Late onset Pompe disease- new genetic variant: Case report

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Abstract

Pompe's disease (acidmaltase deficiency, glycogen storage disease type II) is an autosomal recessive disorder caused by a deficiency of lysosomal acid-1, 4-glucosidase, resulting in excessive accumulation of glycogen in the lysosomes and cytoplasm of all tissues, most notably in skeletal muscles. A case is presented of late-onset Pompe's disease with progressive respiratory failure for about 2 years requiring constant Oxygen supplementation. On physical exams except weight loss and breathlessness everything else was normal.

Alpha glucosidase enzyme activity was reduced 22 (56-296). GAA gene mutation showed a heterozygous missence variation in exon 9 of the GAA gene (chr17.78083769;C>C/G; Depth:141x) that results in the amino acid substitution of Arginine for Proline at codon 451 (p.Pro451Arg:ENST00000302262) was detected. The variant c.1352C>C/G (p.Pro451Arg) detected had an autosomal recessive inheritance pattern. This mutation has not been reported before and it presents with severe progressive respiratory failure. The patient was not given enzyme replacement therapy due to cost but received high protein therapy and Oxygen supplementation using Oxygen extractor machine. She is worsening due to respiratory failure.

Conclusion: This is a new genetic variant isolated of late-onset Pompe disease which presents with almost pure progressive respiratory failure.

Introduction

Pompe disease is a lysosomal storage disorder caused by the deficiency of acid α-glucosidase[1-4]. Deficiency of the lysosomal acid alpha-glucosidase enzyme causes accumulation of glycogen in the lysosomes. The build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly in the heart, skeletal muscles, liver and the nervous system.

The clinical spectrum of Pompe disease is very heterogeneous with regard to the age of onset, disease manifestations and rate of disease progression[3,5]. A vacuolar myopathy is the classic description of the pathology, but in clinical practice the findings can vary substantially from virtually normal muscle to severely abnormal, "end-stage muscle," with prominent necrosis[6]. Muscle biopsy findings vary not only from one patient to the next, but also from one muscle to the next within an individual patient[7]. If the muscle chosen for biopsy is clinically unaffected, a falsely normal biopsy result may be obtained. Thus, a normal muscle biopsy does not exclude the possibility of late-onset Pompe's disease, and clinical suspicion must remain high in patients with appropriate phenotypes despite normal biopsy results. Muscle imaging may allow a more accurate selection of muscle biopsy sites.

A case is presented of adult-onset Pompe disease with an uncommon clinical presentation characterized by severe isolated respiratory failure. The patient has normal muscle biopsy but deficient alpha glucosidase enzyme activity.

Case report

This was a 54 year old black African lady, who suffered from asthma since childhood and is on seretide inhaler. Informed consent was obtained from the patient before publication. Since December 2015, she presented with history of progressive difficulty in breathing and breathlessness which was not remitting on anti-asthma treatment. She has never smoked but

she was living with her husband who stopped smoking 10 years ago. By February 2016 her Oxygen saturations were low to 69% room air and she started depending on Oxygen supplementation. Other diagnosis entertained were Chronic Obstructive Pulmonary Disease (COPD), sarcoidosis, connective tissue disease and probable small septum primum defect due to severe RA overload. No family history of similar illness was elicited.

On investigation, a CT pulmonary angiogram was suggestive of possible pulmonary sarcoidosis. A chest X-ray and lower limb dopplers ultra sound were reported to be normal. Bronchoscopy also revealed a normal airway. Bronchial aspirate was negative for Tuberculosis (TB) stain, TB Polymerase Chain Reaction (PCR) was not detected and culture showed no growth of any organisms, cytology was normal and negative for fungal staining. Echocardiography showed severe pulmonary hypertension, PASP 117mmhg (millimeter of mercury), severely dilated Right Atrium with Tricupsid Regurgitation+++ and Right Ventricular overload with flattening and paradoxical motion of the septum. Left ventricle size was normal with EF 65%.

Other tests done were full blood count, urinalysis, kidney functions, calcium levels, D-dimers, International Normalized Ratio (INR), Aldolase level, Creatine phosphokinase (CPK) level, Lactate Dehydrogenase *(*LDH) level, blood sugar level, liver function tests, Erythrocyte Sedimentation Rate (ESR), Angiotensin Converting Enzyme, serum proteins and magnesium levels which were all normal. Human Immunodeficiency Virus *(*HIV*)* test, anti-double stranded DNA (anti-dsDNA), antinuclear antibody (ANA), Lupus anticoagulant, Anti-phospholipid antibodies, Venereal Disease Research Laboratory test (VDRL), Perinuclear Anti-Neutrophil Cytoplasmic Antibodies (p-ANCA), Cytoplasmic Antineutrophil Cytoplasmic Antibodies (c-ANCA), Extractable Nuclear Antigens (ENA) and Anti-Cyclic Citrullinated Peptide (anti-CCP) were done and were reported negative. Only C-reactive protein was slightly elevated to 8.05mg/L. Nerve conduction study and electromyography done was normal. Muscle biopsy done of biceps muscles showed no muscle abnormality and lipofuscin staining was negative. Glucosidase level was found to be deficient at 22 (56-296) suggestive of POMBE Disease. GAA gene mutation showed a heterozygous missence variation in exon 9 of the Acid Alpha-Glucosidase (GAA) gene (chr17.78083769;C>C/G; Depth:141x) that results in the amino acid substitution of arginine for proline at codon 451(p.Pro451Arg:ENST00000302262) was detected. The variant c.1352C>C/G(p.Pro451Arg) detected had an autosomal recessive inheritance pattern and it suggested a new variant of Pompe disease with severe respiratory involvement. She could not start on myozyme due to cost. She is currently not able to walk for 20 metres without Oxygen and clinically she is deteriorating.

Discussion

Pompe disease is an autosomal recessive metabolic disorder[8] which damages muscle and nerve cells throughout the body. It is caused by an accumulation of glycogen in the lysosome due to deficiency of the lysosomal acid alpha-glucosidase enzyme. It is the only glycogen storage disease with a defect in lysosomal metabolism, and the first glycogen storage disease to be identified, in 1932 by the Dutch pathologist J. C. Pompe.

The build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly in the heart, skeletal muscles, liver and nervous system. More alpha glucosidase present in the individual's muscles means symptoms occur later in life and progress more slowly. Type of Pombe depends on onset i.e infantile-onset form and late onset.

Respiratory symptoms may occur during the night, with apnoea or hypoventilation worsening the clinical course[9]. Hagemans *et al*[10] did not find any correlation between the age of 29 patients with late-onset Pompe disease and the presence, in some cases, of severe respiratory insufficiency without severe limb girdle muscle weakness, and highlighted that respiratory function should be monitored independently from the degree of peripheral muscle weakness. The case presented has basically respiratory failure.

The following is a list of symptoms seen in Pompe disease[10-14] starting with musculoskeletal system. A patient can present with musculoskeletal progressive proximal muscle weakness (trunk and lower limbs), gait abnormalities, muscle pain, difficulty when climbing stairs, frequent falls, scapular winging and difficulty chewing or jaw muscle fatigue. Respiratory system patient can present with respiratory complications caused by weakening of the diaphragm and other respiratory muscles, respiratory failure, orthopnea, exertional dyspnea, respiratory tract infections, daytime somnolence, morning headache and nocturnal hypoventilation. In cardiac they may have arrhythmias. Gastrointestinal system patients can present with feeding and swallowing difficulties and poor weight gain/maintenance. Creatine Kinase (CK) levels may be normal to elevated, with or without symptoms.

The disease is caused by a mutation in a gene (acid alpha-glucosidase: also known as acid maltase) on long arm of chromosome 17 at 17q25.2-q25.3 (base pair 75,689,876 to 75,708,272). To date, almost 300 distinct GAA mutations have been identified, although not all are considered pathogenic[15]. Muscle biopsy depends on muscle isolated, severity of disease and duration of disease. The occurrence of progressive, sometimes fatal, respiratory failure is primarily due to the inability of the respiratory muscles to generate normal levels of pressure and airflow during in- and expiration. These events significantly impair the removal of airway secretions and, therefore, recurrent infections, even pneumonia and atelectasis, which can eventually result in severe respiratory failure, were reported[16]. Respiratory symptoms may occur during the night, with apnoea or hypoventilation worsening the clinical course[17]. Pellegrini *et al*[18] did not find any correlation between the age of 29 patients with late-onset Pompe disease and the presence, in some cases, of severe respiratory insufficiency without severe limb girdle muscle weakness, and highlighted that respiratory function should be monitored independently from the degree of peripheral muscle weakness. When Pompe disease presents in children or adults, the predominant sign is usually progressive muscle weakness, generally beginning with the trunk and proximal muscles of the lower limbs[17]. Early respiratory involvement resulting from degeneration of the diaphragm and other respiratory muscles may manifest as respiratory insufficiency, including orthopnea and indications of sleep-disordered breathing such as morning headaches and daytime fatigue[18].

Treatment of Pompe disease: Cardiac and respiratory complications are treated symptomatically. Physical and occupational therapy may be beneficial for some patients. Myozyme was FDA approved for Pompe disease in 2006

Prognosis: The prognosis for individuals with Pompe disease varies according to the onset and severity of symptoms. Without treatment the outcome is poor. On myozyme (enzyme replacement herapy) it can delay onset of use of ventilator.

Investigational therapies: Gene therapy is also being studied as another approach to therapy for individuals with Pompe disease. In gene therapy, the defective gene present in a patient is replaced with a normal gene to enable the produce of the active enzyme and prevent the development and progression of the disease in question. Modifications to existing enzyme replacement therapy in an effort to improve effectiveness includes exploring ways to improve the uptake of recombinant acid alpha-glucosidase by muscle cells.

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