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Child Neurology: Pompe disease

New horizons

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Case part 1. A 10-month-old full-term baby girl was transferred to our tertiary care hospital for respiratory distress and hypoxemia. Developmental history revealed significant motor delay. On physical examination, she was noted to be hypotonic, to be dysmorphic with macroglossia, and to have hepatomegaly.

DIFFERENTIAL DIAGNOSES The table lists the differential for infants presenting with the above clinical features. In this patient, the history of mild motor delay along with the findings of hypotonia and hepatomegaly should point to possible underlying congenital or metabolic disease.

Case part 2. Chest x-ray revealed cardiomegaly and EKG showed shortened PR interval with biventricular hypertrophy. Initial laboratory tests revealed normal blood count and cultures, normal electrolytes, elevated liver transaminases, and elevated creatine kinase. Echocardiogram revealed dilated and hypertrophic ventricular walls with an ejection fraction of 40%.

The presence of dysmorphism, hypotonia, and hepatomegaly in an infant suggests possible storage disorder. The elevated creatine kinase and transaminases suggest possible muscular involvement. These findings, along with cardiomegaly on chest x-ray and shortened PR interval on EKG, should raise suspicion for a metabolic myopathy, with Pompe disease being the most common disease in this age group (figure).

CLINICAL FEATURES Pompe disease (acid maltase deficiency, glycogen storage disorder type II) is an autosomal recessive condition caused by deficiency of the lysosomal acid α-glucosidase (GAA). Accumulation of glycogen in the lysosomes accounts for Pompe disease being classified as both a glycogen storage disorder and a lysosomal storage disorder.

J.C. Pompe, a Dutch pathologist, first described in 1932 what is now known as the classic infantile form of Pompe disease.[1] This form presents in infancy with cardiac symptoms, hypotonia, hepatomegaly, macroglossia, and failure to thrive. The natural history is characterized by its uniformly rapid progressive nature and death in the first year of life due to cardiorespiratory failure.[2] Other forms of this disease include the following:

1. Variant infantile form, which presents in the first year of life but has slower progression and less severe cardiac involvement.
2. Late-onset form (figure), which includes childhood, juvenile, and adult forms, all of which have a variable natural course. They are usually slowly progressive. Apart from the limb-girdle distribution and diaphragmatic muscle weakness, these have been recognized to have multisystemic involvement as well.

PATHOPHYSIOLOGY Deficiency of the lysosomal enzyme GAA leads to accumulation of glycogen in the lysosomes and subsequently in the cytoplasm of tissues, most notably in the skeletal and cardiac muscles. Glycogen accumulation has also been detected in the CNS including the cortical neurons, cerebellum, brainstem, and anterior horn cells in the spinal cord. Characteristic histopathologic findings include vacuolated muscle fibers that stain positive with periodic acid–Schiff staining. The role of autophagy in Pompe disease is currently an area of active research interest and may explain the accumulation of toxin aggregated in the myofibers.[3]

A possible genotype–phenotype correlation in Pompe disease has also been proposed, with the classic infantile form having 2 pathogenic alleles, one in each gene for the enzyme.[4] This leads to near-total to total absence of the enzyme and hence severe clinical manifestations. Similar correlation has not been well-documented in the late-onset phenotype, since minor genotypic abnormalities have been seen in patients with severe clinical presentations, suggesting a potential role for environmental modifying factors.[4]

Case part 3. Given the clinical suspicion for Pompe disease, enzyme analysis on dried blood sample confirmed decreased activity of GAA. Subsequent skin biopsy confirmed the diagnosis and the mutation analysis revealed homozygous mutation in the *GAA* gene compatible with Pompe disease.

LABORATORY DIAGNOSIS Initial workup of suspected patients should include chest x-ray (cardiomegaly

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Table Clinical manifestations and differential diagnoses of Pompe disease

Initial manifestations in Pompe disease	Differential diagnoses
Classic infantile Pompe disease	
Hypotonia	Spinal muscular atrophy type 1
	Congenital muscular dystrophy
	Glycogen storage disorders
	Mitochondrial disorders
	Peroxisomal disorders
	Hypothyroidism
Cardiac symptoms with cardiomegaly	Idiopathic hypertrophic cardiomyopathy
	Glycogen storage disorders
	Mitochondrial diseases
	Danon disease
	Endocardial fibroelastosis
	Myocarditis
Hepatomegaly	Glycogen storage disorders
	Mitochondrial disorders
	Peroxisomal disorder
Macroglossia	Hypothyroidism
	Glycogen storage disorders
Late-onset Pompe disease	
Progressive muscle weakness	Limb-girdle muscular dystrophy
	Becker muscular dystrophy
	Myasthenia gravis
	Polymyositis
	Late-onset glycogen storage disorders
	Late-onset mitochondriopathies

in the classic infantile form), EKG (ventricular hypertrophy and shortened PR interval), and enzymes reflecting muscle destruction (creatine kinase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase).

Measurement of GAA activity in skin fibroblast culture is the gold standard of diagnosis for Pompe disease. Newer methods for detection of enzyme activity in dried blood samples and leukocytes from whole blood, after blocking of neutral maltases, have been developed. Once validated, these new tests will have the advantage of being more expeditious than fibroblast cultures.

Recently, urinary glucose tetrasaccharide has been shown to have high sensitivity. When combined with dried blood enzyme assay, it also has high negative predictive value.[5] Urine glucose tetrasaccharide has also been shown to be a marker of disease severity and hence might be useful in monitoring patient response to enzyme replacement therapy (ERT).

Given the feasibility of dried blood sample testing, pilot programs are currently looking into the reliability and the benefits of adding Pompe disease to newborn screening, although this cannot distinguish between the infantile and adult-onset forms of the disease.

Case part 4. Initial management of the patient included supportive care for respiratory distress and congestive heart failure. Fibroblast cultures reconfirmed diagnosis of Pompe disease and Western blots for band pattern revealed positive cross-reactive immunologic material (CRIM). The patient was subsequently started on ERT.

MANAGEMENT The approval of ERT (Myozyme and Lumizyme) by the US Food and Drug Administration has heralded a new era in the management of Pompe disease. Given the uniformly dismal prognosis, the initial trials in ERT used historical controls to compare treatment outcomes in patients with the classic infantile form. ERT reduced the risk of death by 99%, the risk of death or invasive ventilation by 92%, and the risk of death and any type of ventilation by 88%.[6]

Over the last decade, CRIM status has been well-recognized as a predictive factor in immune responses to ERT in patients with infantile Pompe disease.[7] CRIM status is determined by testing for residual enzyme activity using Western blot analysis. Patients with CRIM-negative status have no residual enzyme activity and are at high risk for mounting a strong antibody response to ERT. Development of a strong antibody response has been shown to be associated with poor clinical outcome, independent of the CRIM status (figure). Multiple immune modulatory regimens are currently being used to optimize the effect of ERT in such patients with high antibody titers. Commonly used regimens include rituximab and methotrexate with or without IV immunoglobulin[8] (figure). Though ERT in adult-onset Pompe disease has shown some improvement, given the variability in baseline presentation and progression of the late-onset disease, assessment of efficacy is more difficult. The emergence of ERT in the last decade has changed the natural course of infantile Pompe disease. Previously unnoticed cognitive changes and brainstem involvement including hearing loss, dysphagia, and bulbar symptoms, as well as residual muscle weakness, have now been recognized in patients treated with ERT.[9]

Despite new advances in treatment, persisting questions have led to novel avenues of research to help optimize therapy. Approaches currently under investigation include gene therapy, chaperone-mediated therapy, adjunctive therapy to ERT, and alternative immune modulatory regimens for patient with antibodies to ERT.

Even though ERT has brought about improved treatment options for Pompe disease, multidisciplinary supportive treatment of the systemic symptoms involved continues to be an essential part of management.[10] Baseline evaluations in cardiorespiratory functions must be established. A baseline chest x-ray, Holter monitoring, and echocardiogram along with regular follow-up with a cardiologist to address cardiac manifestations including

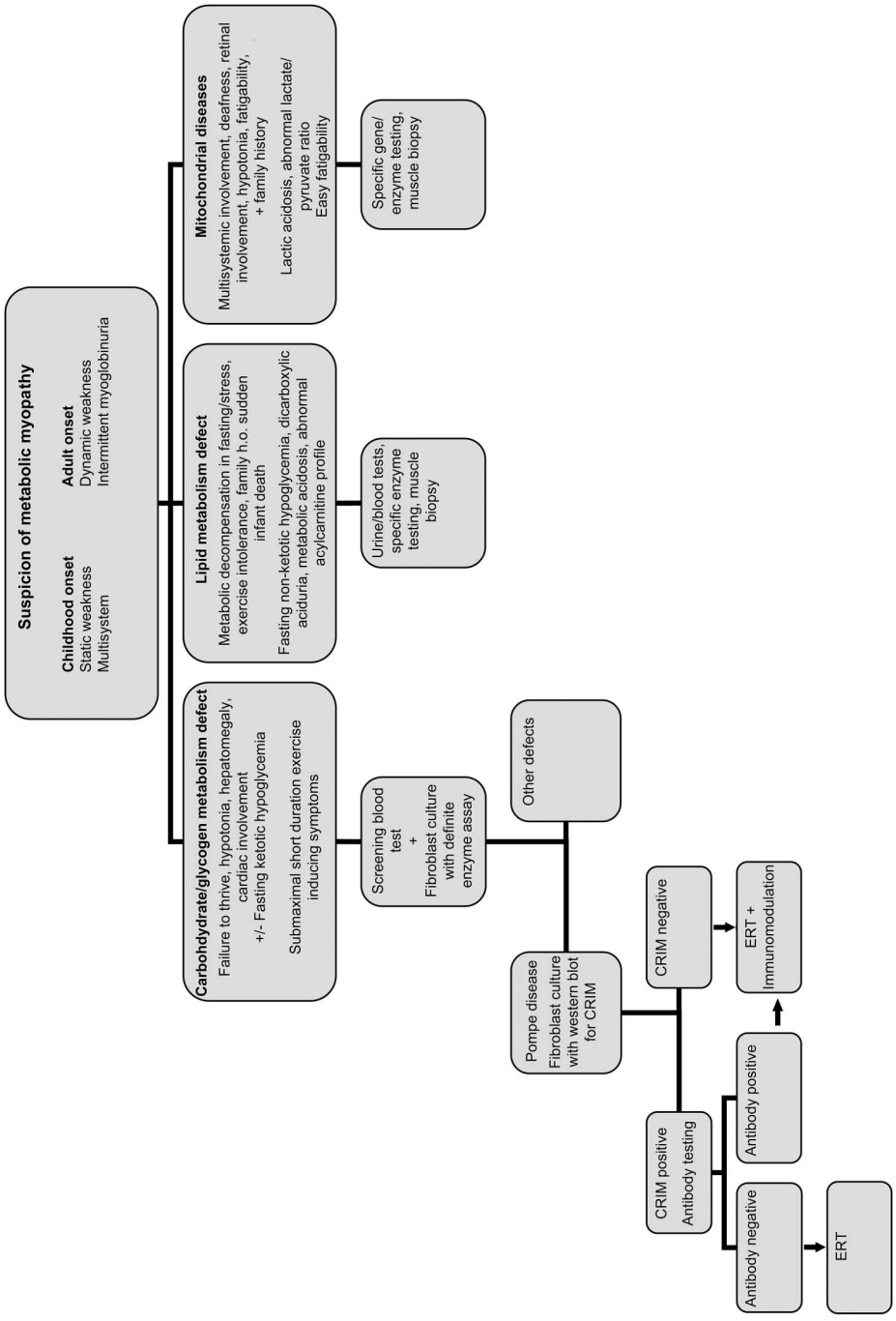

Figure Differential diagnoses of metabolic myopathy and management of Pompe disease based on cross-reactive immunologic material (CRIM)/antibody status

cardiomyopathy, heart failure, and arrhythmias are indicated. Baseline pulmonary function testing and polysomnography establish pulmonary status. Regular screening for daytime sleepiness and fatigue by pulmonary specialists should be conducted to assess the need for supplemental ventilator devices. Testing to ensure safe and adequate nutrition should include a detailed nutritional assessment, evaluation for gastroesophageal reflux, videofluoroscopic swallow assessment, and dual x-ray absorptiometry scan screening for osteopenia.

Given the significant neuromuscular involvement in Pompe disease, a baseline evaluation and follow-up care by a neurologist cannot be overemphasized. An EMG/nerve conduction study may help with diagnosis and assessment for spinal cord involvement or for an alternative diagnosis. Though a muscle biopsy is frequently a part of the workup for weakness, a high clinical suspicion for Pompe disease can alternatively be evaluated by enzyme analysis on blood and a skin biopsy instead. Motor and functional assessments should be monitored at regular intervals to optimize muscle function and to prevent contractures. Age-appropriate hearing assessments need to be conducted at baseline and followed at least annually.

A new exciting phase has emerged in the management of chronic complex storage disorders in the last decade. Along with improving the survival and quality of life, these therapies have changed the natural course

of these diseases. These new horizons emphasize the importance of keeping up to date with novel research in the future, giving hope of cure for a once uniformly fatal disease.

Case follow-up. The patient is currently 15 months old and is able to sit up independently, crawl, and stand without support. She continues to receive ERT every 2 weeks and her cardiac function is much improved.

AUTHOR CONTRIBUTIONS

Deepa S. Rajan: article concept, literature search, and drafting the manuscript. Hoda Abdel-Hamid: manuscript review.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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