Research

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Pompe Disease in Morocco A New Mutation Causing Severe Infantile-Onset

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1. Abstract

Pompe disease is an autosomal recessive disorder caused by a deficiency in 1,4-a-glucosidase, characterized by progressive glycogen accumulation in cellular lysosomes. It ultimately leads to cellular damage. Infantile-onset Pompe disease (IOPD) is the most severe type of this disease and is characterized by severe hypertrophic cardiomyopathy and generalized hypotonia.

To date, approximately 400 pathogenic mutations have been reported in the GAA gene. we identified a novel mutation in the acid alpha-glucosidase (GAA) gene: C.[236_246del11], The patient was a 5 months years old female with hypertrophic cardiomyopathy and a family history of sister dead at earlier age. After definite diagnosis, enzyme-replacement therapy (ERT) was started for the patient. But unfortunately, she dead 4 months after beginning of the treatment by decompensation of her heart diseases by viral bronchiolitis.

2. Keywords:
Enzyme replacement therapy, Glycogen storage disease type II, GAA protein, Human, Cardiomyopathy

3. Introduction

Pompe disease was described by Dutch pathologist J. C. Pompe18 in 1932, is a rare autosomal recessive disorder caused by a deficiency of the enzyme acid alpha-glucosidase leading to glycogen accumulation in cellular lysosomes and finally cellular damage. (1) The gene has been localized to chromosome 17q25.

The spectrum of disease severity varies among patients and has been historically classified as either infantile or late-onset (juvenile or adult), based on age of onset and clinical ,(2)sever infantile GSDII results from complete or near complete deficiency of acid a-glucosidase, the disease presents during the first months of life with severe hypotonia, cardiomegaly, macroglossia, and mild hepatomegaly. the x-ray usually reveals massive cardiac enlargement. [3]

The diagnosis “Pompe disease” is confirmed by the finding of a complete deficiency of acid α-glucosidase activity in all classic-infantile cases or a markedly reduced activity (usually <30% of average normal).[3] The development of the enzyme-replacement therapy (ERT) since 2006 had improve the outcome of this patients.[4] Approximately 400 pathogenic mutations have been reported in the GAA gene [5]. we identified a novel mutation in the acid alpha-glucosidase (GAA) gene: C.[236_246del11].

4. Case Report

A 5-month-old girl was referred to our institution from her community hospital due to a respiratory distress. With medical history of consanguinity first degree and sister died at the age of 7 months, victim of sudden death. On physical examination she was found with heart failure, hepatomegaly and severe cardiomegaly with macroglossia and generalized hypotonia without facial deformation. The echocardiography showed hypertrophic cardiomyopathy.

The diagnosis was confirmed through enzyme assay on a dried blood specimen, which revealed decreased alpha-glucosidase activity. A definite diagnosis was made through molecular analysis. The GAA gene was analyzed by polymerase chain reaction (PCR), The result of the molecular analysis is the following mutation: C.[236_246del11].

As soon as the diagnosis was confirmed, Myozyme® (alglucosidase alfa, Sanofi Genzyme, USA) was initiated for the patient (20 mg/kg, every 2 wk). At 8 months of age, after 3 months of treatment we had notice decrease of cyanosis during breast feeding and the respiratory distress with obtention of head control. But fortunately, she dead at the age of 10 months by decompensation of his cardiopathy by viral bronchiolitis.

To the best of our knowledge, this mutation is a novel, previously undetected, pathogenic nonsense mutation, associated with severe, classical IOPD with a bad prognosis. Written consent was taken from the parents for the presentation of this case.

5. Discussion

We identified a novel disease-causing nonsense mutation in exon 4 of the *GAA* gene. This mutation led to a premature stop codon, which

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very likely resulted in a truncated protein or loss of protein production. Consequently, as was expected, the disease outcome was very severe and had an early infantile onset. This finding supports the previous view that IOPD is a result of truncating mutations. [6]

The phenotype of classical early-onset Pompe cases is almost identical to that of our case, with severe cardiomyopathy, progressive muscle weakness, organomegaly and fatal outcome before the age of 1 year. A number of conditions affecting this age group may have similar findings including metabolic and non-metabolic neuromuscular disorders. A systematic multistep approach is recommended to reach a definite diagnosis, starting with a complete general and neurological examination followed by the measure of CK serum activity. Immediately after this initial approach it is suggested to store blood samples for DBS and leucocytes to perform alpha-glucosidase enzymatic assay and DNA testing, as necessary. The diagnostic approach must continue through careful electrophysiological or pathological investigations.[7]

Currently as many as 400 pathogenic mutations have been deleted. Most mutations are unique to each patient; nevertheless, some of them are more prevalent in certain populations [8]. For example among Caucasians, the c.-32-13T>G mutation is the most common. [9] In 2006 Rachel E. Palmer reported an Argentinean case of IOPD with the same novel homozygous frameshift mutation **C.[236_246del11].** [10]

Our case has responded well to ERT in the beginning of treatment but unfortunately, she dead at the age of 10 months by decompensation of his cardiopathy by viral bronchiolitis.

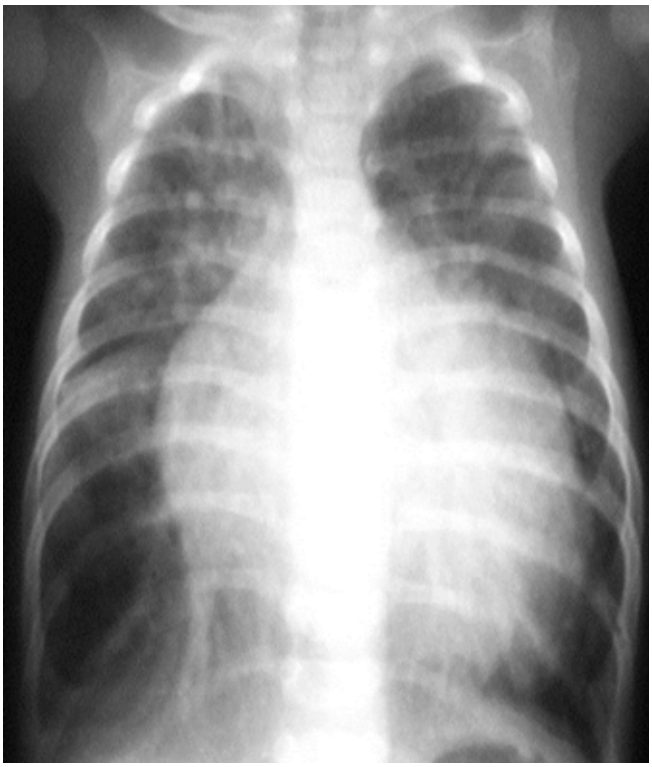
Several articles have been published on response to ERT among IOPD patients. A review article performed by Chien YH et al. showed that ERT was overall beneficial. The authors reported that ERT was able to cause a gradual decrease in heart size 3 months after treatment commencement. Additionally, mortality in their report was also decreased up to 99%. However, response to treatment was variable among the patients, with the treatment being more effective if started early before the destruction of the muscle architecture.[11]

As any protein infusion, it may cause allergic reactions due to immunoglobulin G (IgG) antibodies.[12] In general, these are mild or moderate reactions and are controlled by slowing the infusion rate or temporarily interrupting it until manifestations are resolved; also, antihistamines and corticosteroids may be used as premedication. As an isolated event, a severe anaphylactic reaction may occur due to immunoglobulin E (IgE) antibodies, which reinforces the need for infusion in a hospital setting.

Other specific treatments [13] are being developed, including gene therapy, autologous hematopoietic cell transplantation in association with lentivirus, chaperone use, second generation recombinant ERT, and substrate reduction therapy, but their clinical benefits have not been demonstrated yet.

Treatment effectiveness should be assessed through a careful, regulated follow-up by a multidisciplinary team coordinated by a health care provider with experience in PD, improvement or stabilization give the indication to continue with ERT.[14]

Figure 1: Simple A-P radiograms showing conspicuous cardiomegaly



6. Conclusion

A female patient with a new homozygous mutation in exon 4 of the *GAA* gene (c. **236_246del11.**) was herein introduced. She doesn't survive despite beginning ERT at 6 months old. As a result, future possible patients with this mutation must begin treatment earlier with regulated follow-up.

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