Adult Acid Maltase Deficiency

Bashar Katirji, MD, FACP

No one involved in the planning of this CME activity had any relevant financial relationships to disclose.
Authors / faculty had nothing to disclose.

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American Association of Neuromuscular and Electrodiagnostic Medicine

2621 Superior Dr NW Rochester, MN 55901

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CME Information
Product: CS20 - Adult Acid Maltase Deficiency

Course Description
Intended Audience
This course is intended for Neurologists, Physiatrists, and others who practice neuromuscular, musculoskeletal, and electrodiagnostic medicine with the intent to improve the quality of medical care to patients with muscle and nerve disorders.

Learning Objectives
Upon conclusion of this program, participants should be able to:
1. differentiate the various neuromuscular causes of respiratory failure.
2. identify the clinical presentations and manifestations of Pompe disease (acid maltase deficiency).
3. describe the basic pathophysiology and treatment options of Pompe disease (acid maltase deficiency).

Release Date: 3/16/2008
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Duration/Completion Time: 1 hour

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March 2008

CME Available from March 2008 through March 2011

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Presenting Symptom: Respiratory failure and hypercapnea

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Professor of Neurology, Case Western Reserve University School of Medicine

Disclosures: No one involved in the planning of this CME activity had any relevant financial relationships to disclose. Authors / faculty had nothing to disclose.

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Appropriate Audience: Residents, fellows, and practicing physicians.

Learning Objectives: After completing this educational activity, participants will be able to:

1) Differentiate the various neuromuscular causes of respiratory failure.
2) Identify the clinical presentations and manifestations of Pompe disease (acid maltase deficiency).
3) Describe the basic pathophysiology and treatment options of Pompe disease (acid maltase deficiency).
Adult Acid Maltase Deficiency

History

A 37 year-old man developed exertional shortness of breath and early morning headache. He was found
to have hypercarbic respiratory failure (PCO2) with mental status change. He was admitted to an outside
hospital and required endotracheal intubation with mechanical ventilation. He was then transferred to our
institution. The patient was in the medical intensive care unit on mechanical ventilation for 8 days and
was then successfully extubated and switched over to BIPAP.

His past medical history was relevant for chronic obstructive pulmonary disease and chronic bronchitis.
He smoked heavily for about 25 years (>30 years pack).

Commentary I

At this point, this case may represent only a patient with hypercarbic respiratory failure related to chronic
obstructive pulmonary disease or other pulmonary disorder. The early morning headaches are consistent
with hypercarbia.

History, continued

Additional history was obtained from the patient (after extubation) and his spouse. He has had shortness
of breath for 2 years, and weakness and fatigue for last 6 months. He was seen six months prior to
admission by his primary care physician, had a pulse O2 of 75 and was diagnosed with COPD. Since
then, he has noted weakness, manifesting with difficulty climbingstairs and lifting up heavy objects. At the
same time, he has experienced frequent nocturnal arousals, morning headaches, daytime somnolence,
orthopnea, and exertional shortness of breath. He had a normal developmental history and played
football and baseball in childhood. He admits, however, to never been able to sit up from supine position
without using his hands.

Upon review of systems, he denied weight loss, loss of appetite, joint pain, skin rash, fever, and chills.
There is no history of myalgia, muscle cramps or urine discoloration.

His family history reveals that he had no siblings although he had a brother who was born premature and
died few days after birth. He has an 18 year-old son who has normal motor development.

Physical Examination

His blood pressure was 140/80 and heart rate was 68 bpm. His chest was clear on auscultation and there
was no paradoxical breathing. Cardiac auscultation showed normal S1 and S2 sounds and regular
rhythm.

On neurological examination, he was alert and oriented. Visual acuity showed OD 20/20 OS 20/25. Fundi
were normal with no disk edema. Extraocular muscles were normal with no ptosis or facial weakness or
asymmetry. Facial sensation was intact. Tongue and palate were normal.

Muscle bulk and tone normal with no fasciculations. Muscle strength was normal except for mild
weakness (Modified MRC = 5-5) of the iliopsoas, deltoid, infraspinatus muscles bilaterally. On functional
exam, patient used upper extremities in order to get up from chair and was unable to sit up from supine
position without assistance. He had a positive Gowers’ maneuver.
Sensory examination showed position and vibration sensation, proprioception is normal. His deep tendon reflexes were trace throughout. Toes were downgoing.

Coordination was intact on finger to nose and heel to shin test. Gait was slightly waddling. He was able to walk on heels, toes and tandem.

**Commentary II**

The additional findings, obtained from a more detailed history, family history and neurological examination, raise the question of a neuromuscular disorder as the underlying cause of hypercapneic respiratory failure, mild proximal weakness and truncal weakness.

Chronic neuromuscular disorders that may present with chronic respiratory failure include several disorders that affect different components of the motor unit:

1) Anterior horn cell disease (Amyotrophic lateral sclerosis)
2) Peripheral polyneuropathy (Porphyria, Charcot-Marie-Tooth disease, or chronic inflammatory demyelinating Polyradiculoneuropathy)
3) Disorder of neuromuscular junction (Myasthenia gravis, Lambert Eaton myasthenic syndrome, congenital myasthenia syndromes)
4) Myopathy and muscular dystrophy (Myotonic dystrophy, Acid maltase deficiency (Pompe disease), carnitine palmitoyl transferase deficiency)

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**Electrophysiologic Data**

**SENSORY NERVE CONDUCTION STUDIES**

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INSEr tional activity: N, sust, unsust
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OTHer: 0 or fascic, myotonia, myokymia
EFFort: N, decr
RECruitment: N, inc or dec 1+, 2+, 3+, 4+
AMPitude: N, inc or dec 1+, 2+, 3+, 4+
DURation: N, inc or dec 1+, 2+, 3+, 4+
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Diagnostic Impression

EMG examination revealed (a) normal sensory and motor nerve conduction studies, (b) myotonic discharges in deltoid muscles and small motor unit action potentials in the infraspinatus. (c) Marked decrease in the insertional activity of all the cervical, thoracic and lumbar paraspinal muscles with no voluntary motor units consistent with end-stage muscle atrophy. These findings point to a possible myopathy with subtle myotonia and end-stage atrophy of paraspinal muscles.

Further Investigations

Further investigations were done in the following order:

The following tests were slightly elevated: Creatine kinase varied between 162 and 704 IU/L (N = 0-232 IU/L); ESR -15 (0-10), Lactate dehydrogenase- 229 (100-190); Aldolase -19.5 (1.2-7.6); AST 41 (10-37), ALT- 133 (10-65); CRP- 3.40 (0-1.50)

The following were normal or negative: Carnitine total 53.05 (29.11-73.04), Carnitine free 38.94 (23.29 - 57.92).
Pulmonary function tests revealed a restrictive disorder with FVC of 34% of predicted and FEV1 of -37% of predicted, maximal inspiratory pressure (cm H2O) of 38% of predicted, and maximal expiratory pressure of 30% of predicted.

Arterial blood gases on 35% O2, revealed a pH of 7.36, PCO2 62, PO2 78 and O2 Saturation of 95%.

Transthoracic echocardiogram revealed a left ventricular ejection fraction of 50-60%, mild aortic root dilatation, and a moderately increased peak pulmonary artery systolic pressure.

A CT scan of the chest showed bilateral lower lobe consolidation and diffuse muscle atrophy of the paraspinal muscles (Figure 1).

Figure 1

A non-contrasted computerized tomography scan of the chest showing severe atrophy with fat replacement of the paraspinal (arrows) and chest wall muscles in patient (A) compared to an aged matched normal subject (B).

Commentary III

This patient has findings that are most consistent with a myopathy with predominant involvement of respiratory and trunk muscles. The EMG showed subtle myotonic discharges in few proximal muscles.

The differential diagnosis of myopathy with myotonia includes the following:

- Myotonic dystrophies, including DM1 and DM2
- Myotonia congenita, including Thomsen’s disease (dominant) and Becker’s disease (recessive).
- Muscle channelopathies, including Paramyotonia congenital and hyperkalemic periodic paralysis.
- Acid maltase deficiency
- Myotubular myopathy
- Colchicine myopathy
- Other myotonic disorders (Atypical painful myotonia and myotonia fluctuans)

Further Diagnostic Investigations

Based on the two differential diagnostic lists (Commentary II and III), acid maltase deficiency was the most likely diagnosis, causing truncal and respiratory muscle weakness in this patients.

Further tests were done to confirm the diagnosis:
1) Muscle biopsy. Light microscopy was normal with no lumps or vacuoles, including PAS staining. Electron microscopy increased intra-lysosomal glycogen (Figure 2 and 3).
2) Dried blood test for alpha glucosidase was significantly decreased in leukocytes consistent with acid maltase deficiency.
Infantile AMD (Pompe's disease) manifests in the first weeks or months of life with diffuse hypotonia and weakness, giving these infants a "rag doll" appearance (floppy infant syndrome). Muscle bulk may be increased, however, and macroglossia is common. There is massive cardiomegaly and less severe hepatomegaly.

The clinical hallmark of adult onset AMD is a slowly progressive myopathy, starting in the third or fourth decade, but occasionally later, including a few patients with onset in the sixth or seventh decade. Weakness predominates in truncal and proximal muscles, but respiratory muscles are also selectively affected and respiratory insufficiency may be the presenting complaint, with morning headache or exertional dyspnea. The initial diagnosis in most cases is limb-girdle dystrophy or polymyositis. There is no visceromegaly. Serum CK is variably increased in most patients. The ischemic forearm exercise test causes a normal rise of venous lactate, indicating that phosphorolytic glycogen breakdown and glycolysis are normal. On EMG, fibrillation potentials, positive waves, and myotonic discharges are useful clues to the diagnosis, and may be more evident in paraspinal muscles. Studies of pulmonary function show restrictive ventilatory insufficiency, with reduced maximal static inspiratory and expiratory pressures, and
early diaphragmatic fatigue.

Acid maltase deficiency is a hereditary condition transmitted as an autosomal recessive trait. The gene encoding acid maltase is localized on the long arm of chromosome 17.

The difference in clinical expression and pathology between infantile and later-onset forms of acid maltase deficiency has been attributed to the presence of a small but crucial amount of residual acid maltase activity in childhood and adult cases but not in infantile acid maltase deficiency.

Adult AMD is an important consideration in patients thought to have limb-girdle dystrophy or polymyositis. The early and often selective involvement of respiratory muscles and the EMG features, especially in paraspinal muscles (fibrillation potentials, positive waves, complex repetitive discharges, and myotonic discharges), are useful clues to acid maltase deficiency.

Muscle biopsy shows a vacuolar myopathy in all three forms of AMD. In the infantile form, all muscles and all fibers contain many, often confluent vacuoles, resulting in a “lacing” appearance. In childhood and adult AMD, vacuoles are less numerous and tend to be smaller. Furthermore, in adult AMD, biopsies from clinically unaffected muscles may appear normal, despite the marked decrease of AM activity. The vacuoles contain PAS-positive material, and stain intensely for acid phosphatase, another lysosomal enzyme. The positive acid phosphatase stain is a useful diagnostic clue in otherwise normal biopsy specimens. In agreement with morphological appearance, glycogen content is massively increased in muscle from patients with infantile AMD, often reaching a level 10 times higher than normal. Muscle glycogen concentrations are generally lower in childhood AMD and may be normal in adult AMD. Electron microscopy shows that much of the glycogen is contained within single membrane-limited lysosomal “sacs”.

The definite diagnosis of AMD include measuring acid alpha-glucosidase (GAA) activity in muscle (absent in infants; residual activity observed in later onset forms), in leukocytes (may be normal), in cultured skin fibroblasts (technically demanding), or in dried blood spots (most sensitive and specific). Prenatal diagnosis is possible by DNA analysis if the mutation in the family is known. If the genetic defect is not known, acid maltase activity can be measured in cultured amniocytes or chorionic villus samples.

Until recently clinical management consisted solely of palliative care. In 2006, the FDA approved Myozyme® (alg glucosidase) for treatment of infantile Pompe disease. Myozyme consists of the human enzyme acid alpha-glucosidase (rhGAA) produced by recombinant DNA technology in a Chinese hamster ovary cell line.

A multicenter, multinational, open-label, clinical trial examined the safety and efficacy of Myozyme treatment in 18 severely affected patients with Pompe disease who began treatment prior to 6 months of age (Neurology 2007;68(2):88-89). Eligible patients had documented symptoms of infantile-onset Pompe disease, including GAA activity <1% of the normal mean and hypertrophic cardiomyopathy. Patients were randomized equally to either 20 mg/kg or 40 mg/kg IV infusion of Myozyme every two weeks, with length of treatment ranging from 52 to 106 weeks. Efficacy was assessed by comparing the proportions of Myozyme-treated patients who died or needed ventilator support, with mortality of historical cohort (61 untreated patients with infantile-onset Pompe disease). All treated patients survived to 18 months of age. In contrast, there was 98% mortality in historical control group (only 1 of 61 patients survived to the age of 18 months). Six of the 18 patients in the study required some type of ventilator support (3- invasive, 3- noninvasive). Improvement in cardiomyopathy observed in response to rhGAA treatment almost certainly contributes to the prolonged survival. 13 of the 18 treated patients acquired substantial motor and functional skills (7 pts. walked independently). All 18 patients in this study made more motor gains than patients in previous clinical trials with rhGAA possibly because treatment was initiated at such an early age and early stage of disease progression. The conclusion was that treatment with Myozyme reduced the risk of death by 99%, reduced the risk of death or invasive ventilation by 92%, and reduced the risk of death or any type of ventilation by 88%, as compared to an untreated historical control group.

The recommended dosage regimen is 20 mg/kg body weight administered every 2 weeks as an
intravenous infusion. The total volume of infusion is determined by the patient’s body weight and should be administered over approximately 4 hours. The initial infusion rate should be no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes until a maximum rate of 7 mg/kg/hr is reached.

Approximately 15% of patients treated with MYOZYME have developed infusion reactions that involve cardiovascular system (hypo/hypertension, tachy/bradycardia, ventricular extrasystoles), respiratory system (tachypnea, dyspnea, bronchospasm, oxygen desaturation, hypoxia) and cutaneous system (angioneurotic edema, urticaria, rash, erythema, pruritus, livedo reticularis). Few patients (3%), experienced serious hypersensitivity reactions, including anaphylactic reactions. The majority of these reactions occurred in first two hours of the infusion and were typically managed by slowing, interrupting infusions, or symptomatic treatment, such as antihistaminics, acetaminophen, or glucocorticosteroids.

The majority of patients (89%) tested positive for IgG antibodies toward alglucosidase. Most patients who develop anti-alglucosidase antibodies do so within the first 3 months of exposure. There is evidence to suggest that patients developing sustained high titers may have a poorer clinical response to treatment, or may lose motor function as antibody titers increase. Also, infusion reactions appear to be more common in antibody-positive patients.

### Bibliography