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Case Series

Clinical Presentation of Some Cases of Lysosomal Storage Diseases that Can Use Enzyme Replace Therapy (ERT)

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Abstract

Lysosomal Storage Diseases (LSD) are caused by changes in the functioning of the lysosome. Most are of autosomal recessive transmission. Three of the LSD (Fabry, Hunter and Danon) have a transmission linked to the X chromosome. In some LSD diseases, we can use enzyme replace therapy (ERT).

We reviewed the clinical presentation of six diseases, that can be treated by ERT. They are: Fabry, Gaucher, Pompe, Hunter, Morquio and Maroteaux-Lamy.

The results showed that Fabry disease took so many years until the final diagnose was performed. The first symptoms of hands pain was confused at 3 years of age with juvenile rheumatoid arthritis. The timing of the clinical presentation of Pompe, Gaucher, Morquio and Maroteaux-Lamy cases, were compatible with what is described in the literature. The clinical signs of Hunter case appeared when the child is one-year old. What is described is that the first physical signs are detected at two years of age.

Keywords: *Faby; Gaucher; Pompe; Hunter; Morquio; Maroteaux-Lamy; Clinical Symptoms*

Introduction

Lysosomal Storage Diseases (LSD) are a group of about 50 metabolic diseases, caused by changes in the functioning of the lysosome. Most are of autosomal recessive transmission. Three of the LSD (Fabry, Hunter and Danon) have a transmission linked to the X chromosome. Around 90% of LSD, so far does not have specific treatment. In some cases, we can use enzyme replace therapy (ERT) [1-5].

Purpose of the Study

We reviewed the clinical presentation of six diseases, that can be treated by ERT. They are: Fabry, Gaucher, Pompe, Hunter, Morquio and Maroteaux-Lamy.

Cases Reports

Fabry

A 31 years old male, presented with history of anhidrosis since 9 years of age, even after vigorous physical exercise associated with xerostomy. His past history revealed hands pain at 3 years of age that was diagnosed as juvenile rheumatoid arthritis. He has also a well-

defined subcutaneous fatty cystic image (0.2 x 0.6 x 0.6 cm) in dorsal part of left foot and punctiform purpuric macules (< 1 mm) involving the lips, hands and trunk since that time but classified as folliculitis after biopsy. A second skin biopsy was done recently in the purpuric macules and showed thin epidermis and mild hyperkeratosis. This was compatible with angiokeratoma. Abdomen CT scan revealed hepatic and left renal cyst. The blood spot test showed low enzyme activity of α-Galactosidase A: 0.13 (N: > 1.8 uM/hr). The molecular study confirmed GLA gene hemizygous mutation in exon 7.

Gaucher

A 6 years old girl, presented with lip pallor for the last 2 months, without any other symptoms until one week before admission, when she started to have easy fatigue. She was admitted for study. During the examination, despite pallor in skin, eyelids and lips, splenomegaly (3 cm) was observed. She has fever- 38.5°C. The blood test revealed Hemoglobin- 5.5 g/dl, Reticulocytes count 0.001 (N: 0.005 - 0.02), RBC- 2.18 x 10^12/L, MCV- 77.1, WBC- 4.12, Neutrophils- 49.3%, Lymphocytes- 46.4%, Platelets- 339 x 10^9/L. Coagulation test - normal. ESR- 8, Ferritin- 168 ug/L (N: 13 - 68), Iron- 30 umol/L (7.2 - 26.9). Immune test for IgA, IgG, IgM, ANA, C3 and C4 were all negative. Thalassemia screening was negative. All biochemical tests were also normal. Blood and urine culture were both negatives. Parvovirus, Flu test, RSV, CMV, EBV and Toxoplasmosis were also negative. *Mycoplasma pneumonia* IgM titer showed positive- 1:1280. Abdominal ultrasound confirmed splenomegaly. The child start treatment with blood transfusion and azithromycin for 5 days because the anemia and splenomegaly at that moment, seems caused by *Mycoplasma* infection. The patient few days later after complete antibiotic treatment, restart again signs of anemia and the hemoglobin level dropped to 4.4 g/dl. After new red blood transfusion, increased to 7.2 g/dl but dropped again to 6.8 g/dl, few days later. At that moment, was decided to do bone marrow aspiration and found active marrow with left shifted erythropoiesis and iron block. Because the spleen was increasing (4.5 cm) and persistent anemia, with poor respond to blood transfusion, Gaucher disease was suspected. The result showed reduced B-Glucosidase activity- 0.65 (N: > 1.8 uM/hr), compatible with Gaucher disease. The gene test for GBA confirmed the diagnosis.

Pompe

A 2 years old boy, showed muscle weakness and difficulty in climbing stairs. His CK was not too high: 236 (N: < 190 U/L). The acid α-glucosidase enzyme was low, compatible with Pompe disease. The gene test confirmed the diagnosis with GAA, c.2237G>C(p.Trp746Ser),c.1757C>(p.Ala586Val).

Hunter

A 13 months old boy, had global development delay, coarse face, tick hair, severe adenoid hypertrophy and history of left hydronephrosis and ureter pelvic junction obstruction. The blood spots showed GAGS elevated in urine: heparin sulphate - 203 ng/mL (N: 3.21 - 23.87) and dermatan sulphate - 379 ng/mL) (N: 0.43 - 6.32). The iduronate-2-sulphate sulphatase was low: 0.18 (N:>4.45 uM/hr). These results were compatible with Hunter disease. A hemizygous IDS/IDSP1 rearrangement was detected confirming the disease.

Morquio

A 3 years old boy was sent to Metabolic consultation, because of short stature (83 cm - Percentile < 3), low growth velocity (1 cm/year), macrocephaly, pectus carinatum and genu valgum. MRI of the brain showed mega cisterna magna. Skeletal x ray, revealed typical features of dysostosis multiplex with breaking metacarpals and lumbar vertebral bodies, genu valgum and flattened acetabulum. Cervical CT scan revealed flat cervical vertebra, hypoplasia of the odontoid process and the corresponding spinal canal is narrowed. Spinal stenosis in C1. Heart echo showed mild redundant tricuspid leaflet with trivial regurgitation and also mitral regurgitation. GAGS in urine showed increase level: 31.5 umol/mmol Cr (n: < 15.7). All clinical and radiological features pointed for a storage disease, like mucopolysaccharidoses type IV or Morquio disease. The DNA study confirm type A one: GALNS gene; c.115 116delGA; pAsp39ArgfsX6; EX1/CDS1, chr16:88923170..88923171; homozygous, likely pathogenic.

Maroteaux-Lamy

A 15 months old boy presented with hypotonia, umbilical hernia, hip dislocation. At that moment he didn't have coarse face or dysostosis multiplex. Because he relapsed again the hip dislocation at 24 months of age and started to show some features reminding storage disease, like mild coarse face and thick hair, we checked urine GAGS: 43 (N: 4 - 11 mg/nmol creatinine). The Arylsulfatase B showed: 0 nmol/h/mg protein in the leucocytes (N: 109 - 522) and 0 nm/h/mg in the fibroblasts (N: 122 - 664), compatible with Maroteaux-Lamy disease.

Discussion

Fabry, Gaucher, Pompe, Hunter (Mucopolysaccharidosis type 2 - MPS2), Morquio A (MPS4A), Marateaux-Lamy (MPS6), are a group of lysosomal disorders (LSD) that we can use enzyme replacement therapy.

Fabry disease is an inherited X-linked autosomal recessive disease caused by an inability to produce an enzyme called alpha-galactosidase or alpha-GAL. Without this enzyme, globotriaosylceramide or GL-3, accumulate in the blood vessels, leading to malfunctioning of the kidneys, heart and brain. Pain is considered the first and most common of all symptoms and appear around 6 to 9 years of age. There are two types of pain: acroparasthesia and "Fabry crises". In acroparasthesia, pain affects the hands and feet. It is described as burning pain and may be intermittent or daily. In "Fabry crises", the episodes are intense, with burning pain, initially in the hands and feet and radiating to other parts of the body. They can last from a few minutes to a few days. Other symptoms are: hypohidrosis/anhidrosis, frequent fevers, overheating with physical exercise and intolerance to hot weather, angiokeratoma characteristic purple-red rash, is the most visible sign of Fabry's disease are found from the navel to the knees and in some cases, only on the elbows or knees. Cornea verticillate is similar to the rays of a bicycle wheel (does not affect the vision) and ophthalmoscopy of slit lamp confirm the diagnosis. Other symptoms included, epigastric pain, diarrhea and nausea after meal, renal insufficiency due to excess proteinuria, cardiomyopathy, arrhythmias, heart failure, dizziness, headache, stroke and depression.

Our case 1 (Fabry), the symptoms appeared at 3 years of age and the supposed juvenile rheumatoid arthritis was already acroparasthesia that is the first presentation of Fabry disease. The others symptoms, particularly anhidrosis and the skin changes, were presented in our case too. Even with these classical symptoms, the diagnosis was done only at the age of 33 years of age.

Gaucher disease, is caused by enzymatic deficiency of glucocerebrosidase. This enzyme is not digested within the lysosome, progressively accumulating in the macrophages. These macrophages are increasing in size, being called "Gaucher cells". These cells accumulate mainly in the liver, spleen, marrow, and may cause spontaneous bone fractures. There are 3 types of Gaucher disease: Type 1, is the most frequent, is non-neuropathic or chronic non-neuropathic adult form. Patients may be asymptomatic or present with various forms of hepatosplenomegaly, hematological alterations or bone atrophy. Type 2: acute neuropathy or neuropathic infant form, hepatosplenomegaly, severe hematological changes and death, especially in the first two years of life. Type 3: neuropathic subacute or juvenile neuropathic form with hepatosplenomegaly, anemia, thrombocytopenia, osteopenia, slowly progressive neuropathy symptoms from childhood and death between 20 and 40 years.

Our case 2 (Gaucher), pallor and fatigue were the main symptoms, associated with splenomegaly and anemia. The persistent relapse of anemia was the key point for the diagnosis associated with increase spleen in the patient.

Pompe disease, is caused by decreased activity of alpha-glucosidase-acid. There are two forms of clinical presentation. The infantile form revealed progressive muscle weakness, hypotonia, motor delay, macroglossia, areflexia, progressive respiratory weakness, respiratory insufficiency, frequent respiratory infections, cardiorespiratory insufficiency, cardiomegaly, difficulty swallowing, sucking and/or feeding.

Our case 3 (Pompe), the child has weakness and difficulty in climbing stairs. The mild elevation of CK levels are not common, because generally the values are higher. The ERT will reduce the risk of the symptoms to appear earlier.

Hunter disease is x-linked disease. At birth, they don't show any features of the condition. After 2 years of age, we can find full lips, large rounded cheeks and macroglossia, cornea opacity, umbilical hernia, dysostosis multiplex, hepatosplenomegaly, psychomotor regression, claw hands and carpal tunnel syndrome. They can have also sleep apnea, narrowing of the spinal canal (spinal stenosis) in the neck and can compress and damage the spinal cord. Heart valve abnormalities can cause ventricular hypertrophy. Children with MPS II grow steadily until about age 5 and then their growth slows and they develop short stature. Individuals with this condition have joint deformities (contractures) that significantly affect mobility.

Our case 4 (Hunter), the child showed early signs at 13 months with global delay, tick hair and coarse face. For this reason, we can diagnosis the disease and later start ERT.

Morquio disease or MPS IV has two types: A, more frequent and B that is less common. MPS IV A, results from mutations in the gene encoding galactosamine-6-sulfatase (GALNS), and MPS IV B is secondary to beta-galactosidase (GLB1) deficiency. The clinical features result from accumulation of keratan sulfate and chondroitin-6-sulfate. Clinically, at one year of age, we can find short stature, pectus carinatum, kyphoscoliosis and genu valgum. C1-C2 subluxation can result in cervical cord compression due to atlantoaxial instability and odontoid dysplasia, beginning with fatigue and progressing to weakness and later respiratory arrest. Mild corneal opacities, hepatosplenomegaly and valvular heart disease may occur in Morquio disease. Some patients develop progressive hearing loss. Enamel hypoplasia is seen in MPS IV A but not IV B. In our case, the patient showed short stature, pectus carinatum, genu valgum, mild mitral and tricuspid regurgitation, but no eyes, hearing, liver or spleen involvement.

Our case 5 (Morquio), the patient has short stature, macrocephaly, pectus carinatum and genu valgum. The physical signs were important for the suspicious of the disease, but the normal intelligence is a clinical All others symptoms didn't appear probably because the diagnosis was done so early. The heart ultrasound has also mild changes. After ERT, these symptoms are expected to stabilize and can reduce the risk of heart failure after some years.

Maroteaux-Lamy disease or MPS VI, also known as, is an autosomal recessive inherited lysosomal disorder. The deficient enzyme is Arylsulfatase B. This result in multisystem accumulation of dermatan sulfate, one of the glycosaminoglycans (GAGS). The child presented with coarse face, macrocephaly, corneal clouding, glaucoma, impaired hearing, enlarged tongue, sleep apnea, obstructive and restrictive airway disease, cardiomyopathy, cardiac arrhythmia, pulmonary hypertension, hepatosplenomegaly, umbilical and inguinal hernias, hip dysplasia, joint stiffness, spinal cord compression and carpal tunnel syndrome. The intelligence is normal, like in Morquio disease.

Our case 6 (Maroteaux-Lamy), a 15 months old boy presented with hypotonia, umbilical hernia, hip dislocation. We only found mild coarse face when he was 24 months of age. When we have a patient this phenotype and motor regression, we need to do for screening GAGS in the urine. If positive, we need to advance for another test, that is enzyme active in blood and later on, gene study for confirmation.

Conclusion

Some LSD disorders are nowadays possible to do the ERT. To avoid complications and severe sequela, an early diagnosis is the main point for the success of the treatment.

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