of burden of disease from mortality to morbidity is legitimate, but should only lead to further improving our skills and wisely directing our resources to provide our patients with early access to effective therapies, while curative treatments continue to be sought.

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